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2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis (JIA): Therapeutic Approaches for Oligoarthritis, Temporomandibular Joint (TMJ) Arthritis and Systemic JIA

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ABSTRACT

Objective: To provide updated guidelines for pharmacologic management of juvenile idiopathic arthritis (JIA), focusing on treatment of oligoarthritis, temporomandibular (TMJ) arthritis and systemic JIA (sJIA), with and without macrophage activation syndrome (MAS).

Recommendations regarding tapering and discontinuing treatment in inactive systemic JIA are also provided.

Methods: We developed clinically relevant **p**opulation, **i**ntervention, **c**omparator, and **o**utcomes (PICO) questions. After conducting a systematic literature review, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was used to rate the quality of evidence (high, moderate, low, very low). A voting panel including clinicians and patients/caregivers achieved consensus on the direction (for or against) and strength (strong or conditional) of recommendations.

Results: Similar to those published in 2019, recommendations are based on clinical phenotypes of people with JIA, rather than a specific classification schema. These guidelines provide recommendations for initial and subsequent treatment of JIA with oligoarthritis, TMJ arthritis and sJIA as well as for tapering and discontinuing treatment in inactive sJIA. Other aspects of disease management, including factors that influence treatment choice and medication tapering are discussed. Evidence for all recommendations was graded as low or very low in quality. For that reason, more than half of the recommendations are conditional.

Discussion: This clinical practice guideline complements the 2019 American College of Rheumatology (ACR) JIA and uveitis guidelines which covered polyarthritis, sacroiliitis, enthesitis and uveitis. It serves as a tool to support clinicians, patients and caregivers in decision-making. These recommendations take into consideration the severity of both articular and non-articular manifestations as well as patient quality of life. Although evidence is generally

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low quality and many recommendations are conditional, the inclusion of caregivers and patients in the decision-making process strengthens the relevance and applicability of the guideline. It is important to remember that these are recommendations. Clinical decision-making, as always, remains in the hands of the treating clinician and patient/caregiver.

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SIGNIFICANCE

These treatment recommendations emphasize:

- Decreased reliance on long-term nonsteroidal anti-inflammatory drugs and oral glucocorticoids.
- Early use of conventional synthetic and biologic disease-modifying antirheumatic drugs.
- Importance of shared decision-making with the patient/caregiver.

INTRODUCTION

Reflecting the changing medical landscape, the American College of Rheumatology (ACR) regularly updates clinical practice guidelines and plans to review these annually and update, as needed. The process for updating the 2011 and 2013 JIA guidelines began in 2017[1, 2]. Important clinical topics for consideration were first identified at a meeting to define the scope of the guidelines. Advances in the treatment of JIA and better understanding of pathogenesis dictated separating this clinical practice guideline into several parts due to the breadth of topics. The first part, addressing polyarthritis, sacroiliitis, enthesitis and uveitis, was published in two manuscripts in 2019[3, 4]. The second part, presented here in 2 papers, covers a) oligoarthritis, temporomandibular joint (TMJ) arthritis, systemic arthritis (sJIA) and b) non-pharmacologic treatments, patient monitoring, immunizations and imaging. .[5]. The methods and literature review described below reflects the unified process used for the second part of these guidelines, including both manuscripts. Recommendations were intended to be complementary to the 2019 guidelines and are grouped based on disease phenotypes and severity, not by specific classification criteria, reflecting decision-making in clinical practice.

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Following the selection of topics, we developed clinically relevant **p**opulation, **i**ntervention, **c**omparator and **o**utcomes (PICO) questions. Using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, recommendations were then developed based on the best available evidence for commonly encountered clinical scenarios. Prior to final voting, input was sought from relevant stakeholders including a panel of young adults with JIA and caregivers of children with JIA to consider their values and perspectives in making recommendations. Both the patient/caregiver and guideline voting panels stressed the need for individualized treatment while being mindful of available evidence.

METHODS

This guideline follows the ACR guideline development process and ACR policy guiding management of conflicts of interest and disclosures (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines), which includes GRADE methodology [6, 7] and adheres to AGREE criteria[8]. Supplementary Appendix 1 includes a detailed description of the methods. Briefly, the core leadership team (KO, DH, DL, SS) drafted clinical PICO questions. PICO questions were revised and finalized based on feedback from the entire guideline development group and the public. The literature review team performed systematic literature reviews for each PICO, graded the quality of evidence (high, moderate, low, very low) and produced the evidence report (see Supplementary Appendix 2). Note that GRADE methodology does not distinguish between lack of evidence (i.e., none) and very low-quality evidence.

The core team defined multiple critical study outcome(s) for PICOs relevant to each JIA phenotype (see Supplementary Appendix 3).

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A virtual panel of 15 members, including young adults with JIA and caregivers of children with JIA, moderated by the principal investigator (KO), reviewed the evidence report and provided input to the voting panel. Two members of this panel (JH, KM) were also members of the voting panel, to ensure that the patient voice was part of the entire process. The voting panel reviewed the evidence report and patient/caregiver perspectives and then discussed and voted on recommendation statements. Consensus required ≥70% agreement on both direction (for or against) and strength (strong or conditional) of each recommendation as per ACR practice. A recommendation could be either in favor of or against the proposed intervention and either strong or conditional. According to GRADE, a recommendation is categorized as strong if the panel is very confident that the benefits of an intervention clearly outweigh the harms (or vice versa); a conditional recommendation denotes uncertainty regarding the balance of benefits and harms, such as when the evidence quality is low or very low, or when the decision is sensitive to individual patient preferences, or when costs are expected to impact the decision. Thus, conditional recommendations refer to decisions in which incorporation of patient preferences is a particularly essential element of decision making.

Rosters of the core leadership, literature review team and both panels are included in Supplementary Appendix 4.

Guiding Principles

1) Consistent with the ACR's 2019 JIA guidelines, these recommendations are for persons diagnosed with JIA.

2) Aside from poor prognostic features specified within the recommendations themselves (e.g., specific joints for oligoarthritis, MAS), extra-articular coexisting conditions that would influence disease management, such as uveitis, psoriasis or inflammatory bowel disease, are not addressed within these guidelines.

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3) Recommendations are intended to be used by all clinicians caring for persons with JIA and assume that patients do not have contraindications to the recommended pharmacologic treatments

4) Longer-term glucocorticoid therapy in childhood is not appropriate because of its effects on bone health and growth. Thus, wherever glucocorticoids are suggested, recommended treatment should be limited to the lowest effective dose for the shortest duration possible.

5) Shared decision-making with families and patients is important when considering treatment options.

RESULTS/RECOMMENDATIONS

The initial literature review included topics addressed in this manuscript and in the second paper (add ref to other JIA GL paper), identified 4308 manuscripts in searches for all PICO questions through August 7, 2019. A July 9, 2020 search update identified 367 more references, for a total of 4675 papers after duplicates and non-English publications were removed. After excluding 2291 titles and abstracts, 2384 full-text articles were screened. Of these, 1939 were excluded (see Supplemental Appendix 5, leaving 445 articles to be considered for the evidence report. In the end, 406 papers were matched to PICO questions and included in the final evidence report. Quality of evidence was uniformly low or very low; 17 PICO questions lacked any associated evidence (Tables 1 and 3-7). The following recommendations are based on 62 PICO questions. Several PICO questions were split into 24 sub-PICO questions to improve specificity. Nine questions initially posed were discarded by the voting panel because of redundancy or lack of relevance.

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Final recommendations are described below and in Tables 3-7, which include reference(s) to which PICO question(s) in the evidence report correspond to the recommendation statement.

ACTIVE OLIGOARTHRITIS (Figure 1)

Oligoarthritis refers to children presenting with involvement of 4 or fewer joints without systemic manifestations. It may include patients categorized in different categories of JIA[9] but share in common limited numbers of joints involved; guidance for patients with active uveitis, sacroiliitis or enthesitis can be found in the 2019 guidelines[3, 4]. TMJ arthritis is discussed separately.

NSAIDs

A trial of scheduled NSAIDs is conditionally recommended as part of initial therapy for active oligoarthritis.

NSAIDs have long been the cornerstone of treatment for oligoarthritis and can ease discomfort[10-12]. However, the initial NSAID trial should be brief due to potential adverse effects (e.g., gastritis, bruising) and limited efficacy (unless inactive disease is achieved). Voting panelists could not agree on the appropriate duration of initial use before escalating therapy, as some panelists choose to avoid the use of NSAIDs altogether.

Glucocorticoids

Intra-articular glucocorticoids (IAGCs) are strongly recommended as part of initial therapy for active oligoarthritis.

Triamcinolone hexacetonide is strongly recommended as the preferred agent.

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Despite low-quality evidence, IAGCs are strongly recommended due to low potential of adverse effects and high likelihood of sustained response[13-15]**.** Patients and caregivers agreed as to the utility of IAGC but voiced concerns over the need for sedation in younger children and associated risks.

Despite an overall grading of evidence as low, the panel was convinced by published randomized trials and large observational studies that triamcinolone hexacetonide leads to more durable clinical responses than triamcinolone acetonide, leading to the strong recommendation[16-18]. Triamcinolone hexacetonide has been unavailable in the US for several years. However, very recently, the FDA has allowed the importation of one particular formulation of triamcinolone hexacetonide specifically for joint injections in patients with JIA, to address this identified unmet medical need.

Oral glucocorticoids are conditionally recommended *against*, as part of initial therapy for active oligoarthritis.

Despite recommendations against, if oral glucocorticoids are given to quickly alleviate severe symptoms when IAGC is not available or feasible, or prior to the onset of action of DMARDs, treatment should be limited to the lowest effective dose for the shortest duration possible[19, 20].

Conventional synthetic DMARDs (csDMARDs)

csDMARDs are strongly recommended if there is an inadequate response to scheduled NSAIDs and/or IAGCs for active oligoarthritis.

Methotrexate is conditionally recommended as a preferred agent over leflunomide, sulfasalazine or hydroxychloroquine (in that order).

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Despite absence of comparator trials, methotrexate is the preferred agent given preponderance of evidence showing long-term safety and efficacy in childhood[21-23]. Because methotrexate tolerability is variable, additional treatment options are provided[24-27].

As for route of methotrexate, the 2019 JIA guidelines conditionally recommended subcutaneous methotrexate over oral methotrexate for polyarthritis[3]. This recommendation was conditional because the supporting evidence was of very low quality and patient preferences may guide choice of route of administration. There is little reason to suggest that methotrexate should be used differently in oligoarthritis than in polyarthritis.

Biologic DMARDs (bDMARDs)

bDMARDs are strongly recommended if there is inadequate response or intolerance to NSAIDs and/or IAGC and at least one csDMARD for active oligoarthritis.

There is no preferred bDMARD.

bDMARDs are preferred over combining csDMARDs or switching to a different csDMARD due to bDMARDs' having a greater likelihood of yielding rapid and sustained improvement in JIA[28, 29]. While combination csDMARDs have been used for adults with RA, in children the combination appears to be less effective and less tolerable. For these reasons, this recommendation is strong[30].

Although tumor necrosis factor inhibitors (TNFi) are the most commonly used bDMARDs in childhood[31-33], other bDMARDs of proven efficacy in the treatment of JIA may be used. In the absence of head-to-head trials for children with oligoarthritis[34], bDMARD selection may be driven by specific provider and patient/caregiver preferences and circumstances with the exception of IL-1 inhibitors, which are preferentially used for the treatment of sJIA[28, 35-37]

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Risk factors for poor prognosis and disease activity measures

Consideration of risk factors for poor outcome (e.g., involvement of ankle, wrist, hip, sacroiliac joint and/or TMJ, presence of erosive disease or enthesitis, delay in diagnosis, elevated inflammatory markers, symmetric disease) is conditionally recommended to guide treatment decisions.

Use of validated disease activity measures is conditionally recommended to guide treatment decisions, especially to facilitate treat-to-target (T2T) approaches.

Treatment for oligoarthritis can and should be modified based on the involvement of specific joints or disease features[38, 39]. This could include rapid escalation of treatment (e.g., if there is TMJ involvement or erosive disease at presentation) or alternative medication choice (e.g., sulfasalazine or bDMARD rather than methotrexate for sacroiliitis)[3].

Voting panelists conditionally recommended formal assessment of disease activity using validated measures. Several validated disease activity measures for childhood arthritis exist[40]. The lack of demonstrated superiority of specific measures and the likelihood of future changes led voting panelists to defer stating formal preferences for particular measures. Measures that can be considered include Wallace preliminary criteria for Clinical Remission, ACR preliminary criteria for inactive disease, Juvenile Arthritis Disease Activity Score (JADAS) and clinical cJADAS, amongst others[41-43].

T2T approaches have been strongly endorsed for polyarticular JIA[41], and preliminary data has demonstrated feasibility as well as improved outcomes[44, 45]. Despite limited studies in oligoarticular disease, one would expect a similar response. Presence of risk factors for poor outcomes may justify rapid escalation of treatment.

ACTIVE TMJ ARTHRITIS (Figure 2)

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TMJ disease may be isolated or part of generalized arthritis. Treatment of TMJ arthritis is critical, as patients/caregivers noted high impact on oral health related quality of life (QOL) and challenges with diagnosis and effective pharmacologic treatment[46, 47]. This guideline, therefore, suggests treating TMJ arthritis regardless of presence of clinical symptoms. While NSAIDs and/or IAGCs may be sufficient treatment for some patients, rapid escalation to bDMARDs (potentially in combination with csDMARDs) is often appropriate, given the impact and destructive nature of TMJ arthritis, despite limited evidence[48].

NSAIDs

A trial of scheduled NSAIDs is conditionally recommended as part of initial therapy for active TMJ arthritis.

NSAIDs have long been the cornerstone of treatment for JIA and can ease discomfort[10]. However, the initial NSAID trial should be brief due to potential adverse effects (e.g., gastritis, bruising) and limited efficacy (unless inactive disease is achieved). Voting panelists could not agree on the appropriate duration of initial use before escalating therapy as some panelists avoid the use of NSAIDs altogether.

Glucocorticoids

IAGCs are conditionally recommended as part of initial therapy for active TMJ arthritis.

There is no preferred agent.

IAGCs may alleviate joint symptoms and help restore function. This recommendation is conditional as there have been unique TMJ specific serious adverse events, including heterotopic ossification and impaired growth[48-51]. Therefore, IAGCs for TMJ arthritis should be

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used sparingly for symptomatic children, preferably those who are skeletally mature[49, 52]. There is no comparative data between different IAGC formulations for TMJ injections.

Oral glucocorticoids are conditionally recommended *against* as part of initial therapy for active TMJ arthritis.

Despite recommendations against, if oral glucocorticoids are given to quickly alleviate severe symptoms prior to the onset of action of DMARDs, treatment should be limited to the lowest effective dose for the shortest duration possible[19].

csDMARDs

csDMARDs are strongly recommended for inadequate response or intolerance to NSAIDs and/or IAGCs for active TMJ arthritis.

Methotrexate is conditionally recommended as a preferred agent over leflunomide.

TMJ is a high-risk joint due to major impact on activities of daily living, and, thus, early use of csDMARD therapy is encouraged. The limited evidence available supports the use of methotrexate[53]. However, because not all patients tolerate methotrexate well, leflunomide is recommended as an alternative, if needed.

bDMARDs

bDMARDs are conditionally recommended for inadequate response or intolerance to NSAIDs and/or IAGCs and/or at least one csDMARD for active TMJ arthritis.

There is no preferred bDMARD.

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Voting panelists deferred recommending a specific bDMARD because current studies of TMJ arthritis have been small and observational[48, 54]. TNFi have been most commonly used. As noted earlier, the use of IL-1 inhibitors is restricted to the treatment of sJIA.

CF Note

SYSTEMIC JIA (sJIA) WITH AND WITHOUT MACROPHAGE ACTIVATION SYNDROME (MAS) (Figure 3)

sJIA is recognized as distinct from all other categories of JIA due to fever, rash and visceral involvement and is considered by some to be an autoinflammatory disorder[55]. Disease pathogenesis and cytokine involvement are different from other categories[56-58]. Up to 40% of cases of sJIA are associated with MAS, a secondary hemophagocytic syndrome that is a life-threatening complication requiring urgent recognition and treatment. MAS presents with fevers, high ferritin, cytopenias, elevated liver function tests (LFTs), low fibrinogen and high triglycerides[59, 60]. As MAS may occur at any point during the disease course, careful monitoring is necessary for children with or without MAS at presentation.

Initial therapy: sJIA without MAS

bDMARDs

IL-1 and IL-6 inhibitors are conditionally recommended as initial monotherapy for sJIA without MAS.

There is no preferred agent.

IL-1 and IL-6 inhibitors are extremely effective and well-tolerated treatments for sJIA [56-58] and have been rapidly adopted in clinical practice[61, 62]. Use of IL-1 and IL-6 inhibitors to treat sJIA has allowed for marked reduction in glucocorticoid use[56, 57, 63]. Patients/caregivers agreed

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with this recommendation, given historical delays and limits in clinical response and toxicities from other medications before the bDMARD era.

Some voting panelists preferred starting with a short-acting agent such as anakinra, but in the absence of controlled studies, no preferred agent was endorsed. Patients/caregivers noted preference for fewer injections, if possible. As response to individual agents is variable, switching amongst and between IL-1 and IL-6 inhibitors, when needed, for lack of efficacy or poor tolerability is appropriate.

Concerns were expressed about a highly fatal lung disease observed in some children with sJIA, most treated with bDMARDs. Observed risk factors include younger children with MAS, children with a history of reactions to tocilizumab and those with trisomy 21[64, 65]. The exact etiology for sJIA-associated lung disease and recommendations for screening remain under investigation. Affected children often present with acute digital clubbing, which should raise immediate concern[64, 65]. However, voting panelists noted the need to balance the effectiveness and relative safety of bDMARDs with the rarity of this serious outcome. Voting panelists were also motivated by the extent of morbidity from undertreated sJIA and glucocorticoid-associated toxicities before the bDMARD era[66, 67].

NSAIDs are conditionally recommended as initial monotherapy for sJIA without MAS.

Studies suggest that a small proportion of patients with sJIA will respond to NSAIDs alone[68]. Patients/caregivers agreed with a short trial of NSAIDs for those children. If clinical response is not rapid and complete, rapid escalation of therapy is recommended. Voting panelists could not agree on the appropriate duration of initial use before escalating therapy, as many panelists avoid the use of NSAIDs altogether for sJIA.

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Glucocorticoids

Oral glucocorticoids are conditionally recommended *against* as initial monotherapy for sJIA without MAS.

In most cases, oral glucocorticoids should not be used as initial monotherapy and, if used, should be limited to the lowest effective dose for the shortest duration possible. This recommendation is conditional as bDMARDs may not always be immediately available, and glucocorticoids may help control systemic and joint manifestations until IL-1 or IL-6 inhibitors can be started.

csDMARDs

csDMARDs are strongly recommended *against* as initial monotherapy for sJIA without MAS.

This recommendation is strong despite limited evidence as authors took note of multiple small studies of sJIA that documented lack of efficacy at controlling systemic features that are typically present at onset of disease, leading to a continued need for glucocorticoids[62, 69]. csDMARDs can be considered in combination with bDMARDs for children with prominent arthritis[70]. In areas where biologic therapy is not rapidly attainable, thalidomide has been used to treat sJIA[71]. However, given ready bDMARD availability in North America and risks of thalidomide toxicity, use of thalidomide was not considered as part of these guidelines.

Subsequent therapy: sJIA without MAS

IL-1 and IL-6 inhibitors are strongly recommended over a single or combination of csDMARDs for inadequate response or intolerance to NSAIDs and/or glucocorticoids for sJIA without MAS.

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Most physicians and patients/caregivers preferred quickly starting IL-1 or IL-6 inhibitors for insufficient response to NSAIDs or glucocorticoids[62]. Panel members were persuaded by trials that documented resolution of systemic signs and ability to discontinue glucocorticoids [56, 72-74]

For sJIA without MAS with an inadequate response to IL-1 or IL-6 inhibitors and residual arthritis, the addition of a csDMARD or a switch to different bDMARD is strongly recommended over use of chronic glucocorticoids.

There is no preferred agent.

Given the potential toxicities from chronic glucocorticoids[19], patients should receive steroid-sparing treatments for residual arthritis. Many options exist (e.g., adding methotrexate, switching to abatacept or TNFi) and ample evidence supports the use of DMARDs for sJIA-associated synovitis[22, 75].

Initial therapy: sJIA with MAS

bDMARDs

Infections can trigger MAS; therefore, all persons with MAS should be evaluated for infection concurrently with or prior to therapy[76, 77].

IL-1 or IL-6 inhibitors are conditionally recommended over calcineurin inhibitors alone to achieve inactive disease and resolution of MAS for sJIA and MAS.

There is no preferred agent.

IL-1 and IL-6 inhibitors have proven to be very helpful in the treatment of sJIA and MAS[78-80]. Some voting panelists noted that monotherapy may not be sufficient for severely ill

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individuals[79]. Some may require bDMARDs combined with glucocorticoids and calcineurin inhibitors to control MAS[81].

Glucocorticoids

Glucocorticoids are conditionally recommended as part of initial treatment of sJIA with MAS.

The benefits of glucocorticoids for MAS often outweigh their risks, even in patients whose MAS is triggered by infection. Systemic glucocorticoids may be necessary for severely ill individuals because they can have a rapid onset of action. However, although treatment with high dose glucocorticoids may be required for disease control, subsequent glucocorticoid therapy should be limited to the lowest effective dose for the shortest duration possible. Longer-term glucocorticoid therapy in childhood is not appropriate because of its effects on bone health and growth[19].

Inactive sJIA with or without history of MAS

Tapering and discontinuing glucocorticoids is strongly recommended after inactive disease has been attained for sJIA.

The risk of flare from sJIA that is well controlled is considerably outweighed by possible harms from chronic glucocorticoid use, even at low doses, accounting for this strong recommendation[82]. If a patient is on both DMARDs and glucocorticoids, systemic glucocorticoids should be tapered and discontinued first before attempting to taper bDMARDs or csDMARDs. It is unclear how soon or rapidly these can be safely discontinued in inactive disease for sJIA.

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Tapering and discontinuing bDMARDs is conditionally recommended after inactive disease has been attained for sJIA.

Children with sJIA and inactive disease states may be able to maintain these states on lower doses of bDMARDS or after stopping them[70,83]. It is unclear how soon after achievement of inactive disease these can be tapered. No method of tapering is specified (e.g., decreasing dosage vs. spacing out intervals between doses) given lack of evidence, but patients/caregivers tended to prefer spacing out intervals[82].

DISCUSSION

The recommendations presented in this work are a companion to those published in 2019[3, 4] and cover areas not previously addressed: oligoarthritis, TMJ arthritis and sJIA with and without MAS. In many ways, one must view this guideline as a map for future study. Most of the available evidence was very low quality for the relevant PICO questions, contributing to 22/33 of the recommendations being conditional. None of the recommendations was supported by moderate or high-quality evidence. Similar to the 2019 guidelines, recommendations are grouped based on disease phenotype and not by specific classification criteria, reflecting clinical practice where disease characteristics, severity and risk of damage generally drive treatment decisions. These recommendations differ quite substantially from those published in 2011 and 2013[1, 2], reflecting increased experience with and availability of bDMARDs as well as a deeper understanding of JIA pathogenesis and long-term risks of undertreatment.

The voting and patient/caregiver panels both engaged in vigorous discussions over the use of NSAIDs and oral glucocorticoids[84] in the treatment of JIA, regardless of phenotype. Given the availability of safer, effective alternatives, both panels agreed that these medications should be

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used sparingly and largely as a bridge until more definitive treatment is available. This is a marked change from previous clinical practice where both were mainstays of treatment and subsequent risk of chronic disability was high.[85, 86]

Another major change in recommendation for the treatment of sJIA is the use of bDMARDs as initial treatment or upon inadequate response to a short course of NSAIDs. The addition of csDMARDs is only recommended for persistent synovitis despite treatment with bDMARDs. This recommendation reflects growing understanding about the roles of specific cytokines in this disease and the ability to induce remission with targeted therapy against IL-6 and IL-1[58, 70, 87]. Reports of a highly fatal lung disease in some bDMARD-treated young children with sJIA temper this enthusiasm, and additional investigation is required to determine what role, if any, bDMARDs play in the pathogenesis of this complication[64, 65].

This guideline's focus on oligoarthritis complements previously published recommendations for polyarthritis[3]. However, it was clear in voting panel discussions that the number of involved joints alone was insufficient to tailor treatment decisions. Specific involvement of key joints (e.g., TMJ, wrist, sacroiliac, hip and ankle) and other features (e.g., erosions) were considered reasonable justification for early escalation of therapy[88]. This approach is reflected in a distinct set of recommendations specifically addressing TMJ arthritis.

The use of IAGCs was extensively discussed. Recommendations from 2011 and 2019 to preferentially use triamcinolone hexacetonide for oligoarthritis were reaffirmed, [1, 3] while no specific formulation for TMJ IAGC injection was noted. Triamcinolone hexacetonide has been

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shown to be superior to alternative injectable glucocorticoids in achieving and maintaining remission in children with JIA[16-18]. Triamcinolone hexacetonide has been commercially unavailable in the U.S. for many years, forcing physicians to consider less effective, more toxic or more costly alternatives. However, very recently the FDA allowed the importation of one particular formulation of triamcinolone hexacetonide specifically for joint injections in patients with JIA, to address an identified unmet medical need[89].

There is much that remains to be learned. Studies that lead to high quality data to fill in the evidentiary gaps must be done (see Supplemental Appendix 6). Important areas remain with little or no evidence to guide management, setting a road map for future investigation. Head-to-head trials are needed to understand the optimal order and roles of csDMARDs and bDMARDs for children with JIA. We need improved understanding of which class of medication is best for a particular child allowing for more precise treatment and less time before remission is attained. Biosimilars were not addressed in these guidelines, as these medications were not included in the literature review, and there was no available evidence assessing their use in JIA. More widespread use of biosimilars will add more questions about their relative safety and effectiveness in children who start or switch to them for JIA.

Patient/caregiver input was instrumental in creating these recommendations. Several major themes emerged from their participation. Patients/caregivers stressed the need for individualizing treatments because what works for one does not work for all[90]. To facilitate individualization, no rigid time frames were required for an advancement of treatment. Moving quickly may be needed for a patient who is rapidly worsening, while moving slower may be appropriate for somebody who has improved substantially but not fully. Panel participants emphasized the critical importance of shared decision-making that considers patients' and caregivers' values, goals, and preferences[91]. The depth and breadth of impact that JIA has on

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the lives and well-being of affected children and their families cannot be overstated[92, 93]. Hopefully in the future, more effective, reliable treatments will be available for JIA[94].

This guideline breaks new ground in recommending treatment withdrawal for children with sJIA, who may have lower risks of flare than other forms of JIA[95, 96]. As we look toward the future, we can only hope that similar recommendations around tapering medications can be made for every JIA category. Biomarkers are needed that can help distinguish between disease that is treated from that which has completely resolved as currently the risk of relapse remains high upon medication tapering.

The low quality of evidence supporting these recommendations underscores the importance of clinical judgment and shared decision-making in everyday care of individuals with JIA. Similarly, these guidelines and the many uncertainties therein represent a powerful reminder of the need for more high-quality evidence to support (or refute) current practices and improve the management and well-being of all individuals living with JIA.

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Table 1: Strength of recommendations/quality of supporting evidence

Arthritis Phenotype	Strength of Recommendation			Quality of Supporting Evidence			
	Number of Recommendations	Conditional	Strong	Very Low	Low	Moderate	High
Oligoarthritis	9	4	4	6	2	0	0
TMJ Arthritis	6	4	1	5	0	0	0
Systemic JIA	10	5	4	9	0	0	0
Total	22	13	9	20	2	0	0

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Table 2: Classes of interventions	
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Any at therapeutic dosing [Ibuprofen, Naproxen, Tolmetin, Indomethacin, Meloxicam, Nabumetone, Diclofenac, Piroxicam, Etodolac, Celecoxib]
Conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs)	Methotrexate, Sulfasalazine, Hydroxychloroquine, Leflunomide, Calcineurin inhibitors [cyclosporin A, tacrolimus]
Biologic DMARDs (bDMARDs)	Tumor necrosis factor alpha inhibitors (TNFi): Adalimumab, Etanercept, Infliximab, Golimumab, Certolizumab pegol Other Biologic Response Modifiers (OBRM): Abatacept, Tocilizumab, Anakinra, Canakinumab
Targeted synthetic DMARD (tsDMARD)	JAK inhibitor: Tofacitinib
Glucocorticoids	Oral: Any Intravenous: Any Intraarticular: Triamcinolone Acetonide, Triamcinolone Hexacetonide

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Table 3: Oligoarthritis			
Recommendations	**Certainty of Evidence**	**Based on the evidence report(s) of the following PICO(s)**	**Evidence table(s) on page(s)**
A trial of consistent NSAIDs is **conditionally** recommended as part of initial therapy.	Very Low	PICO 1: In children with oligoarticular JIA, should a trial of consistent NSAIDs be recommended?	6-9
Intra-articular glucocorticoids (IAGCs) are **strongly** recommended as part of initial therapy.	Very Low	PICO 2: In children with oligoarticular JIA, should adding intraarticular glucocorticoids to initial therapy be recommended?	10-19
Triamcinolone hexacetonide (THA) is **strongly** recommended as the preferred agent.	Low	PICO 4: In children with oligoarticular JIA, should a specific steroid type be recommended for intraarticular injection?	21-27
Oral glucocorticoids are **conditionally** recommended *against* as part of initial therapy	Very low	PICO 3: In children with oligoarticular JIA, should adding oral steroids to initial therapy be recommended?	19-20
csDMARDs are **strongly** recommended if there is an inadequate response to scheduled NSAIDs and/or IAGCs.	Low (MTX) Very Low (Lef, Sulfa, Hydroxy)	PICO 5. In children with oligoarticular JIA, should DMARD therapies be recommended, and should there be any preferred order of treatment: methotrexate (subcutaneous or oral),	28-41

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Methotrexate is *conditionally* recommended as a preferred agent over leflunomide, sulfasalazine and hydroxychloroquine (in that order).		leflunomide, sulfasalazine, and/or hydroxychloroquine?	
bDMARDs are **strongly** recommended if there is an inadequate response or intolerance to NSAIDs and/or IAGC and at least one csDMARD. ---------- There is no preferred bDMARD.	Very Low	PICO 6. In children with oligoarticular JIA, should biologic therapies be recommended, and should there be any preferred order of treatment: anti-TNF treatment, biologic treatments with other mechanisms of action?	42-47
Consideration of risk factors for poor outcome (e.g., involvement of ankle, wrist, hip and/or TMJ, presence of erosive disease, delay in diagnosis, elevated inflammatory markers, symmetric disease) is **conditionally** recommended to guide treatment decisions.	Very low	PICO 9. In children with oligoarticular JIA, should poor prognostic features alter the treatment paradigm? ---------- PICO 19. In children with JIA with active TMJ arthritis, should poor prognostic features alter the treatment paradigm?	51-52, 60
Use of validated disease activity measures is **conditionally** recommended to guide treatment decisions, especially to facilitate treat-to-target approaches.	Very low	PICO 10. In children with oligoarticular JIA, should disease activity measures alter the treatment paradigm?	52

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Table 4: TMJ arthritis			
Recommendations	**Certainty of Evidence**	**Based on the evidence report(s) of the following PICO(s)**	**Evidence table(s) on page(s)**
A trial of consistent NSAIDs is **conditionally** recommended as part of initial therapy.	Very Low	PICO 11. In children with JIA with active TMJ arthritis, should a trial of consistent NSAIDs be recommended and should there be any preferred NSAID treatment?	53
IAGCs are **conditionally** recommended as part of initial therapy. --- There is no preferred agent.	Very low Very low	PICO 12. In children with JIA with active TMJ arthritis, should adding intraarticular glucocorticoids to initial therapy be recommended? --- PICO 14. In children with JIA with active TMJ arthritis, should a specific steroid type be recommended for intraarticular injection?	53-57 58
Oral glucocorticoids are **conditionally** recommended *against* as part of initial therapy.	Very low	PICO 13. In children with JIA with active TMJ arthritis, should adding oral glucocorticoids to initial therapy be recommended?	58
csDMARDs are **strongly** recommended for inadequate response or intolerance to NSAIDs and/or IAGCs. ---	Very low	PICO 15. In children with JIA with active TMJ arthritis, should DMARD therapies be recommended, and should there be any preferred order of treatment: methotrexate	58-59

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Methotrexate is **conditionally** recommended as a preferred agent over leflunomide.		(subcutaneous and oral), leflunomide, sulfasalazine, and/or hydroxychloroquine?	
bDMARDs are **conditionally** recommended for inadequate response or intolerance to NSAIDs and/or IAGCs and at least one csDMARD. --- There is no preferred biologic agent.	Very low	PICO 16. In children with JIA with active TMJ arthritis, should systemic biologic therapies be recommended, and should there be any preferred order of treatment: anti TNF, biologic treatments with other mechanisms of action?	59
Consideration of poor prognostic features (e.g., involvement of ankle, wrist, hip and/or TMJ, presence of erosive disease, delay in diagnosis, elevated inflammatory markers, symmetric disease) is **conditionally** recommended to guide treatment decisions.	Very low	PICO 19. In children with JIA with active TMJ arthritis, should poor prognostic features alter the treatment paradigm?	60

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Table 5: sJIA without MAS			
Recommendations	**Certainty of Evidence**	**Based on the evidence report(s) of the following PICO(s)**	**Evidence table(s) on page(s)**
NSAIDs are **conditionally** recommended as initial monotherapy. Oral glucocorticoids are **conditionally** recommended *against* as initial monotherapy.	Very low	PICO 20: In patients with treatment naïve, newly diagnosed sJIA without MAS, should non-DMARD treatment (NSAIDs, glucocorticoids) be used as initial therapy?	61-67
csDMARDs are **strongly** recommended against as initial monotherapy.	Very low	PICO 21. In patients with treatment naïve, newly diagnosed sJIA without MAS, should DMARD treatment (methotrexate, calcineurin inhibitor) be used as initial therapy and is there a preferred order?	67-68
Biologic DMARDs (IL-1 and IL-6 inhibitors) are **conditionally** recommended as initial monotherapy. ---------- There is no preferred agent	Very low	PICO 22. In patients with treatment naïve, newly diagnosed sJIA without MAS, should biologic treatment (Anakinra, Canakinumab, Tocilizumab or others) be used as initial therapy and is there a preferred order?	69-71
IL-1 and IL-6 inhibitors are **strongly** recommended over a single or combination of csDMARDs for inadequate response or intolerance to	Very low	PICO 23. In patients with sJIA without MAS who do not respond to initial therapy with non-biologic treatments (NSAIDs, glucocorticoids, DMARDs), should	72-130

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NSAIDs and/or glucocorticoids.		non-biologic treatments be combined or biologic treatment started?	
For sJIA without MAS with an inadequate response to IL-1 or IL-6 inhibitors and residual arthritis, the addition of a csDMARD or a switch to a different bDMARD is **strongly** recommended over use of chronic glucocorticoids. --- There is no preferred agent.	Very low	PICO 27. In sJIA patients who cannot achieve inactive disease despite treatment with both IL-1 and IL-6 agents and/or are chronically steroid dependent, is chronic stable steroid treatment superior to non-steroid treatments (cytoxan or abatacept or rituximab or IVIG or mesenchymal stem cell transplant or bone marrow transplant) at achievement of inactive disease, achievement of partial response, growth, ability to taper/discontinue steroids, and minimize side effects/medication toxicity?	138

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Table 6: sJIA with MAS			
Recommendations	**Certainty of Evidence**	**Based on the evidence report(s) of the following PICO(s)**	**Evidence table(s) on page(s)**
*Formal recommendation deferred	Very low	PICO 24. In patients with sJIA, does the presence of subclinical MAS alter the treatment paradigm?	130
IL-1 and IL-6 inhibitors are **conditionally** recommended over calcineurin inhibitors alone, in order to achieve inactive disease and resolution of MAS. --- There is no preferred agent. Glucocorticoids are **conditionally** recommended as part of initial treatment of sJIA with MAS	Very low	PICO 25. In patients with sJIA and overt MAS, Is biologic therapy superior to calcineurin inhibitors in achievement of inactive disease and resolution of MAS?	131-136
*Formal recommendation deferred	Very low	PICO 26. For non-response or partial response to biologic therapy, is addition of calcineurin inhibitor superior to etoposide or IVIG or plasmapheresis at achievement of inactive disease, resolution of MAS?	137-138
bDMARDs or csDMARDs are **strongly** recommended over chronic glucocorticoids	Very low	PICO 27. In sJIA patients who cannot achieve inactive disease despite treatment with both IL-1 and	138

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for residual arthritis and an incomplete response to IL-1 and/or IL-6 inhibitors. ---------- There is no preferred agent.		IL-6 agents and/or are chronically steroid dependent, is chronic stable steroid treatment superior to non-steroid treatments (cytoxan or abatacept or rituximab or IVIG or mesenchymal stem cell transplant or bone marrow transplant) at achievement of inactive disease, achievement of partial response, growth, ability to taper/discontinue steroids, and minimize side effects/medication toxicity?	

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Table 7: sJIA inactive disease			
Recommendations	**Certainty of Evidence**	**Based on the evidence report(s) of the following PICO(s)**	**Evidence table(s) on page(s)**
Tapering and discontinuing glucocorticoids is **strongly** recommended after inactive disease has been attained	Very low	PICO 28. In sJIA patients with inactive disease treated with oral steroids, is taper to discontinuation of steroids superior to continuing long-term stable dose steroids for preventing disease flare and minimizing side effects/medication toxicity?	139
Tapering and discontinuing bDMARDs is **conditionally** recommended after inactive disease has been attained.	Very low	PICO 29: In sJIA patients in clinical remission on biologic monotherapy, is tapering by decreasing dose superior to tapering dosing interval at preventing disease exacerbation, preventing development of anti-drug antibodies and minimizing medication toxicity?	140-143

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REFERENCES

1. Beukelman T, Patkar NM, Saag KG, et al. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. *Arthritis Care Res (Hoboken)*.2011;63(4):465-82.
2. Ringold S, Weiss PF, Beukelman T, et al. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. *Arthritis Care Res (Hoboken)*.2013;65(10):1551-63.
3. Ringold S, Angeles-Han ST, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis. *Arthritis Rheumatol*.2019;71(6):846-863.
4. Angeles-Han ST, Ringold S, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Screening, Monitoring, and Treatment of Juvenile Idiopathic Arthritis-Associated Uveitis. *Arthritis Care Res (Hoboken)*.2019;71(6):703-716.
5. Onel KH, D.;Shenoi,S;. 2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis (JIA): Therapeutic Approaches for Oligoarthritis, Temporomandibular Joint Arthritis (TMJ), and Systemic JIA, Medication Monitoring, Immunizations and Non-Pharmacologic Therapies. presented at: ACR Convergence; 11/08/2020 2020;
6. Andrews JC, Schunemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *J Clin Epidemiol*.2013;66(7):726-35.
7. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*.2008;336(7650):924-6.
8. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ*.2010;182(18):E839-42.
9. Petty RE, Southwood TR, Baum J, et al. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. *J Rheumatol*.1998;25(10):1991-4.
10. Chhabra A, Oen K, Huber AM, et al. Real-World Effectiveness of Common Treatment Strategies for Juvenile Idiopathic Arthritis: Results From a Canadian Cohort. *Arthritis Care Res (Hoboken)*.2020;72(7):897-906.
11. Brik R, Gepstein V, Berkovitz D. Low-dose methotrexate treatment for oligoarticular juvenile idiopathic arthritis nonresponsive to intra-articular corticosteroids. *Clin Rheumatol*.2005;24(6):612-4.
12. Kvien TK, Hoyeraal HM, Sandstad B. Naproxen and acetylsalicylic acid in the treatment of pauciarticular and polyarticular juvenile rheumatoid arthritis. Assessment of tolerance and efficacy in a single-centre 24-week double-blind parallel study. *Scand J Rheumatol*.1984;13(4):342-50.
13. de Oliveira Sato J, Albuquerque Pedrosa Fernandes T, Bicalho do Nascimento C, et al. Probability of remission of juvenile idiopathic arthritis following treatment with steroid joint injection. *Clin Exp Rheumatol*.2014;32(2):291-6.
14. Marti P, Molinari L, Bolt IB, et al. Factors influencing the efficacy of intra-articular steroid injections in patients with juvenile idiopathic arthritis. *Eur J Pediatr*.2008;167(4):425-30.

For peer review only

15. Breit W, Frosch M, Meyer U, et al. A subgroup-specific evaluation of the efficacy of intraarticular triamcinolone hexacetonide in juvenile chronic arthritis. *J Rheumatol*.2000;27(11):2696-702.
16. Zulian F, Martini G, Gobber D, et al. Comparison of intra-articular triamcinolone hexacetonide and triamcinolone acetonide in oligoarticular juvenile idiopathic arthritis. *Rheumatology (Oxford)*.2003;42(10):1254-9.
17. Zulian F, Martini G, Gobber D, et al. Triamcinolone acetonide and hexacetonide intra-articular treatment of symmetrical joints in juvenile idiopathic arthritis: a double-blind trial. *Rheumatology (Oxford)*.2004;43(10):1288-91.
18. Eberhard BA, Sison MC, Gottlieb BS, et al. Comparison of the intraarticular effectiveness of triamcinolone hexacetonide and triamcinolone acetonide in treatment of juvenile rheumatoid arthritis. *J Rheumatol*.2004;31(12):2507-12.
19. Guzman J, Kerr T, Ward LM, et al. Growth and weight gain in children with juvenile idiopathic arthritis: results from the ReACCh-Out cohort. *Pediatr Rheumatol Online J*.2017;15(1):68.
20. Sadeghi P AY, Ziaee V, Moayeri H. Adrenal Insufficiency in Children with Juvenile Idiopathic Arthritis (JIA) Treated with Prednisolone. *J Compr Ped*.2019;10(2):e64681.
21. Ravelli A, Davi S, Bracciolini G, et al. Intra-articular corticosteroids versus intra-articular corticosteroids plus methotrexate in oligoarticular juvenile idiopathic arthritis: a multicentre, prospective, randomised, open-label trial. *Lancet*.2017;389(10072):909-916.
22. Albarouni M, Becker I, Horneff G. Predictors of response to methotrexate in juvenile idiopathic arthritis. *Pediatr Rheumatol Online J*.2014;12:35.
23. Bava C, Mongelli F, Pistorio A, et al. A prediction rule for lack of achievement of inactive disease with methotrexate as the sole disease-modifying antirheumatic therapy in juvenile idiopathic arthritis. *Pediatr Rheumatol Online J*.2019;17(1):50.
24. Franova J, Fingerhutova S, Kobrova K, et al. Methotrexate efficacy, but not its intolerance, is associated with the dose and route of administration. *Pediatr Rheumatol Online J*.2016;14(1):36.
25. Imundo LF, Jacobs JC. Sulfasalazine therapy for juvenile rheumatoid arthritis. *J Rheumatol*.1996;23(2):360-6.
26. Foeldvari I, Wierk A. Effectiveness of leflunomide in patients with juvenile idiopathic arthritis in clinical practice. *J Rheumatol*.2010;37(8):1763-7.
27. Haapasaari J, Kautiainen H, Isomaki H, et al. Hydroxychloroquine does not decrease serum methotrexate concentrations in children with juvenile idiopathic arthritis. *Arthritis Rheum*.2005;52(5):1621-2.
28. Alexeeva E, Dvoryakovskaya T, Denisova R, et al. Comparative analysis of the etanercept efficacy in children with juvenile idiopathic arthritis under the age of 4 years and children of older age groups using the propensity score matching method. *Mod Rheumatol*.2019;29(5):848-855.
29. Anink J, Otten MH, Prince FH, et al. Tumour necrosis factor-blocking agents in persistent oligoarticular juvenile idiopathic arthritis: results from the Dutch Arthritis and Biologicals in Children Register. *Rheumatology (Oxford)*.2013;52(4):712-7.
30. Tynjala P, Vahasalo P, Tarkiainen M, et al. Aggressive combination drug therapy in very early polyarticular juvenile idiopathic arthritis (ACUTE-JIA): a multicentre randomised open-label clinical trial. *Ann Rheum Dis*.2011;70(9):1605-12.
31. Lovell DJ, Giannini EH, Reiff A, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. *N Engl J Med*.2000;342(11):763-9.
32. Mannion ML, Xie F, Horton DB, et al. Biologic Switching among Non-Systemic Juvenile Idiopathic Arthritis Patients: A Cohort Study in the Childhood Arthritis and Rheumatology Research Alliance Registry. *J Rheumatol*.2020;

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33. Armaroli G, Klein A, Ganser G, et al. Long-term safety and effectiveness of etanercept in JIA: an 18-year experience from the BiKeR registry. *Arthritis Res Ther*.2020;22(1):258.
34. Horneff G, Klein A, Klotsche J, et al. Comparison of treatment response, remission rate and drug adherence in polyarticular juvenile idiopathic arthritis patients treated with etanercept, adalimumab or tocilizumab. *Arthritis Res Ther*.2016;18(1):272.
35. Minden K, Horneff G, Niewerth M, et al. Time of Disease-Modifying Antirheumatic Drug Start in Juvenile Idiopathic Arthritis and the Likelihood of a Drug-Free Remission in Young Adulthood. *Arthritis Care Res (Hoboken)*.2019;71(4):471-481.
36. Kearsley-Fleet L, Davies R, Lunt M, et al. Factors associated with improvement in disease activity following initiation of etanercept in children and young people with Juvenile Idiopathic Arthritis: results from the British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study. *Rheumatology (Oxford)*.2016;55(5):840-7.
37. Ilowite N, Porras O, Reiff A, et al. Anakinra in the treatment of polyarticular-course juvenile rheumatoid arthritis: safety and preliminary efficacy results of a randomized multicenter study. *Clin Rheumatol*.2009;28(2):129-37.
38. Rypdal V, Arnstad ED, Aalto K, et al. Predicting unfavorable long-term outcome in juvenile idiopathic arthritis: results from the Nordic cohort study. *Arthritis Res Ther*.2018;20(1):91.
39. Rypdal V, Guzman J, Henrey A, et al. Validation of prediction models of severe disease course and non-achievement of remission in juvenile idiopathic arthritis: part 1-results of the Canadian model in the Nordic cohort. *Arthritis Res Ther*.2019;21(1):270.
40. Trincianti C, Consolaro A. Outcome Measures for Juvenile Idiopathic Arthritis Disease Activity. *Arthritis Care Res (Hoboken)*.2020;72 Suppl 10:150-162.
41. Ravelli A, Consolaro A, Horneff G, et al. Treating juvenile idiopathic arthritis to target: recommendations of an international task force. *Ann Rheum Dis*.2018;77(6):819-828.
42. Consolaro A, Ruperto N, Bazso A, et al. Development and validation of a composite disease activity score for juvenile idiopathic arthritis. *Arthritis Rheum*.2009;61(5):658-66.
43. Tibaldi J, Pistorio A, Aldera E, et al. Development and initial validation of a composite disease activity score for systemic juvenile idiopathic arthritis. *Rheumatology (Oxford)*.2020;59(11):3505-3514.
44. Klein A, Minden K, Hospach A, et al. Treat-to-target study for improved outcome in polyarticular juvenile idiopathic arthritis. *Ann Rheum Dis*.2020;79(7):969-974.
45. Buckley L, Ware E, Kreher G, et al. Outcome Monitoring and Clinical Decision Support in Polyarticular Juvenile Idiopathic Arthritis. *J Rheumatol*.2020;47(2):273-281.
46. Rahimi H, Twilt M, Herlin T, et al. Orofacial symptoms and oral health-related quality of life in juvenile idiopathic arthritis: a two-year prospective observational study. *Pediatr Rheumatol Online J*.2018;16(1):47.
47. Frid P, Nordal E, Bovis F, et al. Temporomandibular Joint Involvement in Association With Quality of Life, Disability, and High Disease Activity in Juvenile Idiopathic Arthritis. *Arthritis Care Res (Hoboken)*.2017;69(5):677-686.
48. Bollhalder A, Patcas R, Eichenberger M, et al. Magnetic Resonance Imaging Followup of Temporomandibular Joint Inflammation, Deformation, and Mandibular Growth in Juvenile Idiopathic Arthritis Patients Receiving Systemic Treatment. *J Rheumatol*.2020;47(6):909-916.
49. Stoll ML, Amin D, Powell KK, et al. Risk Factors for Intraarticular Heterotopic Bone Formation in the Temporomandibular Joint in Juvenile Idiopathic Arthritis. *J Rheumatol*.2018;45(9):1301-1307.
50. Ringold S, Thapa M, Shaw EA, et al. Heterotopic ossification of the temporomandibular joint in juvenile idiopathic arthritis. *J Rheumatol*.2011;38(7):1423-8.
51. Lochbuhler N, Saurenmann RK, Muller L, et al. Magnetic Resonance Imaging Assessment of Temporomandibular Joint Involvement and Mandibular Growth Following Corticosteroid Injection in Juvenile Idiopathic Arthritis. *J Rheumatol*.2015;42(8):1514-22.

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52. Resnick CM, Vakilian PM, Kaban LB, et al. Quantifying the Effect of Temporomandibular Joint Intra-Articular Steroid Injection on Synovial Enhancement in Juvenile Idiopathic Arthritis. *J Oral Maxillofac Surg*.2016;74(12):2363-2369.
53. Ince DO, Ince A, Moore TL. Effect of methotrexate on the temporomandibular joint and facial morphology in juvenile rheumatoid arthritis patients. *Am J Orthod Dentofacial Orthop*.2000;118(1):75-83.
54. Stoustrup P, Twilt M, Herlin T. Systemic Treatment for Temporomandibular Joint Arthritis in Juvenile Idiopathic Arthritis. *J Rheumatol*.2020;47(6):793-795.
55. Ombrello MJ, Arthur VL, Remmers EF, et al. Genetic architecture distinguishes systemic juvenile idiopathic arthritis from other forms of juvenile idiopathic arthritis: clinical and therapeutic implications. *Ann Rheum Dis*.2017;76(5):906-913.
56. De Benedetti F, Brunner HI, Ruperto N, et al. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. *N Engl J Med*.2012;367(25):2385-95.
57. Ruperto N, Brunner HI, Quartier P, et al. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. *N Engl J Med*.2012;367(25):2396-406.
58. Pascual V, Allantaz F, Arce E, et al. Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade. *J Exp Med*.2005;201(9):1479-86.
59. Ravelli A, Minoia F, Davi S, et al. 2016 Classification Criteria for Macrophage Activation Syndrome Complicating Systemic Juvenile Idiopathic Arthritis: A European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. *Ann Rheum Dis*.2016;75(3):481-9.
60. Minoia F, Davi S, Horne A, et al. Clinical features, treatment, and outcome of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a multinational, multicenter study of 362 patients. *Arthritis Rheumatol*.2014;66(11):3160-9.
61. DeWitt EM, Kimura Y, Beukelman T, et al. Consensus treatment plans for new-onset systemic juvenile idiopathic arthritis. *Arthritis Care Res (Hoboken)*.2012;64(7):1001-10.
62. Kimura Y, Grevich S, Beukelman T, et al. Pilot study comparing the Childhood Arthritis & Rheumatology Research Alliance (CARRA) systemic Juvenile Idiopathic Arthritis Consensus Treatment Plans. *Pediatr Rheumatol Online J*.2017;15(1):23.
63. Vastert SJ, de Jager W, Noordman BJ, et al. Effectiveness of first-line treatment with recombinant interleukin-1 receptor antagonist in steroid-naive patients with new-onset systemic juvenile idiopathic arthritis: results of a prospective cohort study. *Arthritis Rheumatol*.2014;66(4):1034-43.
64. Schulert GS, Yasin S, Carey B, et al. Systemic Juvenile Idiopathic Arthritis-Associated Lung Disease: Characterization and Risk Factors. *Arthritis Rheumatol*.2019;71(11):1943-1954.
65. Saper VE, Chen G, Deutsch GH, et al. Emergent high fatality lung disease in systemic juvenile arthritis. *Ann Rheum Dis*.2019;78(12):1722-1731.
66. Bsila RS, Inglis AE, Ranawat CS. Joint replacement surgery in patients under thirty. *J Bone Joint Surg Am*.1976;58(8):1098-104.
67. Mertelsmann-Voss C, Lyman S, Pan TJ, et al. US trends in rates of arthroplasty for inflammatory arthritis including rheumatoid arthritis, juvenile idiopathic arthritis, and spondyloarthritis. *Arthritis Rheumatol*.2014;66(6):1432-9.
68. Sura A, Failing C, Sturza J, et al. Patient characteristics associated with response to NSAID monotherapy in children with systemic juvenile idiopathic arthritis. *Pediatr Rheumatol Online J*.2018;16(1):2.
69. Woo P, Southwood TR, Prieur AM, et al. Randomized, placebo-controlled, crossover trial of low-dose oral methotrexate in children with extended oligoarticular or systemic arthritis. *Arthritis Rheum*.2000;43(8):1849-57.
70. Ter Haar NM, van Dijkhuizen EHP, Swart JF, et al. Treatment to Target Using Recombinant Interleukin-1 Receptor Antagonist as First-Line Monotherapy in New-Onset

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Systemic Juvenile Idiopathic Arthritis: Results From a Five-Year Follow-Up Study. *Arthritis Rheumatol*.2019;71(7):1163-1173.
71. Lehman TJ, Schechter SJ, Sundel RP, et al. Thalidomide for severe systemic onset juvenile rheumatoid arthritis: A multicenter study. *J Pediatr*.2004;145(6):856-7.
72. Ruperto N, Quartier P, Wulffraat N, et al. A phase II, multicenter, open-label study evaluating dosing and preliminary safety and efficacy of canakinumab in systemic juvenile idiopathic arthritis with active systemic features. *Arthritis Rheum*.2012;64(2):557-67.
73. Lovell DJ, Giannini EH, Reiff AO, et al. Long-term safety and efficacy of rilonacept in patients with systemic juvenile idiopathic arthritis. *Arthritis Rheum*.2013;65(9):2486-96.
74. Quartier P, Allantaz F, Cimaz R, et al. A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). *Ann Rheum Dis*.2011;70(5):747-54.
75. Otten MH, Prince FH, Anink J, et al. Effectiveness and safety of a second and third biological agent after failing etanercept in juvenile idiopathic arthritis: results from the Dutch National ABC Register. *Ann Rheum Dis*.2013;72(5):721-7.
76. Davies SV, Dean JD, Wardrop CA, et al. Epstein-Barr virus-associated haemophagocytic syndrome in a patient with juvenile chronic arthritis. *Br J Rheumatol*.1994;33(5):495-7.
77. McPeake JR, Hirst WJ, Brind AM, et al. Hepatitis A causing a second episode of virus-associated haemophagocytic lymphohistiocytosis in a patient with Still's disease. *J Med Virol*.1993;39(2):173-5.
78. Aytac S, Batu ED, Unal S, et al. Macrophage activation syndrome in children with systemic juvenile idiopathic arthritis and systemic lupus erythematosus. *Rheumatol Int*.2016;36(10):1421-9.
79. Eloseily EM, Weiser P, Crayne CB, et al. Benefit of Anakinra in Treating Pediatric Secondary Hemophagocytic Lymphohistiocytosis. *Arthritis Rheumatol*.2020;72(2):326-334.
80. Ohmura SI, Uehara K, Yamabe T, et al. Successful use of short-term add-on tocilizumab for refractory adult-onset still's disease with macrophage activation syndrome despite treatment with high-dose glucocorticoids, cyclosporine, and etoposide. *Mod Rheumatol Case Rep*.2020;4(2):202-207.
81. Sonmez HE, Demir S, Bilginer Y, et al. Anakinra treatment in macrophage activation syndrome: a single center experience and systemic review of literature. *Clin Rheumatol*.2018;37(12):3329-3335.
82. Shenoi S, Nanda K, Schulert GS, et al. Physician practices for withdrawal of medications in inactive systemic juvenile arthritis, Childhood Arthritis and Rheumatology Research Alliance (CARRA) survey. *Pediatr Rheumatol Online J*.2019;17(1):48.
83. Quartier P, Alexeeva E, Tamas C, et al. Tapering Canakinumab Monotherapy in Patients with Systemic Juvenile Idiopathic Arthritis in Clinical Remission: Results from an Open-label, Randomized Phase IIIb/IV Study. *Arthritis Rheumatol*.2020;
84. Rice JB, White AG, Scarpati LM, et al. Long-term Systemic Corticosteroid Exposure: A Systematic Literature Review. *Clin Ther*.2017;39(11):2216-2229.
85. Zak M, Pedersen FK. Juvenile chronic arthritis into adulthood: a long-term follow-up study. *Rheumatology (Oxford)*.2000;39(2):198-204.
86. Oen K, Malleson PN, Cabral DA, et al. Disease course and outcome of juvenile rheumatoid arthritis in a multicenter cohort. *J Rheumatol*.2002;29(9):1989-99.
87. Yokota S, Imagawa T, Mori M, et al. Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. *Lancet*.2008;371(9617):998-1006.
88. Al-Matar MJ, Petty RE, Tucker LB, et al. The early pattern of joint involvement predicts disease progression in children with oligoarticular (pauciarticular) juvenile rheumatoid arthritis. *Arthritis Rheum*.2002;46(10):2708-15.

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89. Triamcinolone Hexacetonide. https://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Triamcinolone%20Hexacetonide%20Injectable%20Suspension%20(Aristospan)&st=c
90. Lipstein EA, Muething KA, Dodds CM, et al. "I'm the one taking it": adolescent participation in chronic disease treatment decisions. *J Adolesc Health*.2013;53(2):253-9.
91. Lipstein EA, Lovell DJ, Denson LA, et al. Parents' information needs and influential factors when making decisions about TNF-alpha inhibitors. *Pediatr Rheumatol Online J*.2016;14(1):53.
92. Foster HE, Marshall N, Myers A, et al. Outcome in adults with juvenile idiopathic arthritis: a quality of life study. *Arthritis Rheum*.2003;48(3):767-75.
93. Gomez-Ramirez O, Gibbon M, Berard R, et al. A recurring rollercoaster ride: a qualitative study of the emotional experiences of parents of children with juvenile idiopathic arthritis. *Pediatr Rheumatol Online J*.2016;14(1):13.
94. Brunner HI, Schanberg LE, Kimura Y, et al. New Medications Are Needed for Children With Juvenile Idiopathic Arthritis. *Arthritis Rheumatol*.2020;72(11):1945-1951.
95. Glerup M, Rypdal V, Arnstad ED, et al. Long-Term Outcomes in Juvenile Idiopathic Arthritis: Eighteen Years of Follow-Up in the Population-Based Nordic Juvenile Idiopathic Arthritis Cohort. *Arthritis Care Res (Hoboken)*.2020;72(4):507-516.
96. Guzman J, Oen K, Huber AM, et al. The risk and nature of flares in juvenile idiopathic arthritis: results from the ReACCh-Out cohort. *Ann Rheum Dis*.2016;75(6):1092-8.

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2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis (JIA): Recommendations for Non-Pharmacologic Therapies, Medication Monitoring, Immunizations, and Imaging

Tables 1-7

Table 1: Strength of recommendations/quality of supporting evidence							
		Strength of Recommendation		Quality of Supporting Evidence			
Topic	Recs	Cond	Str	VL	L	Mod	Hi
Non-pharmacologic therapies	4	2	2	4		0	0
Medication Monitoring	20	17	3	17	0	0	0
Infection Surveillance/Immunizations	7	3	4	5	2	0	0
Imaging	2	1	1	2	0	0	0
Total	33	23	10	28	2	0	0

Key:
Recs-Recommendations
Cond-Conditional
Str-Strong
VL-Very Low
L-Low
Mod-Moderate
Hi-High

Note: Lack of evidence for Tofacitinib given FDA approval date.

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Table 2: Classes of interventions	
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Any at therapeutic dosing [Ibuprofen, Naproxen, Tolmetin, Indomethacin, Meloxicam, Nabumetone, Diclofenac, Piroxicam, Etodolac, Celecoxib]
Conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs)	Methotrexate, Sulfasalazine, Hydroxychloroquine, Leflunomide, Calcineurin inhibitors [cyclosporin A, tacrolimus]
Biologic DMARDs (bDMARDs)	Tumor necrosis factor alpha inhibitors (TNFi): Adalimumab, Etanercept, Infliximab, Golimumab, Certolizumab pegol Other Biologic Response Modifiers (OBRM): Abatacept, Tocilizumab, Anakinra, Canakinumab,
Targeted synthetic DMARD	JAK inhibitor: Tofacitinib
Glucocorticoids	Oral: Any Intravenous: Any Intraarticular: Triamcinolone Acetonide, Triamcinolone Hexacetonide
Immunizations	Live attenuated Inactivated
Non-pharmacologic therapies	Physical Therapy (PT) Occupational Therapy (OT) Dietary changes Herbal supplements

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Table 3: Non-Pharmacologic Therapies			
Recommendations	**Certainty of Evidence**	**Based on the evidence report(s) of the following PICO(s)**	**Evidence table(s) on page(s)**
A discussion of healthy, age-appropriate diet is **strongly** recommended. --- Use of a specific diet to treat JIA is **strongly** recommended *against*. --- Use of supplemental or herbal interventions specifically to treat JIA is **conditionally** recommended *against*.	Very Low	PICO 7: In children with oligoarticular JIA, should dietary or herbal interventions be recommended, in addition to whatever other therapeutic options are given, versus not recommending them? --- PICO 17. In children with JIA with active TMJ arthritis, should dietary or herbal interventions be recommended, in addition to whatever other therapeutic options are given, versus not recommending them?	48-49 60
Physical and occupational therapy (PT/OT) are **conditionally** recommended regardless of concomitant pharmacologic therapy.	Very low	PICO 8. In children with oligoarticular JIA, regardless of disease activity and poor prognostic features, should PT/OT versus no PT/OT (regardless of concomitant medical therapy) be recommended? --- PICO 18. In children with JIA with active TMJ arthritis, regardless of disease activity and poor prognostic features, should PT versus no PT (regardless of concomitant medical therapy) be recommended?	49-51 60

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Table 4: Medication monitoring			
Recommendations	**Certainty of Evidence**	**Based on the evidence report(s) of the following PICO(s)[7]**	**Evidence table(s) on page(s)**
NSAIDS: CBC, LFTs and renal function tests are **conditionally** recommended to be monitored every 6-12 months.	Very low	PICO 30: Is there a recommended laboratory screening schedule (complete blood count, comprehensive metabolic panel and urinalysis) for children receiving chronic daily NSAIDs?	144-145
Methotrexate: CBC, LFTs and renal function are **strongly** recommended to be monitored within the first 1-2 months of usage and every 3-4 months thereafter.	Very low	PICO 31: Is there a recommended laboratory screening schedule (complete blood count, comprehensive metabolic panel) for children being treated with methotrexate (po or sq)?	145-150
Decreasing or holding the methotrexate dose is **conditionally** recommended if a clinically relevant elevation in LFTs or decreased neutrophil or platelet count is found.	Very low	PICO 32: After methotrexate (po or sq) is initiated, is there a recommended medication change secondary to elevated liver function tests and decreased neutrophil or platelet count?	150-153
Use of folic/folinic acid is **strongly** recommended in conjunction with methotrexate.	Very low	PICO 7: In children with oligoarticular JIA, should dietary or herbal interventions be recommended, in addition to whatever other therapeutic options are given, versus not recommending them?	60

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Sulfasalazine: CBC, LFTs and renal function are **conditionally** recommended to be monitored within the first 1-2 months of usage and every 3-4 months thereafter.	Very low	PICO 33. Is there a recommended laboratory screening schedule (complete blood count, comprehensive metabolic panel) for children with JIA being treated with sulfasalazine?	153-155
Decreasing or holding the sulfasalazine dose is **conditionally** recommended if a clinically relevant elevation in LFTs or decreased neutrophil or platelet count is found.	Very low	PICO 34. After sulfasalazine is initiated, is there a recommended medication change in response to elevated liver function tests and decreased neutrophil or platelet count?	155-157
Leflunomide: CBC and LFTs are **conditionally** recommended to be monitored within the first 1-2 months of usage and every 3-4 months thereafter.	Very low	PICO 35. Should children with JIA receiving leflunomide have serum creatinine, urinalysis, complete blood count and liver enzymes before and during treatment, per manufacturer's recommendations?	157-158
Altering leflunomide administration is **conditionally** recommended if a clinically relevant elevation in LFTs occurs (temporary hold of leflunomide for ALT> 3X the upper limit of normal [ULN]), as per package insert.	Very low	PICO 36. After leflunomide is initiated, should medication dosage be altered according to the package insert secondary to elevated liver function tests?	158-159
Baseline and annual retinal screening are **conditionally** recommended after starting hydroxychloroquine.	Very low	PICO 37. Should children with JIA receiving treatment with hydroxychloroquine have annual screening tests with automated visual fields, if age appropriate, plus spectral-domain optical coherence tomography (SD OCT) versus starting annual screening 5 years after treatment onset?	159

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Hydroxychloroquine: CBC and LFTs are **conditionally** recommended to be monitored annually.	Very low	PICO 38. Is there a recommended laboratory screening schedule (complete blood count, comprehensive metabolic panel) for children with JIA being treated with hydroxychloroquine?	159
TNFi: CBC and LFTs are **conditionally** recommended to be monitored annually.	Very low	PICO 39. Is there a recommended laboratory screening schedule (complete blood count, comprehensive metabolic panel and urinalysis) for children with JIA receiving TNF inhibitor treatment?	160-161
Abatacept: Doing no routine laboratory monitoring is **conditionally** recommended.	Very low	PICO 40. Is there a recommended laboratory screening schedule (complete blood count, comprehensive metabolic panel and urinalysis) for children with JIA receiving abatacept treatment?	161-162
Tocilizumab: CBC and LFTs are **conditionally** recommended to be monitored within the first 1-2 months of usage and every 3-4 months thereafter. Lipids are **conditionally** recommended to be monitored every 6 months, as per package insert.	Very low	PICO 41. Should children with JIA receiving tocilizumab have serum creatinine, urinalysis, complete blood cell count, and liver enzymes before and during treatment, per manufacturer's recommendations?	162
Altering tocilizumab administration is **conditionally** recommended after starting tocilizumab if monitoring reveals elevated LFTs (1-3X ULN decrease dose or interval, 3XULN hold dose, 5XULN discontinue treatment), neutropenia (500-1000/mm^3), or thrombocytopenia (50,000-100,000/mm^3), as per package insert.	Very low	PICO 42. After tocilizumab is initiated, should medication dosage be altered according to the package insert secondary to elevated liver function tests, neutropenia and/or thrombocytopenia?	163

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Anakinra: CBC and LFTs are **conditionally** recommended to be monitored within the first 1-2 months of usage and every 3-4 months thereafter.	Very low	PICO 43. Is there a recommended laboratory screening schedule (complete blood count, comprehensive metabolic panel and urinalysis) for children with JIA receiving anakinra treatment?	163-164
Canakinumab: CBC and LFTs are **conditionally** recommended to be monitored within the first 1-2 months of usage and every 3-4 months thereafter.	Very low	PICO 44. Is there a recommended laboratory screening schedule (complete blood count, comprehensive metabolic panel and urinalysis) for children with JIA receiving canakinumab treatment?	164
Tofacitinib: CBC and LFTs are **conditionally** recommended to be monitored within the first 1-2 months of usage and every 3-4 months thereafter. Lipids are **conditionally** recommended to be monitored 1-2 months after starting treatment, as per package insert. Altering medication administration as per package insert is **strongly** recommended after starting tofacitinib; medication should be discontinued if hemoglobin is less than 8 g/dl or decreases more than 2 g/dl, or for severe neutropenia(<500/mm^3) or lymphopenia(<500/mm^3).	*	*Given recent approval for JIA and limited experience, recommendations are as per clinical trial, FDA guidance and evidence in adults	*

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Table 5: Infection Surveillance/Immunizations			
Recommendations	**Certainty of Evidence**	**Based on the evidence report(s) of the following PICO(s)[7]**	**Evidence table(s) on page(s)**
No consensus achieved	Very low	PICO 45: Should all children with JIA have infection titers (measles, varicella, hepatitis B, hepatitis C) checked prior to starting immunosuppressive medication?	164-166
Immunization is **conditionally** recommended for children with active non-systemic JIA who have not yet been immunized for Measles, Mumps, Rubella and/or Varicella prior to starting immunosuppressive medications.	Very low	PICO 46. Should children with JIA with no evidence of immunity to important infections have a booster immunization prior to starting immunosuppressive medication?	166
TB screening is **conditionally** recommended prior to starting biologic DMARD therapy and when there is a concern for TB exposure thereafter.	Very low	PICO 47: Should screening for TB be done prior to starting biologic DMARD therapy and then annually in children with JIA?	167-169
	Very low	PICO 48: In children with JIA receiving biologic DMARD therapy, is there a preferred method of TB screening?	169-171
Immunizations (live and inactivated) are **strongly** recommended for children with JIA not on immunosuppression.	Very low	PICO 49. In children with JIA not on immunosuppression, do inactivated or live	172-175

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		attenuated vaccines result in flare of disease?	
Annual influenza immunization is **strongly** recommended for all children with JIA.	Low	PICO 50. In children with JIA not on immunosuppression, are patients able to develop protective antibodies against infections targeted by the vaccine? PICO 52: In children with JIA on immunosuppression, are patients able to develop protective antibodies against infections targeted by the vaccine?	175 – 179 184-195
Inactivated vaccines are **strongly** recommended for children with JIA on immunosuppression.	Very low	PICO 51: In children with JIA on immunosuppression, do inactivated vaccines result in flare of disease?	180-184
Live attenuated vaccines are **conditionally** recommended *against* for children with JIA on immunosuppression.	Low	PICO 53. In children with JIA on immunosuppression, can treatment with live attenuated vaccines be given safely (initial dose, booster dose)?	195-198
Live attenuated vaccines are **strongly** recommended in the household of children with JIA on immunosuppression as per CDC guidelines.	Very Low	PICO 54. Can live attenuated vaccines be used safely in the households of children with JIA on immunosuppression?	198

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Table 6: Imaging			
Recommendations	**Certainty of Evidence**	**Based on the evidence report(s) of the following PICO(s)[7]**	**Evidence table(s) on page(s)**
Use of radiographs as a screening test prior to advanced imaging, for the purpose of identifying active synovitis or enthesitis, is **strongly** recommended *against*.	Very low	PICO 55: In children with JIA, is any specific imaging technique recommended to best detect inflammation and damage, make a diagnosis, predict structural damage, flare or treatment response?	199-268
Imaging guidance is **conditionally** recommended for use with IAGC injections of joints that are difficult to access, or to specifically localize the distribution of inflammation.	Very low	PICO 56: In children with JIA who require IA corticosteroid (IAC) injections, should injections be done with imaging guidance?	269-279

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Table 7: Medication Monitoring*

	Methotrexate***#	Sulfasalazine**	Leflunomide#	Tocilizumab	Anakinra	Tofacitinib	Canakinumab	NSAIDs**	Hydroxychloroquine	TNFi	Abatacept
CBC /diff and LFTs -Baseline -1-2 months after starting -Every 3-4months thereafter***	X	X	X	X	X	X	X				
CBC/diff and LFTs -Baseline -Every 6-12 months								X			
CBC/diff and LFTs -Baseline -Once yearly									X	X	
Lipid panel -Baseline -Every 6 months				X							
Lipid panel -Baseline -4-8 weeks after starting						X					
Eye exam -Baseline -Once yearly									X		
Not None required											X

*If patient is on more than one medication, a more restrictive schedule should be used

**Include Renal function with lab work

***Should be rechecked sooner if dose increased

#Pregnancy test should be considered before use, and counseling as to use of effective methods of contraception is recommended

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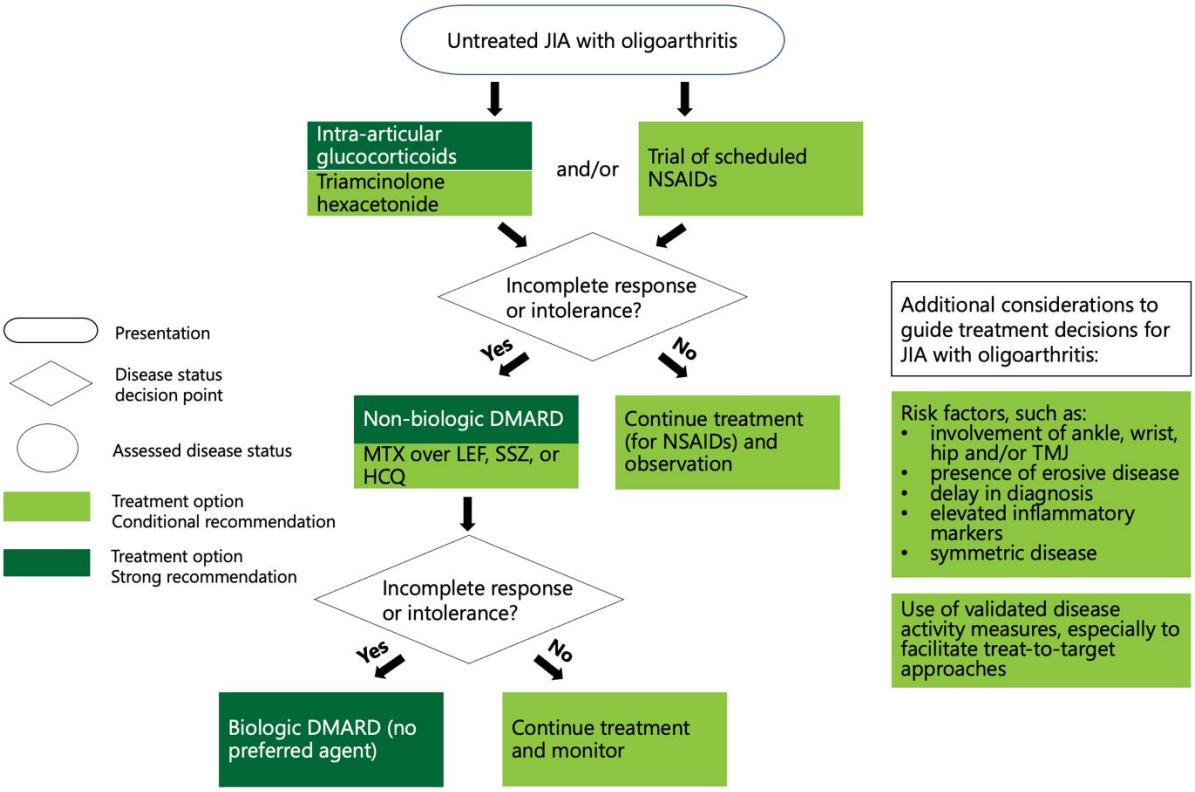
Figure 1. Treatment algorithm for oligoarthritis



DMARD = disease-modifying antirheumatic drug, HCQ = hydroxychloroquine, LEF = leflunomide, MTX = methotrexate, NSAIDs = non-steroid anti-inflammatories, SSZ = sulfasalazine, TMJ = temporomandibular joint

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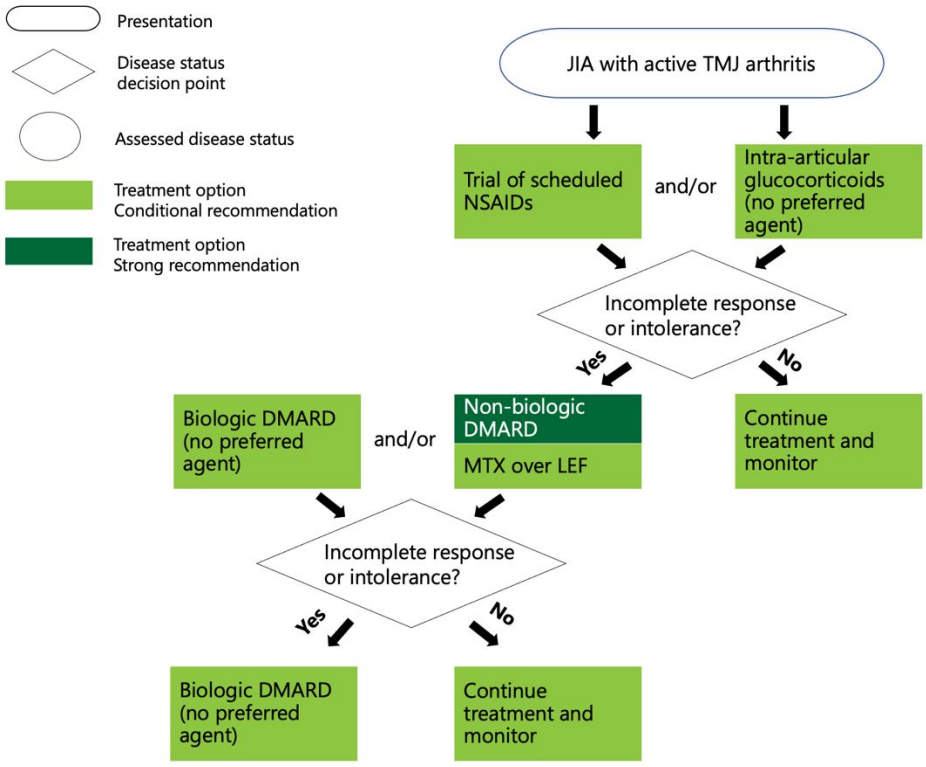
Figure 2. Treatment algorithm for TMJ arthritis



DMARD = disease-modifying antirheumatic drug, LEF = leflunomide, MTX = methotrexate, NSAIDs = non-steroid anti-inflammatories, TMJ = temporomandibular joint

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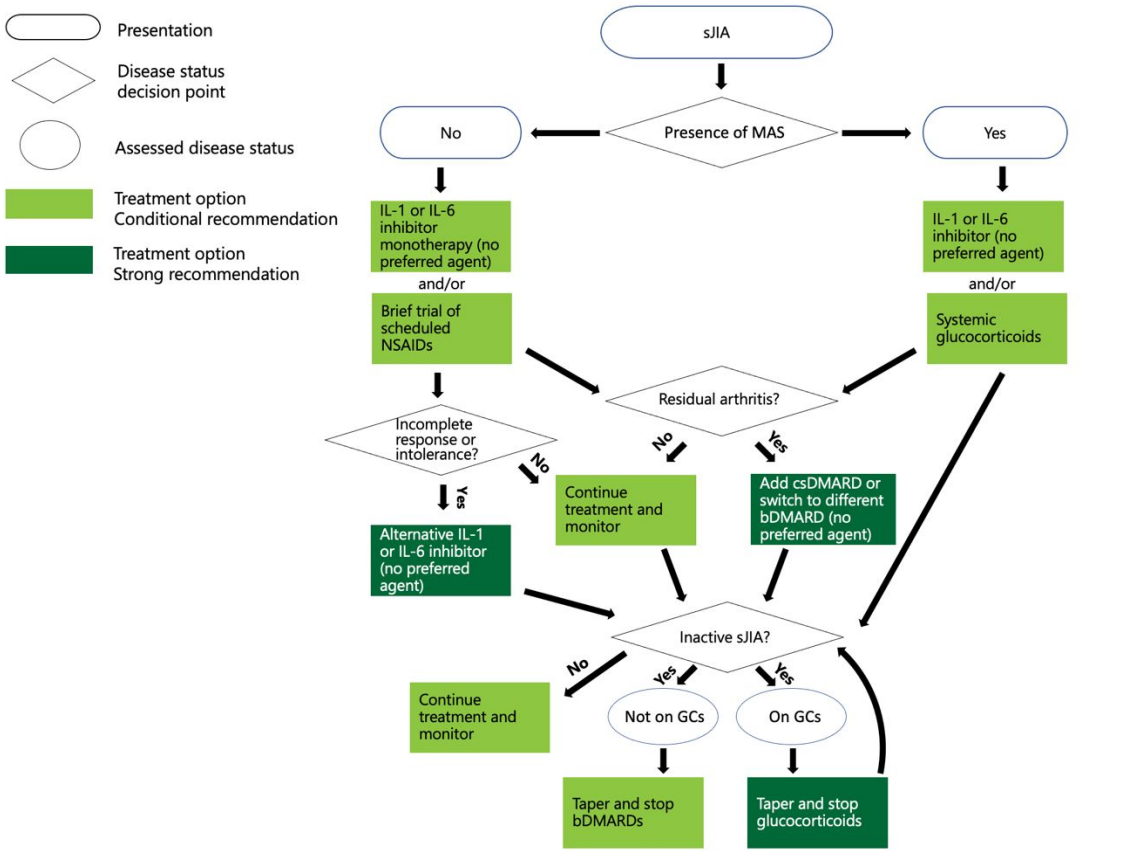
Figure 3. Treatment algorithm for systemic JIA



bDMARD = biologic disease-modifying antirheumatic drug, csDMARD = conventional synthetic disease-modifying antirheumatic drug, GCs = glucocorticoids, IL = interleukin, NSAIDs = non-steroid anti-inflammatories

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Supplementary Appendix 7: Search Strategies

2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis (JIA): Recommendations for Non-Pharmacologic Therapies, Medication Monitoring, Immunizations, and Imaging

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PUBMED

Search Name: JIA PT 2

From database inception to August 3, 2019, then updated on July 8, 2020

Search Strategy:

((((((ARTHRIT*[TW] AND ("COSTEN'S SYNDROME"[TIAB] OR COSTEN SYNDROME[TIAB] OR TEMPOROMANDIBULAR[TW] OR TMJ[TIAB])) OR (OJIA[TIAB] OR ("ARTHRITIS, JUVENILE"[MESH] OR JUVENILE ARTHRIT*[TIAB] OR JUVENILE CHRONIC ARTHRIT*[TIAB] OR JIA[TIAB] OR JRA[TIAB] OR JUVENILE RHEUMATOID ARTHRIT*[TIAB]) AND (OLIGO ARTICULAR*[TW] OR OLIGO-ARTICULAR*[TW] OR OLIGOARTICULAR*[TW]) OR (OLIGOARTHRIT*[TIAB] OR OLIGO-ARTHRIT*[TIAB])) OR ((ARTHRITIS, JUVENILE[MESH] AND (JIA[TIAB] OR JRA[TIAB] OR IDIOPATHIC*[TIAB])) OR (JUVENILE IDIOPATHIC ARTHRIT*[TIAB] OR JUVENILE CHRONIC ARTHRIT*[TIAB] OR CHRONIC JUVENILE ARTHRIT*[TIAB] OR JUVENILE RHEUMATOID ARTHRIT*[TW] OR JUVENILE IDIOPATHIC ARTHROS*[TIAB])) AND (ENGLISH[LANG])) NOT (CASE REPORT*[PT] OR LETTER*[PT] OR COMMENT*[PT] OR EDITORIAL*[PT])) NOT ("ANIMALS"[MESH] NOT ("ANIMALS"[MESH] AND "HUMANS"[MESH]))) NOT ("ADULT"[MESH] NOT ("ADULT"[MESH] AND "CHILD"[MESH] OR "INFANT"[MESH] OR "ADOLESCENT"[MESH]))) AND (("DIETARY SUGARS"[MESH] OR DIETARY SUGAR*[TIAB] OR LOW SUGAR[TIAB] OR GLUTEN FREE*[TW] OR DAIRY FREE*[TIAB] OR LACTOSE FREE*[TIAB] OR "DIETARY SUPPLEMENTS"[MESH] OR "DIET THERAPY"[SUBHEADING] OR FOOD SUPPLEMENT*[TIAB] OR NUTRACEUTICAL*[TW] OR NUTRICEUTICAL*[TW] OR NEUTRACEUTICAL*[TW] OR HERBAL*[TW] OR "FOOD"[MESH] OR "DIET"[MESH] OR DIET[TIAB] OR DIETS[TIAB] OR DIETARY[TW] OR "VITAMINS"[MESH] OR VITAMIN*[TW] OR PREBIOTIC*[TIAB] OR PROBIOTIC*[TIAB] OR NUTRITION THERAPY[MESH] OR VACCINIUM[TW] OR BLUEBERR*[TW] OR "CURCUMA"[MESH] OR CURCUMA[TIAB] OR TURMERIC*[TW] OR ZEDOARY ZEDOARIA*[TIAB] OR HORSE NETTLE*[TIAB] OR HORSENETTLE*[TIAB] OR TROMPILLO*[TIAB] OR NIGHTSHADE*[TW] OR TART CHERR*[TIAB]) OR (LEFLUNOMIDE[TW] OR HWA-486[TIAB] OR HWA486[TIAB] OR SU101[TIAB] OR ARAVA[TIAB] OR HYDROXYCHLOROQUINE[TW] OR OXYCHLOROQUINE[TIAB] OR PLAQUENIL[TIAB] OR SULFASALAZINE[TW] OR SALICYLAZOSULFAPYRIDINE[TIAB] OR AZOPYRIN OR AZOPYRINE OR AZULFIDE OR AZULFIDINA OR AZULFIN OR BENZOSULFA OR

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COLOPLEON OR DISALAZIN OR GASTROPYRIN OR PYRALIN OR RORASUL OR ROSULFANT OR SALAZINE OR SALAZO OR SALAZODIN OR SALAZOPIRINA OR SALAZOPYRIDIN OR SALAZOSULFA* OR SALISULF OR SALOPYR OR SARIDINE OR SAS-500 OR SULCOLON OR ZOPYRIN OR SULPHASALAZINE[TIAB] OR SALAZOSULFAPYRIDINE[TIAB] OR "PYRALIN EN"[TIAB] OR AZULFIDINE[TIAB] OR ASULFIDINE[TIAB] OR COLO-PLEON[TIAB] OR PLEON[TIAB] OR "SULFASALAZIN MEDAC"[TIAB] OR "SULFASALAZIN-HEYL"[TIAB] OR UCINE[TIAB] OR SALAZOPYRIN[TIAB] OR METHOTREXATE[TW] OR AMETHOPTERIN[TIAB] OR MEXATE[TIAB] OR ARBITREXATE OR METHOPTERINE OR ANTIFOLAN OR BIOTREXATE OR CANCEREN OR CL-14377 OR CL14377 OR EMTEXATE OR EMTHEXAT OR EMTHEXATE OR EMTREXATE OR ENTHEXATE OR FARMITREXAT OR FARMITREXATE OR FARMOTREX OR FOLEX OR IFAMET OR IMETH OR JYLAMVO OR LANTAREL OR LEDERTREXATE OR MAXTREX OR METEX OR METHOBLASTIN OR METHOHEXATE OR METHOTRATE OR METHOTREXATE OR METHOTREXATE OR METHROTREXATE OR METHYLAMINOPTERIN OR METHYLAMINOPTERINE OR METICAL OR METOJECT OR METOTREXAT OR METOTREXATE OR METOTREXIN OR METREX OR MPI-504 OR MPI504 OR "MTX" OR NEOTREXATE OR NORDIMET OR NOVATREX OR NSC-740 OR NSC740 OR OTREXUP OR RASUVO OR REUMATREX OR RHEUMATREX OR TEXATE* OR TEXORATE OR TREXALL OR XAKEN OR XATMEP OR ZEXATE) OR (BRIDGE[TIAB] OR BRIDGING[TIAB] OR BRIDGED[TIAB] OR BRIDGES[TIAB] OR PREDNISONE*[TW] OR DEHYDROCORTISONE[TIAB] OR DELTA-CORTISONE[TIAB] OR RECTODELT[TIAB] OR PREDNISON*[TIAB] OR STERAPRED[TIAB] OR ULTRACORTEN[TIAB] OR WINPRED[TIAB] OR APO-PREDNISONE[TIAB] OR CORTAN[TIAB] OR CORTANCYL[TIAB] OR PANAFCORT[TIAB] OR DECORTIN[TIAB] OR DACORTIN[TIAB] OR DECORTISYL[TIAB] OR DELTASONE[TIAB] OR ENCORTONE[TIAB] OR ENCORTON[TIAB] OR METICORTEN[TIAB] OR ORASONE[TIAB] OR PANASOL[TIAB] OR PREDNIDIB[TIAB] OR PRONISONE[TIAB]) OR (BIOLOGIC DISEASE MODIF*[TIAB] OR BIOLOGIC RESPONSE MODIF*[TIAB] OR BIOLOGIC AGENT*[TIAB] OR BIOLOGIC DRUG*[TIAB] OR DISEASE-MODIFYING ANTIRHEUMATIC*[TIAB] OR DISEASE-MODIFYING ANTI-RHEUMATIC*[TIAB] OR DMARD*[TIAB] OR "RECEPTORS, INTERLEUKIN-6/ANTAGONISTS AND INHIBITORS"[MESH] OR "RECEPTORS, INTERLEUKIN-1/ANTAGONISTS AND INHIBITORS"[MESH] OR INTERLEUKIN-1 BLOCKER*[TIAB] OR IL-1 BLOCKER*[TIAB] OR IL-1 BLOCKADE*[TIAB] OR INTERLEUKIN-1 BLOCKADE*[TIAB] OR INTERLEUKIN-6 BLOCKER*[TIAB] OR IL-6 BLOCKER*[TIAB] OR IL-6 BLOCKADE*[TIAB] OR INTERLEUKIN-6 BLOCKADE*[TIAB] OR "CANAKINUMAB"[SUPPLEMENTARY CONCEPT] OR CANAKINUMAB[TIAB] OR ILARIS[TIAB] OR ACZ-885[TIAB] OR ACZ885[TIAB] OR ANTI-INTERLEUKIN-1*[TIAB] OR ANTI-IL-1*[TIAB] OR ANTI-INTERLEUKIN-6*[TIAB] OR ANTI-IL-6*[TIAB] OR ANAKINRA[TW] OR KINERET[TW] OR ANTRIL[TW] OR "INTERLEUKIN-6/ANTAGONISTS AND INHIBITORS"[MESH] OR INTERLEUKIN-6 INHIBITOR*[TIAB] OR IL-6 INHIBITOR*[TIAB] OR INTERLEUKIN-1 INHIBITOR*[TIAB] OR "INTERLEUKIN-1/ANTAGONISTS AND INHIBITORS"[MESH] OR IL-1 INHIBITOR*[TIAB] OR "RILONACEPT"[SUPPLEMENTARY CONCEPT] OR RILONACEPT[TIAB] OR TUMOR NECROSIS FACTOR INHIBITOR*[TIAB] OR TUMOUR NECROSIS FACTOR INHIBITOR*[TIAB] OR TNFALPHA INHIBITOR*[TIAB] OR TNF-ALPHA INHIBITOR*[TIAB] OR TNF INHIBITOR*[TIAB] OR ANTI-TUMOR NECROSIS FACTOR*[TIAB] OR ANTI-TUMOUR NECROSIS FACTOR*[TIAB] OR ANTI-TNF*[TIAB] OR "TUMOR NECROSIS FACTOR-

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ALPHA/ANTAGONISTS AND INHIBITORS"[MESH] OR TNFI[TIAB] OR "ADALIMUMAB"[MESH] OR ADALIMUMAB[TIAB] OR HUMIRA[TIAB] OR ADALIMUMAB-ADBM[TIAB] OR AMJEVITA[TIAB] OR ADALIMUMAB-ATTO[TIAB] OR CYLTEZO[TIAB] OR ETANERCEPT[TIAB] OR "TNFR-FC FUSION PROTEIN"[TIAB] OR "TNR 001"[TIAB] OR "TNT RECEPTOR FUSION PROTEIN"[TIAB] OR TNR-001[TIAB] OR ETANERCEPT-SZZS[TIAB] OR "TNF RECEPTOR TYPE II-IGG FUSION PROTEIN"[TIAB] OR ERELZI[TIAB] OR ENBREL[TIAB] OR INFLIXIMAB*[TW] OR "MONOCLONAL ANTIBODY CA2"[TIAB] OR "MAB CA2"[TIAB] OR RENFLEXIS[TIAB] OR INFLECTRA[TIAB] OR REMICADE[TIAB] OR "GOLIMUMAB"[SUPPLEMENTARY CONCEPT] OR GOLIMUMAB[TIAB] OR "CERTOLIZUMAB PEGOL"[TW] OR CIMZIA[TIAB] OR CDP870[TIAB] OR ABATACEPT[TW] OR LEA29Y[TIAB] OR BMS224818[TIAB] OR BMS-224818[TIAB] OR BELATACEPT[TIAB] OR ORENCIA[TIAB] OR BMS-188667[TIAB] OR CTLA-4-IG[TIAB] OR "CYTOTOXIC T LYMPHOCYTE-ASSOCIATED ANTIGEN 4-IMMUNOGLOBULIN"[TIAB] OR CTLA4-IG*[TIAB] OR CTLA4-FC[TIAB] OR NULOJIX[TIAB] OR "TOCILIZUMAB"[SUPPLEMENTARY CONCEPT] OR TOCILIZUMAB[TIAB] OR ATLIZUMAB[TIAB] OR ACTEMRA[TIAB] OR RITUXIMAB[TW] OR MABTHERA[TIAB] OR IDEC-C2B8 ANTIBODY[TIAB] OR IDEC-C2B8[TIAB] OR GP2013[TIAB] OR RITUXAN[TIAB] OR "TOFACITINIB"[SUPPLEMENTARY CONCEPT] OR TOFACITINIB[TW] OR TASOCITINIB[TIAB] OR XELJANZ[TIAB] OR CP690550[TIAB] OR CP-690550[TIAB] OR CP 690550[TIAB] OR "SECUKINUMAB"[SUPPLEMENTARY CONCEPT] OR SECUKINUMAB[TIAB] OR COSENTYX[TIAB] OR AIN457[TIAB] OR AIN-457[TIAB]) OR (LEFLUNOMIDE[TW] OR HWA-486[TIAB] OR HWA486[TIAB] OR SU101[TIAB] OR ARAVA[TIAB] OR HYDROXYCHLOROQUINE[TW] OR OXYCHLOROQUINE[TIAB] OR PLAQUENIL[TIAB] OR SULFASALAZINE[TW] OR SALICYLAZOSULFAPYRIDINE[TIAB] OR SULPHASALAZINE[TIAB] OR SALAZOSULFAPYRIDINE[TIAB] OR "PYRALIN EN"[TIAB] OR AZULFIDINE[TIAB] OR ASULFIDINE[TIAB] OR COLO-PLEON[TIAB] OR PLEON[TIAB] OR "SULFASALAZIN MEDAC"[TIAB] OR "SULFASALAZIN-HEYL"[TIAB] OR UCINE[TIAB] OR SALAZOPYRIN[TIAB] OR METHOTREXATE[TW] OR AMETHOPTERIN[TIAB] OR MEXATE[TIAB] OR CALCINEURIN INHIBITOR*[TW] OR PROTEIN PHOSPHATASE-2B INHIBITOR*[TIAB] OR PROTEIN PHOSPHATASE 3 INHIBITOR*[TIAB] OR CALCINEURIN ANTAGONIST*[TIAB] OR CALCINEURIN BLOCKER*[TIAB] OR PROGRAF[TIAB] OR PROGRAFT[TIAB] OR FR-900506[TIAB] OR FR900506[TIAB] OR FK-506[TIAB] OR FK506[TIAB] OR "33-EPI-CHLORO-33-DESOXYASCOMYCIN"[TIAB] OR SDZ-ASM-981[TIAB] OR "ASM 981"[TIAB] OR ELIDEL[TIAB] OR CYCLOSPORIN[TIAB] OR CICLOSPORIN[TIAB] OR NEORAL[TIAB] OR CYA-NOF[TIAB] OR SANDIMMUNE[TIAB] OR SANDIMMUN[TIAB] OR CSA-NEORAL[TIAB] OR "OL 27-400"[TIAB] OR "OL 27400"[TIAB] OR PIMECROLIMUS[TW] OR TACROLIMUS[TW]) OR (JOINT INJECTION*[TIAB] OR STEROID INJECTION*[TIAB] OR CORTICOSTEROID INJECTION*[TIAB] OR INTRA-ARTICULAR*[TIAB] OR INTRAARTICULAR*[TW] OR "METHYLPREDNISOLONE ACETATE"[MESH] OR METHYLPREDNISOLONE*[TW] OR "ACETYL-METHYLPREDNISOLONE"[TIAB] OR DEPO-MEDRONE[TIAB] OR DEPO-MEDROL[TIAB] OR "TRIAMCINOLONE HEXACETONIDE"[SUPPLEMENTARY CONCEPT] OR ARISTOSPAN[TIAB] OR "TRIAMCINOLONE ACETONIDE"[MESH] OR TRICORT-40[TIAB] OR KENALOG*[TIAB] OR AZMACORT[TIAB] OR "KENACORT A"[TIAB] OR TRIAMCINOLONE*[TW]) OR ("OCCUPATIONAL THERAPY"[MESH] OR OCCUPATIONAL THERAP*[TIAB] OR "PHYSICAL THERAPY MODALITIES"[MESH] OR PHYSICAL THERAP*[TIAB] OR PHYSIOTHERAP*[TIAB] OR

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"EXERCISE"[MESH] OR EXERCISE*[TIAB] OR PHYSICAL ACTIVIT*[TIAB] OR MOUTH PROTECTOR*[TW] OR MOUTH GUARD*[TIAB] OR MOUTHGUARD*[TIAB] OR PROTECTIVE MOUTH PIECE*[TIAB] OR PROTECTIVE MOUTHPIECE*[TIAB] OR ERGOTHERAP*[TW] OR PT/OT[TIAB] OR "ACTIVITIES OF DAILY LIVING"[MESH] OR "ACTIVITIES OF DAILY LIVING"[TIAB])))
OR (((ARTHRITIS, JUVENILE[MESH] AND (JIA[TIAB] OR JRA[TIAB] OR IDIOPATHIC*[TIAB])) OR (JUVENILE IDIOPATHIC ARTHRIT*[TIAB] OR JUVENILE CHRONIC ARTHRIT*[TIAB] OR CHRONIC JUVENILE ARTHRIT*[TIAB] OR JUVENILE RHEUMATOID ARTHRIT*[TW] OR JUVENILE IDIOPATHIC ARTHROS*[TIAB]) OR (SJIA[TIAB] OR STILLS DISEASE*[TIAB] OR "STILL'S DISEASE"[TIAB] OR STILL DISEASE*[TIAB] OR JUVENILE SYSTEMIC ARTHRIT*[TIAB] OR SYSTEMIC JUVENILE ARTHRIT*[TIAB] OR JUVENILE SYSTEMIC IDIOPATHIC ARTHRIT*[TIAB] OR SYSTEMIC JUVENILE IDIOPATHIC ARTHRIT*[TIAB] OR SYSTEMIC JIA[TIAB] OR SYSTEMIC JRA[TIAB] OR SYSTEMIC JUVENILE RHEUMATOID ARTHRIT*[TIAB] OR JUVENILE SYSTEMIC RHEUMATOID ARTHRIT*[TIAB] OR "RHEUMATOID ARTHRITIS, SYSTEMIC JUVENILE"[SUPPLEMENTARY CONCEPT] OR JUVENILE ONSET SYSTEMIC ARTHRIT*[TIAB] OR SYSTEMIC JUVENILE ONSET ARTHRIT*[TIAB]) AND (ENGLISH[LANG]) NOT (LETTER*[PT] OR COMMENT*[PT] OR EDITORIAL*[PT] OR CASE REPORT*[PT]) NOT ("ANIMALS"[MESH] NOT ("ANIMALS"[MESH] AND "HUMANS"[MESH]))) AND ((BIOLOGIC DISEASE MODIF*[TIAB] OR BIOLOGIC RESPONSE MODIF*[TIAB] OR BIOLOGIC AGENT*[TIAB] OR BIOLOGIC DRUG*[TIAB] OR DISEASE-MODIFYING ANTIRHEUMATIC*[TIAB] OR DISEASE-MODIFYING ANTI-RHEUMATIC*[TIAB] OR DMARD*[TIAB] OR "RECEPTORS, INTERLEUKIN-6/ANTAGONISTS AND INHIBITORS"[MESH] OR "RECEPTORS, INTERLEUKIN-1/ANTAGONISTS AND INHIBITORS"[MESH] OR INTERLEUKIN-1 BLOCKER*[TIAB] OR IL-1 BLOCKER*[TIAB] OR IL-1 BLOCKADE*[TIAB] OR INTERLEUKIN-1 BLOCKADE*[TIAB] OR INTERLEUKIN-6 BLOCKER*[TIAB] OR IL-6 BLOCKER*[TIAB] OR IL-6 BLOCKADE*[TIAB] OR INTERLEUKIN-6 BLOCKADE*[TIAB] OR "CANAKINUMAB"[SUPPLEMENTARY CONCEPT] OR CANAKINUMAB[TIAB] OR ILARIS[TIAB] OR ACZ-885[TIAB] OR ACZ885[TIAB] OR ANTI-INTERLEUKIN-1*[TIAB] OR ANTI-IL-1*[TIAB] OR ANTI-INTERLEUKIN-6*[TIAB] OR ANTI-IL-6*[TIAB] OR ANAKINRA[TW] OR KINERET[TW] OR ANTRIL[TW] OR "INTERLEUKIN-6/ANTAGONISTS AND INHIBITORS"[MESH] OR INTERLEUKIN-6 INHIBITOR*[TIAB] OR IL-6 INHIBITOR*[TIAB] OR INTERLEUKIN-1 INHIBITOR*[TIAB] OR "INTERLEUKIN-1/ANTAGONISTS AND INHIBITORS"[MESH] OR IL-1 INHIBITOR*[TIAB] OR "RILONACEPT"[SUPPLEMENTARY CONCEPT] OR RILONACEPT[TIAB] OR TUMOR NECROSIS FACTOR INHIBITOR*[TIAB] OR TUMOUR NECROSIS FACTOR INHIBITOR*[TIAB] OR TNFALPHA INHIBITOR*[TIAB] OR TNF-ALPHA INHIBITOR*[TIAB] OR TNF INHIBITOR*[TIAB] OR ANTI-TUMOR NECROSIS FACTOR*[TIAB] OR ANTI-TUMOUR NECROSIS FACTOR*[TIAB] OR ANTI-TNF*[TIAB] OR "TUMOR NECROSIS FACTOR-ALPHA/ANTAGONISTS AND INHIBITORS"[MESH] OR TNFI[TIAB] OR "ADALIMUMAB"[MESH] OR ADALIMUMAB[TIAB] OR HUMIRA[TIAB] OR ADALIMUMAB-ADBM[TIAB] OR AMJEVITA[TIAB] OR ADALIMUMAB-ATTO[TIAB] OR CYLTEZO[TIAB] OR ETANERCEPT[TIAB] OR "TNFR-FC FUSION PROTEIN"[TIAB] OR "TNR 001"[TIAB] OR "TNT RECEPTOR FUSION PROTEIN"[TIAB] OR TNR-001[TIAB] OR ETANERCEPT-SZZS[TIAB] OR "TNF RECEPTOR TYPE II-IGG FUSION PROTEIN"[TIAB] OR ERELZI[TIAB] OR ENBREL[TIAB] OR INFLIXIMAB*[TW] OR "MONOCLONAL ANTIBODY CA2"[TIAB] OR "MAB CA2"[TIAB] OR RENFLEXIS[TIAB] OR INFLECTRA[TIAB] OR REMICADE[TIAB]

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OR "GOLIMUMAB"[SUPPLEMENTARY CONCEPT] OR GOLIMUMAB[TIAB] OR "CERTOLIZUMAB PEGOL"[TW] OR CIMZIA[TIAB] OR CDP870[TIAB] OR ABATACEPT[TW] OR LEA29Y[TIAB] OR BMS224818[TIAB] OR BMS-224818[TIAB] OR BELATACEPT[TIAB] OR ORENCIA[TIAB] OR BMS-188667[TIAB] OR CTLA-4-IG[TIAB] OR "CYTOTOXIC T LYMPHOCYTE-ASSOCIATED ANTIGEN 4-IMMUNOGLOBULIN"[TIAB] OR CTLA4-IG*[TIAB] OR CTLA4-FC[TIAB] OR NULOJIX[TIAB] OR "TOCILIZUMAB"[SUPPLEMENTARY CONCEPT] OR TOCILIZUMAB[TIAB] OR ATLIZUMAB[TIAB] OR ACTEMRA[TIAB] OR RITUXIMAB[TW] OR MABTHERA[TIAB] OR IDEC-C2B8 ANTIBODY[TIAB] OR IDEC-C2B8[TIAB] OR GP2013[TIAB] OR RITUXAN[TIAB] OR "TOFACITINIB"[SUPPLEMENTARY CONCEPT] OR TOFACITINIB[TW] OR TASOCITINIB[TIAB] OR XELJANZ[TIAB] OR CP690550[TIAB] OR CP-690550[TIAB] OR CP 690550[TIAB] OR "SECUKINUMAB"[SUPPLEMENTARY CONCEPT] OR SECUKINUMAB[TIAB] OR COSENTYX[TIAB] OR AIN457[TIAB] OR AIN-457[TIAB]) OR (("ANTI-INFLAMMATORY AGENTS, NON-STEROIDAL"[MESH] OR NSAID*[TIAB] OR NON-STEROIDAL ANTI-INFLAMMATOR*[TW]) OR (NONSTEROIDAL ANTI-INFLAMMATORY AGENT*[TIAB] OR NONSTEROIDAL ANTIINFLAMMATORY AGENT*[TIAB] OR ANTI-INFLAMMATORY ANALGESIC*[TIAB]) OR ("ANTI-INFLAMMATORY AGENTS, NON-STEROIDAL"[PHARMACOLOGICAL ACTION]) OR (ACECLOFENAC OR ACEMETACIN OR ACETOSYRINGONE OR ACETOVANILLONE OR ADAPALENE OR ALCLOFENAC OR ALMINOPROFEN OR AMIPRILOSE OR AMPYRONE OR ANDROGRAPHOLIDE OR ANISODAMINE OR ANISODINE OR ANTIPYRINE OR APAZONE OR APREMILAST OR ARTEPARON OR ARTHROTEC OR ASPIRIN OR ATRINOSITOL OR AZULENE OR BAICALIN OR BALSALAZIDE OR BENDAZAC OR BENDAZAC LYSINE OR BENORILATE OR BENOXAPROFEN OR BENZOBARBITAL OR BERBAMINE OR BEVONIUM OR BOLDINE OR BROMFENAC OR BUCILLAMINE OR BUFEXAMAC OR BUMADIZONE OR BUTIBUFEN OR CARPROFEN OR CARYOPHYLLENE OR CASTANOSPERMINE OR CELECOXIB OR CEPHARANTHINE OR CHLOROQUINE DIPHOSPHATE OR CHOLINE MAGNESIUM TRISALICYLATE OR CHRYSAROBIN OR CLONIXIN OR CURCUMIN OR DAURICINE OR DEXKETOPROFEN TROMETAMOL OR DICLOFENAC OR DIFENPIRAMIDE OR DIFLUNISAL OR DIMEPHOSPHON OR DIPYRONE OR DIUCIFON OR DROXICAM OR EBSELEN OR ECALLANTIDE OR ELTENAC OR EPIRIZOLE OR ETANERCEPT OR ETHENZAMIDE OR ETHONIUM OR ETODOLAC OR ETOFENAMATE OR ETORICOXIB OR FENBUFEN OR FENCLOFENAC OR FENFLUMIZOLE OR FENOPROFEN OR FENTIAZAC OR FEPRADINOL OR FEPRAZONE OR FLOCTAFENINE OR FLOSULIDE OR FLUNIXIN OR FLUNOXAPROFEN OR FLUPROQUAZONE OR FLURBIPROFEN OR GLUCAMETACIN OR GUACETISAL OR HELENALIN OR HELIODERMIN OR HEMODES OR HIGENAMINE OR IBUPROFEN OR IBUPROXAM OR ICATIBANT OR INDOBUFEN OR INDOMETHACIN OR INDOPROFEN OR IODOANTIPYRINE OR ISOXICAM OR KEBUZONE OR KETOPROFEN OR KETOROLAC OR LICOFELONE OR LISOFYLLINE OR LOBENZARIT OR LONAZOLAC OR LORNOXICAM OR LOXOPROFEN OR LUMIRACOXIB OR MAGNOLOL OR MANOALIDE OR MASOPROCOL OR MELOXICAM OR MESALAMINE OR MIZORIBINE OR MOFEBUTAZONE OR MOFEZOLAC OR NABUMETONE OR NAFAMOSTAT OR NAPROXEN OR NEBACETIN OR NEPAFENAC OR NIFENAZONE OR NIMESULIDE OR NITROASPIRIN OR OLSALAZINE OR OLVANIL OR ORGOTEIN OR OXAPROZIN OR OXYPHENBUTAZONE OR PALMIDROL OR PARECOXIB OR PARTHENOLIDE OR PEONIFLORIN OR PHENIDONE OR PHENYLBUTAZONE OR PIMECROLIMUS OR PIRFENIDONE OR

PIROXICAM OR PIRPROFEN OR PROGLUMETACIN OR PROPACETAMOL OR PROPIONYLCARNITINE OR PROPYPHENAZONE OR PROQUAZONE OR PYRANOPROFEN OR PYRAZOLONE OR PYROGENAL OR RESVERATROL OR RNS60 OR ROFECOXIB OR RUMALON OR SAIKO-KEISHI-TO OR SAIKOSAPONIN OR SALICIN OR SALICYLAMIDE OR SALICYLATES OR "SALICYLSALICYLIC ACID" OR SEMAPIMOD OR SERATRODAST OR SERRATIOPEPTIDASE OR SHIKONIN OR SINAPALDEHYDE OR SODIUM SALICYLATE OR SUL-121 OR SULFASALAZINE OR SULINDAC OR SUPROFEN OR SUXIBUZONE OR TANSHINONE OR TAXIFOLIN OR TENIDAP OR TENOXICAM OR TEPOXALIN OR TIARAMIDE OR TINORIDINE OR TOLMETIN OR TRANILAST OR TRIBENOSIDE OR VALDECOXIB OR ZILEUTON OR ZOMEPIRAC) OR (CELEBREX OR SC-58635 OR SC58635) OR (ETODOLIC* OR ULTRADOL OR LODINE OR RAMODAR OR AY-24236) OR (CP-16171 OR CP16171 OR FELDENE) OR (DICLOPHENAC OR DICROFENAC OR DICHLOFENAL OR "DICLONATE P" OR FELORAN OR VOLTAROL OR NOVAPIRINA OR ORTHOFEN OR ORTOFEN OR ORTHOPHEN OR SR-38 OR VOLTAREN) OR (NABUMETON OR RELIFEX OR RELIF OR APO-NABUMETONE OR APONABUMETONE OR MEBUTAN OR LISTRAN OR GEN-NABUMETONE OR ARTHRAXAN OR RHOXAL-NABUMETONE OR RELAFEN OR NABUCOX) OR (MILOXICAM OR PAROCIN OR MOBIC OR MOBICOX OR MOBEC OR MASFLEX OR MOVICOX OR REUMOXICAM OR UTICOX OR MOVALIS) OR ("INDOMETHACIN"[MESH] OR INDOMETACIN OR OSMOSIN OR INDOCID OR METINDOL OR AMUNO OR INDOCIN) OR (TOLECTIN OR MCN-2559) OR (MOTRIN OR NUPRIN OR RUFEN OR SALPROFEN OR BRUFEN) OR (METHOXYPROPIOCIN OR ANAPROX OR ALEVE OR PROXEN OR SYNFLEX OR NAPROSIN OR NAPROSYN)) OR (Search AND (CORTICOSTEROID*[TW] AND ORAL*[TIAB]) OR (STEROID*[TW] AND ORAL*[TIAB]) OR (FLUBENISOLONE[TIAB] OR BETADEXAMETHASONE[TIAB] OR CELESTONA[TIAB] OR CELESTON[TIAB] OR CELESTONE[TIAB] OR "BETAMETHASONE 17-VALERATE"[TIAB] OR FLUBENISOLONVALERATE[TIAB] OR BETNOVATE[TIAB] OR METHYLFLUORPREDNISOLONE[TIAB] OR HEXADECADROL[TIAB] OR DECAMETH[TIAB] OR DECASPRAY[TIAB] OR DEXASONE[TIAB] OR DEXPAK[TIAB] OR MAXIDEX[TIAB] OR MILLICORTEN[TIAB] OR ORADEXON[TIAB] OR DECAJECT[TIAB] OR DECAJECT-L.A.[TIAB] OR DECAJECT L.A.[TIAB] OR HEXADROL[TIAB] OR HE-111[TIAB] OR HE111[TIAB] OR AUXISON[TIAB] OR MELENGESTROL[TIAB] OR METIPRED[TIAB] OR 6-METHYLPREDNISOLONE[TIAB] OR URBASON[TIAB] OR MEDROL[TIAB] OR PREDATE[TIAB] OR PREDONINE[TIAB] OR DI-ADRESON-F[TIAB] OR DEHYDROCORTISONE[TIAB] OR DELTA-CORTISONE[TIAB] OR RECTODELT[TIAB] OR "PREDNISON HEXAL"[TIAB] OR STERAPRED[TIAB] OR ULTRACORTEN[TIAB] OR WINPRED[TIAB] OR APO-PREDNISONE[TIAB] OR CORTAN[TIAB] OR CORTANCYL[TIAB] OR PANAFCORT[TIAB] OR DECORTIN[TIAB] OR DACORTIN[TIAB] OR DECORTISYL[TIAB] OR DELTASONE[TIAB] OR ENCORTONE[TIAB] OR ENCORTON[TIAB] OR "LIQUID PRED"[TIAB] OR METICORTEN[TIAB] OR ORASONE[TIAB] OR PANASOL[TIAB] OR "PREDNI TABLINEN"[TIAB] OR PREDNIDIB[TIAB] OR "PREDNISON ACSIS"[TIAB] OR PRONISONE[TIAB] OR SONE[TIAB] OR "PREDNISON GALEN"[TIAB] OR VOLON[TIAB] OR ARISTOCORT[TIAB]) OR (ALCLOMETASONE DIPROPIONATE[TIAB] OR AMCINONIDE[TIAB] OR BETAMETHASONE[MESH] OR BETAMETHASONE[TW] OR BETAMETHASONE VALERATE[MESH] OR CICLESONIDE[TIAB] OR CLOBETASONE BUTYRATE[TIAB] OR CLOCORTOLONE*[TIAB] OR DEXAMETHASONE[MESH] OR DEXAMETHASONE*[TW] OR DEXAMETHASONE

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ISONICOTINATE[MESH] OR DICHLORISONE ACETATE[TIAB] OR DIFLORASONE[TIAB] OR DIFLUPREDNATE[TIAB] OR DROCINONIDE PHOSPHATE POTASSIUM[TIAB] OR FLUOCORTIN BUTYL ESTER[TIAB] OR FLUPEROLONE ACETATE[TIAB] OR FLUPREDNIDENE ACETATE[TIAB] OR FLUPREDNISOLONE[MESH] OR FX006[TIAB] OR HALOMETASONE[TIAB] OR MEDRYSONE[TIAB] OR MELENGESTROL ACETATE[MESH] OR METHYLPREDNISOLONE[MESH] OR METHYLPREDNISOLONE[TW] OR PARAMETHASONE[MESH] OR PREDNICARBATE[TIAB] OR PREDNISOLONE[MESH] OR PREDNISOLONE*[TW] OR PREDNISONE[MESH] OR PREDNISONE[TW] OR RIMEXOLONE[TIAB] OR TRIAMCINOLONE[MESH] OR TRIAMCINOLONE*[TW]) OR (GLUCOCORTICOID*[TW])) OR ("METHOTREXATE"[MESH] OR METHOTREXATE*[TIAB] OR AMETHOPTERIN[TIAB] OR MEXATE[TIAB] OR "RILONACEPT"[SUPPLEMENTARY CONCEPT] OR RILONACEPT[TIAB] OR ANAKINRA[TW] OR KINERET[TIAB] OR ANTRIL[TIAB] OR "CANAKINUMAB"[SUPPLEMENTARY CONCEPT] OR CANAKINUMAB[TIAB] OR ILARIS[TIAB] OR ACZ-885[TIAB] OR ACZ885[TIAB] OR "TOCILIZUMAB"[SUPPLEMENTARY CONCEPT] OR TOCILIZUMAB[TIAB] OR ATLIZUMAB[TIAB] OR ACTEMRA[TIAB]) OR ("ETOPOSIDE"[MESH] OR ETOPOSIDE[TIAB] OR EPOSIDE[TIAB] OR "ETOPOSIDO FERRER FARMA"[TIAB] OR LASTET[TIAB] OR NSC-141540[TIAB] OR TOPOSAR[TIAB] OR VEPESID[TIAB] OR "VP 16-213"[TIAB] OR "VP 16 213"[TIAB] OR "VP 16213"[TIAB] OR VP-16[TIAB] OR VP16[TIAB] OR "VEPESIDE-SANDOZ"[TIAB] OR CELLTOP[TIAB]) OR ("IMMUNOGLOBULINS, INTRAVENOUS"[MESH] OR INTRAVENOUS IMMUNOGLOBULIN*[TIAB] OR "INTRAVENOUS IG"[TIAB] OR INTRAVENOUS ANTIBOD*[TIAB] OR IVIG[TIAB] OR INTRAVENOUS IMMUNE GLOBULIN*[TIAB] OR IV IMMUNOGLOBULIN*[TIAB] OR "FLEBOGAMMA DIF"[TIAB] OR GAMUNEX[TIAB] OR GLOBULIN-N[TIAB] OR INTRAGLOBIN*[TIAB] OR GAMMAGARD[TIAB] OR GAMIMUNE[TIAB] OR GAMIMMUNE[TIAB] OR PRIVIGEN[TIAB] OR SANDOGLOBULIN[TIAB] OR VENOGLOBULIN*[TIAB] OR IVEEGAM[TIAB] OR ALPHAGLOBIN[TIAB] OR ENDOBULIN[TIAB] OR "GAMIMUNE N"[TIAB] OR "GAMIMMUNE N"[TIAB] OR GAMMONATIV[TIAB]) OR ("PLASMAPHERESIS"[MESH] OR PLASMAPHERES*[TIAB]) OR (DISEASE ACTIVITY SCORE*[TIAB] OR JADA[TIAB] OR JADAS*[TIAB] OR JADI[TIAB] OR DISEASE ACTIVITY INDEX[TIAB] OR PATIENT GLOBAL ASSESSMENT*[TIAB] OR PHYSICAL GLOBAL ASSESSMENT*[TIAB] OR PHYSICIAN GLOBAL ASSESSMENT*[TIAB] OR PGA-VAS[TIAB] OR PtGA[TIAB]) OR ("SEROSITIS"[MESH] OR SEROSIT*) OR (INTERLEUKIN-6 INHIBITOR*[TIAB] OR IL-6 INHIBITOR*[TIAB] OR INTERLEUKIN-1 INHIBITOR*[TIAB] OR IL-1 INHIBITOR*[TIAB] OR "INTERLEUKIN-6/ANTAGONISTS AND INHIBITORS"[MESH] OR "INTERLEUKIN-1/ANTAGONISTS AND INHIBITORS"[MESH] OR "RECEPTORS, INTERLEUKIN-6/ANTAGONISTS AND INHIBITORS"[MESH] OR "RECEPTORS, INTERLEUKIN-1/ANTAGONISTS AND INHIBITORS"[MESH] OR "RILONACEPT"[SUPPLEMENTARY CONCEPT] OR RILONACEPT[TIAB] OR INTERLEUKIN-1 BLOCKER*[TIAB] OR IL-1 BLOCKER*[TIAB] OR IL-1 BLOCKADE*[TIAB] OR INTERLEUKIN-1 BLOCKADE*[TIAB] OR INTERLEUKIN-6 BLOCKER*[TIAB] OR IL-6 BLOCKER*[TIAB] OR IL-6 BLOCKADE*[TIAB] OR INTERLEUKIN-6 BLOCKADE*[TIAB] OR "CANAKINUMAB"[SUPPLEMENTARY CONCEPT] OR CANAKINUMAB[TIAB] OR ILARIS[TIAB] OR ACZ-885[TIAB] OR ACZ885[TIAB] OR ANTI-INTERLEUKIN-1*[TIAB] OR ANTI-IL-1*[TIAB] OR ANTI-INTERLEUKIN-6*[TIAB] OR ANTI-IL-6*[TIAB] OR ANAKINRA[TW] OR KINERET[TW] OR ANTRIL[TW] OR SARILUMAB[SUPPLEMENTARY CONCEPT] OR SARILUMAB[TIAB]) OR

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(SENDOXAN[TIAB] OR B-518[TIAB] OR B518[TIAB] OR CYTOPHOSPHANE[TIAB] OR CYTOXAN[TIAB] OR ENDOXAN[TIAB] OR NEOSAR[TIAB] OR NSC-26271[TIAB] OR NSC26271[TIAB] OR PROCYTOX[TIAB] OR CYCLOPHOSPHANE[TIAB] OR CYCLOPHOSPHAMIDE[MESH] OR CYCLOPHOSPHAMIDE*[TIAB]) OR (ABATACEPT[TW] OR LEA29Y[TIAB] OR BMS224818[TIAB] OR BMS-224818[TIAB] OR BELATACEPT[TIAB] OR ORENCIA[TIAB] OR BMS-188667[TIAB] OR CTLA-4-IG[TIAB] OR "CYTOTOXIC T LYMPHOCYTE-ASSOCIATED ANTIGEN 4-IMMUNOGLOBULIN"[TIAB] OR CTLA4-IG*[TIAB] OR CTLA4-FC[TIAB] OR NULOJIX[TIAB]) OR (RITUXIMAB[TW] OR MABTHERA[TIAB] OR IDEC-C2B8 ANTIBODY[TIAB] OR IDEC-C2B8[TIAB] OR GP2013[TIAB] OR RITUXAN[TIAB]) OR ("BONE MARROW TRANSPLANTATION"[MESH] OR BONE MARROW TRANSPLANT*[TIAB] OR BONE MARROW GRAFT*[TIAB] OR BONE MARROW CELL TRANSPLANT*[TIAB] OR "MESENCHYMAL STEM CELL TRANSPLANTATION"[MESH] OR MESENCHYMAL STEM CELL TRANSPLANTATION*[TIAB]) OR ("S100A12 PROTEIN"[MESH] OR "S100 A12"[TIAB] OR MRP-6 PROTEIN[TIAB] OR CALGRANULIN C PROTEIN[TIAB] OR EN-RAGE PROTEIN[TIAB] OR CAAF1 PROTEIN[TIAB] OR S100A12[TIAB]) OR (TAPERING[TIAB] OR TAPER[TIAB] OR TAPERS[TIAB] OR TAPERED[TIAB])))) OR ((((ARTHRITIS, JUVENILE[MESH] AND (JIA[TIAB] OR JRA[TIAB] OR IDIOPATHIC*[TIAB])) OR (JUVENILE IDIOPATHIC ARTHRIT*[TIAB] OR JUVENILE CHRONIC ARTHRIT*[TIAB] OR CHRONIC JUVENILE ARTHRIT*[TIAB] OR JUVENILE RHEUMATOID ARTHRIT*[TW] OR JUVENILE IDIOPATHIC ARTHROS*[TIAB]) OR (SJIA[TIAB] OR STILLS DISEASE*[TIAB] OR "STILL'S DISEASE"[TIAB] OR STILL DISEASE*[TIAB] OR JUVENILE SYSTEMIC ARTHRIT*[TIAB] OR SYSTEMIC JUVENILE ARTHRIT*[TIAB] OR JUVENILE SYSTEMIC IDIOPATHIC ARTHRIT*[TIAB] OR SYSTEMIC JUVENILE IDIOPATHIC ARTHRIT*[TIAB] OR SYSTEMIC JIA[TIAB] OR SYSTEMIC JRA[TIAB] OR SYSTEMIC JUVENILE RHEUMATOID ARTHRIT*[TIAB] OR JUVENILE SYSTEMIC RHEUMATOID ARTHRIT*[TIAB] OR "RHEUMATOID ARTHRITIS, SYSTEMIC JUVENILE"[SUPPLEMENTARY CONCEPT] OR JUVENILE ONSET SYSTEMIC ARTHRIT*[TIAB] OR SYSTEMIC JUVENILE ONSET ARTHRIT*[TIAB]) AND (ENGLISH[LANG]) NOT (LETTER*[PT] OR COMMENT*[PT] OR EDITORIAL*[PT] OR CASE REPORT*[PT]) NOT ("ANIMALS"[MESH] NOT ("ANIMALS"[MESH] AND "HUMANS"[MESH]))) AND ("MACROPHAGE ACTIVATION SYNDROME"[MESH] OR MACROPHAGE ACTIVATION*[TIAB] OR "LYMPHOHISTIOCYTOSIS, HEMOPHAGOCYTIC"[MESH] OR HEMOPHAGOCYTIC LYMPHOHISTIOCYTOS*[TIAB] OR MAS[TIAB])) AND (("PULSE THERAPY, DRUG"[MESH] OR PULSE DOSE*[TIAB] OR PULSED[TIAB] OR PULSE THERAP*[TIAB] OR "ADMINISTRATION, INTRAVENOUS"[MESH] OR INTRAVENOUS*[TW] OR IV[TIAB]) OR (CALCINEURIN INHIBITOR*[TW] OR PROTEIN PHOSPHATASE-2B INHIBITOR*[TIAB] OR PROTEIN PHOSPHATASE 3 INHIBITOR*[TIAB] OR CALCINEURIN ANTAGONIST*[TIAB] OR CALCINEURIN BLOCKER*[TIAB] OR PROGRAF[TIAB] OR PROGRAFT[TIAB] OR FR-900506[TIAB] OR FR900506[TIAB] OR FK-506[TIAB] OR FK506[TIAB] OR "33-EPI-CHLORO-33-DESOXYASCOMYCIN"[TIAB] OR SDZ-ASM-981[TIAB] OR "ASM 981"[TIAB] OR ELIDEL[TIAB] OR TACROLIMUS OR CYCLOSPORIN OR CYCLOSPORINE OR CICLOSPORINE OR "MUSTOPIC OINT" OR TSUKUBAENOLIDE OR CIPOL OR CYCLOKAT OR DEXIMUNE OR IMPLANTA OR IMMUNOSPORIN OR IMUSPORIN OR VEKACIA OR PROGRAF OR ADVAGRAF OR HECORIA OR GENGRAF OR ASTAGRAF OR "OL-27-400" OR "CSA-NEORAL" OR "CYA-NOF" OR NEURAL))) OR (("LEUKOCYTE COUNT"[MESH] OR LEUKOCYTE

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COUNT*[TIAB] OR LEUKOCYTE NUMBER*[TIAB] OR WHITE BLOOD CELL COUNT*[TIAB] OR "PLATELET COUNT"[MESH] OR PLATELET COUNT*[TIAB] OR PLATELET NUMBER*[TIAB] OR POLYMORPHONUCLEAR LEUKOCYTE*[TIAB] OR LE CELLS[TIAB] OR LE CELL[TIAB] OR "LIVER FUNCTION TESTS"[MESH] OR LIVER ENZYME*[TW] OR LIVER FUNCTION TEST*[TIAB] OR "BLOOD CELL COUNT"[MESH] OR CBC[TIAB] OR COMPLETE BLOOD COUNT*[TIAB] OR BLOOD CELL COUNT*[TIAB] OR BLOOD CELL NUMBER*[TIAB] OR "URINALYSIS"[MESH] OR URINALYS*[TW] OR "CREATININE"[MESH] OR CREATININE[TW] OR KREBIOZEN OR LOW DENSITY LIPOPROTEIN*[TIAB] OR HIGH DENSITY LIPOPROTEIN*[TIAB] OR LDL CHOLESTEROL[TIAB] OR HDL CHOLESTEROL[TIAB] OR "TRIGLYCERIDES"[MESH] OR TRIGLYCERIDE* OR "CHOLESTEROL"[MESH:noexp] OR TOTAL CHOLESTEROL[TIAB] OR "CHOLESTEROL, HDL"[MESH] OR "CHOLESTEROL, LDL"[MESH] OR LIPID PANEL*[TIAB]) AND ((((((ARTHRIT*[TW] AND ("COSTEN'S SYNDROME"[TIAB] OR COSTEN SYNDROME[TIAB] OR TEMPOROMANDIBULAR[TW] OR TMJ[TIAB])) OR (OJIA[TIAB] OR ("ARTHRITIS, JUVENILE"[MESH] OR JUVENILE ARTHRIT*[TIAB] OR JUVENILE CHRONIC ARTHRIT*[TIAB] OR JIA[TIAB] OR JRA[TIAB] OR JUVENILE RHEUMATOID ARTHRIT*[TIAB]) AND (OLIGO ARTICULAR*[TW] OR OLIGO-ARTICULAR*[TW] OR OLIGOARTICULAR*[TW]) OR (OLIGOARTHRIT*[TIAB] OR OLIGO-ARTHRIT*[TIAB])) OR ((ARTHRITIS, JUVENILE[MESH] AND (JIA[TIAB] OR JRA[TIAB] OR IDIOPATHIC*[TIAB])) OR (JUVENILE IDIOPATHIC ARTHRIT*[TIAB] OR JUVENILE CHRONIC ARTHRIT*[TIAB] OR CHRONIC JUVENILE ARTHRIT*[TIAB] OR JUVENILE RHEUMATOID ARTHRIT*[TW] OR JUVENILE IDIOPATHIC ARTHROS*[TIAB])) AND (ENGLISH[LANG])) NOT (CASE REPORT*[PT] OR LETTER*[PT] OR COMMENT*[PT] OR EDITORIAL*[PT])) NOT ("ANIMALS"[MESH] NOT ("ANIMALS"[MESH] AND "HUMANS"[MESH]))) NOT ("ADULT"[MESH] NOT ("ADULT"[MESH] AND "CHILD"[MESH] OR "INFANT"[MESH] OR "ADOLESCENT"[MESH]))) OR ((ARTHRITIS, JUVENILE[MESH] AND (JIA[TIAB] OR JRA[TIAB] OR IDIOPATHIC*[TIAB])) OR (JUVENILE IDIOPATHIC ARTHRIT*[TIAB] OR JUVENILE CHRONIC ARTHRIT*[TIAB] OR CHRONIC JUVENILE ARTHRIT*[TIAB] OR JUVENILE RHEUMATOID ARTHRIT*[TW] OR JUVENILE IDIOPATHIC ARTHROS*[TIAB]) OR (SJIA[TIAB] OR STILLS DISEASE*[TIAB] OR "STILL'S DISEASE"[TIAB] OR STILL DISEASE*[TIAB] OR JUVENILE SYSTEMIC ARTHRIT*[TIAB] OR SYSTEMIC JUVENILE ARTHRIT*[TIAB] OR JUVENILE SYSTEMIC IDIOPATHIC ARTHRIT*[TIAB] OR SYSTEMIC JUVENILE IDIOPATHIC ARTHRIT*[TIAB] OR SYSTEMIC JIA[TIAB] OR SYSTEMIC JRA[TIAB] OR SYSTEMIC JUVENILE RHEUMATOID ARTHRIT*[TIAB] OR JUVENILE SYSTEMIC RHEUMATOID ARTHRIT*[TIAB] OR "RHEUMATOID ARTHRITIS, SYSTEMIC JUVENILE"[SUPPLEMENTARY CONCEPT] OR JUVENILE ONSET SYSTEMIC ARTHRIT*[TIAB] OR SYSTEMIC JUVENILE ONSET ARTHRIT*[TIAB]) AND (ENGLISH[LANG]) NOT (LETTER*[PT] OR COMMENT*[PT] OR EDITORIAL*[PT] OR CASE REPORT*[PT]) NOT ("ANIMALS"[MESH] NOT ("ANIMALS"[MESH] AND "HUMANS"[MESH])))) AND (("METHOTREXATE"[MESH] OR METHOTREXATE*[TIAB] OR AMETHOPTERIN[TIAB] OR MEXATE[TIAB] OR "SULFASALAZINE"[MESH] OR SULFASALAZINE*[TIAB] OR SALICYLAZOSULFAPYRIDINE[TIAB] OR SULPHASALAZINE[TIAB] OR SALAZOSULFAPYRIDINE[TIAB] OR "PYRALIN EN"[TIAB] OR AZULFIDINE[TIAB] OR ASULFIDINE[TIAB] OR COLO-PLEON[TIAB] OR PLEON[TIAB] OR "SULFASALAZIN MEDAC"[TIAB] OR "SULFASALAZIN-HEYL"[TIAB] OR UCINE[TIAB] OR SALAZOPYRIN[TIAB] OR LEFLUNOMIDE[TW] OR HWA-486[TIAB] OR

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HWA486[TIAB] OR SU101[TIAB] OR ARAVA[TIAB] OR "HYDROXYCHLOROQUINE"[TW] OR OXYCHLOROQUINE[TIAB] OR PLAQUENIL[TIAB] OR TUMOR NECROSIS FACTOR INHIBITOR*[TIAB] OR TUMOUR NECROSIS FACTOR INHIBITOR*[TIAB] OR TNFALPHA INHIBITOR*[TIAB] OR TNF-ALPHA INHIBITOR*[TIAB] OR TNF INHIBITOR*[TIAB] OR ANTI-TUMOR NECROSIS FACTOR*[TIAB] OR ANTI-TUMOUR NECROSIS FACTOR*[TIAB] OR ANTI-TNF*[TIAB] OR "TUMOR NECROSIS FACTOR-ALPHA/ANTAGONISTS AND INHIBITORS"[MESH] OR TNFI[TIAB] OR ABATACEPT[TW] OR LEA29Y[TIAB] OR BMS224818[TIAB] OR BMS-224818[TIAB] OR BELATACEPT[TIAB] OR ORENCIA[TIAB] OR BMS-188667[TIAB] OR CTLA-4-IG[TIAB] OR "CYTOTOXIC T LYMPHOCYTE-ASSOCIATED ANTIGEN 4-IMMUNOGLOBULIN"[TIAB] OR CTLA4-IG*[TIAB] OR CTLA4-FC[TIAB] OR NULOJIX[TIAB] OR "TOCILIZUMAB"[SUPPLEMENTARY CONCEPT] OR TOCILIZUMAB[TIAB] OR ATLIZUMAB[TIAB] OR ACTEMRA[TIAB] OR ANAKINRA[TW] OR KINERET[TIAB] OR ANTRIL[TIAB] OR "CANAKINUMAB"[SUPPLEMENTARY CONCEPT] OR CANAKINUMAB[TIAB] OR ILARIS[TIAB] OR ACZ-885[TIAB] OR ACZ885[TIAB]) OR (("ANTI-INFLAMMATORY AGENTS, NON-STEROIDAL"[MESH] OR NSAID*[TIAB] OR NON-STEROIDAL ANTI-INFLAMMATOR*[TW]) OR (NONSTEROIDAL ANTI-INFLAMMATORY AGENT*[TIAB] OR NONSTEROIDAL ANTIINFLAMMATORY AGENT*[TIAB] OR ANTI-INFLAMMATORY ANALGESIC*[TIAB]) OR ("ANTI-INFLAMMATORY AGENTS, NON-STEROIDAL"[PHARMACOLOGICAL ACTION]) OR (ACECLOFENAC OR ACEMETACIN OR ACETOSYRINGONE OR ACETOVANILLONE OR ADAPALENE OR ALCLOFENAC OR ALMINOPROFEN OR AMIPRILOSE OR AMPYRONE OR ANDROGRAPHOLIDE OR ANISODAMINE OR ANISODINE OR ANTIPYRINE OR APAZONE OR APREMILAST OR ARTEPARON OR ARTHROTEC OR ASPIRIN OR ATRINOSITOL OR AZULENE OR BAICALIN OR BALSALAZIDE OR BENDAZAC OR BENDAZAC LYSINE OR BENORILATE OR BENOXAPROFEN OR BENZOBARBITAL OR BERBAMINE OR BEVONIUM OR BOLDINE OR BROMFENAC OR BUCILLAMINE OR BUFEXAMAC OR BUMADIZONE OR BUTIBUFEN OR CARPROFEN OR CARYOPHYLLENE OR CASTANOSPERMINE OR CELECOXIB OR CEPHARANTHINE OR CHLOROQUINE DIPHOSPHATE OR CHOLINE MAGNESIUM TRISALICYLATE OR CHRYSAROBIN OR CLONIXIN OR CURCUMIN OR DAURICINE OR DEXKETOPROFEN TROMETAMOL OR DICLOFENAC OR DIFENPIRAMIDE OR DIFLUNISAL OR DIMEPHOSPHON OR DIPYRONE OR DIUCIFON OR DROXICAM OR EBSELEN OR ECALLANTIDE OR ELTENAC OR EPIRIZOLE OR ETANERCEPT OR ETHENZAMIDE OR ETHONIUM OR ETODOLAC OR ETOFENAMATE OR ETORICOXIB OR FENBUFEN OR FENCLOFENAC OR FENFLUMIZOLE OR FENOPROFEN OR FENTIAZAC OR FEPRADINOL OR FEPRAZONE OR FLOCTAFENINE OR FLOSULIDE OR FLUNIXIN OR FLUNOXAPROFEN OR FLUPROQUAZONE OR FLURBIPROFEN OR GLUCAMETACIN OR GUACETISAL OR HELENALIN OR HELIODERMIN OR HEMODES OR HIGENAMINE OR IBUPROFEN OR IBUPROXAM OR ICATIBANT OR INDOBUFEN OR INDOMETHACIN OR INDOPROFEN OR IODOANTIPYRINE OR ISOXICAM OR KEBUZONE OR KETOPROFEN OR KETOROLAC OR LICOFELONE OR LISOFYLLINE OR LOBENZARIT OR LONAZOLAC OR LORNOXICAM OR LOXOPROFEN OR LUMIRACOXIB OR MAGNOLOL OR MANOALIDE OR MASOPROCOL OR MELOXICAM OR MESALAMINE OR MIZORIBINE OR MOFEBUTAZONE OR MOFEZOLAC OR NABUMETONE OR NAFAMOSTAT OR NAPROXEN OR NEBACETIN OR NEPAFENAC OR NIFENAZONE OR NIMESULIDE OR NITROASPIRIN OR OLSALAZINE OR OLVANIL OR ORGOTEIN OR

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OXAPROZIN OR OXYPHENBUTAZONE OR PALMIDROL OR PARECOXIB OR PARTHENOLIDE OR PEONIFLORIN OR PHENIDONE OR PHENYLBUTAZONE OR PIMECROLIMUS OR PIRFENIDONE OR PIROXICAM OR PIRPROFEN OR PROGLUMETACIN OR PROPACETAMOL OR PROPIONYLCARNITINE OR PROPYPHENAZONE OR PROQUAZONE OR PYRANOPROFEN OR PYRAZOLONE OR PYROGENAL OR RESVERATROL OR RNS60 OR ROFECOXIB OR RUMALON OR SAIKO-KEISHI-TO OR SAIKOSAPONIN OR SALICIN OR SALICYLAMIDE OR SALICYLATES OR "SALICYLSALICYLIC ACID" OR SEMAPIMOD OR SERATRODAST OR SERRATIOPEPTIDASE OR SHIKONIN OR SINAPALDEHYDE OR SODIUM SALICYLATE OR SUL-121 OR SULFASALAZINE OR SULINDAC OR SUPROFEN OR SUXIBUZONE OR TANSHINONE OR TAXIFOLIN OR TENIDAP OR TENOXICAM OR TEPOXALIN OR TIARAMIDE OR TINORIDINE OR TOLMETIN OR TRANILAST OR TRIBENOSIDE OR VALDECOXIB OR ZILEUTON OR ZOMEPIRAC) OR (CELEBREX OR SC-58635 OR SC58635) OR (ETODOLIC* OR ULTRADOL OR LODINE OR RAMODAR OR AY-24236) OR (CP-16171 OR CP16171 OR FELDENE) OR (DICLOPHENAC OR DICROFENAC OR DICHLOFENAL OR "DICLONATE P" OR FELORAN OR VOLTAROL OR NOVAPIRINA OR ORTHOFEN OR ORTOFEN OR ORTHOPHEN OR SR-38 OR VOLTAREN) OR (NABUMETON OR RELIFEX OR RELIF OR APO-NABUMETONE OR APONABUMETONE OR MEBUTAN OR LISTRAN OR GEN-NABUMETONE OR ARTHRAXAN OR RHOXAL-NABUMETONE OR RELAFEN OR NABUCOX) OR (MILOXICAM OR PAROCIN OR MOBIC OR MOBICOX OR MOBEC OR MASFLEX OR MOVICOX OR REUMOXICAM OR UTICOX OR MOVALIS) OR ("INDOMETHACIN"[MESH] OR INDOMETACIN OR OSMOSIN OR INDOCID OR METINDOL OR AMUNO OR INDOCIN) OR (TOLECTIN OR MCN-2559) OR (MOTRIN OR NUPRIN OR RUFEN OR SALPROFEN OR BRUFEN) OR (METHOXYPROPIOCIN OR ANAPROX OR ALEVE OR PROXEN OR SYNFLEX OR NAPROSIN OR NAPROSYN)))) OR (((((((ARTHRIT*[TW] AND ("COSTEN'S SYNDROME"[TIAB] OR COSTEN SYNDROME[TIAB] OR TEMPOROMANDIBULAR[TW] OR TMJ[TIAB])) OR (OJIA[TIAB] OR ("ARTHRITIS, JUVENILE"[MESH] OR JUVENILE ARTHRIT*[TIAB] OR JUVENILE CHRONIC ARTHRIT*[TIAB] OR JIA[TIAB] OR JRA[TIAB] OR JUVENILE RHEUMATOID ARTHRIT*[TIAB]) AND (OLIGO ARTICULAR*[TW] OR OLIGO-ARTICULAR*[TW] OR OLIGOARTICULAR*[TW]) OR (OLIGOARTHRIT*[TIAB] OR OLIGO-ARTHRIT*[TIAB])) OR ((ARTHRITIS, JUVENILE[MESH] AND (JIA[TIAB] OR JRA[TIAB] OR IDIOPATHIC*[TIAB])) OR (JUVENILE IDIOPATHIC ARTHRIT*[TIAB] OR JUVENILE CHRONIC ARTHRIT*[TIAB] OR CHRONIC JUVENILE ARTHRIT*[TIAB] OR JUVENILE RHEUMATOID ARTHRIT*[TW] OR JUVENILE IDIOPATHIC ARTHROS*[TIAB])) AND (ENGLISH[LANG])) NOT (CASE REPORT*[PT] OR LETTER*[PT] OR COMMENT*[PT] OR EDITORIAL*[PT])) NOT ("ANIMALS"[MESH] NOT ("ANIMALS"[MESH] AND "HUMANS"[MESH]))) NOT ("ADULT"[MESH] NOT ("ADULT"[MESH] AND "CHILD"[MESH] OR "INFANT"[MESH] OR "ADOLESCENT"[MESH]))) OR ((ARTHRITIS, JUVENILE[MESH] AND (JIA[TIAB] OR JRA[TIAB] OR IDIOPATHIC*[TIAB])) OR (JUVENILE IDIOPATHIC ARTHRIT*[TIAB] OR JUVENILE CHRONIC ARTHRIT*[TIAB] OR CHRONIC JUVENILE ARTHRIT*[TIAB] OR JUVENILE RHEUMATOID ARTHRIT*[TW] OR JUVENILE IDIOPATHIC ARTHROS*[TIAB]) OR (SJIA[TIAB] OR STILLS DISEASE*[TIAB] OR "STILL'S DISEASE"[TIAB] OR STILL DISEASE*[TIAB] OR JUVENILE SYSTEMIC ARTHRIT*[TIAB] OR SYSTEMIC JUVENILE ARTHRIT*[TIAB] OR JUVENILE SYSTEMIC IDIOPATHIC ARTHRIT*[TIAB] OR SYSTEMIC JUVENILE IDIOPATHIC ARTHRIT*[TIAB] OR SYSTEMIC JIA[TIAB] OR SYSTEMIC JRA[TIAB] OR SYSTEMIC JUVENILE RHEUMATOID ARTHRIT*[TIAB] OR JUVENILE

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SYSTEMIC RHEUMATOID ARTHRIT*[TIAB] OR "RHEUMATOID ARTHRITIS, SYSTEMIC JUVENILE"[SUPPLEMENTARY CONCEPT] OR JUVENILE ONSET SYSTEMIC ARTHRIT*[TIAB] OR SYSTEMIC JUVENILE ONSET ARTHRIT*[TIAB]) AND (ENGLISH[LANG]) NOT (LETTER*[PT] OR COMMENT*[PT] OR EDITORIAL*[PT] OR CASE REPORT*[PT]) NOT ("ANIMALS"[MESH] NOT ("ANIMALS"[MESH] AND "HUMANS"[MESH]))))) AND (SERIOUS INFECTION*[TIAB] OR HERPES VIRUS VARICELLAE[TIAB] OR HERPESVIRUS 3[TIAB] OR ZONA VIRUS[TIAB] OR VARICELLA*[TW] OR HERPES ZOSTER[TW] OR "HEPATITIS C"[MESH] OR HEPATITIS C[TIAB] OR PT-NANBH[TIAB] OR "HEPATITIS B"[MESH] OR HEPATITIS B[TIAB] OR "CHICKENPOX"[MESH] OR CHICKENPOX OR HERPESVIRUS 3[TIAB] OR CHICKEN POX[TIAB] OR "MEASLES"[MESH] OR MEASLES[TIAB] OR RUBEOLA[TIAB] OR RUBELLA[TIAB])) OR (((((((ARTHRIT*[TW] AND ("COSTEN'S SYNDROME"[TIAB] OR COSTEN SYNDROME[TIAB] OR TEMPOROMANDIBULAR[TW] OR TMJ[TIAB])) OR (OJIA[TIAB] OR ("ARTHRITIS, JUVENILE"[MESH] OR JUVENILE ARTHRIT*[TIAB] OR JUVENILE CHRONIC ARTHRIT*[TIAB] OR JIA[TIAB] OR JRA[TIAB] OR JUVENILE RHEUMATOID ARTHRIT*[TIAB]) AND (OLIGO ARTICULAR*[TW] OR OLIGO-ARTICULAR*[TW] OR OLIGOARTICULAR*[TW]) OR (OLIGOARTHRIT*[TIAB] OR OLIGO-ARTHRIT*[TIAB])) OR ((ARTHRITIS, JUVENILE[MESH] AND (JIA[TIAB] OR JRA[TIAB] OR IDIOPATHIC*[TIAB])) OR (JUVENILE IDIOPATHIC ARTHRIT*[TIAB] OR JUVENILE CHRONIC ARTHRIT*[TIAB] OR CHRONIC JUVENILE ARTHRIT*[TIAB] OR JUVENILE RHEUMATOID ARTHRIT*[TW] OR JUVENILE IDIOPATHIC ARTHROS*[TIAB])) AND (ENGLISH[LANG])) NOT (CASE REPORT*[PT] OR LETTER*[PT] OR COMMENT*[PT] OR EDITORIAL*[PT])) NOT ("ANIMALS"[MESH] NOT ("ANIMALS"[MESH] AND "HUMANS"[MESH]))) NOT ("ADULT"[MESH] NOT ("ADULT"[MESH] AND "CHILD"[MESH] OR "INFANT"[MESH] OR "ADOLESCENT"[MESH]))) OR ((ARTHRITIS, JUVENILE[MESH] AND (JIA[TIAB] OR JRA[TIAB] OR IDIOPATHIC*[TIAB])) OR (JUVENILE IDIOPATHIC ARTHRIT*[TIAB] OR JUVENILE CHRONIC ARTHRIT*[TIAB] OR CHRONIC JUVENILE ARTHRIT*[TIAB] OR JUVENILE RHEUMATOID ARTHRIT*[TW] OR JUVENILE IDIOPATHIC ARTHROS*[TIAB]) OR (SJIA[TIAB] OR STILLS DISEASE*[TIAB] OR "STILL'S DISEASE"[TIAB] OR STILL DISEASE*[TIAB] OR JUVENILE SYSTEMIC ARTHRIT*[TIAB] OR SYSTEMIC JUVENILE ARTHRIT*[TIAB] OR JUVENILE SYSTEMIC IDIOPATHIC ARTHRIT*[TIAB] OR SYSTEMIC JUVENILE IDIOPATHIC ARTHRIT*[TIAB] OR SYSTEMIC JIA[TIAB] OR SYSTEMIC JRA[TIAB] OR SYSTEMIC JUVENILE RHEUMATOID ARTHRIT*[TIAB] OR JUVENILE SYSTEMIC RHEUMATOID ARTHRIT*[TIAB] OR "RHEUMATOID ARTHRITIS, SYSTEMIC JUVENILE"[SUPPLEMENTARY CONCEPT] OR JUVENILE ONSET SYSTEMIC ARTHRIT*[TIAB] OR SYSTEMIC JUVENILE ONSET ARTHRIT*[TIAB]) AND (ENGLISH[LANG]) NOT (LETTER*[PT] OR COMMENT*[PT] OR EDITORIAL*[PT] OR CASE REPORT*[PT]) NOT ("ANIMALS"[MESH] NOT ("ANIMALS"[MESH] AND "HUMANS"[MESH]))))) AND ("TUBERCULOSIS"[MESH] OR TUBERCULOS* OR "KOCH'S DISEASE"[TIAB] OR KOCH DISEASE[TIAB] OR KOCHS DISEASE[TIAB] OR MYCOBACTERIUM[TW] OR "TUBERCULIN TEST"[MESH] OR TUBERCULIN TEST*[TIAB] OR LTBI[TIAB]) AND (BIOLOGIC DISEASE MODIF*[TIAB] OR BIOLOGIC RESPONSE MODIF*[TIAB] OR BIOLOGIC AGENT*[TIAB] OR BIOLOGIC DRUG*[TIAB] OR DISEASE-MODIFYING ANTIRHEUMATIC*[TIAB] OR DISEASE-MODIFYING ANTI-RHEUMATIC*[TIAB] OR DMARD*[TIAB] OR "RECEPTORS, INTERLEUKIN-6/ANTAGONISTS AND INHIBITORS"[MESH] OR "RECEPTORS, INTERLEUKIN-1/ANTAGONISTS AND INHIBITORS"[MESH] OR INTERLEUKIN-1 BLOCKER*[TIAB]

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OR IL-1 BLOCKER*[TIAB] OR IL-1 BLOCKADE*[TIAB] OR INTERLEUKIN-1 BLOCKADE*[TIAB] OR INTERLEUKIN-6 BLOCKER*[TIAB] OR IL-6 BLOCKER*[TIAB] OR IL-6 BLOCKADE*[TIAB] OR INTERLEUKIN-6 BLOCKADE*[TIAB] OR "CANAKINUMAB"[SUPPLEMENTARY CONCEPT] OR CANAKINUMAB[TIAB] OR ILARIS[TIAB] OR ACZ-885[TIAB] OR ACZ885[TIAB] OR ANTI-INTERLEUKIN-1*[TIAB] OR ANTI-IL-1*[TIAB] OR ANTI-INTERLEUKIN-6*[TIAB] OR ANTI-IL-6*[TIAB] OR ANAKINRA[TW] OR KINERET[TW] OR ANTRIL[TW] OR "INTERLEUKIN-6/ANTAGONISTS AND INHIBITORS"[MESH] OR INTERLEUKIN-6 INHIBITOR*[TIAB] OR IL-6 INHIBITOR*[TIAB] OR INTERLEUKIN-1 INHIBITOR*[TIAB] OR "INTERLEUKIN-1/ANTAGONISTS AND INHIBITORS"[MESH] OR IL-1 INHIBITOR*[TIAB] OR "RILONACEPT"[SUPPLEMENTARY CONCEPT] OR RILONACEPT[TIAB] OR TUMOR NECROSIS FACTOR INHIBITOR*[TIAB] OR TUMOUR NECROSIS FACTOR INHIBITOR*[TIAB] OR TNFALPHA INHIBITOR*[TIAB] OR TNF-ALPHA INHIBITOR*[TIAB] OR TNF INHIBITOR*[TIAB] OR ANTI-TUMOR NECROSIS FACTOR*[TIAB] OR ANTI-TUMOUR NECROSIS FACTOR*[TIAB] OR ANTI-TNF*[TIAB] OR "TUMOR NECROSIS FACTOR-ALPHA/ANTAGONISTS AND INHIBITORS"[MESH] OR TNFI[TIAB] OR "ADALIMUMAB"[MESH] OR ADALIMUMAB[TIAB] OR HUMIRA[TIAB] OR ADALIMUMAB-ADBM[TIAB] OR AMJEVITA[TIAB] OR ADALIMUMAB-ATTO[TIAB] OR CYLTEZO[TIAB] OR ETANERCEPT[TIAB] OR "TNFR-FC FUSION PROTEIN"[TIAB] OR "TNR 001"[TIAB] OR "TNT RECEPTOR FUSION PROTEIN"[TIAB] OR TNR-001[TIAB] OR ETANERCEPT-SZZS[TIAB] OR "TNF RECEPTOR TYPE II-IGG FUSION PROTEIN"[TIAB] OR ERELZI[TIAB] OR ENBREL[TIAB] OR INFLIXIMAB*[TW] OR "MONOCLONAL ANTIBODY CA2"[TIAB] OR "MAB CA2"[TIAB] OR RENFLEXIS[TIAB] OR INFLECTRA[TIAB] OR REMICADE[TIAB] OR "GOLIMUMAB"[SUPPLEMENTARY CONCEPT] OR GOLIMUMAB[TIAB] OR "CERTOLIZUMAB PEGOL"[TW] OR CIMZIA[TIAB] OR CDP870[TIAB] OR ABATACEPT[TW] OR LEA29Y[TIAB] OR BMS224818[TIAB] OR BMS-224818[TIAB] OR BELATACEPT[TIAB] OR ORENCIA[TIAB] OR BMS-188667[TIAB] OR CTLA-4-IG[TIAB] OR "CYTOTOXIC T LYMPHOCYTE-ASSOCIATED ANTIGEN 4-IMMUNOGLOBULIN"[TIAB] OR CTLA4-IG*[TIAB] OR CTLA4-FC[TIAB] OR NULOJIX[TIAB] OR "TOCILIZUMAB"[SUPPLEMENTARY CONCEPT] OR TOCILIZUMAB[TIAB] OR ATLIZUMAB[TIAB] OR ACTEMRA[TIAB] OR RITUXIMAB[TW] OR MABTHERA[TIAB] OR IDEC-C2B8 ANTIBODY[TIAB] OR IDEC-C2B8[TIAB] OR GP2013[TIAB] OR RITUXAN[TIAB] OR "TOFACITINIB"[SUPPLEMENTARY CONCEPT] OR TOFACITINIB[TW] OR TASOCITINIB[TIAB] OR XELJANZ[TIAB] OR CP690550[TIAB] OR CP-690550[TIAB] OR CP 690550[TIAB] OR "SECUKINUMAB"[SUPPLEMENTARY CONCEPT] OR SECUKINUMAB[TIAB] OR COSENTYX[TIAB] OR AIN457[TIAB] OR AIN-457[TIAB])) OR (((((((ARTHRIT*[TW] AND ("COSTEN'S SYNDROME"[TIAB] OR COSTEN SYNDROME[TIAB] OR TEMPOROMANDIBULAR[TW] OR TMJ[TIAB])) OR (OJIA[TIAB] OR ("ARTHRITIS, JUVENILE"[MESH] OR JUVENILE ARTHRIT*[TIAB] OR JUVENILE CHRONIC ARTHRIT*[TIAB] OR JIA[TIAB] OR JRA[TIAB] OR JUVENILE RHEUMATOID ARTHRIT*[TIAB]) AND (OLIGO ARTICULAR*[TW] OR OLIGO-ARTICULAR*[TW] OR OLIGOARTICULAR*[TW]) OR (OLIGOARTHRIT*[TIAB] OR OLIGO-ARTHRIT*[TIAB])) OR ((ARTHRITIS, JUVENILE[MESH] AND (JIA[TIAB] OR JRA[TIAB] OR IDIOPATHIC*[TIAB])) OR (JUVENILE IDIOPATHIC ARTHRIT*[TIAB] OR JUVENILE CHRONIC ARTHRIT*[TIAB] OR CHRONIC JUVENILE ARTHRIT*[TIAB] OR JUVENILE RHEUMATOID ARTHRIT*[TW] OR JUVENILE IDIOPATHIC ARTHROS*[TIAB])) AND (ENGLISH[LANG])) NOT (CASE REPORT*[PT] OR LETTER*[PT] OR COMMENT*[PT] OR EDITORIAL*[PT])) NOT

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("ANIMALS"[MESH] NOT ("ANIMALS"[MESH] AND "HUMANS"[MESH]))) NOT ("ADULT"[MESH] NOT ("ADULT"[MESH] AND "CHILD"[MESH] OR "INFANT"[MESH] OR "ADOLESCENT"[MESH]))) OR ((ARTHRITIS, JUVENILE[MESH] AND (JIA[TIAB] OR JRA[TIAB] OR IDIOPATHIC*[TIAB])) OR (JUVENILE IDIOPATHIC ARTHRIT*[TIAB] OR JUVENILE CHRONIC ARTHRIT*[TIAB] OR CHRONIC JUVENILE ARTHRIT*[TIAB] OR JUVENILE RHEUMATOID ARTHRIT*[TW] OR JUVENILE IDIOPATHIC ARTHROS*[TIAB]) OR (SJIA[TIAB] OR STILLS DISEASE*[TIAB] OR "STILL'S DISEASE"[TIAB] OR STILL DISEASE*[TIAB] OR JUVENILE SYSTEMIC ARTHRIT*[TIAB] OR SYSTEMIC JUVENILE ARTHRIT*[TIAB] OR JUVENILE SYSTEMIC IDIOPATHIC ARTHRIT*[TIAB] OR SYSTEMIC JUVENILE IDIOPATHIC ARTHRIT*[TIAB] OR SYSTEMIC JIA[TIAB] OR SYSTEMIC JRA[TIAB] OR SYSTEMIC JUVENILE RHEUMATOID ARTHRIT*[TIAB] OR JUVENILE SYSTEMIC RHEUMATOID ARTHRIT*[TIAB] OR "RHEUMATOID ARTHRITIS, SYSTEMIC JUVENILE"[SUPPLEMENTARY CONCEPT] OR JUVENILE ONSET SYSTEMIC ARTHRIT*[TIAB] OR SYSTEMIC JUVENILE ONSET ARTHRIT*[TIAB]) AND (ENGLISH[LANG]) NOT (LETTER*[PT] OR COMMENT*[PT] OR EDITORIAL*[PT] OR CASE REPORT*[PT]) NOT ("ANIMALS"[MESH] NOT ("ANIMALS"[MESH] AND "HUMANS"[MESH]))))) AND ("VACCINES"[MESH:noexp] OR VACCIN*[TW] OR "VACCINATION"[MESH] OR IMMUNIZ*[TW] OR IMMUNIS*[TW])) OR (((((((ARTHRIT*[TW] AND ("COSTEN'S SYNDROME"[TIAB] OR COSTEN SYNDROME[TIAB] OR TEMPOROMANDIBULAR[TW] OR TMJ[TIAB])) OR (OJIA[TIAB] OR ("ARTHRITIS, JUVENILE"[MESH] OR JUVENILE ARTHRIT*[TIAB] OR JUVENILE CHRONIC ARTHRIT*[TIAB] OR JIA[TIAB] OR JRA[TIAB] OR JUVENILE RHEUMATOID ARTHRIT*[TIAB]) AND (OLIGO ARTICULAR*[TW] OR OLIGO-ARTICULAR*[TW] OR OLIGOARTICULAR*[TW]) OR (OLIGOARTHRIT*[TIAB] OR OLIGO-ARTHRIT*[TIAB])) OR ((ARTHRITIS, JUVENILE[MESH] AND (JIA[TIAB] OR JRA[TIAB] OR IDIOPATHIC*[TIAB])) OR (JUVENILE IDIOPATHIC ARTHRIT*[TIAB] OR JUVENILE CHRONIC ARTHRIT*[TIAB] OR CHRONIC JUVENILE ARTHRIT*[TIAB] OR JUVENILE RHEUMATOID ARTHRIT*[TW] OR JUVENILE IDIOPATHIC ARTHROS*[TIAB])) AND (ENGLISH[LANG])) NOT (CASE REPORT*[PT] OR LETTER*[PT] OR COMMENT*[PT] OR EDITORIAL*[PT])) NOT ("ANIMALS"[MESH] NOT ("ANIMALS"[MESH] AND "HUMANS"[MESH]))) NOT ("ADULT"[MESH] NOT ("ADULT"[MESH] AND "CHILD"[MESH] OR "INFANT"[MESH] OR "ADOLESCENT"[MESH]))) OR ((ARTHRITIS, JUVENILE[MESH] AND (JIA[TIAB] OR JRA[TIAB] OR IDIOPATHIC*[TIAB])) OR (JUVENILE IDIOPATHIC ARTHRIT*[TIAB] OR JUVENILE CHRONIC ARTHRIT*[TIAB] OR CHRONIC JUVENILE ARTHRIT*[TIAB] OR JUVENILE RHEUMATOID ARTHRIT*[TW] OR JUVENILE IDIOPATHIC ARTHROS*[TIAB]) OR (SJIA[TIAB] OR STILLS DISEASE*[TIAB] OR "STILL'S DISEASE"[TIAB] OR STILL DISEASE*[TIAB] OR JUVENILE SYSTEMIC ARTHRIT*[TIAB] OR SYSTEMIC JUVENILE ARTHRIT*[TIAB] OR JUVENILE SYSTEMIC IDIOPATHIC ARTHRIT*[TIAB] OR SYSTEMIC JUVENILE IDIOPATHIC ARTHRIT*[TIAB] OR SYSTEMIC JIA[TIAB] OR SYSTEMIC JRA[TIAB] OR SYSTEMIC JUVENILE RHEUMATOID ARTHRIT*[TIAB] OR JUVENILE SYSTEMIC RHEUMATOID ARTHRIT*[TIAB] OR "RHEUMATOID ARTHRITIS, SYSTEMIC JUVENILE"[SUPPLEMENTARY CONCEPT] OR JUVENILE ONSET SYSTEMIC ARTHRIT*[TIAB] OR SYSTEMIC JUVENILE ONSET ARTHRIT*[TIAB]) AND (ENGLISH[LANG]) NOT (LETTER*[PT] OR COMMENT*[PT] OR EDITORIAL*[PT] OR CASE REPORT*[PT]) NOT ("ANIMALS"[MESH] NOT ("ANIMALS"[MESH] AND "HUMANS"[MESH]))))) AND ("RADIOLOGY"[MESH:noexp] OR RADIOLOG*[TIAB] OR "MAGNETIC RESONANCE IMAGING"[MESH:noexp] OR MAGNETIC

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RESONANCE[TIAB] OR MR TOMOGRAPH*[TIAB] OR NMR TOMOGRAPH*[TIAB] OR ZEUGMATOGRAPH*[TIAB] OR PROTON SPIN TOMOGRAPH*[TIAB] OR MRI SCAN*[TIAB] OR FMRI[TIAB] OR FUNCTIONAL MRI*[TIAB] OR IMAGING*[TW] OR "ULTRASONOGRAPHY"[MESH:noexp] OR ULTRASONOGRAPH*[TIAB] OR ECHOGRAPH*[TIAB] OR ULTRASOUND*[TIAB] OR MEDICAL SONOGRAPH*[TIAB] OR ECHOTOMOGRAPH*[TIAB] OR ULTRASONIC DIAGNOS*[TIAB] OR ULTRASONIC TOMOGRAPH*[TIAB] OR "RADIOGRAPHY"[MESH] OR RADIOGRAPH*[TW] OR ROENTGENOGRAPH*[TIAB] OR "X-RAYS"[MESH] OR X-RAY*[TW] OR XRAY*[TIAB] OR ROENTGEN RAY*[TIAB]))

Cochrane

Search Name: JIA PT 2

From database inception to August 3, 2019, then updated on July 8, 2020

ID	Search
#1	MeSH descriptor: [Arthritis, Juvenile] explode all trees
#2	JUVENILE ARTHRIT* OR JUVENILE CHRONIC ARTHRIT* OR JIA OR JRA OR JUVENILE RHEUMATOID ARTHRIT*
#3	OLIGO ARTICULAR* OR OLIGO-ARTICULAR* OR OLIGOARTICULAR*
#4	(#1 or #2) and #3
#5	oligoarthrit* OR OLIGO-ARTHRIT*
#6	#4 OR #5
#7	temporomandibular* OR TMJ
#8	ARTHRIT*
#9	"COSTEN'S SYNDROME" OR "COSTENS SYNDROME"
#10	#7 OR #9
#11	MeSH descriptor: [Arthritis, Juvenile] explode all trees
#12	(#8 OR #11)

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#13 #10 AND #12

#14 MeSH descriptor: [Arthritis, Juvenile] explode all trees

#15 JIA OR JRA OR IDIOPATHIC*

#16 #14 and #15

#17 juvenile idiopathic arthrit* OR JUVENILE RHEUMATOID ARTHRIT*

#18 JUVENILE CHRONIC ARTHRIT* OR CHRONIC JUVENILE ARTHRIT*

#19 JUVENILE IDIOPATHIC ARTHROS*

#20 #16 OR #17 OR #18 OR #19

#21 #6 OR #13 OR #20 in Trials

#22 EMBASE OR PUBMED

#23 #21 NOT #22

#24 SJIA

#25 "STILLS DISEASE" OR "STILL'S DISEASE" OR "STILL DISEASE" OR "SYSTEMIC-ONSET JUVENILE ARTHRITIS" OR "JUVENILE SYSTEMIC-ONSET ARTHRITIS" OR "JUVENILE SYSTEMIC-ONSET IDIOPATHIC ARTHRITIS" OR "SYSTEMIC-ONSET JUVENILE IDIOPATHIC ARTHRITIS" OR "JUVENILE SYSTEMIC ARTHRITIS" OR "SYSTEMIC JUVENILE ARTHRITIS" OR "JUVENILE SYSTEMIC IDIOPATHIC ARTHRITIS" OR "SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS" OR "SYSTEMIC JIA" OR "SYSTEMIC-ONSET JIA" OR "SYSTEMIC-ONSET JRA" OR "SYSTEMIC-ONSET JUVENILE RHEUMATOID ARTHRITIS" OR "JUVENILE SYSTEMIC-ONSET RHEUMATOID ARTHRITIS" OR "SYSTEMIC JRA" OR "SYSTEMIC JUVENILE RHEUMATOID ARTHRITIS" OR "JUVENILE SYSTEMIC RHEUMATOID ARTHRITIS"

#26 #24 OR #25

#27 EMBASE OR PUBMED

#28 #26 NOT #27

#29 #28 OR #23

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Embase

From 1974 to August 5, 2019, then updated on July 8, 2020

Search Strategy:

1 juvenile idiopathic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. or exp juvenile rheumatoid arthritis/ (20816)

2 juvenile chronic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. and (JIA or JRA or IDIOPATHIC).ti,ab. (109)

3 JUVENILE https://protect-us.mimecast.com/s/ee-1CkRoJ1Hl0xltVGL4i?domain=arthritis.mp. and (JIA or JRA or IDIOPATHIC).ti,ab. (965)

4 1 or 2 or 3 (20836)

5 https://protect-us.mimecast.com/s/r7x0ClYpK1HGKQGfyk_ye?domain=temporomandibular.mp. (27542)

6 TMJ.ti,ab. (9139)

7 ARTHRIT*.mp. (325914)

8 (costen's syndrome or COSTEN SYNDROME).ti,ab. (37)

9 5 or 6 or 8 (28456)

10 7 and 9 (1945)

11 (oligoarthrit* or oligo-arthrit*).mp. (1898)

12 (oligoarticular* or "oligo-articular" or "oligo articular").ti,ab. (1821)

13 juvenile idiopathic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. or juvenile rheumatoid arthritis/ (20816)

14 (JIA or JRA).ti,ab. (9864)

15 13 or 14 (22532)

16 12 and 15 (1339)

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17 11 or 16 (3111)

18 10 or 17 (4997)

19 adult/ or middle aged/ or young adult/ (6884305)

20 exp juvenile/ (3257587)

21 19 not (19 and 20) (5731897)

22 18 not 21 (3867)

23 4 not 21 (18650)

24 22 or 23 (20308)

25 limit 24 to (abstracts and human and english language and (article or article in press or "review")) (8795)

26 juvenile idiopathic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. or exp juvenile rheumatoid arthritis/ (20816)

27 juvenile chronic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. and (JIA or JRA or IDIOPATHIC).ti,ab. (109)

28 JUVENILE https://protect-us.mimecast.com/s/ee-1CkRoJ1Hl0xltVGL4i?domain=arthritis.mp. and (JIA or JRA or IDIOPATHIC).ti,ab. (965)

29 26 or 27 or 28 (20836)

30 https://protect-us.mimecast.com/s/r7x0ClYpK1HGKQGfyk_ye?domain=temporomandibular.mp. (27542)

31 TMJ.ti,ab. (9139)

32 ARTHRIT*.mp. (325914)

33 (costen's syndrome or COSTEN SYNDROME).ti,ab. (37)

34 30 or 31 or 33 (28456)

35 32 and 34 (1945)

36 (oligoarthrit* or oligo-arthrit*).mp. (1898)

37 (oligoarticular* or "oligo-articular" or "oligo articular").ti,ab. (1821)

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38 juvenile idiopathic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. or juvenile rheumatoid arthritis/ (20816)

39 (JIA or JRA).ti,ab. (9864)

40 38 or 39 (22532)

41 37 and 40 (1339)

42 36 or 41 (3111)

43 35 or 42 (4997)

44 adult/ or middle aged/ or young adult/ (6884305)

45 exp juvenile/ (3257587)

46 44 not (44 and 45) (5731897)

47 43 not 46 (3867)

48 29 not 46 (18650)

49 47 or 48 (20308)

50 limit 49 to (abstracts and human and english language and (article or article in press or "review")) (8795)

51 exp sugar intake/ (7416)

52 exp dietary supplement/ (9719)

53 https://protect-us.mimecast.com/s/O8k4CmZEL5UXYOXH9M72b?domain=neutraceutical.mp. (204)

54 https://protect-us.mimecast.com/s/oB8zCn5zM1CwL8wUmoC16?domain=herbal.mp. (60728)

55 exp diet/ (300636)

56 exp vitamin/ (598919)

57 LOW-SUGAR*.mp. (508)

58 GLUTEN-FREE*.mp. (10521)

59 DAIRY-FREE*.mp. (79)

60 LACTOSE-FREE*.mp. (680)

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61 nutraceutical/ (4097)

62 food/ (71574)

63 food supplement*.mp. (4870)

64 DIET*.mp. (925897)

65 VITAMIN*.mp. (319538)

66 PROBIOTIC*.mp. or probiotic agent/ (38371)

67 prebiotic agent/ or PREBIOTIC*.mp. (11133)

68 NUTRITION https://protect-us.mimecast.com/s/JOYuCo2ON1f9GO9iox5-R?domain=therapy.mp. or diet therapy/ (51479)

69 vaccinium/ or blueberry/ or BLUEBERR*.ti,ab. (2832)

70 exp Curcuma/ or https://protect-us.mimecast.com/s/JAoqCpYzO1HkLYkf7zxIm?domain=curcuma.mp. (6661)

71 turmeric/ (1685)

72 HORSE https://protect-us.mimecast.com/s/5V6iCqx2P1fBrqBCvRX3u?domain=nettle.mp. (0)

73 https://protect-us.mimecast.com/s/XeLrCrkYQ1iMjgMHLVHaf?domain=trompillo.mp. (2)

74 https://protect-us.mimecast.com/s/buG4Cv2jX1f1gQ1HEJqVA?domain=nightshade.mp. (314)

75 TART CHERR*.mp. (146)

76 *"cherry juice"/ (7)

77 exp Solanum/ (31895)

78 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 (1646460)

79 https://protect-us.mimecast.com/s/yI6qCwpkY1f6QB6HXUF8Z?domain=leflunomide.mp. or leflunomide/ (11450)

80 https://protect-us.mimecast.com/s/BuHtCxklZgi80Y8f08XNE?domain=arava.tn. (538)

81 https://protect-us.mimecast.com/s/cKZvCyPm1jfDWxDSvpik9?domain=arabloc.mp. (6)

82 (hwa 486 or hwa486 or repso or rs 34821 or rs34821 or su 101 or su101).tn. (200)

83 hydroxychloroquine/ (22365)

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84 https://protect-us.mimecast.com/s/pDRhCzpn2kfDB5DSWp7Kd?domain=hydroxychloroquine.mp. (23217)

85 https://protect-us.mimecast.com/s/c3hkCADmJpC0ok0f1DcgK?domain=chloroquinol.mp. (4)

86 https://protect-us.mimecast.com/s/1eCWCBBnKqSqmYqfXC3l0?domain=hydrochloroquine.mp. (53)

87 https://protect-us.mimecast.com/s/2KZbCDk0Mvipm4psX-gGP?domain=oxychloroquine.mp. (6)

88 (ercoquin or plaquenil or quensyl or "sn 8137").tn,mp. (1315)

89 https://protect-us.mimecast.com/s/T1FnCERPNwHyGEyi0BQG_?domain=sulfasalazine.mp. or salazosulfapyridine/ (25013)

90 (azopyrin or azopyrine or azosulfidine or azulfide or azulfidina or azulfidine* or azulfin).mp. (691)

91 (benzosulfa or colo pleon or colo-pleon or colopleon or disalazin or gastropyrin).mp. (72)

92 (pleon ra or pyralin en or rorasul or rosulfant or salazine or salazo sulfapyridine).mp. (29)

93 (salazodin or salazopirina or salazopyridin or salazopyridine or salazopyrin* or salazosulfa pyridine or salazosulfpyridine or salicyl azo sulfapyridine or salicylazosulfapyridin* or salisulf or salopyr or saridine or sas 500 or sulcolon or sulfasalizine or sulfosalazine or sulphasalazine or zopyrin).mp. (2842)

94 methotrexate/ or https://protect-us.mimecast.com/s/3DL7CG69P0tnlvnCOtwNS?domain=methotrexate.mp. (175129)

95 (a methopterine or abitrexate or amethopterin or amethopterine or ametopterine or antifolan or biotrexate or canceren or cl 14377 or cl14377 or emtexate or emthexat or emthexate or emtrexate or enthexate or farmitrexat or farmitrexate or farmotrex or folex or ifamet or imeth or jylamvo or lantarel or ledertrexate or maxtrex or metex or methoblastin or methohexate or methotrate or methotrexat or methotrexato or methrotrexate or methylaminopterin or methylaminopterine or meticil or metoject or metothrexate or metotrexat or metotrexate or metotrexin or metrex or mexate or mexate-aq or mexate-aq* or mpi 5004 or mpi5004 or MTX or neotrexate or nordimet or novatrex or nsc 740 or nsc740 or otrexup or rasuvo or reumatrex or rheumatrex or texate or texate-t or texorate or trexall or xaken or xatmep or zexate).mp. (24750)

96 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 (207088)

97 BRIDG*.ti,ab. (133562)

98 prednisone acetate/ or prednisone/ or https://protect-us.mimecast.com/s/Rw-zCJ6PVBtOzNOi362jT?domain=prednisone.mp. (168721)

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99 (DEHYDROCORTISONE or DELTA-CORTISONE or RECTODELT or PREDNISON* or STERAPRED or ULTRACORTEN or WINPRED or APO-PREDNISONE or CORTAN or CORTANCYL or PANAFCORT or DECORTIN or DACORTIN or DECORTISYL or DELTASONE or ENCORTONE or ENCORTON or METICORTEN or ORASONE or PANASOL or PREDNIDIB or PRONISONE).mp. (169281)

100 (Ancortone or biocortone or colisone or cortidelt or cortiprex or cutason or deltacorten or deltacortene or deltacortisone or deltacortone or deltison or deltisona or deltra or di adreson or diadreson or drazone or enkorton or fernisone or hostacortin or insone or lodotra or me-korti or meprison or metacorandracin or meticortine or nisona or nsc-10023 or nsc10023 or orisane or paracort or pehacort or precort or precortal or prednicenm or prednicorn or prednicot or prednidib or prednitone or pronison or pronisone or pronizone or pulmison or rayos or rectodelt or servisone or steerometz or sterapred or ultracorten or urtilone or winpred).mp. (693)

101 97 or 98 or 99 or 100 (302644)

102 (INTERLEUKIN-6 adj3 (INHIBITOR* or ANTAGONIST*)).mp. (803)

103 (INTERLEUKIN-1 adj3 (INHIBITOR* or ANTAGONIST*)).mp. (4677)

104 (INTERLEUKIN-1 RECEPTOR* adj3 (INHIBITOR* or ANTAGONIST*)).mp. (4100)

105 (INTERLEUKIN-6 RECEPTOR* adj3 (INHIBITOR* or ANTAGONIST*)).mp. (194)

106 exp tumor necrosis factor inhibitor/ or https://protect-us.mimecast.com/s/UxQnCKr6WDHKwVKfwOuyb?domain=tnfi.mp. (84349)

107 https://protect-us.mimecast.com/s/FBkFCL9PXEFqO6qfNGyt3?domain=infliximab.mp. or infliximab/ (48723)

108 CERTOLIZUMAB https://protect-us.mimecast.com/s/CvDLCM89YGfP8NPUMgO6i?domain=pegol.mp. or certolizumab pegol/ (6062)

109 https://protect-us.mimecast.com/s/Z4M1CNk8ZJiLx4Lfv7cBA?domain=abatacept.mp. or abatacept/ (8753)

110 rituximab/ (72964)

111 https://protect-us.mimecast.com/s/xWshCOYZ1KHYXWYH3NsYt?domain=rituximab.mp. (76089)

112 https://protect-us.mimecast.com/s/LtAKCPNY2Ligmpgtw0lIL?domain=tofacitinib.mp. or tofacitinib/ (3626)

113 https://protect-us.mimecast.com/s/JgEZCQWO3MHVq0VhgxAf_?domain=canakinumab.mp. or canakinumab/ (2750)

114 https://protect-us.mimecast.com/s/wIaUCR6L4NtYl2YH6jfPx?domain=rilonacept.mp. or rilonacept/ (836)

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115 https://protect-us.mimecast.com/s/FmouCVON8RHBKGBCPqAVh?domain=golimumab.mp. or golimumab/ (6324)

116 https://protect-us.mimecast.com/s/bsSECW68gVt3YJ3HQu0eV?domain=tocilizumab.mp. or tocilizumab/ (10496)

117 https://protect-us.mimecast.com/s/PN9TCXDMjWCANwAHN1MuR?domain=secukinumab.mp. or secukinumab/ (2857)

118 (BIOLOGIC DISEASE MODIF* or BIOLOGIC RESPONSE MODIF* or DISEASE-MODIFYING ANTIRHEUMATIC* or DISEASE-MODIFYING ANTI-RHEUMATIC* or DMARD*).mp. (25544)

119 disease modifying antirheumatic drug/ (15443)

120 (INTERLEUKIN-1 BLOCKER* or IL-1 BLOCKER* or IL-1 BLOCKADE* or INTERLEUKIN-1 BLOCKADE* or INTERLEUKIN-6 BLOCKER* or IL-6 BLOCKER* or IL-6 BLOCKADE* or INTERLEUKIN-6 BLOCKADE* or ILARIS or ACZ-885 or ACZ885 or ANTI-INTERLEUKIN-1* or ANTI-IL-1* or ANTI-INTERLEUKIN-6* or ANTI-IL-6*).mp. (9604)

121 https://protect-us.mimecast.com/s/8DrtCYEMk8iYZrYH5GQTv?domain=anakinra.mp. or anakinra/ (4519)

122 (KINERET or ANTRIL or INTERLEUKIN-6 INHIBITOR* or IL-6 INHIBITOR* or INTERLEUKIN-1 INHIBITOR* or IL-1 INHIBITOR* or TUMOR NECROSIS FACTOR INHIBITOR* or TUMOUR NECROSIS FACTOR INHIBITOR*).mp. (15168)

123 (TNFALPHA INHIBITOR* or TNF-ALPHA INHIBITOR* or TNF INHIBITOR* or ANTI-TUMOR NECROSIS FACTOR* or ANTI-TUMOUR NECROSIS FACTOR* or ANTI-TNF* or HUMIRA or ADALIMUMAB-ADBM or AMJEVITA).mp. (36953)

124 (ADALIMUMAB-ATTO or CYLTEZO or ETANERCEPT or "TNFR-FC FUSION PROTEIN" or "TNR 001" or "TNT RECEPTOR FUSION PROTEIN" or TNR-001 or ETANERCEPT-SZZS or "TNF RECEPTOR TYPE II-IGG FUSION PROTEIN" or ERELZI or ENBREL).mp. (30938)

125 ("MONOCLONAL ANTIBODY CA2" or "MAB CA2" or RENFLEXIS or INFLECTRA or REMICADE or CIMZIA or CDP870 or LEA29Y or BMS224818 or BMS-224818 or BELATACEPT or ORENCIA or BMS-188667 or CTLA-4-IG).mp. (7707)

126 ("CYTOTOXIC T LYMPHOCYTE-ASSOCIATED ANTIGEN 4-IMMUNOGLOBULIN" or CTLA4-IG* or CTLA4-FC or NULOJIX or ATLIZUMAB or ACTEMRA or MABTHERA or IDEC-C2B8 ANTIBODY or IDEC-C2B8 or GP2013 or RITUXAN or TASOCITINIB or XELJANZ or CP690550 or CP-690550 or CP 690550 or COSENTYX or AIN457 or AIN-457).mp. (7476)

127 interleukin-1 receptor block*.mp. or interleukin 1 receptor blocking agent/ (18273)

128 interleukin 6/ and receptor blocking agent/ (205)

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129 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 (214157)

130 CALCINEURIN INHIBITOR*.mp. or exp calcineurin inhibitor/ (91432)

131 (PROTEIN PHOSPHATASE-2B INHIBITOR* or PROTEIN PHOSPHATASE 3 INHIBITOR* or CALCINEURIN ANTAGONIST* or CALCINEURIN BLOCKER* or PROGRAF or PROGRAFT or FR-900506 or FR900506 or FK-506 or FK506 or "33-EPI-CHLORO-33-DESOXYASCOMYCIN" or SDZ-ASM-981 or "ASM 981" or ELIDEL or TACROLIMUS or CYCLOSPORIN or CYCLOSPORINE or CICLOSPORINE or "MUSTOPIC OINT" or TSUKUBAENOLIDE or CIPOL or CYCLOKAT or DEXIMUNE or IMPLANTA or IMMUNOSPORIN or IMUSPORIN or VEKACIA or PROGRAF or ADVAGRAF or HECORIA or GENGRAF or ASTAGRAF or "OL-27-400" or "CSA-NEORAL" or "CYA-NOF" or NEURAL).mp. (557556)

132 130 or 131 (564945)

133 https://protect-us.mimecast.com/s/yI6qCwpkY1f6QB6HXUF8Z?domain=leflunomide.mp. or leflunomide/ (11450)

134 https://protect-us.mimecast.com/s/BuHtCxklZgi80Y8f08XNE?domain=arava.tn. (538)

135 https://protect-us.mimecast.com/s/cKZvCyPm1jfDWxDSvpik9?domain=arabloc.mp. (6)

136 (hwa 486 or hwa486 or repso or rs 34821 or rs34821 or su 101 or su101).tn. (200)

137 hydroxychloroquine/ (22365)

138 https://protect-us.mimecast.com/s/pDRhCzpn2kfDB5DSWp7Kd?domain=hydroxychloroquine.mp. (23217)

139 https://protect-us.mimecast.com/s/c3hkCADmJpC0ok0f1DcgK?domain=chloroquinol.mp. (4)

140 https://protect-us.mimecast.com/s/1eCWCBBnKqSqmYqfXC3l0?domain=hydrochloroquine.mp. (53)

141 https://protect-us.mimecast.com/s/2KZbCDk0Mvipm4psX-gGP?domain=oxychloroquine.mp. (6)

142 (ercoquin or plaquenil or quensyl or "sn 8137").tn,mp. (1315)

143 https://protect-us.mimecast.com/s/T1FnCERPNwHyGEyi0BQG_?domain=sulfasalazine.mp. or salazosulfapyridine/ (25013)

144 (azopyrin or azopyrine or azosulfidine or azulfide or azulfidina or azulfidine* or azulfin).mp. (691)

145 (benzosulfa or colo pleon or colo-pleon or colopleon or disalazin or gastropyrin).mp. (72)

146 (pleon ra or pyralin en or rorasul or rosulfant or salazine or salazo sulfapyridine).mp. (29)

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147 (salazodin or salazopirina or salazopyridin or salazopyridine or salazopyrin* or salazosulfa pyridine or salazosulfpyridine or salicyl azo sulfapyridine or salicylazosulfapyridin* or salisulf or salopyr or saridine or sas 500 or sulcolon or sulfasalizine or sulfosalazine or sulphasalazine or zopyrin).mp. (2842)

148 methotrexate/ or https://protect-us.mimecast.com/s/3DL7CG69P0tnlvnCOtwNS?domain=methotrexate.mp. (175129)

149 (a methopterine or abitrexate or amethopterin or amethopterine or ametopterine or antifolan or biotrexate or canceren or cl 14377 or cl14377 or emtexate or emthexat or emthexate or emtrexate or enthexate or farmitrexat or farmitrexate or farmotrex or folex or ifamet or imeth or jylamvo or lantarel or ledertrexate or maxtrex or metex or methoblastin or methohexate or methotrate or methotrexat or methotrexato or methrotrexate or methylaminopterin or methylaminopterine or meticil or metoject or metothrexate or metotrexat or metotrexate or metotrexin or metrex or mexate or mexate-aq or mexate-aq* or mpi 5004 or mpi5004 or MTX or neotrexate or nordimet or novatrex or nsc 740 or nsc740 or otrexup or rasuvo or reumatrex or rheumatrex or texate or texate-t or texorate or trexall or xaken or xatmep or zexate).mp. (24750)

150 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 (207088)

151 132 or 150 (735676)

152 exp intraarticular drug administration/ or https://protect-us.mimecast.com/s/PxHDCZ6Wl1tvRJvf2VL07?domain=intraarticular.mp. (20936)

153 METHYLPREDNISOLONE https://protect-us.mimecast.com/s/EtKKC1w9mLFgmVgtZmkqx?domain=acetate.mp. or methylprednisolone acetate/ (3615)

154 TRIAMCINOLONE https://protect-us.mimecast.com/s/D7uOC2k9nMirGMrSwEVCr?domain=acetonide.mp. or triamcinolone acetonide/ (14974)

155 methylprednisolone/ or https://protect-us.mimecast.com/s/SQZbC319oNf3Mn3H3S1Ri?domain=methylprednisolone.mp. (100135)

156 https://protect-us.mimecast.com/s/JZbIC4x9pOfPWXPUvTHfU?domain=triamcinolone.mp. or triamcinolone/ (28328)

157 TRIAMCINOLONE https://protect-us.mimecast.com/s/A6QZC5yWqPF8KB8f5Jhws?domain=hexacetonide.mp. or triamcinolone hexacetonide/ (1163)

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158 (JOINT INJECTION* or STEROID INJECTION* or CORTICOSTEROID INJECTION* or INTRA-ARTICULAR* or "ACETYL-METHYLPREDNISOLONE" or DEPO-MEDRONE or DEPO-MEDROL or ARISTOSPAN or TRICORT-40 or KENALOG* or AZMACORT or "KENACORT A").mp. (30145)

159 152 or 153 or 154 or 155 or 156 or 157 or 158 (160451)

160 OCCUPATIONAL THERAP*.mp. or occupational therapy/ (29387)

161 physiotherapy/ or home physiotherapy/ or joint mobilization/ or pediatric physiotherapy/ (81126)

162 PHYSICAL THERAP*.mp. (33750)

163 exercise/ or aquatic exercise/ or arm exercise/ or dynamic exercise/ or isokinetic exercise/ or leg exercise/ or muscle exercise/ or pilates/ or resistance training/ or static exercise/ (283834)

164 EXERCISE*.mp. (493092)

165 physical activity/ or "physical activity, capacity and performance"/ or stretching/ or swimming/ or walking/ or weight bearing/ or weight lifting/ (254597)

166 PHYSICAL ACTIVIT*.mp. (195592)

167 ACTIVITIES OF DAILY https://protect-us.mimecast.com/s/na3JC680rQfk95kfr3DAQ?domain=living.mp. or daily life activity/ (93255)

168 https://protect-us.mimecast.com/s/BrNXC73AvRUM6DMHO8Sp_?domain=mouthguard.mp. or mouth protector/ (1237)

169 MOUTH GUARD*.mp. (219)

170 (MOUTH PROTECTOR* or PROTECTIVE MOUTH PIECE* or PROTECTIVE MOUTHPIECE* or ERGOTHERAP*).mp. (2039)

171 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 (874207)

172 78 or 96 or 101 or 129 or 151 or 159 or 171 (3515998)

173 50 and 172 (4304)

174 (INTERLEUKIN-6 adj3 (INHIBITOR* or ANTAGONIST*)).mp. (803)

175 (INTERLEUKIN-1 adj3 (INHIBITOR* or ANTAGONIST*)).mp. (4677)

176 (INTERLEUKIN-1 RECEPTOR* adj3 (INHIBITOR* or ANTAGONIST*)).mp. (4100)

177 (INTERLEUKIN-6 RECEPTOR* adj3 (INHIBITOR* or ANTAGONIST*)).mp. (194)

178 exp tumor necrosis factor inhibitor/ or https://protect-us.mimecast.com/s/UxQnCKr6WDHKwVKfwOuyb?domain=tnfi.mp. (84349)

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179 https://protect-us.mimecast.com/s/FBkFCL9PXEFqO6qfNGyt3?domain=infliximab.mp. or infliximab/ (48723)

180 CERTOLIZUMAB https://protect-us.mimecast.com/s/CvDLCM89YGfP8NPUMgO6i?domain=pegol.mp. or certolizumab pegol/ (6062)

181 https://protect-us.mimecast.com/s/Z4M1CNk8ZJiLx4Lfv7cBA?domain=abatacept.mp. or abatacept/ (8753)

182 rituximab/ (72964)

183 https://protect-us.mimecast.com/s/xWshCOYZ1KHYXWYH3NsYt?domain=rituximab.mp. (76089)

184 https://protect-us.mimecast.com/s/LtAKCPNY2Ligmpgtw0lIL?domain=tofacitinib.mp. or tofacitinib/ (3626)

185 https://protect-us.mimecast.com/s/JgEZCQWO3MHVq0VhgxAf_?domain=canakinumab.mp. or canakinumab/ (2750)

186 https://protect-us.mimecast.com/s/wIaUCR6L4NtYl2YH6jfPx?domain=rilonacept.mp. or rilonacept/ (836)

187 https://protect-us.mimecast.com/s/FmouCVON8RHBKGBCPqAVh?domain=golimumab.mp. or golimumab/ (6324)

188 https://protect-us.mimecast.com/s/bsSECW68gVt3YJ3HQu0eV?domain=tocilizumab.mp. or tocilizumab/ (10496)

189 https://protect-us.mimecast.com/s/PN9TCXDMjWCANwAHN1MuR?domain=secukinumab.mp. or secukinumab/ (2857)

190 (BIOLOGIC DISEASE MODIF* or BIOLOGIC RESPONSE MODIF* or DISEASE-MODIFYING ANTIRHEUMATIC* or DISEASE-MODIFYING ANTI-RHEUMATIC* or DMARD*).mp. (25544)

191 disease modifying antirheumatic drug/ (15443)

192 (INTERLEUKIN-1 BLOCKER* or IL-1 BLOCKER* or IL-1 BLOCKADE* or INTERLEUKIN-1 BLOCKADE* or INTERLEUKIN-6 BLOCKER* or IL-6 BLOCKER* or IL-6 BLOCKADE* or INTERLEUKIN-6 BLOCKADE* or ILARIS or ACZ-885 or ACZ885 or ANTI-INTERLEUKIN-1* or ANTI-IL-1* or ANTI-INTERLEUKIN-6* or ANTI-IL-6*).mp. (9604)

193 https://protect-us.mimecast.com/s/8DrtCYEMk8iYZrYH5GQTv?domain=anakinra.mp. or anakinra/ (4519)

194 (KINERET or ANTRIL or INTERLEUKIN-6 INHIBITOR* or IL-6 INHIBITOR* or INTERLEUKIN-1 INHIBITOR* or IL-1 INHIBITOR* or TUMOR NECROSIS FACTOR INHIBITOR* or TUMOUR NECROSIS FACTOR INHIBITOR*).mp. (15168)

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195 (TNFALPHA INHIBITOR* or TNF-ALPHA INHIBITOR* or TNF INHIBITOR* or ANTI-TUMOR NECROSIS FACTOR* or ANTI-TUMOUR NECROSIS FACTOR* or ANTI-TNF* or HUMIRA or ADALIMUMAB-ADBM or AMJEVITA).mp. (36953)

196 (ADALIMUMAB-ATTO or CYLTEZO or ETANERCEPT or "TNFR-FC FUSION PROTEIN" or "TNR 001" or "TNT RECEPTOR FUSION PROTEIN" or TNR-001 or ETANERCEPT-SZZS or "TNF RECEPTOR TYPE II-IGG FUSION PROTEIN" or ERELZI or ENBREL).mp. (30938)

197 ("MONOCLONAL ANTIBODY CA2" or "MAB CA2" or RENFLEXIS or INFLECTRA or REMICADE or CIMZIA or CDP870 or LEA29Y or BMS224818 or BMS-224818 or BELATACEPT or ORENCIA or BMS-188667 or CTLA-4-IG).mp. (7707)

198 ("CYTOTOXIC T LYMPHOCYTE-ASSOCIATED ANTIGEN 4-IMMUNOGLOBULIN" or CTLA4-IG* or CTLA4-FC or NULOJIX or ATLIZUMAB or ACTEMRA or MABTHERA or IDEC-C2B8 ANTIBODY or IDEC-C2B8 or GP2013 or RITUXAN or TASOCITINIB or XELJANZ or CP690550 or CP-690550 or CP 690550 or COSENTYX or AIN457 or AIN-457).mp. (7476)

199 interleukin-1 receptor block*.mp. or interleukin 1 receptor blocking agent/ (18273)

200 interleukin 6/ and receptor blocking agent/ (205)

201 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 or 196 or 197 or 198 or 199 or 200 (214157)

202 "stills disease".mp. (2591)

203 exp systemic juvenile idiopathic arthritis/ (1083)

204 SYSTEMIC-ONSET JUVENILE ARTHRIT*.mp. (23)

205 (JUVENILE SYSTEMIC-ONSET ARTHRIT* or JUVENILE SYSTEMIC-ONSET IDIOPATHIC ARTHRIT* or SYSTEMIC-ONSET JUVENILE IDIOPATHIC ARTHRITIS or JUVENILE SYSTEMIC ARTHRIT* or SYSTEMIC JUVENILE ARTHRIT* or JUVENILE SYSTEMIC IDIOPATHIC ARTHRIT* or SYSTEMIC JUVENILE IDIOPATHIC ARTHRIT* or SYSTEMIC JIA or SYSTEMIC-ONSET JIA or SYSTEMIC-ONSET JRA or SYSTEMIC-ONSET JUVENILE RHEUMATOID ARTHRIT* or JUVENILE SYSTEMIC-ONSET RHEUMATOID ARTHRIT* or SYSTEMIC JRA or SYSTEMIC JUVENILE RHEUMATOID ARTHRIT* or JUVENILE SYSTEMIC RHEUMATOID ARTHRIT*).mp. (2778)

206 202 or 203 or 204 or 205 (5106)

207 juvenile idiopathic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. or exp juvenile rheumatoid arthritis/ (20816)

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208 juvenile chronic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. and (JIA or JRA or IDIOPATHIC).ti,ab. (109)

209 JUVENILE https://protect-us.mimecast.com/s/ee-1CkRoJ1Hl0xltVGL4i?domain=arthritis.mp. and (JIA or JRA or IDIOPATHIC).ti,ab. (965)

210 207 or 208 or 209 (20836)

211 206 or 210 (22378)

212 limit 211 to (abstracts and english language and (article or article in press or "review")) (10297)

213 NSAID*.mp. or exp nonsteroid antiinflammatory agent/ (713203)

214 https://protect-us.mimecast.com/s/RmZ9C829wVf3Mo3HB_94I?domain=indomethacin.mp. (41524)

215 (NON-STEROIDAL ANTI-INFLAMMATOR* or NONSTEROIDAL ANTI-INFLAMMATORY AGENT* or NONSTEROIDAL ANTIINFLAMMATORY AGENT* or ANTI-INFLAMMATORY ANALGESIC or ACECLOFENAC or ACEMETACIN or ACETOSYRINGONE or ACETOVANILLONE or ADAPALENE or ALCLOFENAC or ALMINOPROFEN or AMIPRILOSE or AMPYRONE or ANDROGRAPHOLIDE or ANISODAMINE or ANISODINE or ANTIPYRINE or APAZONE or APREMILAST or ARTEPARON or ARTHROTEC or ASPIRIN or ATRINOSITOL or AZULENE or BAICALIN or BALSALAZIDE or BENDAZAC or BENDAZAC LYSINE or BENORILATE or BENOXAPROFEN or BENZOBARBITAL or BERBAMINE or BEVONIUM or BOLDINE or BROMFENAC or BUCILLAMINE or BUFEXAMAC or BUMADIZONE or BUTIBUFEN or CARPROFEN or CARYOPHYLLENE or CASTANOSPERMINE or CELECOXIB or CEPHARANTHINE or CHLOROQUINE DIPHOSPHATE or CHOLINE MAGNESIUM TRISALICYLATE or CHRYSAROBIN or CLONIXIN or CURCUMIN or DAURICINE or DEXKETOPROFEN TROMETAMOL or DICLOFENAC or DIFENPIRAMIDE or DIFLUNISAL or DIMEPHOSPHON or DIPYRONE or DIUCIFON or DROXICAM or EBSELEN or ECALLANTIDE or ELTENAC or EPIRIZOLE or ETANERCEPT or ETHENZAMIDE or ETHONIUM or ETODOLAC or ETOFENAMATE or ETORICOXIB or FENBUFEN or FENCLOFENAC or FENFLUMIZOLE or FENOPROFEN or FENTIAZAC or FEPRADINOL or FEPRAZONE or FLOCTAFENINE or FLOSULIDE or FLUNIXIN or FLUNOXAPROFEN or FLUPROQUAZONE or FLURBIPROFEN or GLUCAMETACIN or GUACETISAL or HELENALIN or HELIODERMIN or HEMODES or HIGENAMINE or IBUPROFEN or IBUPROXAM or ICATIBANT or INDOBUFEN or INDOMETHACIN or INDOPROFEN or IODOANTIPYRINE or ISOXICAM or KEBUZONE or KETOPROFEN or KETOROLAC or LICOFELONE or LISOFYLLINE or LOBENZARIT or LONAZOLAC or LORNOXICAM or LOXOPROFEN or LUMIRACOXIB or MAGNOLOL or MANOALIDE or MASOPROCOL or MELOXICAM or MESALAMINE or MIZORIBINE or MOFEBUTAZONE or MOFEZOLAC or NABUMETONE or NAFAMOSTAT or NAPROXEN or NEBACETIN or NEPAFENAC or NIFENAZONE or NIMESULIDE or NITROASPIRIN or OLSALAZINE or OLVANIL or ORGOTEIN or OXAPROZIN or OXYPHENBUTAZONE or PALMIDROL or PARECOXIB or PARTHENOLIDE or PEONIFLORIN or PHENIDONE or PHENYLBUTAZONE or PIMECROLIMUS or PIRFENIDONE or PIROXICAM or PIRPROFEN or PROGLUMETACIN or PROPACETAMOL or PROPIONYLCARNITINE or PROPYPHENAZONE or PROQUAZONE or PYRANOPROFEN or PYRAZOLONE or PYROGENAL or RESVERATROL or RNS60 or

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ROFECOXIB or RUMALON or SAIKO-KEISHI-TO or SAIKOSAPONIN or SALICIN or SALICYLAMIDE or SALICYLATES or "SALICYLSALICYLIC ACID" or SEMAPIMOD or SERATRODAST or SERRATIOPEPTIDASE or SHIKONIN or SINAPALDEHYDE or SODIUM SALICYLATE or SUL-121 or SULFASALAZINE or SULINDAC or SUPROFEN or SUXIBUZONE or TANSHINONE or TAXIFOLIN or TENIDAP or TENOXICAM or TEPOXALIN or TIARAMIDE or TINORIDINE or TOLMETIN or TRANILAST or TRIBENOSIDE or VALDECOXIB or ZILEUTON or ZOMEPIRAC or CELEBREX or SC-58635 or SC58635 or ETODOLIC* or ULTRADOL or LODINE or RAMODAR or AY-24236 or CP-16171 or CP16171 or FELDENE or DICLOPHENAC or DICROFENAC or DICHLOFENAL or "DICLONATE P" or FELORAN or VOLTAROL or NOVAPIRINA or ORTHOFEN or ORTOFEN or ORTHOPHEN or SR-38 or VOLTAREN or NABUMETON or RELIFEX or RELIF or APO-NABUMETONE or APONABUMETONE or MEBUTAN or LISTRAN or GEN-NABUMETONE or ARTHRAXAN or RHOXAL-NABUMETONE or RELAFEN or NABUCOX or MILOXICAM or PAROCIN or MOBIC or MOBICOX or MOBEC or MASFLEX or MOVICOX or REUMOXICAM or UTICOX or MOVALIS or INDOMETACIN or OSMOSIN or INDOCID or METINDOL or AMUNO or INDOCIN or TOLECTIN or MCN-2559 or MOTRIN or NUPRIN or RUFEN or SALPROFEN or BRUFEN or METHOXYPROPIOCIN or ANAPROX or ALEVE or PROXEN or SYNFLEX or NAPROSIN or NAPROSYN).mp. (474369)

216 213 or 214 or 215 (841632)

217 immunoglobulin/iv [Intravenous Drug Administration] (30481)

218 (IMMUNOGLOBULIN* adj3 (INTRAVENOUS* or IV)).mp. (21787)

219 ("INTRAVENOUS IG" or INTRAVENOUS ANTIBOD* or IVIG or INTRAVENOUS IMMUNE GLOBULIN* or IV IMMUNOGLOBULIN* or "FLEBOGAMMA DIF" or GAMUNEX or GLOBULIN-N or INTRAGLOBIN* or GAMMAGARD or GAMIMUNE or GAMIMMUNE or PRIVIGEN or SANDOGLOBULIN or VENOGLOBULIN* or IVEEGAM or ALPHAGLOBIN or ENDOBULIN or "GAMIMUNE N" or "GAMIMMUNE N" or GAMMONATIV).mp. (19714)

220 217 or 218 or 219 (51936)

221 ((CORTICOSTEROID* or STEROID*) adj4 ORAL*).mp. (18564)

222 https://protect-us.mimecast.com/s/g2bJC9r2xWHnKGnC8FMiq?domain=betamethasone.mp. or betamethasone/ (22539)

223 dexamethasone/ or https://protect-us.mimecast.com/s/wtDyC0R9lKHvW1vfY1WHi?domain=dexamethasone.mp. (156317)

224 https://protect-us.mimecast.com/s/vfk5CgJkB0t6WM6HNrQnyA?domain=fluprednisolone.mp. or fluprednisolone/ (109)

225 methylprednisolone/ or https://protect-us.mimecast.com/s/SQZbC319oNf3Mn3H3S1Ri?domain=methylprednisolone.mp. (100135)

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226 https://protect-us.mimecast.com/s/hI0_CjRnG1HEJWEfWWLiAm?domain=paramethasone.mp. or paramethasone/ (493)

227 prednisolone/ or https://protect-us.mimecast.com/s/bRkWCkRoJ1Hl0xlt2VPn43?domain=prednisolone.mp. (131228)

228 prednisone acetate/ or prednisone/ or https://protect-us.mimecast.com/s/Rw-zCJ6PVBtOzNOi362jT?domain=prednisone.mp. (168721)

229 https://protect-us.mimecast.com/s/JZbIC4x9pOfPWXPUvTHfU?domain=triamcinolone.mp. or triamcinolone/ (28328)

230 GLUCOCORTICOID*.mp. (128860)

231 (FLUBENISOLONE or BETADEXAMETHASONE or CELESTONA or CELESTON or CELESTONE or FLUBENISOLONVALERATE or BETNOVATE or METHYLFLUORPREDNISOLONE or HEXADECADROL or DECAMETH or DECASPRAY or DEXASONE or DEXPAK or MAXIDEX or MILLICORTEN or ORADEXON or HEXADROL or HE-111 or HE111 or AUXISON or METIPRED or 6-METHYLPREDNISOLONE or URBASON or MEDROL or PREDATE or PREDONINE or DEHYDROCORTISONE or DELTA-CORTISONE or RECTODELT or "PREDNISON HEXAL" or STERAPRED or ULTRACORTEN or WINPRED or APO-PREDNISONE or CORTAN or CORTANCYL or PANAFCORT or DECORTIN or DACORTIN or DECORTISYL or DELTASONE or ENCORTONE or ENCORTON or "LIQUID PRED" or METICORTEN or ORASONE or PANASOL or "PREDNI TABLINEN" or PREDNIDIB or "PREDNISON ACSIS" or PRONISONE or SONE or "PREDNISON GALEN" or VOLON or ARISTOCORT or ALCLOMETASONE DIPROPIONATE or AMCINONIDE or CICLESONIDE or CLOBETASONE BUTYRATE or CLOCORTOLONE* or DICHLORISONE ACETATE or DIFLORASONE or DIFLUPREDNATE or DROCINONIDE PHOSPHATE POTASSIUM or FLUOCORTIN BUTYL ESTER or FLUPEROLONE ACETATE or FLUPREDNIDENE ACETATE or FX006 or HALOMETASONE or MEDRYSONE or PREDNICARBATE or RIMEXOLONE).mp. (14871)

232 221 or 222 or 223 or 224 or 225 or 226 or 227 or 228 or 229 or 230 or 231 (602929)

233 methotrexate/ or https://protect-us.mimecast.com/s/3DL7CG69P0tnlvnCOtwNS?domain=methotrexate.mp. (175129)

234 https://protect-us.mimecast.com/s/JgEZCQWO3MHVq0VhgxAf_?domain=canakinumab.mp. or canakinumab/ (2750)

235 https://protect-us.mimecast.com/s/bsSECW68gVt3YJ3HQu0eV?domain=tocilizumab.mp. or tocilizumab/ (10496)

236 https://protect-us.mimecast.com/s/wIaUCR6L4NtYl2YH6jfPx?domain=rilonacept.mp. or rilonacept/ (836)

237 https://protect-us.mimecast.com/s/8DrtCYEMk8iYZrYH5GQTv?domain=anakinra.mp. or anakinra/ (4519)

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238 (AMETHOPTERIN or MEXATE or KINERET or ANTRIL or ILARIS or ACZ-885 or ACZ885 or ATLIZUMAB or ACTEMRA).mp. (2473)

239 (atlizumab or lusinex or r1569 or roactemra).mp. (771)

240 https://protect-us.mimecast.com/s/T9yNClYpK1HGKQGfGyDu_q?domain=arcalyst.mp. (135)

241 il 1 https://protect-us.mimecast.com/s/mDD0CmZEL5UXYOXHG9d3W9?domain=trap.mp. (51)

242 (A METHOPTERINE or ABITREXATE or AMETHOPTERIN or AMETHOPTERINE or AMETOPTERINE or ANTIFOLAN or BIOTREXATE or CANCEREN or CL 14377 or CL14377 or EMTEXATE or EMTHEXAT or EMTHEXATE or EMTREXATE or ENTHEXATE or FARMITREXAT or FARMITREXATE or FARMOTREX or FOLEX or FOLEX PFS or IFAMET or IMETH or JYLAMVO or LANTAREL or LEDERTREXATE or MAXTREX or METEX or METHOBLASTIN or METHOHEXATE or METHOTRATE or METHOTREXAT or METHOTREXAT EBEWE or METHOTREXATO or METHOXTREXATE or METHROTREXATE or METHYLAMINOPTERIN or METHYLAMINOPTERINE or METICIL or METOJECT or METOTHREXATE or METOTHREXATE SODIUM or METOTREXAT or METOTREXATE or METOTREXIN or METREX or MEXATE* or MPI 5004 or MPI5004 or MTX or NEOTREXATE or NORDIMET or NOVATREX or NSC 740 or NSC740 or OTREXUP or RASUVO or REUMATREX or RHEUMATREX or TEXATE or TEXATE-T or TEXORATE or TREXALL or XAKEN or XATMEP or ZEXATE).mp. (24751)

243 233 or 234 or 235 or 236 or 237 or 238 or 239 or 240 or 241 or 242 (188442)

244 https://protect-us.mimecast.com/s/YnhBCn5zM1CwL8wU9mB15i?domain=etoposide.mp. or etoposide/ (87211)

245 (CITODOX or EPOSIN or EPSIDOX or ETOMEDAC or ETOMEDEC or ETOPHOS or ETOPOL or ETOPOS or ETOPOSID or ETOPOSIDO or ETOPOXAN or ETOSID or NEXVEP or NK 171 or NK171 or NSC 141540 or NSC141540 or POSID or TOPRESID or VESPID or VP 16 or VP-TEC or VP16 213 or VP16-213 or VP16213).mp. (9622)

246 (EPOSIDE or "ETOPOSIDO FERRER FARMA" or LASTET* or NSC-141540 or TOPOSAR or VEPESID* or "VP 16-213" or "VP 16 213" or "VP 16213" or VP-16 or VP16 or "VEPESIDE-SANDOZ" or CELLTOP).mp. (12989)

247 244 or 245 or 246 (89891)

248 PLASMAPHERES*.mp. or exp plasmapheresis/ (40670)

249 (plasma pheresis or plasmaphores*).mp. (220)

250 248 or 249 (40718)

251 DISEASE ACTIVITY SCORE*.mp. or disease activity score/ (13729)

252 PATIENT GLOBAL ASSESSMENT*.mp. (2192)

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253 PHYSICAL GLOBAL ASSESSMENT*.mp. (19)

254 PHYSICIAN GLOBAL ASSESSMENT*.mp. (2448)

255 DISEASE ACTIVITY https://protect-us.mimecast.com/s/Y2-fCo2ON1f9GO9i1o9X5-?domain=index.mp. (16621)

256 (JADA or JADAS).mp. (466)

257 (JADI or PGA-VAS or PtGA).mp. (592)

258 251 or 252 or 253 or 254 or 255 or 256 or 257 (30621)

259 https://protect-us.mimecast.com/s/8DrtCYEMk8iYZrYH5GQTv?domain=anakinra.mp. or anakinra/ (4519)

260 https://protect-us.mimecast.com/s/wdIkCpYzO1HkLYkfP7RnlO?domain=sarilumab.mp. or sarilumab/ (415)

261 https://protect-us.mimecast.com/s/JgEZCQWO3MHVq0VhgxAf_?domain=canakinumab.mp. or canakinumab/ (2750)

262 https://protect-us.mimecast.com/s/wIaUCR6L4NtYl2YH6jfPx?domain=rilonacept.mp. or rilonacept/ (836)

263 (INTERLEUKIN-6 INHIBITOR* or IL-6 INHIBITOR* or INTERLEUKIN-1 INHIBITOR* or IL-1 INHIBITOR* or INTERLEUKIN-1 BLOCKER* or IL-1 BLOCKER* or IL-1 BLOCKADE* or INTERLEUKIN-1 BLOCKADE* or INTERLEUKIN-6 BLOCKER* or IL-6 BLOCKER* or IL-6 BLOCKADE* or INTERLEUKIN-6 BLOCKADE* or ILARIS or ACZ-885 or ACZ885 or ANTI-INTERLEUKIN-1* or ANTI-IL-1* or ANTI-INTERLEUKIN-6* or ANTI-IL-6* or KINERET or ANTRIL).mp. (11220)

264 (BI 61012 or BI61012 or LEUKINE or PROKINE or SARGRASTIM or ARCALYST or IL 1 TRAP).mp. (726)

265 interleukin-1 receptor blocking https://protect-us.mimecast.com/s/D8OyCqx2P1fBrqBCZvSxNd?domain=agent.mp. or interleukin 1 receptor blocking agent/ (18268)

266 interleukin 6/ and receptor blocking agent/ (205)

267 (INTERLEUKIN-1 adj3 (INHIBITOR* or ANTAGONIST*)).mp. (4677)

268 (INTERLEUKIN-6 adj3 (INHIBITOR* or ANTAGONIST*)).mp. (803)

269 259 or 260 or 261 or 262 or 263 or 264 or 265 or 266 or 267 or 268 (32323)

270 cyclophosphamide/ or https://protect-us.mimecast.com/s/o87lCrkYQ1iMjgMH7LCZHB?domain=cyclophosphamide.mp. (215464)

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271 (SENDOXAN or B-518 or B518 or CYTOXAN or ENDOXAN* or NEOSAR or NSC-26271 or NSC26271 or PROCYTOX or CYCLOPHOSPHAN*).mp. (9655)

272 (alkyroxan or b 518 or b 518 asta or b518 or b518 asta or carloxan or ciclofosfamida or ciclolen or cicloxal or clafen or cyclo-cell or cycloblastin or cycloblastine or cyclofos amide or cyclofosfamid or cyclofosfamide or cyclophar or cyclophosphamid or cyclophosphamides or cyclophosphan or cyclophosphane or cyclostin or cycloxan or cyphos or cytophosphan or cytophosphane or cytoxan or endocyclo phosphate or endoxan* or enduxan or genoxal or ledoxan or ledoxina or mitoxan or neosan or neosar or noristan or nsc 26271 or nsc 2671 or procytox or procytoxide or semdoxan or sendoxan or syklofosfamid).mp. (10662)

273 270 or 271 or 272 (215846)

274 https://protect-us.mimecast.com/s/Z4M1CNk8ZJiLx4Lfv7cBA?domain=abatacept.mp. or abatacept/ (8753)

275 (LEA29Y or BMS224818 or BMS-224818 or BELATACEPT or ORENCIA or BMS-188667 or CTLA-4-IG or "CYTOTOXIC T LYMPHOCYTE-ASSOCIATED ANTIGEN 4-IMMUNOGLOBULIN" or CTLA4-IG* or CTLA4-FC or NULOJIX).mp. (3702)

276 (BMS 188667 or BMS188667 or CTLA4 or CTLA4IG).mp. (6375)

277 274 or 275 or 276 (15879)

278 https://protect-us.mimecast.com/s/xWshCOYZ1KHYXWYH3NsYt?domain=rituximab.mp. or rituximab/ (76089)

279 (MABTHERA or IDEC-C2B8 ANTIBODY or IDEC-C2B8 or GP2013 or RITUXAN).mp. (4742)

280 (blitzima or ct p10 or ctp10 or idec 102 or idec c2b8 or idec102 or idecc2b8 or monoclonal antibody idec c2b8 or r 105 or r105 or reditux or rg 105 or rg105 or ritemvia or rituxin or rituzena or rixathon or riximyo or ro 452294 or ro452294 or truxima or tuxella).mp. (525)

281 278 or 279 or 280 (76333)

282 BONE MARROW TRANSPLANT*.mp. or exp bone marrow transplantation/ (71757)

283 MESENCHYMAL STEM CELL https://protect-us.mimecast.com/s/3QsCCv2jX1f1gQ1HQEN93h?domain=transplantation.mp. or mesenchymal stem cell transplantation/ (10760)

284 (BONE MARROW GRAFT* or BONE MARROW CELL TRANSPLANT* or mesenchymal stem cell therap* or bone marrow cell transfer* or bone marrow transfusion*).mp. (2391)

285 282 or 283 or 284 (82208)

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286 S100A12 https://protect-us.mimecast.com/s/T21yCwpkY1f6QB6HVXF_AE?domain=protein.mp. or calgranulin C/ (616)

287 (MRP-6 PROTEIN or EN-RAGE PROTEIN or CAAF1 PROTEIN or S100A12 or migration inhibitory factor related protein 6 or MRP 6 or S 100A12 protein or S100 A12 protein or S100 calcium binding protein A12).mp. (933)

288 286 or 287 (1127)

289 (TAPERING or TAPER or TAPERS or TAPERED).mp. (29166)

290 SEROSIT* {No Related Terms} (1972)

291 201 or 216 or 220 or 232 or 243 or 247 or 250 or 258 or 269 or 273 or 277 or 281 or 285 or 288 or 289 or 290 (1711219)

292 212 and 291 (5249)

293 "stills disease".mp. (2591)

294 exp systemic juvenile idiopathic arthritis/ (1083)

295 SYSTEMIC-ONSET JUVENILE ARTHRIT*.mp. (23)

296 (JUVENILE SYSTEMIC-ONSET ARTHRIT* or JUVENILE SYSTEMIC-ONSET IDIOPATHIC ARTHRIT* or SYSTEMIC-ONSET JUVENILE IDIOPATHIC ARTHRITIS or JUVENILE SYSTEMIC ARTHRIT* or SYSTEMIC JUVENILE ARTHRIT* or JUVENILE SYSTEMIC IDIOPATHIC ARTHRIT* or SYSTEMIC JUVENILE IDIOPATHIC ARTHRIT* or SYSTEMIC JIA or SYSTEMIC-ONSET JIA or SYSTEMIC-ONSET JRA or SYSTEMIC-ONSET JUVENILE RHEUMATOID ARTHRIT* or JUVENILE SYSTEMIC-ONSET RHEUMATOID ARTHRIT* or SYSTEMIC JRA or SYSTEMIC JUVENILE RHEUMATOID ARTHRIT* or JUVENILE SYSTEMIC RHEUMATOID ARTHRIT*).mp. (2778)

297 293 or 294 or 295 or 296 (5106)

298 juvenile idiopathic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. or exp juvenile rheumatoid arthritis/ (20816)

299 juvenile chronic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. and (JIA or JRA or IDIOPATHIC).ti,ab. (109)

300 JUVENILE https://protect-us.mimecast.com/s/ee-1CkRoJ1Hl0xltVGL4i?domain=arthritis.mp. and (JIA or JRA or IDIOPATHIC).ti,ab. (965)

301 298 or 299 or 300 (20836)

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302 297 or 301 (22378)

303 limit 302 to (abstracts and english language and (article or article in press or "review")) (10297)

304 (exp hemophagocytic syndrome/ and https://protect-us.mimecast.com/s/Aa9rCxklZgi80Y8f80XxW4?domain=secondary.mp.) or exp macrophage activation syndrome/ (2843)

305 (hemophagocytic syndrome and secondary).mp. (1252)

306 (HEMOPHAGOCYTIC LYMPHOHISTIOCYTOS* and SECONDARY).mp. (1080)

307 MACROPHAGE ACTIVATION*.mp. (26216)

308 304 or 305 or 306 or 307 (27470)

309 303 and 308 (516)

310 CALCINEURIN INHIBITOR*.mp. or exp calcineurin inhibitor/ (91432)

311 (PROTEIN PHOSPHATASE-2B INHIBITOR* or PROTEIN PHOSPHATASE 3 INHIBITOR* or CALCINEURIN ANTAGONIST* or CALCINEURIN BLOCKER* or PROGRAF or PROGRAFT or FR-900506 or FR900506 or FK-506 or FK506 or "33-EPI-CHLORO-33-DESOXYASCOMYCIN" or SDZ-ASM-981 or "ASM 981" or ELIDEL or TACROLIMUS or CYCLOSPORIN or CYCLOSPORINE or CICLOSPORINE or "MUSTOPIC OINT" or TSUKUBAENOLIDE or CIPOL or CYCLOKAT or DEXIMUNE or IMPLANTA or IMMUNOSPORIN or IMUSPORIN or VEKACIA or PROGRAF or ADVAGRAF or HECORIA or GENGRAF or ASTAGRAF or "OL-27-400" or "CSA-NEORAL" or "CYA-NOF" or NEURAL).mp. (557556)

312 310 or 311 (564945)

313 (PULSE THERAP* or PULSE DRUG THERAP* or DRUG PULSE THERAP*).mp. (9914)

314 INTRAVENOUS https://protect-us.mimecast.com/s/0oKMCyPm1jfDWxDSZvgKMr?domain=administration.mp. or exp intravenous drug administration/ (380567)

315 (PULSE DOSE* or PULSED or PULSE THERAP* or INTRAVENOUS* or IV THERAP*).mp. (1161823)

316 313 or 314 or 315 (1161876)

317 312 or 316 (1678528)

318 309 and 317 (272)

319 juvenile idiopathic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. or exp juvenile rheumatoid arthritis/ (20816)

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320 juvenile chronic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. and (JIA or JRA or IDIOPATHIC).ti,ab. (109)

321 JUVENILE https://protect-us.mimecast.com/s/ee-1CkRoJ1Hl0xltVGL4i?domain=arthritis.mp. and (JIA or JRA or IDIOPATHIC).ti,ab. (965)

322 319 or 320 or 321 (20836)

323 https://protect-us.mimecast.com/s/r7x0ClYpK1HGKQGfyk_ye?domain=temporomandibular.mp. (27542)

324 TMJ.ti,ab. (9139)

325 ARTHRIT*.mp. (325914)

326 (costen's syndrome or COSTEN SYNDROME).ti,ab. (37)

327 323 or 324 or 326 (28456)

328 325 and 327 (1945)

329 (oligoarthrit* or oligo-arthrit*).mp. (1898)

330 (oligoarticular* or "oligo-articular" or "oligo articular").ti,ab. (1821)

331 juvenile idiopathic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. or juvenile rheumatoid arthritis/ (20816)

332 (JIA or JRA).ti,ab. (9864)

333 331 or 332 (22532)

334 330 and 333 (1339)

335 329 or 334 (3111)

336 328 or 335 (4997)

337 adult/ or middle aged/ or young adult/ (6884305)

338 exp juvenile/ (3257587)

339 337 not (337 and 338) (5731897)

340 336 not 339 (3867)

341 322 not 339 (18650)

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342 340 or 341 (20308)

343 limit 342 to (abstracts and human and english language and (article or article in press or "review")) (8795)

344 "stills disease".mp. (2591)

345 exp systemic juvenile idiopathic arthritis/ (1083)

346 SYSTEMIC-ONSET JUVENILE ARTHRIT*.mp. (23)

347 (JUVENILE SYSTEMIC-ONSET ARTHRIT* or JUVENILE SYSTEMIC-ONSET IDIOPATHIC ARTHRIT* or SYSTEMIC-ONSET JUVENILE IDIOPATHIC ARTHRITIS or JUVENILE SYSTEMIC ARTHRIT* or SYSTEMIC JUVENILE ARTHRIT* or JUVENILE SYSTEMIC IDIOPATHIC ARTHRIT* or SYSTEMIC JUVENILE IDIOPATHIC ARTHRIT* or SYSTEMIC JIA or SYSTEMIC-ONSET JIA or SYSTEMIC-ONSET JRA or SYSTEMIC-ONSET JUVENILE RHEUMATOID ARTHRIT* or JUVENILE SYSTEMIC-ONSET RHEUMATOID ARTHRIT* or SYSTEMIC JRA or SYSTEMIC JUVENILE RHEUMATOID ARTHRIT* or JUVENILE SYSTEMIC RHEUMATOID ARTHRIT*).mp. (2778)

348 344 or 345 or 346 or 347 (5106)

349 juvenile idiopathic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. or exp juvenile rheumatoid arthritis/ (20816)

350 juvenile chronic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. and (JIA or JRA or IDIOPATHIC).ti,ab. (109)

351 JUVENILE https://protect-us.mimecast.com/s/ee-1CkRoJ1Hl0xltVGL4i?domain=arthritis.mp. and (JIA or JRA or IDIOPATHIC).ti,ab. (965)

352 349 or 350 or 351 (20836)

353 348 or 352 (22378)

354 limit 353 to (abstracts and english language and (article or article in press or "review")) (10297)

355 343 or 354 (10870)

356 LEUKOCYTE https://protect-us.mimecast.com/s/k4O2Czpn2kfDB5DS4WuPbQ?domain=count.mp. or exp leukocyte count/ (201647)

357 PLATELET https://protect-us.mimecast.com/s/k4O2Czpn2kfDB5DS4WuPbQ?domain=count.mp. or platelet count/ (47162)

358 LIVER FUNCTION TEST*.mp. or liver function test/ (43004)

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359 BLOOD CELL https://protect-us.mimecast.com/s/k4O2Czpn2kfDB5DS4WuPbQ?domain=count.mp. or exp blood cell count/ (260752)

360 URINALYS*.mp. or exp urinalysis/ (105056)

361 https://protect-us.mimecast.com/s/cHKxCADmJpC0ok0fG1pKts?domain=creatinine.mp. (256079)

362 https://protect-us.mimecast.com/s/7TpQCBBnKqSqmYqfzX8N10?domain=triglycerides.mp. or triacylglycerol/ (200299)

363 https://protect-us.mimecast.com/s/LhvpCDk0Mvipm4psWXx3FJ?domain=cholesterol.mp. (404322)

364 lipid https://protect-us.mimecast.com/s/NORgCERPNwHyGEyiN0NsGw?domain=panel.mp. (1122)

365 LOW DENSITY https://protect-us.mimecast.com/s/dddVCG69P0tnlvnCKOykXp?domain=lipoprotein.mp. or low density lipoprotein/ (199791)

366 high density https://protect-us.mimecast.com/s/h_rVCJ6PVBtOzNOiV3gDSr?domain=lipoprotein.mp. or high density lipoprotein/ (159947)

367 kidney function https://protect-us.mimecast.com/s/vQmlCKr6WDHKwVKfMwgITe?domain=test.mp. or kidney function test/ (11143)

368 serum https://protect-us.mimecast.com/s/vFmXCL9PXEFqO6qfBNThOy?domain=creatinine.mp. or creatinine blood level/ (119446)

369 (LEUKOCYTE NUMBER* or WHITE BLOOD CELL COUNT* or PLATELET NUMBER* or POLYMORPHONUCLEAR LEUKOCYTE* or LE CELLS or LE CELL or LIVER ENZYME* or CBC or COMPLETE BLOOD COUNT* or BLOOD CELL COUNT* or BLOOD CELL NUMBER* or KREBIOZEN).mp. (135783)

370 (URINARY ANALYSIS or URINARY TEST or URINE ANALYSIS or URINE EXAMINATION or URINE INVESTIGATION or URINE TEST or URINE TESTING or WBC COUNT or WBC COUNTS or WHITE BLOOD COUNT or WHITE CELL COUNT or BLOOD PLATELET COUNT or PLATELET NUMBER or HEPATIC FUNCTION TEST).mp. (27818)

371 356 or 357 or 358 or 359 or 360 or 361 or 362 or 363 or 364 or 365 or 366 or 367 or 368 or 369 or 370 (1195321)

372 355 and 371 (845)

373 NSAID*.mp. or exp nonsteroid antiinflammatory agent/ (713203)

374 https://protect-us.mimecast.com/s/RmZ9C829wVf3Mo3HB_94I?domain=indomethacin.mp. (41524)

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375 (NON-STEROIDAL ANTI-INFLAMMATOR* or NONSTEROIDAL ANTI-INFLAMMATORY AGENT* or NONSTEROIDAL ANTIINFLAMMATORY AGENT* or ANTI-INFLAMMATORY ANALGESIC or ACECLOFENAC or ACEMETACIN or ACETOSYRINGONE or ACETOVANILLONE or ADAPALENE or ALCLOFENAC or ALMINOPROFEN or AMIPRILOSE or AMPYRONE or ANDROGRAPHOLIDE or ANISODAMINE or ANISODINE or ANTIPYRINE or APAZONE or APREMILAST or ARTEPARON or ARTHROTEC or ASPIRIN or ATRINOSITOL or AZULENE or BAICALIN or BALSALAZIDE or BENDAZAC or BENDAZAC LYSINE or BENORILATE or BENOXAPROFEN or BENZOBARBITAL or BERBAMINE or BEVONIUM or BOLDINE or BROMFENAC or BUCILLAMINE or BUFEXAMAC or BUMADIZONE or BUTIBUFEN or CARPROFEN or CARYOPHYLLENE or CASTANOSPERMINE or CELECOXIB or CEPHARANTHINE or CHLOROQUINE DIPHOSPHATE or CHOLINE MAGNESIUM TRISALICYLATE or CHRYSAROBIN or CLONIXIN or CURCUMIN or DAURICINE or DEXKETOPROFEN TROMETAMOL or DICLOFENAC or DIFENPIRAMIDE or DIFLUNISAL or DIMEPHOSPHON or DIPYRONE or DIUCIFON or DROXICAM or EBSELEN or ECALLANTIDE or ELTENAC or EPIRIZOLE or ETANERCEPT or ETHENZAMIDE or ETHONIUM or ETODOLAC or ETOFENAMATE or ETORICOXIB or FENBUFEN or FENCLOFENAC or FENFLUMIZOLE or FENOPROFEN or FENTIAZAC or FEPRADINOL or FEPRAZONE or FLOCTAFENINE or FLOSULIDE or FLUNIXIN or FLUNOXAPROFEN or FLUPROQUAZONE or FLURBIPROFEN or GLUCAMETACIN or GUACETISAL or HELENALIN or HELIODERMIN or HEMODES or HIGENAMINE or IBUPROFEN or IBUPROXAM or ICATIBANT or INDOBUFEN or INDOMETHACIN or INDOPROFEN or IODOANTIPYRINE or ISOXICAM or KEBUZONE or KETOPROFEN or KETOROLAC or LICOFELONE or LISOFYLLINE or LOBENZARIT or LONAZOLAC or LORNOXICAM or LOXOPROFEN or LUMIRACOXIB or MAGNOLOL or MANOALIDE or MASOPROCOL or MELOXICAM or MESALAMINE or MIZORIBINE or MOFEBUTAZONE or MOFEZOLAC or NABUMETONE or NAFAMOSTAT or NAPROXEN or NEBACETIN or NEPAFENAC or NIFENAZONE or NIMESULIDE or NITROASPIRIN or OLSALAZINE or OLVANIL or ORGOTEIN or OXAPROZIN or OXYPHENBUTAZONE or PALMIDROL or PARECOXIB or PARTHENOLIDE or PEONIFLORIN or PHENIDONE or PHENYLBUTAZONE or PIMECROLIMUS or PIRFENIDONE or PIROXICAM or PIRPROFEN or PROGLUMETACIN or PROPACETAMOL or PROPIONYLCARNITINE or PROPYPHENAZONE or PROQUAZONE or PYRANOPROFEN or PYRAZOLONE or PYROGENAL or RESVERATROL or RNS60 or ROFECOXIB or RUMALON or SAIKO-KEISHI-TO or SAIKOSAPONIN or SALICIN or SALICYLAMIDE or SALICYLATES or "SALICYLSALICYLIC ACID" or SEMAPIMOD or SERATRODAST or SERRATIOPEPTIDASE or SHIKONIN or SINAPALDEHYDE or SODIUM SALICYLATE or SUL-121 or SULFASALAZINE or SULINDAC or SUPROFEN or SUXIBUZONE or TANSHINONE or TAXIFOLIN or TENIDAP or TENOXICAM or TEPOXALIN or TIARAMIDE or TINORIDINE or TOLMETIN or TRANILAST or TRIBENOSIDE or VALDECOXIB or ZILEUTON or ZOMEPIRAC or CELEBREX or SC-58635 or SC58635 or ETODOLIC* or ULTRADOL or LODINE or RAMODAR or AY-24236 or CP-16171 or CP16171 or FELDENE or DICLOPHENAC or DICROFENAC or DICHLOFENAL or "DICLONATE P" or FELORAN or VOLTAROL or NOVAPIRINA or ORTHOFEN or ORTOFEN or ORTHOPHEN or SR-38 or VOLTAREN or NABUMETON or RELIFEX or RELIF or APO-NABUMETONE or APONABUMETONE or MEBUTAN or LISTRAN or GEN-NABUMETONE or ARTHRAXAN or RHOXAL-NABUMETONE or RELAFEN or NABUCOX or MILOXICAM or PAROCIN or MOBIC or MOBICOX or MOBEC or MASFLEX or MOVICOX or REUMOXICAM or UTICOX or MOVALIS or INDOMETACIN or OSMOSIN or INDOCID or METINDOL or AMUNO or INDOCIN or TOLECTIN or MCN-2559 or MOTRIN or NUPRIN or RUFEN or SALPROFEN or BRUFEN or METHOXYPROPIOCIN or ANAPROX or ALEVE or PROXEN or SYNFLEX or NAPROSIN or NAPROSYN).mp. (474369)

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376 373 or 374 or 375 (841632)

377 https://protect-us.mimecast.com/s/yI6qCwpkY1f6QB6HXUF8Z?domain=leflunomide.mp. or leflunomide/ (11450)

378 https://protect-us.mimecast.com/s/BuHtCxklZgi80Y8f08XNE?domain=arava.tn. (538)

379 https://protect-us.mimecast.com/s/cKZvCyPm1jfDWxDSvpik9?domain=arabloc.mp. (6)

380 (hwa 486 or hwa486 or repso or rs 34821 or rs34821 or su 101 or su101).tn. (200)

381 hydroxychloroquine/ (22365)

382 https://protect-us.mimecast.com/s/pDRhCzpn2kfDB5DSWp7Kd?domain=hydroxychloroquine.mp. (23217)

383 https://protect-us.mimecast.com/s/c3hkCADmJpC0ok0f1DcgK?domain=chloroquinol.mp. (4)

384 https://protect-us.mimecast.com/s/1eCWCBBnKqSqmYqfXC3l0?domain=hydrochloroquine.mp. (53)

385 https://protect-us.mimecast.com/s/2KZbCDk0Mvipm4psX-gGP?domain=oxychloroquine.mp. (6)

386 (ercoquin or plaquenil or quensyl or "sn 8137").tn,mp. (1315)

387 https://protect-us.mimecast.com/s/T1FnCERPNwHyGEyi0BQG_?domain=sulfasalazine.mp. or salazosulfapyridine/ (25013)

388 (azopyrin or azopyrine or azosulfidine or azulfide or azulfidina or azulfidine* or azulfin).mp. (691)

389 (benzosulfa or colo pleon or colo-pleon or colopleon or disalazin or gastropyrin).mp. (72)

390 (pleon ra or pyralin en or rorasul or rosulfant or salazine or salazo sulfapyridine).mp. (29)

391 (salazodin or salazopirina or salazopyridin or salazopyridine or salazopyrin* or salazosulfa pyridine or salazosulfpyridine or salicyl azo sulfapyridine or salicylazosulfapyridin* or salisulf or salopyr or saridine or sas 500 or sulcolon or sulfasalizine or sulfosalazine or sulphasalazine or zopyrin).mp. (2842)

392 methotrexate/ or https://protect-us.mimecast.com/s/3DL7CG69P0tnlvnCOtwNS?domain=methotrexate.mp. (175129)

393 (a methopterine or abitrexate or amethopterin or amethopterine or ametopterine or antifolan or biotrexate or canceren or cl 14377 or cl14377 or emtexate or emthexat or emthexate or emtrexate or enthexate or farmitrexat or farmitrexate or farmotrex or folex or ifamet or imeth or jylamvo or lantarel or ledertrexate or maxtrex or metex or methoblastin or methohexate or methotrate or methotrexat or methotrexato or methrotrexate or methylaminopterin or methylaminopterine or meticil or metoject or metothrexate or metotrexat or metotrexate or metotrexin or metrex or mexate or mexate-aq or mexate-aq* or mpi 5004 or mpi5004 or MTX or neotrexate or nordimet or novatrex or nsc 740 or nsc740

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or otrexup or rasuvo or reumatrex or rheumatrex or texate or texate-t or texorate or trexall or xaken or xatmep or zexate).mp. (24750)

394 377 or 378 or 379 or 380 or 381 or 382 or 383 or 384 or 385 or 386 or 387 or 388 or 389 or 390 or 391 or 392 or 393 (207088)

395 methotrexate/ or https://protect-us.mimecast.com/s/3DL7CG69P0tnlvnCOtwNS?domain=methotrexate.mp. (175129)

396 https://protect-us.mimecast.com/s/JgEZCQWO3MHVq0VhgxAf_?domain=canakinumab.mp. or canakinumab/ (2750)

397 https://protect-us.mimecast.com/s/bsSECW68gVt3YJ3HQu0eV?domain=tocilizumab.mp. or tocilizumab/ (10496)

398 https://protect-us.mimecast.com/s/wIaUCR6L4NtYl2YH6jfPx?domain=rilonacept.mp. or rilonacept/ (836)

399 https://protect-us.mimecast.com/s/8DrtCYEMk8iYZrYH5GQTv?domain=anakinra.mp. or anakinra/ (4519)

400 (AMETHOPTERIN or MEXATE or KINERET or ANTRIL or ILARIS or ACZ-885 or ACZ885 or ATLIZUMAB or ACTEMRA).mp. (2473)

401 (atlizumab or lusinex or r1569 or roactemra).mp. (771)

402 https://protect-us.mimecast.com/s/T9yNClYpK1HGKQGfGyDu_q?domain=arcalyst.mp. (135)

403 il 1 https://protect-us.mimecast.com/s/mDD0CmZEL5UXYOXHG9d3W9?domain=trap.mp. (51)

404 (A METHOPTERINE or ABITREXATE or AMETHOPTERIN or AMETHOPTERINE or AMETOPTERINE or ANTIFOLAN or BIOTREXATE or CANCEREN or CL 14377 or CL14377 or EMTEXATE or EMTHEXAT or EMTHEXATE or EMTREXATE or ENTHEXATE or FARMITREXAT or FARMITREXATE or FARMOTREX or FOLEX or FOLEX PFS or IFAMET or IMETH or JYLAMVO or LANTAREL or LEDERTREXATE or MAXTREX or METEX or METHOBLASTIN or METHOHEXATE or METHOTRATE or METHOTREXAT or METHOTREXAT EBEWE or METHOTREXATO or METHOXTREXATE or METHROTREXATE or METHYLAMINOPTERIN or METHYLAMINOPTERINE or METICIL or METOJECT or METOTHREXATE or METOTHREXATE SODIUM or METOTREXAT or METOTREXATE or METOTREXIN or METREX or MEXATE* or MPI 5004 or MPI5004 or MTX or NEOTREXATE or NORDIMET or NOVATREX or NSC 740 or NSC740 or OTREXUP or RASUVO or REUMATREX or RHEUMATREX or TEXATE or TEXATE-T or TEXORATE or TREXALL or XAKEN or XATMEP or ZEXATE).mp. (24751)

405 395 or 396 or 397 or 398 or 399 or 400 or 401 or 402 or 403 or 404 (188442)

406 https://protect-us.mimecast.com/s/Z4M1CNk8ZJiLx4Lfv7cBA?domain=abatacept.mp. or abatacept/ (8753)

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407 (LEA29Y or BMS224818 or BMS-224818 or BELATACEPT or ORENCIA or BMS-188667 or CTLA-4-IG or "CYTOTOXIC T LYMPHOCYTE-ASSOCIATED ANTIGEN 4-IMMUNOGLOBULIN" or CTLA4-IG* or CTLA4-FC or NULOJIX).mp. (3702)

408 (BMS 188667 or BMS188667 or CTLA4 or CTLA4IG).mp. (6375)

409 406 or 407 or 408 (15879)

410 TUMOR NECROSIS FACTOR ALPHA https://protect-us.mimecast.com/s/rojzCM89YGfP8NPUwMvWwg?domain=inhibitor.mp. or exp tumor necrosis factor inhibitor/ (86651)

411 (TUMOR NECROSIS FACTOR INHIBITOR* or TUMOUR NECROSIS FACTOR INHIBITOR* or TNFALPHA INHIBITOR* or TNF-ALPHA INHIBITOR* or TNF INHIBITOR* or ANTI-TUMOR NECROSIS FACTOR* or ANTI-TUMOUR NECROSIS FACTOR* or ANTI-TNF* or TNFI).mp. (40949)

412 (ANTI TUMOR NECROSIS FACTOR AGENT or ANTI TUMOUR NECROSIS FACTOR AGENT or TNF ALPHA INHIBITOR or TNF INHIBITOR or TUMOR NECROSIS FACTOR ALPHA INHIBITOR or TUMOUR NECROSIS FACTOR ALPHA INHIBITOR or TUMOUR NECROSIS FACTOR INHIBITOR or ADALIMUMAB or BELANTAMAB or BELANTAMAB MAFODOTIN or BLESELUMAB or CD24FC or DENOSUMAB or EFIZONERIMOD ALFA or ETANERCEPT or GOLIMUMAB or INFLIXIMAB or PEGILODECAKIN or RAVAGALIMAB or REMTOLUMAB or SELICRELUMAB or TAVOLIMAB or TIBULIZUMAB or VANALIMAB).mp. (82355)

413 405 or 406 or 407 or 408 or 409 or 410 or 411 or 412 (264696)

414 376 or 394 or 413 (925195)

415 414 and 372 (529)

416 juvenile idiopathic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. or exp juvenile rheumatoid arthritis/ (20816)

417 juvenile chronic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. and (JIA or JRA or IDIOPATHIC).ti,ab. (109)

418 JUVENILE https://protect-us.mimecast.com/s/ee-1CkRoJ1Hl0xltVGL4i?domain=arthritis.mp. and (JIA or JRA or IDIOPATHIC).ti,ab. (965)

419 416 or 417 or 418 (20836)

420 https://protect-us.mimecast.com/s/r7x0ClYpK1HGKQGfyk_ye?domain=temporomandibular.mp. (27542)

421 TMJ.ti,ab. (9139)

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422 ARTHRIT*.mp. (325914)

423 (costen's syndrome or COSTEN SYNDROME).ti,ab. (37)

424 420 or 421 or 423 (28456)

425 422 and 424 (1945)

426 (oligoarthrit* or oligo-arthrit*).mp. (1898)

427 (oligoarticular* or "oligo-articular" or "oligo articular").ti,ab. (1821)

428 juvenile idiopathic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. or juvenile rheumatoid arthritis/ (20816)

429 (JIA or JRA).ti,ab. (9864)

430 428 or 429 (22532)

431 427 and 430 (1339)

432 426 or 431 (3111)

433 425 or 432 (4997)

434 adult/ or middle aged/ or young adult/ (6884305)

435 exp juvenile/ (3257587)

436 434 not (434 and 435) (5731897)

437 433 not 436 (3867)

438 419 not 436 (18650)

439 437 or 438 (20308)

440 limit 439 to (abstracts and human and english language and (article or article in press or "review")) (8795)

441 "stills disease".mp. (2591)

442 exp systemic juvenile idiopathic arthritis/ (1083)

443 SYSTEMIC-ONSET JUVENILE ARTHRIT*.mp. (23)

444 (JUVENILE SYSTEMIC-ONSET ARTHRIT* or JUVENILE SYSTEMIC-ONSET IDIOPATHIC ARTHRIT* or SYSTEMIC-ONSET JUVENILE IDIOPATHIC ARTHRITIS or JUVENILE SYSTEMIC ARTHRIT* or SYSTEMIC

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JUVENILE ARTHRIT* or JUVENILE SYSTEMIC IDIOPATHIC ARTHRIT* or SYSTEMIC JUVENILE IDIOPATHIC ARTHRIT* or SYSTEMIC JIA or SYSTEMIC-ONSET JIA or SYSTEMIC-ONSET JRA or SYSTEMIC-ONSET JUVENILE RHEUMATOID ARTHRIT* or JUVENILE SYSTEMIC-ONSET RHEUMATOID ARTHRIT* or SYSTEMIC JRA or SYSTEMIC JUVENILE RHEUMATOID ARTHRIT* or JUVENILE SYSTEMIC RHEUMATOID ARTHRIT*).mp. (2778)

445 441 or 442 or 443 or 444 (5106)

446 juvenile idiopathic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. or exp juvenile rheumatoid arthritis/ (20816)

447 juvenile chronic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. and (JIA or JRA or IDIOPATHIC).ti,ab. (109)

448 JUVENILE https://protect-us.mimecast.com/s/ee-1CkRoJ1Hl0xltVGL4i?domain=arthritis.mp. and (JIA or JRA or IDIOPATHIC).ti,ab. (965)

449 446 or 447 or 448 (20836)

450 445 or 449 (22378)

451 limit 450 to (abstracts and english language and (article or article in press or "review")) (10297)

452 440 or 451 (10870)

453 exp hepatitis C/ or HEPATITIS https://protect-us.mimecast.com/s/HfJHCNk8ZJiLx4Lfmv8zom?domain=c.mp. (146595)

454 HEPATITIS https://protect-us.mimecast.com/s/RJ6ZCOYZ1KHYXWYHE3ZaLG?domain=b.mp. or exp hepatitis B/ (152991)

455 https://protect-us.mimecast.com/s/RSfwCPNY2LigmpgtzwhRPN?domain=chickenpox.mp. or chickenpox/ (13480)

456 measles/ or https://protect-us.mimecast.com/s/BSpqCQWO3MHVq0VhxgchYa?domain=measles.mp. (34449)

457 HERPES https://protect-us.mimecast.com/s/DeThCR6L4NtYl2YH96ShuF?domain=zoster.mp. or herpes zoster/ (25559)

458 (SERIOUS INFECTION* or HERPES VIRUS VARICELLAE or HERPESVIRUS 3 or ZONA VIRUS or VARICELLA* or PT-NANBH or HERPESVIRUS 3 or CHICKEN POX or RUBEOLA or RUBELLA or morbilli).mp. (52829)

459 453 or 454 or 455 or 456 or 457 or 458 (347741)

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460 452 and 459 (483)

461 juvenile idiopathic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. or exp juvenile rheumatoid arthritis/ (20816)

462 juvenile chronic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. and (JIA or JRA or IDIOPATHIC).ti,ab. (109)

463 JUVENILE https://protect-us.mimecast.com/s/ee-1CkRoJ1Hl0xltVGL4i?domain=arthritis.mp. and (JIA or JRA or IDIOPATHIC).ti,ab. (965)

464 461 or 462 or 463 (20836)

465 https://protect-us.mimecast.com/s/r7x0ClYpK1HGKQGfyk_ye?domain=temporomandibular.mp. (27542)

466 TMJ.ti,ab. (9139)

467 ARTHRIT*.mp. (325914)

468 (costen's syndrome or COSTEN SYNDROME).ti,ab. (37)

469 465 or 466 or 468 (28456)

470 467 and 469 (1945)

471 (oligoarthrit* or oligo-arthrit*).mp. (1898)

472 (oligoarticular* or "oligo-articular" or "oligo articular").ti,ab. (1821)

473 juvenile idiopathic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. or juvenile rheumatoid arthritis/ (20816)

474 (JIA or JRA).ti,ab. (9864)

475 473 or 474 (22532)

476 472 and 475 (1339)

477 471 or 476 (3111)

478 470 or 477 (4997)

479 adult/ or middle aged/ or young adult/ (6884305)

480 exp juvenile/ (3257587)

For Peer Review Only

481 479 not (479 and 480) (5731897)

482 478 not 481 (3867)

483 464 not 481 (18650)

484 482 or 483 (20308)

485 limit 484 to (abstracts and human and english language and (article or article in press or "review")) (8795)

486 "stills disease".mp. (2591)

487 exp systemic juvenile idiopathic arthritis/ (1083)

488 SYSTEMIC-ONSET JUVENILE ARTHRIT*.mp. (23)

489 (JUVENILE SYSTEMIC-ONSET ARTHRIT* or JUVENILE SYSTEMIC-ONSET IDIOPATHIC ARTHRIT* or SYSTEMIC-ONSET JUVENILE IDIOPATHIC ARTHRITIS or JUVENILE SYSTEMIC ARTHRIT* or SYSTEMIC JUVENILE ARTHRIT* or JUVENILE SYSTEMIC IDIOPATHIC ARTHRIT* or SYSTEMIC JUVENILE IDIOPATHIC ARTHRIT* or SYSTEMIC JIA or SYSTEMIC-ONSET JIA or SYSTEMIC-ONSET JRA or SYSTEMIC-ONSET JUVENILE RHEUMATOID ARTHRIT* or JUVENILE SYSTEMIC-ONSET RHEUMATOID ARTHRIT* or SYSTEMIC JRA or SYSTEMIC JUVENILE RHEUMATOID ARTHRIT* or JUVENILE SYSTEMIC RHEUMATOID ARTHRIT*).mp. (2778)

490 486 or 487 or 488 or 489 (5106)

491 juvenile idiopathic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. or exp juvenile rheumatoid arthritis/ (20816)

492 juvenile chronic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. and (JIA or JRA or IDIOPATHIC).ti,ab. (109)

493 JUVENILE https://protect-us.mimecast.com/s/ee-1CkRoJ1Hl0xltVGL4i?domain=arthritis.mp. and (JIA or JRA or IDIOPATHIC).ti,ab. (965)

494 491 or 492 or 493 (20836)

495 490 or 494 (22378)

496 limit 495 to (abstracts and english language and (article or article in press or "review")) (10297)

497 485 or 496 (10870)

498 (INTERLEUKIN-6 adj3 (INHIBITOR* or ANTAGONIST*)).mp. (803)

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499 (INTERLEUKIN-1 adj3 (INHIBITOR* or ANTAGONIST*)).mp. (4677)

500 (INTERLEUKIN-1 RECEPTOR* adj3 (INHIBITOR* or ANTAGONIST*)).mp. (4100)

501 (INTERLEUKIN-6 RECEPTOR* adj3 (INHIBITOR* or ANTAGONIST*)).mp. (194)

502 exp tumor necrosis factor inhibitor/ or https://protect-us.mimecast.com/s/UxQnCKr6WDHKwVKfwOuyb?domain=tnfi.mp. (84349)

503 https://protect-us.mimecast.com/s/FBkFCL9PXEFqO6qfNGyt3?domain=infliximab.mp. or infliximab/ (48723)

504 CERTOLIZUMAB https://protect-us.mimecast.com/s/CvDLCM89YGfP8NPUMgO6i?domain=pegol.mp. or certolizumab pegol/ (6062)

505 https://protect-us.mimecast.com/s/Z4M1CNk8ZJiLx4Lfv7cBA?domain=abatacept.mp. or abatacept/ (8753)

506 rituximab/ (72964)

507 https://protect-us.mimecast.com/s/xWshCOYZ1KHYXWYH3NsYt?domain=rituximab.mp. (76089)

508 https://protect-us.mimecast.com/s/LtAKCPNY2Ligmpgtw0lIL?domain=tofacitinib.mp. or tofacitinib/ (3626)

509 https://protect-us.mimecast.com/s/JgEZCQWO3MHVq0VhgxAf_?domain=canakinumab.mp. or canakinumab/ (2750)

510 https://protect-us.mimecast.com/s/wIaUCR6L4NtYl2YH6jfPx?domain=rilonacept.mp. or rilonacept/ (836)

511 https://protect-us.mimecast.com/s/FmouCVON8RHBKGBCPqAVh?domain=golimumab.mp. or golimumab/ (6324)

512 https://protect-us.mimecast.com/s/bsSECW68gVt3YJ3HQu0eV?domain=tocilizumab.mp. or tocilizumab/ (10496)

513 https://protect-us.mimecast.com/s/PN9TCXDMjWCANwAHN1MuR?domain=secukinumab.mp. or secukinumab/ (2857)

514 (BIOLOGIC DISEASE MODIF* or BIOLOGIC RESPONSE MODIF* or DISEASE-MODIFYING ANTIRHEUMATIC* or DISEASE-MODIFYING ANTI-RHEUMATIC* or DMARD*).mp. (25544)

515 disease modifying antirheumatic drug/ (15443)

516 (INTERLEUKIN-1 BLOCKER* or IL-1 BLOCKER* or IL-1 BLOCKADE* or INTERLEUKIN-1 BLOCKADE* or INTERLEUKIN-6 BLOCKER* or IL-6 BLOCKER* or IL-6 BLOCKADE* or INTERLEUKIN-6 BLOCKADE* or ILARIS

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or ACZ-885 or ACZ885 or ANTI-INTERLEUKIN-1* or ANTI-IL-1* or ANTI-INTERLEUKIN-6* or ANTI-IL-6*).mp. (9604)

517 https://protect-us.mimecast.com/s/8DrtCYEMk8iYZrYH5GQTv?domain=anakinra.mp. or anakinra/ (4519)

518 (KINERET or ANTRIL or INTERLEUKIN-6 INHIBITOR* or IL-6 INHIBITOR* or INTERLEUKIN-1 INHIBITOR* or IL-1 INHIBITOR* or TUMOR NECROSIS FACTOR INHIBITOR* or TUMOUR NECROSIS FACTOR INHIBITOR*).mp. (15168)

519 (TNFALPHA INHIBITOR* or TNF-ALPHA INHIBITOR* or TNF INHIBITOR* or ANTI-TUMOR NECROSIS FACTOR* or ANTI-TUMOUR NECROSIS FACTOR* or ANTI-TNF* or HUMIRA or ADALIMUMAB-ADBM or AMJEVITA).mp. (36953)

520 (ADALIMUMAB-ATTO or CYLTEZO or ETANERCEPT or "TNFR-FC FUSION PROTEIN" or "TNR 001" or "TNT RECEPTOR FUSION PROTEIN" or TNR-001 or ETANERCEPT-SZZS or "TNF RECEPTOR TYPE II-IGG FUSION PROTEIN" or ERELZI or ENBREL).mp. (30938)

521 ("MONOCLONAL ANTIBODY CA2" or "MAB CA2" or RENFLEXIS or INFLECTRA or REMICADE or CIMZIA or CDP870 or LEA29Y or BMS224818 or BMS-224818 or BELATACEPT or ORENCIA or BMS-188667 or CTLA-4-IG).mp. (7707)

522 ("CYTOTOXIC T LYMPHOCYTE-ASSOCIATED ANTIGEN 4-IMMUNOGLOBULIN" or CTLA4-IG* or CTLA4-FC or NULOJIX or ATLIZUMAB or ACTEMRA or MABTHERA or IDEC-C2B8 ANTIBODY or IDEC-C2B8 or GP2013 or RITUXAN or TASOCITINIB or XELJANZ or CP690550 or CP-690550 or CP 690550 or COSENTYX or AIN457 or AIN-457).mp. (7476)

523 interleukin-1 receptor block*.mp. or interleukin 1 receptor blocking agent/ (18273)

524 interleukin 6/ and receptor blocking agent/ (205)

525 498 or 499 or 500 or 501 or 502 or 503 or 504 or 505 or 506 or 507 or 508 or 509 or 510 or 511 or 512 or 513 or 514 or 515 or 516 or 517 or 518 or 519 or 520 or 521 or 522 or 523 or 524 (214157)

526 https://protect-us.mimecast.com/s/O49ECVON8RHBKGBCGPpTla?domain=tuberculosis.mp. or exp tuberculosis/ (233236)

527 https://protect-us.mimecast.com/s/drZQCW68gVt3YJ3H6QUcHh?domain=mycobacterium.mp. or Mycobacterium/ (123983)

528 TUBERCULIN https://protect-us.mimecast.com/s/nBp1CXDMjWCANwAH6NNGPK?domain=test.mp. or tuberculin test/ (16950)

529 ("KOCH'S DISEASE" or KOCH DISEASE or KOCHS DISEASE or LTBI).mp. (3038)

530 (tuberculous infection or tuberculous lesion).mp. (2052)

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531 526 or 527 or 528 or 529 or 530 (276546)

532 497 and 525 and 531 (347)

533 juvenile idiopathic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. or exp juvenile rheumatoid arthritis/ (20816)

534 juvenile chronic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. and (JIA or JRA or IDIOPATHIC).ti,ab. (109)

535 JUVENILE https://protect-us.mimecast.com/s/ee-1CkRoJ1Hl0xltVGL4i?domain=arthritis.mp. and (JIA or JRA or IDIOPATHIC).ti,ab. (965)

536 533 or 534 or 535 (20836)

537 https://protect-us.mimecast.com/s/r7x0ClYpK1HGKQGfyk_ye?domain=temporomandibular.mp. (27542)

538 TMJ.ti,ab. (9139)

539 ARTHRIT*.mp. (325914)

540 (costen's syndrome or COSTEN SYNDROME).ti,ab. (37)

541 537 or 538 or 540 (28456)

542 539 and 541 (1945)

543 (oligoarthrit* or oligo-arthrit*).mp. (1898)

544 (oligoarticular* or "oligo-articular" or "oligo articular").ti,ab. (1821)

545 juvenile idiopathic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. or juvenile rheumatoid arthritis/ (20816)

546 (JIA or JRA).ti,ab. (9864)

547 545 or 546 (22532)

548 544 and 547 (1339)

549 543 or 548 (3111)

550 542 or 549 (4997)

551 adult/ or middle aged/ or young adult/ (6884305)

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552 exp juvenile/ (3257587)

553 551 not (551 and 552) (5731897)

554 550 not 553 (3867)

555 536 not 553 (18650)

556 554 or 555 (20308)

557 limit 556 to (abstracts and human and english language and (article or article in press or "review")) (8795)

558 "stills disease".mp. (2591)

559 exp systemic juvenile idiopathic arthritis/ (1083)

560 SYSTEMIC-ONSET JUVENILE ARTHRIT*.mp. (23)

561 (JUVENILE SYSTEMIC-ONSET ARTHRIT* or JUVENILE SYSTEMIC-ONSET IDIOPATHIC ARTHRIT* or SYSTEMIC-ONSET JUVENILE IDIOPATHIC ARTHRITIS or JUVENILE SYSTEMIC ARTHRIT* or SYSTEMIC JUVENILE ARTHRIT* or JUVENILE SYSTEMIC IDIOPATHIC ARTHRIT* or SYSTEMIC JUVENILE IDIOPATHIC ARTHRIT* or SYSTEMIC JIA or SYSTEMIC-ONSET JIA or SYSTEMIC-ONSET JRA or SYSTEMIC-ONSET JUVENILE RHEUMATOID ARTHRIT* or JUVENILE SYSTEMIC-ONSET RHEUMATOID ARTHRIT* or SYSTEMIC JRA or SYSTEMIC JUVENILE RHEUMATOID ARTHRIT* or JUVENILE SYSTEMIC RHEUMATOID ARTHRIT*).mp. (2778)

562 558 or 559 or 560 or 561 (5106)

563 juvenile idiopathic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. or exp juvenile rheumatoid arthritis/ (20816)

564 juvenile chronic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. and (JIA or JRA or IDIOPATHIC).ti,ab. (109)

565 JUVENILE https://protect-us.mimecast.com/s/ee-1CkRoJ1Hl0xltVGL4i?domain=arthritis.mp. and (JIA or JRA or IDIOPATHIC).ti,ab. (965)

566 563 or 564 or 565 (20836)

567 562 or 566 (22378)

568 limit 567 to (abstracts and english language and (article or article in press or "review")) (10297)

569 557 or 568 (10870)

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570 https://protect-us.mimecast.com/s/nz4RCYEMk8iYZrYH05IOv7?domain=vaccines.mp. or vaccine/ (149029)

571 VACCINATION*.mp. or exp vaccination/ (211144)

572 live vaccine/ (14134)

573 INACTIVATED VACCINE*.mp. or inactivated vaccine/ (6748)

574 https://protect-us.mimecast.com/s/fDTmCZ6Wl1tvRJvfz22tui?domain=immunization.mp. or immunization/ (165691)

575 (VACCIN* or IMMUNIS* or reimmunisation or reimmunization).mp. (447382)

576 570 or 571 or 572 or 573 or 574 or 575 (513476)

577 MAGNETIC RESONANCE https://protect-us.mimecast.com/s/cU3cC1w9mLFgmVgtLZG1m2?domain=imaging.mp. or exp nuclear magnetic resonance imaging/ (923493)

578 X-RAY*.mp. or X ray/ (553949)

579 https://protect-us.mimecast.com/s/5K9JC2k9nMirGMrSnw1wik?domain=ultrasonography.mp. or echography/ (386023)

580 radiography/ or joint radiography/ (193597)

581 RADIOGRAPH*.mp. (639585)

582 radiology/ or https://protect-us.mimecast.com/s/9AkYC319oNf3Mn3Hg32pue?domain=radiology.mp. (122263)

583 https://protect-us.mimecast.com/s/cU3cC1w9mLFgmVgtLZG1m2?domain=imaging.mp. (1689000)

584 (MAGNETIC RESONANCE or MR TOMOGRAPH* or NMR TOMOGRAPH* or ZEUGMATOGRAPH* or PROTON SPIN TOMOGRAPH* or MRI SCAN* or FMRI or FUNCTIONAL MRI* or ULTRASONOGRAPH* or ECHOGRAPH* or ULTRASOUND* or MEDICAL SONOGRAPH* or ECHOTOMOGRAPH* or ULTRASONIC DIAGNOS* or ULTRASONIC TOMOGRAPH* or ROENTGENOGRAPH* XRAY* or ROENTGEN RAY* or magnetic resonance tomograph* or magnetization transfer imaging or MRI or NMR imaging or doptone or sonogram or sonograph* or ultrasonic detection* or ultrasonic scan*).mp. (1953129)

585 577 or 578 or 579 or 580 or 581 or 582 or 583 or 584 (3487175)

586 576 or 585 (3984532)

587 569 and 586 (2229)

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588 https://protect-us.mimecast.com/s/pDRhCzpn2kfDB5DSWp7Kd?domain=hydroxychloroquine.mp. or hydroxychloroquine/ (23217)

589 (CHLOROQUINOL or ERCOQUIN or HYDROCHLOROQUINE or HYDROCLOROQUINE or OXYCHLOROQUINE or PLAQUENIL or QUENSYL or SN 8137).mp. (1374)

590 588 or 589 (23239)

591 VISION SCREEN*.mp. or exp vision test/ (35560)

592 VISUAL FIELD TEST*.mp. or perimetry/ (12107)

593 exp optical coherence tomography/ or OPTICAL COHERENCE TOMOGRAPH*.mp. (59536)

594 (CAMPIMETR*OR PERIMETR* or VISUAL SCREEN* or OCT TOMOGRAPH* or SD OCT or vision test* or visual field exam* or visual field test*).mp. (20065)

595 591 or 592 or 593 or 594 (94350)

596 590 and 595 (422)

597 juvenile idiopathic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. or exp juvenile rheumatoid arthritis/ (20816)

598 juvenile chronic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. and (JIA or JRA or IDIOPATHIC).ti,ab. (109)

599 JUVENILE https://protect-us.mimecast.com/s/ee-1CkRoJ1Hl0xltVGL4i?domain=arthritis.mp. and (JIA or JRA or IDIOPATHIC).ti,ab. (965)

600 597 or 598 or 599 (20836)

601 https://protect-us.mimecast.com/s/r7x0ClYpK1HGKQGfyk_ye?domain=temporomandibular.mp. (27542)

602 TMJ.ti,ab. (9139)

603 ARTHRIT*.mp. (325914)

604 (costen's syndrome or COSTEN SYNDROME).ti,ab. (37)

605 601 or 602 or 604 (28456)

606 603 and 605 (1945)

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607 (oligoarthrit* or oligo-arthrit*).mp. (1898)

608 (oligoarticular* or "oligo-articular" or "oligo articular").ti,ab. (1821)

609 juvenile idiopathic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. or juvenile rheumatoid arthritis/ (20816)

610 (JIA or JRA).ti,ab. (9864)

611 609 or 610 (22532)

612 608 and 611 (1339)

613 607 or 612 (3111)

614 606 or 613 (4997)

615 adult/ or middle aged/ or young adult/ (6884305)

616 exp juvenile/ (3257587)

617 615 not (615 and 616) (5731897)

618 614 not 617 (3867)

619 600 not 617 (18650)

620 618 or 619 (20308)

621 limit 620 to (abstracts and human and english language and (article or article in press or "review")) (8795)

622 "stills disease".mp. (2591)

623 exp systemic juvenile idiopathic arthritis/ (1083)

624 SYSTEMIC-ONSET JUVENILE ARTHRIT*.mp. (23)

625 (JUVENILE SYSTEMIC-ONSET ARTHRIT* or JUVENILE SYSTEMIC-ONSET IDIOPATHIC ARTHRIT* or SYSTEMIC-ONSET JUVENILE IDIOPATHIC ARTHRITIS or JUVENILE SYSTEMIC ARTHRIT* or SYSTEMIC JUVENILE ARTHRIT* or JUVENILE SYSTEMIC IDIOPATHIC ARTHRIT* or SYSTEMIC JUVENILE IDIOPATHIC ARTHRIT* or SYSTEMIC JIA or SYSTEMIC-ONSET JIA or SYSTEMIC-ONSET JRA or SYSTEMIC-ONSET JUVENILE RHEUMATOID ARTHRIT* or JUVENILE SYSTEMIC-ONSET RHEUMATOID ARTHRIT* or SYSTEMIC JRA or SYSTEMIC JUVENILE RHEUMATOID ARTHRIT* or JUVENILE SYSTEMIC RHEUMATOID ARTHRIT*).mp. (2778)

626 622 or 623 or 624 or 625 (5106)

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627 juvenile idiopathic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. or exp juvenile rheumatoid arthritis/ (20816)

628 juvenile chronic https://protect-us.mimecast.com/s/vHjYCjRnG1HEJWEfWKdp0?domain=arthritis.mp. and (JIA or JRA or IDIOPATHIC).ti,ab. (109)

629 JUVENILE https://protect-us.mimecast.com/s/ee-1CkRoJ1Hl0xltVGL4i?domain=arthritis.mp. and (JIA or JRA or IDIOPATHIC).ti,ab. (965)

630 627 or 628 or 629 (20836)

631 626 or 630 (22378)

632 limit 631 to (abstracts and english language and (article or article in press or "review")) (10297)

633 621 or 632 (10870)

634 596 and 633 (3)

635 173 or 292 or 318 or 415 or 460 or 532 or 587 or 634 (6996)

636 case report/ (2386151)

637 editorial/ (617847)

638 letter/ (1025956)

639 636 or 637 or 638 (3822370)

640 635 not 639 (5651)

641 limit 640 to exclude medline journals (442)

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SUPPLEMENTARY APPENDIX 2: Evidence Report

2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis (JIA): Recommendations for Non-Pharmacologic Therapies, Medication Monitoring, Immunizations, and Imaging

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Prepared for: American College of Rheumatology

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Introduction

Critical outcomes

- Each table reports the summary of findings from randomized trials and/or observational studies reporting the critical outcomes. The critical outcomes, as chosen by the Core Team, varied among the different subgroups of pediatric patients with JIA (oligoarticular JIA, active TMJ arthritis, and systemic JIA with or without macrophage activation syndrome [MAS]).
- For oligoarticular JIA and TMJ arthritis, critical outcomes included quality of life measures, disease activity measures (pediatric ACR response, JADAS, active joint count, ESR/CRP, patient/parent global, MD global), ACR provisional criteria for clinical inactive disease, functional ability (CHAQ, PROMIS), joint damage requiring surgical intervention, significant limb length discrepancy, and significant or life-threatening adverse events (e.g. hospitalization, infection, malignancy). An additional critical outcome for TMJ arthritis was resolution of MRI findings consistent with active TMJ arthritis.
- For systemic JIA with or without MAS, critical outcomes included achievement of inactive disease, avoiding emergence of MAS, resolution of subclinical MAS, prevention or re-emergence/progression to overt MAS, resolution of overt MAS, mortality, ICU admission, hospital admission, prediction of persistent systemic disease activity at 6 months, response to treatment/inactive disease, sustained response to medication (no development of tolerance/antibodies), growth, ability to taper/discontinue steroids, prevention of exacerbation, minimizing side effects/medication toxicity (steroids), prediction of ability to wean treatment without disease flare, and proportion of durable inactive disease off therapy.
- Note that serious adverse events are rare, and thus it is quite difficult to achieve a statistically significant difference between groups for this outcome in randomized trials powered for efficacy outcomes that occur much more often.
- Not every study identified examined all critical outcomes. Each outcome was analyzed separately.

Interventions

- The following interventions were within the scope of this guideline:
    - NSAIDs
    - Glucocorticoids (oral and intra-articular injections for oligo JIA and TMJ arthritis; oral and intravenous for systemic JIA)
    - Non-biologic disease modifying anti-rheumatic drugs (DMARDs): this includes methotrexate, sulfasalazine, hydroxychloroquine and leflunomide for oligo JIA and TMJ arthritis, and methotrexate and calcineurin inhibitors for systemic JIA.
    - TNF inhibitors – only for oligo JIA and TMJ arthritis (adalimumab, etanercept, infliximab, golimumab, and certolizumab pegol).

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- Other biological response modifiers (OBRM) for oligo JIA and TMJ arthritis: abatacept, tocilizumab, rituximab, tofacitinib, and secukinumab).
- OBRM for systemic JIA: IL-1 inhibitors, IL-6 inhibitors, IL-18 inhibitors, JAK inhibitors, interferon gamma inhibitors, B cell inhibitors, and abatacept.
- Non-medical interventions for oligo JIA and TMJ arthritis: physical therapy, occupational therapy (oligo JIA only), dietary changes, and herbal supplements

Systematic Literature Review

- While randomized controlled trials (RCTs) were the preferred source of evidence, observational studies that directly or indirectly addressed PICO questions with little or no RCT evidence were also included.

Quality Assessment

- Quality assessment was performed separately for each outcome using the GRADE system, which results in one of four possible evidence grades that reflect level of confidence in the effect estimate: high, moderate, low, and very low.
- Study design is the starting point for quality assessment: randomized controlled trials (RCTs) start at high quality and observational studies start at low quality.
- Five factors can lower the quality of evidence grade: risk of bias, inconsistency, indirectness, imprecision, and publication bias.
- Risk of bias refers to limitations in study design or execution (e.g. lack of allocation concealment or blinding).
- Inconsistency refers to unexplained heterogeneity in results of studies evaluating the same outcome.
- Indirectness refers to lack of direct comparisons of interventions of interest (e.g. studies comparing drug A vs. placebo and drug B vs. placebo when the comparison of interest is drug A vs. drug B), lack of applicability in the interventions or populations being evaluated, or use of indirect (surrogate) outcome measures.
- Imprecision refers to uncertainty in the estimate of effect due to very low numbers of patients or events and/or wide 95% confidence intervals that cross a clinical decision threshold (i.e. between recommending and not recommending treatment).
- Publication bias refers to selective publication of studies that show greater treatment effects (i.e. negative studies are suppressed).
- Quality of evidence can vary from outcome to outcome. The final quality assessment for the PICO question is based on the critical outcome with the lowest quality assessment.
- The level of evidence listed in this report for either an individual paper or a group of papers is not meant to be an absolute statement about the quality of the study (or studies) under consideration. Rather, the intention is to rate the paper(s) *in relation to the question being asked in this guideline*. Because of this, a very well conducted study might actually be rated down in this evidence report, possible reasons including that the population or intervention being studied does not completely match the population or intervention being

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examined by the PICO question in this guideline (in other words, downgrading for indirectness). The level of evidence may also be downgraded due to imprecision in the effect estimate (wide confidence intervals that cross the line of no effect, or a low number of patients or events). A combination of these factors may result in quality of evidence from a well-conducted study being rated as low.

Presentation of effects

- The treatment effects from binary (yes or no) outcomes are presented as relative effects and absolute effects.
- Relative effects capture the difference between intervention and control in relative terms. For example, a 10% event rate in controls and a 5% event rate in the intervention represents a 50% relative risk reduction (10% - 5%/ 10%)
- The same difference represents a 5% absolute risk reduction (10% - 5% = 5%). In general, for patients, the absolute effect is the most important.
- Relative effects for dichotomous outcomes in the tables are expressed as relative risk (RR) or odds ratio (OR). RR is the default effect size because it is more easily interpretable, but under some circumstances RRs can lead to impossible numbers when calculating absolute risk differences. In such instances ORs were used instead of RRs.
- In the tables, when RR or OR is specified, the first drug (e.g. tocilizumab vs methotrexate, or methotrexate vs placebo) is the reference drug.

Evidence Summaries including Summary of Findings (= Tables under each PICO question, except some PICO questions for which no evidence was available)

- Direct comparisons are situations where trials directly compare drug A to drug B within one of the patient subgroups covered in this guideline.
- Indirect comparisons: Some studies do not include a direct comparison of drugs or interventions specified in a given PICO question. An example of this is trials that compare drug A to placebo, or an observational study where all patients received drug A and a pre-post comparison is made.

Interpreting the evidence

- It is important to take into account the information presented specifically as it relates to the question of interest. For example, when the only evidence for a given PICO question is indirect due to the comparison or patient population, it appropriately gets downgraded for indirectness as shown under the column labeled “indirectness.” Also, if the 95% confidence interval around an effect size is wide and crosses the line of no difference between treatments, the evidence for that outcome is downgraded due to imprecision. Study design and risk of bias also may result in downgrades in the quality of evidence. The overall quality of evidence takes all these factors into account, and is appropriately rated as high, moderate, low or very low. This quality of evidence is key to your decisions.

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Moving from evidence to recommendations

- In GRADE, recommendations can be either strong or conditional. Generally, strong recommendations are restricted to high or moderate quality evidence. Low quality evidence almost invariably mandates a weak recommendation.
- There are, however, situations in which low quality evidence can lead to strong recommendations. For instance, if there is low quality evidence favoring an intervention but high quality evidence of important harm then a strong recommendation against the intervention may be appropriate.

Bibliography of included studies

- Separate reference lists of studies included for each PICO question with an evidence base appear at the end of the summaries for each question. For two questions with a very large evidence base (PICO 23 and 55), we have placed reference lists after specific subsections rather than a single overall reference list for each question.

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Oligoarticular JIA

PICO 1: In children with oligoarticular JIA, should a trial of consistent NSAIDs be recommended?

Summary: The literature search revealed one randomized controlled trial (RCT)[1] and 2 observational studies[2, 3] that addressed this PICO question. The small, single center RCT provided indirect evidence by comparing scheduled naproxen (10mg/kg/day) to scheduled aspirin in 80 patients with JIA (65% oligoarticular). Aspirin as the comparator is not representative of current clinical practice. More subjects in the naproxen arm (30% compared to 5.3%) discontinued medication by week 24 for lack of response (RR 5.7); however, less in the naproxen group (12.5% compared to 52.6%) discontinued for side effects (RR 0.24). (Table 1). Definitions of improvement and lack of response were not described in detail and appear inconsistent with measures used in contemporary trials. Absolute change in patient global, physician global and active joint count at weeks 12 and 24 were reported, but no additional statistical analysis of these results was available (Table 2). There was no sub-analysis of oligoarticular patients.

One observational study provided direct comparison of three NSAIDs (ibuprofen, naproxen, indomethacin) as monotherapy in JIA, reporting no significant differences in "success" of NSAID trials (defined as attainment of inactive disease) among the three medications (52.6%, 54.1%, 54%, respectively).[3] 52% of these NSAID trials were in patients with oligoarticular JIA- sub-analysis comparing the three medications was not performed for oligoarticular JIA specifically. The overall success rate of NSAID monotherapy in patients with less than 5 affected joints was 59.5%. In a small prospective cohort of oligoarticular JIA patients, only 10.5% achieved clinical remission on NSAID (naproxen 20mg/kg/day or ibuprofen 30 mg/kg/day) monotherapy.[2]

Quality of evidence across all critical outcomes: Very low

Table 1. Data from RCT - Naproxen compared to Aspirin for Oligoarticular JIA [1]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Naproxen	Aspirin	Relative (95% CI)	Absolute (95% CI)		
Withdrawals due to side effects at week 24												

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Naproxen	Aspirin	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	not serious	not serious	serious [a]	serious[b]	none	5/40 (12.5%)	20/38 (52.6%)	**RR 0.24** (0.10 to 0.57)	**400 fewer per 1,000** (from 474 fewer to 226 fewer)	⊕⊕⊕◯ LOW	Favors naproxen
Improvement at week 24												
1	randomized trials	not serious	not serious	serious [a]	serious [b,c]	none	13/40 (32.5%)	8/38 (21.1%)	**RR 1.54** (0.72 to 3.30)	**114 more per 1,000** (from 59 fewer to 484 more)	⊕⊕◯◯ VERY LOW	
Lack of response at week 2												
1	randomized trials	not serious	not serious	serious [a]	serious [b]	none	12/40 (30.0%)	2/38 (5.3%)	**RR 5.70** (1.36 to 23.81)	**247 more per 1,000** (from 19 more to 1,000 more)	⊕⊕⊕◯ LOW	Favors aspirin

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Outdated comparator (aspirin)

b. Single small study

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c. Wide CI crosses significant effect and no-effect lines

Table 2. Additional data from observational studies and RCT data not suitable for GradePro

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
2329, Brik, 2005 [2]	Prospective cohort	5 years	19 oligoarticular JIA (16 persistent, 3 extended), age 2-14 with 5.1 +/- 3.3 years disease duration	Stepwise therapy: NSAID (naproxen 20mg/kg/day OR ibuprofen 30mg/kg/day) X 6-12 weeks, followed by methylprednisolone acetate IASI if not in clinical remission, followed by methotrexate 0.2mg/kg/week po for at least 6 months if steroid injection non-responder (defined as improvement for <4 weeks for each of 2 consecutive steroid injections)	2 (10.5%) responded to NSAIDs.
2581, Kvien, 1984 [1]	Single center randomized controlled trial	24 weeks	80 patients with oligo (52) or polyarticular (28) JIA	1:1 randomization to naproxen 10mg/kg/day or aspirin 75mg/kg/day	Change at week 12 from baseline (median values): - Patient global assessment: naproxen 0 aspirin 0 - Physician global assessment: naproxen –1.5, aspirin - 1 - Active Joint count: naproxen 0 aspirin 0 Change at week 24 from baseline (median values): - Patient global assessment: naproxen 0 aspirin 0 - Physician global assessment: naproxen -2, aspirin -2 - Active Joint count: naproxen – 1 aspirin -1 Patients with adverse reactions: naproxen 12, aspirin 30

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					* No additional statistical analysis was provided for these results.
3244, Chhabra, 2019 [3]	Retrospective analysis of prospective inception cohort	Median 10.1 mos (IQR 5.9, 14.9) for successful trials, 3.9 mos (2.4, 7) for unsuccessful trials	1352 JIA patients in inception cohort with adequate data to assess response to treatment trial using an n-of-1 approach. 532 (39.3%) oligo, with total 1635 medication trials in oligo JIA evaluated.	586 naproxen trials 67 indomethacin trials 26 ibuprofen trials 52.2% of all NSAID trials were in oligo JIA	NSAID success rate for joint count <5 was 59.5% (95%CI 55-64) Success of specific NSAIDs (in all patients, not oligoarticular specifically): Naproxen monotherapy: 54.1% success (49.5-58.6 95%CI) indomethacin monotherapy: 54% success (39.7-68.3) Ibuprofen monotherapy: 52.6% success (27.9-77.4)

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References:

1. Kvien, T. K., et al. (1984). "Naproxen and acetylsalicylic acid in the treatment of pauciarticular and polyarticular juvenile rheumatoid arthritis. Assessment of tolerance and efficacy in a single-centre 24-week double-blind parallel study." Scand J Rheumatol **13**(4): 342-350.
2. Brik, R., et al. (2005). "Low-dose methotrexate treatment for oligoarticular juvenile idiopathic arthritis nonresponsive to intra-articular corticosteroids." Clin Rheumatol **24**(6): 612-614.
3. Chhabra, A., et al. (2019). "Real-World Effectiveness of Common Treatment Strategies for Juvenile Idiopathic Arthritis: Results from a Canadian Cohort." Arthritis Care Res (Hoboken).

PICO 2: In children with oligoarticular JIA, should adding intraarticular glucocorticoids to initial therapy be recommended?

Summary: The literature search identified 14 observational studies that evaluated outcomes of intraarticular (IA) steroid injections in patients with oligo JIA; most studies used triamcinolone hexacetonide (THA) or triamcinolone acetonide (TA).

Two studies compared the use of THA versus TA in patients with oligo JIA and both found significantly better outcomes with THA[1, 2].

Breit et al.[3] compared IA THA in early onset oligo JIA to late onset oligo JIA and showed a longer duration of improvement in early onset; for early onset, the effect of IA steroids lasted a median of 121 weeks with late onset only lasting a median of 47 weeks. Another study[4] using IA THA that did not specify length of follow-up did not find a significant correlation between age of onset and treatment outcome.

Lanni et al.[5] evaluated freedom from synovitis flare at 1, 2 and 3 years respectively following IA THA injections and divided into those having 1 joint injected, 2 joints injected or 3 or more joints injected. At one year 70% of those with 1 joint injected remained free of synovitis flare, 61% at two years and 37% at three. The patients who had 2 or 3 or more joints injected had lower rates of freedom from synovitis flare, with lasting results decreased to 45/32/22% for 2 joints at years 1, 2 and 3 and 44/30/19% for those with 3 or more injected joints. Another study[6] that used both IA THA and TA injections reported that 41% of patients with persistent oligo JIA remained in remission (on and off medication) at a mean follow-up of 4 years.

Five studies looked at sustained remission at 6 months and all showed favorable and lasting benefit of IA steroid injections: one study[7] showed 69% lasting remission with IA THA, while another study[8] using IA THA reported remission in 81.6% of injected joints. A study[9] using IA TA found 65% overall but 81% for oligo JIA and only 59% for the other JIA types. The remaining study[10] used IA TA and showed 70% lasting remission at 6 months. One study[11] used IA THA for large joints and IA methylprednisolone for small or difficult to access joints. This study reported a remission rate of 59% for patients with oligo JIA.

Two studies evaluated different aspects of growth and development. Padeh et al.[12] conducted a retrospective cohort study comparing rates of growth retardation in patients with persistent oligo JIA who received either intraarticular TA (group I) or intraarticular TA plus DMARDs (group II; 75% of patients in this group received methotrexate) during a mean follow-up of 6 years. In group I, 30.6% had any growth retardation and 6.5% had severe growth retardation, while in group II, 44.4% had any growth retardation and 21.2% had severe growth retardation. However, a retrospective chart review comparing patients who did and did not receive IA THA showed a significant decrease in leg length discrepancies with the use of IA THA [13].

A prospective cohort study by Brik et al.[14] used IA methylprednisolone acetate and reported that 64% (11/17 patients) did not respond to this treatment. Nine of the non-responders were treated with low-dose MTX for a median duration of 15±3.8 months. Except for one patient with an extended disease course, all responded very well to treatment and went into remission after a median of 6.4±2.9 months, and none required additional IA injections after initiation of MTX treatment.

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Overall these studies support benefit for the use of IA THA or TA in early onset oligo JIA compared to other types of JIA and all studies showed minimal side effects. However, the evidence is very low quality due to the lack of control groups in most studies, confounding due to concomitant treatments (usually MTX) and because these studies do not specifically address the comparison of using IA steroids first to using other treatment regimens first.

Quality of evidence across all critical outcomes: Very low

Table 1. Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
1446 Marti 2008 [1]	Retrospective chart review	4 years	202 injections in 60 pts Oligo JIA -37 polyJIARF—15 4SOJIA 4ERA	THA /TA whichever was available	JIA significantly longer remission in joints of the upper extremities, followed by the knees Oligoarticular JIA: 102 injected joints; number of joints with flare: 67 (65.7%); duration of remission: mean 6.5 months. Concomitant use of methotrexate was the strongest predictive factor in the study and was highly significantly associated with a longer duration of remission both in the total cohort and in the subgroup of knee joints, whereas use of NSAR was not. Use of THA was significantly associated with longer remission (RR 0.77, p = 0.04 in Cox regression analysis, but this included all JIA subtypes in the study). No major side effects, such as infections, skin necrosis or avascular necrosis related to the steroid injections, were observed in our cohort Our results confirm the findings of the superiority of triamcinolone hexacetonide over triamcinolone acetonide for the knee joints.

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
785 Zulian 2003 [**Error! Reference source not found.**]	Prospective cohort	4 years	130 joints of 85 pts with oligo JIA: Persistent 87% Extended 13% ANA pos67% HLA B27+4.7% IA steroids given due to inadequate response to NSAIDs or persistent arthritis of single joint	70 THA or 60 TA (whichever available)	Compared groups: Response rate higher for THA (81.4%) versus TA 53.3% (6 months). THA 67.1% vs TA 43.3% at 12 months. THA 60% vs TA 33.3% at 24 months. The results showed that TH is more effective than TA in both short- and long-term follow-up. this study shows that IACS are effective and safe for the treatment of joint inflammation in JIA and may be used as the first-line therapy for the oligoarticular subtype
3684, Breit, 2000 [**Error! Reference source not found.**]	Cohort study	Multiple time points with longest being a mean of 64 (+/- 23.4) weeks	194 patients with JIA for a total of 1439 injected joints; 121 pts (62%) had oligo JIA, 20 pts (10%) had sJIA. All patients had insufficient response to oral or parental drug treatment (NSAID, DMARD, or corticosteroids)	Intraarticular triamcinolone hexacetonide	Children with early onset pauciarticular arthritis (EOPA) had the longest median duration of effect (121 weeks). Children with late onset pauciarticular arthritis (LOPA) had a median duration of effect of 47 weeks. In each group, the first injections had the longest median duration of improvement (EOPA 152 weeks, LOPA 50 weeks).
4007 Lepore 2002 [1]	Prospective cohort	Not reported	37 patients (81% fe m a l e s , 56% A NA+) with oligo JIA involving knees	IA TH after failing to respond to NSAIDs for two months.	Mean duration of remission was 13.9 months. 12 pts (7 ANA+) remission after a single injection; 13 patients (3 ANA+) had more than 6 months' remission then relapsed

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
			were treated. 18 pts were treated within 6 months of onset, 19 were treated more than 6 months after onset		12 patients (11 ANA+) relapse within 6 months of injection. Of 20 patients treated within 6 months of onset, 17 had remission 8 out of 17 retreated during relapse in remission (p = 0.03). The mean % of T + and of B CD5+ lymphocytes in synovial fluid was the same as nml subjects. The study did not find a significant correlation between age of onset and treatment response.
2747 Lanni, 2011 [5]	Retrospective cohort study	6 months to 3 years	440 JIA patients (171 persistent OJIA, 147 extended OJIA, 20 SJIA, 72 polyJIA)	Triamcinolone hexacetonide injected into one joint (n = 215), two joints (n = 107), three or more joints (n = 118)	The cumulative probability of survival without synovitis flare for patients injected in one, two, or three or more joints was 70, 45 and 44%, respectively, at 1 year; 61, 32 and 30%, respectively, at 2 years; and 37, 22 and 19%, respectively, at 3 years. Subcutaneous atrophy 2%.
3058 J. de Oliveira Sato 2014 [**Error! Reference source not found.**]	Retrospective analysis cohort	4 years	77 patients 254 treated joints, were reviewed. 83% oligoarticular subtype 57% had persistent oligoarticular course.	Triamcinolone hexacetonide was the most frequently used drug, though when it was unavailable, triamcinolone acetonide was used. Seventy-seven patients were submitted to 116 joint injection sessions,	41% of patients with persistent oligo JIA remained in remission (on and off medication) at a mean follow-up of 4 years.

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				with at least one treated joint. Twenty-three (29.9%) were submitted to one repeated session, 12 (15.6%) were submitted to two repeated joint injection sessions, three (3.9%) were submitted to three repeated sessions, and only one (1.3%) to more than three repeated sessions	
1439 A.Ravelli et.al. 2001 [7]	Prospective cohort	Enrolled from February 1996 - June 1999 Followed for 6 months	94 patients with JIA: 81 oligoarticular (66 persistently,15 extended) 4 RF-poly 5systemic 4 ERA	dose of 1 mg/kg (maximum 40 mg) triamcinolone hexacetonide with 0.5 ml lidocaine (2%) IA injections	The primary outcome measure was persistence of complete clinical response at 6 months, i.e., no evidence of synovitis clinically. At 6 months after the IAC injection, 65 (69%) patients showed a sustained complete clinical response, whereas 29 (31%) had had a recurrence of signs of synovitis.
1952 Padeh, 1998 [**Error!**	Single-arm study	More than 6 months	43 (60%) oligo JIA, 13 (18%) sJIA, poly JIA 5(7%), other 10(14%)	141 joints in OJIA patients were injected with	Full remission on oligo JIA patients: 115 (81.6%) of joints Failure in oligo JIA patients: 26 (18.1%)

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Reference source not found.]				triamcinolone hexacetonide.	Discontinuation of oral medication in 32 (74.4%) oligo JIA patients No infection or other serious complications occurred in any of the patients following the procedure.
1973 E. Unsal, 2008 [9]	Retrospective chart review	2000 to 2005. Tx w/IA TA at least 1 year prior to2000 were eligible	37 patients (15 girls, 22 boys; mean age 7.3 ± 3.7 yr) with JIA one or more intra-articular TA injections. The mean duration of illness was 4.7±2.9 yr. Ninety-five joints were injected with a total number of 125 injections.	A dose of 0.5 mg/kg and 1mg/kg of triamcinolone acetonide was injected for the small and large joints, respectively	Complete remission of the joint inflammation lasting at least for 6 months was obtained in 62 of 95 injections (65%). In patients with oligoarthritis, 21 of 26 injected joints (81%) were in full remission at six-months. However, only 41 of 69 (59%) injected joints in the other subtypes of JIA were in remission at six-month time period, and this rate was significantly lower ($P<0.01$).
1970 Hertzberger-ten Cate, 1991 [10]	Single-arm study	40 months	21 children with type 1 pauciarticular JIA.	20mg triamcinolone-acetonide and 1ml lidocaine (1%).	Signs of active arthritis resolved in all cases for 1-40 months (mean 15.2 months). Remission exceeding 6 months was seen in 19 knees (70%). Arthritis flared after 1-30 months in 17 knees (63%). No significant adverse reactions

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
950, Papadopoulo, 2013 [11]	Cohort study	At least 6 months	220 children with JIA, for a total of 1096 injected joints; 15 patients (6.8%) had sJIA, 109 (49.6%) had oligoJIA	Intraarticular joint injections simultaneously of at least 3 joints: triamcinolone hexacetonide for large joints; methylprednisolone for small or difficult to access joints	After injection, 14 out of 34 persistent oligo JIA patients experienced a flare, and 20 out of 34 patients were in remission. No serious adverse events or deaths occurred.
617 Padeh, 2011 [12]	Retrospective cohort study	Mean follow-up 6 (SD 3.7) years	95 patients with persistent oligo JIA	Patients treated by triamcinolone acetonide alone (group I) or by triamcinolone acetonide plus DMARDs (group II) 75% of group II patients received methotrexate.	Growth retardation was found in 35.8% of patients (z-score <0.3), including 11.6% with severe growth retardation (z-score <1.0). Growth retardation in each group: group I: any growth retardation, 30.6%; severe growth retardation, 6.5%; group II: any growth retardation, 44.4%; severe growth retardation, 21.2%. group II had a significantly higher rate of severe growth retardation than group I ($p < 0.05$). Elevated erythrocyte sedimentation rate values (≥40mm/1sth) indicated a significantly higher risk for growth retardation. All other clinical variables had no association with growth retardation.
3051 D.D. Sherry et.al.	Retrospective chart review	Diagnosed between January	30 children with oligo JRA <7 y.o.	WA children were given IA triamcinolone hexacetonide within 2 months of diagnosis	12 children received IA steroid injections; they had significantly less leg length discrepancy (LLD) compared to the control group ($p = 0.0005$). 50% (7/14) of control

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
1999 [13]		1990 and March 1995 LLD evaluation summer 1997	2 geographic groups: WA compared to NC	and repeated if synovitis recurred. Compared with NC children who were not treated with IA steroids LLD/TCM measured in 1997 Pts who rec'd IA steroids compared to those who had not: (leg length discrepancy=LLD, thigh circumference discrepancy=TCD)	group children had LLD compared to 0% in the IA steroid group (p = 0.002).
2329 Brik 2005 [14]	Prospective cohort	4 years	19 patients (age: 2–14 years, 18 females) with oligo JIA, 16 had a persistent course and 3 had an extended course of the disease	Low dose MTX given to pts who did not respond to IA methylprednisolone acetate injections (defined as duration of improvement lasting less than 4 weeks for 2 consecutive injections)	Forty-eight IA methylprednisolone injections were given to 17 patients; 11 (64%) of them did not respond to this treatment. Nine of the non-responders were treated with low-dose MTX for a median duration of 15±3.8 months. Except for one patient with an extended disease course, all responded very well to treatment and went into remission after a median of 6.4±2.9 months, and none required additional IA injections after initiation of MTX treatment.

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References:

1. Marti, P., Molinari, L., Bolt, I. B., Seger, R., & Saurenmann, R. K. (2008). Factors influencing the efficacy of intra-articular steroid injections in patients with juvenile idiopathic arthritis. Eur J Pediatr, 167(4), 425-430. doi:10.1007/s00431-007-0525-9

2. Zulian, F., Martini, G., Gobber, D., Agosto, C., Gigante, C., & Zacchello, F. (2003). Comparison of intra-articular triamcinolone hexacetonide and triamcinolone acetonide in oligoarticular juvenile idiopathic arthritis. Rheumatology (Oxford), 42(10), 1254-1259. doi:10.1093/rheumatology/keg358

3. Breit, W., Frosch, M., Meyer, U., Heinecke, A., & Ganser, G. (2000). A subgroup-specific evaluation of the efficacy of intraarticular triamcinolone hexacetonide in juvenile chronic arthritis. J Rheumatol, 27(11), 2696-2702.

4. Lepore, L., Del Santo, M., Malorgio, C., Presani, G., Perticarari, S., Prodan, M., . . . Tommasini, A. (2002). Treatment of juvenile idiopathic arthritis with intra-articular triamcinolone hexacetonide: evaluation of clinical effectiveness correlated with circulating ANA and T gamma/delta + and B CD5+ lymphocyte populations of synovial fluid. Clin Exp Rheumatol, 20(5), 719-722.

5. Lanni, S., Bertamino, M., Consolaro, A., Pistorio, A., Magni-Manzoni, S., Galasso, R., . . . Ravelli, A. (2011). Outcome and predicting factors of single and multiple intra-articular corticosteroid injections in children with juvenile idiopathic arthritis. Rheumatology (Oxford), 50(9), 1627-1634. doi:10.1093/rheumatology/ker165

6. de Oliveira Sato, J., Albuquerque Pedrosa Fernandes, T., Bicalho do Nascimento, C., Corrente, J. E., & Saad-Magalhaes, C. (2014). Probability of remission of juvenile idiopathic arthritis following treatment with steroid joint injection. Clin Exp Rheumatol, 32(2), 291-296.

7. Ravelli, A., Manzoni, S. M., Viola, S., Pistorio, A., Ruperto, N., & Martini, A. (2001). Factors affecting the efficacy of intraarticular corticosteroid injection of knees in juvenile idiopathic arthritis. J Rheumatol, 28(9), 2100-2102.

8. Padeh, S., & Passwell, J. H. (1998). Intraarticular corticosteroid injection in the management of children with chronic arthritis. Arthritis Rheum, 41(7), 1210-1214.

9. N., Günay, T., . . . Unsal, E. (2011). Performance of tuberculin skin test and interferon gamma assay for the diagnosis of latent tuberculosis infection in juvenile idiopathic arthritis. Clin Rheumatol, 30(9), 1189-1193.

10. Hertzberger-ten Cate, R., de Vries-van der Vlugt, B. C., van Suijlekom-Smit, L. W., & Cats, A. (1991). Intra-articular steroids in pauciarticular juvenile chronic arthritis, type 1. Eur J Pediatr, 150(3), 170-172. doi:10.1007/bf01963559

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11. Papadopoulou, C., Kostik, M., Gonzalez-Fernandez, M. I., Bohm, M., Nieto-Gonzalez, J. C., Pistorio, A., . . . Ravelli, A. (2013). Delineating the role of multiple intraarticular corticosteroid injections in the management of juvenile idiopathic arthritis in the biologic era. Arthritis Care Res (Hoboken), 65(7), 1112-1120.

12. Padeh, S., Pinhas-Hamiel, O., Zimmermann-Sloutskis, D., & Berkun, Y. (2011). Children with oligoarticular juvenile idiopathic arthritis are at considerable risk for growth retardation. J Pediatr, 159(5), 832-837.e831-832.Camlar, S. A., Makay, B., Appak, O., Appak, Y. C., Esen,

13. Sherry, D. D., Stein, L. D., Reed, A. M., Schanberg, L. E., & Kredich, D. W. (1999). Prevention of leg length discrepancy in young children with pauciarticular juvenile rheumatoid arthritis by treatment with intraarticular steroids. Arthritis Rheum, 42(11), 2330-2334.

14. Brik, R., Gepstein, V., & Berkovitz, D. (2005). Low-dose methotrexate treatment for oligoarticular juvenile idiopathic arthritis nonresponsive to intra-articular corticosteroids. Clin Rheumatol, 24(6), 612-614. doi:10.1007/s10067-005-1116-7

PICO 3: In children with oligoarticular JIA, should adding oral steroids to initial therapy be recommended?

Summary: The literature search identified one retrospective, cross-sectional study that indirectly addressed this PICO question.[1] This study showed that the development of adrenal insufficiency (AI) in JIA patients was a rare occurrence when low dose glucocorticoids (<7.5mg prednisolone) was used. Signs of AI occurred in only 4/61 patients. Those who had AI all had oligo-articular JIA, were female, and were younger at the time of their JIA diagnosis and at the time of this study. All patients were treated for at least 6 months with low dose steroids and were off steroids for 3 months when AI was assessed. There was no statistical difference in the development of AI in relationship to steroid duration or period of cessation.

Quality of evidence across all critical outcomes: Very Low

Table 1. Data from Observational Study

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
87, Sadeghi et al. 2019	Cross sectional study	2 year study period 2014-2016	36 patients with JIA 25 females (69.4%)	Study designed to assess adrenal	The AI diagnosis was made if the first level of plasma cortisol was less than 3 micrograms/dL and the second level was less than 20 micrograms/dL.

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
			Mean age 8.2 years at time of study +/- 3.4 years. The mean age at the time of diagnosis was 6.3 +/-3.2 years. Oligoarticular (32 cases, 88.9%) Systemic (4 cases, 11.1%)	insufficiency (AI) in children with JIA undergoing treatment with low-dose corticosteroids All were treated with prednisolone (maximum dose of 7.5 mg for at least six months); AI was tested via blood samples at least 3 months after stopping steroids.	The mean plasma cortisol level was 13.1 +/-6.2 micrograms/dL before ACTH administration and 30.8+/-10.5micrograms/dL after ACTH administration. Four cases had AI, all of whom were female with oligo-articular arthritis. The age at the time of study (p 0.049) and the age at disease onset (p 0.043) were significantly different between cases with and without AI. Cases with AI had younger ages for disease onset (3.6 +/- 1.9 years vs 6.6 +/- 3.1 years) and younger ages at time of study (5.2 +/- 2.3 years vs. 8.6 +/-3.3 years) The duration of steroid therapy for those with AI vs no AI (19.9 +/-3 months vs 17.6 +/- 5.6 months) and steroid cessation (3.5 +/- 1 month vs 3 +/- 1 month) was not statistically significant among those with AI vs those without AI.

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References

1. Sadeghi P, Yahya A, Vahid Z, Moayeri Z. Adrenal Insufficiency in Children with Juvenile Idiopathic Arthritis (JIA) Treated with Prednisolone. J Compr Ped. In Press(In Press):e64681.;113:860-864. May, 2019.

PICO 4: In children with oligoarticular JIA, should a specific steroid type be recommended for intraarticular injection?

Summary: The literature search identified one prospective controlled cohort study[1], one randomized controlled trial (RCT)[2] and one retrospective cohort study[3] that addressed this PICO question. All studies provided a direct drug comparison (triamcinolone hexacetonide vs triamcinolone acetonide). The prospective cohort study[1] exclusively enrolled patients with oligo JIA (87% persistent oligo, 13% extended oligo), while the RCT[2] included only 59% of patients with persistent oligo JIA (the remainder had extended oligo or poly JIA). The RCT enrolled patients with symmetrical joints with a similar degree of inflammation; the joints were randomized to receive acetonide or hexacetonide. Both studies showed superiority of hexacetonide over acetonide in response rates and relapse rates from 6 to 24 months, even when the dose of acetonide was doubled relative to hexacetonide. Since both studies were conducted by the same group of authors at the same institution, the reproducibility of the findings at other institutions is unclear. The results of the retrospective cohort study were not presented by disease type and included sJIA, polyarticular JIA, and oligoarticular JIA. The time to relapse for all first joint injections and all first knee injections was longer with triamcinolone hexacetonide compared to triamcinolone acetonide.

Although the prospective cohort study and the RCT had risk of bias and imprecision in effect estimates, the consistency of the results that remained unchanged even when the acetonide dose was doubled provided low-quality evidence that hexacetonide is superior to acetonide for intraarticular injection in patients with oligo JIA.

Quality of evidence across all critical outcomes: Low

Table 1. Triamcinolone Hexacetonide vs. Triamcinolone Acetonide (equal doses) – Prospective Controlled Cohort Study with Blinding[1]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TH	TA	Relative (95% CI)	Absolute (95% CI)		
Response rate at 6 months												
1	Prospective cohort study	serious [a]	not serious	not serious	serious [b]	none	59/70 (84.3%)	32/60 (53.3%)	**RR 1.58** (1.22 to 2.04)	**309 more per 1,000** (from 117 more to 555 more)	⊕⊕◯◯ LOW	Favors TH

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TH	TA	Relative (95% CI)	Absolute (95% CI)		
Response rate at 12 months												
1	Prospective cohort study	serious [a]	not serious	not serious	serious [b]	none	47/70 (67.1%)	26/60 (43.3%)	**RR 1.55** (1.11 to 2.16)	**238 more per 1,000** (from 48 more to 503 more)	⊕⊕◯◯ LOW	Favors TH
Response rate at 24 months												
1	Prospective cohort study	serious [a]	not serious	not serious	serious [b]	none	42/70 (60.0%)	20/60 (33.3%)	**RR 1.8** (1.2 to 2.7)	**267 more per 1,000** (from 67 more to 567 more)	⊕⊕◯◯ LOW	Favors TH
Relapse at 6 months												
1	Prospective cohort study	serious [a]	not serious	not serious	serious [b]	none	13/70 (18.6%)	28/60 (46.7%)	**RR 0.40** (0.23 to 0.70)	**280 fewer per 1,000** (from 359 fewer to 140 fewer)	⊕⊕◯◯ LOW	Favors TH
Relapse at 12 months												

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TH	TA	Relative (95% CI)	Absolute (95% CI)		
1	Prospective cohort study	serious [a]	not serious	not serious	serious [b]	none	23/70 (32.9%)	34/60 (56.7%)	**RR 0.58** (0.39 to 0.87)	**238 fewer per 1,000** (from 346 fewer to 74 fewer)	⨁⨁◯◯ LOW	Favors TH

Relapse at 24 months

1	Prospective cohort study	serious [a]	not serious	not serious	serious [b]	none	28/70 (40.0%)	40/60 (66.7%)	**RR 0.60** (0.43 to 0.84)	**267 fewer per 1,000** (from 380 fewer to 107 fewer)	⨁⨁◯◯ LOW	Favors TH

Kaplan–Meier estimate of incidence rate of arthritis flare (months of follow-up*0.1)

1	Prospective cohort study	serious [a]	not serious	not serious	serious [b]	none	14/1000 (1.4%)	42/1000 (4.2%)	**RR 0.33** (0.18 to 0.61)	**28 fewer per 1,000** (from 34 fewer to 16 fewer)	⨁⨁◯◯ LOW	Favors TH

Survival rate at 24 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TH	TA	Relative (95% CI)	Absolute (95% CI)		
1	Prospective cohort study	serious [a]	not serious	not serious	serious [b]	none	46/70 (65.7%)	24/60 (40.0%)	**RR 1.64** (1.15 to 2.34)	**256 more per 1,000** (from 60 more to 536 more)	⨁⨁◯◯ LOW	Favors TH

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. No randomization or allocation concealment

b. Single study

Table 2. Triamcinolone Hexacetonide vs. Triamcinolone Acetonide (double dose of TA) – Randomized Controlled Trial[2]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TH 1 mg/kg	TA 2 mg/kg	Relative (95% CI)	Absolute (95% CI)		
Relapse by 24 months												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	6/39 (15.4%)	21/39 (53.8%)	**RR 0.29** (0.13 to 0.63)	**382 fewer per 1,000** (from 468 fewer to 199 fewer)	⨁◯◯◯ VERY LOW	Favors TH

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TH 1 mg/kg	TA 2 mg/kg	Relative (95% CI)	Absolute (95% CI)		
Sustained response at 6 months												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	35/39 (89.7%)	24/39 (61.5%)	**RR 1.46** (1.11 to 1.91)	**283 more per 1,000** (from 68 more to 560 more)	⨁◯◯◯ VERY LOW	Favors TH
Sustained response at 12 months												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	33/39 (84.6%)	19/39 (48.7%)	**RR 1.74** (1.23 to 2.46)	**361 more per 1,000** (from 112 more to 711 more)	⨁◯◯◯ VERY LOW	Favors TH
Sustained response at 24 months												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	30/39 (76.9%)	15/39 (38.5%)	**RR 2.00** (1.30 to 3.08)	**385 more per 1,000** (from 115 more to 800 more)	⨁◯◯◯ VERY LOW	Favors TH

Kaplan–Meier estimate of incidence rate of arthritis flare (months of follow-up*0.1)

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TH 1 mg/kg	TA 2 mg/kg	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	16/1000 (1.6%)	43/1000 (4.3%)	**RR 0.37** (0.21 to 0.66)	**27 fewer per 1,000** (from 34 fewer to 15 fewer)	⊕◯◯◯ VERY LOW	Favors TH

Survival (no flare) by 24 months

1	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	25/39 (64.1%)	13/39 (33.3%)	**RR 1.92** (1.16 to 3.18)	**307 more per 1,000** (from 53 more to 727 more)	⊕◯◯◯ VERY LOW	Favors TH

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Randomization, allocation concealment not described

b. Only 59% of patients have persistent oligo JIA

c. Single study

Table 3. Data from Other Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
1096 Eberhard 2012 [3]	Retrospective Cohort study	8 year period, 15 month	186 patients, 794 joint injections	IA joint injections: TH – 40mg knee, 30mg ankle and elbow, 20mg wrist	(Results not presented by disease type) Time to relapse: (all first joint injections)

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		minimum follow up	(15 sJIA, 49 poly, 179 oligo)	TA – 80mg knee, 60mg ankle and elbow, 40mg wrist	TH (n=111) = 10.47 ± 0.42 months TA (n=70) = 8.66 ± 0.59 months, p<0.001 (first knee injection only) TH (n=89) = 11.04 ± 0.44 months TA (n=56) = 8.99 ± 0.65 months, p <0.001

References:

1. Zulian, F., et al. Comparison of intra-articular triamcinolone hexacetonide and triamcinolone acetonide in oligoarticular juvenile idiopathic arthritis. Rheumatology 2003;42:1254–1259.
2. Zulian, F. et al. Triamcinolone acetonide and hexacetonide intra-articular treatment of symmetrical joints in juvenile idiopathic arthritis: a double-blind trial. Rheumatology 2004 Oct;43(10):1288-91.
3. Eberhard, B. A., et al. (2011). A dose schedule for intraarticular steroids in juvenile arthritis. J Rheumatol 2011;39(2): 374-376.

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PICO 5. In children with oligoarticular JIA, should DMARD therapies be recommended, and should there be any preferred order of treatment: methotrexatate (subcutaneous or oral), leflunomide, sulfasalazine, and/or hydroxychloroquine?

Summary: Literature searches identified one randomized controlled trial (RCT)[1] and 12 observational studies addressing this PICO question. There were 4 prospective cohorts [3, 6, 11, 12] and 8 retrospective cohorts [2, 4, 5, 7, 8, 9, 10, 13].

Ravelli et al.[1] prospectively randomized children at 10 hospital units in Italy with oligoarticular JIA to receive either intraarticular corticosteroid joint injections alone or injections in combination with oral methotrexate (MTX) therapy. The primary outcome was remission of disease at 12 months. Multivariable analysis (that accounted for treatment effect and ESR) showed that the addition of MTX was protective against arthritis flare (OR 0.53, 95% CI 0.27-1.01; p=0.05). In the intention to treat analysis for remission of all joints at 12 months, there was no significant difference (p=0.48) between those that received steroid injections alone compared to those who also received MTX in addition to injections. Time to arthritis flare was found to be longer for those who had the addition of MTX (median 10.1 months, 95% CI 7.6 to > 16) vs those with injections alone (median 6 months, 95% CI 4.6-8.2).

Collectively, 8 cohort studies [2, 3, 4, 5, 6, 7, 8, 9] evaluated MTX in the setting of JIA. Bava et al.[2] found that those with oligoarticular JIA had a higher proportion of patients achieve inactive disease on MTX compared to their systemic and ERA counterparts. In total, 54.8% of oligoJIA patients were able to achieve inactive disease. van Dijkhuizen et al.[3] did not study efficacy but looked at MTX tolerance. They found that 54.5% of oligoJIA patients tolerated MTX, whether oral or subcutaneous. No subanalysis was done in this population to ascertain which formulation (SC or PO) was more tolerated in those with oligo JIA. Albarouni et al.[4] reported that 70% of oligo JIA patients achieved an ACR Pedi 70 response to MTX at 12 months. Klein et al.[5] reported no significant difference between oral and subcutaneous administration of methotrexate on the ACR Pedi 50 and 70 scores at 6 and 12 months. Franova et al.[6] aimed to ascertain the benefit of adding MTX to achieve an inactive disease state, however, limited oligo JIA data makes this study less relevant to the PICO question. Two other cohort studies[7, 8] also had a small percentage of oligo JIA patients but reported remission rates of 54% to 58% following MTX treatment. Finally, Padeh et al.[9] conducted a retrospective cohort study comparing rates of growth retardation in patients with persistent oligo JIA who received either intraarticular triamcinolone acetonide (TA) (group I) or intraarticular TA plus DMARDs (group II; 75% of patients in this group received methotrexate) during a mean follow-up of 6 years. In group I, 30.6% had any growth retardation and 6.5% had severe growth retardation, while in group II, 44.4% had any growth retardation and 21.2% had severe growth retardation.

Three cohort studies [10, 11, 12] focused on sulfasalazine treatment. Chen et al. [10] reported that 100% of oligoarticular JRA patients demonstrated clinical improvement and 90.9% achieved clinical remission by a mean of 4.7 months on sulfasalazine. Varbanova et al. [11] concluded that children with pauciarticular JRA showed the highest prevalence of responders (90%) compared to the systemic and polyarticular subgroups. In the study by Imundo et al.[12], most of the pauciarticular JRA patients showed clinical improvement (77%) and a small number achieved remission (26%). When examining ANA positive female patients in this subgroup, 88% showed significant improvement and 44% achieved remission.

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Foeldvari et al.[13] was the only study identified that examined leflunomide. This study was limited in that only 25.9% of the JIA patients had persistent oligoarticular disease and there was limited subgroup analysis data available. The authors reported that 20% of those with persistent oligoJIA achieved disease remission. Several concomitant medications were permitted to be given during this study making it difficult to ascertain the true benefit of leflunomide.

No studies were identified which evaluated hydroxychloroquine in the oligoarticular JIA population.

The RCT was rated as low quality evidence (Table 1) and the remaining studies were rated as very low due to the observational design and lack of relevant control groups. The quality of evidence score for methotrexate was based on the evidence from the RCT.

Quality of evidence across all critical outcomes: Low for methotrexate, Very low for other DMARDs

Table 1. Data from Randomized Controlled Trials[1]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Steroids + MTX	Steroids	Relative (95% CI)	Absolute (95% CI)		
Inactive disease at 12 months												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	38/105 (36.2%)	27/102 (26.5%)	**OR 1.58** (0.87 to 2.85)	**98 more per 1,000** (from 26 fewer to 242 more)	⊕⊕◯◯ LOW	
New-onset arthritis after treatment initiation												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	38/102 (37.3%)	38/105 (36.2%)	**OR 1.05** (0.59 to 1.84)	**11 more per 1,000** (from 111 fewer to 149 more)	⊕⊕◯◯ LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Steroids + MTX	Steroids	Relative (95% CI)	Absolute (95% CI)		
Time to arthritis flare in months												
1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	105	102	-	MD **4.1 higher** (1.27 higher to 6.93 higher)	⨁⨁◯◯ LOW	Favors steroids + MTX

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference; **MTX**: Methotrexate

Explanations

a. Open-label RCT

b. Wide CI crosses significant effect and no-effect lines

c. Single study

Table 2. Additional Data from RCT and Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
1960, Ravelli, 2017 [1]	Prospective, randomized open label trial	4 years	Children younger than 18 years of age with oligoarticular JIA (per ILAR criteria) who were candidates to receive joint injection in at least 2 or more	Intra-articular steroids: triamcinolone hexacetonide for large jts at a dose of 1 mg/kg (max 40 mg) in knees and shoulders; 0.75 mg/kg (max 30 mg) in ankles and elbows and 0.25-0.5 mg/kg (max 20 mg) in wrists	There were 102 patients in intraarticular steroids alone group and 105 patients in the steroids + MTX group There was a lower cumulative probability of remission of arthritis in all injected joints at 6 months and 12 months in children allocated to steroids alone (49%, CI 39-58; 35%, 25-44 respectively) than in children assigned intraarticular steroids + MTX (67%, 56-75 and 46%, 35-56) Analysis of imputed covariate and outcome data in a univariable logisitic regression model showed no significant effect for the addition of MTX (OR 0.69, 95% CI 0.38-1.24,

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
			joints or in 1 joint if they had had a prior joint injection in the previous 12 months; patients who received an intraarticular steroid injection in 1 knee in the previous 12 months were excluded Exclusion criteria included: prior treatment w/ MTX or a biologic, administration of systemic or intraarticular steroids in the 3 months before enrollment Patients could be on concomitant NSAIDs at outset, but these had to be discontinued at enrollment	Methylprednisolone acetate for smaller jts at a dose of 5-10 mg for small hand and foot joints and 20-40 mg for subtalar and intertarsal jts Methotrexate was given orally at a dose of 15 mg/m2 (max 20 mg) once a week plus folinic acid (25-50% of the methotrexate dose in mg) MTX was started w/in 1 week of jt injections Clinical assessments performed at 1, 3, 6, 12 mos	p=0.22). However, multivariable analysis that included treatment effect and ESR showed that concomitant administration of MTX was protective against arthritis flare (OR 0.53, 95% CI 0.27-1.01, P=0.05) Hazard ratio of flare of arthritis in injected joints for intra articular steroids plus MTX vs steroids alone in univariable analysis was 0.67 (95% CI 0.46-0.97, p=0.0321). In multivariable models, the HR adjusted for ESR was 0.55 (95% CI 0.37-0.81, p=0.003). A higher ESR was a/w greater risk of flare HR 1.02 (95% CI 1.01-1.02, p=0.0002)

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
2991, Bava, 2019 [2]	Retrospective cohort, single arm	13 years	JIA patients (defined via ILAR criteria) that were using MTX as sole DMARD were included. Patients previously treated with any biologic DMARD were excluded. Previous treatment with other synthetic DMARDs or concomitant or previous administration of nonsteroidal anti-inflammatory drugs and systemic or intra-articular corticosteroids was allowed. In total, there were 375 patients included of which 24% had persistent oligoarthritis	Median MTX dose was 12.8 mg/m2 for all patients State of inactive disease was evaluated per Wallace criteria In patients with oligoarthritis at presentation, all active joints were injected with corticosteroid	Methotrexate was more commonly administered subcutaneously. Of the 174 total oligoarthritis patients studied (includes persistent and extended), 49 (33.8%) did not achieve inactive disease while 125 (54.8%) did. 61% of patients achieved ID after a median of 1.7 years from the start of MTX therapy. The relative frequency of favorable outcome was higher among patients with oligoarthritis than in those with ERA or systemic arthritis; an equal proportion of patients with polyarthritis reached or did not reach ID. It appears that persistent and extended oligo were investigated together as they studied patients according to 'functional phenotypes.'

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
			patients were grouped in the functional phenotypes of oligoarthritis (4 or fewer affected joints), polyarthritis (5 or more affected joints), systemic arthritis, and ERA		
2478, van Dijkhuizen, 2016 [3]	Prospective, Cross sectional, observational cohort study	4 years	190 JIA patients (defined by ILAR criteria) of which 44 (23%) had persistent oligo JIA; methotrexate could be given PO or subcutaneously; additional meds were permitted and included: NSAIDs, prednisone, folic acid, etanercept, adalimumab, sulfasalazine, hydroxychloroquine; Route of administration	methotrexate intolerance severity score (MISS) was obtained on each of the patients; The MISS consists of 12 questions distributed over four domains, being abdominal pain, nausea, vomiting and behavioural symptoms. The first three domains each assess experiencing symptoms after intake of MTX, anticipatory (before intake) and/or associative (when thinking of MTX) complaints. The behavioural domain assesses crying, irritability,	24 patients (54.5%) were tolerant to methotrexate, while 20 (45%) were intolerant 17 patients with oligo JIA were exclusively PO while 18 patients were exclusively given the subcutaneous form. The odds of MTX intolerance were higher in patients using MTX exclusively SC compared to exclusively PO (adjusted odds ratio 3.37 [95% confidence interval 1.19–10.0]). THIS STAT IS FOR MTX INTOLERANCE OVERALL, NOT JUST FOR OLIGO JIA.

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
			was categorised as exclusively PO, exclusively SC, switch from PO to SC and switch from SC to PO	restlessness and refusal to take MTX. The items can be assigned 0 (no symptoms), 1 (mild), 2 (moderate) or 3 (severe) points. The MISS was calculated as the sum of the questionnaire, while blank questions were assigned 0 points. The score could range from 0 to 36. A patient was considered intolerant if she had a score above the validated cut point of 6 points in concert with at least one associative, anticipatory or behavioural symptom	
3002 Albarouni, 2014 [4]	Retrospective cohort study	3-12 months	731 JIA patients (207 oligoarticular, 25 sJIA)	MTX (dose unclear)	PedACR 30 Response at 3 mos: Oligo: 159/207 PedACR 70 Response at 12mos: Oligo: 145/207
1246, Klein, 2012 [5]	Retrospective cohort study	4 years	411 eligible patients, patients with JIA (all subtypes, diagnosis made by ILAR criteria) who had newly started	259 patients (63%) received oral methotrexate and 152 (37%) received subcutaneous methotrexate; in both a comparable weekly dose was used (0.4 mg/kg for those with oral and 0.42 for those with subcutaneous); ACR	*In both groups, persistent oligoarthritis was the predominant JIA subtype *ACR Pedi 30 scores were reached slightly more frequently in the subcutaneous treatment group *ACR Pedi 50 and 70 scores were documented in 64 and 51% of the patients in the oral group and 76 and 54% of the subcutaneous group. None of the differences were significant.

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
			methotrexate and were documented in the registry, consecutively studied; 94 (36%) had persistent oligoarthritis and were on oral methotrexate, 42 patients (28%) were taking subcutaneous methotrexate Patients had no previous or concomitant treatment with biologic agents. Steroids (either oral or intraarticular) were permitted.	Pedi 30/50/70 was assessed after 6 and 12 months of therapy	**OF NOTE STUDY HAS FEWER THAN 50% (ONLY 33%) PERSISTENT OLIGOARTHRITIS PATIENTS OF THE TOTAL # OF PATIENTS STUDIED
2463, Franova, 2016 [6]	Prospective cohort study	1 year	55 JIA patients starting MTX treatment for active disease (at least 1 joint with synovitis), recruited consecutively, under 18 years of age; 45	Patients on oral or subcutaneous methotrexate, dosed weekly at ~ 15 mg/m2; Patients evaluated every 3 months for 1 year; ACRPedi, JADAS, Clinically inactive disease, methotrexate intolerance severity score and adverse events were recorded	32.7% (n=18) of the patients had persistent oligoarticular disease At 12 months of follow up, the median JADAS score for those with persistent oligoarthritis (10 patients at that point responded) was 5.6 Clinically inactive disease was reached in 17 patients (30.9% of all the JIA patients studied, not just oligo) at month 6 and in 31 (56.4%) at month 12. There was no differene in the time to inactivity btwn various JIA subtypes.

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
			patients received subcutaneous MTX, 10 received oral Concomitant medications included: oral corticosteroids and intraarticular corticosteroids		Neither the rate nor the extent of therapeutic response was influenced by JIA subtype or the route of MTX administration. Persistent decrease in JADAS seen over a 12 monthtime frame for those with persistent oligoarthritis.
1244 Lin, 2000 [7]	Retrospective cohort study	1.3-18.6 years	52 JIA patients (13 oligoarticular, 17 sJIA)	MTX 9-10mg/m2/week	Safety: 25% of patients had adverse effects, all minor aside from 1 patient with HSV reactivation - Clinical improvement: oligo 11/13; - Remission: oligo 7/13; - A significant number of patients had reduction of steroid dose or discontinuation of steroids
1048 Gottlieb, 1997 [8]	Retrospective cohort study	1-62 months	101 JIA patients (19 oligoarticular, 25 sJIA); 25 JIA patients for withdrawal portion (6 oligoarticular, 4 sJIA)	MTX 0.2-0.7mg/m2/dose – outcomes after discontinuation	Response to MTX: - Oligo: 0/19 none, 2/19 mild, 6/19 moderate, 11/19 complete; mean 9 months to control After discontinuation of MTX: - Oligo: 3/6 remission, 3/6 relapse
617 Padeh, 2011 [9]	Retrospective cohort study	Mean follow-up 6 (SD 3.7) years	95 patients with persistent oligo JIA	Patients treated by triamcinolone acetonide alone (group I) or by triamcinolone acetonide plus DMARDs (group II) 75% of group II patients received methotrexate.	Growth retardation was found in 35.8% of patients (z-score <0.3), including 11.6% with severe growth retardation (z-score <1.0). Growth retardation in each group: group I: any growth retardation, 30.6%; severe growth retardation, 6.5%; group II: any growth retardation, 44.4%; severe growth retardation, 21.2%.

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					group II had a significantly higher rate of severe growth retardation than group I ($p < 0.05$). Elevated erythrocyte sedimentation rate values (≥40mm/1sth) indicated a significantly higher risk for growth retardation. All other clinical variables had no association with growth retardation.
3704, Chen, 2002 [10]	Retrospective cohort study	7 years	24 children with JRA (diagnosis made according to ACR criteria) treated with oral sulfasalazine; All patients had received NSAIDs, 17 received sulfasalazine and azathioprine; there were 11 with oligoarticular disease, 6 polyarticular and 7 systemic	Initial dose of sulfasalazine averaged 21.6 mg/kg/day; clinical and lab assessments of disease activity were performed at baseline and repeated monthly for 3 months following initiation of SSZ; thereafter, evaluations were completed every 3 months or when a flare was suspected; evaluated # of jts with active arthritis, lab parameters; clinical improvement was defined as the absence of systemic features for at least 2 consecutive months and a more than 50% reduction in the # of jts with active arthritis	Of oligoarticular patients: 100% (11 patients) showed clinical improvement, with a mean duration of 3.2 months before improvement 90.9% (10 patients) exhibited clinical remission with a mean duration of 4.7 months before clinical remission 81.8% (9 patients) showed improvement in their labs on treatment with a mean duration of 7.1 months before laboratory improvement 63.6% (7 patients) showed laboratory remission with a mean duration of 6.4 months before laboratory remission **OF NOTE, STUDY HAS FEWER THAN 50% (ONLY 45%) WITH PERSISTENT OLIGOARTHRITIS OF THE TOTAL # OF PATIENTS STUDIED
3711, Varbanova, 1999 [11]	Prospective cohort	Unclear	32 JCA children (using EULAR criteria); (10 poly, 21 pauci, 1 systemic) Concomitant medication: NSAIDs	Sulfasalazine given as 40 mg/kg in 2-3 divided doses, titrating up by 1/3 to achieve maximal dose at 3 weeks; if patients entered remission in the 1st year, they were given 25 mg/kg/day; obtained labs twice during the first month, once a month up to the third	Those w/ pauciarthrits showed the greatest response to the treatment in that 19/21 (90%) showed response (this was the only outcome shared for this subgroup)

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				month, and then every 3 months following that Disease severity was assessed based on 1) # jts with active synovitis, 2) # jts with limited ROM, 3) ESR, 4) pain, 5) physician's global, 6) patient/parent global; assessment was conducted q3 months; a point was given for each parameter if it improved > 50% Nonresponders: < 50% or fewer than 3 pts (within this were insignificant responders which showed > 30% but < 50% improvement; unchanged < 30% improvement; deterioration > 30% worsening of the indices) Complete Remission: if 5 of the following signs were absent for at least 2 months: 1) symptoms of inflammatory joint pain, 2) morning stiffness, 3) fatigue, 4) synovitis on jt exam, 5) progression of radiographic damage on sequential radiographs, 6) elevated ESR or CRP	
3705, Imundo, 1996 [12]	Prospective cohort	3 years	139 JRA children (using ACR criteria) that	Sulfasalazine given as a mean dose of 31 mg/kg/day divided BID, max 3g/day;	There were 69 pauciarticular patients. 16 of these were ANA positive females < 8 years of age.

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
			demonstrated active arthritis (persistent effusion, limited ROM, pain; patients were allowed to be on other agents concomitantly including: NSAIDs, prednisone, hydroxychloroquine, auranofin, penicillamine, methotrexate, aspirin	blood tests were performed monthly x 3 months and then every 3 months thereafter Significant improvement defined as achievement of 1 or more of the following in the 1st year of tx: 1) 50% or more decrease in number of active joints (defined as pain, limited ROM or effusion), 2) 50% or more decrease in total number of joints with effusion, 3) 50% or more decrease in total degree of flexion contracture, 4) decrease in ESR to < 20 mm/hr (of those that had an abnormal one to begin with)	77% of the total pauciarticular patients showed significant improvement over 12 months. 88% of the ANA positive females showed significant improvement over 12 months. 26% of the total pauciarticular patients entered remission. 44% of the ANA positive females w/ pauciarticular disease entered remission. 7% of the pauciarticular patients were considered treatment failures. 0% of the ANA positive females were considered treatment failures. 17% of patients in the pauciarticular group had an adverse reaction. 19% in the ANA positive female group had an adverse reaction. The average length of treatment to remission (for all JRA disease groups studied together was 12 months). **OF NOTE, JUST ABOUT 50% (49.6%) OF TOTAL PATIENTS STUDIED HAD PAUCIARTICULAR DISEASE
1201, Foeldvari, 2010 [13]	Retrospective cohort, single arm	5 years	58 total JIA patients (using ILAR criteria); 15 with persistent oligoarthritis (25.9%); all patients had at least 1 active joint at starting leflunomide (defined as swollen, tender, or limited ROM); all patients had received methotrexate	Leflunomide administered with a mean dose of 16.64 mg/day. No loading dose was given. Baseline characteristics, reason for starting leflunomide, adverse events, joint outcomes, CHAQ, VAS, well being scores and treatment status were all obtained On average, patient evaluations and labs were done every 4-12 weeks	Patients mainly dc'd MTX and switched to leflunomide due to GI intolerance. The remainder were due to treatment failure. 4 (20%) oligoarticular patients discontinued leflunomide as they achieved remission **OF NOTE, THERE WAS LIMITED SUBTYPE ANALYSIS IN PAPER AND FEWER THAN 50% (25.9%) OF PATIENTS IN GROUP HAD OLIGOARTICULAR DISEASE

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
			prior to leflunomide Concomitant medications were permitted including: methotrexate (10 patients took both leflunomide and MTX); etanercept, infliximab, adalimumab, rituximab, anakinra, cyclosporine, sulfasalazine, hydroxychloroquine		

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References:

1. Ravelli, A., Davì, S., Bracciolini, G., Pistorio, A., Consolaro, A., van Dijkhuizen, E. H. P., . . . Martini, A. (2017). Intra-articular corticosteroids versus intra-articular corticosteroids plus methotrexate in oligoarticular juvenile idiopathic arthritis: a multicentre, prospective, randomised, open-label trial. Lancet, 389(10072), 909-916. doi:10.1016/s0140-6736(17)30065-x
2. Bava, C., Mongelli, F., Pistorio, A., Bertamino, M., Bracciolini, G., Dalprà, S., . . . Ravelli, A. (2019). A prediction rule for lack of achievement of inactive disease with methotrexate as the sole disease-modifying antirheumatic therapy in juvenile idiopathic arthritis. Pediatr Rheumatol Online J, 17(1), 50. doi:10.1186/s12969-019-0355-0

3. van Dijkhuizen, E. H., Pouw, J. N., Scheuern, A., Hügle, B., Hardt, S., Ganser, G., . . . Wulffraat, N. M. (2016). Methotrexate intolerance in oral and subcutaneous administration in patients with juvenile idiopathic arthritis: a cross-sectional, observational study. Clin Exp Rheumatol, 34(1), 148-154.
4. Albarouni, M., Becker, I., & Horneff, G. (2014). Predictors of response to methotrexate in juvenile idiopathic arthritis. Pediatr Rheumatol Online J, 12, 35. doi:10.1186/1546-0096-12-35
5. Klein, A., Kaul, I., Foeldvari, I., Ganser, G., Urban, A., & Horneff, G. (2012). Efficacy and safety of oral and parenteral methotrexate therapy in children with juvenile idiopathic arthritis: An observational study with patients from the German Methotrexate Registry. Arthritis Care Res (Hoboken), 64(9), 1349-1356. doi:10.1002/acr.21697
6. Fráňová, J., Fingerhutová, Š., Kobrová, K., Srp, R., Němcová, D., Hoza, J., . . . Doležalová, P. (2016). Methotrexate efficacy, but not its intolerance, is associated with the dose and route of administration. Pediatric rheumatology, 14(1), 36. doi:10.1186/s12969-016-0099-z
7. Lin, Y. T., Tsai, M. J., Wang, L. H., Huang, M. T., Yang, Y. H., & Chiang, B. L. (2000). Efficacy and safety of methotrexate therapy for juvenile rheumatoid arthritis. J Formos Med Assoc, 99(8), 623-629.
8. Gottlieb, B. S., Keenan, G. F., Lu, T., & Ilowite, N. T. (1997). Discontinuation of methotrexate treatment in juvenile rheumatoid arthritis. Pediatrics, 100(6), 994-997. doi:10.1542/peds.100.6.994
9. Padeh, S., Pinhas-Hamiel, O., Zimmermann-Sloutskis, D., & Berkun, Y. (2011). Children with oligoarticular juvenile idiopathic arthritis are at considerable risk for growth retardation. J Pediatr, 159(5), 832-837.e831-832. doi:10.1016/j.jpeds.2011.04.012
10. Chen, C.-C., Lin, Y.-T., Yang, Y.-H., & Chiang, B.-L. (2002). Sulfasalazine therapy for juvenile rheumatoid arthritis. Journal of the Formosan Medical Association, 101(2), 110-116.
11. Varbanova, B. B., & Dyankov, E. D. (1999). Sulphasalazine. An alternative drug for second-line treatment of juvenile chronic arthritis. Adv Exp Med Biol, 455, 331-336.
12. Imundo, L. F., & Jacobs, J. C. (1996). Sulfasalazine therapy for juvenile rheumatoid arthritis. J Rheumatol, 23(2), 360-366.
13. Foeldvari, I., & Wierk, A. (2010). Effectiveness of leflunomide in patients with juvenile idiopathic arthritis in clinical practice. J Rheumatol, 37(8), 1763-1767. doi:10.3899/jrheum.090874

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PICO 6. In children with oligoarticular JIA, should biologic therapies be recommended, and should there be any preferred order of treatment: anti-TNF treatment, biologic treatments with other mechanisms of action?

Summary: A literature review search identified 8 cohort studies (most single arm)[1-8] and one case series[9] addressing the treatment of JIA patients with biologic therapy. Minden et al.[1] reported outcomes of bDMARDs (missed with csDMARDs) in JIA patients over a 10-year period. Symptom relief and disease activity appeared to be good in patients with persistent oligo JIA. An analysis that combined all JIA subtypes found that patients who began bDMARD treatment within 2 years of symptom onset (G1 0 to 2 years) were significantly more likely to be in drug-free remission than those patients who began bDMARD treatment later (G2 >2 to 5 years, G3 >5 years). G1 patients also had lower disease activity, higher functional status, overall well-being, and lower rates of arthroplasty than other groups. Anink et al.[9] looked at 16 persistent oligo patients all previously treated with MTX with 14 being treated with Enbrel and 2 with Humira. Looking at both 3- and 15-month outcomes, there were decreases in active count joints, CHAQ scores, ESR levels, as well pain. Ten out of 16 achieved inactive disease at 3 months, 9/10 at 15 months. Etanercept was the most commonly used TNF-inhibitor in the cohort studies. Alexeeva et al.[2] evaluated 32 oligoarticular patients who received etanercept 0.4 mg/kg twice a week with ACR 30/50/70/90s of 97%/97%/94%/88%. Inactive disease in the persistent oligo JIA patients was 88% according to Wallace criteria and 50% according to JADAS71 criteria. Stable remission at the end of follow up was 56%. In another study by Alexeeva et al.[3], 84 patients with persistent Oligo JIA given etanercept twice a week had a reduction in active joint count, physician global, CHAQ and JADAS-71 with ACR Pedi 30/50/70/90 of 90.5%/90.5%/88.1%/77.4% with 86.9% achieving inactive disease. Kearsley-Fleet et al.[4] evaluated 496 JIA patients, 12 with oligo JIA on Etanercept and found JADAS-71 decreased from median 7.2 (IQR 3.8-10.2) to 3.1 at 1 year (IQR 0.7-5.6), which was not statistically significant. ACR Pedi's of 30/50/70/90 were 80%/78%/70%/62% with minimal disease activity at 1 year of 74%. Minden et al.[5] conducted a prospective cohort study evaluating 346 patients with JIA, 11 with oligo JIA, treated with etanercept who achieved HAQ disability indices of 60% 0, 20% >0 to 0.5, 10% >0.5 to 1.0, 10% >1.0 to 3.0. Zuber et al.[7] evaluated 27 patients with oligo JIA who achieved ACR 30/50/70/90/100 scores of 80%/80%/50%/35%/35% at 12 months. In Horneff et al.[8], 10 patients with persistent oligo JIA receiving etanercept 0.4 mg/kg twice weekly with complete remission in 62% of patients. Donnithorne et al.[6] evaluated 125 patients with JIA, 26 with persistent oligo JIA, treated with etanercept (83%), infliximab (6%) and adalimumab (11%) with 64% of patients achieving inactive disease at 1 year and 62% achieving inactive disease ever. Given that all of the studies lacked a comparison group, the risk of bias was high and the quality of evidence very low.

Quality of evidence across all critical outcomes: Very low

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Table 1. Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
3889 Minden, 2019[1]	Prospective cohort study	mean ± SD 9.1 ± 3.7 years	40 SJIA patients, 43 with persistent OJIA, 128 with extended OJIA	bDMARDS (mixed with csDMARDs)	PhGA of disease activity (mean ± SD): Persistent OJIA 1.5 ± 1.9 PhGA CID, n (%): Persistent OJIA 15 (36.6%) cJADAS-10: Persistent OJIA 4.3 ± 5.0 cJADAS-10 remission off drugs, no. (%): Persistent OJIA 1 (2.4%) HAQ total: Persistent OJIA 0.15 ± 0.40 Patient reported pain: Persistent OJIA 1.8 ± 2.3 At the 10-year time point, patients who began bDMARD treatment within 2 years of symptom onset (G1 0 to 2 years) were significantly more likely to be in drug-free remission than those patients who began treatment later (G2 >2 to 5 years, G3 >5 years). G1 patients also had lower disease activity, higher functional status, overall well-being, and lower rates of arthroplasty than other groups. However, this data combines different JIA subtypes (persistent OJIA, extended OJIA, sJIA, poly JIA, enthesitis, psoriatic arthritis)
763 Alexeeva, 2017[2]	Retrospective cohort study, propensity score matching	Unclear	49 patients with JIA (17 polyarticular, the rest oligoarticular)	Etanercept SQ 0.4mg/kg (max single dose 25mg), twice a week	- ACR 30/50/70/90 at the end of follow-up, n (%): Persistent oligo: 31/31/30/27 (97%/97%/94%/88%) - Inactive disease (according to the Wallace criteria) at the end of follow-up, n (%): Persistent oligo: 28 (88%); - Inactive disease (according to the JADAS71 cut-off point), n (%): Persistent oligo: 16 (50%); - Stable remission at the end of follow-up, n (%): Persistent oligo: 18 (56%);
3003, E. I. Alexeeva et al., 2017[3]	Single-arm cohort study	12 months	197 patients with non-systemic JIA (n = 84	Etanercept via subcutaneous injection at a dose of 0.4 mg per kg	**Oligoarticular JIA subgroup:** Active joint count decreased from median of 2 (IQR 2-4) to 0 (IQR 0-0), painful joint count

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
			persistent oligoarticular JIA)	body weight (maximum single dose, 25 mg) twice a week	decreased from 2 (IQR 1.5-3) to 0 (IQR 0-0), physician global decreased from 50 (IQR 42-70) to 0 (IQR 0-4), CHAQ decreased from 0.78 (IQR 0.5-1.5) to 0 (IQR 0-0.25), JADAS-71 decreased from 14.9 (11.7 – 18.9) to 0.5 (0-1.1) 90.5% of patients reached ACR Pedi 30 response, 90.5% ACR Pedi 50, 88.1% ACR Pedi 70, 77.4% ACR Pedi 90, 86.9% inactive disease
1442, L Kearsley-Fleet et al., 2016[4]	Single-arm cohort study	1 year	496 patients with JIA (n = 12 with oligoarticular JIA)	Etanercept	**Oligoarticular JIA outcomes:** JADAS-71 decreased from median 7.2 (IQR 3.8-10.2) to 3.1 at 1 year (IQR 0.7-5.6) (not statistically significant) ACR Pedi 30 at 1 year: 80% ACR Pedi 50 at 1 year: 78% ACR Pedi 70 at 1 year: 70% ACR Pedi 90 at 1 year: 62% MDA at 1 year: 74% **AEs (all patients):** 9 (2%) stopped due to adverse events
4076, J. Anink et al., 2013[9]	Case series	Median follow-up 13.7 months (IQR 8.3-16.7 months)	16 persistent oligoarticular JIA patients	Etanercept (n = 14), adalimumab (n = 2; both with arthritis + uveitis). All previously treated with MTX	**3 month outcomes (n = 16)** Active joint count decreased from median of 2 (IQR 1-3) to 0 (IQR 0-1) Pain decreased from 51 on VAS (IQR 0-71) to 6 (IQR 0-75) CHAQ decreased from 0.3 (IQR 0-0.9) to 0.1 (0-1.0) 10/16 with inactive disease at 3 months ESR decreased from 10 (IQR 2-60) to 3 (IQR 2-30); 11/15 normalized

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					15 month outcomes (n = 10) Active joint count decreased from median of 2 (IQR 1-3) to 0 (IQR 0-2) Pain decreased from 51 on VAS (IQR 0-71) to 0 (IQR 0-34) CHAQ decreased from 0.3 (IQR 0-0.9) to 0.1 (0-0.6) 9/10 with inactive disease at 3 months ESR decreased from 10 (IQR 2-60) to 3 (IQR 2-29); 9/10 normalized No permanent discontinuation due to AEs
2294, K. Minden et al., 2012[5]	Prospective cohort	Median treatment duration with ETA of 4.1 years (IQR 2-6 years)	346 patients with JIA (n = 11 with persistent oligoarticular JIA)	Etanercept	**Oligoarticular JIA outcomes:** SF-36 PCS mean score 48.5 (SD 10.1) SF-36 MCS mean score 51.4 (SD 10.5) HAQ disability index: 60% 0, 20% >0 to 0.5, 10% >0.5 to 1.0, 10% >1.0 to 3.0 **SAE's (all patients):** 7 infections (2.1/100 patient-years) 1 death due to suicide
348, K.J. Donnithorne et al., 2011[6]	Single-arm cohort study	Median follow up 14.0 months (IQR 9-21 months); 16/26 patients with oligoarticular JIA with 1-	125 patients with JIA (n = 26 with persistent oligoarticular JIA)	TNF-alpha inhibitors (83% etanercept, 6% infliximab, 11% adalimumab)	**Oligoarticular JIA outcomes:** 9/14 (64%) with inactive disease at 1 year and 16/26 (62%) with inactive disease ever.

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
		year follow up data			
1346, Zuber, 2011[7]	Cohort	Jan 2003 thru March 2010, 72 month safety observation period	188 patients (27 patients with oligo JIA)	Patients were given etanercept after being unresponsive or intolerant to methotrexate	At 12 months, persistent oligo JIA showed ACR 30, 50, 70, 90 and 100 responses in 80%, 80%, 50%, 35% and 35% of patients, respectively (data extrapolated from Figure 1). 2 patients with oligo JIA discontinued treatment due to adverse events (unclear whether patients had persistent or extended oligo).
1552, G. Horneff et al., 2004[8]	Single-arm cohort study	1 to 48 months (mean (SD) length of treatment, 13.4 (10.5) months, median 12 months)	322 patients with JIA (n = 10 persistent oligoarticular JIA)	Recommended dosage and treatment schedule of etanercept is 0.4 mg/kg twice weekly (actual dosing not reported)	**All JIA patients:** Significant improvements in the number of tender and swollen joints, duration of morning stiffness, and physician's and parent's global assessment were seen after 1, 3, 6, 12, 18, 24, and 30 months ($p<0.0001$ for all except for swollen joint count and ESR at 30 months ($p<0.0005$) and duration of morning stiffness at 30 months ($p<0.001$) A significant improvement in the CHAQ was observed after 6, 12, 18, 24, and 30 months ($p<0.0001$ at 1 to 24 months and $p<0.01$ at 30 months) **Oligoarticular patients only:** Complete remission in 5/10 with persistent oligoarticular JIA (62%)

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References

1. Minden K, Horneff G, Niewerth M, Seipelt E, Aringer M, Aries P, et al. Time of Disease-Modifying Antirheumatic Drug Start in Juvenile Idiopathic Arthritis and the Likelihood of a Drug-Free Remission in Young Adulthood. Arthritis care & research. 2018;71(4):471-481.

2. Alexeeva E, Dvoryakovskaya T, Denisova R, Sleptsova T, Isaeva K, Chomahidze A, et al. Comparative Analysis of the Etanercept Efficacy in Children with Juvenile Idiopathic Arthritis Under the Age of 4 Years and Children of Older Age Groups Using the Propensity Score Matching Method. Modern rheumatology. 2018:1-20.
3. Alexeeva EI, Namazova-Baranova LS, Bzarova TM, Valieva SI, Denisova RV, Sleptsova TV, et al. Predictors of the response to etanercept in patients with juvenile idiopathic arthritis without systemic manifestations within 12 months: results of an open-label, prospective study conducted at the National Scientific and Practical Center of Children's Health, Russia. Pediatric rheumatology online journal. 2017;15(1):51.
4. Kearsley-Fleet L, Davies R, Lunt M, Southwood TR, Hyrich KL. Factors associated with improvement in disease activity following initiation of etanercept in children and young people with Juvenile Idiopathic Arthritis: results from the British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study. Rheumatology (Oxford, England). 2016;55(5):840-847.
5. Minden K, Niewerth M, Zink A, Seipelt E, Foeldvari I, Girschick H, et al. Long-term outcome of patients with JIA treated with etanercept, results of the biologic register JuMBO. Rheumatology (Oxford, England). 2012;51(8):1407-1415.
6. Donnithorne KJ, Cron RQ, Beukelman T. Attainment of inactive disease status following initiation of TNF-alpha inhibitor therapy for juvenile idiopathic arthritis: enthesitis-related arthritis predicts persistent active disease. The Journal of rheumatology. 2011;38(12):2675-2681.
7. Zuber Z, Rutkowska-Sak L, Postepski J, Dobrzyniecka B, Opoka-Winiarska V, Kobusinska K, et al. Etanercept treatment in juvenile idiopathic arthritis: the Polish registry. Medical science monitor : international medical journal of experimental and clinical research. 2011;17(12):Sr35-42.
8. Horneff G, Schmeling H, Biedermann T, Foeldvari I, Ganser G, Girschick HJ, et al. The German etanercept registry for treatment of juvenile idiopathic arthritis. Annals of the rheumatic diseases. 2004;63(12):1638-1644.
9. Anink J, Otten MH, Prince FH, Hoppenreijs EP, Wulffraat NM, Swart JF, et al. Tumour necrosis factor-blocking agents in persistent oligoarticular juvenile idiopathic arthritis: results from the Dutch Arthritis and Biologicals in Children Register. Rheumatology (Oxford, England). 2012;52(4):712-717.

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PICO 7: In children with oligoarticular JIA, should dietary or herbal interventions be recommended, in addition to whatever other therapeutic options are given, versus not recommending them?

Summary: The literature search identified one randomized controlled trial[1] and one single-arm cohort study[2] that addressed this PICO question. The RCT provided indirect evidence by looking at the use of MTX with or without folic acid in a small group of patients with mostly poly JIA (only 5 patients had oligo JIA). The study found no significant differences between the folic acid group and the placebo group with respect to transaminase levels, morning stiffness, patient or physician global, swollen joint count or CRP.

The single-arm observational study evaluated the use of omega 3 fatty acids in 27 JIA patients (9 with oligo JIA); for patients with oligo JIA, 3/9 had ACR50 response, 5/9 ACR 30 and 1/9 no response.

Quality of evidence across all critical outcomes: Very low

Table 1. Data from Randomized Controlled Trials

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
1210 Hunt, 1997 [1]	Double-blind placebo-controlled RCT	13 weeks	18 JIA patients on MTX for at least 6 months (oligo 5, poly 12, systemic 2)	9 patients MTX + folic acid 1mg/day vs 10 patients MTX + placebo	No patients had abnormal transaminase levels during the trial. Mean (SD) AST levels: baseline 28 (6), folic acid 27 (7), placebo 29 (14). Mean (SD) ALT levels: baseline 28 (8), folic acid 30 (14), placebo 27 (10). Morning stiffness, min (SD): folic acid group 13 (28), placebo 24 (57) Patient global assessment, mm: folic acid group 30 (17), placebo 35 (21). Physician global assessment, mm: folic acid group 11 (10), placebo 35 (21). Swollen joint count: folic acid group 3 (4), placebo 3 (5). CRP, mg/dl: folic acid group 0.6 (1), placebo 0.7 (1

Table 2. Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results

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2696, Gheita et al, 2012 [2]	Single-arm cohort study	12 weeks	27 patients with JIA (n = 9 oligoarticular JIA)	Omega-3 fatty acids 2 g/day	**Oligoarticular outcomes (extrapolated from Fig 3):** 3/9 patients (33.3%) Pediatric ACR50 response 5/9 patients (55.56%) Pediatric ACR30 response 1/9 patients (11.11%) No response

References:

1. Hunt PG, Rose CD, McIlvain-Simpson G, Tejani S. The effects of daily intake of folic acid on the efficacy of methotrexate therapy in children with juvenile rheumatoid arthritis. A controlled study. J Rheumatol. 1997 Nov;24(11):2230-2.
2. Gheita T, Kamel S, Helmy N, El-Laithy N, Monir A. Omega-3 fatty acids in juvenile idiopathic arthritis: effect on cytokines (IL-1 and TNF-alpha), disease activity and response criteria. Clin Rheumatol. 2012 Feb;31(2):363-6. doi: 10.1007/s10067-011-1848-5. Epub 2011 Sep 16.

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PICO 8. In children with oligoarticular JIA, regardless of disease activity and risk factors, should PT/OT versus no PT/OT (regardless of concomitant medical therapy) be recommended?

Summary: Literature searches led to one randomized controlled trial [4482] which indirectly answered the PICO question. This study included patients with JIA as well as those with cerebral palsy and brachial plexus birth injury, although data for JIA was reported separately. The aim was to include all patients with at least one distal upper extremity joint involved. Patients were randomly allocated to either complete 8 weeks of leap motion controller based training (LMCBT) or a conventional rehabilitation program. The LMCBT program employed elements of virtual reality. The system could purportedly detect finger movements with submillimeter accuracy. The program included 2 games that were developed for the purposes of this study. Conventional therapy included “re-education of muscles using a sensorimotor approach to control motor output.” In looking strictly at the data for JIA patients, it appeared that both the LMCBT based rehabilitation and traditional rehabilitation both led to statistically significant improvements in CHAQ total, CHAQ pain, CHAQ well-being, hand grip, tip grip, lateral grip and triple grip. LCMBT showed a statistically significant improvement in Duruoz Hand Index (DHI) scoring compared to traditional rehabilitation. There was no significant difference in the outcomes of the therapy methods in the remaining categories (Jebson Taylor Hand Function Test, Nine-Hole Peg Test, CHAQ), grip strength). Regarding JIA specifically, there was no evidence to suggest that LMCBT was more effective than conventional therapy.

This paper very indirectly addresses this PICO question. It suggests that rehabilitation is beneficial, though there was no negative control group (no one without therapy) with which to compare. This paper also considered a virtual reality method which was not considered in this particular

PICO question. Furthermore, this PICO asks specifically about oligoarticular JIA and this paper considered JIA as a whole. There is no reported subgroup analysis for oligo JIA. Nonetheless, there is a significant improvement in patients' CHAQ scores before and after 8 weeks of traditional rehabilitation engagement.

This study had several limitations in addition to indirectness of the patient population and comparison. Allocation was unconcealed and patients and practitioners were not blinded (although the outcome assessor was blinded). Since this is a single small study there is also serious imprecision in effect estimates.

Quality of evidence across all critical outcomes: Very low

Table 1. Data from randomized controlled trials

Ref ID, Author, year	Study type	Duration	Population Description	Monitoring given to relevant population	Results
4482, Tarakci 2019 [1]	Randomized controlled trial	1 year of study, 8 week program conducted for participants	Pediatric patients between 5 and 17 with JIA, cerebral palsy or brachial plexus birth injury with at least one affected distal joint in upper extremity (wrist and/or finger joints) Patients were excluded if they had undergone botox injections, intraarticular injection, surgery or hand rehabilitation within the previous 1 year	This was a randomized parallel group trial. Patients either underwent a leap motion controller based training program (LMCBT) or conventional rehabilitation for 8 weeks. Each program took place for 1 hour sessions 3 times weekly for 8 weeks. *LMCBT is a method which uses virtual reality to influence movement outcomes. In this case, a leap motion controller device was employed which could track hand and finger movements with purported submillimeter accuracy. Two games were "academically developed" for the purposes of the study *The conventional rehabilitation program aimed to re-educate muscles using a sensorimotor approach to control motor output	18 patients with JIA underwent LMCBT and 25 patients with JIA underwent traditional rehab There were significantly improved scores for CHAQ total, CHAQ pain, CHAQ well being and Duruoz Hand Index (DHI) in both LMCBT and traditional rehab groups when comparing pre and post-treatment scores for patients. There was a statistically significant improvement in hand grip, tip grip, lateral grip and triple grip in both LCMBT and traditional rehab pre and post treatment groups. There was a statistically significant difference in the DHI between the LMCBT and traditional rehabilitation group in favor of LMCBT. There was no statistically significant difference in the remainder of the outcome measures when comparing the two methods of rehabilitation.

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References:

1. Tarakci E, Arman N, Tarakci D, Kasapcopur O. Leap Motion Controller-based training for upper extremity rehabilitation in children and adolescents with physical disabilities: A randomized controlled trial. J Hand Ther. Apr-Jun 2020;33(2):220-228.

PICO 9. In children with oligoarticular JIA, should *risk factors* alter the treatment paradigm?

Summary: The literature search identified one observational study[1] that addressed this PICO question. The observational study was retrospective but included 205 pts. Results were significant showing that symmetric disease was a predictor of extension to >10 joints, the need to use DMARDs, erosive disease on radiographs, continued active disease, lack of remission and disability based on CHAQ. Ankle or wrist involvement was a predictor of extension and erosions. Wrist involvement was a predictor of need for DMARDs and continued active disease. Elevated ESR was a predictor of extension, need for DMARDs and lack of remission.

Quality of evidence across all critical outcomes: Very low

Table 1. Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
1135, Al-Matar et a., 2002 [1]	Single-arm retrospective cohort study	At least 5 years Median 10.8 years (range 5-26.6 years)	205 patients with oligoarticular JIA	N/A	**All below features present in first 6 months of disease; results taken from multivariate logistic regression model (disease duration included as confounder)** Symmetric disease predictor of extension to >= 10 joints (OR 19.2, 95% CI [5.46-67.8], p = 0.000), need to use DMARDs (OR 11.5, 95% CI [4.22-31.33], p = 0.000), erosive disease on radiographs (OR 4.73, 95% CI [1.47-15.2], p = 0.009), inflammatory activity at last follow up visit (OR 3.23, 95% CI [1.45-7.2]), no remission of disease (OR 4.73, 95% CI [2.15-10.4]), disability as measured by C-HAQ>0.12 (OR 2.95, 95% CI [1.01-8.6]) Ankle and/or wrist disease predictor of extension (OR 6.61, 95% CI [1.97-22.1]) and erosions (OR 3.59, 95% CI [1.15-11.2], p = 0.027)

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					Wrist disease predictor of need to use DMARDs (OR 5.87, 95% CI [1.51-22.8]) and inflammatory disease activity at last follow up visit (OR 4.01, 95% CI [1.16-13.8], p = 0.004) Elevated ESR predictive of extension (OR 3.76, 95% CI [1.09-12.9], p = 0.036), need to use DMARDs (OR 6.47, 95% CI [2.2-18.9], p = 0.001), and no remission of disease (OR 2.30, 95% CI [1.04-5.08], p = 0.039)

References:

1. Al-Matar MJ, Petty RE, Tucker LB, Malleson PN, Schroeder ML, Cabral DA. The early pattern of joint involvement predicts disease progression in children with oligoarticular (pauciarticular) juvenile rheumatoid arthritis. Arthritis Rheum. 2002 Oct;46(10):2708-15.

PICO 10. In children with oligoarticular JIA, should *disease activity measures* alter the treatment paradigm?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

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Active TMJ Arthritis

PICO 11. In children with JIA with active TMJ arthritis, should a trial of consistent NSAIDs be recommended and should there be any preferred NSAID treatment?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 12. In children with JIA with active TMJ arthritis, should adding intraarticular glucocorticoids to initial therapy be recommended?

Summary: The literature search identified seven observational studies[1-7] that addressed this PICO question, including one prospective pilot study, 2 prospective cohort studies, 2 retrospective cohort studies and 2 retrospective reviews. Some of the observational studies looked at radiographic benefit, others looked at clinical markers including improvement in pain or improved MIO. Three studies showed radiographic benefit with improvement in MRI findings.[1,2,6] Improvements in pain were more varied. In two studies[1,3] pain was significantly decreased. One study[5] showed initial improvement in pain-frequency, pain-intensity and pain-index, but by long term follow-up only pain frequency was still improved. One study[2] showed all groups had a decrease in pain intensity (measured by VAS) but there was no statistically significant difference between groups including control group. Another study[7] showed mean increase in MIO (maximal incisal opening) of 6.9 mm (p = 0.002; 95% CI 3, 10.7), but with subsequent injections the increase was only 0.4 mm (p = 0.8; 95% CI –3.5, 4.4).

Two studies reported potential serious adverse events of IA steroid injections of TMJs. In one[4], 33/238 patients developed heterotopic bone formation (HBF), bilateral in 36%. The study found a 25% increase in hazard of HBF for every additional injection (steroid and infliximab injections analyzed together) (HR 1.254, 95%CI 1.04-1.512, p= 0.0184) and a 56% *decrease* in hazard for each year increase in delay between JIA diagnosis and first injection. (HR 0.44, 95% CI 0.296-0.655, p not reported). In the other study[7], one patient developed subcutaneous atrophy at the injection site. Two patients developed small, asymptomatic intraarticular calcifications.

Since all studies were observational and all but one lacked a control group, the risk of bias was high.

Quality of evidence across all critical outcomes: Very low

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Table 1. Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
3157, Resnick, 2016[1]	Retrospective cohort	Post-injection follow-up MRI performed at 6.4+/-2.4 mos	29 patients with JIA and TMJ synovitis (MRI proven); excluded patients with previous TMJ IASI. 21 bilateral injections. Total TMJ injections= 50.	50 ml sterile saline flush followed by 10 mg triamcinolone hexacetonide TMJ injection (without radiologic guidance)	Resolution of MRI findings of active TMJ disease: Post injection MRI enhancement ratio (ER) decreased in all patients but only fell below the established threshold for pathologic synovial enhancement (<1.55) in 18% joints (9/50). Univariate regression analysis showed strong association between decrease in ER and increase in maximal incisor opening. Arthritis-related pain: Pain was reported by 66% of patients before injection, 11% after (P<0.001)
397, Antonarakis, 2018[2]	Prospective cohort	6 months	41 patients with JIA and TMJ arthritis	- 21 patients: lavage (with 2-3 ml 0.9% NaCl) and triamcinolone acetonide (20mg) injection - 8 patients: lavage only - 12 patients: monitored without intervention	Improvement of MRI findings at 6 months: - 42.9% of lavage + injection - 31.3% lavage only - 27.8% no intervention Multilevel regression showed a relevant difference between the lavage + injection and lavage (P=0.03), and no treatment (P=0.004) groups. No difference between lavage and no treatment groups (P=1). Arthritis-related pain: all groups had a decrease in pain intensity (measured by VAS). No intervention (-0.4) Lavage (-1) Lavage+ Injection (-2.6), no statistically significant difference between groups.
748, Olsen-Bergem, 2014[3]	Prospective cohort	8 months	21 patients with JIA and TMJ arthritis (38 joints)	17 joints: arthrocentesis using “push and pull method” with B12 and physiologic salt water. 21 joints: arthrocentesis + triamcinolone hexacetonide injection	Arthritis-related pain: At 3 months, mean pain VAS improved from 49 to 18 (P<0.0005) overall. At 8 months, pain VAS further improved to 8 (P=0.05 compared to 3 months). Functional ability: (as measured by patient-reported function VAS). At 3 months, improved from 41 to 19 (P<0.005). At 8 months, further improved to 4 (P<0.05 compared to 3 months).

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					No significant differences between the 2 treatment arms.
3395, Stoll, 2018[4]	Retrospective cohort	2.1 +/- 1.3 years from 1st injection to last MRI	238 JIA patients	All patients received 1 or more TMJ corticosteroid injections (triamcinolone hexacetonide or triamcinolone acetonide). 23% had also received intra-articular infliximab.	33 patients developed heterotopic bone formation (HBF) bilateral in 36%. Cox proportional hazard modeling was performed to identify risk factors for development of HBF. 28% increase in hazard of developing HBF for every 1 year increase in age at diagnosis (HR 1.279, 95%CI 1.169-1.398, p <0.0001) 25% increase in hazard of HBF for every additional injection (steroid and infliximab injections analyzed together) (HR 1.254, 95%CI 1.04-1.512, p= 0.0184) 56% ***decrease*** in hazard for each year increase in delay between JIA diagnosis and first injection. (HR 0.44, 95% CI 0.296-0.655, p not reported) HBF was associated with decreased mouth opening, presence of jaw deviation, and 3 of 33 patients with HBF required joint replacement.
3845 P.Stoustrup et.al. 2015[5]	prospective pilot study	February 2011 - July 2012 3 exams: T1-pre T2- 34 days T3-333days	Thirteen patients with JIA and arthritis-related orofacial signs and symptoms (median 17.2 years, IQR 15–18.4 years).	All patients received TMJ IACI (11 bilateral and two unilateral) due to an insufficient response to previous pain-management treatments. (non-imaging guided IACI) with triamcinolone hexacetonide (20 mg/injection) Eleven patients received bilateral TMJ injections	High pre-treatment pain levels were seen at T1 with a mean pain intensity of 62.7 (VAS scale 0–100 mm) and a reported average pain frequency of “several times a day”. At the short-term follow-up (T2) pain-frequency, pain-intensity and pain-index were all significantly reduced when compared to the pre-treatment T1 levels. At long-term T3 follow-up only the pain frequency remained significantly reduced compared to the pre-treatment T1 level. The pain-intensity and also the pain-index variables significantly worsened between T2 and T3 The ANOVA test documented no significant intra-group changes in any of the outcome variables reflecting TMJ mobility

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				and two had unilateral injections Three exams: T1 pre tx, T2 short-term F/U:(mean 34 days T3 long-term F/U(mean 333 days	
901 A.M.Cahill et.al. 2007[6]	Retrospective review	From October 2002 to February 2004,	14 girls/1 boy JIA: 9 oligo 4 poly 1 sJIA 1 pJIA	Pre-procedure MRI showed signs of inflammatory arthropathy in all 27 joints considered for treatment 27 CT guided intraarticular TMJ steroid injections were performed	Results support intraarticular TMJ injection of a long-acting steroid in children is a safe procedure even in patients with joint space deformities Many patients w/improved clinical symptoms: reduction in acute and subacute inflammatory changes on MRI. "Because our cohort had severe disease involvement by the time of entry into the study, we did not study whether intervention earlier in the course of disease prevents disease progression."
1954 S.Ringold et.al. 2008[7]	Retrospective chart review	January 2000-January 2006	Twenty-five patients, 21F/4M 14ANA+ 5HLA B27 The mean age at dx 8.9 years (range 1–16 yrs, median 8.4). The mean duration of time from initial diagnosis of JIA to the onset of TMJ symptoms or suspected TMJ arthritis	TMJ IAS injections by OMF surgeon with GA/no imaging. Each TMJ was injected with 0.5–1 ml triamcinolone acetonide (40 mg/ml) or triamcinolone hexacetonide (20 mg/ml)	When baseline MIO (maximal incisal opening), measurements were compared to the last MIO measurements of the study period, there was a mean increase in MIO of 6.9 mm ($p = 0.002$; 95% CI 3, 10.7). There was a mean increase in MIO of 3.8 mm following each IAS injection ($p = 0.003$; 95% CI 1.4, 6.2). Patients who underwent multiple IAS injections had a mean increase in MIO after first injection of 6.6 mm ($p < 0.001$; 95% CI 4.1, 9.1); however, the mean increase in MIO after subsequent injections was 0.4 mm ($p = 0.8$; 95% CI –3.5, 4.4). One patient developed subcutaneous atrophy at the injection site. Two patients developed small, asymptomatic intraarticular calcifications. No additional adverse events were reported

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			was 11 months (range 0–55 mo, median 2). Ten patients (40%) had TMJ complaints or suspected TMJ arthritis at their first visit		

References:

1. Resnick CM, Vakilian PM, Kaban LB, Peacock ZS. Quantifying the Effect of Temporomandibular Joint Intra-Articular Steroid Injection on Synovial Enhancement in Juvenile Idiopathic Arthritis. Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons. 2016;74(12):2363-2369.
2. Antonarakis GS, Courvoisier DS, Hanquinet S, Dhouib A, Carlomagno R, Hofer M, et al. Benefit of Temporomandibular Joint Lavage With Intra-Articular Steroids Versus Lavage Alone in the Management of Temporomandibular Joint Involvement in Juvenile Idiopathic Arthritis. Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons. 2018;76(6):1200-1206.
3. Olsen-Bergem H, Bjornland T. A cohort study of patients with juvenile idiopathic arthritis and arthritis of the temporomandibular joint: outcome of arthrocentesis with and without the use of steroids. International journal of oral and maxillofacial surgery. 2014;43(8):990-995.
4. Stoll ML, Amin D, Powell KK, Poholek CH, Strait RH, Aban I, et al. Risk Factors for Intraarticular Heterotopic Bone Formation in the Temporomandibular Joint in Juvenile Idiopathic Arthritis. The Journal of rheumatology. 2018;45(9):1301-1307.
5. Stoustrup P, Kristensen KD, Kuseler A, Pedersen TK, Herlin T. Temporomandibular joint steroid injections in patients with juvenile idiopathic arthritis: an observational pilot study on the long-term effect on signs and symptoms. Pediatric rheumatology online journal. 2015;13:62.
6. Cahill AM, Baskin KM, Kaye RD, Arabshahi B, Cron RQ, Dewitt EM, et al. CT-guided percutaneous steroid injection for management of inflammatory arthropathy of the temporomandibular joint in children. AJR. American journal of roentgenology. 2006;188(1):182-186.
7. Ringold S, Torgerson TR, Egbert MA, Wallace CA. Intraarticular corticosteroid injections of the temporomandibular joint in juvenile idiopathic arthritis. The Journal of rheumatology. 2008;35(6):1157-1164.

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PICO 13. In children with JIA with active TMJ arthritis, should adding oral glucocorticoids to initial therapy be recommended?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 14. In children with JIA with active TMJ arthritis, should a specific steroid type be recommended for intraarticular injection?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 15. In children with JIA with active TMJ arthritis, should DMARD therapies be recommended, and should there be any preferred order of treatment: methotrexate (subcutaneous and oral), leflunomide, sulfasalazine, and/or hydroxychloroquine?

Summary: The literature search identified one observational study[1] that addressed this PICO question. This study only evaluated MTX and does not address order of treatment. The study included 45 pts (40%oligo/60% poly). All patients in the MTX group had poly JIA and the MTX group had a higher dysfunction index (DI) than the non-MTX group. This was consistent with a higher DI in the poly JIA group. It is likely that patients with a higher dysfunction index were given MTX. However, Poly JIA patients receiving MTX showed less severe TMJ involvement compared to poly JIA patients not receiving MTX. Nevertheless, the cross-sectional design prevents determination of a possible causal effect of MTX on TMJ outcomes.

Quality of evidence across all critical outcomes: Very low

Table 1. Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment	Results
1175, Ince et al., 2000 [1]	Cross-sectional	N/A	45 patients with JIA (40% oligoarticular, 60% polyarticular)	18 with MTX exposure, 27 without MTX exposure	TMJ involvement on tomography in 63% of patients (at least grade 1 involvement) - 33% in oligoarticular group - 80% in polyarticular group

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					75% with vertical height asymmetry and symphysis deviation, 70% with smaller mandibular length, 60% with shorter ramus height, and 75% ANB angles greater than normative values **Clinical outcomes** Non-MTX group with less dysfunction index (DI) value than MTX group (mean 0.12 vs. 0.21, p = 0.02). This was consistent with a higher DI in the poly JIA group (0.19 vs 0.09 in oligo JIA group, p = 0.01). All patients in the MTX group had poly JIA. **Radiographic outcomes** Moderately strong correlation between craniomandibular index (CMI) and right and left condylar lesions (0.36) Moderate to strong correlation between tomographic TMJ data and lateral cephalometric measurements (0.3 to 0.6) and between tomographic TMJ findings and asymmetry of lower face (0.5). Poly JIA patients receiving MTX showed less severe TMJ involvement compared to poly JIA patients not receiving MTX.

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References:

1. Ince DO, Ince A, Moore DL. Effect of methotrexate on the temporomandibular joint and facial morphology in juvenile rheumatoid arthritis patients. Am J Orthod Dentofacial Orthop. 2000 Jul;118(1):75-83.

PICO 16. In children with JIA with active TMJ arthritis, should systemic biologic therapies be recommended, and should there be any preferred order of treatment: anti TNF, biologic treatments with other mechanisms of action?

Summary: The literature search did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 17. In children with JIA with active TMJ arthritis, should dietary or herbal interventions be recommended, in addition to whatever other therapeutic options are given, versus not recommending them?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 18. In children with JIA with active TMJ arthritis, regardless of disease activity and risk factors, should PT versus no PT (regardless of concomitant medical therapy) be recommended?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 19. In children with JIA with active TMJ arthritis, should risk factors alter the treatment paradigm?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

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Systemic JIA (sJIA) with and without Macrophage Activation Syndrome (MAS)

PICO 20: In patients with treatment naïve, newly diagnosed sJIA without MAS, should non-DMARD treatment (NSAIDs, glucocorticoids) be used as initial therapy?

Summary: The literature searches identified 11 observational studies (Table 1) that directly or indirectly addressed the question of whether non-DMARD treatment (NSAIDS, glucocorticoids) should be used as initial therapy in treatment naïve, newly diagnosed sJIA without MAS. Only one of these studies involved children with sJIA[1], the remaining studies involved patients with Adult Onset Still's Disease (AOSD)[2, 3, 4, 5, 6, 7, 8, 9, 10]. Studies were limited by retrospective treatment comparisons or lack of any control groups.

Sura et al.[1] observed 87 children newly diagnosed with sJIA between 2000-2014; 51 children received a trial of NSAID monotherapy with only 13 (25.5%) achieving clinically inactive disease [CID] for the duration of the study. Initial joint count was the only statistically significant predictor ($p = 0.01$) of CID on NSAIDs alone.

Most of the studies in AOSD highlighted poor response to NSAID monotherapy, although Wouters' study in 1986 highlighted variable effect of different NSAIDS on fever with best response noted with naproxen use [fever improved in 29 % with aspirin, 70% with indomethacin and 86% with naproxen][3]. In Kim et al.'s 2012 study, the authors concluded that NSAID monotherapy was not effective when used as monotherapy in AOSD[4]. In Franchini et al.[5], Gerfand-Valentin et al.[3] and Kalyoncu et al.[2], only 16% to 25% of patients with AOSD went into clinical remission following use of NSAID monotherapy.

Corticosteroids showed varying response rates across studies in patients with AOSD. Ruscitti et al.[7] assessed the role of high dose corticosteroid therapy in AOSD. They concluded that first-line treatment with high dosage of corticosteroids was a significant predictor of the achievement of clinical remission during the first 6 months of observation ($P < .001$). In contrast, Hu et al.[8] assessed a Chinese cohort of 517 AOSD patients in whom glucocorticoids were used most frequently (498/517, 96.3%) for disease control, followed by methotrexate (273/517, 52.8%) and hydroxychloroquine (174/517, 33.7%). 357/423 (84.4%) of AOSD cases were able to achieve initial remission with different regimens, mostly including glucocorticoids, methotrexate or hydroxychloroquine. Patients who required higher dose of glucocorticoids to induce remission had a poor response to treatment. Disease features associated with need for high dose steroids to induce remission: presence of skin rash, pericarditis, splenomegaly and delayed diagnosis (both more than 3 months and more than 6 months). Kong et al.[10] reported that 50% of 104 AOSD patients achieved remission after 2 weeks of corticosteroid treatment. In 1-month treatment, partial remission and complete remission rates were 92% and 71%, respectively. In the same cohort, cumulative relapse rate of 46.9% was observed after treatment with corticosteroids. In contrast, Kalyoncu et al.[2] found that 87% of AOSD patients receiving moderate-high dose corticosteroids went into remission with initial treatment compared to 26% patients receiving NSAIDs alone who went into remission with initial treatment.

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A prospective cohort study by Ter Haar et al.[111] assessed the use of rIL-1Ra (Anakinra) in sJIA at 2 mg/kg which was escalated for incomplete response to 4 mg/kg or additional prednisolone or switched to alternative therapy. The authors found that 76% of patients had inactive disease 1 year after the initiation of rIL-1Ra; 96% patients with inactive disease at 1 month had sustained inactive disease at 1 year, compared to only 47% of patients with active disease at 1 month (OR 27.0 [95% CI 4.17, 539.74], P = 0.003). Only 33% of patients required systemic glucocorticoids to achieve or sustain inactive disease. Patients with persistent arthritis after 1 month of rIL-1Ra treatment were at risk of prolonged disease activity). Among 6 patients who did not respond to initial treatment with rIL-1Ra, Inactive disease was ultimately achieved with tocilizumab (n = 2), canakinumab (n = 2), or the combination of MTX and prednisolone (n = 2). The ability to achieve inactive disease without glucocorticoids was also associated with sustained inactive disease at 1 year.

Quality of evidence across all critical outcomes: Very low

Table 1. Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
2822 Sura et al. 2018 [1]	Cohort study	14 years (2000-2014)	87 children w ere newly diagnosed with sJIA 2000-2014	NSAID monotherapy	51 children received a trial of NSAID monotherapy and 13 (25.5%) achieved CID. Initial joint count was the only statistically significant predictor (p = 0.01) of CID on NSAIDs alone. Age at presentation, ferritin, and CRP were trending towards significance (p = 0.10, p = 0.08, p = 0.14 respectively).
3323 Kalyoncu et al. 2016 [2]	Multicenter cohort	0-180 mo median f/u time 22 mo	356 AOSD Mostly females 59 % median age 32 years	NSAID, moderate-high dose corticosteroids	52 (86.7%) of 60 pts receiving moderate-high dose corticosteroids went into remission with initial treatment. 5 (26.3%) of 19 patients receiving NSAIDs alone went into remission with initial treatment.

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
114, Gerfand-Valentin, 2014 [3]	Retrospective cohort	Mean 8.4 years	57 patients with AOSD	NSAIDs 28 patients received NSAIDs (6 indomethacin, 9 ketoprofen, 7 aspirin, 3 diclofenac, 3 other) Corticosteroids 51 patients received CS (49 as first- or second-line treatment).	NSAIDs Only 5/28 (18%) were controlled with NSAID monotherapy. 6 had gastrointestinal AE, 4 requiring PPIs Corticosteroids 23/51 (45%) has "steroid-dependent disease"/unable to discontinue steroids 75% had CS-related AEs
3869 Kim et al. 2012 [4]	Cohort/ retrospective analysis	Unclear	54 Korean patients with AOSD (met Yamaguchi's criteria)	NSAID monotherapy, high-dose corticosteroids	NSAID monotherapy was tried in 42 patients without any efficacy. Of the 50 patients treated with high-dose corticosteroids, 21 patients (42%) were resistant and 29 showed a response. Elevated ESR and corticosteroids refractoriness were associated with poor prognosis (P = 0.023 and P = 0.009, respectively).
1270, Franchini, 2010 [5]	Retrospective cohort	Mean 56 months	45 patients with AOSD	NSAIDs 25 trials of NSAID monotherapy Corticosteroids 56 trials of steroid monotherapy	NSAIDs Inactive disease at least 2 months in 4/25 (all responders were patients without chronic articular involvement) Corticosteroids Inactive disease at least 2 months in 35/56 (63%), most responders had systemic disease without chronic articular disease.
144 Wouters, 1986 [6]	Cohort Study	6 months	45 pts with Adult-Onset Still's disease (AOSD)	NSAIDs, corticosteroids	Fever improved in 29 % with aspirin, 70% with indomethacin and 86% with naproxen. In 76% of patients, glucocorticoids reduced the systemic and/or joint symptoms. 3 patients febrile on glucocorticoids, indomethacin reduced temperature to normal. 8 patients who improved on steroids later developed severe joint destruction.

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					13 patients received one or several slow-acting antirheumatic drugs.
2411 Ruscitti et al. 2019 [7]	Cohort study	18 months	80 pts with AOSD	High dosages of corticosteroids (0.8–1 mg/kg/day of prednisone-equivalent) versus low dosage of CCSs (0.2–0.3 mg/kg/day of prednisone-equivalent) at disease onset	25 (64.79%) patients treated with the first-line treatment with high dosage of corticosteroids reached the primary endpoint of clinical remission at 6 months, a significantly higher percentage when compared with 8 (22.85%) patients treated with the first-line treatment with low dosage of corticosteroids (P <.001). First-line treatment with high dosage of corticosteroids was a significant predictor of the achievement of clinical remission during the first 6 months of observation. At 18 months follow-up, 17 (44.73%) pts treated with high dosage of corticosteroids maintained clinical remission, being classified as monocyclic pattern, a significant higher percentage when compared with 3 (8.57%) patients treated with the first-line treatment with low dosage of corticosteroids (P: .001), Side effects: 7% of enrolled patients experienced minor adverse events. No severe adverse events or deaths were observed.
4371 Hu et al, 2019 [8]	Retrospective Cohort study	Unclear	517 AOSD patients (Chinese Cohort)	Corticosteroids, methotrexate, hydroxychloroquine	Glucocorticoids were used most frequently (498/517, 96.3%) for disease control, followed by methotrexate (273/517, 52.8%) and hydroxychloroquine (174/517, 33.7%). 84.4%. 357/423 of AOSD cases were able to achieve initial remission with different regimens, mostly including glucocorticoids, methotrexate or hydroxychloroquine.

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					Biological agents e.g., TNF-α and IL-6 receptor blocker, were rarely used in first-line or second-line treatments. Patients who require a higher dose of glucocorticoids to induce remission usually had a poor response to treatment Disease features associated with need for high dose steroids to induce remission: presence of skin rash, pericarditis, splenomegaly and delayed diagnosis (both more than 3 months and more than 6 months)
681 Kim et al. 2014 [9]	Cohort, retrospective	1-year observation	82 pt with AOSD seen between 1992-2012)	Corticosteroids	Patients were divided into those with a favorable (monocyclic course; n=33) and an unfavorable (chronic, polycyclic, or death; n=49) course. polyarthralgia (p=0.01), and high LDH (p=0.03) were significantly associated with an unfavorable disease course Insufficient starting dosage of prednisolone or its equivalent (<30 mg/day) was the most significant predictive factor (OR 6.476, p=0.007) for chronic and relapsing disease, markedly decreasing response rates.
682 Kong, 2010 [10]	Cohort Study	5.6 years	104 pts with Adult-Onset Still's disease (AOSD)	Corticosteroids	Prognosis: 52% and 39% of AOSD patients achieved partial remission and complete remission respectively after 2 weeks of corticosteroid treatment. In 1-month treatment, partial remission and complete remission rates were 92% and 71%, respectively. Cumulative relapse rate of 46.9% (46 patients). 34 relapsed once, 12 relapsed twice or more.
4040 Ter Haar et al. 2019 [111]	Prospective cohort (single center)	Median f/u 5.8 yrs	42 patients with sJIA	2 mg/kg rIL-1Ra escalated for incomplete response to 4 mg/kg rIL-1Ra or additional prednisolone or switched to alternative therapy.	32 patients (76%) had inactive disease 1 year after the initiation of rIL1-Ra. 24 /25 (96%) patients in whom inactive disease was achieved at 1 month had sustained inactive disease at 1 year, compared to only 8 (47%) of 17 patients with active disease at 1 month (OR 27.0 [95% CI 4.17, 539.74], *P* = 0.003). Only 33% of patients required systemic glucocorticoids to achieve or sustain inactive disease.

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				When inactive disease was achieved, rIL-1Ra was tapered after 3 months and subsequently stopped.	Patients with persistent arthritis after 1 month of rIL-1Ra treatment were at risk of prolonged disease activity; Inactive disease was achieved in 1 of 6 patients at 1 year (OR 0.03 [95% CI 0.00, 0.25], *P* = 0.004). Inactive disease was ultimately achieved in these 6 patients with tocilizumab (n = 2), canakinumab (n = 2), or the combination of MTX and prednisolone (n = 2). The ability to achieve inactive disease without glucocorticoids was also associated with sustained inactive disease at 1 year.

References:

1. Sura, A., Failing, C., Sturza, J., Stannard, J., & Riebschleger, M. (2018). Patient characteristics associated with response to NSAID monotherapy in children with systemic juvenile idiopathic arthritis. Pediatr Rheumatol Online J, 16(1), 2-2. doi:10.1186/s12969-017-0219-4
2. Kalyoncu, U., Solmaz, D., Emmungil, H., Yazici, A., Kasifoglu, T., Kimyon, G., . . . Pay, S. (2016). Response rate of initial conventional treatments, disease course, and related factors of patients with adult-onset Still's disease: Data from a large multicenter cohort. J Autoimmun, 69, 59-63. doi:10.1016/j.jaut.2016.02.010
3. Gerfaud-Valentin, M., Maucort-Boulch, D., Hot, A., Iwaz, J., Ninet, J., Durieu, I., . . . Sève, P. (2014). Adult-onset still disease: manifestations, treatment, outcome, and prognostic factors in 57 patients. Medicine (Baltimore), 93(2), 91-99. doi:10.1097/md.0000000000000021
4. Kim, H. A., Sung, J. M., & Suh, C. H. (2012). Therapeutic responses and prognosis in adult-onset Still's disease. Rheumatol Int, 32(5), 1291-1298. doi:10.1007/s00296-011-1801-6
5. Franchini, S., Dagna, L., Salvo, F., Aiello, P., Baldissera, E., & Sabbadini, M. G. (2010). Efficacy of traditional and biologic agents in different clinical phenotypes of adult-onset Still's disease. Arthritis Rheum, 62(8), 2530-2535. doi:10.1002/art.27532
6. Wouters, J. M., & van de Putte, L. B. (1986). Adult-onset Still's disease; clinical and laboratory features, treatment and progress of 45 cases. Q J Med, 61(235), 1055-1065.
7. Ruscitti, P., Cipriani, P., Liakouli, V., Guggino, G., Carubbi, F., Berardicurti, O., . . . Giacomelli, R. (2019). Managing Adult-onset Still's disease: The effectiveness of high-dosage of corticosteroids as first-line treatment in inducing the clinical remission. Results from an observational study. Medicine, 98(15), e15123-e15123. doi:10.1097/MD.0000000000015123
8. Hu, Q. Y., Zeng, T., Sun, C. Y., Luo, C. N., Liu, S., Ding, T. T., . . . Liu, H. L. (2019). Clinical features and current treatments of adult-onset Still's disease: a multicentre survey of 517 patients in China. Clin Exp Rheumatol, 37 Suppl 121(6), 52-57.
9. Kim, Y. J., Koo, B. S., Kim, Y. G., Lee, C. K., & Yoo, B. (2014). Clinical features and prognosis in 82 patients with adult-onset Still's disease. Clin Exp Rheumatol, 32(1), 28-33.
10. Kong, X. D., Xu, D., Zhang, W., Zhao, Y., Zeng, X., & Zhang, F. (2010). Clinical features and prognosis in adult-onset Still's disease: a study of 104 cases. Clin Rheumatol, 29(9), 1015-1019. doi:10.1007/s10067-010-1516-1

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11. Ter Haar, N. M., van Dijkhuizen, E. H. P., Swart, J. F., van Royen-Kerkhof, A., El Idrissi, A., Leek, A. P., . . . Vastert, S. J. (2019). Treatment to Target Using Recombinant Interleukin-1 Receptor Antagonist as First-Line Monotherapy in New-Onset Systemic Juvenile Idiopathic Arthritis: Results From a Five-Year Follow-Up Study. Arthritis Rheumatol, 71(7), 1163-1173. doi:10.1002/art.40865

PICO 21. In patients with treatment naïve, newly diagnosed sJIA without MAS, should DMARD treatment (methotrexate, calcineurin inhibitor) be used as initial therapy and is there a preferred order?

Summary: The literature search revealed three observational studies [**Error! Reference source not found.**, 2, 3] that addressed this PICO question. Hu et al. (2019) assessed a Chinese cohort of 517 patients with adult onset stills disease (AOSD). Glucocorticoids were used most frequently (498/517, 96.3%) for disease control, followed by methotrexate (273/517, 52.8%) and hydroxychloroquine (174/517, 33.7%). A total of 357/423 (84.4%) patients were able to achieve initial remission with different regimens, mostly including glucocorticoids, methotrexate or hydroxychloroquine. Biological agents (e.g. TNF-α and IL-6 receptor blocker) were rarely used in first-line or second-line treatments.[1] A retrospective cohort study provided indirect evidence of methotrexate efficacy in AOSD, reporting that 87.6% of patients achieved clinical remission with initial combination corticosteroid and methotrexate combination therapy.[2] Another retrospective cohort study provided indirect evidence of methotrexate and cyclosporine efficacy in AOSD patients with steroid-refractory or steroid-dependent disease (73% and 75%, respectively).[3] No studies were identified that directly evaluated DMARD monotherapy in treatment naïve patients.

Quality of evidence across all critical outcomes: Very low

Table 1. Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
4371 Hu et al, 2019 [1]	Retrospective Cohort study	Unclear	517 AOSD patients (Chinese Cohort)	Clinical and laboratory features, treatment of AOSD	Glucocorticoids were used most frequently (498/517, 96.3%) for disease control, followed by methotrexate (273/517, 52.8%) and hydroxychloroquine (174/517, 33.7%). 84.4% (357/423) of AOSD cases were able to achieve initial remission with different regimens, mostly including glucocorticoids, methotrexate or hydroxychloroquine. Biological agents, e.g., TNF-α and IL-6 receptor blocker, were rarely used in first-line or second-line treatments.

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					Disease features associated with need for high dose steroids to induce remission: presence of skin rash, pericarditis, splenomegaly and delayed diagnosis (both more than 3 months and more than 6 months)
3323 Kalyoncu et al. 2016 [2]	Multicenter observational cohort	median f/u time 22 mo (0-180 mo)	356 patients with AOSD	Corticosteroids plus methotrexate	85/97 (87.6%) pts went into remission with initial treatment of corticosteroids plus methotrexate.
1270, Franchini, 2010 [3]	Retrospective cohort	Mean 56 months	45 patients with AOSD	DMARDs including methotrexate and cyclosporine were used in 35 patients with steroid-resistant or steroid-dependent disease	"Therapeutic success" (absence of joint swelling, inflammatory joint pain, systemic signs/symptoms and normal ESR/CRP for at least 2 months) achieved in 33/55 DMARD trials (60%). DMARDs with highest efficacy were methotrexate (16/22=73% efficacy) and cyclosporine (9/12= 75% efficacy).

References:

1. Hu QY et al. (2019). "Clinical features and current treatments of adult-onset Still's disease: a multicentre survey of 517 patients in China." Clin Exp Rheumatol **37**(6):52-57.

2. Kalyoncu, U., et al. (2016). "Response rate of initial conventional treatments, disease course, and related factors of patients with adult-onset Still's disease: Data from a large multicenter cohort." J Autoimmun **69**: 59-63.

3. Franchini, S., et al. (2010). "Efficacy of traditional and biologic agents in different clinical phenotypes of adult-onset Still's disease." Arthritis Rheum **62**(8): 2530-2535.

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PICO 22. In patients with treatment naïve, newly diagnosed sJIA without MAS, should biologic treatment (Anakinra, Canakinumab, Tocilizumab or others) be used as initial therapy and is there a preferred order?

Summary: Literature searches identified three observational cohort studies that indirectly addressed whether biologic treatment (Anakinra, Canakinumab, Tocilizumab or others) should be used as initial therapy for sJIA and whether there is a preferred order. None of these trials included a comparison treatment group.

A prospective cohort study by Ter Haar et al.[11] assessed the use of rIL-1Ra (Anakinra) in sJIA at 2 mg/kg which was escalated for incomplete response to 4 mg/kg or additional prednisolone or switched to alternative therapy. The authors found that 76% of patients had inactive disease 1 year after the initiation of rIL-1Ra; 96% patients with inactive disease at 1 month had sustained inactive disease at 1 year, compared to only 47% of patients with active disease at 1 month (OR 27.0 [95% CI 4.17, 539.74], P = 0.003). Patients with persistent arthritis after 1 month of rIL-1Ra treatment were at risk of prolonged disease activity). Among 6 patients who did not respond to initial treatment with rIL-1Ra, Inactive disease was ultimately achieved with tocilizumab (n = 2), canakinumab (n = 2), or the combination of MTX and prednisolone (n = 2). The ability to achieve inactive disease without glucocorticoids was also associated with sustained inactive disease at 1 year.

Vastert et al.[2] investigated IL-1Ra [Anakinra 2mg/kg] as first-line therapy in patients with sJIA. The authors observed excellent response in about 85% of patients within 3 months. Reported side effects included local skin reactions in 65% of patients, without report of serious invasive infections. The authors noted mild cutaneous or upper airway infection and reactivation of infection with herpes simplex virus type 1 in several patients, none of whom required hospitalization or IV antibiotic treatment.

Pacharapakornpong et al.[3] investigated the effect of Tocilizumab in 23 patients with sJIA as a first line therapy when indicated versus greater than 6 months after indicated; 54% of patients who received early treatment with tocilizumab achieved remission whereas no patients who received the dose late achieved remission. Patients who received early treatment had a significant difference from baseline to 12 months in joint count (p=0.003), number of limited joints (p=0.011), patient global (p=0.003), physician global (p=0.003), ESR (p=0.003). For those who received late treatment, there were statistically significant differences from baseline to 12 months in number of active joints (p=0.026), patient global (p=0.014), physician global (p=0.003), ESR (p=0.002), and CHAQ (p=0.017).

The identified studies supported use of biologic treatment (Anakinra, Canakinumab, Tocilizumab) as initial therapy. Although two studies investigated IL-1Ra as initial therapy, no studies evaluated a preferred order for starting these medications. The observational study designs and lack of comparison groups rendered the quality of evidence as very low.

Quality of evidence across all critical outcomes: Very low

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Table 1. Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
4040 Ter Haar et al. 2019 [11]	Prospective cohort (single center)	Median f/u 5.8 yrs	42 patients with sJIA	2 mg/kg rIL-1Ra escalated for incomplete response to 4 mg/kg rIL-1Ra or additional prednisolone or switched to alternative therapy. When inactive disease was achieved, rIL-1Ra was tapered after 3 months and subsequently stopped.	32 patients (76%) had inactive disease 1 year after the initiation of rIL1-Ra. 24 /25 (96%) patients in whom inactive disease was achieved at 1 month had sustained inactive disease at 1 year, compared to only 8 (47%) of 17 patients with active disease at 1 month (OR 27.0 [95% CI 4.17, 539.74], *P* = 0.003). Patients with persistent arthritis after 1 month of rIL-1Ra treatment were at risk of prolonged disease activity; Inactive disease was achieved in 1 of 6 patients at 1 year (OR 0.03 [95% CI 0.00, 0.25], *P* = 0.004). Inactive disease was ultimately achieved in these 6 patients with tocilizumab (n = 2), canakinumab (n = 2), or the combination of MTX and prednisolone (n = 2). The ability to achieve inactive disease without glucocorticoids was also associated with sustained inactive disease at 1 year.
1200 Vastert et al. 2014 [2]	Prospective cohort	32 mo (12-54 mo)	20 patients with sJIA	IL-1Ra (Anakinra) 2 mg/kg	85% of patients showed an adapted ACR Pedi 90 response or had inactive disease at 3 months. 73% of patients with at least an adapted ACR Pedi 90 response at 3 months could stop recombinant IL-1Ra treatment within 1 year. After 2 years, 12 (86%) of 14 patients met the criteria for disease remission, either while receiving (n = 4) or not receiving (n = 8) medication. After 3 years, 10 (91%) of 11 patients met the criteria for disease remission, either while receiving (n = 2) or not receiving (n = 8) medication. Side effects: Local skin reactions in 13/20 pts. No serious invasive infections. Mild cutaneous or upper airway infection and reactivation of infection with herpes simplex virus type 1 in several patients, none of whom required hospitalization or IV antibiotic treatment.
803 Pacharapa kornpong	Retrospective cohort	4 years	23 patients with sJIA	Tocilizumab; first line therapy/when indicated v greater than 6 months	54.5% of patients who received early treatment with tocilizumab achieved remission where no patients who received the dose late achieved remission.

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
2017 [3]				after indicated	- Patients who received early treatment had a significant difference from baseline to 12 months in joint count (p=0.003), number of limited joints (p=0.011), patient global (p=0.003), physician global (p=0.003), ESR (p=0.003). - For those who received late treatment, there were statistically significant differences from baseline to 12 months in number of active joints (p=0.026), patient global (p=0.014), physician global (p=0.003), ESR (p=0.002), and CHAQ (p=0.017)

References:

1. Ter Haar, N. M., van Dijkhuizen, E. H. P., Swart, J. F., van Royen-Kerkhof, A., El Idrissi, A., Leek, A. P., . . . Vastert, S. J. (2019). Treatment to Target Using Recombinant Interleukin-1 Receptor Antagonist as First-Line Monotherapy in New-Onset Systemic Juvenile Idiopathic Arthritis: Results From a Five-Year Follow-Up Study. Arthritis Rheumatol, 71(7), 1163-1173. doi:10.1002/art.40865
2. Vastert, S. J., de Jager, W., Noordman, B. J., Holzinger, D., Kuis, W., Prakken, B. J., & Wulffraat, N. M. (2014). Effectiveness of first-line treatment with recombinant interleukin-1 receptor antagonist in steroid-naive patients with new-onset systemic juvenile idiopathic arthritis: results of a prospective cohort study. Arthritis Rheumatol, 66(4), 1034-1043. doi:10.1002/art.38296
3. Pacharapakornpong, T., Vallibhakara, S. A.-O., Lerkvaleekul, B., & Vilaiyuk, S. (2017). Comparisons of the outcomes between early and late tocilizumab treatment in systemic juvenile idiopathic arthritis. Rheumatol Int, 37(2), 251-255. doi:10.1007/s00296-016-3595-z

PICO 23. In patients with sJIA without MAS who do not respond to initial therapy with non-biologic treatments (NSAIDs, glucocorticoids, DMARDs), should non-biologic treatments be combined or biologic treatment started?

Summary: The literature search identified 50 studies that addressed this question in patients with sJIA: X RCTS, X open label trials, and X observational cohort studies about treatment of sJIA with corticosteroids, conventional DMARDS (mostly MTX), and biologics. Studies of patients with Adult Onset Still's Disease (AOSD) are summarized in a separate section following the sJIA tables.

Corticosteroids: One RCT [1] compared IV methylprednisolone to oral prednisone in 24 patients with sJIA who had failed NSAID therapy, and showed that the IV methylprednisolone group had lower disease activity and received less steroids. There were also 3 cohort studies about treatment with steroids. Two [2, 3] showed that intra-articular steroids were not effective for sJIA, and one [4] showed that growth was affected when oral prednisone was given, but that catch-up growth occurred in 17/24 sJIA patients when steroids were discontinued (Table 1).

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Conventional DMARDs: One RCT [5] found that MTX was marginally better than placebo for sJIA, but the finding was inconclusive due to serious imprecision in the effect estimate (Table 2). Five observational cohort studies [6, 7, 8, 9, 10] discussed the efficacy of MTX in sJIA, and found improvement/response/remission that ranged 63%-88% (Table 3). One study [7] stated that steroids were reduced because of MTX. One cohort study [11] showed that Cyclosporin A was effective in ~50% of 34 patients with sJIA and that steroid dose was reduced; however, was discontinued in many due to side effects. Finally, one cohort study [12] evaluated infection risk with different medications. Found that aHR was ~1.2 with anti-TNF OR anti-TNF +MTX vs. MTX. aHR was ~2 for steroids vs. MTX, and highest aHR for sJIA was 2.7 for Anakinra vs. MTX.

IL-1 inhibitors: Two RCTs[13, 14] compared IL-1 inhibitors (anakinra or canakinumab) to placebo in children with sJIA (Table 4). Il-1 inhibitors showed superiority over placebo for improvement in modified ACR Pedi 30, 50, 70, 90 and inactive disease at 1 month. Two additional RCTs[15,16] compared rilonacept to placebo and found superiority of rilonacept over placebo for ACR 30, 50, 70, and 90 at 1 month, but the difference in inactive disease did not reach statistical significance (Table 5).

Four observational studies specifically evaluated anakinra (Table 6). One retrospective cohort study[17] that used anakinra monotherapy in 10 patients reported a complete response in 80% of patients at a median follow-up of 14.5 months. Another cohort study[18] with a minimum 1-month follow-up reported a complete response to anakinra in 10/22 patients (45.5%). One study[19] found that earlier treatment with anakinra (closer to time of disease onset) led to higher likelihood of treatment response when compared to later treatment with anakinra. Another study[20] identified shorter disease duration as a factor increasing the likelihood of complete clinical response.

Three studies specifically evaluated canakinumab (Table 6). One prospective cohort study[21] reported that 69% of patients achieved remission with canakinumab and allowed tapering of corticosteroids by 48 weeks. However, serious adverse events occurred in 8/19 patients. A 5-year open label extension of two RCTs reported that 48.6% patients achieved remission at 2 years and was sustained until the study's end, but 58% of patients discontinued treatment during the follow-up[22]. A smaller cohort study with 6 months follow-up reported an ACR pedi 90 rate of 20% after canakinumab initiation[23].

One cohort study[24] compared anakinra to canakinumab; the study found a higher rate of drug retention for canakinumab than anakinra, with a difference that was almost statistically significant ($p = 0.056$). Two cohort studies compared anakinra to tocilizumab; one study found no difference in treatment efficacy but did note patients were significantly more likely to continue tociluzumab than anakinra[25] The other study reported more non-responders among patients taking anakinra; some of these patients showed a treatment response when switched to tocilizumab (Table 6).[26]

IL-6 inhibitors (Tocilizumab): Two RCTs[28, 29] compared tocilizumab to placebo in patients with sJIA (Table 7); a meta-analysis of both trials showed that tocilizumab led to significantly greater improvement in ACR pedi 30, 50, 70, and 90 compared to placebo at 12 weeks, but the rate of infection with tocilizumab was also significantly higher compared to placebo. Five serious adverse events occurred in the tocilizumab group and none in the placebo group.

Eleven observational studies specifically evaluated tocilizumab (Table 8). One cohort study [30] showed that tocilizumab was safe and effective for sJIA patients, with 8/11 achieving inactive disease at 6 months. Another cohort study [31] showed that IV tocilizumab in children <2 years old

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was equivalent to treatment of older children aged 2-17 years. Kostic et al.[32] reported that 40/48 patients with sJIA achieved inactive by approximately 4 months after tocilizumab initiation. One cohort study[33] reported that 54.5% of patients who received early treatment (within 6 months of indication for treatment) with tocilizumab achieved remission while no patients who received the dose late (>6 months after indication) achieved remission. A controlled cohort study[34] compared two different tocilizumab dosing schedules (every 2 weeks versus every 4 weeks). Patients in the 4-week group had a milder sJIA course on average and were less likely to have hepatosplenomegaly, coagulopathy, and central nervous system dysfunction. An open-label extension of an RCT[35] reported that patients who received tocilizumab had significant catch up growth when comparing pre-treatment to post treatment height velocity after one and two years. Another cohort study[36] reported that improvement in height velocity was associated with a decrease in corticosteroid dose after tocilizumab initiation. The remaining studies[37, 38, 39, 40] focused on adverse events related to tocilizumab therapy. Adverse events were mostly mild, but there were cases of serious adverse events including MAS. One study[40] of 66 patients reported serious adverse events in 32 patients, but stated that 54% of serious events were "mild."

B cell inhibitors (Rituximab): One prospective cohort study[41] evaluated rituximab (1 IV infusion per week for 4 successive weeks) in 55 children with JIA (84% had sJIA). The study exclusively enrolled patients who had not responded to NSAIDs, corticosteroids, methotrexate, and TNF inhibitors. By 24 weeks 98% of patients achieved ACR 30 response and 25% achieved remission; by 48 weeks 52% achieved remission. At 96 weeks only 25 patients remained, and 44% were in remission (Table 8).

Nine studies evaluated multiple biologics within the same study[42, 43, 44, 45, 46, 47, 48, 49, 50] (Table 9). One cohort study evaluated predictors of need for biologic therapy, with baseline of steroids + MTX [42], and found that elevated ESR and neutrophil/lymphocyte ratio predicted need for biologic treatment. One study [43] reported that serious adverse event rates were higher with canakinumab and tocilizumab than anakinra and etanercept, although serious adverse event rates with etanercept and tocilizumab were highest when steroids were added. The remaining studies reported data that is more difficult to interpret.

Since most studies were observational designs that lacked relevant comparison groups and the few RCTs also provided only indirect evidence, the quality of evidence was very low.

Quality of evidence across all critical outcomes: Very low

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Table 1. Intraarticular Corticosteroids – Data from RCT and Observational Studies

Ref ID, Author, Year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
9, Picco, 1996 [1]	RCT	6 months and if completed study, 12 months	22 patients with sJIA in whom 3-6 months of NSAIDs were unsuccessful	Randomized to receive: Group A - methylprednisolone IV pulses for 3 days at 5 mg/kg/day and for 3 days at 2.5 mg/kg/day, afterwards 1 mg/kg/day of prednisone which was tapered Group B – Prednisone 1 mg/kg/day which was tapered the same as in group A	Group A showed improvement of clinical and biological parameters of inflammation with a persistence of benefit for 6 months; Group A required a lower cumulative steroid daily dose than Group B.
950, Papadopoulo, 2013 [2]	Cohort study	At least 6 months	220 children with JIA, for a total of 1096 injected joints;	Intraarticular joint injections simultaneously of at least 3	After injection, 11 out of 15 sJIA patients experienced a flare, while the other 4 remained in remission. No serious adverse events or deaths occurred.

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Ref ID, Author, Year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
			15 patients (6.8%) had sJIA, 109 (49.6%) had oligoJIA	joints: triamcinolone hexacetonide for large joints; methylprednisolone for small or difficult to access joints	
3684, Breit, 2000 [3]	Cohort study	Multiple time points with longest being a mean of 64 (+/- 23.4) weeks	194 patients with JIA for a total of 1439 injected joints; 20 pts (10%) had sJIA All patients had insufficient response to oral or parental drug treatment (NSAID, DMARD, or corticosteroids)	Intraarticular triamcinolone hexacetonide	Children with sJIA had the shortest median duration of effect (36 weeks). The first injections had the longest median duration of improvement (sJIA 57 weeks).
2242, Simon, 2002 [4]	Cohort study	Mean 13.6 (+/- 5) years	24 patients with sJIA	Daily oral prednisone in a mean dose of 0.2 mg/kg or more during	During steroid therapy, the mean loss of the height standard deviation score for chronological age was -2.7 +/- 1.5 and positively correlated with steroid duration. After discontinuation, 17 patients (705) had catch up growth. Mean final height was -2.8 +/- 1.8

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Ref ID, Author, Year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
				at least the first 2 years. Height was measured at regular intervals.	

Table 2. MTX vs placebo – Data from Randomized Controlled Trial [5]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	placebo	Relative (95% CI)	Absolute (95% CI)		
Clinical improvement												
1	randomised trials	not serious	not serious	very serious [a]	serious [b]	none	11/44 (25.0%)	7/44 (15.9%)	**RR 1.57** (0.67 to 3.68)	**91 more per 1,000** (from 52 fewer to 426 more)	⊕◯◯◯ VERY LOW	

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Mixed population and comparison to placebo

b. Wide CI crosses significant effect and no-effect lines

Table 3. Conventional DMARDs – Data from Observational Studies

Ref ID, Author, Year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
3002 Albarouni, 2014 [6]	Retrospective cohort study	3-12 months	731 JIA patients (207 oligoarticular, 25 sJIA)	MTX (dose unclear)	PedACR 30 Response at 3 mos: -sJIA 21/24; PedACR 70 Response at 12mos: - sJIA: 13/17;
1244 Lin, 2000 [7]	Retrospective cohort study	1.3-18.6 years	52 JIA patients (13 oligoarticular, 17 sJIA)	MTX 9-10mg/m2/week	Safety: 25% of patients had adverse effects, all minor aside from 1 patient with HSV reactivation - Clinical improvement: sJIA 9/17 - Remission: sJIA 4/17 - A significant number of patients had reduction of steroid dose or discontinuation of steroids
1048 Gottlieb, 1997 [8]	Retrospective cohort study	1-62 months	101 JIA patients (19 oligoarticular, 25 sJIA); 25 JIA patients for withdrawal portion (6	MTX 0.2-0.7mg/m2/dose – outcomes after discontinuation	Response to MTX: - sJIA: 2/25 none, 6/25 mild, 7/25 moderate, 10/25 complete; mean 25.5 months to achieve control After discontinuation of MTX: - sJIA: 2/4 remission, 2/4 relapse

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Ref ID, Author, Year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
			oligoarticular, 4 sJIA)		
1443 Ravelli, 1994 [9]	Retrospective cohort study	6 months	19 patients with sJIA	MTX 7.5-11mg/m2/week	12/19 (63%) patients were responders (>50% reduction in the number of joints with active arthritis and/or an articular severity score Predictors of response to MTX: shorter disease duration, fewer radiographic lesions, fewer joints with limitation of motion, lower functional limitation score, and lower articular severity score.
3486 Rose, 1990 [10]	Cohort study	8-39 months	29 patients with JIA (12 with sJIA)	MTX 5-15mg/m2/week (mean dose 7.1mg/m2/week)	10/12 sJIA patients had clinical improvement in fever and rash, and 1/12 achieved clinical remission 6/12 patients with sJIA had persistent arthritis 8/29 total patients had some adverse effects; however, most were mild and resolved with medication discontinuation or dose decrease
1254 Gerloni, 2001 [11]	Cohort study	4mos-8 years	34 patients with sJIA and 7 with chronic anterior uveitis	Cyclosporin A 3-5mg/kg PO BID	Reduction of fever in 52% of patients 50% reduction in arthritis in 12/28 patients at 1 yr. Improvement in ESR and Hb in ~40% of patients The mean prednisone dose was decreased from 0.34mg/kg/day at baseline to 0.14mg/kg/day

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Ref ID, Author, Year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
					Cyclosporin discontinued in 32/34 patients, 8 due to remission, but 15 because of disease flare/inefficacy and 9 because of side effects.
3399 Beukelman, 2016 [12]	Retrospective cohort study	Up to 10 years (2000-2010)	6,035 JIA patients	MTX, anti-TNFs, and Anakinra (evaluating infection rates)	Risk of infection associated with TNFi monotherapy versus MTX: aHR 1.19 (0.72–1.94) TNFi + MTX combination therapy versus MTX: aHR 1.23 (0.69–2.17). Baseline high-dose oral glucocorticoid use (≥10 mg/day of prednisone): aHR 2.03 (1.21–3.39) Anakinra versus MTX: aHR 3.53 (1.83–6.82); but less so compared with MTX users with SJIA [aHR 2.69 (0.82–8.82)]

Table 4. Anakinra or Canakinumab vs Placebo – Data from Randomized Controlled Trials[13, 14]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Biologic	placebo	Relative (95% CI)	Absolute (95% CI)		
ACR Pedi 30 at 4 weeks												

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Biologic	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious [a]	serious [b,c]	none	11/12 (91.7%)	7/12 (58.3%)	**RR 1.57** (0.95 to 2.61)	**333 more per 1,000** (from 29 fewer to 939 more)	⊕⊕◯◯ LOW	

Modified ACR Pedi 30 at 4 weeks

2	randomised trials	not serious	not serious	serious [a]	not serious	none	43/55 (78.2%)	5/53 (9.4%)	**RR 8.28** (3.55 to 19.27)	**687 more per 1,000** (from 241 more to 1,000 more)	⊕⊕⊕◯ MODERATE	Favors IL-1 inhibitors

Modified ACR Pedi 50 at 4 weeks

2	randomised trials	not serious	not serious	serious [a]	not serious	none	36/55 (65.5%)	2/53 (3.8%)	**RR 14.05** (4.13 to 47.84)	**492 more per 1,000** (from 118 more to 1,000 more)	⊕⊕⊕◯ MODERATE	Favors IL-1 inhibitors

Modified ACR pedi 70 at 4 weeks

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Biologic	placebo	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	not serious	not serious	serious [a]	not serious	none	34/55 (61.8%)	1/53 (1.9%)	**RR 20.45** (4.14 to 100.97)	**367 more per 1,000** (from 59 more to 1,000 more)	⊕⊕⊕◯ MODERATE	Favors IL-1 inhibitors
Modified ACR Pedi 90 at 4 weeks												
1	randomised trials	not serious	not serious	serious [a]	serious [c]	none	20/43 (46.5%)	1/41 (2.4%)	**RR 19.07** (2.68 to 135.69)	**441 more per 1,000** (from 41 more to 1,000 more)	⊕⊕◯◯ LOW	Favors IL-1 inhibitors
Inactive disease at 4 weeks												
1	randomised trials	not serious	not serious	serious [a]	serious [c]	none	13/43 (30.2%)	0/41 (0.0%)	**RR 25.77** (1.58 to 419.95)	**Cannot calculate**	⊕⊕◯◯ LOW	Favors IL-1 inhibitors

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Indirect comparison to placebo

b. Wide CI crosses significant effect and no-effect lines

c. Single small study

Table 5. Rilonacept vs Placebo – Data from Randomized Controlled Trials[15, 16]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rilonacept	Placebo	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events												
2	randomised trials	not serious	not serious	serious [a]	serious [b]	none	3/53 (5.7%)	1/42 (2.4%)	**OR 1.45** (0.18 to 11.88)	**10 more per 1,000** (from 19 fewer to 201 more)	⊕⊕◯◯ LOW	
ACR 30 at 4 wks												
2	randomised trials	not serious	not serious	serious [a]	not serious	none	37/52 (71.2%)	15/40 (37.5%)	**OR 4.48** (1.81 to 11.09)	**354 more per 1,000** (from 146 more to 494 more)	⊕⊕⊕◯ MODERATE	Favors rilonacept
ACR 50 at 4 wks												
2	randomised trials	not serious	not serious	serious [a]	not serious	none	30/52 (57.7%)	11/40 (27.5%)	**OR 3.84** (1.53 to 9.64)	**318 more per 1,000** (from 92 more to 510 more)	⊕⊕⊕◯ MODERATE	Favors rilonacept
ACR 70 at 4 wks												

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rilonacept	Placebo	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	not serious	not serious	serious [a]	not serious	none	20/52 (38.5%)	5/40 (12.5%)	**OR 4.43** (1.48 to 13.31)	**263 more per 1,000** (from 50 more to 530 more)	⊕⊕⊕◯ MODERATE	Favors rilonacept

Inactive Disease at 4 wks

1	randomised trials	not serious	not serious	serious [a]	serious [b]	none	2/36 (5.6%)	0/34 (0.0%)	**OR 5.00** (0.23 to 108.01)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕◯◯ LOW	

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Comparison to placebo

b. Wide CI crosses significant effect and no-effect lines

Table 6. IL-1 Inhibitors (Anakinra and Canakinumab) – Data from Observational Studies

Ref ID, Author, Year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
182 Nigrovic, 2011 [17]	Retrospective single arm cohort	median follow-up interval of 14.5 months	46 SJIA patients	Anakinra monotherapy was used in 10 patients (22%), while 67% received	Complete response to initial therapy 27/46 (59%); Partial response 18/46 (39%). Complete response with anakinra monotherapy 8/10 (80%) Serious infection 3/46 (7%)

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Ref ID, Author, Year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
				corticosteroids and 33% received additional DMARDs.	
2833 Gattorno 2008 [18]	Single Arm Cohort	Minimum 1 month	22 patients with sJIA selected for treatment with anakinra	Anakinra 1mg/kg/day SQ (max dose 100mg), increases allowed to 3-4mg/kg/day	Complete response in 10/22 patients (45.5%). 2 groups of responders Good responders: reduction in joint count and CRP@1 week (p=0.005), @1 month (p=0.005), and follow up (p=0.005). Incomplete responders: reduction in joint count @1 week (p=0.002), @1 month (p=0.046), follow up (p=NS), reduction in CRP @1 week (p=0.01), @1 month and follow up (p=NS) 2 patients developed MAS and discontinued anakinra, 1 restarted without MAS, 1 did not restart
187 Pardeo, 2015 [19]	Case series	6 months	25 SJIA patients	Anakinra plus concomitant medications	The only variable significantly associated with response was the time from disease onset to receiving anakinra, with earlier treatment being associated with a better outcome: in patients with inactive disease 1.9 (0.8–5.4), in patients with active disease 24.5 (6.2–58.4) months.
2995 Saccomanno, 2019 [20]	Case series	12 months	62 SJIA patients	Anakinra plus concomitant medications	On multivariable analysis, independent correlations with achievement of complete clinical response were identified for shorter disease duration, lower active joint count, higher ferritin level, and greater activity of systemic manifestations. 10 patients had adverse events (including 5 who developed MAS).
4420 Nisimura 2020 [21]	Single-arm prospective cohort study	48 weeks	19 sJIA patients aged 2-20yo	Canakinumab 4mg/kg q4weeks	19/19 achieved ACRpedi30 at week 8, and 14/19 completed steroids by week 28 Week 48 ACRpedi50/70/90/100: 100%/100%/88%/69% Safety: 8/19 had SAE: 2 flares (as above), 4 serious infections, 2 MAS (3 discontinued prior to week 28 as a result) Many mild AEs, but no malignancy or anaphylaxis
522, Ruperto 2018 [22]	5-year open-label extension of 2 RCTs	5 years	144 SJIA patients	Canakinumab	At 2 years, aJIA-ACR 50/70/90 response rates were 62%, 61% and 54%. Clinically inactive disease was 48.6% at 2 years and was sustained until the end of the study. 102 (58%) discontinued, with 63/102 (62%) due to inefficacy.

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Ref ID, Author, Year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
					Proportion of patients for ACR50, ACR70 and ACR90 significantly dropped from 69% at year 3.5-4 to 48% at years 4-4.5. Proportion of patients with CID reached maximum in 1.5 years reaching 62%, and significantly dropped in years 4.5-5 down to 18%
2900 Ruperto, 2011 [23]	Single-arm cohort	6 months	25 SJIA patients	Canakinumab at doses 0.5, 1.5 and 4.5 mg/kg given subcutaneously during first 15 days, and then 4mg/kg every 4 weeks	ACRPedi30 – 15/25 (60%) ACRPedi50 – 15/25 (60%) ACRPedi90 - 5/25 (20%) Tapered of the steroid dose – 8 of 11 responders (73%); 4/11 of those discontinued steroid treatment by the end of the study.
1105 Sota 2018 [24]	Single Arm Cohort	8 years	77 patients with sJIA receiving IL-1i	Anakinra 1-4mg/kg Canakinumab 2mg/kg every 8 weeks to 4mg/kg every 4 weeks	Drug retention rate for IL-1i at 12, 24, 48, 60 months (%): 79.9, 59.5, 53.5, 53.5 DRR higher for biologic naïve vs prior biologic, p=0.038 DRR higher for no AEs vs AEs, p=0.004 DRR higher for canakinumab vs anakinra, p=0.056 DRR higher for monotherapy vs combo with DMARD, p=0.058 Cox regression variables associated with drug withdrawal: biologic exposed (HR 3.37 (1.341-8.406) p=0.01) and AEs (HR 2.970 (1.186-7.435) p=0.020) Reduction in corticosteroid requirement, p=0.025 16/63 (27%) discontinued CS No serious AEs, no MAS
3596 Kearsley-Fleet, 2019 [25]	Single arm cohort	12 months	76 SJIA patients	Anakinra (86%) and tocilizumab (63%)	ACR Pedi 90: 42% Clinically inactive disease: 39% No significant difference between anakinra and tocilizumab on primary treatment outcomes. Treatment survival (patients continuing their biologic treatment) was better with tocilizumab (89%) compared with anakinra (59%; P = 0.002).

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Ref ID, Author, Year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
1725 Arthur 2018 [26]	Single arm Cohort	unknown	52 patients with sJIA (38 anakinra, 14 tocilizumab)	No doses provided	Anakinra: 9 nonresponders, 23 “any responder” Tocilizumab: 3 nonresponders, 11 “any responder” 8 tocilizumab patients were anakinra non-responders, 6 of these were any responders to tocilizumab.
1416 Horneff 2017 [27]	Single Arm Cohort	15 years of study, each patient observed for 24 months	245 patients with sJIA exposed to etanercept (143), tocilizumab (71), or IL-1i (anakinra 38, canakinumab 22)	Biologic per treating physician – data recorded in BIKER. Anakinra, canakinumab, tocilizumab,	ACR response criteria ACR70 @months 3, 6, 12, 18, 24 IL-1i (%): 47, 45, 44, 59, 47 TOC (%): 47, 45, 44, 59, 47 ACR90 @ months 3, 6, 12, 18, 24 IL-1i (%): 34, 36, 35, 51, 41 TOC (%): 31, 31, 27, 34, 35 JADAS-10 (minimal disease activity ≤3.8 and remission on drug ≤1.0) IL-1i: decrease from median 13.0 (6.7-20.6) to 0.6 (0.2-2.0) TOC: decrease from median 16.9 (8.1-24.8) to 1.5 (0.2-2.0) @month 6 JADAS10 MDA TOC:IL-1a OR=1.06 (95%CI 0.96-1.16) @month 6 JADAS10 remission TOC:IL-1i OR=1.01 (0.94-1.09) ACR preliminary criteria for inactive disease @ months 3, 6, 12, 18, 24: TOC 19/49, 29/63, 32/67, 24/53, 20/60 IL-1i 17/34, 28/43, 28/47, 20/38, 19/34 Number/rate of patients without systemic symptoms @ months 0, 3, 6, 12, 18, 24: TOC 41/58%, 30/86%, 45/94%, 42/93%, 35/95%, 27/96% IL-1i 24/37%, 19/68%, 28/78%, 31/79%, 23/74%, 19/83%

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Ref ID, Author, Year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
					Rates of AE (per patient-year) were significantly higher with TOC (risk ratio (RR) 5.3; p < 0.0001) compared to ETA and serious AE were also more frequent with TOC (RR 2.5; p = 0.01) and IL-1i (2.9; p < 0.01) compared to ETA.

Table 7. Tocilizumab vs Placebo – Data from Randomized Controlled Trials[28, 29]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCZ	placebo	Relative (95% CI)	Absolute (95% CI)		
ACR-Pedi30 at 12 weeks												
2	randomised trials	not serious	not serious	serious [a]	not serious	none	80/95 (84.2%)	13/60 (21.7%)	**RR 3.77** (2.31 to 6.13)	**600 more per 1,000** (from 284 more to 1,000 more)	⊕⊕⊕◯ MODERATE	Favors TCZ
ACR-Pedi50 at 12 weeks												
1	randomised trials	not serious	not serious	serious [a]	serious [b]	none	16/20 (80.0%)	4/23 (17.4%)	**RR 4.60** (1.84 to 11.51)	**626 more per 1,000** (from 146 more to 1,000 more)	⊕⊕◯◯ LOW	Favors TCZ
ACR-Pedi70 at 12 weeks												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCZ	placebo	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	not serious	not serious	serious [a]	not serious	none	68/95 (71.6%)	6/60 (10.0%)	**RR 7.07** (3.27 to 15.27)	**607 more per 1,000** (from 227 more to 1,000 more)	⊕⊕⊕◯ MODERATE	Favors TCZ
SAE at 12 weeks												
2	randomised trials	not serious	not serious	serious [a]	serious [c]	none	5/95 (5.3%)	0/60 (0.0%)	**RR 4.46** (0.55 to 36.10)	**Cannot calculate**	⊕⊕◯◯ LOW	
ACR-Pedi 90 at 12 weeks												
1	randomised trials	not serious	not serious	serious [a]	serious [b]	none	28/75 (37.3%)	2/37 (5.4%)	**RR 6.91** (1.74 to 27.44)	**319 more per 1,000** (from 40 more to 1,000 more)	⊕⊕◯◯ LOW	Favors TCZ
Infection at 12 weeks												
1	randomised trials	not serious	not serious	serious [a]	serious [b]	none	41/75 (54.7%)	11/37 (29.7%)	**RR 1.84** (1.08 to 3.14)	**250 more per 1,000** (from 24 more to 636 more)	⊕⊕◯◯ LOW	Favors placebo

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Comparison to placebo

b. Single small study

c. Wide CI crosses significant effect and no-effect lines

Table 8. Tocilizumab – Data from Observational Studies

Ref ID, Author, Year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
4643 Demir 2019 [30]	Cohort study	Unclear	20 JIA patients, 13 of these sJIA (only reporting about these)	TCZ q2weeks 10mg/kg for <30kg, 8mg/kg for >30kg	2 sJIA patients had anaphylaxis and had to discontinue treatment. Of the remaining 11 sJIA patients: - all had improvements in ESR/CRP/platelet count/active joint count/JADAS-71 - 8/11 had inactive disease at 6 months, off of steroids, while 3/11 had CID but high CRP and still required prednisone 0.05-0.25mg/kg - adverse events: In addition to anaphylaxis, 2 with thrombocytopenia, 1 with MAS, and 1 with transaminitis
4468 Mallalieu 2019 [31]	Prospective cohort study	12 weeks	11 sJIA patients <2yo	TCZ 12mg/kg IV q2weeks (and then compared to sJIA patients aged 2-17yo)	Primary outcome: Pharmacodynamics were similar to children aged 2-17yo Secondary outcome: Similar decreases in JADAS-71, rash, and fever, as children aged 2-17yo Safety: Similar safety profile, aside from more hypersensitivity in children <2yo

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Ref ID, Author, Year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
3247, Kostik 2018 [32]	Single arm cohort study	Unclear	48 active soJIA patients	Patients who had failed corticosteroids, MTX, and CSA. Dosing for TCZ was 12 mg/kg for pts <30kg and 8 mg/kg in pts >30 kg	40/48 patients achieved inactive disease (defined by Wallace criteria) in approximately 4 months. Flares occurred in 31.8% of patients and were determined by 30% worsening of ACR pedi measurements. 7 pts d/c treatment due to adverse reactions and 8 d/c due to remission. 2 pts died, one due to MAS and fungal infection and the other d/t amyloidosis. Those who were more likely to have inactive disease were those with a milder disease course with less frequent HSM, pulmonary, cardiac, and MAS features. Predictors of inactive disease were CRP <82 mg/L (p=0.016), ESR <32 mm/hr (p=0.014), ferritin <273 ng/mL (p=0.0001), Hb >11.3 g/L (0.014), LDH <676 U/L (p=0.000014), plt >335x10^9/L (p=0.11) and depression of WBC 2 weeks after TCZ infusion (p=0.05).
803 Pacharapakornpong 2017 [33]	Observational cohort	4 years	23 systemic onset JIA patients	Tocilizumab; first line therapy/when indicated vs greater than 6 months after indicated; 8 mg/kg for those >30kg and 12 mg/kg for <30 kg	54.5% of patients who received early treatment with tocilizumab achieved remission where no patients who received the dose late achieved remission. - Patients who received early treatment had a significant difference from baseline to 12 months in joint count (p=0.003), number of limited joints (p=0.011), patient global (p=0.003), physician global (p=0.003), ESR (p=0.003). - For those who received late treatment, there were statistically significant differences from baseline to 12 months in number of active joints (p=0.026), patient global (p=0.014), physician global (p=0.003), ESR (p=0.002), and CHAQ (p=0.017)

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Ref ID, Author, Year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
3699 Kostik 2015 [34]	Controlled cohort	Not disclosed, median treatment was 665 days	37 pts with SoJIA	Dosing for TCZ was 12 mg/kg for pts <30kg and 8 mg/kg in pts >30 kg	TCZ was given either every 2 weeks (n=8) or every 4 weeks (n=26). Those receiving q4week dosing had a milder course and Q2 vQ4 week treatment was up to the discretion of the treating physician. -10/20 stopped CSA in a mean of 53 days. - Steroids were stopped in 21/26 in a mean of 66 days. - MTX stopped in 9/32 in a mean of 11.5 months. - Inactive disease obtained in 12 pts. - Those who were successfully treated with Q4 dosing were less likely to have hepatosplenomegaly (p=0.003), coagulopathy (p=0.005), CNS dysfunction (p=0.0001), ILD (p=0.005), ferritin <605 ug/L (p=0.0001), LDH <571 U/L (p=0.001), albumin > 2.8 g/dL (p=0.001), ESR <26 mm/hr (0.001), granulocytes <9792 cells/uL (0.0015), platelets >208x10^9/L (p=0.005), and CRP <82.2 mg/L (0.001). -4 patients withdrew due to infusion reactions and a diagnosis of early MAS. One patient died after 5 months TCZ treatment due to severe uncontrolled MAS.
555 De Benedetti 2015 [35]	Trials with open label extension	Up to 5 years	83 systemic onset JIA patients	Tocilizumab dosing per TENDER study protocol	Those patients who received tocilizumab had significant catch up growth when comparing pre-treatment to post treatment height velocity after one and two years. - Pre-treatment velocity 3 cm/year and post 6.6 cm/yr and 6.8 cm/year, respectively (p = <0.0001, paired t test). - There were also increases in TGF-1 when comparing pre and post

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Ref ID, Author, Year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
					treatment (p = <0.0001). - Reduction in glucocorticoids when comparing pre and post treatment (p = <0.001)
1185 Miyamae 2014 [36]	Single arm cohort study	About 3 years	45 sJIA pts, boys under 10 yrs and girls under 8 yrs	TCZ 8 mg/kg every 2 weeks	- 38 (84.4%) achieved ACR pedi 0 response - mean standard deviation score for height was -2.67+/1.97 and mean disease duration was 4.1+/-3.2 yrs - no clear correlation between baseline corticosteroid use and height, but pts with less than median corticosteroid exposure had significant improvement in standard deviation score for height compared to those with higher corticosteroid exposure; equivalent dose <6.7 mg/person/day (n=22) v ≥ 6.7 mg/person/day (n=23), p=0.001 - mean standard deviation of height improved from -5.96+/-3.93 in the year prior to TCZ to -2.51+/-4.77, n=28; paired t test w p=0.0064 - only factor that showed correlation with improvement in height velocity was a decrease in steroid dose after TCZ initiation - extension over 3 years of TCZ treatment showed standardization by 3rd year of treatment
3394 Yasuoka 2019 [37]	Cohort study	July 2004-December 2015 (137 months)	40 pts with soJIA	All patients received TCZ 8 mg/kg at intervals	Pts who developed fever, respiratory, GI, cardiovascular, and dermatologic symptoms were deemed to have had a hypersensitivity reaction. 5 of 50 patients experienced reaction after the 3rd dose. Lower age, lower body weight, and shorter height were associated with those patients who had reaction; p=0.1, .02, and .02 respectively. 4/5

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Ref ID, Author, Year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
				between 7 and 14 days.	patients with hypersensitivity reactions were also noted to have elevated IgE and anti TCZ antibodies.
735 Xiao 2016 [38]	Cross sectional study	104 weeks	112 patients with soJIA and 118 patients with polyarticular JIA	Tocilizumab used in patients with both systemic JIA (12 mg/kg for patients <30 kg and 8 mg/kg for patients >30 kg) q2 weeks and polyarticular JIA (8 mg/kg for patients >30 kg and 10 mg/kg for patients <30 kg) q4 weeks; open label extension from both TENDER and CHERISH trials	- 50 sJIA patients (21 pts <30 kg and 29 pts >30 kgs) had grade 0-1 neutropenia (defined as 1.5 x10^9/L – normal). - 34 sJIA patients (16 pts <30kg and 18 pts >30 kg) had grade 2 neutropenia (defined as 1.0-<1.5x10^9/L). - 26 sJIA patients (19 pts < 30kg and 7 pts >30 kg) had grade 3 neutropenia (defined as 0.5-<1.0x10^9/L) - 2 sJIA patients <30 kg and grade 4 neutropenia. There is no direct relationship between the dose of tocilizumab and the development of neutropenia or infections. Neutropenia was noted to be worse in patients who were receiving methotrexate and had soJIA, but not those who had poly JIA and were on combination therapy. It appears methotrexate use was associated with neutropenia in soJIA patients. In both soJIA and poly JIA it seems as though patients with a lower body weight had a higher risk of neutropenia. This paper suggests that the risk of infection is related to underlying JIA and less related to treatment. Neutropenia seems to be transient and not directly related to infections.
3929 Yokota 2016 [39]	Single arm cohort	52 weeks	417 soJIA pts	TCZ 8 mg/kg every 8 weeks	-30.5% (127) pts enrolled from previous clinical trial - 16 (3.8%) were lost to follow up

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Ref ID, Author, Year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
					- 17 (4.1%) had AEs that lead to discontinuation of treatment - most common AE was infection/infestation at 69.8/100 PYs - 2nd most common AE was respiratory, thoracic, and mediastinal disorders w rate of 34.9/100 PYs - MSK disorders 19.7/100 PYs - connective tissue disorders 17/100 PYs - blood/lymphatic disorders 14/100 PYs - GI disorders 13.8/100 PYs - decreased platelet count 2.9/100 PYs - decreased white count 4.2/100 PYs - for serious AEs incidence rate is 54.5/100 PYs, 3.4% of pts discontinued TCZ due to SAE - most common SAE was infection/infestation at 18.2/100 PYs - 2nd most common SAE was blood/lymphatic disorders at 9.8/100 PYs - MSK disorders 4.4/100 PYs - connective tissue disorders 4.2/100 PYs - GI disorders 3.7/100 PYs - 2 deaths, one d/t vasculitis and cardiac failure and the other d/t pseudomonas, ILD, and sepsis

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Ref ID, Author, Year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
					- 26 reported cases of MAS in 24 pts; 2 definite MAS, 15 probable, 3 events viral related hemophagocytic syndrome and 6 were possible or non MAS - 25 required treatment including cyclosporine and IV steroids - 30 pts (7.2%) had infusion reactions a a rate of 11.3/100 PYs - 8 pts had 14 serious infusion reactions, rate of 3.4/100 PYs; all required steroids and antihistamines and only 3 received epinephrine -⅝ of anti TCZ antibodies (only 6 tested) - 7 continued treatment, but 3/7 later discontinued treatment secondary to subsequent infusion reactions, 2 of these had anti TCZ antibodies - all between 2nd and 4th infusions 1 pt discontinued TCZ -mean CRP levels decreased from 2.7 mg/dL to 0.5 mg/dL after 4 weeks of treatment and levels remained normal from week 8 to 52 - at 4 weeks 90.5% of patients had normal CRP, at 8 weeks it was 96.2% and at 52 weeks it was 99% -baseline steroid dose was 0.9 mg/kg/day and decreased to 0.7 mg.kg/day at 4 weeks with further decrease to 0.5 mg/kg/day at 8 weeks and was down to 0.2 mg/kg/day at 52 weeks -155 pts were receiving steroids at baseline and received TCZ for 48

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Ref ID, Author, Year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
					weeks, of those 19 d/c steroids completely - 251 pts reported systemic features at baseline and week 52; 54.6% (137/251) had fever and this decreased to 5.6% (14/251) -125 pts had fever resolve by wk 52 - reports of rash decreased from 43% (108/251) at baseline to 5.6% (14/251) at week 52 - mean systemic feature score decreased from 1.6+/-1.7 to 0.2+/-0.6 at week 52 (p<0.0001)
2306 Yokota 2014 [40]	Secondary analysis of RCT	Unclear, median exposure 3.4 years	11 pts from phase II open label dose escalation study and 56 pts from phase III study including open label lead in phase and a randomized, double blind placebo controlled withdrawal phase	TCZ 8 mg/kg every 2 weeks, DMARDS discontinued before entry into the study	- 32 pts reported serious AEs and 54% of serious AEs were mild - no pts developed pulmonary hypertension or malignant tumors - 1 case of definite MAS and 1 case of probable MAS developed - 5 pts developed anti TCZ antibodies - 2 pts w no anti TCZ abs developed infusion reactions - grade 3 neutropenia developed in 12 pts and grade 4 in pt - LFT elevation occurred but typically was precipitated by infection or flare, although causal relationship not excluded Week 168 -ACR 30: 80.3% (49/61, 95% CI 68.2-89.4) -ACR 50: 80.3% (49/61, 95% CI 68.2-89.4)

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Ref ID, Author, Year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
					-ACR 70: 74.5% (46/61, 95% CI 62.7-85.5) -ACR 90: 60.7% (37/61, 95% CI 47.3-72.8) -ACR 100: 18% (11/61, 95% CI 9.4-30) - no difference noted between biologic naive and biologic prior use patients - 22 pts (32.8%) completely stopped steroids, 16 patients (23.9%) decreased dose by 70% and 9 pts (13.4%) by 50% - mean treatment interval was 15.2 days, shortened to <10 days in 35 pts - mean hemoglobin concentration inc by about 2 g/dL
1247, Alexeeva, 2011 [41]	Open label prospective cohort study	96 weeks	Children from 2.3 years to 17 years of age diagnosed w/ poly, oligo or systemic JIA…55 patients total, 46 with sJIA (84%); pts had to be diagnosed > 1 yr prior and had to fail steroids, NSAIDs, and at	Rituximab 375 mg/m2 weekly x 4 weeks; repeated if patients had persistent systemic manifestations, 'active' joints, elevated CRP and increased ESR at 24 wks	No cases of exacerbation with severe systemic manifestation or polyarthritis w/ severe functional impairment were observed. At week 12, rash went from 55% to 10% of patients (p<0.001) and carditis and polyserositis were resolved in all patients. At week 24, 98% of patients achieved ACR 30 response and 25% achieved remission. No patient had carditis; 65% had inactive joints; but 2 out of 46 patients continued to have fever. At 48 weeks, 52% of patients achieved remission. At 96 wks there were 25 pts remaining, and the remission rate was 44%.

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Ref ID, Author, Year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
			least 2 other immunosuppressants including MTX and were also not responsive to TNFi	Pre-med with IV methylpred given as needed Background immunosuppressant therapy was permitted	Of those on prednisolone at the start, there was no dose escalation and it was not prescribed for those who had never received it before.

Table 9. Multiple Biologic Medications – Data from Observational Studies

Ref ID, Author, Year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
4653 Dundar 2020 [42]	Cohort study	2-6.8 years, median 3.3 years	50 sJIA patients	All received steroids + MTX, biologic was initiated in some as needed	58 total episodes of sJIA disease activity, biologic required in 17 Predictors of need for biologic therapy: elevated ESR and high neutrophil/lymphocyte ratio
4487 Klein 2019 [43]	Cohort study	Mean follow-up 4.3 years	260 sJIA patients	Etanercept (151), TCZ (109), anakinra (71), canakinumab (51)	Rates of serious adverse events (SAE) highest with canakinumab and TCZ (20/100 person years and 21/100PY) vs. anakinra and etanercept (7/100PY and 4/100PY) SAE rates higher when steroids added to etanercept or TCZ, but SAE rate did not change when steroids added to anakinra or canakinumab

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Ref ID, Author, Year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
1191, Otten, 2013 [44]	Cohort	F/U at 3 months, 15 months, yearly	307 patients (51 systemic, 256 non systemic JIA)	After failing etanercept, 80% switched to a second, 22% switched to a third biologic agent; During 1030 patient years of follow up, 49 switches to adalimumab, 28 infliximab, 17 anakinra, four to abatacept and 4 drug trials were evaluated.	84% of patients who started etanercept as a first biologic agent were, after 12 months, still on the drug compared to 47% who started a second and 51% who started a third. Patients who switched because of primary ineffectiveness continued the second agent less often. After etanercept failure, drug continuation of adalimumab was similar to infliximab for patients with non systemic JIA. Anakinra was superior to a second TNF blocker for systemic JIA. AE rates within the first 12 months after initiation were comparable for each course and biologic agent.
3071 Barut, 2019 [45]	Single arm study	3-27 months (median)	165 Patients with systemic JIA	Corticosteroids 168 (100%) for median 12 months; Methotrexate 126 (75%) for median 27 months; Cyclosporine A 29 (17.3%) for median 8 months; Anakinra 27 (16.1%) for median 3 months; Canakinumab 27 (16.1%) for median 19.5 months; Tocilizumab 18 (10.7%) for median 7 months; Etanercept 50 (29.8%) for median 25 months; Adalimumab 7 (4.2%) for median 6 months; IVIG 19 (11.3%)	Remission: Methotrexate 47/125 (37.6%) Anakinra 7/27 (25.9%) Canakinumab 3/30 (11.5%) Etanercept 6/50 (12%) Adalimumab 1/7 (14.3%) Tocilizumab 2/18 (11.1%) Cyclosporine A 12/29 (41.4%) Minimal disease activity: Methotrexate, 78/125 (62.4%); Anakinra, 20/27 (74.1%); Canakinumab, 23/30 (88.5%); Etanercept, 44/50 (88%); Adalimumab, 6/7 (85.7%); Tocilizumab, 16/18 (88.9%); Cyclosporine A, 17/29 (58.6%).
2933 Kimura, 2017 [46]	Single arm study	9 months	30 patients with systemic JIA	GC (N = 2), MTX (N = 6), IL1 Inhibitor (N = 12), IL6 Inhibitor (N = 10)	Clinically inactive disease (CID): IL-1i 5/12 (41.7%); IL-6i 6/10 (60.0%); Non-biologic 2/8 (25.0%); Biologic 11/22 (50.0%) Off GC: IL-1i - 10/12 (83.3%); IL-6i - 8/10 (80.0%); CID off GC: IL-1i - 5/12 (41.7%); IL-6i - 6/10 (60.0%);

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Ref ID, Author, Year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
					CID off GC and, no CTP change: IL-1i 3/12 (25.0%); IL-6i 5/10 (50.0%) SAE: IL-1i - 2/12 (17%) (infections); IL-6i - 1/10 (10%) (MAS)
3889 Minden, 2019 [47]	Prospective cohort study	mean ± SD 9.1 ± 3.7 years	40 SJIA patients, 43 with persistent OJIA, 128 with extended OJIA	bDMARDS (mixed with csDMARDs)	PhGA of disease activity (mean ± SD): Systemic 1.4 ± 1.3; Persistent OJIA 1.5 ± 1.9; Extended OJIA 2.1 ± 2.3 PhGA CID, n (%): Systemic JIA 17 (42.5%); Persistent OJIA 15 (36.6%); Extended OJIA 49 (39.5%); PhGA remission off drugs, no. (%): Systemic JIA 5 (12.5%); Extended OJIA 14 (10.9%). cJADAS-10: Systemic JIA 4.4 ± 4.1; Persistent OJIA 4.3 ± 5.0; Extended OJIA 5.7 ± 5.2. cJADAS-10 remission off drugs, no. (%): Systemic JIA 5 (12.5%); Persistent OJIA 1 (2.4%); Extended OJIA8 (6.3%). HAQ total: Systemic JIA 0.34 ± 0.61; Persistent OJIA 0.15 ± 0.40; Extended OJIA 0.26 ± 0.42. Patient reported pain: Systemic JIA 2.0 ± 2.2; Persistent OJIA 1.8 ± 2.3; Extended OJIA 2.9 ± 2.3. At the 10-year time point, patients who began bDMARD treatment within 2 years of symptom onset (G1 0 to 2 years) were significantly more likely to be in drug-free remission than those patients who began treatment later (G2 >2 to 5 years, G3 >5 years). G1 patients also had lower disease activity, higher functional status, overall well-being, and lower rates of arthroplasty than other groups. However, this data combines different JIA subtypes (persistent OJIA, extended OJIA, sJIA, poly JIA, enthesitis, psoriatic arthritis)
432 Woerner, 2015 [48]	Retrospective single arm study	6.7 months (range 0.5–55.0) under the first BA, 12.0 months (range 0.5–	77 SJIA patients	Anakinra, Canakinumab, Tocilizumab, Etanercept	Inactive disease at last follow-up was achieved in 37 patients with a first biologic, 43 (55.8%) with a second BA, 49(63.6%) with a third and 50 (64.9%) under a fourth BA, and was 44.1% for anakinra (as a first, second, third or fourth BA), 41.9% for canakinumab, 45% for tocilizumab, and only 5.9% for etanercept.

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Ref ID, Author, Year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
		73.6) under the second and 10.6 months (range 2.0–56.2) under the third BA.			Inactive disease with canakinumab or tocilizumab as second, third or fourth biologic in 6/19 (31.6%) and 7/17 (41%), respectively. No significant differences in SAE between the different biologic treatments. 11/24 SAE (46%) under concomitant GC, 1 (4%) under MTX, and 3 (13%) under GC + MTX.
1158 Uettwiller, 2014 [49]	Retrospective single arm study	Median 2.92 years	10 SJIA patients with growth retardation	1 or more biologics	10/29 (33%) SJIA patients had growth retardation as opposed to 7/36 (19%) with PolyJIA and 1/27 (4%) with OJIA. Patients who required several biologics and systemic patients had a significantly lower growth velocity after the onset of biologic treatment.
1808 Baris, 2018 [50]	Retrospective case series	Median follow-up 69 months	77 SJIA patients	70 (92%) oral steroids, 39 with IV steroids (51%), 14 (18%) with IVIG, 66 (87%) with MTX, 25 (33%) with non-MTX CDMARDs, and 50 (66%) with BDMARDs (Anakinra, 28 (37%); IFX, 25 (33%); ETA, 21 (28%); TCZ, 11 (15%); canakinumab, 11 (15%); ADA, 9 (12%); abatacept, 2 (3%).	Duration of treatment with GC: No biologic – 5.5 months Anakinra – 6.5 months Infliximab – 20 months Etanercept – 36 months

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References:

1. Picco, P., Gattorno, M., Buoncompagni, A., Pistoia, V., & Borrone, C. (1996). 6-methylprednisolone 'Mini-pulses': A New Modality of Glucocorticoid Treatment in Systemic Onset Juvenile Chronic Arthritis. Scandinavian Journal of Rheumatology, 25(1), 24-27.

2. Papadopoulou, C., Kostik, M., Gonzalez-Fernandez, M. I., Bohm, M., Nieto-Gonzalez, J. C., Pistorio, A., . . . Ravelli, A. (2013). Delineating the role of multiple intraarticular corticosteroid injections in the management of juvenile idiopathic arthritis in the biologic era. Arthritis Care Res (Hoboken), 65(7), 1112-1120. doi:10.1002/acr.21947
3. Breit, W., Frosch, M., Meyer, U., Heinecke, A., & Ganser, G. (2000). A subgroup-specific evaluation of the efficacy of intraarticular triamcinolone hexacetonide in juvenile chronic arthritis. J Rheumatol, 27(11), 2696-2702.
4. Simon, D., Fernando, C., Czernichow, P., & Prieur, A. M. (2002). Linear growth and final height in patients with systemic juvenile idiopathic arthritis treated with longterm glucocorticoids. J Rheumatol, 29(6), 1296-1300.
5. Woo, P., Southwood, T. R., Prieur, A. M., Doré, C. J., Grainger, J., David, J., . . . Lemelle, I. (2000). Randomized, placebo-controlled, crossover trial of low-dose oral methotrexate in children with extended oligoarticular or systemic arthritis. Arthritis Rheum, 43(8), 1849-1857. doi:10.1002/1529-0131(200008)43:8<1849::aid-anr22>3.0.co;2-f
6. Albarouni, M., Becker, I., & Horneff, G. (2014). Predictors of response to methotrexate in juvenile idiopathic arthritis. Pediatr Rheumatol Online J, 12, 35. doi:10.1186/1546-0096-12-35
7. Lin, Y. T., Tsai, M. J., Wang, L. H., Huang, M. T., Yang, Y. H., & Chiang, B. L. (2000). Efficacy and safety of methotrexate therapy for juvenile rheumatoid arthritis. J Formos Med Assoc, 99(8), 623-629.
8. Gottlieb, B. S., Keenan, G. F., Lu, T., & Ilowite, N. T. (1997). Discontinuation of methotrexate treatment in juvenile rheumatoid arthritis. Pediatrics, 100(6), 994-997. doi:10.1542/peds.100.6.994
9. Ravelli, A., Ramenghi, B., Di Fuccia, G., Ruperto, N., Zonta, L., & Martini, A. (1994). Factors associated with response to methotrexate in systemic-onset juvenile chronic arthritis. Acta Paediatr, 83(4), 428-432. doi:10.1111/j.1651-2227.1994.tb18135.x
10. Rose, C. D., Singsen, B. H., Eichenfield, A. H., Goldsmith, D. P., & Athreya, B. H. (1990). Safety and efficacy of methotrexate therapy for juvenile rheumatoid arthritis. J Pediatr, 117(4), 653-659. doi:https://doi.org/10.1016/S0022-3476(05)80709-7
11. Gerloni, V., Cimaz, R., Gattinara, M., Arnoldi, C., Pontikaki, I., & Fantini, F. (2001). Efficacy and safety profile of cyclosporin A in the treatment of juvenile chronic (idiopathic) arthritis. Results of a 10-year prospective study. Rheumatology (Oxford), 40(8), 907-913. doi:10.1093/rheumatology/40.8.907
12. Beukelman, T., Xie, F., Baddley, J. W., Chen, L., Mannion, M. L., Saag, K. G., . . . Curtis, J. R. (2016). The risk of hospitalized infection following initiation of biologic agents versus methotrexate in the treatment of juvenile idiopathic arthritis. Arthritis Res Ther, 18(1), 210. doi:10.1186/s13075-016-1109-8
13. Quartier, P., Allantaz, F., Cimaz, R., Pillet, P., Messiaen, C., Bardin, C., . . . Pascual, V. (2011). A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). Ann Rheum Dis, 70(5), 747-754. doi:10.1136/ard.2010.134254
14. Ruperto, N., Brunner, H. I., Quartier, P., Constantin, T., Wulffraat, N., Horneff, G., . . . Lovell, D. J. (2012). Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. N Engl J Med, 367(25), 2396-2406. doi:10.1056/NEJMoa1205099

For Peer Review Only

15. Lovell, D. J., Giannini, E. H., Reiff, A. O., Kimura, Y., Li, S., Hashkes, P. J., . . . Radin, A. R. (2013). Long-term safety and efficacy of rilonacept in patients with systemic juvenile idiopathic arthritis. Arthritis Rheum, 65(9), 2486-2496. doi:10.1002/art.38042
16. Ilowite, N. T., Prather, K., Lokhnygina, Y., Schanberg, L. E., Elder, M., Milojevic, D., . . . Sandborg, C. I. (2014). Randomized, double-blind, placebo-controlled trial of the efficacy and safety of rilonacept in the treatment of systemic juvenile idiopathic arthritis. Arthritis Rheumatol, 66(9), 2570-2579. doi:10.1002/art.38699
17. Nigrovic, P. A., Mannion, M., Prince, F. H., Zeft, A., Rabinovich, C. E., van Rossum, M. A., . . . Higgins, G. C. (2011). Anakinra as first-line disease-modifying therapy in systemic juvenile idiopathic arthritis: report of forty-six patients from an international multicenter series. Arthritis Rheum, 63(2), 545-555. doi:10.1002/art.30128
18. Gattorno, M., Piccini, A., Lasigliè, D., Tassi, S., Brisca, G., Carta, S., . . . Rubartelli, A. (2008). The pattern of response to anti-interleukin-1 treatment distinguishes two subsets of patients with systemic-onset juvenile idiopathic arthritis. Arthritis Rheum, 58(5), 1505-1515. doi:10.1002/art.23437
19. Pardeo, M., Pires Marafon, D., Insalaco, A., Bracaglia, C., Nicolai, R., Messia, V., & De Benedetti, F. (2015). Anakinra in Systemic Juvenile Idiopathic Arthritis: A Single-center Experience. J Rheumatol, 42(8), 1523-1527. doi:10.3899/jrheum.141567
20. Saccomanno, B., Tibaldi, J., Minoia, F., Bagnasco, F., Pistorio, A., Guariento, A., . . . Ravelli, A. (2019). Predictors of Effectiveness of Anakinra in Systemic Juvenile Idiopathic Arthritis. J Rheumatol, 46(4), 416-421. doi:10.3899/jrheum.180331
21. Nishimura, K., Hara, R., Umebayashi, H., Takei, S., Iwata, N., Imagawa, T., . . . Yokota, S. (2020). Efficacy and safety of canakinumab in systemic juvenile idiopathic arthritis: 48-week results from an open-label phase III study in Japanese patients. Mod Rheumatol, 1-9. doi:10.1080/14397595.2020.1783163
22. Ruperto, N., Brunner, H. I., Quartier, P., Constantin, T., Wulffraat, N. M., Horneff, G., . . . Lovell, D. J. (2018). Canakinumab in patients with systemic juvenile idiopathic arthritis and active systemic features: results from the 5-year long-term extension of the phase III pivotal trials. Ann Rheum Dis, 77(12), 1710-1719. doi:10.1136/annrheumdis-2018-213150
23. Ruperto, N., Brunner, H. I., Quartier, P., Constantin, T., Wulffraat, N., Horneff, G., . . . Lovell, D. J. (2012). Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. N Engl J Med, 367(25), 2396-2406. doi:10.1056/NEJMoa1205099
24. Sota, J., Insalaco, A., Cimaz, R., Alessio, M., Cattalini, M., Gallizzi, R., . . . Cantarini, L. (2018). Drug Retention Rate and Predictive Factors of Drug Survival for Interleukin-1 Inhibitors in Systemic Juvenile Idiopathic Arthritis. Front Pharmacol, 9, 1526. doi:10.3389/fphar.2018.01526
25. Kearsley-Fleet, L., Beresford, M. W., Davies, R., De Cock, D., Baildam, E., Foster, H. E., . . . Hyrich, K. L. (2018). Short-term outcomes in patients with systemic juvenile idiopathic arthritis treated with either tocilizumab or anakinra. Rheumatology, 58(1), 94-102. doi:10.1093/rheumatology/key262
26. Arthur, V. L., Shuldiner, E., Remmers, E. F., Hinks, A., Grom, A. A., Foell, D., . . . Ombrello, M. J. (2018). IL1RN Variation Influences Both Disease Susceptibility and Response to Recombinant Human Interleukin-1 Receptor Antagonist Therapy in Systemic Juvenile Idiopathic Arthritis. Arthritis Rheumatol, 70(8), 1319-1330. doi:10.1002/art.40498

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For Peer Review Only

27. Horneff, G., Schulz, A. C., Klotsche, J., Hospach, A., Minden, K., Foeldvari, I., . . . Haas, J. P. (2017). Experience with etanercept, tocilizumab and interleukin-1 inhibitors in systemic onset juvenile idiopathic arthritis patients from the BIKER registry. Arthritis Res Ther, 19(1), 256. doi:10.1186/s13075-017-1462-2
28. De Benedetti, F., Brunner, H. I., Ruperto, N., Kenwright, A., Wright, S., Calvo, I., . . . Martini, A. (2012). Randomized Trial of Tocilizumab in Systemic Juvenile Idiopathic Arthritis. New England Journal of Medicine, 367(25), 2385-2395. doi:10.1056/NEJMoa1112802
29. Yokota, S., Imagawa, T., Mori, M., Miyamae, T., Aihara, Y., Takei, S., . . . Kishimoto, T. (2008). Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. Lancet, 371(9617), 998-1006. doi:10.1016/s0140-6736(08)60454-7
30. Demir, S., Sönmez, H. E., Arslanoğlu-Aydın, E., Özen, S., & Bilginer, Y. (2019). Tocilizumab treatment in juvenile idiopathic arthritis patients: A single center experience. Turk J Pediatr, 61(2), 180-185. doi:10.24953/turkjped.2019.02.005
31. Mallalieu, N. L., Wimalasundera, S., Hsu, J. C., Douglass, W., Wells, C., Penades, I. C., . . . Wouters, C. (2019). Intravenous dosing of tocilizumab in patients younger than two years of age with systemic juvenile idiopathic arthritis: results from an open-label phase 1 clinical trial. Pediatr Rheumatol Online J, 17(1), 57. doi:10.1186/s12969-019-0364-z
32. Kostik, M. M., Isupova, E. A., Chikova, I. A., Dubko, M. F., Masalova, V. V., Snegireva, L. S., . . . Chasnyk, V. G. (2018). Reasons for inactive disease and flare in systemic onset juvenile idiopathic arthritis patients during tocilizumab treatment. Clin Exp Rheumatol, 36(2), 335-341.
33. Pacharapakornpong, T., Vallibhakara, S. A.-O., Lerkvaleekul, B., & Vilaiyuk, S. (2017). Comparisons of the outcomes between early and late tocilizumab treatment in systemic juvenile idiopathic arthritis. Rheumatol Int, 37(2), 251-255. doi:10.1007/s00296-016-3595-z
34. Kostik, M. M., Dubko, M. F., Masalova, V. V., Snegireva, L. S., Kornishina, T. L., Chikova, I. A., . . . Chasnyk, V. G. (2015). Successful treatment with tocilizumab every 4 weeks of a low disease activity group who achieve a drug-free remission in patients with systemic-onset juvenile idiopathic arthritis. Pediatric rheumatology, 13(1), 4. doi:10.1186/1546-0096-13-4
35. De Benedetti, F., Brunner, H., Ruperto, N., Schneider, R., Xavier, R., Allen, R., . . . Lovell, D. (2015). Catch-up growth during tocilizumab therapy for systemic juvenile idiopathic arthritis: results from a phase III trial. Arthritis Rheumatol, 67(3), 840-848. doi:10.1002/art.38984
36. Miyamae, T., Yokoya, S., Yamanaka, H., & Yokota, S. (2014). Effect of tocilizumab on growth impairment in systemic juvenile idiopathic arthritis with long-term corticosteroid therapy. Mod Rheumatol, 24(4), 567-571. doi:10.3109/14397595.2013.844404
37. Yasuoka, R., Iwata, N., Abe, N., Kohagura, T., Nakaseko, H., Shimizu, M., & Kawabe, S. (2019). Risk factors for hypersensitivity reactions to tocilizumab introduction in systemic juvenile idiopathic arthritis. Mod Rheumatol, 29(2), 324-327. doi:10.1080/14397595.2018.1457490
38. Haijuan Xiao, Mingsheng Ma, Hongmei Song, Ji Li, Xiaoyan Tang, Chen Wang, Lejia Zhang, Yanyan He, Min Wei: Clinically inactive disease status with tocilizumab every 4 weeks in refractory systemic-onset juvenile idiopathic arthritis. Int J Clin Exp Med 2016;9(7):14132-14140.

For Peer Review Only

39. Yokota, S., Itoh, Y., Morio, T., Origasa, H., Sumitomo, N., Tomobe, M., . . . Minota, S. (2016). Tocilizumab in systemic juvenile idiopathic arthritis in a real-world clinical setting: results from 1 year of postmarketing surveillance follow-up of 417 patients in Japan. Ann Rheum Dis, 75(9), 1654-1660. doi:10.1136/annrheumdis-2015-207818
40. Yokota, S., Imagawa, T., Mori, M., Miyamae, T., Takei, S., Iwata, N., . . . Kishimoto, T. (2014). Longterm safety and effectiveness of the anti-interleukin 6 receptor monoclonal antibody tocilizumab in patients with systemic juvenile idiopathic arthritis in Japan. J Rheumatol, 41(4), 759-767. doi:10.3899/jrheum.130690
41. Alexeeva, E. I., Valieva, S. I., Bzarova, T. M., Semikina, E. L., Isaeva, K. B., Lisitsyn, A. O., . . . Chistyakova, E. G. (2011). Efficacy and safety of repeat courses of rituximab treatment in patients with severe refractory juvenile idiopathic arthritis. Clin Rheumatol, 30(9), 1163-1172. doi:10.1007/s10067-011-1720-7
42. Adiguzel Dundar, H., Acari, C., Turkucar, S., & Unsal, E. (2020). Treatment of Systemic JIA: When do we need a biologic? Real world data of a single center. Mod Rheumatol, 1-16. doi:10.1080/14397595.2020.1761079
43. Klein, A., Klotsche, J., Hügle, B., Minden, K., Hospach, A., Weller-Heinemann, F., . . . Horneff, G. (2019). Long-term surveillance of biologic therapies in systemic-onset juvenile idiopathic arthritis: data from the German BIKER registry. Rheumatology (Oxford). doi:10.1093/rheumatology/kez577
44. Otten, M. H., Prince, F. H., Anink, J., Ten Cate, R., Hoppenreijs, E. P., Armbrust, W., . . . van Suijlekom-Smit, L. W. (2013). Effectiveness and safety of a second and third biological agent after failing etanercept in juvenile idiopathic arthritis: results from the Dutch National ABC Register. Ann Rheum Dis, 72(5), 721-727. doi:10.1136/annrheumdis-2011-201060
45. Barut, K., Adrovic, A., Sahin, S., Tarcin, G., Tahaoglu, G., Koker, O., . . . Kasapcopur, O. (2019). Prognosis, complications and treatment response in systemic juvenile idiopathic arthritis patients: A single-center experience. Int J Rheum Dis, 22(9), 1661-1669. doi:10.1111/1756-185x.13649
46. Kimura, Y., Grevich, S., Beukelman, T., Morgan, E., Nigrovic, P. A., Mieszkalski, K., . . . Schanberg, L. E. (2017). Pilot study comparing the Childhood Arthritis & Rheumatology Research Alliance (CARRA) systemic Juvenile Idiopathic Arthritis Consensus Treatment Plans. Pediatr Rheumatol Online J, 15(1), 23. doi:10.1186/s12969-017-0157-1
47. Minden, K., Horneff, G., Niewerth, M., Seipelt, E., Aringer, M., Aries, P., . . . Klotsche, J. (2019). Time of Disease-Modifying Antirheumatic Drug Start in Juvenile Idiopathic Arthritis and the Likelihood of a Drug-Free Remission in Young Adulthood. Arthritis Care Res (Hoboken), 71(4), 471-481. doi:10.1002/acr.23709
48. Woerner, A., Uettwiller, F., Melki, I., Mouy, R., Wouters, C., Bader-Meunier, B., & Quartier, P. (2015). Biological treatment in systemic juvenile idiopathic arthritis: achievement of inactive disease or clinical remission on a first, second or third biological agent. RMD Open, 1(1), e000036. doi:10.1136/rmdopen-2014-000036
49. Uettwiller, F., Perlbarg, J., Pinto, G., Bader-Meunier, B., Mouy, R., Compeyrot-Lacassagne, S., . . . Quartier, P. (2014). Effect of biologic treatments on growth in children with juvenile idiopathic arthritis. J Rheumatol, 41(1), 128-135. doi:10.3899/jrheum.130311

For Peer Review Only

50. Baris, H. E., Anderson, E., Sozeri, B., & Dedeoglu, F. (2018). Impact of biologics on disease course in systemic onset juvenile idiopathic arthritis. Clin Rheumatol, 37(12), 3263-3273. doi:10.1007/s10067-018-4297-6.

Summary of AOSD studies: The literature search identified 26 studies that addressed this question in patient with Adult Onset Still's Disease (AOSD).

Combined non-biologic treatments: One observational study addressed the use of combined non-biologic DMARDS in refractory AOSD.[1] This small retrospective study indirectly evaluated combination non-biologic therapy, reporting remission in 69% and successful discontinuation of steroids in 42% of patients treated with methotrexate (Table 1).

IL-1 inhibitors (Anakinra): The literature search revealed one RCT [2] and 12 observational studies [4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 13, 18] that addressed the use of anakinra in AOSD. The small, open label randomized trial compared anakinra to DMARD therapy (methotrexate, cyclosporine, azathioprine, sulfasalazine or leflunomide) in patients refractory to glucocorticoids. This study reported that the anakinra arm had more subjects in remission at weeks 4, 8 and 24, more who were able to discontinue steroids, and fewer adverse events, but findings did not reach statistical significance (Table 2).

Twelve additional observational studies evaluating anakinra in AOSD are outlined in Table 3. A multicenter retrospective cohort provided indirect evidence by reporting a significant decrease in Pouchot's score as a measure of disease activity at 3 months in 140 refractory AOSD patients (P<.0001); 28% of patients were ultimately able to stop therapy due to inactive disease. [12] A multicenter open label study of 41 patients with refractory AOSD provided indirect evidence, reporting a significant steroid sparing effect of anakinra at 3, 6 and 12 months (P<.001) and a 34% rate of remission off medication at 1 year. [10] A retrospective cohort of 141 AOSD patients provided indirect evidence by evaluating drug retention rates in long-term follow up: 14.2% withdrew due to long-term treatment induced remission (at 35.95 +/-36.05 months), 11.3% for primary inefficacy, 7.8% for secondary inefficacy, 17.7% for side effects. [10] Seven small, retrospective cohorts provided additional indirect evidence by reporting complete response to anakinra (inactive disease) in 70-100% of patients previously refractory to NSAIDs, glucocorticoids, and/or DMARDs. [4, 5, 5, 8, 8, 11, 13]. Only two of these studies reported steroid-free remission rates: 28.6% [3] and 35% [8]. One study found that patients presenting without arthritis were more likely to respond to anakinra than those presenting with arthritis (OR 10, p=0.017) [3]. An additional retrospective cohort of 28 patients reported a lower complete response of 54% with partial response in an additional 32%; however, half of the patients in this study had already failed another biologic DMARD. [6] A retrospective cohort of 141 patients found no significant difference in overall response, drug retention rate or primary/secondary inefficacy based on timing of anakinra initiation with regards to disease duration. [18] Four of these cohorts reported on adverse events: 2/28 patients stopped therapy for side effects not specified [6], 3/25 stopped for severe urticaria and 7/25 stopped after infections [7], 2 deaths from macrophage activation syndrome (present before initiation of anakinra) among 20 patients [11], and no serious adverse events reported among 13 patients [13].

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Four additional observational studies provided indirect evidence by evaluating anakinra efficacy in both children with SJIA and adults with AOSD (Table 4) [15,16,17, 17]. Patients experienced a rapid improvement in systemic features and a significant decrease in corticosteroid dose was reported in children (p=0.05) and adults (p=0.0047) in the Lequerre study. [14] Sota, et al reported a significant reduction in corticosteroid (p=0.033) and cDMARD (p<0.0001) requirement, an 18.2% discontinuation of anakinra for clinical remission. [17] Complete response was reported in 42.3%-86.4% of SJIA patients and 54.3-78.2% of AOSD patients. [15,16] 88 % of SJIA and 73.5% of AOSD patients were able to taper corticosteroids in one study. [16]

IL-1 inhibitors (Canakinumab)*:* The literature search revealed 1 RCT and 2 observational studies that provide indirect evidence by reporting efficacy and safety of canakinumab in both AOSD and SJIA (Table 5) [15, 16, 19]. In the RCT, compared to placebo, canakinumab was superior in efficacy, had more adverse events but due to small sample size the results are imprecise across all outcomes [19]. (Table 4) 14.2-60% of SJIA patients and 50-66.7% of AOSD patients had a complete response to canakinumab. One study reported a 5% medication discontinuation rate for adverse events. [15]

IL-6 inhibitors (Tocilizumab)*:* The literature search identified one RCT [24] and six observational studies [3, 11, 21,22,23, 25] that evaluated tocilizumab. The RCT [20] provided indirect evidence by comparing tocilizumab to placebo and by evaluating tocilizumab efficacy in an open label extension. In the RCT, compared to placebo, tocilizumab was superior in producing ACR 20, 50 and 70 responses at weeks 4 and 12, decreasing systemic features at weeks 4 and 12, and decreasing prednisolone dose but due to small sample size the results are imprecise across all outcomes. (Table 6). During the open label extension, rates of ACR20, ACR50 and ACR70 were 84.6%, 84.6% and 61.5%, respectively. Serious adverse events were infections, aseptic necrosis in the hips, exacerbation of adult-onset Still's disease, drug eruption and anaphylactic shock (Table 7).

Three small observational studies provided indirect evidence, reporting complete response (clinical remission) in 82.4-100% of patients treated with tocilizumab (Table 7) [3, 11, 21] Another cohort of 28 patients reported rapid, statistically significant improvement in fever, rash and arthritis at 2 weeks (P<0.05) sustained at 12, 24, 36, and 48 weeks.[25] Five cohorts provided indirect evidence by reporting success in tapering or stopping corticosteroids. [3, 21, 22, 23, 25].

IL-18 inhibitors (Tadekenig alpha): The literature search identified one phase 2, open label trial study that provided indirect evidence by reporting safety and efficacy of the interleukin-18 inhibitor tadekenig alpha in 23 patients with AOSD (Table 8). 10 of 22 patients included in efficacy assessment (45.5%) met pre-defined response criteria at 12 weeks (≥20% reduction in joint count AND 70% decrease in CRP (or reduction to normal level) or normalization of ferritin. 47 drug-related AEs were reported (4 leading to drug discontinuation, 1 serious). [26]

Since most studies were observational designs that lacked relevant comparison groups and all but one RCT provided only indirect evidence, the quality of evidence was very low.

Quality of evidence across all critical outcomes: Very low

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Table 1. AOSD- Combined Non-biologic Treatments- Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
867, Fautrel, 1999 [1]	Cohort Study	48.9 months	26 pts with Adult-Onset Still's disease	Corticosteroid sparing effect of low dose methotrexate treatment: 7.5 mg-17.5 mg weekly	23/26 patients responded to MTX; 18 (69%) had complete remission. 11 patients (42%) stopped taking corticosteroids. One patient with AA amyloidosis renal failure died of neutropenia: this was the only serious adverse event.

Table 2. AOSD- Anakinra Compared to DMARDs – Data from Randomized Controlled Trial[2]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anakinra	DMARD for disease remission in AOSD	Relative (95% CI)	Absolute (95% CI)		
Disease remission at 8 weeks												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	7/12 (58.3%)	5/10 (50.0%)	**RR 1.17** (0.53 to 2.55)	**85 more per 1,000** (from 235 fewer to 775 more)	⨁⨁◯◯ LOW	
Disease remission at 24 weeks												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anakinra	DMARD for disease remission in AOSD	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	6/12 (50.0%)	2/10 (20.0%)	**RR 2.50** (0.64 to 9.77)	**300 more per 1,000** (from 72 fewer to 1,000 more)	⨁⨁◯◯ LOW	

Oral steroid discontinuation

1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	3/12 (25.0%)	0/10 (0.0%)	**OR 7.74** (0.35 to 170.10)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	

Serious adverse events

1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	1/12 (8.3%)	2/10 (20.0%)	**OR 0.36** (0.03 to 4.74)	**117 fewer per 1,000** (from 193 fewer to 342 more)	⨁⨁◯◯ LOW	

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CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

Explanations

a. Open-label trial

b. Wide CI crosses significant effect and no-effect lines

Table 3. AOSD- Anakinra- Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
123, Vercruysse, 2019 [3]	Retrospective cohort	Median 6 years (IQR 4-9)	27 patients with refractory AOSD, after steroid and DMARD failure	Anakinra used in 15 patients Tocilizumab used in 17 patients	13/15 (87.5%) had full response to anakinra. - 4 (28.6%) stopped steroids - 3/13 responders (23%) stopped anakinra without recurrence at last follow-up. - Patients presenting without arthritis more likely to respond to anakinra than those with arthritis (OR 10 [1.22-92.6] p=0.017) 14/17 (82.4%) had full response to tocilizumab. - 10 (71.4%) stopped steroids - 5/14 responders (35.7%) stopped tocilizumab without recurrence at last follow-up
136, Sfriso, 2016 [4]	Retrospective cohort	unclear	245 patients with AOSD	35 patients received anakinra (dose not specified) for refractory disease	26/35 (74.3%) complete response 7/35 (20%) partial response 1/35 (2.9%) no response
138, Iliou et al. 2013 [5]	Retrospective cohort	1985-2011	44 patients with adult onset Still's Disease 21 males 23 females	(68.2%) non-steroidal anti-inflammatory drugs or aspirin with or without corticosteroids. Refractory to above-> DMARD added (mostly MTX)	Response to corticosteroids (23/39, 58.9%) MTX response rate (7/11, 63.6%) Anakinra response rate (10/10, 100%)

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				Refractory to DMARD-> Anakinra added 10/44 patients (22.7%)	
185 Giampietro et al. 2013 [6]	Retrospective cohort	23 months	28 pts with AOSD ages (23-72 years) Mean 40.3 years Men to women 1:2 Disease years (mean) at start of anakinra 9.3 years All patients refractory to conventional therapy of NSAIDs, DMARDs, steroids. 50% had failed other biologic agents.	Anakinra 100mg/day 19 treated in combination with MTX 7.5-40mg/week 1 treated with plaquenil, 1 imuran, 1 cellcept. 6 using Anakinra as monotherapy	All 28 patients showed rapid clinically significant response to anakinra. At 3 months 86% still being treated with anakinra. 54% in complete remission 32% with partial response -mainly still had arthritis symptoms The 6 using monotherapy 5 complete remission 1 partial remission At last follow-up 23 months 57% still being treated with anakinra 42% still in complete remission 14% partial remission 43% had discontinued 2 due to partial response, considered failure 3 complete remission and stopped 2 side effect 1 due to pregnancy 4 due to flare after complete remission, considered failure
1233, Lasari et al 2011 [7]	Case series, retrospective	>1 year of treatment Median of 15 months of treatment	25 patients with refractory stills disease (NSAIDs, steroids, DMARDs or anti-tnf)	Anakinra (dose not provided)	Efficacy and safety of anakinra 16 received as adjunct therapy 9 monotherapy 84% clinical activity resolved in a few days (median 0.2 months). 80% complete response symptoms/labs at 3 months.

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					Proportion achieving ACR 20 at 1 month: 82% 1 year: 100% At end of study: 80% (20 pt) had complete lab normalization 16% (4pt) partial lab response 4% (1 pt) with active disease. 84% (21 patients) clinical activity resolved completely and maintained in all but 1 at last visit. Safety 3 patients severe urticarial reaction and d/c therapy 7 (28%) developed infections (H1N1, URI, GI, UTI) which led to discontinuing therapy.
1237, Cavalli, 2015 [8]	Retrospective cohort	Median 5 years (1-9 years)	20 patients with AOSD (all refractory to NSAIDs, steroids and DMARDs)	Anakinra 100 mg daily was used in 20 patients (first -line biologic in 16) Tocilizumab was used in 4 patients	14/20 (70%) full response to anakinra, 2 partial response - 7 discontinued steroids - 8 reduced steroids by 25% - 9 discontinued methotrexate - 5 discontinued cyclosporine 2/4 (50%) complete response, 1 partial response, 1 treatment failure - 1 discontinued steroids - 1 reduced steroids by 25% - 2 discontinued methotrexate - 1 discontinued cyclosporine 3 cases of reactivation of latent herpes zoster (2 anakinra, 1 toci)
1256 Ortiz-Sanjuan et al., 2015 [9]	Retrospective, open label multicenter study	1 year from start of treatment with anakinra	41 patients with refractory AOSD 26 women	Anakinra 100mg at initiation 12 monotherapy 29 combined	1 year of treatment After 1 year of therapy, the Frequency compared to baseline of joint and cutaneous manifestations had decreased to 41.5% and to 7.3% respectively,

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
			15 men		fever from 78% to 14.6%, anemia from 56.1% to 9.8%, and lymphadenopathy from 26.8% to 4.9%. Rapid and maintained improvement in labs: Ferritin, CRP, WBC. Significant steroid sparing effect from baseline to all follow-ups 3, 6, 12 months (p <.01) 34% discontinued drug at 1 year due to remission.
2304 Vitale et al. 2019 [10]	Retrospective observational	120 months	141 AOSD patients (48 males, 93 females) treated with anakinra for a mean period of 35.96 +/- 36.05 months were enrolled	Anakinra. Screening for Drug Retention Rate (DRR)	20 patients (14.2%) withdrew from anakinra treatment due to long-term treatment-induced remission, 16 cases (11.3%) withdrew due to primary inefficacy and 11 (7.8%) cases because of secondary inefficacy. 25 (17.7%) patients discontinued anakinra due to side effects. DRR for Anakinra = 44.6% and 30.5% at the 60 and 120 month assessments (all patients). Risk for loss of efficacy was low with less than 4% cumulative risk identified during the first year of follow-up and 13.5% at 5 years.
3018, Ruscitti, 2019 [11]	Retrospective cohort	Median 4.9 years (IQR 14.4)	44 patients with AOSD refractory to steroids (93% had also been treated with traditional DMARDs)	Anakinra used in 20 patients Tocilizumab used in 13 patients	14/20 (70%) full response - 3 had MAS prior to starting anakinra (reason for biologic initiation)- 2 deaths. 11/13 (84.6 %) full response
3325 Colafrancesco, 2017 [12]	Cohort Study	72 months	140 Pts with refractory AOSD	Anakinra for all 140 pts and canakinumab for 4 pts who failed anakinra	Good response, drop in Puochot's score, at 3 months in both groups: anakinra: p < 0.0001, canakinumab: p < 0.0001. 28% were able to discontinue therapy in follow up. 5 cases of MAS occurred following treatment with anakinra; 2 of these patients died.

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
3344, Dall'Ara, 2016 [13]	Retrospective cohort	Median 61 months (41-100)	39 patients with AOSD	Anakinra (dose unspecified) used in 13 patients Tocilizumab (dose unspecified) used in 5 patients	12/13 (92%) achieved clinical remission on anakinra 4/5 (80%) achieved clinical remission on tocilizumab 1/5 stopped medication due to cutaneous reaction No serious adverse events reported with anakinra or tocilizumab
1914, T. Lequerre et al., 2008 [14]	Single-arm retrospective cohort	At least one assessment following treatment onset; mean follow-up 14.7 months (range 2-27) in SoJIA and 14.3 months (1-27) in AoSD	20 patients with systemic JIA, 15 with adult-onset Still's. All SJIA patients on steroids at baseline (mean 5.7 yrs), 12/15 AOSD on steroids at baseline (mean 4.6 yrs).	Anakinra 1-2 mg/kg/day in children (started with 1 mg/kg, advanced to 2 m/kg in 4 patients); 100 mg/day in adults (advanced to 100 mg BID in 1 AoSD patient) All treated with corticosteroids before starting anakinra **Complete response definition = resolution of systemic symptoms and improvement of ACR score or ACR pediatric score by at least 50%	sJIA - Fever/rash: resolved in 14/20 within 3 mos - ACR Pedi 30: 55% at 3 mos, 50% at 6 mos - ACR Pedi 50: 30% at 3 mos, 25% at 6 mos - ACR Pedi 70: 0% at 3 mos, 10% at 6 mos - Steroid exposure: dose reduced by 15% to 78% at 5 mos in 9/20 patients; mean dose 0.50 +/- 0.32 mg/kg → 0.24 +/- 0.22 mg/kg (p= 0.05) AOSD - 11/15 (73%) prompt/ dramatic improvement in all disease markers - Complete response: 9/11 of responders (81.8%) at 3 months, 10/11 (90.9%) at 6 months, 9/11 (81.82%) at 9 months - Steroid exposure: stopped in 2/11 patients, reduced by 45 to 95% in relation to baseline in 8/11 patients; mean dose 26.8 +/- 20.1 mg → 8.6 +/- 7.6 (p = 0.0047) Adverse events: 1 tx withdrawal in SJIA group due to intolerance, 2 withdrawals in AOSD group due to side-effects, 1 child visceral Leishmania infection, 2 varicella, 2 rhinopharyngitis, 1 non-extensive labial herpes, 1 bronchitis, 1 hepatitis A, 1 cutaneous infection
3622, A. Vitale et al., 2016 [15]	Retrospective cohort	The mean ± SD duration of treatment was 24.4 ± 27 months	475 patients treated with IL-1 inhibitor; 78 patients with AOSD (16%), 72	Canakinumab (dosage range 150 mg q4, q6, and q8 weeks), Anakinra (dosage range 30-200	sJIA - Anakinra: 38/44 (86.36%) complete response, 4/44 (9.09%) partial response, 2/44 (4.54%) failure

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
		for both IL-1 inhibitors, corresponding to 24.34 ± 27.03 months for Anakinra and 24.52 ± 27.06 months for Canakinumab, as well as 26.6 ± 28.6 months for pediatric patients and 24.39 ± 27.04 months for adults.	patients with SJIA (15%)	mg/day for adults, 2-4 mg/kg/day for children)	- Canakinumab: 12/20 (60%) complete response, 7/20 (35%) partial response, 1/20 (5%) failure AoSD - Anakinra: 61/78 (78.2%) complete response, 10/78 (12.82%) partial response, 7/78 (8.97%) failure - Canakinumab: 2/3 (66.7%) complete response, 1/3 (33.3%) partial response, 0/3 (0%) failure Adverse events: - 76/475 patients (14.4%) - 10/475 patients with severe AE (1.9%) - More common in patients >65 years-old - 17% discontinued anakinra due to AE 5% discontinued canakinumab due to AE
3947, L. Rossi-Semerano et al., 2015 [**Error! Reference source not found.**]	Cross-sectional	N/A (physician questionnaire)	189 patients on IL-1 inhibition (n = 35 AOSD, 26 SJIA)	Anakinra (185 patients), Canakinumab (25 patients)	Anakinra efficacy in sJIA: - 3/26 (11.5%) no response, 12/26 (46.2%) partial response, 11/26 (42.3%) complete response - Median treatment duration 502 days (IQR 1154) - 20 of 22 patients on associated treatment on corticosteroids (90.1%) - 22 of 25 patients (88%) had reduction in their associated treatment regimen - Withdrawal due to inefficacy in 7/26 patients Anakinra efficacy in AoSD - 3/35 (8.6%) no response, 12/35 (34.3%) partial response, 19/35 (54.3%) complete response - Median treatment duration 461 days (IQR 1164) - 24/28 patients on associated treatment on corticosteroids (85.7%)

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					- 25 of 34 patients (73.5%) had associated treatment reduction - Withdrawal due to inefficacy in 14/35 patients Canakinumab efficacy in sJIA - 3/7 patients with no clinical response, 3/7 with partial clinical response, 1/7 with total clinical response Canakinumab efficacy in AoSD - 1/2 patients with no clinical response, 1/2 patients with total clinical response Adverse events - 58% at least one adverse event, minor injection-site reactions most common - Canakinumab better cutaneous tolerance, similar non-cutaneous and severe adverse events Withdrawal of anakinra due to adverse event in 3/26 patients with sJIA and 3/35 patients with AoSD
4327, J.Sota, 2019 [**Error! Reference source not found.**]	Retrospective cohort	60 months	76 AOSD patients, 61 SJIA patients	Anakinra 100 mg daily ASOD; 1-4mg/kg/day (SJIA). 42 received concomitant cDMARDs (mtx 18, CsA 4, SSZ 1, LFN 2, HCQ 7)	- Cumulative retention rate at 12, 24, 48, 60 months: 74.3%, 62.9%, 49.4%, 49.4%. - Treatment withdrawal statistically higher in patients with previous biologic therapy than biologic-naïve [HR 1.818 (CI 1.007-3.282) p= 0.047]. - Significant reduction in corticosteroid requirement (p=0.033) and cDMARD requirement (p<0.0001). - 25 (18.2%) stopped anakinra for remission. - AEs in 29.2%, 6 serious AEs, 4 deaths
4376, A. Vitale, 2020 [**Error! Reference source not found.**]	Retrospective cohort	12 months	141 AOSD patients	Anakinra 100 mg daily in 128, 200 mg daily in 4, less than 100 mg per day in 9.	- Regression analysis did not find timing of anakinra initiation, daily corticosteroid dose, concomitant DMARDs predictive of overall response at 6 or 12 months; however, Pouchot systemic score decrease at 3,6, 12 months significantly higher in patients treated within 6 months of disease onset (p=0.006, p<0.001, p=0.001).

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					- No statistically significant difference between primary or secondary inefficacy between patients receiving anakinra after NSAIDs/CS, after cDMARDs or after other biologics. - No differences in drug retention rates between patients treated before and after 6 months, before and after 12 months

Table 4. AOSD- Canakinumab Compared to Placebo- Data from Randomized Controlled Trial[19]

Certainty assessment							Summary of findings				
							Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Placebo	With Canakimumab		Risk with Placebo	Risk difference with Canakimumab
DAS28(ESR), 12 weeks											
36 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	7/17 (41.2%)	12/19 (63.2%)	**RR 1.53** (0.79 to 2.98)	412 per 1,000	**218 more per 1,000** (from 86 fewer to 815 more)
DAS28(CRP), 12 weeks											
36 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	7/17 (41.2%)	12/19 (63.2%)	**RR 1.53** (0.79 to 2.98)	412 per 1,000	**218 more per 1,000** (from 86 fewer to 815 more)
ACR20, 12 weeks											

Certainty assessment							Summary of findings				
36 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	7/17 (41.2%)	11/19 (57.9%)	**RR 1.41** (0.71 to 2.79)	412 per 1,000	**169 more per 1,000** (from 119 fewer to 737 more)

ACR30, 12 weeks

36 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	5/17 (29.4%)	11/19 (57.9%)	**RR 1.97** (0.86 to 4.52)	294 per 1,000	**285 more per 1,000** (from 41 fewer to 1,000 more)

ACR30 modified, 12 weeks

36 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	4/17 (23.5%)	10/19 (52.6%)	**RR 2.24** (0.86 to 5.83)	235 per 1,000	**292 more per 1,000** (from 33 fewer to 1,000 more)

ACR50, 12 weeks

36 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	3/17 (17.6%)	9/19 (47.4%)	**RR 2.68** (0.87 to 8.32)	176 per 1,000	**296 more per 1,000** (from 23 fewer to 1,000 more)

ACR70, 12 weeks

36 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	2/17 (11.8%)	5/19 (26.3%)	**RR 2.24** (0.50 to 10.06)	118 per 1,000	**146 more per 1,000** (from 59 fewer to 1,000 more)

EULAR, 12 weeks

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Certainty assessment							Summary of findings				
36 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	9/17 (52.9%)	14/19 (73.7%)	**RR 1.39** (0.83 to 2.35)	529 per 1,000	**206 more per 1,000** (from 90 fewer to 715 more)

EULAR DAS(CRP), 12 weeks

36 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	8/17 (47.1%)	13/19 (68.4%)	**RR 1.45** (0.81 to 2.62)	471 per 1,000	**212 more per 1,000** (from 89 fewer to 762 more)

SAE, 12 weeks

36 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	0/17 (0.0%)	2/19 (10.5%)	**RR 4.50** (0.23 to 87.61)	0 per 1,000	**0 fewer per 1,000** (from 0 fewer to 0 fewer)

SAE, 24 weeks

36 (1 RCT)	not serious	not serious	serious [a]	serious [b]	none	⨁⨁◯◯ LOW	1/17 (5.9%)	4/19 (21.1%)	**RR 3.58** (0.44 to 28.97)	59 per 1,000	**152 more per 1,000** (from 33 fewer to 1,000 more)

CI: Confidence interval; **RR:** Risk ratio; **SAE**: Serious adverse events

Explanations

a. Indirect comparison to placebo

b. Wide CI crosses significant effect and no-effect lines

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Table 5. AOSD- Canakinumab- Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
3622, A. Vitale et al., 2016 [15]	Retrospective cohort	The mean ± SD duration of treatment was 24.4 ± 27 months for both IL-1 inhibitors, corresponding to 24.34 ± 27.03 months for Anakinra and 24.52 ± 27.06 months for Canakinumab, as well as 26.6 ± 28.6 months for pediatric patients and 24.39 ± 27.04 months for adults.	475 patients treated with IL-1 inhibitor; 78 patients with AOSD (16%), 72 patients with SJIA (15%)	Canakinumab (dosage range 150 mg q4, q6, and q8 weeks), Anakinra (dosage range 30-200 mg/day for adults, 2-4 mg/kg/day for children)	SJIA - Anakinra: 38/44 (86.36%) complete response, 4/44 (9.09%) partial response, 2/44 (4.54%) failure - Canakinumab: 12/20 (60%) complete response, 7/20 (35%) partial response, 1/20 (5%) failure AoSD - Anakinra: 61/78 (78.2%) complete response, 10/78 (12.82%) partial response, 7/78 (8.97%) failure - Canakinumab: 2/3 (66.7%) complete response, 1/3 (33.3%) partial response, 0/3 (0%) failure Adverse events: - 76/475 patients (14.4%) - 10/475 patients with severe AE (1.9%) - More common in patients >65 years-old - 17% discontinued anakinra due to AE 5% discontinued canakinumab due to AE
3947, L. Rossi-Semerano et al., 2015 [16]	Cross-sectional	N/A (physician questionnaire)	189 patients on IL-1 inhibition (n = 35 AOSD, 26 SJIA)	Anakinra (185 patients), Canakinumab (25 patients)	Anakinra efficacy in sJIA: - 3/26 (11.5%) no response, 12/26 (46.2%) partial response, 11/26 (42.3%) complete response - Median treatment duration 502 days (IQR 1154) - 20 of 22 patients on associated treatment on corticosteroids (90.1%) - 22 of 25 patients (88%) had reduction in their associated treatment regimen - Withdrawal due to inefficacy in 7/26 patients Anakinra efficacy in AoSD - 3/35 (8.6%) no response, 12/35 (34.3%) partial response, 19/35 (54.3%) complete response - Median treatment duration 461 days (IQR 1164)

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					- 24/28 patients on associated treatment on corticosteroids (85.7%) - 25 of 34 patients (73.5%) had associated treatment reduction - Withdrawal due to inefficacy in 14/35 patients Canakinumab efficacy in sJIA - 3/7 patients with no clinical response, 3/7 with partial clinical response, 1/7 with total clinical response Canakinumab efficacy in AoSD - 1/2 patients with no clinical response, 1/2 patients with total clinical response Adverse events - 58% at least one adverse event, minor injection-site reactions most common - Canakinumab better cutaneous tolerance, similar non-cutaneous and severe adverse events Withdrawal of anakinra due to adverse event in 3/26 patients with sJIA and 3/35 patients with AoSD

Table 6. AOSD-Tocilizumab vs. Placebo – Data from Randomized Controlled Trial[20]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCZ	Placebo	Relative (95% CI)	Absolute (95% CI)		
ACR-20 week 4												

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCZ	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious [a]	serious [b]	none	10/13 (76.9%)	5/13 (38.5%)	**RR 2.00** (0.95 to 4.23)	**385 more per 1,000** (from 19 fewer to 1,000 more)	⨁⨁◯◯ LOW	

ACR-50 week 4

1	randomised trials	not serious	not serious	serious [a]	serious [b]	none	8/13 (61.5%)	4/13 (30.8%)	**RR 2.00** (0.80 to 5.03)	**308 more per 1,000** (from 62 fewer to 1,000 more)	⨁⨁◯◯ LOW	

ACR-70 week 4

1	randomised trials	not serious	not serious	serious [a]	serious [b]	none	5/13 (38.5%)	4/13 (30.8%)	**RR 1.25** (0.43 to 3.63)	**77 more per 1,000** (from 175 fewer to 809 more)	⨁⨁◯◯ LOW	

ACR-20 week 12

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCZ	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious [a]	serious [b]	none	8/13 (61.5%)	4/13 (30.8%)	**RR 2.00** (0.80 to 5.03)	**308 more per 1,000** (from 62 fewer to 1,000 more)	⨁⨁◯◯ LOW	

ACR-50 week 12

1	randomised trials	not serious	not serious	serious [a]	serious [b]	none	8/13 (61.5%)	4/13 (30.8%)	**RR 2.00** (0.80 to 5.03)	**308 more per 1,000** (from 62 fewer to 1,000 more)	⨁⨁◯◯ LOW	

ACR-70 week 12

1	randomised trials	not serious	not serious	serious [a]	serious [b]	none	6/13 (46.2%)	4/13 (30.8%)	**RR 1.50** (0.55 to 4.10)	**154 more per 1,000** (from 138 fewer to 954 more)	⨁⨁◯◯ LOW	

Decrease in systemic feature score at week 4

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCZ	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious [a]	serious [b]	none	13	13	-	MD **1.4 lower** (2.9 lower to 0.1 higher)	⨁⨁◯◯ LOW	

Decrease in systemic feature score at week 12

1	randomised trials	not serious	not serious	serious [a]	serious [c]	none	13	13	-	MD **1.8 lower** (2.87 lower to 0.73 lower)	⨁⨁◯◯ LOW	

% decrease of prednisolone dose at week 12

1	randomised trials	not serious	not serious	serious [a]	serious [c]	none	13	13	-	MD **25.2 lower** (44.46 lower to 5.94 lower)	⨁⨁◯◯ LOW	

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Indirect comparison to placebo

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b. Wide CI crosses significant effect and no-effect lines

c. Small sample size

Table 7. AOSD-Tocilizumab - Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
123, Vercruysse, 2019 [3]	Retrospective cohort	Median 6 years (IQR 4-9]	27 patients with AOSD	Anakinra used in 15 patients Tocilizumab used in 17 patients	13/15 (87.5%) had full response to anakinra. - 4 (28.6%) stopped steroids - 3/13 responders (23%) stopped anakinra without recurrence at last follow-up. - Patients presenting without arthritis more likely to respond to anakinra than those with arthritis (OR 10 [1.22-92.6] p=0.017) 14/17 (82.4%) had full response to tocilizumab. - 10 (71.4%) stopped steroids - 5/14 responders (35.7%) stopped tocilizumab without recurrence at last follow-up
1186 N.Nishina et.al. 2015 [21]	Retrospective, single center cohort	Median 86 months (IQR 41 – 193)	40 AOSD patients, age at onset avg 39 (17-85). 10 refractory/ recurrent cases tx with TCZ	10 patients received TCZ: -3 every 2 weeks -4 every 4 weeks -1 every 6 weeks	100% had full resolution of disease activity at 6 months except arthralgia in 2 patients. At 6 months, the median (IQR) dose of glucocorticoids was decreased. 4 patients discontinued TCZ due to sustained remission: 2 maintained remission, 2 restarted for recurrent disease activity at 6 and 14 months. None discontinued TCZ for adverse events.
1268 F.Ortiz-Sanjuan et.al., 2014 [22]	Retrospective open-labeled, multicenter	median f/u 19 months	34 AOSD pts (26 F, 8M) Mean age 38.7 +/-16 Refractory to steroids and DMARDS. 50% had received prior biologics.	Tocilizumab: Initial: -8 mg/kg IV every 4 weeks (22) -8 mg/kg IV every 2 weeks (10) -4 mg/kg IV every 4 weeks (2) Maintenance:	Rapid and maintained clinical and laboratory improvement. Joint manifestations were more refractory to treatment than systemic manifestations. At 1 year, median prednisone dose decreased from 13.8 mg/day (IQR 5–45) to 2.5 mg (IQR 0–30). Prednisone dose reduction was significant at 1 month (P <0.01), 3 months (P < 0.01), 6 months (P < 0.01), and 12 months (P< 0.01).

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				4–8 mg/kg every 2 OR 4 weeks.	Infections were the most common complications, severe enough to require TCZ discontinuation in 2.
1269 S.T.Song et al 2016 [23]	Retrospective multicenter	Treatment median 7.5 months (IQR: 4.0- 12.3) Analysis at 6 months and 12 months	22 patients with refractory AOSD Avg Age= 36 Avg duration of disease= 70.5 months	Tocilizumab -8 mg/kg every 4-5 weeks in 18 patients -6 mg/kg every 4 weeks in 2 4 mg/kg every 4 weeks in 2	Decrease in modified Pouchot score >2 (considered good response) in 50.0% at 6 months and in 64.3% at 12 months. Corticosteroid dose reduced from 11.5 mg/day before TCZ therapy to 7.5 mg/day at 6 months and finally to 6.3 mg/day at 12 months. 8 adverse events in 4 patients, none severe. 1 patient stopped tocilizumab for facial swelling and hypertension.
3018, Ruscitti, 2019 [11]	Retrospective cohort	Median 4.9 years (IQR 14.4)	44 patients with AOSD refractory to steroids (93% had previously received DMARDs)	Anakinra used in 20 patients Tocilizumab used in 13 patients	14/20 (70%) full response - 3 had MAS prior to starting anakinra (reason for biologic initiation)- 2 deaths. 11/13 (84.6 %) full response
3924 Kaneko et al. 2018 [24]	Randomized double-blind, placebo-controlled phase III trial with open label extension Open label data shown here.	12-week, double-blind phase, followed by 40 weeks of open-label tocilizumab.	27 AOSD patients refractory to glucocorticoids.	Randomized to tocilizumab 8 mg/kg or placebo intravenously every 2 weeks during the 12-week, double-blind phase, followed by 40 weeks open label tocilizumab.	In the full analysis set, ACR50 response at week 4 was achieved in 61.5% (95% CI 31.6 to 86.1) in the tocilizumab group and 30.8% (95% CI 9.1 to 61.4) in the placebo group (p=0.24). The least squares means for change in systemic feature score at week 12 were –4.1 in the tocilizumab group and –2.3 in the placebo group (p=0.003). Glucocorticoid dose at week 12 decreased by 46.2% in the tocilizumab group and 21% in the placebo group (p=0.017). At week 52, the rates of ACR20, ACR50 and ACR70 were 84.6%, 84.6% and 61.5%, respectively, in both groups. Serious adverse events in all participants who received one dose of tocilizumab were infections, aseptic necrosis in the hips, exacerbation of adult-onset Still's disease, drug eruption and anaphylactic shock

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
4586, C. Wang, 2019 [25]	Prospective observational	48 weeks	28 patients with AOSD refractory to steroids and at least one DMARD	Tocilizumab 8mg/kg IV every 4 weeks and methotrexate 12.5 mg po weekly. Prednisone tapered after clinical remission achieved (1.5-2mg/kg/day at trial start). In patients with 6 months of clinical remission, tocilizumab was spaced to every 8 weeks.	- Improvement of fever, rash and arthritis improved 67.9%, 85.7%, 60.8% at 2 weeks compared to pre-treatment. (p<0.05), sustained at 12, 24, 36, 48 weeks - 12 patients (42.9%) discontinued corticosteroids - 12 AEs reported, no serious AEs

Table 8. AOSD- Tadekenig Alpha – Data from Observational Study

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
2707 Gabay, 2018 [26]	Phase 2, open label trial	20 weeks	23 AOSD pts (22 with previous glucocorticoid tx, 13 previous nonbiologic DMARD, 9 previous biologic)	safety and efficacy of tadekinig alfa: -10 pts given 80mg (6 later up-titrated to 160 mg) - 13 pts 160mg (one discontinued for injection site reaction not included in efficacy assessment)	11/22 achieved 3 wk target (≥50% CRP decrease from baseline and resolution of fever) - 5/10 on 80 mg dose, 6/12 on 160 mg 10/22 achieved 12 wk target (≥20% reduction in joint count and 70% decrease in CRP (or reduction to normal level) or normalization of ferritin) - 2/4 on 80 mg and 8/18 on 160 mg. 47 adverse events thought related to the drug occurred: injection site reactions, upper airway infections, and arthralgia were most common. 4 pts stopped drug because of AEs.

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					1 serious AE thought related to drug: toxic optic neuropathy.

References:

1. Fautrel, B., Borget, C., Rozenberg, S., Meyer, O., Le Loët, X., Masson, C., . . . Bourgeois, P. (1999). Corticosteroid sparing effect of low dose methotrexate treatment in adult Still's disease. J Rheumatol, 26(2), 373-378.
2. Nordström, D., Knight, A., Luukkainen, R., van Vollenhoven, R., Rantalaiho, V., Kajalainen, A., . . . Pettersson, T. Beneficial effect of interleukin 1 inhibition with anakinra in adult-onset Still's disease. An open, randomized, multicenter study. J Rheumatol. 2012 Oct;39(10):2008-11. doi:10.3899/jrheum.111549
3. Vercruysse, F., Barnetche, T., Lazaro, E., Shipley, E., Lifermann, F., Balageas, A., . . . Truchetet, M. E. (2019). Adult-onset Still's disease biological treatment strategy may depend on the phenotypic dichotomy. Arthritis Res Ther, 21(1), 53. doi:10.1186/s13075-019-1838-6
4. Sfriso, P., Priori, R., Valesini, G., Rossi, S., Montecucco, C. M., D'Ascanio, A., . . . Punzi, L. (2016). Adult-onset Still's disease: an Italian multicentre retrospective observational study of manifestations and treatments in 245 patients. Clin Rheumatol, 35(7), 1683-1689. doi:10.1007/s10067-016-3308-8
5. Iliou, C., Papagoras, C., Tsifetaki, N., Voulgari, P. V., & Drosos, A. A. (2013). Adult-onset Still's disease: clinical, serological and therapeutic considerations. Clin Exp Rheumatol, 31(1), 47-52.
6. Giampietro, C., Ridene, M., Lequerre, T., Costedoat Chalumeau, N., Amoura, Z., Sellam, J., . . . Fautrel, B. (2013). Anakinra in adult-onset Still's disease: long-term treatment in patients resistant to conventional therapy. Arthritis Care Res (Hoboken), 65(5), 822-826. doi:10.1002/acr.21901
7. Laskari, K., Tzioufas, A. G., & Moutsopoulos, H. M. (2011). Efficacy and long-term follow-up of IL-1R inhibitor anakinra in adults with Still's disease: a case-series study. Arthritis Res Ther, 13(3), R91. doi:10.1186/ar3366
8. Cavalli, G., Franchini, S., Aiello, P., Guglielmi, B., Berti, A., Campochiaro, C., . . . Dagna, L. (2015). Efficacy and safety of biological agents in adult-onset Still's disease. Scand J Rheumatol, 44(4), 309-314. doi:10.3109/03009742.2014.992949
9. Ortiz-Sanjuán, F., Blanco, R., Riancho-Zarrabeitia, L., Castañeda, S., Olivé, A., Riveros, A., . . . González-Gay, M. A. (2015). Efficacy of Anakinra in Refractory Adult-Onset Still's Disease: Multicenter Study of 41 Patients and Literature Review. Medicine (Baltimore), 94(39), e1554. doi:10.1097/md.0000000000001554
10. Vitale, A., Cavalli, G., Colafrancesco, S., Priori, R., Valesini, G., Argolini, L. M., . . . Cantarini, L. (2019). Long-Term Retention Rate of Anakinra in Adult Onset Still's Disease and Predictive Factors for Treatment Response. Front Pharmacol, 10, 296. doi:10.3389/fphar.2019.00296

For Peer Review Only

11. Ruscitti, P., Cipriani, P., Liakouli, V., Iacono, D., Pantano, I., Caso, F., . . . Giacomelli, R. (2020). Prescribing motivations and patients' characteristics related to the use of biologic drugs in adult-onset Still's disease: analysis of a multicentre "real-life" cohort. Rheumatol Int, 40(1), 107-113. doi:10.1007/s00296-019-04358-w
12. Colafrancesco, S., Priori, R., Valesini, G., Argolini, L., Baldissera, E., Bartoloni, E., . . . Sfriso, P. (2017). Response to Interleukin-1 Inhibitors in 140 Italian Patients with Adult-Onset Still's Disease: A Multicentre Retrospective Observational Study. Front Pharmacol, 8, 369. doi:10.3389/fphar.2017.00369
13. Dall'Ara, F., Frassi, M., Tincani, A., & Airò, P. (2016). A retrospective study of patients with adult-onset Still's disease: is pericarditis a possible predictor for biological disease-modifying anti-rheumatic drugs need? Clin Rheumatol, 35(8), 2117-2123. doi:10.1007/s10067-015-3164-y
14. Lequerré, T., Quartier, P., Rosellini, D., Alaoui, F., De Bandt, M., Mejjad, O., . . . Sibilia, J. (2008). Interleukin-1 receptor antagonist (anakinra) treatment in patients with systemic-onset juvenile idiopathic arthritis or adult onset Still disease: preliminary experience in France. Ann Rheum Dis, 67(3), 302-308. doi:10.1136/ard.2007.076034
15. Vitale, A., Insalaco, A., Sfriso, P., Lopalco, G., Emmi, G., Cattalini, M., . . . Cantarini, L. (2016). A Snapshot on the On-Label and Off-Label Use of the Interleukin-1 Inhibitors in Italy among Rheumatologists and Pediatric Rheumatologists: A Nationwide Multi-Center Retrospective Observational Study. Front Pharmacol, 7, 380. doi:10.3389/fphar.2016.00380
16. Rossi-Semerano, L., Fautrel, B., Wendling, D., Hachulla, E., Galeotti, C., Semerano, L., . . . Koné-Paut, I. (2015). Tolerance and efficacy of off-label anti-interleukin-1 treatments in France: a nationwide survey. Orphanet J Rare Dis, 10, 19. doi:10.1186/s13023-015-0228-7
17. Sota, J., Rigante, D., Ruscitti, P., Insalaco, A., Sfriso, P., de Vita, S., . . . Cantarini, L. (2019). Anakinra Drug Retention Rate and Predictive Factors of Long-Term Response in Systemic Juvenile Idiopathic Arthritis and Adult Onset Still Disease. Front Pharmacol, 10, 918. doi:10.3389/fphar.2019.00918
18. Vitale, A., Cavalli, G., Ruscitti, P., Sota, J., Colafrancesco, S., Priori, R., . . . Cantarini, L. (2020). Comparison of Early vs. Delayed Anakinra Treatment in Patients With Adult Onset Still's Disease and Effect on Clinical and Laboratory Outcomes. Front Med (Lausanne), 7, 42. doi:10.3389/fmed.2020.00042
19. Kedor, C., Listing, J., Zernicke, J., Weiß, A., Behrens, F., Blank, N., . . . Feist, E. (2020). Canakinumab for Treatment of Adult-Onset Still's Disease to Achieve Reduction of Arthritic Manifestation (CONSIDER): phase II, randomised, double-blind, placebo-controlled, multicentre, investigator-initiated trial. Annals of the rheumatic diseases, 79(8), 1090-1097. doi:10.1136/annrheumdis-2020-217155
20. Pham, T., Claudepierre, P., Constantin, A., de Bandt, M., Fautrel, B., Gossec, L., . . . Club Rhumatismes et, I. (2010). Tocilizumab: therapy and safety management. Joint Bone Spine, 77 Suppl 1, S3-100. doi:10.1016/s1297-319x(10)70001-4
21. Nishina, N., Kaneko, Y., Kameda, H., & Takeuchi, T. (2015). The effect of tocilizumab on preventing relapses in adult-onset Still's disease: A retrospective, single-center study. Mod Rheumatol, 25(3), 401-404. doi:10.3109/14397595.2014.973659

For Peer Review Only

22. Ortiz-Sanjuán, F., Blanco, R., Calvo-Rio, V., Narvaez, J., Rubio Romero, E., Olivé, A., . . . González-Gay, M. A. (2014). Efficacy of tocilizumab in conventional treatment-refractory adult-onset Still's disease: multicenter retrospective open-label study of thirty-four patients. Arthritis Rheumatol, 66(6), 1659-1665. doi:10.1002/art.38398
23. Song, S. T., Kim, J. J., Lee, S., Kim, H. A., Lee, E. Y., Shin, K. C., . . . Yoo, D. H. (2016). Efficacy of tocilizumab therapy in Korean patients with adult-onset Still's disease: a multicentre retrospective study of 22 cases. Clin Exp Rheumatol, 34(6 Suppl 102), S64-s71.
24. Kaneko, Y., Kameda, H., Ikeda, K., Ishii, T., Murakami, K., Takamatsu, H., . . . Takeuchi, T. (2018). Tocilizumab in patients with adult-onset still's disease refractory to glucocorticoid treatment: a randomised, double-blind, placebo-controlled phase III trial. Ann Rheum Dis, 77(12), 1720-1729. doi:10.1136/annrheumdis-2018-213920
25. Wang, C. Y., Guo, S. H., Wang, L. P., & Shen, H. L. (2019). Refractory adult-onset Still disease treated by tocilizumab combined with methotrexate: A STROBE-compliant article. Medicine (Baltimore), 98(32), e16682. doi:10.1097/md.0000000000016682
26. Gabay, C., Fautrel, B., Rech, J., Spertini, F., Feist, E., Kötter, I., . . . Schiffrin, E. J. (2018). Open-label, multicentre, dose-escalating phase II clinical trial on the safety and efficacy of tadekinig alfa (IL-18BP) in adult-onset Still's disease. Ann Rheum Dis, 77(6), 840-847. doi:10.1136/annrheumdis-2017-212608

PICO 24. In patients with sJIA, does the presence of subclinical MAS alter the treatment paradigm?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

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PICO 25. In patients with sJIA and overt MAS, Is biologic therapy superior to calcineurin inhibitors in achievement of inactive disease and resolution of MAS?

Summary: This literature search identified two systematic reviews of MAS cases [1, 2], five single arm cohort studies [3, 4, 5, 6, 7], and one case series [2]. There were no direct comparisons made between treatment with biologics and cyclosporin. The systematic review by Grom et al.[1] included 72 patients with sJIA and possible MAS; they reported that clinical features of MAS were not modified by canakinumab compared to placebo. In contrast, Sonmez et al.[2] reported that 33/35 patients with MAS treated with anakinra achieved remission. Similarly, Sonmez et al.[2] evaluated 13 patients at their own institution with MAS secondary to sJIA; after starting anakinra, clinical symptoms resolved, steroids were able to be stopped and lab findings normalized. Two patients developed recurrence of MAS after reduction of anakinra dosage. In a cohort study by Eloseily et al.[3], sJIA patients with secondary HLH/MAS treated with anakinra within five days of hospitalization had the lowest mortality with zero deaths compared to secondary HLH/MAS due to other causes. Early administration of anakinra was associated with reduced mortality. Twenty-five percent of that cohort was treated with concomitant calcineurin inhibitors (cyclosporin A). In a cohort study by Yokota et al.[5] of 417 sJIA patients with 26 reported cases of MAS, cases treated with tocilizumab 8 mg/kg every 8 weeks showed a decrease in CRP, fever, reduction in steroid dose, and a mean reduction in systemic feature score. Another cohort study by Yokota et al.[6] evaluating sJIA patients' treatment with IL-6 inhibition found that definite or probable MAS occurred in 3.6% of sJIA patients. Clinical and lab features appeared to be similar among patients regardless of whether IL-6 inhibition was administered. In one retrospective cohort study [7], 102 children with MAS secondary to JIA (grouped all categories together), 15 patients received IL1 inhibitors with 5 receiving cyclosporine as well.

Overall quality of evidence across all critical outcomes: Very low

Table 1. Data from Observational Studies

Ref ID, Author, Year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
3225, Grom, 2016 [1]	Systematic review	Unclear	72 sJIA with possible MAS	Canakinumab	21 events (19 with canakinumab treatment; 2 with placebo control) in 19 patients were adjudicated as being probable MAS and 10 events in 9 patients as being possible MAS. Sojia was well controlled in majority of canakinumab treated patients at time of MAS. When rates of probable MAS events were compared between canakinumab-treated patients (2.8 per 100 patient years) and placebo treated patients (7.7 per 100 patient-years), the difference was not significant (-4.9 CI -15.6, 5.9). Three deaths due to MAS related complications (2-canakinumab treated, 1 placebo). Clinical features of MAS were not modified by

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Ref ID, Author, Year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
					canakinumab. Infections were common trigger.
192, Sonmez, 2018 [2]	Case series/ systematic review	Jan 2015 to Jan 2017	MAS patients due to sJIA or AID (13 patients with soJIA)	Anakinra (2mg/kg/day)	Case series: 19 MAS episodes were observed. Anakinra (2mg/kg/day) was started in with a median 1 day after admission. Clinical sx resolved and lab findings normalizied within median 2 (1-4) and 6 (4-9) days after introduction of anakinra. Steroids were stopped in a median of 10 (4-13_ weeks after anakinra tx. Patients were followed up for a median of 13 (6-24 months). Two patients developed recurrence of MAS sx when anakinra was reduced, others in remission. Systematic review: 9 articles, 35 patients with MAS associated with sJIA or AIDS, all patients except 2 reached remission.
4342, Eloseily, 2020 [3]	Single arm cohort study	January 2008 to December 2016	All patients who presented with secondary HLH/MAS 44 patients, 13 with sJIA	Anakinra; concomitant therapies included steroids (73%), cyclosporin A (25%), IVIG (9%), etoposide (9%), tocilizumab (5%) and abatacept, rituximab, cyclophosphamide, and plasmapheresis in one patient each.	Early administration of anakinra (within 5 days of hospitalization) was associated with reduced mortality (p=0.046). Those patients with sJIA had the lowest mortality rate with no deaths among them (P=0.006)
2352, Aytac, 2016 [4]	Retrospective cohort	2009-2015	MAS patients secondary to sJIA (28) and lupus (6) 37 Mas	Multiple treatments	All patients received steroids. Cyclosporine was given in 74.2% of soJIA-MAS. Intravenous immunoglobulin, anakinra, and etoposide was given during 67.7, 41,9, and 32.3% of sJIA MAS. Plasmapheresis was performed during 41.9% of sJIA MAS and was performed more frequently (p=0.021) in patients who died compared to patients who

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Ref ID, Author, Year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
			episodes		were cured.
3929 Yokota 2016 [5]	Single arm cohort	52 weeks	417 sJIA pts	TCZ 8 mg/kg every 8 weeks	-30.5% (127) pts enrolled from previous clinical trial - 16 (3.8%) were lost to follow up - 17 (4.1%) had AEs that lead to discontinuation of treatment - most common AE was infection/infestation at 69.8/100 PYs - 2nd most common AE was respiratory, thoracic, and mediastinal disorders w rate of 34.9/100 PYs - MSK disorders 19.7/100 PYs - connective tissue disorders 17/100 PYs - blood/lymphatic disorders 14/100 PYs - GI disorders 13.8/100 PYs - decreased platelet count 2.9/100 PYs - decreased white count 4.2/100 PYs - for serious AEs incidence rate is 54.5/100 PYs, 3.4% of pts discontinued TCZ due to SAE - most common SAE was infection/infestation at 18.2/100 PYs - 2nd most common SAE was blood/lymphatic disorders at 9.8/100 PYs - MSK disorders 4.4/100 PYs - connective tissue disorders 4.2/100 PYs - GI disorders 3.7/100 PYs

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Ref ID, Author, Year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
					- 2 deaths, one d/t vasculitis and cardiac failure and the other d/t pseudomonas, ILD, and sepsis - 26 reported cases of MAS in 24 pts; 2 definite MAS, 15 probable, 3 events viral related hemophagocytic syndrome and 6 were possible or non MAS - 25 required treatment including cyclosporine and IV steroids - 30 pts (7.2%) had infusion reactions a a rate of 11.3/100 PYs - 8 pts had 14 serious infusion reactions, rate of 3.4/100 PYs; all required steroids and antihistamines and only 3 received epinephrine -⅝ of anti TCZ antibodies (only 6 tested) - 7 continued treatment, but 3/7 later discontinued treatment secondary to subsequent infusion reactions, 2 of these had anti TCZ antibodies - all between 2nd and 4th infusions 1 pt discontinued TCZ -mean CRP levels decreased from 2.7 mg/dL to 0.5 mg/dL after 4 weeks of treatment and levels remained normal from week 8 to 52 - at 4 weeks 90.5% of patients had normal CRP, at 8 weeks it was 96.2% and at 52 weeks it was 99% -baseline steroid dose was 0.9 mg/kg/day and decreased to 0.7 mg.kg/day at 4 weeks with further decrease to 0.5 mg/kg/day at 8 weeks and was down to 0.2 mg/kg/day at 52 weeks -155 pts were receiving steroids at baseline and received TCZ for 48 weeks, of those 19 d/c steroids completely

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Ref ID, Author, Year	Study Type	Duration	Population Description	Treatment given to relevant population	Results
					- 251 pts reported systemic features at baseline and week 52; 54.6% (137/251) had fever and this decreased to 5.6% (14/251) -125 pts had fever resolve by wk 52 - reports of rash decreased from 43% (108/251) at baseline to 5.6% (14/251) at week 52 - mean systemic feature score decreased from 1.6+/-1.7 to 0.2+/-0.6 at week 52 (p<0.0001)
2358, Yokota, 2015 [6]	Cohort	April 2008, followed 52 weeks	All sJIA patients tx with TCZ	TCZ	Definite or probably MAS occurred in 3.6% of patients with sJIA (14/394) Clinical and laboratory features in the course of MAS appear to be similar among patients regardless of whether TCZ Is administered. TCZ was reinitiated after improvement or resolution of MAS in 18/23 patients and did not seem to induce MAS. In patients treated with canakinumab, MAS developed in 1/43 (2.3%) in trial 1 and in 4 of 177 patients (2.3%) in trial 2.
2353, Bennett, 2012 [7]	Retrospective cohort study	October 1, 2006 to Sept 30, 2010	121 children with MAS secondary to sle or JIA (102 with JIA)	Cyclosporin, IL-1	Mortality rate for entire cohort was 7%, children with JIA 6%, SLE 11%, p=0.6. ICU admission was common 33%. Children with SLE had a higher ICU admission rate (63% versus 27%, p=0.002). Higher percentages of children with SLE received mechanical ventilation (53% versus 21%; p=0.02) than children with JIA. Most patients received steroids (83%). Fifteen patients with JIA received IL-1 antagonist. Of those, 14 patients also received steroids, 5 received cyclosporine, 1 received etoposide. Approx half (47%) of all patients received either cyclosporine or etoposide with most of those 42% receiving cyclosporine alone, only 2% receiving etoposide alone and 2% receving both. Other than a modest decrease in steroid use over time, there did not appear to be consistent trends in immunosuppressant use over time.

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References:

1. Grom, A. A., Ilowite, N. T., Pascual, V., Brunner, H. I., Martini, A., Lovell, D., . . . Abrams, K. (2016). Rate and Clinical Presentation of Macrophage Activation Syndrome in Patients With Systemic Juvenile Idiopathic Arthritis Treated With Canakinumab. Arthritis Rheumatol, 68(1), 218-228. doi:10.1002/art.39407
2. Sönmez, H. E., Demir, S., Bilginer, Y., & Özen, S. (2018). Anakinra treatment in macrophage activation syndrome: a single center experience and systemic review of literature. Clin Rheumatol, 37(12), 3329-3335. doi:10.1007/s10067-018-4095-1
3. Eloseily, E. M., Weiser, P., Crayne, C. B., Haines, H., Mannion, M. L., Stoll, M. L., . . . Cron, R. Q. (2020). Benefit of Anakinra in Treating Pediatric Secondary Hemophagocytic Lymphohistiocytosis. Arthritis Rheumatol, 72(2), 326-334. doi:10.1002/art.41103
4. Aytaç, S., Batu, E. D., Ünal, Ş., Bilginer, Y., Çetin, M., Tuncer, M., . . . Özen, S. (2016). Macrophage activation syndrome in children with systemic juvenile idiopathic arthritis and systemic lupus erythematosus. Rheumatol Int, 36(10), 1421-1429. doi:10.1007/s00296-016-3545-9
5. Yokota, S., Itoh, Y., Morio, T., Origasa, H., Sumitomo, N., Tomobe, M., . . . Minota, S. (2016). Tocilizumab in systemic juvenile idiopathic arthritis in a real-world clinical setting: results from 1 year of postmarketing surveillance follow-up of 417 patients in Japan. Ann Rheum Dis, 75(9), 1654-1660. doi:10.1136/annrheumdis-2015-207818
6. Yokota, S., Itoh, Y., Morio, T., Sumitomo, N., Daimaru, K., & Minota, S. (2015). Macrophage Activation Syndrome in Patients with Systemic Juvenile Idiopathic Arthritis under Treatment with Tocilizumab. J Rheumatol, 42(4), 712-722. doi:10.3899/jrheum.140288
7. Bennett, T. D., Fluchel, M., Hersh, A. O., Hayward, K. N., Hersh, A. L., Brogan, T. V., . . . Bratton, S. L. (2012). Macrophage activation syndrome in children with systemic lupus erythematosus and children with juvenile idiopathic arthritis. Arthritis Rheum, 64(12), 4135-4142. doi:10.1002/art.34661

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PICO 26. For non-response or partial response to biologic therapy, is addition of calcineurin inhibitor superior to etoposide or IVIG or plasmapheresis at achievement of inactive disease, resolution of MAS?

Summary: The literature search identified 2 cohort studies[1,2] and one case series[3] addressing this question. Aytac et al.[1] included 28 soJIA patients with MAS, all of whom received steroids in addition to 74.2% receiving cyclosporine, 67.7% receiving IVIG, and 32.3% receiving etoposide. Plasmapheresis was performed in 41.9% of patients, being done more frequently in patients who died. In a retrospective cohort including 102 children with MAS secondary to JIA (grouped subtypes together)[2], 15 patients with JIA received IL-1 antagonist with 5 receiving cyclosporine and 1 receiving etoposide as well. A modest decrease in steroid use over time was seen but there were no trends in use of immunosuppressant use over time. In a case series looking at 6 patients with MAS associated with soJIA,[3] 2/6 received IVIG where the outcome was favorable in all patients. These non-comparative observational study designs had a high risk of bias and the quality of evidence was very low.

Quality of evidence across all critical outcomes: Very low

Table 1. Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
2352, Aytac, 2016[1]	Retrospective chart review/cohort	2009-2015	MAS patients secondary to sJIA (28) and lupus (6) 37 MAS episodes	Multiple treatments including plasmapheresis	All patients received steroids. Cyclosporine was given in 74.2% of soJIA-MAS. Intravenous immunoglobulin, anakinra, and etoposide was given during 67.7, 41,9, and 32.3% of sJIA MAS. Plasmapheresis was performed during 41.9% of sJIA MAS and was performed more frequently (p=0.021) in patients who died compared to cured.
2353, Bennett, 2012[2]	Retrospective cohort study	October 1, 2006 to Sept 30, 2010	121 children with MAS secondary to SLE or JIA (102 with JIA)	Cyclosporine	Mortality rate for entire cohort was 7%, children with JIA 6%, SLE 11%, p=0.6. ICU admission was common 33%. Children with SLE had a higher ICU admission rate (63% versus 27%, p=0.002). Higher percentages of children with SLE received mechanical ventilation (53% versus 21%; p=0.02) than children with JIA. Most patients received steroids (83%). Fifteen patients with JIA received IL-1 antagonist. Of those, 14 patients also received steroids, 5 received cyclosporine, 1 received etoposide. Approximately half (47%) of all patients received either cyclosporine or etoposide with most of those 42% receiving cyclosporine alone, only 2% receiving etoposide alone and 2% receiving both. Other than a modest decrease in steroid use

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					over time, there did not appear to be consistent trends in immunosuppressant use over time.
2354, Singh, 2012[3]	Case series	Jan 1995-Dec 2008	6 SoJIA with MAS	IVIG	MAS was first manifestation in 4 patients. Intravenous methylprednisone was used in 4/6, oral prednisone 2/6, and immunoglobulin in 2/6. Outcome favorable in all patients but one who died of progressive disease

References

1. Aytac S, Batu ED, Unal S, Bilginer Y, Cetin M, Tuncer M, et al. Macrophage activation syndrome in children with systemic juvenile idiopathic arthritis and systemic lupus erythematosus. Rheumatology international. 2016;36(10):1421-1429.
2. Bennett TD, Fluchel M, Hersh AO, Hayward KN, Hersh AL, Brogan TV, et al. Macrophage activation syndrome in children with systemic lupus erythematosus and children with juvenile idiopathic arthritis. Arthritis and rheumatism. 2012;64(12):4135-4142.
3. Singh S, Chandrakasan S, Ahluwalia J, Suri D, Rawat A, Ahmed N, et al. Macrophage activation syndrome in children with systemic onset juvenile idiopathic arthritis: clinical experience from northwest India. Rheumatology international. 2011;32(4):881-886.

PICO 27. In sJIA patients who cannot achieve inactive disease despite treatment with both IL-1 and IL-6 agents and/or are chronically steroid dependent, is chronic stable steroid treatment superior to non-steroid treatments (cytoxan or abatacept or rituximab or IVIG or mesenchymal stem cell transplant or bone marrow transplant) at achievement of inactive disease, achievement of partial response, growth, ability to taper/discontinue steroids, and minimize side effects/medication toxicity?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

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PICO 28. In sJIA patients with inactive disease treated with oral steroids, is taper to discontinuation of steroids superior to continuing long-term stable dose steroids for preventing disease flare and minimizing side effects/medication toxicity?

Summary: The literature review identified one case series[1] which included 20 patients with soJIA where symptoms of fever and rash flared up when prednisone was tapered. Five patients who had been off steroids for 4 to 24 months prior had recurrence of their disease.

Quality of evidence across all critical outcomes: Very low

Table 1. Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
1472, Pelkonen, 1986	Case series	1974-1983	20 patients with sJIA	40 of 42 episodes of systemic systems in the patients were treated with steroids	Initial steroid dose ranged from 0.6-1.8 mg.kg/day. All patients had normalization of serum ferritin during the first few weeks of treatment. Fever and rash flared up when prednisone was tapered. Fifteen patients had one or several exacerbations of the disease. Five patients had been off steroids for 4 to 24 months prior to the recurrence.

References:

1. Pelkonen P, Swanljung K, Siimes MA. Ferritinemia as an indicator of systemic disease activity in children with systemic juvenile rheumatoid arthritis. Acta Paediatr Scand. 1986 Jan;75(1):64-8.

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PICO 29: In sJIA patients in clinical remission on biologic monotherapy, is tapering by decreasing dose superior to tapering dosing interval at preventing disease exacerbation, preventing development of anti-drug antibodies and minimizing medication toxicity?

Summary: The literature search revealed one randomized controlled trial (RCT)[1] and one observational study[2] that addressed this PICO question. The RCT was a double-blind, placebo control, abatacept withdrawal study that indirectly addressed the question of abatacept withdrawal; 190 patients, ages 6-17 years with mostly polyarticular JIA (only 18% had sJIA) and with prior inadequate response to at least one DMARD were given abatacept 10mg/kg for 4 months in an open label phase. 47 did not respond in the open label phase and were excluded. Of the remaining patients, 60 were assigned to continue abatacept 10mg/kg every 28 days x 6 months and 62 were assigned placebo for the same timing. Flares of arthritis occurred in 33 of 62 (53%) patients who were given placebo and 12 of 60 (20%) abatacept patients during the double-blind treatment (p=0.0003). Median time to flare of arthritis was 6 months for patients given placebo (insufficient events to calculate IQR); insufficient events had occurred in the abatacept group for median time to flare to be assessed (p=0.0002). The risk of flare in patients who continued abatacept was less than a third of that for controls during that double-blind period (hazard ratio 0.31, 95% CI 0.16–0.95). Only two serious adverse events were reported, both in controls (p=0.50).

For the observational study[2], 42 systemic onset JIA (sJIA) patients refractory to 2mg/kg recombinant interleukin 1 receptor antagonist (rIL-1Ra) escalated their treatment to 4 mg/kg or additional prednisolone or switched to alternative therapy. For patients with inactive disease at 3 months while receiving rIL-1Ra only therapy, rIL-1Ra was tapered for a month (alternate-day regimen) and subsequently stopped. This tapering regimen was effective. Thirty-one patients were able to stop rIL-1Ra, and 29 did so within the first year of therapy. There were 18/31 patients that remained free of flares after stopping rIL-1Ra. There were 13/31 patients that experienced a flare after stopping rIL-1Ra. The median total duration of rIL-1Ra treatment was 6.1 months (IQR 4.4, 9.5 months).

Quality of evidence across all critical outcomes: Very low

Table 1. Data from Randomized Trials

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	abatacept	placebo	Relative (95% CI)	Absolute (95% CI)		
Flare of arthritis in abatacept vs placebo phase												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	abatacept	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	very serious [a]	not serious	none	12/60 (20.0%)	33/62 (53.2%)	**RR 0.38** (0.22 to 0.66)	**330 fewer per 1,000** (from 415 fewer to 181 fewer)	⊕⊕◯◯ LOW	Favors abatacept
Serious adverse events												
1	randomised trials	not serious	not serious	very serious [a]	serious [b]	none	0/60 (0.0%)	2/62 (3.2%)	**OR 0.20** (0.01 to 4.25)	**26 fewer per 1,000** (from 32 fewer to 92 more)	⊕◯◯◯ VERY LOW	
ACR 30 response												
1	randomised trials	not serious	not serious	very serious [a]	serious [b]	none	49/60 (81.7%)	43/62 (69.4%)	**RR 1.18** (0.96 to 1.44)	**125 more per 1,000** (from 28 fewer to 305 more)	⊕◯◯◯ VERY LOW	
ACR 50 Response												
1	randomised trials	not serious	not serious	very serious [a]	not serious	none	46/60 (76.7%)	32/62 (51.6%)	**RR 1.49** (1.12 to 1.96)	**253 more per 1,000** (from 62 more to 495 more)	⊕⊕◯◯ LOW	Favors abatacept
ACR 70 response												
1	randomised trials	not serious	not serious	very serious [a]	not serious	none	32/60 (53.3%)	19/62 (30.6%)	**RR 1.74** (1.12 to 2.71)	**227 more per 1,000** (from 37 more to 524 more)	⊕⊕◯◯ LOW	Favors abatacept

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	abatacept	placebo	Relative (95% CI)	Absolute (95% CI)		
ACR 90 response												
1	randomised trials	not serious	not serious	very serious [a]	not serious	none	24/60 (40.0%)	10/62 (16.1%)	**RR 2.48** (1.30 to 4.73)	**239 more per 1,000** (from 48 more to 602 more)	⊕⊕◯◯ LOW	Favors abatacept
ACR inactive disease												
1	randomised trials	not serious	not serious	very serious [a]	not serious	none	18/60 (30.0%)	7/62 (11.3%)	**RR 2.66** (1.20 to 5.90)	**187 more per 1,000** (from 23 more to 553 more)	⊕⊕◯◯ LOW	Favors abatacept

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

Explanations

a. Indirect comparison to placebo, only 18% of patients had sJIA

b. Wide CI crosses significant effect and no-effect lines

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Table 2. Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment (screening/monitoring) given to relevant population	Results
4040 Ter Haar et al. 2019	Prospective cohort (single center)	Median f/u 5.8 yrs	42 SOJIA	2 mg/kg rIL-1Ra escalated for incomplete response to 4 mg/kg rIL-1Ra or additional prednisolone or switched to alternative therapy.	After a median period of 3.7 months, rIL-1Ra tapering was started in 33 patients. Two patients experienced recurrent disease activity while rIL1-Ra was being tapered and continued IL-1 blockade. Thirty-one patients were able to stop rIL-1Ra, and 29 did so within the first year of therapy. The median total duration of rIL-1Ra treatment was

				If patients had inactive disease at 3 months while receiving rIL-1Ra only, rIL-1Ra was tapered for a month (alternate-day regimen) and subsequently stopped.	6.1 months (IQR 4.4, 9.5 months). Eighteen of the 31 patients remained free of flares after stopping rIL-1Ra (including 2 patients who received rIL-1Ra for >1 year) and have been in remission without therapy for years. Thirteen of the 31 patients experienced a flare after stopping rIL-1Ra.

References:

1. Ruperto et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet 2008 Jul; 372:383-391.
2. Ter Haar NM et al. Treatment to Target Using Recombinant Interleukin-1 Receptor Antagonist as First-Line Monotherapy in New-Onset Systemic Juvenile Idiopathic Arthritis: Results From a Five-Year Follow-Up Study. Arthritis Rheumatol. 2019 Jul; 71 (7):1163-1173.

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Specific Medication Screening Irrespective of Disease Subtype

PICO 30: Is there a recommended laboratory screening schedule (complete blood count, comprehensive metabolic panel and urinalysis) for children receiving chronic daily NSAIDs?

Summary: The literature search revealed two studies that directly/indirectly addressed this question by monitoring for lab abnormalities while on treatment with NSAIDs. Neither study compared different screening schedules. A retrospective cohort study[1] most directly addressed this question of whether routine screening of hemoglobin, Transaminases, BUN, creatinine, and urinalysis was indicated in asymptomatic JIA patients. The authors reported that while 24/91 patients had lab abnormalities none of them correlated with adverse clinical signs or symptoms. Consequently, they concluded that routine monitoring may not be needed in asymptomatic patients. The second study[2] was a randomized, single center, controlled trial that indirectly addressed this PICO question by looking at lab abnormalities for patients on naproxen vs. aspirin at baseline, 12 weeks, and 24 weeks. Pathological elevations of liver enzymes occurred in the aspirin treated patients (14/30) but no clinical abnormalities occurred in the naproxen treated patients. Consequently, this study indirectly concluded that lab monitoring may vary by type of NSAID used. However, aspirin is not representative of current clinical practice, and the randomization was for comparison of different treatments rather than screening schedules. Therefore, the quality of evidence is very low.

Quality of evidence across all critical outcomes: Very low

Table 1. Data from Relevant Studies

Ref ID, Author, year	Study type	Duration	Population Description	Screening given to relevant population	Results
1393, Vora et al. 2010 [1]	Retrospective Cohort	10 years 1996-2006	91 JIA patients Oligo 62% Poly 29%	Screening for lab abnormalities or adverse events on NSAIDs for at least 1 month Median duration of tx (1.5 years) oligo 0.58 years poly	24/91 patients had lab abnormalities during the study period Nearly all were mild and not associated with adverse clinical concerns All continued treatment except for 1 patient Study proposes that routine lab monitoring in asymptomatic pts being treated with NSAIDs is of questionable utility
2581, Kvien, 1984 [2]	Single center randomized	24 weeks	80 patients with oligo (52) or	1:1 randomization to naproxen 10mg/kg/day or aspirin 75mg/kg/day	Patients with adverse reactions: naproxen 12, aspirin 30 Discontinuation due to adverse reactions: naproxen 5, aspirin 20.

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	controlled trial		polyarticular (28) JIA	Laboratory screening at baseline, 12 weeks and 24 weeks	Pathologically elevated liver enzymes occurred in 14/30 aspirin-treated patients. There was no elevation of ALT and AST levels of clinical importance in the naproxen-treated patients (0/12 patients).

References:

1. Vora S, Bengston C, Syverson G, Nocton J. An evaluation of the utility of routine laboratory monitoring of juvenile idiopathic arthritis (JIA) patients using non-steroidal anti-inflammatory drugs (NSAIDs): a retrospective review. Pediatric Rheumatology 2010; 8:11.
2. Kvien TK, Hoyeraal HM, Sandstad B. Naproxen and acetylsalicylic acid in the treatment of pauciarticular and polyarticular juvenile rheumatoid arthritis. Assessment of tolerance and efficacy in a single centre 24-week double-blind parallel study. Scand J Rheumatol. 1984; 13 (4): 342-50.

PICO 31: Is there a recommended laboratory screening schedule (complete blood count, comprehensive metabolic panel) for children being treated with methotrexate (po or sq)?

Summary: The literature search revealed 8 observational studies which addressed this question.[1, 2, 3, 4, 5, 6, 7, 8] They were primarily retrospective and prospective cohort studies and one cross sectional study. None of the studies compared different laboratory screening schedules. Mild laboratory changes were not infrequent but were considered mild. Liver enzyme elevations were the most frequent. Abnormalities normalized in the majority of patients. Higher doses of methotrexate were associated with greater lab abnormalities in one study [3] and changes on liver biopsy in one study [6]. Differences between lab abnormalities were noted in one study between po and sq MTX [2]. There was no standard interval for laboratory testing among the studies as a whole; the shortest reported regular screening interval was every 4 weeks[8] and the longest was every 6 months (after one 3 and 6 month screening after MTX initiation).[2] One prospective cohort study suggested a screening interval of every 2-3 months in otherwise healthy JIA patients [5]. No study found evidence that a screening interval of less than 2 months was necessary in patients with JIA who did not have comorbid conditions that put them at risk of laboratory abnormalities.

Quality of evidence across all critical outcomes: Very Low

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Table 1. Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Screening given to relevant population	Results
2463, Franova, 2016 [1]	Prospective cohort study	1 year	55 JIA patients starting MTX treatment for active disease (at least 1 joint with synovitis), recruited consecutively, under 18 years of age; 45 patients received subcutaneous MTX, 10 received oral	Patients on oral or subcutaneous methotrexate, dosed weekly at ~ 15 mg/m2; Patients evaluated every 3 months for 1 year; ACRPedi, JADAS, Clinically inactive disease, methotrexate intolerance severity score and adverse events were recorded	Laboratory data and patient-reported outcomes were recorded within ± 2 weeks of the first MTX administration and then every 3 months. Measurable toxicity of methotrexate was identified in 8 patients (15.4%). Transaminases were elevated in 7 patients. Cytopenias were identified in 1 patient. In 3 cases the adverse events led to MTX withdrawal. In the remaining 5, results normalized after a short treatment interruption or MTX dose reduction.
1246, Klein, 2012 [2]	Retrospective cohort study	4 years	411 eligible patients, patients with JIA (all subtypes, diagnosis made by ILAR criteria) who had newly started methotrexate and were documented in the registry, consecutively studied	259 patients (63%) received oral methotrexate and 152 (37%) received subcutaneous methotrexate; in both a comparable weekly dose was used (0.4 mg/kg for those with oral and 0.42 for those with subcutaneous); do not give a time frame during which the lab results are obtained “laboratory results, which are done routinely, were documented”	Laboratory screening tests were performed at 3 and 6 months after the start of therapy and then every 6 months. 22% of patients in the oral group and 27% in the subcutaneous group had at least 1 documented adverse event 7 patients (2.7%) in the oral MTX group demonstrated elevated liver enzymes vs 8 patients (5.2%) in the subcutaneous group had elevated liver enzymes 2 patients (0.8%) in the oral MTX group demonstrated abnormal blood counts vs 1 patient (0.66%) in the subcutaneous group 0 patients in the oral group and 1 patient (0.66%) in the subcutaneous group had abnormalities in the serum creatinine

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Ref ID, Author, year	Study type	Duration	Population Description	Screening given to relevant population	Results
1194, Becker et al. 2010 [3]	Retrospective (Comparative cohort)	6 months	220 patients with JIA 126 (Cohort 1) 94 (Cohort 2)	Cohort 1: High dose MTX >0.5mg/kg/week Cohort 2: Low dose MTX <0.5mg/kg/week NSAIDs Screening: AST, ALT	At 6 months, the high-dose group was more likely to have an elevated AST or ALT (adjusted OR 3.89, 95% CI 1.82–8.29, p < 0.0001) with no significant improvement in joint count compared to the low dose MTX group. Females >males had higher risk of toxicity Based on more toxicity in the high dose group, the study suggests that these patients may need more frequent monitoring than the low dose group.
2523, Kocharla et al 2009 [4]	Cross-sectional study	2002-2007	588 patients eligible JIA patients 336 had complete data and were evaluated 198 on MTX 138 on other tx	Screening lab tests compared for patients on MTX + folic acid vs patients not treated with MTX Abnormal AST/ALT (>2x upper limit)	MTX Group 44/2650 (1.7%) AST results were abnormal 90/2647 (3.4%) ALT results were abnormal These results occurred in a total of 30 JIA patients (30%) AST or ALT tests at > 2 ULN occurred more often with systemic JIA (p = 0.04) macrophage activation syndrome, during infections, in systemic antibiotic use, and after intensifying JIA drug regimens. AST or ALT results at > 2 ULN were as frequent among MTX-treated children as those not treated with MTX. Study concluded that adult standards of checking MTX labs q4-8 weeks is unnecessary for JIA patients.
1611, Ortiz et al. 2004 [5]	Prospective cohort study	>1 month of MTX treatment (duration of monitoring not noted)	89 patients with JIA	Screening Labs: AST, ALT, and CBCD for patients taking Methotrexate	40 % of patients had a significantly abnormal blood test (SABT) -14% had elevated liver enzymes (defined as >2x upper limit of normal) -26% had hematologic abnormalities (defined as granulocyte count < 1.5 · 10⁹/l; lymphocyte count < 0.9 · 10⁹/l; or hemoglobin decreased by > 2 g/l from previous level

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Ref ID, Author, year	Study type	Duration	Population Description	Screening given to relevant population	Results
					95% of patients had viral symptoms at time of the abnormal blood test; MTX withheld until results normalized Significantly abnormal blood tests persisted beyond 2 months in only two patients with normalization by 6 months, no cause identified No difference of SABT with cumulative or current dose of MTX Probability of having a SABT at 3 months =11% compared to chance of 10% Authors recommend MTX screening labs every 2-3 months in patients without comorbid conditions which could also put them at risk for lab abnormalities. They did not find any convincing evidence that a lab check at 4 weeks is necessary.
1652 Lahdenne 2002 [6]	Single Arm Cohort study	5 years	34 Patients with polyarticular course JIA (3 sJIA, 23 poly, 8 oligo)	Percutaneous liver biopsy for all patients on long term MTX (>2.4 years) Low dose MTX (<20mg/m2)=24 patients High dose MTX (>20mg/m2) = 10 patients	Liver enzyme tests were routinely performed every 4 to 6 weeks one or 2 days before the next weekly MTX dose. Low dose MTX – 10 patients with liver enzymes > 2.5 times the ULN, all biopsies grade I High dose MTX – 4 patients with liver enzymes >2.5 times the ULN, 5 with biopsy grade I, 4 with biopsy grade II, 1 biopsy unclassified due to extensive steatosis High dose MTX correlated with grade II (p = 0.003) Higher cumulative MTX associated with grade II (p = 0.005) Liver enzymes >2.5 times the ULN not associated with grade (p=0.63) In 2 cases with > 20 mg/m2 MTX doses, portal inflammation was moderate to severe. The portal inflammation resolved when MTX was discontinued for 6 months. Higher MTX doses may increase the risk for histopathologic liver changes. However, these changes seem to be reversible, because regardless of high doses of MTX, cumulative doses up to 6 g, and the use of MTX in combination with other DMARD, the authors did not find any case of fibrosis or cirrhosis.

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Ref ID, Author, year	Study type	Duration	Population Description	Screening given to relevant population	Results
2528, Graham et al. 1992 [7]	Retrospective Cohort	84-296 weeks of MTX tx (1985-1990)	62 patients with poly JIA	Screening for adverse events/lab abnormalities	9/62 had elevated liver enzymes during the study period not clearly attributed to MTX MTX able to be continued in all patients Hematologic abnormalities were rare 1 patient had a macrocytic anemia when taking Bactrim No neutropenia or thrombocytopenia seen No recommendation given on frequency of lab monitoring, but authors felt lab changes were rare.
3486 Rose, 1990 [8]	Cohort study	8-39 months	29 patients with JIA (12 with sJIA)	MTX 5-15mg/m2/week (mean dose 7.1mg/m2/week) Screening for adverse events/lab abnormalities	Lab screening was done every 4 weeks. Two children had moderate gastrointestinal upset; one of them also had mild stomatitis. These two patients had initially been given MTX as a single weekly oral pulsed dose, and symptoms resolved in both cases after the dose was divided into three equal parts. One child had abnormal levels of serum liver enzymes in week 8 of treatment that returned to normal within 2 weeks of stopping MTX therapy; no recurrence of liver involvement was observed after MTX therapy was reinstituted at a 30% lower dose. No manifestations of pulmonary, cutaneous, renal, or hematologic toxicity were observed during the follow-up period.

References:

1. Fráňová, J., Fingerhutová, Š., Kobrová, K., Srp, R., Němcová, D., Hoza, J., . . . Doležalová, P. (2016). Methotrexate efficacy, but not its intolerance, is associated with the dose and route of administration. Pediatric rheumatology, 14(1), 36. doi:10.1186/s12969-016-0099-z
2. Klein, A., Kaul, I., Foeldvari, I., Ganser, G., Urban, A., & Horneff, G. (2012). Efficacy and safety of oral and parenteral methotrexate therapy in children with juvenile idiopathic arthritis: An observational study with patients from the German Methotrexate Registry. Arthritis Care Res (Hoboken), 64(9), 1349-1356. doi:10.1002/acr.21697
3. ECKER, M. L., ROSÉ, C. D., CRON, R. Q., SHERRY, D. D., BILKER, W. B., & LAUTENBACH, E. (2010). Effectiveness and Toxicity of Methotrexate in Juvenile Idiopathic Arthritis: Comparison of 2 Initial Dosing Regimens. J Rheumatol, 37(4), 870-875. doi:10.3899/jrheum.090826

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4. KOCHARLA, L., TAYLOR, J., WEILER, T., TING, T. V., LUGGEN, M., & BRUNNER, H. I. (2009). Monitoring Methotrexate Toxicity in Juvenile Idiopathic Arthritis. J Rheumatol, 36(12), 2813-2818. doi:10.3899/jrheum.090482
5. Ortiz-Alvarez, O., Morishita, K., Avery, G., Green, J., Petty, R. E., Tucker, L. B., . . . Cabral, D. A. (2004). Guidelines for blood test monitoring of methotrexate toxicity in juvenile idiopathic arthritis. J Rheumatol, 31(12), 2501-2506.
6. Lahdenne, P., Rapola, J., Ylijoki, H., & Haapasaari, J. (2002). Hepatotoxicity in patients with juvenile idiopathic arthritis receiving longterm methotrexate therapy. J Rheumatol, 29(11), 2442-2445.
7. Graham, L. D., Myones, B. L., Rivas-Chacon, R. F., & Pachman, L. M. (1992). Morbidity associated with long-term methotrexate therapy in juvenile rheumatoid arthritis. J Pediatr, 120(3), 468-473. doi:10.1016/s0022-3476(05)80923-0
8. Rose, C. D., Singsen, B. H., Eichenfield, A. H., Goldsmith, D. P., & Athreya, B. H. (1990). Safety and efficacy of methotrexate therapy for juvenile rheumatoid arthritis. J Pediatr, 117(4), 653-659. doi:https://doi.org/10.1016/S0022-3476(05)80709-7

PICO 32: After methotrexate (po or sq) is initiated, is there a recommended medication change secondary to elevated liver function tests and decreased neutrophil or platelet count?

Summary: The literature search revealed 5 observational cohort studies which indirectly addressed this question.[1, 2, 3, 4, 5] Higher doses of methotrexate were associated with greater lab abnormalities in one study[2] compared to lower dose methotrexate without change in joint count. Consequently, this difference prompted the authors to suggest use of low dose methotrexate over high dose methotrexate (>20mg/m2). One study showed more changes on liver biopsy with higher doses of methotrexate[4]; however, the changes seemed to be reversible. In some instances, lab abnormalities improved after holding methotrexate temporarily [1, 3] before restarting it at the same dose or improved with methotrexate dose reduction in other cases [1, 5].

Quality of evidence across all critical outcomes: Very Low

Table 1. Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Screening in relevant population	Results
2463, Franova, 2016 [1]	Prospective cohort study	1 year	55 JIA patients starting MTX treatment for active disease (at least 1 joint with synovitis),	Patients on oral or subcutaneous methotrexate, dosed weekly at ~ 15 mg/m2; Patients	Measurable toxicity of methotrexate was identified in 8 patients (15.4%). Transaminases were elevated in 7 patients (defined as increase of at least 1 liver transaminase above 2x the upper limit of normal). Cytopenias were identified in 1 patient. In 3 cases the adverse events led to MTX withdrawal. In the remaining 5,

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Ref ID, Author, year	Study type	Duration	Population Description	Screening in relevant population	Results
			recruited consecutively, under 18 years of age; 45 patients received subcutaneous MTX, 10 received oral	evaluated every 3 months for 1 year; ACRPedi, JADAS, Clinically inactive disease, methotrexate intolerance severity score and adverse events were recorded	results normalized after a short treatment interruption or MTX dose reduction. In the majority of cases, intolerance was managed to the patient and family satisfaction by treatment modifications and various other actions and their combinations: change in the route and/or timing of MTX administration, MTX dose reduction, addition of antiemetics, counseling. Methotrexate withdrawal was the ultimate solution in 2 patients only (8%).
1194, Becker et al. 2010 [2]	Retrospective (Comparative cohort)	1 year of MTX treatment	220 patients with JIA 126 (Cohort 1) 94 (Cohort 2)	Cohort 1: High dose MTX >0.5mg/kg/week Cohort 2: Low dose MTX <0.5mg/kg/week NSAIDs were allowed in each group	At 6 months, the high-dose group was more likely to have an elevated AST or ALT (adjusted OR 3.89, 95% CI 1.82–8.29, p < 0.0001) with NO statistically significant improvement in joint count compared to the low dose MTX group. Five of 126 (4%) patients in the high-dose group discontinued MTX due to hepatic toxicity. No medication substitution was mentioned.
1611, Ortiz et al. 2004 [3]	Prospective cohort study	>1 month of MTX treatment (duration of monitoring not noted)	89 patients with JIA	Screening Labs: AST, ALT, and CBCD for patients taking Methotrexate	40 % of patients had a significantly abnormal blood test (SABT) -14% had elevated liver enzymes (defined as >2x upper limit of normal) -26% had hematologic abnormalities (defined as granulocyte count $< 1.5 \cdot 10^9$/l; lymphocyte count $< 0.9 \cdot 10^9$/l; or hemoglobin decreased by > 2 g/l from previous level When a SABT was identified, patients were instructed to stop taking MTX and have the blood test repeated within one to 2 weeks of the last abnormal test. 95% of patients had viral symptoms at time of the abnormal blood test; MTX withheld until results normalized and MTX was able to be restarted in most at the previous dose. In 2 patients, MTX was withheld for 6

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Ref ID, Author, year	Study type	Duration	Population Description	Screening in relevant population	Results
					months. No other patient had MTX withheld for longer than a month. No medication substitution was mentioned. No difference of SABT with cumulative or current dose of MTX. Probability of having a SABT at 3 months =11% compared to chance of 10%. Overall, study shows that most lab changes are minor and MTX can be continued in most patients.
1652 Lahdenne 2002 [4]	Single Arm Cohort study	5 years	34 Patients with polyarticular course JIA (3 sJIA, 23 poly, 8 oligo)	Percutaneous liver biopsy for all patients on long term MTX (>2.4 years) Low dose MTX (<20mg/m2)=24 patients High dose MTX (>20mg/m2) = 10 patients	Liver enzyme tests were routinely performed every 4 to 6 weeks one or 2 days before the next weekly MTX dose. Low dose MTX – 10 patients with liver enzymes > 2.5 times the ULN, all biopsies grade I High dose MTX – 4 patients with liver enzymes >2.5 times the ULN, 5 with biopsy grade I, 4 with biopsy grade II, 1 biopsy unclassified due to extensive steatosis High dose MTX correlated with grade II (p = 0.003) Higher cumulative MTX associated with grade II (p = 0.005) Liver enzymes >2.5 times the ULN not associated with grade (p=0.63) In 2 cases with > 20 mg/m2 MTX doses, portal inflammation was moderate to severe. The portal inflammation resolved when MTX was discontinued for 6 months. Higher MTX doses may increase the risk for histopathologic liver changes. However, these changes seem to be reversible, because regardless of high doses of MTX, cumulative doses up to 6 g, and the use of MTX in combination with other DMARD, the authors did not find any case of fibrosis or cirrhosis.
3486 Rose, 1990 [5]	Cohort study	8-39 months	29 patients with JIA (12 with sJIA)	MTX 5-15mg/m2/week (mean dose 7.1mg/m2/week)	Two children had moderate gastrointestinal upset; one of them also had mild stomatitis. These two patients had initially been given MTX as a single weekly oral pulsed dose, and symptoms resolved in both cases after the dose was divided into three equal parts. One child had abnormal levels of serum liver enzymes in week 8 of treatment that returned to normal within

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Ref ID, Author, year	Study type	Duration	Population Description	Screening in relevant population	Results
					2 weeks of stopping MTX therapy; no recurrence of liver involvement was observed after MTX therapy was reinstituted at a 30% lower dose.

1. Franova et al. Methotrexate Efficacy, but Not Its Intolerance, Is Associated with the Dose and Route of Administration. Pediatr Rheumatol Online J. 2016 Jun; 14 (1):36.
2. Becker ML, Rose CD, Cron RQ, Sherry DD, Bilker WB, Lautenbach E. Effectiveness and Toxicity of Methotrexate in Juvenile Idiopathic Arthritis: Comparison of 2 Initial Dosing Regimens. J Rheumatol. 2010 Apr; 37 (4) 870-5.
3. Ortiz-Alvarez O et al. Guidelines for Blood Test Monitoring of Methotrexate Toxicity in Juvenile Idiopathic Arthritis. J Rheumatol. 2004 Dec; 31 (12): 2501-6.
4. Lahdenne P, Rapola J, Heikki Y, Haapasaari J. Hepatotoxicity in Patients with Juvenile Idiopathic Arthritis Receiving Longterm Methotrexate Therapy. J Rheumatol.2002 Nov; 29 (11):2442-5.
5. Rose, C. D., Singsen, B. H., Eichenfield, A. H., Goldsmith, D. P., & Athreya, B. H. (1990). Safety and efficacy of methotrexate therapy for juvenile rheumatoid arthritis. J Pediatr, 117(4), 653-659. doi:https://doi.org/10.1016/S0022-3476(05)80709-7

PICO 33. Is there a recommended laboratory screening schedule (complete blood count, comprehensive metabolic panel) for children with JIA being treated with sulfasalazine?

Summary: Literature searches identified three observational studies (1 retrospective [1] and 2 prospective [2, 3] cohorts) which indirectly answered the PICO question. The laboratory screening schedule was not the aim of these studies and none of them compared different screening schedules. Each of the studies permitted for concomitant therapy administration including the use of NSAIDs [1, 3, 2], azathioprine [1, 3, 2], prednisone [3], anti-malarial [3, 2], auranofin [3], penicillamine [3], methotrexate [3] or aspirin [3]. In the study conducted by Chen et al., [1] labs were obtained baseline and then monthly thereafter. Each blood draw consisted of a CBC as well as renal and liver function tests. None of the patients developed leukopenia, thrombocytopenia, or hepatitis (1). In the study by Varbanova et al. [2] labs were obtained twice during the 1st through 3rd months and then every 3 months thereafter. Two cases of reversible neutropenia (following discontinuation of therapy) were identified. No specific list of screening tests was identified [2]. Finally, the study performed by Imundo et al. [3] drew screening tests monthly for 3 months followed by a q3 month schedule. No specific laboratory screening measures were identified, but the authors noted that three patients were found to have transaminitis and 5 had leukopenia with neutropenia.

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Quality of evidence across all critical outcomes: Very low

Table 1. Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Monitoring given to relevant population	Results
3704, Chen, 2002 [1]	Retrospective cohort study	7 years	24 children with JRA (diagnosis made according to ACR criteria) treated with oral sulfasalazine; All patients had received NSAIDs, 17 received sulfasalazine and azathioprine	Initial dose of sulfasalazine averaged 21.6 mg/kg/day; drug safety was monitored at baseline before treatment and then monthly thereafter using history, physical exam, CBC, renal and liver function tests	SSZ adverse effects were found in 3 patients (12.5%) None of the patients developed leukopenia, thrombocytopenia, or hepatitis The combination of SSZ and AZA did not show any serious adverse effects compared to using the therapies singly
3711, Varbanova, 1999 [2]	Prospective cohort	Unclear	32 JCA children (using EULAR criteria); (10 poly, 21 pauci, 1 systemic); permitted for NSAIDs, azathioprine or antimalarial therapy	Sulfasalazine given as 40 mg/kg in 2-3 divided doses, titrating up by 1/3 to achieve maximal dose at 3 weeks; if patients entered remission in the 1st year, they were given 25 mg/kg/day; obtained labs twice during the first month, once a month up to the third month, and then every 3 months following that	2 cases had reversible neutropenia requiring discontinuation of therapy
3705, Imundo, 1996 [3]	Prospective cohort	3 years	139 JRA children (using ACR criteria) that demonstrated active arthritis (persistent effusion, limited ROM, pain; patients were allowed to be on other agents concomitantly including: NSAIDs,	Sulfasalazine given as a mean dose of 31 mg/kg/day divided BID, max 3g/day; blood tests were performed monthly x 3 months and then every 3 months thereafter	3 patients had transaminitis (LFTs 3-17 x normal), these usually resolved within 3 months of drug discontinuation 5 patients had leukopenia and neutropenia (ANC range 1000-1500). Medication was stopped until all symptoms resolved. Authors state that in cases where adverse reactions were 'mild' or not thought to be related to the drug that sulfasalazine was either: resumed at full dose, resumed at reduced dose, or changed to the enteric coated form…however, they do not identify which patients and the neutropenic patients are reported with

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Ref ID, Author, year	Study type	Duration	Population Description	Monitoring given to relevant population	Results
			prednisone, hydroxychloroquine, auranofin, penicillamine, methotrexate, aspirin		the other patients who had adverse effects (rash, GI upset, headache, fever). There was no difference in the initial dose between patients that had an adverse reaction and those who did not.

References:

1. Chen, C.-C., Lin, Y.-T., Yang, Y.-H., & Chiang, B.-L. (2002). Sulfasalazine therapy for juvenile rheumatoid arthritis. Journal of the Formosan Medical Association, 101(2), 110-116.
2. Varbanova, B. B., & Dyankov, E. D. (1999). Sulphasalazine. An alternative drug for second-line treatment of juvenile chronic arthritis. Adv Exp Med Biol, 455, 331-336.
3. Imundo, L. F., & Jacobs, J. C. (1996). Sulfasalazine therapy for juvenile rheumatoid arthritis. J Rheumatol, 23(2), 360-366.

PICO 34. After sulfasalazine is initiated, is there a recommended medication change in response to elevated liver function tests and decreased neutrophil or platelet count?

Summary: Literature searches identified two prospective observational cohorts which indirectly answered the PICO question. The change of medication in response to abnormal labs was an indirect outcome of these studies. Varbanova et al. [1] reported 2 cases (6.25%) of reversible neutropenia. They noted that the neutropenia resolved with discontinuation of sulfasalazine treatment; they did not indicate what alternative treatment these patients received following discontinuation. Imundo et al.[2] reported that 3 patients (2.2%) had transaminitis (LFTs ranging 3 to 17 times normal) which resolved by 3 months upon sulfasalazine discontinuation. Five patients (3.6%) had neutropenia. In all these patients sulfasalazine was discontinued for some period of time. the authors mention that some patients with 'mild' adverse reactions were restarted on medication, some at full dose, some at reduced dose and some with the enteric coated form. However, this study is unclear regarding which of these treatment modifications was given to the patients with neutropenia.

Quality of evidence across all critical outcomes: Very low

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Table 1. Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Monitoring given to relevant population	Results
3711, Varbanova, 1999 [1]	Prospective cohort	Unclear	32 JCA children (using EULAR criteria); (10 poly, 21 pauci, 1 systemic)	Sulfasalazine given as 40 mg/kg in 2-3 divided doses, titrating up by 1/3 to achieve maximal dose at 3 weeks; if patients entered remission in the 1st year, they were given 25 mg/kg/day; obtained labs twice during the first month, once a month up to the third month, and then every 3 months following that.	2 cases had reversible neutropenia requiring discontinuation of therapy (did not report what patients were switched to).
3705, Imundo, 1996 [2]	Prospective cohort	3 years	139 JRA children (using ACR criteria) that demonstrated active arthritis (persistent effusion, limited ROM, pain; patients were allowed to be on other agents concomitantly including: NSAIDs, prednisone, hydroxylchloroquine, auranofin, penicillamine, methotrexate, aspirin	Sulfasalazine given as a mean dose of 31 mg/kg/day divided BID, max 3g/day; blood tests were performed monthly x 3 months and then every 3 months thereafter.	3 patients had transaminitis (LFTs 3-17 x normal), these usually resolved within 3 months of drug discontinuation 5 patients had leukopenia and neutropenia (ANC range 1000-1500). Medication was stopped until all symptoms resolved. The authors stated that in cases where adverse reactions were 'mild' or not thought to be related to the drug that sulfasalazine was either: resumed at full dose, resumed at reduced dose, or changed to the enteric coated form. However, the authors did not report which patients received which medication change and the neutropenic patients are reported with the other patients who had adverse effects (rash, GI upset, headache, fever). There was no difference in the initial dose between patients that had an adverse reaction and those who did not.

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References:

1. Varbanova, B. B., & Dyankov, E. D. (1999). Sulphasalazine. An alternative drug for second-line treatment of juvenile chronic arthritis. Adv Exp Med Biol, 455, 331-336.
2. Imundo, L. F., & Jacobs, J. C. (1996). Sulfasalazine therapy for juvenile rheumatoid arthritis. J Rheumatol, 23(2), 360-366.

PICO 35. Should children with JIA receiving leflunomide have serum creatinine, urinalysis, complete blood count and liver enzymes before and during treatment, per manufacturer's recommendations?

The following package insert information provided by the manufacturer regarding laboratory testing of leflunomide (ARAVA) is relevant to this PICO question.

"Hematologic Monitoring: At minimum, patients taking ARAVA should have platelet, white blood cell count and hemoglobin or hematocrit monitored at baseline and monthly for six months following initiation of therapy and every 6 to 8 weeks thereafter.

Bone Marrow Suppression Monitoring: If used concomitantly with immunosuppressants such as methotrexate, chronic monitoring should be monthly.

Liver Enzyme Monitoring: At minimum, ALT (SGPT) must be performed at baseline and at least monthly for six months after starting ARAVA, and thereafter every 6-8 weeks. In addition, if ARAVA and methotrexate are given concomitantly, ACR guidelines for monitoring methotrexate liver toxicity must be followed with ALT, AST, and serum albumin testing every month."

Summary: The literature search identified one study that indirectly addressed the question. The study was a retrospective, single-center cohort study [1] of JIA patients who initiated leflunomide between April 2001 and October 2006. Labs were obtained on patients every 4-12 weeks. The specific set of labs drawn was not reported in the study. Reporting of adverse events indicated that 9 (15.5%) of patients experienced transient transaminitis. This resolved with decreasing the dose.

Quality of evidence across all critical outcomes: Very low

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Table 1. Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Monitoring given to relevant population	Results
1201, Foeldvari, 2010 [1]	Retrospective cohort, single arm	5 years	58 total JIA patients (using ILAR criteria); 15 with oligoarthritis (25.9%); all patients had at least 1 active joint at starting leflunomide (defined as swollen, tender, or limited ROM); all patients had received methotrexate prior to leflunomide	Leflunomide administered with a mean dose of 16.64 mg/day. No loading dose was given. Baseline characteristics, reason for starting leflunomide, adverse events, joint outcomes, CHAQ, VAS, well being scores and treatment status were all obtained On average, patient evaluations and labs were done every 4-12 weeks: did not define what the specific labs obtained were.	9 patients (15.5%) had transient increase in LFTs. No one stopped the medication. Doses were temporarily decreased until LFTs normalized.

References:

1. Foeldvari I, Wierk A. Effectiveness of leflunomide in patients with juvenile idiopathic arthritis in clinical practice. J Rheumatol. 2010 Aug 1;37(8):1763-7.

PICO 36. **After leflunomide is initiated, should medication dosage be altered according to the package insert secondary to elevated liver function tests?**

The following package insert information provided by the manufacturer regarding contraindications and warnings related to leflunomide (ARAVA) is relevant to this PICO question.

“If ALT elevation > 3 fold ULN occurs, interrupt ARAVA therapy while investigating the probable cause of the ALT elevation by close observation and additional tests. If likely leflunomide-induced, start cholestyramine washout and monitor liver tests weekly until normalized. If leflunomide-induced liver injury is unlikely because some other probable cause has been found, resumption of ARAVA therapy may be considered.”

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Summary: This PICO question was indirectly addressed by one single-center retrospective cohort study.[1] All patients in this study failed methotrexate treatment before moving to leflunomide. A mean dose of 16.64 mg/day was administered to patients. Nine out of 58 total patients (15.5%) experienced transaminitis. Per the authors, no patient stopped the medication, but doses were temporarily decreased until LFT normalization occurred. The degree of dosage decrease was not indicated.

Quality of evidence across all critical outcomes: Very low

Table 1. Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
1201, Foeldvari, 2010 [1]	Retrospective cohort, single arm	5 years	58 total JIA patients (using ILAR criteria); 15 with oligoarthritis (25.9%); all patients had at least 1 active joint at starting leflunomide (defined as swollen, tender, or limited ROM); all patients had received methotrexate prior to leflunomide	Leflunomide administered with a mean dose of 16.64 mg/day. No loading dose was given. Baseline characteristics, reason for starting leflunomide, adverse events, joint outcomes, CHAQ, VAS, well being scores and treatment status were all obtained On average, patient evaluations and labs were done every 4-12 weeks	9 patients (15.5%) had transient increase in LFTs. No one stopped the medication. Doses were temporarily decreased until LFTs normalized.

References:

1. Foeldvari I, Wierk A. Effectiveness of leflunomide in patients with juvenile idiopathic arthritis in clinical practice. J Rheumatol. 2010 Aug 1;37(8):1763-7.

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PICO 37. Should children with JIA receiving treatment with hydroxychloroquine have annual screening tests with automated visual fields, if age appropriate, plus spectral-domain optical coherence tomography (SD OCT) versus starting annual screening 5 years after treatment onset?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 38. Is there a recommended laboratory screening schedule (complete blood count, comprehensive metabolic panel) for children with JIA being treated with hydroxychloroquine?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 39. Is there a recommended laboratory screening schedule (complete blood count, comprehensive metabolic panel and urinalysis) for children with JIA receiving TNF inhibitor treatment?

Summary: The literature search identified two observational studies that addressed this PICO question.[1,2] Neither study compared different screening schedules. One single-arm cohort study measured levels of adalimumab or etanercept and anti-drug antibody (ADab) levels at baseline, 3 months and 6 months in a cohort of 59 RA and 11 JIA patients beginning first-line therapy with these drugs. All JIA patients were positive for drug and negative for ADab throughout the study.[1] Another cohort study evaluating etanercept performed labs at baseline, 6 months, 12 months and then yearly.[2] Only 2% of patients stopped etanercept due to AE but the study did not mention if these AE were identified in the lab tests.

Quality of evidence across all critical outcomes: Very low

Table 1. Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Monitoring given to relevant population	Results
4551, Bodio et al., 2020[1]	Single-arm prospective cohort study	6 months	59 RA patients, 11 JIA patients; all starting first-line therapy with	Drug levels and anti-drug antibody (ADAb) levels measured at	**Clinical outcomes of prospective study** RA • Humira: 2 with ADAb and loss of response after 3 months, 2 with ADAb after 6 months (1 moderate

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			adalimumab or etanercept with concomitant MTX	baseline, 3 months and 6 months using ELISA and RGA	response, 1 no response), 2 with primary failure without ADAb • Etanercept: all with moderate to good response; positive for drug and undetectable ADAb JIA • Adalimumab: All positive for drug and negative for ADAb; 2 patients never reached remission; 1 loss of response at 6 months • Etanercept: all improved during treatment Non-responders (n = 10 total; n = 3 had JIA) • 2/10 with high ADAb and low drug levels (both RA patients) • 8/10 without ADAb and drug level therapeutic (including 3 JIA non-responders) **Performance of ELISA and RGA assays (cross-sectional aspect of study):** ELISA • ADAb levels detected in 14.1% (23/163) • Drug levels detected in 83.4% (136/163) • 5.1% (7/136) positive for both ADAb and drug RGA • ADAb detected in 12.9% (21/163) • Drug levels detected in 71.8% (117/163) 0.9% (1/117) positive for both ADAb and drug
1442, L Kearsley-Fleet et al., 2016[2]	Single-arm cohort study	1 year	496 patients with JIA	Etanercept was given to all patients. Lab measures including ESR and CRP were evaluated at baseline, 6 months, 12 months, and annually thereafter.	**AEs (all patients):** 9 (2%) patients stopped taking etanercept due to adverse events.

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References:

1. Bodio C, Grossi C, Pregnolato F, Favalli EG, Biggioggero M, Marchesoni A, et al. Personalized medicine in rheumatoid arthritis: How immunogenicity impacts use of TNF inhibitors. Autoimmunity reviews. 2020;19(5):102509.
2. Kearsley-Fleet L, Davies R, Lunt M, Southwood TR, Hyrich KL. Factors associated with improvement in disease activity following initiation of etanercept in children and young people with Juvenile Idiopathic Arthritis: results from the British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study. Rheumatology (Oxford, England). 2016;55(5):840-847.

PICO 40. Is there a recommended laboratory screening schedule (complete blood count, comprehensive metabolic panel and urinalysis) for children with JIA receiving abatacept treatment?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 41. Should children with JIA receiving tocilizumab have serum creatinine, urinalysis, complete blood cell count, and liver enzymes before and during treatment, per manufacturer's recommendations?

Summary. Our searches identified one retrospective cohort study with 104 patients (86 with JIA) that marginally addressed this question. Aeschlimann et al.[1] evaluated pediatric rheumatology patients who received at least 1 dose of tocilizumab. As noted in Table 1, 3 children with sJIA developed MAS with elevated liver enzymes while on tocilizumab, and a couple children (disease not specified) had elevated liver enzymes or febrile neutropenia while on tocilizumab.

Quality of evidence across all critical outcomes: Very low

Table 1. Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
4608, Aeschlimann, 2020[1]	Retrospective Cohort study	01/2007 to 06/2019	All pediatric rheumatology patients who received at least one dose of tocilizumab:	At least one dose of tocilizumab	3 children with sJIA had MAS while on tocilizumab therapy, with part of the presentation including elevated liver enzymes

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			43 sJIA, 43 pJIA, 12 other autoinflammatory disease, 6 "other"		1 child (disease not stated) had elevated liver enzymes while on tocilizumab 1 child (disease not stated) had febrile neutropenia while on tocilizumab

References

1. Aeschlimann FA, Dumaine C, Wörner A, Mouy R, Wouters C, Melki I, et al. Serious adverse events in children with juvenile idiopathic arthritis and other rheumatic diseases on tocilizumab - a real-world experience. Seminars in arthritis and rheumatism. 2020;50(4):744-748.

PICO 42. After tocilizumab is initiated, should medication dosage be altered according to the package insert secondary to elevated liver function tests, neutropenia and/or thrombocytopenia?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 43. Is there a recommended laboratory screening schedule (complete blood count, comprehensive metabolic panel and urinalysis) for children with JIA receiving anakinra treatment?

Summary. Our searches identified one retrospective cohort study with 77 patients with sJIA treated with anakinra and canakinumab that marginally addressed this question. Sota et al.[1] evaluated drug retention rate and factors that led to stopping the drugs in some patients. Adverse events occurred in 13/77 patients, one of whom had abnormal liver enzymes, but no patients developed MAS or serious adverse events.

Quality of evidence across all critical outcomes: Very low

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Table 1. Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Monitoring given to relevant population	Results
4406 Sota, 2019[1]	Retrospective cohort	7.5 years	77 pediatric systemic JIA pts treated with anakinra and canakinumab	Evaluate drug retention rate of anakinra and canakinumab. Determine factors which led to stopping the drug.	15 centers in Italy retrospectively reviewed. 61 pts received anakinra, 25 canakinumab. 22 pts also received a DMARD concurrently (mtx, cyclosporine, sulfasalazine, leflunomide, or plaquenil). Mean ± SD treatment length 22.67 ± 19.50 months. The retention rate of both anti-IL-1 agents at 12-, 24-, 48-, and 60-months of follow-up was 79.9, 59.5, 53.5, and 53.5%, respectively. The median disease length was significantly higher in pts who stopped IL-1 blockers (5.88 years ± 6.55) vs those that were able to continue these biologic agents (3.17 years ± 3.68) (p = 0.011). 16/63 patients (27%) were able to stop corticosteroids. AEs occurred in 13 out of 77 patients (17.1%) (11 on ANA and 2 on CAN), with injection site-reactions (n = 7) most commonly, then generalized skin rashes (n = 4), respiratory problems (n = 1), and abnormal level of liver enzymes (n = 1). 10 pts stopped treatment because of AEs. No pts had MAS or serious AEs.

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References:

1. Sota J, Insalaco A, Cimaz R, Alessio M, Cattalini M, Gallizzi R, et al. Drug retention rate and predictive factors of drug survival for interleukin-1 inhibitors in systemic juvenile idiopathic arthritis. Frontiers in Pharmacology. 2019;9(JAN):1526.

PICO 44. Is there a recommended laboratory screening schedule (complete blood count, comprehensive metabolic panel and urinalysis) for children with JIA receiving canakinumab treatment?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

PICO 45: Should all children with JIA have infection titers (measles, varicella, hepatitis B, hepatitis C) checked prior to starting immunosuppressive medication?

Summary: The literature search identified two cohort studies[1,2] and one cross-sectional study[3] that addressed this PICO question. These studies reported adverse events related to infectious diseases in patients with JIA receiving a biologic[1] and the incidence of zoster among patients with JIA.[2] The rate of zoster was higher among patients with JIA compared to healthy controls (IRR 2.9 (1.8 – 4.5), p<0.001). The cross-sectional study[3] evaluated the presence of lower genital infections in female JIA patients compared to healthy controls. The frequency of HPV infection was higher in JIA patients compared to controls, but the difference was not statistically significant (30% vs 11%, p=0.155). There was no difference in the frequency of Chlamydia trachomatis or Neisseria gonorrhoeae infection between JIA patients or healthy controls. Current use of MTX (12% vs 44%, p=0.206) and biologic use (37% vs 64%, p=0.238) were not significantly different between JIA patients with abnormal and normal cytopathology.

Quality of evidence across all critical outcomes: Very low

Table 1. Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Monitoring in relevant population	Results
1858 Dumaine 2019[1]	Single Arm Cohort study	14 years	677 patients with JIA and receiving a biologic (177 poly, 137 ERA, 117 sJIA, 108 extended oligo, 87 oligo, 33 psoriatic, 18 unclassified) 90% on combination therapy (MTX, NSAIDs, corticosteroids)	Adverse event related to infectious disease as reported by investigator in the database	184 infectious adverse events, incidence rate 0.17 (95% CI 0.17 ± 0.01) per biological treatment 54 IAE in sJIA (all patients on anakinra and canakinumab): ANA 6.7/100 p-y, CAN 9.6/100 p-y 37 IAE in extended oligo 14 in oligo (no treatment/disease type rates reported) 12 severe or very severe (7 in sJIA) – CAN severe 1 (1.3/100 p-y), very severe 1 (1.3/100 p-y) ANA severe 2 (1.1/100 p-y), very severe 0 24 hospitalization (15 in sJIA) – CAN 2 (2.7/100 p-y), ANA 6 (3.3/100 p-y)
1844 Nimmrich 2015[2]	Cohort Study	12 years	3,042 patients with JIA enrolled in BIKER	Incidence of zoster diagnosed by a physician	(Rate by JIA category not reported) – 17 total cases Overall rate 6/1000 patients (3.5-9.0), incidence 3.1/1000 patient-years (1.9-4.9) – compared to published rate in healthy children IRR 2.9 (1.8-4.5), p<0.001

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Ref ID, Author, year	Study type	Duration	Population Description	Monitoring in relevant population	Results
					4/17 with extended oligo (meds include Prednisone, MTX, AZA, etanercept, intraarticular TH) 3/17 with persistent oligo (meds include prednisone, MTX, etanercept, intraarticular TH)
4489 Ferreira 2019[3]	Cross-sectional study	9/2014 – 6/2016	33 post-pubertal female JIA patients, 28 healthy, age-matched controls	GYN exam with HPV DNA testing, CT DNA testing, and NG DNA testing, Pap smear with cytopathology	Chlamydia trachomatis (CT) was found in 0% JIA vs 7% healthy controls, p=0.207 Neisseria gonorrhoeae (NG) was found in 0% JIA vs 4% healthy controls, p=0.459 HPV infection was found in 30% JIA vs 11% healthy controls, p=0.155 Of JIA patients, abnormal cervical cytopathology had higher HPV infection compared to normal cytopathology (87% vs 12%, p=0.0002) Current use of MTX (12% vs 44%, p=0.206) and biologic use (37% vs 64%, p=0.238) were not significantly different between JIA patients with abnormal and normal cytopathology.

References:

1. Dumaine C, Bekkar S, Belot A, Cabrera N, Malik S, Scheven AV, et al. Infectious adverse events in children with Juvenile Idiopathic Arthritis treated with Biological Agents in a real-life setting: data from the JIRcohorte. Joint, bone, spine : revue du rhumatisme. 2019.
2. Nimmrich S, Horneff G. Incidence of herpes zoster infections in juvenile idiopathic arthritis patients. Rheumatology international. 2015;35(3):465-470.
3. Ferreira GRV, Tomioka RB, Queiroz LB, Kozu K, Aikawa NE, Sallum AME, et al. Lower genital tract infections in young female juvenile idiopathic arthritis patients. Advances in rheumatology (London, England). 2019;59(1):50.

PICO 46. Should children with JIA with no evidence of immunity to important infections have a booster immunization prior to starting immunosuppressive medication?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

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PICO 47: Should screening for TB be done prior to starting biologic DMARD therapy and then annually in children with JIA?

Summary: The literature search identified 5 observational studies that addressed this PICO question.[1, 2, 3, 4, 5] There was 1 study that matched JIA (and other rheumatic diseases) to healthy controls, 3 single arm cohort studies, and 1 case series that evaluated the rates of mycobacterial infection or positive latent tuberculosis infection (LTBI) screening among individuals with JIA on a TNFi. In the matched cohort study[3] over 48 months, the incidence of mycobacterial infection was 1/44 JIA patients, 22.53/100,000 person years (95% CI 13.9 to 61.7/100,000 person years). This incidence was no higher than that observed among healthy controls (35.79/100,000 person-years, 95% CI 12.4 to 69.6/100,000 person-years). The single arm cohort and case series had varying observable time; 3 studies reported initial screening and then clinical evaluation every 2 months [1], every 3 months [5], or every 3 to 6 months.[2] Kilic et al.[4] required subjects to be on TNFi for >6 months before enrollment and then had an evaluation for TB every 6 months. One patient had a positive LTBI screening prior to initiation of TNFi [2]. Ten patients developed positive screening by tuberculin skin test (TST) or interferon gamma release assay (IGRA) [2, 4]; 7 were given INH prophylaxis and none of those 7 had chest X-ray (CXR) changes, 1 patient was treated with anti-TB therapy for 18 months [4]. The timing of the remaining positive screening tests was not specified, 7 were treated with isoniazid (INH) prophylaxis for 9 months [5] and 4 patients with intermediate TST responses were monitored without treatment with no development of symptoms [5]. Three patients had positive LTBI screening by the conclusion of the study (timing not specified) [1].

Quality of evidence across all critical outcomes: Very low

Table 1. Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Monitoring in relevant population	Results
2219 Brunelli 2017 [1]	Single Arm Cohort	8 years	69 JIA patients eligible for TNFi therapy (19 sJIA, 31 pJIA, 12 oJIA, 7 ERA, 1 PsA)	Initial screening then Q2 month clinic evaluation using TST, CXR, history of exposure	At end of study, 3 patients had positive LTBI screening; 1 TST positive and history of TB exposure, 2 only TST positive No active TB diagnosed during study period
4058 Caldaza-Hernandez 2015 [2]	Single Arm Cohort	9 years	221 patients <18yo treated with TNFi (163 JIA – 46 pJIA, 70 oJIA, 24 ERA, 11 PsA, 12 undiff, 1 Blau, 1 TRAPS, 1 PAPA, 1 chronic plantar fasciitis, 46 IBD,	Initial screening then clinical evaluation q3-6 months	3 JIA patients positive for LTBI screening, 1 on initial screening prior to TNFi, 2 with negative TST but positive IGRA after etanercept initiated

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Ref ID, Author, year	Study type	Duration	Population Description	Monitoring in relevant population	Results
			7 uveitis, 1 pars planitis)		
1843 Gomes 2015 [3]	Matched Cohort Study	48 months	262 patients (109 RA, 93 AS, 44 JIA, 16 PsA) on TNFi 215 healthy matched controls	Followed by clinical and lab evaluation to identify active mycobacterial infection	Incidence of mycobacterial infection: 1 of 44 JIA, 22.53/100,000 person years (95% CI 13.9-61.7) In the control group, the active mycobacterial incidence rate was 35.79/100,000 person-years (95% confidence interval 12.4-69.6), which did not differ from the JIA incidence rate.
2023 Kilic 2012 [4]	Single Arm Cohort Study	Not reported	132 Patients with JIA on TNFi for >6 months, (also uveitis 4, FMF 8)	Q6 month evaluation for TB (history, PE, TST, CXR, sputum/aspirate for AFB when needed)	7 patients (4.8%) with a positive TST were given INH ppx, none with CXR changes. Quantiferon TB positive in 1 patient treated with anti-TB therapy x 18 months
3049 Ayaz 2010 [5]	Case series	3-48 months	14 SoJIA pts, 12 ERA pts, 6 poly JIA pts, 3 extended oligos, and 1 psoriatic patient, all Turkish	Screening by history, exam, CXR, TST prior to starting etanercept, then every 3 months. Chest CT was ordered for TST >10mm with prior BCG vaccination	-1 had not received BCG vaccine, 16 had 1 vaccination and 19 had received 2. -7 pts had a TST above 10 mm and INH prophylaxis was started -3 had CT which showed non-specific findings -4 pts with TST 5-10 mm were followed with no symptom development and were not treated - it does not appear that etanercept was held, although this was not explicitly stated

References:

1. Brunelli, J. B., Bonfiglioli, K. R., Silva, C. A., Kozu, K. T., Goldenstein-Schainberg, C., Bonfa, E., & Aikawa, N. E. (2017). Latent tuberculosis infection screening in juvenile idiopathic arthritis patients preceding anti-TNF therapy in a tuberculosis high-risk country. Revista Brasileira de Reumatologia (English Edition), 57(5), 392-396. doi:https://doi.org/10.1016/j.rbre.2016.11.004
2. Calzada-Hernández, J., Anton-López, J., Bou-Torrent, R., Iglesias-Jiménez, E., Ricart-Campos, S., Martín de Carpi, J., . . . Noguera-Julian, A. (2015). Tuberculosis in pediatric patients treated with anti-TNFα drugs: a cohort study. Pediatr Rheumatol Online J, 13, 54-54. doi:10.1186/s12969-015-0054-4

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3. Gomes, C. M. F., Terreri, M. T., Moraes-Pinto, M. I. d., Barbosa, C., Machado, N. P., Melo, M. R., & Pinheiro, M. M. (2015). Incidence of active mycobacterial infections in Brazilian patients with chronic inflammatory arthritis and negative evaluation for latent tuberculosis infection at baseline--a longitudinal analysis after using TNFa blockers. Mem Inst Oswaldo Cruz, 110(7), 921-928. doi:10.1590/0074-02760150235
4. Kilic, O., Kasapcopur, O., Camcioglu, Y., Cokugras, H., Arisoy, N., & Akcakaya, N. (2012). Is it safe to use anti-TNF-α agents for tuberculosis in children suffering with chronic rheumatic disease? Rheumatol Int, 32(9), 2675-2679. doi:10.1007/s00296-011-2030-8
5. Ayaz, N. A., Demirkaya, E., Bilginer, Y., Ozçelik, U., Cobanoğlu, N., Kiper, N., . . . Ozen, S. (2010). Preventing tuberculosis in children receiving anti-TNF treatment. Clin Rheumatol, 29(4), 389-392. doi:10.1007/s10067-009-1334-5

PICO 48: In children with JIA receiving biologic DMARD therapy, is there a preferred method of TB screening?

Summary: The literature search identified 4 observational studies that addressed this PICO question.[1, 2, 5, 4] These studies report the type and frequency of TB screening in single center populations. All studies used the tuberculin skin test (TST), chest X-ray was used in 2 studies[1, 5], 2 studies used Quantiferon Gold (QFT) test[2, 4], and 1 used history of exposure[2210]. No active TB was reported. There were 4 cases where TST was negative but QFT was positive[2, 4]. In one study [4], the correlation between QFT and TST was poor in both the JIA and control group (kappa 0.06 and 0.1, respectively).

Quality of evidence across all critical outcomes: Very low

Table 1. Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Monitoring in relevant population	Results
2219 Brunelli 2017 [1]	Single Arm Cohort	8 years	69 JIA patients eligible for TNFi therapy (19 sJIA, 31 pJIA, 12 oJIA, 7 ERA, 1 PsA)	Initial screening then Q2 month clinic evaluation using TST, CXR, history of exposure	At end of study, 3 patients had positive LTBI screening; 1 TST positive and history of TB exposure, 2 only TST positive. No active TB diagnosed during study period.
4058 Caldaza-Hernandez 2015 [2]	Single Arm Cohort	9 years	221 patients <18 yo treated with TNFi (163 JIA – 46 pJIA, 70 oJIA, 24 ERA, 11 PsA, 12 undiff, 1 Blau, 1 TRAPS, 1	Initial screening by TST and after March 2012 by Quantiferon Gold-in Tube test (QFT) then clinical evaluation q3-6 months	3 JIA patients positive for LTBI screening by IGRA, 1 on initial screening prior to TNFi with TST and IGRA positive, 2 with negative TST but positive IGRA after etanercept initiated. No incident cases of TB disease were observed during follow up.

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Ref ID, Author, year	Study type	Duration	Population Description	Monitoring in relevant population	Results
			PAPA, 1 chronic plantar fasciitis, 46 IBD, 7 uveitis, 1 pars planitis)		
3049 Ayaz 2010 [5]	Case series	3-48 months	14 SoJIA pts, 12 ERA pts, 6 poly JIA pts, 3 extended oligos, and 1 psoriatic pt, all Turkish	Etanercept 0.8 mg/kg weekly or split into 2 doses/week Tuberculin Skin Test (TST) and chest X-rays were routinely carried out in each patient.	-1 had no received BCG vaccine, 16 had 1 vaccination and 19 had received 2 -7 pts had a TST above 10 mm and INH prophylaxis was started -3 had CT which showed non-specific findings -4 pts with TST 5-10 mm were followed with no symptom development and were not treated - it does not appear that etanercept was held, although this was not explicitly stated
2861 Camlar 2011 [4]	Cross sectional study	13 months; June 2008 to July 2009	39 pts with JIA (5 extended oligo, 13 ERA, 3 RF+ poly, 11 RF- poly, 3 psoriatic, 5 systemic). 40 healthy controls	18 on MTX, 8 on sulfasalazine, 2 on steroids, 3 on MTX+steroids, 5 on MTX+ sulfasalazine, and 3 on steroids+ sulfasalazine. TST and QuantiFERON-TB Gold In-Tube	-positive test defined as ≥10mm for JIA and ≥15 mm for controls -median TST induration for JIA pts was 5.8+/-5.7 mm and 10.7+/-4.5 mm for controls (p=0.000) -15/39 (38%) had no reaction to TST and 14/15 (93%) had active JIA -2 patients had positive QFT-GIT test results but negative TST results. - negative correlation noted between TST and ESR (r= -0.325 and p=0.044) - overall agreement between TST and QFT-GIT was low in JIA and control group (κ value =0.06 and 0.10, respectively). - TST might be inadequate to diagnose latent TB in JIA. The IFN-γ assay may be useful to identify false negative TST response in cases with latent M. tuberculosis infection.

References:

1. Brunelli, J. B., Bonfiglioli, K. R., Silva, C. A., Kozu, K. T., Goldenstein-Schainberg, C., Bonfa, E., & Aikawa, N. E. (2017). Latent tuberculosis infection screening in juvenile idiopathic arthritis patients preceding anti-TNF therapy in a tuberculosis high-risk country. Revista Brasileira de Reumatologia (English Edition), 57(5), 392-396. doi:https://doi.org/10.1016/j.rbre.2016.11.004

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2. Calzada-Hernández, J., Anton-López, J., Bou-Torrent, R., Iglesias-Jiménez, E., Ricart-Campos, S., Martín de Carpi, J., . . . Noguera-Julian, A. (2015). Tuberculosis in pediatric patients treated with anti-TNFα drugs: a cohort study. Pediatr Rheumatol Online J, 13, 54-54. doi:10.1186/s12969-015-0054-4
3. Ayaz, N. A., Demirkaya, E., Bilginer, Y., Ozçelik, U., Cobanoğlu, N., Kiper, N., . . . Ozen, S. (2010). Preventing tuberculosis in children receiving anti-TNF treatment. Clin Rheumatol, 29(4), 389-392. doi:10.1007/s10067-009-1334-5
4. Camlar, S. A., Makay, B., Appak, O., Appak, Y. C., Esen, N., Günay, T., . . . Unsal, E. (2011). Performance of tuberculin skin test and interferon gamma assay for the diagnosis of latent tuberculosis infection in juvenile idiopathic arthritis. Clin Rheumatol, 30(9), 1189-1193. doi:10.1007/s10067-011-1724-3.

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Vaccination

PICO 49. In children with JIA not on immunosuppression, do inactivated or live attenuated vaccines result in flare of disease?

Summary: The literature search identified one randomized control trial (RCT)[1] and three observational studies[2-4] that addressed this PICO question. The RCT provided evidence that patients with juvenile idiopathic arthritis (diagnosed using ILAR criteria) who received an MMR booster did not have a significant number of flared of arthritis compared to those who did not receive a booster. Those receiving biologic therapies were asked to hold it for five half-lives prior to repeat vaccination. The study was a modified intention to treat analysis which included 60 patients on methotrexate and 15 on biologic DMARDs. The remaining patients were not on immunosuppressive therapies other than NSAIDs. JADAS-27 scores did not differ between the two groups at the start of the study, with difference of 2.0 set to determine the equivalence margin. Flares were determined by 30% worsening of three of the six core criteria without simultaneous improvement in two of six core criteria with at least two active and/or limited joints if the joint count was used as a criterion of flare. Cutoff values for seroprotection were 0.20 IU/mL for measles and 10 IU/mL for rubella and because no international reference serum for mumps exists, an in-house reference was used, with a seroprotection level of 45 RIVM units (RU)/mL. All vaccinated patients were seroprotected again measles and rubella, but two were seronegative for mumps within one month of vaccination. At three months revaccinated patients had increased antibody concentrations against measles, mumps, and rubella. At 12 months after vaccination antibody concentrations were much higher when compared to the control group. The mean number of flares per patient did not differ significantly between the MMR booster group (0.44; 95% CI, 0.28-0.61) and the control group (0.34; 95% CI, 0.20-0.49), nor did the percentage of patients with one or more flare during follow-up. The relative risk of a flare in revaccinated patients compared with controls was 0.9 (95% CI, 0.4-2.0) at 3 months and 1.3 (95% CI, 0.8-2.1) during total follow-up (Table 1).

The observational studies provided evidence that immunization with the HPV vaccine[2], conjugated meningococcal vaccine[3] or MMR[4] did not result in worsening of disease activity. There were no notable increases in JADAS-27 with HPV vaccine[2] with lower scores seven months after the vaccine (2.8 with IQR 0.2-6.0) v (3.1 w IQR 1.2-6.8) p= 0.007, and at 12 months 1.8 w IQR 0.1-4.6) p=0.006. Patients who received the conjugate meningococcal vaccine were also not noted to have increased disease activity after vaccination and for a total of 12 months, although patient populations were mixed and included both those on immunosuppression and not on immunosuppression[3]. The risk of flare one month after vaccine was 6% while risk of flare for the remaining eleven months was 8.1% with a relative risk of .74 (95% CI 0.39-1.41). The relative risk of flare at two months was 0.81 (95% CI 0.48-1.38), relative risk of flare at three months was 0.76 (95% CI 0.52-1.12), and relative risk of flare at six months at 0.52 (95% CI 0.37-.72). Another observational study following patients six months prior to and six months following MMR vaccine[4] showed no increase in disease activity when compared to disease activity prior to vaccination. In the six months preceding the vaccination there were 40 flares in 36 patients and post vaccination there were 56 flares in 50 patients. Of note, there was no worsening of disease activity in polyarticular JIA patients on NSAIDs or methotrexate (Table 2).

The RCT was the only trial with a relevant control group, and the lack of blinding of patients, practitioners, and assessors of JIA disease activity combined with indirectness in the patient population (half of the patients were on MTX or biologic DMARDs) and imprecision in effect estimates

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rendered the study quality as very low. The observational studies were also very low quality due to lack of relevant controls and inclusion of some patients on immunosuppressive therapy.

Quality of evidence across all critical outcomes: Very low

Table 1. Data from Randomized Controlled Trials

Ref ID, Author, Year	Study Type	Duration	Population Description	Vaccine given to relevant population	Results
1226 Heijstek 2013 [1]	Randomized controlled clinical trial	May 2008 to July 2011	137 JIA pts aged 4-9 yrs	Randomized to 68 who received MMR booster and 69 who did not	-131 analyzed in the modified intention to treat analysis - 60 on methotrexate and 15 on biologics - JADAS did not differ between 63 revaccinated pts (JADAS-27, 2.8 with 95% CI 2.1-3.5) and 68 controls (JADAS 27, 2.4 with 95% CI 1.7-3.1) - The mean number of flares per patient did not differ significantly between the MMR booster group (0.44; 95% CI, 0.28-0.61) and the control group (0.34; 95% CI, 0.20-0.49), nor did the percentage of patients with 1 or more flare during follow-up. - The relative risk of a flare in revaccinated patients compared with controls was 0.9 (95% CI, 0.4-2.0) at 3 months and 1.3 (95% CI, 0.8-2.1) during total follow-up.

Table 2. Data from Observational Studies

Ref ID, Author, Year	Study Type	Duration	Population Description	Vaccination given to relevant population	Results
1780 Heijstek 2014 [2]	Controlled cohort	12 months	68 female JIA pts and 55 healthy female controls age 12-18 yrs	Vaccination for HPV 16/18 given at 0,1, and 6 months	JADAS-27 lower at 7 mos (2.8 with IQR 0.2-6.0) v (3.1 w IQR 1.2-6.8) p= 0.007; and at 12 mos after inclusion 1.8 w IQR 0.1-4.6) p=0.006
3485 Zonneveld	Single arm cohort	1 year	234 JIA pts; SoJIA n=34, persistent	Meningococcal serogroup C	- no worsening of disease noted post vaccination; risk of flare 1 one month after vaccine 6% while risk of flare for the remaining 11 mos

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Ref ID, Author, Year	Study Type	Duration	Population Description	Vaccination given to relevant population	Results
-Huijssoon 2007 [3]			oligo n=103, extended oligo n=25, RF+ poly n=5, RF- poly n=59, psoriatic n=4, ERA n=7	(MenC) conjugate vaccine	was 8.1%. RR .74 (95% CI 0.39-1.41) - RR of flare at 2 months 0.81 (95% CI 0.48-1.38) - RR of flare at 3 mos .76 (95% CI 0.52-1.12) - RR of flare at 6 mos 0.52 (95% CI 0.37-.72) (Note: this analysis mixes patients without immunosuppression with patients on immunosuppression).
3505 Heijstek 2007 [4]	Single arm cohort	Unclear; data collected 6 months before and 6 months after vaccination	207 pts with JIA born between 1989 and 1996; persistent oligo n=101, extended oligo n = 22, RF- poly n=55, RF+ poly n=5, systemic n=17, ERA n=3, psoriatic n=4	MMR vaccine	-no worsening disease activity seen prior to or after MMR vaccine; 40 flares occurred in 36 patients before MMR and 56 flares in 50 pts after MMR -10 flares (4.8) seen in first month after vaccination - no worsening of disease activity in poly pts on MTX and NSAIDs

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References

1. Heijstek MW, Kamphuis S, Armbrust W, Swart J, Gorter S, de Vries LD, et al. Effects of the live attenuated measles-mumps-rubella booster vaccination on disease activity in patients with juvenile idiopathic arthritis: a randomized trial. JAMA. 2013 Jun 19;309(23):2449-56.
2. Heijstek MW, Scherpenisse M, Groot N, Tacke C, Schepp RM, Buisman AM, et al. Immunogenicity and safety of the bivalent HPV vaccine in female patients with juvenile idiopathic arthritis: a prospective controlled observational cohort study. Ann Rheum Dis. 2014 Aug;73(8):1500-7.
3. Zonneveld-Huijssoon E, Ronaghy A, Van Rossum MA, Rijkers GT, van der Klis FR, Sanders EA, et al. Safety and efficacy of meningococcal c vaccination in juvenile idiopathic arthritis. Arthritis Rheum. 2007 Feb;56(2):639-46.

4. Heijstek MW, Pileggi GC, Zonneveld-Huijssoon E, Armbrust W, Hoppenreijs EP, Uiterwaal CS, Safety of measles, mumps and rubella vaccination in juvenile idiopathic arthritis. Ann Rheum Dis. 2007 Oct;66(10):1384-7.

PICO 50. In children with JIA not on immunosuppression, are patients able to develop protective antibodies against infections targeted by the vaccine?

Summary. The literature search identified one randomized controlled trial (RCT)[1] and six observational studies[2-7] that addressed this PICO question. According to the RCT[1], 100% of control patients and 92% of revaccinated JIA patients (95% CI, 84-99%) were noted to have seroconverted 12 months after vaccination; 97% (95% CI 95-100%) of controls and 81% of revaccinated JIA patients (95% CI, 72-93%) were noted to have seroconversion 12 months after mumps vaccination. Finally, 100% of controls and 94% (95% CI 86-100%) of revaccinated patients were noted to have seroconversion at 12 months after vaccination with the rubella vaccine. There seemed to be no difference between patients on methotrexate and biologics, although numbers were too small to be significant.

The observational studies provided evidence that protective antibodies were developed against infections targeted by the vaccines. A controlled cohort study compared response rates to a bivalent HPV vaccine between patients with JIA and healthy controls[2]. All patients were noted to be seropositive at seven months, but one oligoarticular JIA patient was noted to be seronegative at 12 months. An observational study looking at seroconversation in patients who received the H1N1 vaccine showed that patients with arthritis had lower seroconversation rates, compared to healthy controls with the exception of those on TNF therapy (100% seroconversion v 86.1% for those not on anti-TNFs)[3]. Two studies directly addressed inactivated influenza vaccine[4,5] and in one study there was a seroconversion rate of 78.3% which was similar to that of healthy individuals[5]. In the second study protective titers were detected in 77% of children in the JIA group and 79% of children in the healthy control group[4]. Four patients on anti-TNF medications also developed seroprotection at 6 months after vaccination. A cross sectional study assessing response to several vaccines including measles, mumps, rubella, diphtheria and tetanus vaccines showed lowered protection when compared to healthy controls against mumps, rubella, diphtheria and tetanus ($p \leq 0.001$)[6]. Specifically in SoJIA patients there was a lower antibody concentrations against measles ($p=0.025$), mumps ($p=0.018$), and tetanus ($p=0.027$), and rubella ($p=0.007$) but no difference was noted for diphtheria ($p=0.316$)[6].In an observational study addressing seroprotection with the conjugate meningococcal vaccine, patients were divided into four groups based on medical therapy, but overall there was no difference noted between JIA patient responses and healthy controls with regards to increase in titers post vaccination ($p=0.631$)[7].

The RCT had limitations including the lack of blinding of patients, practitioners, and assessors of JIA disease activity, but this is less likely to affect antibody measurement. However, indirectness in the patient population (half of the patients were on MTX or biologic DMARDs) and imprecision in effect estimates mean that the study quality is low. Four observational studies compared seroconversion rates for vaccinated JIA patients and healthy controls, one compared JIA patients without medications and JIA patients on various immunosuppressive medications, the remaining study lacked a control group but the findings were generally consistent across studies. Although some studies did not separate results for patients with or without immunosuppression, the overall quality was low.

Quality of evidence across all critical outcomes: Low

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Table 1. Data from Randomized Controlled Trials

Ref ID, Author, Year	Study Type	Duration	Population Description	Vaccine given to relevant population	Results
1226 Heijstek 2013 [1]	Randomized controlled clinical trial	May 2008 to July 2011	137 JIA pts aged 4-9 yrs	Randomized to 68 who received MMR booster and 69 who did not	A total of 131 patients were analyzed in the modified intention to treat analysis; 60 on methotrexate and 15 on biologic DMARDs. There was no significant difference between re-vaccinated and control groups with regards to intra articular steroid injections or methotrexate (p=0.62 and p=.25, respectively). Two patients were seronegative for mumps at 12 months; one patient was on MTX and had a small increase in immunogenicity but levels below protective were noted at 12 months. An oligoarticular JIA patient started MTX shortly after vaccination and was negative at baseline for MMR; also negative for mumps at follow up but did have increased antibodies to measles and rubella. At 12 months, five controls (12%) were negative for measles, 12 (19%) negative for mumps, and four (6%) seronegative for rubella. Three months after vaccination there were notable increases in antibody concentrations in MMR and at 12 months titers were higher compared with controls. Humoral response to revaccination did not differ significantly between those on MTX or biologics, but numbers were too small to draw conclusions.

Table 2. Data from Observational Studies

Ref ID, Author, Year	Study Type	Duration	Population Description	Vaccination given to relevant population	Results
1780 Heijstek 2014 [2]	Controlled cohort	12 months	68 female JIA pts and 55 healthy female controls age 12-18 yrs	Vaccination for HPV 16/18 given at 0,1, and 6 months	All patients were noted to be seropositive at 7 mos. One oligoarticular JIA patient was noted to be seronegative at 12 months. 50 (91%) healthy control and 66 (97%) JIA pts received all 3 doses Four JIA pts received 1 vaccine at 3 months; 2 were seronegative for

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Ref ID, Author, Year	Study Type	Duration	Population Description	Vaccination given to relevant population	Results
					HPV 16 and 3 seronegative for HPV 18; these pts turned seropositive after the 3rd dose. MTX did not affect HPV16 abs (2578 LU/mL, 95% CI 1338-4967 LU/mL) v (2844 LU/mL, 95% CI 2034-3967 LU/mL), p=.79 or HPV18 abs 860 LU/mL (95% CI 963 - 3595LU/mL) v 1335 LU/mL (95% CI 951-1873LU/mL) p=.37. Avidity of HPV16/18 was comparable in a random sample of 18 JIA pts and 18 healthy controls. In JIA pts memory B cells increased at 3 months (HPV16 p=0.004 and HPV18 p=0.002) and at 7 months HPV16 p=0.15, HPV18 p=0.03) Memory B cells were undetectable in 5 pts and 2 controls for HPV16 and in 3 pts and 21 control for HPV18
1188, Aikawa, 2013 [3]	Cohort	3 weeks	95 JIA patients (24 oligo, 18 systemic) vs healthy controls	Inactivated H1N1 flu vaccine	Healthy controls had 95.6% seroprotection 3 weeks after vaccination; OligoJIA had 87.5% and sJIA had 88.9%. Those on DMARDs had 89.1% conversion vs. 87.5% for those not on DMARDs. Those on MTX had 87.2% conversion v 89.6% for those not on MTX. Those on anti-TNFs had 100% seroconversion v 86.1% for those not on anti-TNFs.
3482, Toplak, 2012 [4]	Cohort	6 months	31 JIA vaccinated (18 oligo, 2 sJIA) v 31 JIA unvaccinated (19 oligo, 3 sJIA) v 14 healthy controls	Inactivated flu vaccine	Protective titers against all three vaccine viruses were detected in 77% of children in the JIA group and 79% in the healthy controls at 6 months post-vaccination. In 4 children on anti-TNF therapy, they had protective titers to all three vaccine viruses 6 months after vaccination. Disease flare was observed 1 month after vaccination in 1 out of 2 sJIA patient; Flare occurred in 1 out of 18 oligo at 2 months; and in 4 out of 18 oligo at 6 months; Disease flare in unvaccinated group occurred within 6 months for 5 out of 19 oligos.
1778 Miraglia 2011 [5]	Single arm cohort study	21 days	83 JIA pts	inactivated, monovalent non adjuvanted H1N1	Seroprotection noted 85.5% in JIA pts and seroconversion 78.3% JIA pts did have high pre vaccination titers for hemagglutination, consistent with data which shows that children ages 5-14 had the

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Ref ID, Author, Year	Study Type	Duration	Population Description	Vaccination given to relevant population	Results
				flu vaccine; pts ages 6-35 mos received 2x.25 mL doses and 36 mos to 8 yrs received 2x0.5 mL doses. Children ages ≥9 received 10.5 mL dose	highest rates of infection with H1N1
1027 Heijstek 2013 [6]	Cross sectional study	Unclear	400 JIA pts; oligo persistent n=159, oligo extended n=38, RF+ poly n=13, RF- poly110, SoJIA n=64, ERA n=10, psoriatic n=6. Compared to healthy controls	Measles, mumps, rubella, diphtheria and tetanus vaccines	Geometric mean concentration (GMC) was higher in pts with JIA than healthy controls, p<0.001, with regards to measles, but against mumps and rubella was lower (p<0.001 for both) There was no noted relationship noted between MTX and glucocorticoid use and pathogen specific GMC There was a weak negative correlation between MTX and antibody concentrations against mumps (r=-0.15), rubella (r=-0.29), diphtheria (r=-0.28), tetanus (r=-0.23), but not for measles (r=0.04), this was significant for rubella (p=0.009) and diphtheria (p=0.007)
3485 Zonneveld-Huijssoon 2007 [7]	Single arm cohort	1 year	234 JIA pts; SoJIA n=34, persistent oligo n=103, extended oligo n=25, RF+ poly n=5, RF- poly n=59, psoriatic n=4, ERA n=7	Meningococcal serogroup C (MenC) conjugate vaccine	Group 1 included patients on no medication. Group 2 included patients on NSAID monotherapy. Group 3 included on low dose (<10 mg/m2/wk) MTX or sulfasalazine, without or without NSAID therapy. Group 4 included patients on high dose MTX, infliximab, etanercept, cyclosporin, or combination MTX and sulfasalazine, with or without NSAID therapy. MenC IgG geometric mean concentrations rose from 0.4 ug.mL pre vaccine to 28. ug/mL post vaccine (range 1.0-1820.5 ug/mL) p<0.0005. Anti-MenC IgG geometric mean concentrations were significantly lower in patients in medication groups 3 (17.53) and 4 (16.28) compared with those in patients in groups 1 (41) and 2 (46.93).

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Ref ID, Author, Year	Study Type	Duration	Population Description	Vaccination given to relevant population	Results
					Four patients on steroids did not have different responses to vaccines than peers on similar maintenance medications (MTX, groups 3 and 4); p=0.63 and p=0.73. Four patients (2 in group 3 and 2 in group 4) were low responders (developed 1.5 fold rise in titers compared to 17 fold rise seen in other patients), but were still able to mount SBA titers ≥8.

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References:

1. Heijstek MW, Kamphuis S, Armbrust W, Swart J, Gorter S, de Vries LD, et al. Effects of the live attenuated measles-mumps-rubella booster vaccination on disease activity in patients with juvenile idiopathic arthritis: a randomized trial. JAMA. 2013 Jun 19;309(23):2449-56.
2. Heijstek MW, Scherpenisse M, Groot N, Tacke C, Schepp RM, Buisman AM, et al. Immunogenicity and safety of the bivalent HPV vaccine in female patients with juvenile idiopathic arthritis: a prospective controlled observational cohort study. Ann Rheum Dis. 2014 Aug;73(8):1500-7.
3. Aikawa NE, Trudes G, Campos LM, Pereira RM, Moraes JC, Ribeiro AC, et al. Immunogenicity and safety of two doses of a non-adjuvanted influenza A H1N1/2009 vaccine in young autoimmune rheumatic diseases patients. Lupus. 2013 Nov;22(13):1394-8.
4. Heijstek MW, Kamphuis S, Armbrust W, Swart J, Gorter S, de Vries LD, et al. Effects of the live attenuated measles-mumps-rubella booster vaccination on disease activity in patients with juvenile idiopathic arthritis: a randomized trial. JAMA. 2013 Jun 19;309(23):2449-56.
5. Toplak N, Subelj V, Kveder T, Cucnik S, Prosenc K, Trampus-Bakija A, et al. Safety and efficacy of influenza vaccination in a prospective longitudinal study of 31 children with juvenile idiopathic arthritis. Clin Exp Rheumatol. 2012 May-Jun;30(3):436-44.
6. Miraglia JL, Abdala E, Hoff PM, Luiz AM, Oliveira DS, Saad CG, et al. Immunogenicity and reactogenicity of 2009 influenza A (H1N1) inactivated monovalent non-adjuvanted vaccine in elderly and immunocompromised patients. PLoS One. 2011;6(11):e27214.
7. Zonneveld-Huijssoon E, Ronaghy A, Van Rossum MA, Rijkers GT, van der Klis FR, Sanders EA, et al. Safety and efficacy of meningococcal c vaccination in juvenile idiopathic arthritis. Arthritis Rheum. 2007 Feb;56(2):639-46.

PICO 51: In children with JIA on immunosuppression, do inactivated vaccines result in flare of disease?

Summary: The literature search identified one randomized controlled trial (RCT) [1] and 7 cohort studies [2, 3, 4, 5, 6, 7, 8] that addressed this PICO question.

The RCT [1] compared 68 JIA patients who received an MMR booster to 69 JIA patients who did not. 131 patients were analyzed in the modified intention to treat analysis. 60 patients were on methotrexate and 15 were on biologics. The JDAS did not differ between the 63 vaccinated patients (JADAS-27 2.8 (95% CI 2.1-3.5) and the 68 unvaccinated patients (JADAS-27 2.4 (95% CI 1.7-3.1). The mean number of flares per patient did not differ significantly between the experiment group (0.44; 95% CI, 0.28-0.61) and the control group (0.34; 95% CI, 0.20-0.49), nor did the percentage of patients with 1 or more flare during follow-up. The relative risk of a flare in revaccinated patients compared with controls was 0.9 (95% CI, 0.4-2.0) at 3 months and 1.3 (95% CI, 0.8-2.1) during total follow-up. Similar results were found in patients using methotrexate or biologics, although small patient numbers precluded definite conclusions.

Four cohort studies evaluated patients who received the flu vaccine. One prospective study by Camacho-Lovillo [2] followed 35 JIA patients for a year after receiving the inactivated flu vaccine; 3 out of 35 patients were not on immunosuppressants. None of the JIA patients had a disease flare 4-8 weeks after vaccination. A prospective study by Ogimi [3] followed 23 patients with JIA for one month after receiving the inactivated flu vaccine. Only one JIA patient had a disease flare 2 weeks after vaccination. It is not clear exactly which immunosuppressants this patient was taking, but they were at least taking prednisolone. The study by Carvalho [4] looked at 70 JIA patients over 2 flu seasons and gave 44 patients the flu vaccine; 70% of vaccinated patients were receiving DMARDs or TNF inhibitors. They reported 50 JIA flares in 44/70 patients during the study. There was no significant difference in the total number of flares related to administration of the flu vaccine. The study by Toplak [5] looked at 31 JIA patients vaccinated v 31 unvaccinated patients v 14 healthy controls. They found that disease flare occurred at 1 month after vaccination in 1 out of 2 sJIA patients, at 2 months in 1 out of 18 oligoJIA patients, and in 4 out of 18 oligoJIA patients at 6 months. In the unvaccinated group, disease flare occurred in 5 out of 19 oligoJIA patients within 6 months. Only 42% of vaccinated JIA patients were on immunosuppression.

A cohort study by Heijstek [6] compared female JIA patients to healthy female controls (not a relevant comparison for this PICO question); all were vaccinated with the HPV vaccine. The JADAS-27 was significantly lower at 7 months and at 12 months as compared to baseline in the JIA group (p=0.007 and 0.006, respectively), indicating that HPV vaccination did not correlate with disease flares. This was also true for 24 patients using methotrexate, disease activity was lower at 7 months and at 12 months (3.0 (IQR 0.2–5.7). [6].

A prospective cohort study by Farmaki [7] compared a study group of 31 JIA patients on an anti-TNF and either methotrexate or cyclosporine (with or without prednisolone) to a control group of 32 JIA patients on methotrexate and/or cyclosporine (with or without prednisolone). All participants received the pneumococcal conjugate vaccine (PCV7). One patient in the control group (not treated with anti-TNF) experienced an exacerbation of the underlying disease at 3 months post-vaccination.

A study by Zonneveld-Huijssoon [8] looked at a cohort of 234 JIA patients (34 sJIA, 128 oligoJIA) who received the meningococcal serogroup C conjugate vaccine. There was no worsening of disease noted post vaccination. The relative risk of a flare within 1 month of vaccination was 0.74

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(95% CI 0.39-1.41). The relative risks of relapse calculated within 2, 4 or 6 months after vaccination were similar (RR 0.81 (95% CI 0.48-1.38), RR 0.76 (95% CI 0.52-1.12), RR 0.52 (95% CI 0.37-0.72), respectively). Results were not reported separately for patients on immunosuppression.

The RCT had limitations that included lack of blinding of patients, practitioners, and assessors of JIA disease activity combined with imprecision in effect estimates, which rendered the study quality as low. The observational studies mostly lacked relevant controls (i.e., unvaccinated JIA patients) and included some patients on immunosuppressive therapy (although some studies reported data separately for patients on immunosuppression, others did not), so their overall quality is very low.

Quality of evidence across all critical outcomes: Very low

Table 1. Data from Randomized Controlled Trials

Ref ID, Author, Year	Study Type	Duration	Population Description	Vaccine given to relevant population	Results
1226 Heijstek 2013 [1]	Randomized controlled clinical trial	May 2008 to July 2011	137 JIA pts aged 4-9 yrs	Randomized to 68 who received MMR booster and 69 who did not	-131 analyzed in the modified intention to treat analysis - 60 on methotrexate and 15 on biologics - JADAS did not differ between 63 revaccinated pts (JADAS-27, 2.8 with 95% CI 2.1-3.5) and 68 controls (JADAS 27, 2.4 with 95% CI 1.7-3.1) - The mean number of flares per patient did not differ significantly between the MMR booster group (0.44; 95% CI, 0.28-0.61) and the control group (0.34; 95% CI, 0.20-0.49), nor did the percentage of patients with 1 or more flare during follow-up. - The relative risk of a flare in revaccinated patients compared with controls was 0.9 (95% CI, 0.4-2.0) at 3 months and 1.3 (95% CI, 0.8-2.1) during total follow-up. Similar results were found in patients using methotrexate or biologics, although small patient numbers precluded definite conclusions.

Table 2. Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
1779, Camacho-	Prospective Cohort	1 year	35 patients with JIA (19 oligoarthritis, 7 systemic)	Inactivated flu vaccine in	No patients had a disease flare 4-8 weeks after vaccination.

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Lovillo, 2017 [2]			v 6 healthy sibling controls	2013/2014 and in 2014/2015	
1785, Ogimi, 2011 [3]	Prospective cohort	1 month	49 children with rheumatic disease (23 with JIA) v 36 healthy controls	Inactivated flu vaccine	One JIA patient had a disease flare 2 weeks after vaccination.
3101, Carvalho, 2013 [4]	Cohort	2 surveillance periods of 5 month duration each, once in 2007 and once in 2008	Surveillance group 1: 61 JIA patients (20 oligo, 13 systemic); Surveillance group 2: 63 JIA patients (23 oligo, 13 systemic).	Inactivated flu vaccine	44/70 patients received the flu vaccine, and 70% of vaccinated patients were receiving DMARDs or TNF inhibitors. There was no significant difference in the total number of flares related to administration of influenza vaccine.
3482, Toplak, 2012 [5]	Cohort	6 months	31 JIA vaccinated (18 oligo, 2 sJIA) v 31 JIA unvaccinated (19 oligo, 3 sJIA) v 14 healthy controls	Inactivated flu vaccine	Disease flare was observed 1 month after vaccination in 1 out of 2 sJIA patient; Flare occurred in 1 out of 18 oligo at 2 months; and in 4 out of 18 oligo at 6 months; Disease flare in unvaccinated group occurred within 6 months for 5 out of 19 oligo patients. Only 42% of vaccinated JIA patients were on immunosuppression.
1780 Heijstek 2014 [6]	Controlled cohort	12 months	68 female JIA pts and 55 healthy female controls age 12-18 yrs	Vaccination for HPV 16/18 given at 0,1, and 6 months	- JADAS-27 lower at 7 mos (2.8 with IQR 0.2-6.0) v (3.1 w IQR 1.2-6.8) p= 0.007; and at 12 mos after inclusion 1.8 w IQR 0.1-4.6) p=0.006. In 24 patients using methotrexate, disease activity was lower at 7 months (JADAS-27 4.0 (IQR 1.0–6.4) vs 4.1 (IQR 2.6–9.8); p=0.02) and at 12 months (3.0 (IQR 0.2–5.7).
1153, Farmaki, 2010 [7]	Prospective Cohort	Up to 8 months	Study group: 31 JIA patients (8 oligo, 2 systemic) on anti-TNF and MTX or cyclosporine with or without prednisone vs Control group: 32 JIA patients (14 oligo) on	PCV7 Vaccine	One patient in the control group experienced exacerbation of the underlying disease at 3 months following completion of vaccination.

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
			MTX and/or cyclosporine with or without prednisone		
3485 Zonneveld-Huijssoon 2007 [8]	Single arm cohort	1 year	234 JIA pts; SoJIA n=34, persistent oligo n=103, extended oligo n=25, RF+ poly n=5, RF- poly n=59, psoriatic n=4, ERA n=7	Meningococcal serogroup C (MenC) conjugate vaccine	- no worsening of disease noted post vaccination; risk of flare 1 one month after vaccine 6% while risk of flare for the remaining 11 mos was 8.1%. RR .74 (95% CI 0.39-1.41) - RR of flare at 2 months 0.81 (95% CI 0.48-1.38) - RR of flare at 3 mos .76 (95% CI 0.52-1.12) - RR of flare at 6 mos 0.52 (95% CI 0.37-.72) (Note: this analysis mixes patients without immunosuppression with patients on immunosuppression).

References:

1. Heijstek, M. W., Kamphuis, S., Armbrust, W., Swart, J., Gorter, S., de Vries, L. D., . . . Wulffraat, N. M. (2013). Effects of the live attenuated measles-mumps-rubella booster vaccination on disease activity in patients with juvenile idiopathic arthritis: a randomized trial. Jama, 309(23), 2449-2456. doi:10.1001/jama.2013.6768
2. Camacho-Lovillo, M. S., Bulnes-Ramos, A., Goycochea-Valdivia, W., Fernández-Silveira, L., Núñez-Cuadros, E., Neth, O., & Pérez-Romero, P. (2017). Immunogenicity and safety of influenza vaccination in patients with juvenile idiopathic arthritis on biological therapy using the microneutralization assay. Pediatr Rheumatol Online J, 15(1), 62. doi:10.1186/s12969-017-0190-0
3. Ogimi, C., Tanaka, R., Saitoh, A., & Oh-Ishi, T. (2011). Immunogenicity of influenza vaccine in children with pediatric rheumatic diseases receiving immunosuppressive agents. Pediatr Infect Dis J, 30(3), 208-211. doi:10.1097/INF.0b013e3181f7ce44
4. Carvalho, L. M., de Paula, F. E., Silvestre, R. V. D., Roberti, L. R., Arruda, E., Mello, W. A., & Ferriani, V. P. L. (2013). Prospective surveillance study of acute respiratory infections, influenza-like illness and seasonal influenza vaccine in a cohort of juvenile idiopathic arthritis patients. Pediatr Rheumatol Online J, 11, 10-10. doi:10.1186/1546-0096-11-10
5. Toplak, N., Subelj, V., Kveder, T., Cucnik, S., Prosenc, K., Trampus-Bakija, A., . . . Avcin, T. (2012). Safety and efficacy of influenza vaccination in a prospective longitudinal study of 31 children with juvenile idiopathic arthritis. Clin Exp Rheumatol, 30(3), 436-444.
6. Heijstek, M. W., Scherpenisse, M., Groot, N., Tacke, C., Schepp, R. M., Buisman, A. M., . . . Wulffraat, N. M. (2014). Immunogenicity and safety of the bivalent HPV vaccine in female patients with juvenile idiopathic arthritis: a prospective controlled observational cohort study. Ann Rheum Dis, 73(8), 1500-1507. doi:10.1136/annrheumdis-2013-203429
7. Farmaki, E., Kanakoudi-Tsakalidou, F., Spoulou, V., Trachana, M., Pratsidou-Gertsi, P., Tritsoni, M., & Theodoridou, M. (2010). The effect of anti-TNF treatment on the immunogenicity and safety of the 7-valent conjugate pneumococcal vaccine in children with juvenile idiopathic arthritis. Vaccine, 28(31), 5109-5113. doi:10.1016/j.vaccine.2010.03.080

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8. Zonneveld-Huijssoon, E., Ronaghy, A., Van Rossum, M. A., Rijkers, G. T., van der Klis, F. R., Sanders, E. A., . . . Wulffraat, N. M. (2007). Safety and efficacy of meningococcal c vaccination in juvenile idiopathic arthritis. Arthritis Rheum, 56(2), 639-646. doi:10.1002/art.22399

PICO 52: In children with JIA on immunosuppression, are patients able to develop protective antibodies against infections targeted by the vaccine?

Summary: The literature search identified 21 studies that addressed this question: 7 cohort studies that looked at the flu vaccine [1, 2, 3, 4, 5, 6, 7], 2 cohort studies [10, 3592] and 1 RCT [8] that looked at the pneumococcal vaccine, 1 cross-sectional study [13], 1 RCT [11], and 1 cohort study [12] that looked at MMR vaccine, 1 cross-sectional study[13] and 1 cohort study[14] that looked at diphtheria and tetanus vaccine, 2 cohort studies that looked at HPV vaccination [15, 16], 2 cohorts that looked at meningococcal vaccination [17, 18], and 3 cohorts that looked at varicella vaccination [19, 20, 21].

Seven cohort studies evaluated the immune response to influenza vaccine in patients with JIA (Table 1). A study by Camacho-Lovillo [1] did not find a statistically different rate of seroprotection for three strains of influenza (A/H1N1, p=0.521, A/H3N2, p=0.565, B, p=0.871) in JIA patients on biological therapy as compared to those on no biologics, and overall, the groups achieved adequate seroprotection. A cohort study by Aikawa [2] found that seroconversion for JIA patients on DMARDs was 89.1% vs 87.2% for those not on DMARDs. Those on methotrexate had 87.2% conversion v 89.6% for those not on methotrexate. Those on anti-TNFs had 100% seroconversion v 86.1% for those not on anti-TNFs. In a cohort study by Carvalho [3], JIA patients on anti-TNF drugs presented lower seroconversion (p=0.03) and seroprotection (60%) responses to the H1N1 strain, but the seroprotection was above the cut-off levels to the other strains, H3N2 (100%) and B/Florida (80%). A cohort study by Dell'Era [4] found that the seroconversion and seroprotective rates 28 +/- 3 days and 90 +/- 3 days after vaccination were 100% in JIA patients receiving DMARDs and the healthy controls. In JIA patients on etanercept, the rates were 100% and 96.7%, respectively. A cohort study by Shinoki [5] compared 27 sJIA patient on tocilizumab with 17 healthy controls. The differences in the seroconversion rates, seroconversion factors, and seroprotection rates between the two groups after influenza vaccination were not statistically significant. Duration of tocilizumab did not have an effect on the ability to develop antibodies, however, those patients on < 0.2 mg/kg prednisolone had a statistically significant lower seroconversion factor for A/H1N1 strain (p=0.03) than those patients on >0.2 mg/kg prednisolone. Another cohort [6] found the geometrical mean values of protective antibody titers at 1 month were significantly higher for all influenza vaccine strains compared to baseline in JIA patients on DMARDs (A/H1N1, p=0.0059, A/H3N2, p=0.044, B, p=0.032). By 6 months, only titers for influenza strain B were statistically higher (p=0.022). Finally, Ogimi et al. [7] compared 31 JIA children on a combination of prednisolone and other immunosuppressive agents with controls. There were no significant differences in seroconversion factor (p>0.21) or seroconversion rates (p>0.26).

One RCT and two cohort studies addressed the antibody response to pneumococcal vaccine in patients with JIA (Table 2). In the RCT comparing anakinra to placebo in sJIA patients [8], the level of post-vaccination antibodies against five pneumococcal capsular polysaccharide serotypes was not significantly different between the two groups. After month 1, all patients received anakinra; 12 patients were tested and had an

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adequate antibody response at month 12. In one cohort [9], the frequencies of patients achieving adequate vaccine response from PPV23 at 2 and 12 months were similar in JIA patients with and without anti-TNF therapy (p=0.424 at 2 months, p=1.0 at 12 months). In another cohort study [10], 52-74% of JIA patients on an anti-TNF and methotrexate or cyclosporine had a 4-fold increase in baseline antibody titers, depending on the serotype.

Three studies evaluated the MMR vaccine in patients with JIA (Table 3). In an RCT by Heijstek et al.[11], 12 month seroprotection rates were higher in revaccinated JIA patients (60 on methotrexate, 15 on biologics) who received the MMR booster vs unvaccinated JIA controls: measles 100% v 92% (95% CI 84-99%), mumps 97% (95% CI, 95-100%) v 81% (95% CI, 72-93%); and rubella 100% v 94% (95% CI, 86-100%). There seemed to be no difference between patients on methotrexate and biologics, although numbers were too small to be significant. One cohort study [12] compared 15 patients with JIA treated with methotrexate with or without etanercept to 22 healthy controls who received the MMR vaccine. Neither low-dose MTX nor etanercept treatment interfered with generation of long-lived virus-restricted T cells and protective levels of virus-specific IgG antibodies. One cross-sectional study [13] looked at measles, mumps, rubella, diptheria, and tetanus vaccines. Systemic JIA patients had lower antibody concentrations against measles (p=0.025), mumps (p=0.018), and tetanus (p=0.027), and rubella (p=0.007) but no difference was noted for diphtheria (p=0.316). There was a weak negative correlation between the methotrexate dose and antibody concentrations against mumps (r=−0.15), rubella (r=−0.29), diphtheria (r=−0.28), tetanus (r=−0.23) but not for measles (r=0.04). This was significant for rubella (p=0.009) and diphtheria (p=0.007). There was no association between the steroid dose and antibody concentrations. The number of patients using anti-TNFα treatment was too small to assess the effect.

In a recent cohort study assessing response to diphtheria and tetanus vaccine in patients receiving abatacept (Table 3), there were no infections with either pathogen during the 24 month period of the study[14]. Patients were vaccinated prior to initiating therapy with abatacept. Protective antibody titers were noted in 29/29 patients against tetanus and 26/29 patients against diphtheria. No significant differences noted between patients on monotherapy versus those on combination therapy with methotrexate and/or glucocorticoids.

Two cohort studies addressed HPV vaccination (Table 4). In one cohort [15], 31 of 32 patients on methotrexate were seropositive at 12 months. All patients on anti-TNFs (n=9) were seropositive after 3 vaccine doses, however the number of patients was too small to draw definite conclusions. JIA patients showed significantly lower anti-HPV16 titers than controls 1 month after the administration of the third dose ($p < 0.05$), whereas no significant difference was observed in anti-HPV18 titers. Only 6 patients were on etanercept, but it didn't seem to influence the immune response.

Two cohort studies addressed meningococcal vaccination (Table 5). In one cohort [17], starting treatment with biologics induced a trend towards accelerated decline of antibodies in 92.6% of patients, in contrast to starting treatment with methotrexate. In another cohort [18], JIA patients on high dose methotrexate, infliximab, etanercept, cyclosporine, or a combination of methotrexate and sulfasalazine had anti-MenC IgG geometric mean concentrations significantly lower than JIA patients on no medications (p=0.01).

Three cohort studies addressed varicella vaccination (Table 6). In one cohort [19], of 23 patients with pediatric rheumatic disease on immunosuppression (17 with JIA), 21 showed a positive vaccination response. In another cohort study [20] of patients with pediatric rheumatic diseases on methotrexate and steroids (not exclusively JIA), vaccine response rates and median postimmunization VZV-IgG titers were not

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different when patients were compared to healthy controls. In a third cohort study [21], in 6 patients with JIA treated with biologics, 5 patients produced protective antibodies against varicella virus 6 weeks after the second vaccination.

In summary, most vaccines appeared to induce protective antibodies in patients with JIA on immunosuppression. Because most studies were observational cohort designs with attendant study limitations, and the two RCTs also had limitations (single small studies with imprecision in effect estimates), the overall quality of evidence is low.

Quality of evidence across all critical outcomes: Low

Table 1. Influenza Vaccine – Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
1779, Camacho-Lovillo, 2017 [1]	Cohort	1 year	35 patients with JIA (19 oligoarthritis, 7 systemic) v 6 healthy sibling controls	Inactivated flu vaccine in 2013/2014 and in 2014/2015	Both groups achieved an adequate seroprotection rate. There were no differences in post-vaccination seroprotection rates or antibody response between patients receiving biological treatment and those receiving no biological treatment
1188, Aikawa, 2013 [2]	Cohort	3 weeks	95 JIA patients (24 oligo, 18 systemic) vs healthy controls	Inactivated H1N1 flu vaccine	Healthy controls had 95.6% seroprotection 3 weeks after vaccination; OligoJIA had 87.5% and systemics had 88.9%. Those on DMARDs had 89.1% conversion vs. 87.5% for those not on DMARDs. Those on MTX had 87.2% conversion v 89.6% for those not on MTX. Those on anti-TNFs had 100% seroconversion v 86.1% for those not on anti-TNFs.
3101, Carvalho, 2013 [3]	Cohort	2 surveillance periods of 5 month duration each, once in 2007 and once in 2008	Surveillance group 1: 61 JIA patients (20 oligo, 13 systemic); Surveillance group 2: 63 JIA patients (23 oligo, 13 systemic)	Inactivated flu vaccine	Patients on anti-TNF drugs presented lower seroconversion and seroprotection responses to H1N1 strain, but the seroprotection was above the cut-off levels to the other strains – H3N2 and B/Florida.
1788, Dell'Era, 2012 [4]	Cohort	3 months	30 JIA patients treated with DMARDs v 30 JIA patients treated with	2010/2011 inactivated flu vaccine	The seroconversion and seroprotective rates 28+/- 3 days and 90 +/- 3 days after vaccination were 100% in the DMARD group and healthy group. In the etanercept group, the rates were 100% at 28 +/- 3 days and 96.7% at 90 +/- 3 days.

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
			etanercept vs 30 healthy controls		At the follow-up visits 4 weeks and 3 months after the vaccination, none of the patients showed any clinical or laboratory change in disease activity.
3494 Shinoki, 2012 [5]	Cohort study	8 weeks	27 sJIA patients receiving tocilizumab and 17 age and sex matched healthy controls	Flu vaccine (A/Solomon/3/2006 (H1N1), A/Hiroshima/52/ 2005(H3N2), and B/Malaysia/2506/2004)	Safety: No sJIA patients had severe adverse reactions or disease exacerbation. Efficacy: efficacy did not differ significantly between the sJIA group and the healthy controls, and duration of tocilizumab administration did not affect response.
3482, Toplak, 2012 [6]	Cohort	6 months	31 JIA vaccinated (18 oligo, 2 sJIA) v 31 JIA unvaccinated (19 oligo, 3 sJIA) v 14 healthy controls	Inactivated flu vaccine	Protective titers against all three vaccine viruses were detected in 77% of children in the JIA group and 79% in the healthy controls at 6 months post-vaccination In 4 children on anti-TNF therapy, they had protective titers to all three vaccine viruses 6 months after vaccination
1785, Ogimi, 2011 [7]	Cohort	1 month	49 children with rheumatic disease (23 with JIA) v 36 healthy controls	Inactivated flu vaccine	After vaccination, antibodies against influenza were produced equally between children who received immunosuppressive agents and controls; Local side effects were seen in 2% of the patient group and 8% in the control group

Table 2. Pneumococcal Vaccine – Data from RCTs and Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
2561 Quartier 2011 [8]	RCT	1 month	Anakinra ((2 mg/kg subcutaneous daily, maximum 100 mg) vs placebo in sJIA (24 patients, 12 per group)	Pneumococcal vaccine	Level of post-vaccination antibodies against five pneumococcal capsular polysaccharide serotypes was not significantly different between the two groups. After month 1, all patients received anakinra; 12 patients were tested and had an adequate antibody response at month 12.
3592, Aikawa, 2015 [9]	Cohort	1 year	17 patients with poly JIA refractory to high doses of	PPV23	The frequencies of patients achieving adequate vaccine response at 2 months and 12 months were similar in JIA patients with and without anti-TNF therapy.

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
			methotrexate immediately before starting etanercept (etanercept started 2 weeks after vaccination) v 10 JIA patients on stable dose of methotrexate		
1153, Farmaki, 2010 [10]	Cohort	6-8 weeks	Study group: 31 JIA patients (8 oligo, 2 systemic) on anti-TNF and MTX or cyclosporine with or without prednisone vs Control group: 32 JIA patients (14 oligo) on MTX and/or cyclosporine with or without prednisone	PCV7 Vaccine	After the first vaccine dose, geometric mean titers (GMTs) of antibodies were significantly increased from baseline for all viral strains in both groups. Protective titers were significantly increased in both groups after vaccination, and there was no significant difference in the percentage of patients with protective titers between the two groups. There was no significant difference between children achieving vaccine response and administration of prednisone or not.

Table 3. Measles, Mumps, Rubella (MMR) Vaccine and Diptheria/Tetanus Vaccine – Data from RCTs and Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
1226 Heijstek 2013 [11]	Randomized controlled clinical trial	May 2008 to July 2011	137 JIA pts aged 4-9 yrs	Randomized to 68 who received booster and 69 who did not	-131 analyzed in the modified intention to treat analysis - 60 on methotrexate and 15 on biologics - at 12 mos seroprotection rates were higher in revaccination pts v control pts; measles 100% v 92% (95% CI 84-99%), mumps 97% (95% CI, 95-100%) v 81% (95% CI, 72-93%); and rubella 100% v 94% (95% CI, 86-100%) - there was no significant difference between re-vaccinated and control groups with regards to intra articular steroid injections of

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					methotrexate (p=0.62 and p=.25, respectively) - all pts were seropositive against measles and rubella -2 pts were seronegative for mumps at 12 months; 1 pt was on MTX and had a small increase in immunogenicity but levels below protective were noted at 12 months. - an oligo patient started MTX shortly after vaccination and was negative at baseline for MMR; also negative for mumps at follow up but did have increased antibodies to measles and rubella - at 12 months 5 controls (12%) were negative for measles, 12 (19%) negative for mumps, and 4 (6%) seronegative for rubella - 3 months after vaccination there were notable increases in antibody concentrations in MMR and at 12 months titers were higher compared with controls - humoral response to revaccination did not differ significantly between those on MTX or biologics, but numbers were too small to draw conclusions.
1263 Borte, 2009 [12]	Cohort study	Unclear	15 patients with JIA treated with MTX and etanercept and 22 healthy controls	MMR vaccine	Virus-specific T-cells and antibodies increased after vaccination Neither low-dose MTX nor etanercept treatment interfered with generation of long-lived virus-restricted T cells and protective levels of virus-specific IgG antibodies
1027 Heijstek 2012 [13]	Cross sectional study	Unclear	400 JIA pts; oligo persistent n=159, oligo extended n=38, RF+ poly n=13, RF- poly110, SoJIA n=64, ERA n=10, psoriatic n=6	Measles, mumps, rubella, diptheria and tetanus vaccines	-Geometric mean concentration (GMC) was higher in pts with JIA than healthy controls, p<0.001, with regards to measles, but but against mumps and rubella was lower (p<0.001 for both) - soJIA pt how lower antibody concentrations against measles (p=0.025), mumps (p=0.018), and tetanus (p=0.027), and rubella (p=0.007) but no difference was noted for diphtheria (p=0316) - no relationship noted between MTX and glucocorticoid use and pathogen specific GMC - weak negative correlation between MTX and antibody concentrations against mumps (r=-0.15), rubella (r=-0.29), diphtheria (r=-0.28), tetanus (r=-0.23), but not for measles (r=0.04), this was significant for rubella (p=0.009) and diphtheria (p=0.007)
4502 Brunner	Single arm cohort	24 months	n=46 with 29 who participated, male	Vaccination with DTaP prior to	All patients were noted to have protective antibodies against tetanus after 2 months of abatacept and 26/29 had protective

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
2020 [14]			and female patients ages 2-5 years; RF – poly n=18, ext oligo n=8, psoriatic n=3	treatment with abatacept with assessment of vaccine response	antibody response to diphtheria after 2 months of abatacept. Concomitant use of MTX and/or low-dose corticosteroids had no evident effect on antibody levels: 19/20 (95.0%) patients receiving MTX and/or low-dose corticosteroids maintained protective levels to diphtheria and tetanus compared with 7/9 (77.8%) patients receiving no MTX or corticosteroids. No cases of diphtheria or tetanus were noted during the 24 months after the study was started.

Table 4. Human Papillomavirus Vaccine – Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
1780 Heijstek 2014 [15]	Controlled cohort	12 months	68 female JIA pts and 55 health female controls age 12-18 yrs	Vaccination for HPV 16/18 given at 0,1, and 6 months	-all pts seropositive at 7 mos -1 pt seronegative at 12 mos; oligo pt -49 (89% and 63 (93% could be analyzed - 50 (91%0 healthy control and 66 (97) JIA pts received all 3 doses -4 JIA pts received 1 vaccine at 3 months; 2 were seronegative for HPV 16 and 3 seronegative for HPV 18; these pts turned seropositive after the 3rd dose - MTX did not affect HPV16 abs (2578 LU/mL, 95% CI 1338-4967 LU/mL) v (2844 LU/mL, 95% CI 2034-3967 LU/mL), p=.79 or HPV18 abs 860 LU/mL (95% CI 963 - 3595LU/mL) v 1335 LU/mL (95% CI 951-1873LU/mL) p=.37 -avidity of HPV16/18 was comparable in a random sample of 18 JIA pts and 18 healthy controls - no of IgG producing b cells in JIA pts GM 7.9 (95% CI 6.8-9.2) v healthy controls GM 6.7 (95% CI 5.6-8.1) - in JIA pts memory B cells increased at 3 months (HPV16 p=0.004 and HPV18 p=0.002) and at 7 months HPV16 p=0.15, HPV18 p=0.03) -memory B cells were undetectable in 5 pts and 2 controls for HPV16 and in 3 pts and 21 control for HPV18

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					- JADAS-27 lower at 7 mos (2.8 with IQR 0.2-6.0) v (3.1 w IQR 1.2-6.8) p= 0.007; and at 12 mos after inclusion 1.8 w IQR 0.1-4.6) p=0.006
1787 Esposito, 2014 [16]	Cohort study	12 months	21 patients with JIA [6 oligoarticular, 10 polyarticular, 5 sJIA) and 21 healthy controls	HPV vaccine (bivalent Cervarix vaccine by GlaxoSmithKline Biologicals, Rixensart, Belgium) in a 0-, 1-, 6-month schedule	All subjects seroconverted after the scheduled doses. JIA patients showed significantly lower anti-HPV16 titers than controls 1 month after the administration of the third dose ($p < 0.05$), whereas no significant difference was observed in anti-HPV18 titers

Table 5. Meningococcal Vaccine – Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
2207 Stoof, 2014 [17]	Retrospective Cohort study	Unclear	127 JIA patients	Meningococcal serogroup C conjugate vaccine (The NeisVac-C vaccine by Baxter Healthcare, Vienna, Austria)	MenC-specific IgG concentrations postvaccination were highest in patients aged 13–19 years at time of vaccination, and gradually waned over time. Estimated antibody concentrations at 4.2 years post-vaccination were similar to those measured in controls. Treatment with biologics induced a trend towards accelerated decline of antibodies (in contrast to treatment with MTX)
3485 Zonneveld-Huijssoon 2007 [18]	Single arm cohort	1 year	234 JIA pts; SoJIA n=34, persistent oligo n=103, extended oligo n=25, RF+ poly n=5, RF- poly n=59, psoriatic n=4, ERA n=7	Meningococcal serogroup C conjugate vaccine	- group 1 pts on no medication - group 2 pts on NSAID monotherapy - group 3 pts on low dose (<10 mg/m2/wk) MTX or SSZ w or w/out NSAID - group 4 pts on high dose MTX, infliximab, etanercept, cyclosporin, or combination MTX and SSZ w or w/out NSAIDs - MenC iGG geometric mean concentrations rose from 0.4 ug/mL pre vaccine to 28. ug/mL post vaccine (range 1.0-1820.5 ug/mL) p<0.0005

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					-Anti-MenC IgG geometric mean concentrations were significantly lower in patients in medication groups 3 (17.53) and 4 (16.28) compared with those in patients in groups 1 (41) and 2 (46.93). - 4 pts on steroids and did not have different responses to vaccines than peers on similar maintenance medications (MTX, groups 3 and 4); p=0.63 and p=0.73 - 4 pts (2 in group 3 and 2 in group 4) were low responders (developed 1.5 fold rise in titers compared to 17 fold rise seen in other patients), but were still able to mount SBA titers ≥8 - no difference noted between JIA pt responses and healthy controls with regards to increase in titers post vaccination (p=0.631)

Table 6. Varicella Vaccine – Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
4253 Speth, 2018 [19]	Cohort study	12 weeks for assessments, one additional interview after 3 years	23 patients with pediatric rheumatic disease (17 with JIA)	VZV vaccine (Varilrix® by Glaxo-Smith-Kline) + pre-vaccine checklist	21/23 patients (91%) showed a positive vaccination response Median VZV-IgG after 1st vaccination: 224 (59-1219) mIU/ml (median (range) After booster: 882 (30-4685) mIU/ml 9/21 patients had received 1st vaccine prior to study, reached high titers of VZV-IgG >500 mIU/ml (1117 (513-4685) mIU/ml) after booster Two patients in the high activity group failed to raise positive VZV-IgG, despite booster immunization
3493 Pileggi, 2010 [20]	Cohort study	2-3 years	25 patients with pediatric rheumatic disease (17 with JIA) and 18 healthy controls	Varicella vaccine, single dose	Efficacy only reported for whole cohort, not for JIA specifically Positive VZV-IgG titers were reached at 4 – 6 weeks after vaccination in 50% of patients and in 72.2% of controls The response was equivocal in 20% of patients and 16.6% of controls; vaccine response rates and median postimmunization

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Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					VZV-IgG titers were not different when patients and controls were compared One year after receiving VV, 8 (80%) of 10 seroconverted patients maintained positive VZV-IgG titers
2311 Toplak, 2015 [21]	Cohort study	3-24 months	6 patients with JIA (2 oligoarticular, 2 sJIA) treated with biologics	Varicella vaccine (varicella–zoster Oka strain virus 103.3 plaque forming units propagated in MRC5 human diploid cells), 2 doses	Five patients produced protective antibodies against varicella virus 6 weeks after the second vaccination One patient with low level of protective antibodies got mild varicella infection 4 months after the second vaccination

References:

1. Camacho-Lovillo, M. S., Bulnes-Ramos, A., Goycochea-Valdivia, W., Fernández-Silveira, L., Núñez-Cuadros, E., Neth, O., & Pérez-Romero, P. (2017). Immunogenicity and safety of influenza vaccination in patients with juvenile idiopathic arthritis on biological therapy using the microneutralization assay. Pediatr Rheumatol Online J, 15(1), 62. doi:10.1186/s12969-017-0190-0
2. Aikawa, N. E., Campos, L. M., Goldenstein-Schainberg, C., Saad, C. G., Ribeiro, A. C., Bueno, C., . . . Bonfá, E. (2013). Effective seroconversion and safety following the pandemic influenza vaccination (anti-H1N1) in patients with juvenile idiopathic arthritis. Scand J Rheumatol, 42(1), 34-40. doi:10.3109/03009742.2012.709272
3. Carvalho, L. M., de Paula, F. E., Silvestre, R. V. D., Roberti, L. R., Arruda, E., Mello, W. A., & Ferriani, V. P. L. (2013). Prospective surveillance study of acute respiratory infections, influenza-like illness and seasonal influenza vaccine in a cohort of juvenile idiopathic arthritis patients. Pediatr Rheumatol Online J, 11, 10-10. doi:10.1186/1546-0096-11-10
4. Dell'Era, L., Corona, F., Daleno, C., Scala, A., Principi, N., & Esposito, S. (2012). Immunogenicity, safety and tolerability of MF59-adjuvanted seasonal influenza vaccine in children with juvenile idiopathic arthritis. Vaccine, 30(5), 936-940. doi:10.1016/j.vaccine.2011.11.083
5. Shinoki, T., Hara, R., Kaneko, U., Miyamae, T., Imagawa, T., Mori, M., & Yokota, S. (2012). Safety and response to influenza vaccine in patients with systemic-onset juvenile idiopathic arthritis receiving tocilizumab. Mod Rheumatol, 22(6), 871-876. doi:10.1007/s10165-012-0595-z
6. Toplak, N., Subelj, V., Kveder, T., Cucnik, S., Prosenc, K., Trampus-Bakija, A., . . . Avcin, T. (2012). Safety and efficacy of influenza vaccination in a prospective longitudinal study of 31 children with juvenile idiopathic arthritis. Clin Exp Rheumatol, 30(3), 436-444.

For Peer Review Only

7. Ogimi, C., Tanaka, R., Saitoh, A., & Oh-Ishi, T. (2011). Immunogenicity of influenza vaccine in children with pediatric rheumatic diseases receiving immunosuppressive agents. Pediatr Infect Dis J, 30(3), 208-211. doi:10.1097/INF.0b013e3181f7ce44
8. Quartier, P., Allantaz, F., Cimaz, R., Pillet, P., Messiaen, C., Bardin, C., . . . Pascual, V. (2011). A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). Ann Rheum Dis, 70(5), 747-754. doi:10.1136/ard.2010.134254
9. Aikawa, N. E., França, I. L., Ribeiro, A. C., Sallum, A. M., Bonfa, E., & Silva, C. A. (2015). Short and long-term immunogenicity and safety following the 23-valent polysaccharide pneumococcal vaccine in juvenile idiopathic arthritis patients under conventional DMARDs with or without anti-TNF therapy. Vaccine, 33(5), 604-609. doi:10.1016/j.vaccine.2014.12.030
10. Farmaki, E., Kanakoudi-Tsakalidou, F., Spoulou, V., Trachana, M., Pratsidou-Gertsi, P., Tritsoni, M., & Theodoridou, M. (2010). The effect of anti-TNF treatment on the immunogenicity and safety of the 7-valent conjugate pneumococcal vaccine in children with juvenile idiopathic arthritis. Vaccine, 28(31), 5109-5113. doi:10.1016/j.vaccine.2010.03.080
11. Heijstek, M. W., Kamphuis, S., Armbrust, W., Swart, J., Gorter, S., de Vries, L. D., . . . Wulffraat, N. M. (2013). Effects of the live attenuated measles-mumps-rubella booster vaccination on disease activity in patients with juvenile idiopathic arthritis: a randomized trial. Jama, 309(23), 2449-2456. doi:10.1001/jama.2013.6768
12. Borte, S., Liebert, U. G., Borte, M., & Sack, U. (2009). Efficacy of measles, mumps and rubella revaccination in children with juvenile idiopathic arthritis treated with methotrexate and etanercept. Rheumatology (Oxford), 48(2), 144-148. doi:10.1093/rheumatology/ken436
13. Heijstek, M. W., van Gageldonk, P. G., Berbers, G. A., & Wulffraat, N. M. (2012). Differences in persistence of measles, mumps, rubella, diphtheria and tetanus antibodies between children with rheumatic disease and healthy controls: a retrospective cross-sectional study. Ann Rheum Dis, 71(6), 948-954. doi:10.1136/annrheumdis-2011-200637
14. Brunner, H. I., Tzaribachev, N., Cornejo, G. V., Joos, R., Gervais, E., Cimaz, R., . . . the Paediatric Rheumatology International Trials, O. (2020). Maintenance of antibody response to diphtheria/tetanus vaccine in patients aged 2–5 years with polyarticular-course juvenile idiopathic arthritis receiving subcutaneous abatacept. Pediatric rheumatology, 18(1), 19. doi:10.1186/s12969-020-0410-x
15. Heijstek, M. W., Scherpenisse, M., Groot, N., Tacke, C., Schepp, R. M., Buisman, A. M., . . . Wulffraat, N. M. (2014). Immunogenicity and safety of the bivalent HPV vaccine in female patients with juvenile idiopathic arthritis: a prospective controlled observational cohort study. Ann Rheum Dis, 73(8), 1500-1507. doi:10.1136/annrheumdis-2013-203429
16. Esposito, S., Corona, F., Barzon, L., Cuoco, F., Squarzon, L., Marcati, G., . . . Principi, N. (2014). Immunogenicity, safety and tolerability of a bivalent human papillomavirus vaccine in adolescents with juvenile idiopathic arthritis. Expert Rev Vaccines, 13(11), 1387-1393.doi:10.1586/14760584.2014.943195
17. Stoof, S. P., Heijstek, M. W., Sijssens, K. M., van der Klis, F., Sanders, E. A. M., Teunis, P. F. M., . . . Berbers, G. A. M. (2014). Kinetics of the long-term antibody response after meningococcal C vaccination in patients with juvenile idiopathic arthritis: a retrospective cohort study. Annals of the rheumatic diseases, 73(4), 728-734. doi:10.1136/annrheumdis-2012-202561
18. Zonneveld-Huijssoon, E., Ronaghy, A., Van Rossum, M. A., Rijkers, G. T., van der Klis, F. R., Sanders, E. A., . . . Wulffraat, N. M. (2007). Safety and efficacy of meningococcal c vaccination in juvenile idiopathic arthritis. Arthritis Rheum, 56(2), 639-646. doi:10.1002/art.22399

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19. Speth, F., Hinze, C. H., Andel, S., Mertens, T., & Haas, J.-P. (2018). Varicella-zoster-virus vaccination in immunosuppressed children with rheumatic diseases using a pre-vaccination check list. Pediatric rheumatology, 16(1), 15. doi:10.1186/s12969-018-0231-3
20. Pileggi, G. S., de Souza, C. B., & Ferriani, V. P. (2010). Safety and immunogenicity of varicella vaccine in patients with juvenile rheumatic diseases receiving methotrexate and corticosteroids. Arthritis Care Res (Hoboken), 62(7), 1034-1039. doi:10.1002/acr.20183
21. Toplak, N., & Avčin, T. (2015). Long-term safety and efficacy of varicella vaccination in children with juvenile idiopathic arthritis treated with biologic therapy. Vaccine, 33(33), 4056-4059. doi:10.1016/j.vaccine.2015.06.086

PICO 53. In children with JIA on immunosuppression, can treatment with live attenuated vaccines be given safely (initial dose, booster dose)?

Summary: The literature search identified one randomized controlled trial (RCT) [1] and six observational cohort studies [2, 3, 4, 5, 6, 7] that addressed this PICO question. In the RCT [1], there were no significant differences in adverse events or disease flare between patients who received the MMR booster and controls who received no MMR booster, and no disease due to infection occurred in JIA patients on immunosuppression (Table 1). All observational studies [2, 3, 4, 5, 6, 7] reported that there was no worsening of disease activity or disease flare after live attenuated vaccines. Further, four observational studies [2, 3, 4, 7] reported no major reactions or adverse events, and four observational studies reported no infections after live attenuated vaccine with Varicella [4, 7], MMR [5, 6, 7], or combination MMR/V [7] (Table 2).

The RCT was the only controlled trial, and the lack of blinding of patients, practitioners, and assessors of JIA disease activity combined with imprecision in effect estimates rendered the study quality as low. Although the cohort studies all lack a control group, the findings are consistent with the findings of the RCT.

Quality of evidence across all critical outcomes: Low

Table 1. Data from Randomized Controlled Trials

Ref ID, Author, Year	Study Type	Duration	Population Description	Vaccine given to relevant population	Results

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1226 Heijstek 2013 [1]	Randomized controlled clinical trial	May 2008 to July 2011	137 JIA pts aged 4-9 yrs	Randomized to 68 who received MMR booster and 69 who did not	-131 analyzed in the modified intention to treat analysis - 60 on methotrexate and 15 on biologics - The mean number of flares per patient did not differ significantly between the MMR booster group (0.44; 95% CI, 0.28-0.61) and the control group (0.34; 95% CI, 0.20-0.49), nor did the percentage of patients with 1 or more flare during follow-up. - The relative risk of a flare in revaccinated patients compared with controls was 0.9 (95% CI, 0.4-2.0) at 3 months and 1.3 (95% CI, 0.8-2.1) during total follow-up. No disease due to infections with attenuated viruses occurred in patients treated with immunosuppressive drugs. Serious events were comparable between groups and were judged unrelated to MMR booster vaccination.

Table 2. Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Vaccine given to relevant population	Results
4253 Speth, 2018 [2]	Cohort study	12 weeks for assessments, one additional interview after 3 years	23 patients with pediatric rheumatic disease (17 with JIA)	VZV vaccine (Varilrix® by Glaxo-Smith-Kline) + pre-vaccine checklist	Safety: no major reactions or disease flare Only these 23 patients met the pre-vaccination checklist criteria (out of thousands)
3493 Pileggi, 2010 [3]	Cohort study	2-3 years	25 patients with pediatric rheumatic disease (17 with JIA) and 18 healthy controls	Varicella vaccine, single dose	Safety: Specifically for JIA, no worsening of disease activity; 2 patients with sJIA developed varicella-like rash; immunosuppressive therapy did not affect safety
2311 Toplak, 2015 [4]	Cohort study	3-24 months	6 patients with JIA (2 oligoarticular, 2 sJIA) treated with biologics	Varicella vaccine (varicella–zoster Oka strain virus 103.3 plaque forming units propagated in MRC5	Safety: No serious side effects, no varicella infection, disease activity remained stable

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Ref ID, Author, year	Study type	Duration	Population Description	Vaccine given to relevant population	Results
				human diploid cells), 2 doses	
1263 Borte, 2009 [5]	Cohort study	Unclear	15 patients with JIA treated with MTX and etanercept and 22 healthy controls	MMR vaccine	Safety: No overt measles, mumps, rubella or secondary severe infections; no increase in disease activity or medication use
3505 Heijstek 2007 [6]	Single arm cohort	Unclear; data collected 6 months before and 6 months after vaccination	207 pts with JIA born between 1989 and 1996; persistent oligo n=101, extended oligo n = 22, RF- poly n=55, RF+ poly n=5, systemic n=17, ERA n=3, psoriatic n=4	MMR vaccine	-no worsening disease activity seen prior to or after MMR vaccine; 40 flares occurred in 36 patients before MMR and 56 flares in 50 pts after MMR. -10 flares (4.8) seen in first month after vaccination. - no worsening of disease activity in poly pts on MTX and NSAIDs - No measles, mumps or rubella infections were reported. This was also true for patients using MTX.
4484 Uziel 2020 [7]	Cohort study	Single questionnaire	234 patients, 211/234 with JIA (oligo n=78, poly n=69, systemic n=18, psoriatic n=6, ERA n=5), treated with combination of MTX alone, combination DMARDs, biologics, or biologics +MTX	MMR or MMR/V vaccine	Safety: No serious adverse events, no MMR or varicella infection, no changes in disease activity - Minimal mild AEs

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References:

1. Heijstek, M. W., Kamphuis, S., Armbrust, W., Swart, J., Gorter, S., de Vries, L. D., . . . Wulffraat, N. M. (2013). Effects of the live attenuated measles-mumps-rubella booster vaccination on disease activity in patients with juvenile idiopathic arthritis: a randomized trial. Jama, 309(23), 2449-2456. doi:10.1001/jama.2013.6768
2. Speth, F., Hinze, C. H., Andel, S., Mertens, T., & Haas, J.-P. (2018). Varicella-zoster-virus vaccination in immunosuppressed children with rheumatic diseases using a pre-vaccination check list. Pediatric rheumatology, 16(1), 15. doi:10.1186/s12969-018-0231-3
3. Pileggi, G. S., de Souza, C. B., & Ferriani, V. P. (2010). Safety and immunogenicity of varicella vaccine in patients with juvenile rheumatic diseases receiving methotrexate and corticosteroids. Arthritis Care Res (Hoboken), 62(7), 1034-1039. doi:10.1002/acr.20183

4. Toplak, N., & Avčin, T. (2015). Long-term safety and efficacy of varicella vaccination in children with juvenile idiopathic arthritis treated with biologic therapy. Vaccine, 33(33), 4056-4059. doi:10.1016/j.vaccine.2015.06.086
5. Borte, S., Liebert, U. G., Borte, M., & Sack, U. (2009). Efficacy of measles, mumps and rubella revaccination in children with juvenile idiopathic arthritis treated with methotrexate and etanercept. Rheumatology (Oxford), 48(2), 144-148. doi:10.1093/rheumatology/ken436
6. Heijstek, M. W., Pileggi, G. C. S., Zonneveld-Huijssoon, E., Armbrust, W., Hoppenreijs, E. P. A. H., Uiterwaal, C. S. P. M., . . . Wulffraat, N. M. (2007). Safety of measles, mumps and rubella vaccination in juvenile idiopathic arthritis. Annals of the rheumatic diseases, 66(10), 1384-1387. doi:10.1136/ard.2006.063586
7. Uziel, Y., Moshe, V., Onozo, B., Kulcsár, A., Tróbert-Sipos, D., Akikusa, J. D., . . . Toplak, N. (2020). Live attenuated MMR/V booster vaccines in children with rheumatic diseases on immunosuppressive therapy are safe: Multicenter, retrospective data collection. Vaccine, 38(9), 2198-2201. doi:10.1016/j.vaccine.2020.01.037

PICO 54. Can live attenuated vaccines be used safely in the households of children with JIA *on immunosuppression*?

Summary: The literature searches did not identify any studies that addressed this PICO question.

Quality of evidence across all critical outcomes: Very low

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Imaging Modalities

PICO 55: In children with JIA, is any specific imaging technique recommended to best detect inflammation and damage, make a diagnosis, predict structural damage, flare or treatment response?

Direct evidence

Summary: Literature searches identified 24 studies that provided direct evidence to address this question by comparing two imaging technologies in patients with JIA. Five studies compared X-ray with MRI. One study showed that 83.3% of patients had erosions by MRI compared to 34.8% by X-ray[1]. In patients without clinical complaints of cervical involvement, MRI of cervical spine showed that 65% had soft tissue involvement, pannus formation and erosions compared to X-ray which showed only erosion in 20% of patients[2]. Cartilage loss was visible on both MRI and X-ray[7] with more severe cartilage loss on MRI. The joint effusions were better detected by MRI than radiography in both hips and knees[7]. One study indicated that MRI is less efficient than conventional radiography in detecting destructive changes over 1 year[19].

In a small study[3] that compared MRI with ultrasound (US) of knee and hip joints before and after IA steroid therapy, MRI was more sensitive in detecting popliteal cyst and lymph nodes, but US was as sensitive as MRI in detecting effusion. In another study[14], the effusion of knee joints was suspected by MRI in 76% and by radiograph in 21% joints. The MRI was more sensitive in detecting TMJ erosions, synovial hypertrophy, synovitis and effusions[10], while US misdiagnosed 67% of patients with TMJ involvement as false-negative[11]. Another study[12] reports that chronic TMJ arthritis was diagnosed in 69% by MRI and in 28% by US. The correlation between US capsular width and MRI assessed amount of synovitis in TMJ was 0.483 at the subcondylar and 0.347 at the condylar level ($p < 0.001$)[13]. In detecting imflammation, US sensitivity was 0%, specificity 36.4%, PPV 0%, NPV 100%, when compared with MRI as the reference standard in a study where MRI detected inflammation in 64.7% of the joints, and power Doppler US detected none [**Error! Reference source not found.**].

The other comparisons were (one study per each comparison): US vs GSUS vs PDUS (60% had abnormal findings in US, 60% had abnormal findings in GSUS, and 30% had abnormal findings in PDUS)[17]; MRI vs orthopantomograms (OPG) with authors' conclusion that MRI was superior to OPG in following changes of the condyle over time[18]; Radiography vs US with no significant differences in joint space width (JSW) or cartilage thickness between finger joints without or with previous arthritis[20]. The pixel by pixel DCE-MRI parameters correlated moderately to significantly with conventional MRI scores for synovitis[**Error! Reference source not found.**]. Diffusion-weighted imaging (DWI) was accurate in detecting arthritis in patients with JIA or suspected of having JIA and showed agreement with contrast-enhanced MRI [**Error! Reference source not found.**].

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The evidence base for comparative imaging in JIA is relatively diffuse in that each study is fairly unique in the combination of imaging techniques compared, the type of JIA being evaluated, the specific joints being evaluated and the purpose of the comparison (e.g., diagnosis, detection of inflammation, treatment response). Also, most of the studies have small patient numbers and have limited generalizability to the broader JIA population. For these reasons, the quality of evidence is very low.

Quality of evidence across all critical outcomes: Very low

Table 1. Studies Comparing Imaging Technologies

Ref ID, Author, year	Study type	Duration	Population Description	Assessment given to relevant population	Results
977, Mallatia, 2011 [1]	Prospective observational	Median 1.2 years (IQR 1.0-1.4) for 39 patients with longitudinal data	66 JIA patients with wrist arthritis	Contrast-enhanced MRI of more clinically affected wrist, using 1.5T scanner. Images were scored using 1) a novel pediatric-targeted scoring system, modified from the OMERACT RAMRIS recommendations [this novel tool was a precursor to the JAMRIS system] and 2) the RAMRIS system.	- 83.3% of patients had erosions by MRI compared to 34.8% by X-ray. Assessment of novel pediatric MRI scoring tool: - MRI erosion score was significantly higher in patients with limited wrist ROM (p=0.0002), and correlated with Sharp (p<0.0001, r_s= 0.61) and Poznanski scores (p<0.0001, r_s= 0.61) and clinical indicators of damage (JADI-A) (p<0.0001, r_s=0.49). -MRI Bone marrow edema score correlated with Sharp (p<0.0001, r_s=0.66) and Poznanski scores (p=0.001, r_s= -0.43) , and JADI-A (p=0.001, r_s= 0.4). - MRI synovitis score significantly higher with higher wrist swelling score (p<0.0001), moderately correlated with total swollen joint count (p=0.0002, r_s=0.45), JADAS-71 (p=0.0006, r_s= 0.41), and physician global (p=0.001, r_s= 0.41). Longitudinal data/sensitivity or scoring tool to change: - Patients meeting ACR30 at follow up had significant decrease in bone marrow edema score (p=0.04, SRM= 0.44) and synovitis score (p=0.01, SRM=0.62) - Patients without clinical improvement had significant increase in erosion score (p=0.03, SRM= 0.57), but the same was seen in patients with clinical improvement (p=0.01, SRM= 0.6)
2192 Oren et. al. 1996 [2]	Prospective cohort	1991 for 32 months	20 pts with “JRA” 7 females, 13	MRI of cervical spine, X-ray	18 pts without clinical complaints of cervical involvement, 13 (65%) had soft tissue involvement, pannus formation and erosions compared to X-ray which showed only erosion in 4 pts

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Ref ID, Author, year	Study type	Duration	Population Description	Assessment given to relevant population	Results
			males, age 3-16,		
2071 Eich, 1994 [3]	Single-arm study	1 month	10 JIA patients	MRI and US of 15 joints before and after Intraarticular steroid therapy	Effusion before therapy: US and MRI 11 knees, 4 hips; Effusion after therapy: US 11 knees, 0 hips; MRI 4 knees, 1 hip; Popliteal cyst before therapy: US 1 knee, MRI 3 knees, clinical exam 0; Popliteal cyst before therapy: US 0 knee, MRI 1 knees, clinical exam 0; Lymph nodes before therapy: US 1 knee, MRI 9 knees; Lymph nodes after therapy: US 0 knees, MRI 6 knees.
644, Koos, 2013 [4]	Retrospective cohort study	Unclear	23 patients with JIA, 23 matched controls	Underwent contrast enhanced MRI or cone beam CT scan (CBCT)	78% of TMJs in control group were considered normal; 83% of the TMJs in the JIA group showed severe changes; difference between TMJ arthritis in control and JIA group was highly significant $p<0.0001$ Paper devises a scoring method for assessing TMJ arthritis that can be used with MRI and CBCT but does not compare them head to head
838, Kuseler, 1998 [5]	Prospective cohort study	3 years	30 TMJ in 15 children diagnosed with JCA (per EULAR criteria) 10 healthy children served as controls	Patients underwent clinical exam, radiographs and contrast enhanced MRI imaging	In control group, MRI showed no erosions, but 3 joints in 2 patients showed an anteriorly displaced disc and one of these discs was folded. In JCA patients, radiographs revealed small erosions (only in the cortical bone, and no changes in the shape of the condyle) in 5 joints (3 patients) and severe erosions (destruction of the trabecular bone and flattening of the condylar head) in 5 joints (3 patients). On MRI in JCA patients, there were small erosions in 5 joints (5 patients) and severe erosions in 5 joints (3 patients). Two joints with small erosions on the radiograph could not be diagnosed on the MRI. Two joints with small erosions on the MRI could not be diagnosed on radiographs.

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Ref ID, Author, year	Study type	Duration	Population Description	Assessment given to relevant population	Results
					Grade 2 condylar changes seen on the radiographs corresponded to the MR images. Of patients with small erosions on MRI, none reported subjective symptoms, 3 were found to have objective signs and 2 had no objective findings. Clinical signs were found in all patients with severe erosions on MRI, but only 2 of them reported subjective symptoms. Slight but clear enhancement of synovial membrane seen after injection of Gd-DTPA in 15 joints (11 patients). A strong enhancement was seen in 8 joints (6 patients). Only 1 of these patients reported subjective symptoms. Pannus was found in 7 joints (5 patients). All the joints with pannus also showed enhancement. All discs had a low signal intensity.
2208 Gylys-Morin et. al. 2001 [6]	Prospective cohort (?)	31 months (6/1996-2/1999)	30 pts with JIA: 21 F/9M Age 5-16 (sx less than a year)	MRI with contrast of more symptomatic knee compared with X-rays in 27 children	Suprapatellar joint effusions in 26/30 (87%) Meniscal hypoplasia in 11/30 (37%) Abnormal epiphyseal marrow in 8/30 (27%) 3 had irregular articular cartilage with fissures/thinning 1 knee had erosion Versus xrays which only showed suprapatellar fullness in 78%, joint space narrowing in 1 with no bony abnml
2539 Senac, 1988 [7]	Cohort Study	Unclear	21 pts with JRA and 3 healthy volunteers	MRI imaging of hips and knees contrasted with X-rays in juvenile rheumatoid arthritis	13/15 hips had cartilage loss on MRI and 12/15 had joint-space narrowing on standard films. 8 hips had more severe cartilage loss on MRI than radiograph. 6 hips had joint Effusions on MRI, but one of which was radiographically visible. 2/15 hips had Avascular necrosis of the femoral head with equivocal plain film findings. 9/15 hips had bone erosions/degenerative changes on both MRI and xray-worse on MRI.

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					14/20 knees had articular and epiphyseal cartilage loss on MRI. 5/14 had focal thinning, and 9/20 had joint-space narrowing on xrays. 13/20 had meniscal changes. 15 knees showed joint effusions on MRI vs 9 on xrays. 1 had avascular necrosis, 3 had intraarticular fragments, and 1 had medullary infarcts on MRI, none visible on corresponding radiographs.
1040, Barendregt, 2016 [8]	Cross sectional study	Feb 2013-Dec 2014	35 patients with JIA (18 MRI active and 17 MRI inactive)	Compared dynamic contrast enhanced MRI (DCE) with diffusion weighted imaging (DWI) in quantifying synovial inflammation in JIA	ME, MIS, TTP. TIC5 and ADC were significantly different when MRI inactive and active JIA were compared. Higher percentages of TIC5 were seen in MRI inactive JIA. Lower ME, MIS, TTP and ADC were found in MRI-inactive JIA as compared to MRI active JIA. In MRI inactive JIA, ME positive correlated with ADC with r=0.49 and p=0.048. TTP positively correlated with ADC with r=0.50, p=0.043 and TIC 4 inversely correlated with ADC with r= -0.55, p= 0.022. ME, MIS and TIC5 significantly correlated to ADC (0.62, 0.45, -0.51 respectively, all p<0.05) when assessing MRI active and inactive JIA together.
546, Pradsgaard, 2015 [9]	Cohort	Nov 2008 to October 2011	23 children with JIA	One knee from each of 23 children with oligo JIA were investigated by both MRI and US. Outcome measure was distal femoral cartilage thickness	High level of agreement between MRI and US measurements of mean cartilage thickness and Rho values between modalities were high (between 0.70 and 0.86, p<0.05 for all) Intercondylar notch of the distal femoral cartilage may be the best anatomical point for cartilage thickness measurements of the knee
799, Laurell, 2012 [10]	Cohort study	2007-2011	10 JIA patients with 11 clinically active joints were assessed by US and MRI	10 patients with JIA were assessed by US and MRI compared to 6 healthy controls with 8 joints	US detected synovial hypertrophy in 22 areas of 11 joints, 86% of which had synovial hyperemia, and MRI revealed synovitis in 36 areas of the same 11 joints. Erosions were identified by US in two areas of two joints and by MRI in 6 areas of four joints. Effusion was shown by US in nine areas of six joints and by MRI in 17 areas of five joints. MRI detected juxta articular bone marrow edema in 16 areas of eight joints.
1126, Muller,	Case series	March and Sept 2006	30 consecutive JIA patients	Patients underwent 4 examinations: Rheum investigation, orthodontic	19/30 (63%) patients and 33/60 (55%) joints had signs of TMJ involvement on MRI. This was associated with condylar deformity in 9/19 (47%) patients and 15/33 (45%) joints.

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2009 [11]				exam, US of TMJs, and MRI of TMJs	Rheumatological, orthodontic, and US examinations correctly diagnosed 11 (58%), 9 (47%) and 6 (33%) patients, respectively, with active arthritis but misdiagnosed 8 (42%), 10 (53%) and 12 (67%) patients, respectively, as having no signs of inflammation. Best predictor for active arthritis on MRI was a reduced maximum mouth opening
1672, Weiss, 2008 [12]	Single arm cohort	Jan 2005 to April 2007	38 newly diagnosed JIA patients	Children with newly diagnosed JIA were prospectively evaluated for TMJ arthritis. Jaw pain and disability were assessed with questionnaires and physician exam TMJs were imagined with MRI and US within 8 weeks of diagnosis	Acute TMJ arthritis was diagnosed in 75% of children by MRI and none by US. Chronic arthritis was diagnosed in 69% by MRI and in 28% by US. Findings of both acute and chronic TMJ disease were detected by MRI in 53% of the patients. Of those with acute arthritis, 71% were asymptomatic and 63% had normal PE.
3835, Kirkhus, 2016 [13]	Case series	2005-2012	55 patients; 48 with JIA; 7 with other diseases including JDM, MCTD, Scleroderma , Sjorgens and Lupus	Ultrasound and MRI of TMJs were obtained within a week for patients referred to radiology due to symptoms or clinical suspicion of TMJ arthritis; 124 ultrasounds and MRIs were done in 55 patients and were scored for subcondylar and condylar capsule width (US) and amount of synovitis (MRI)	Correlation between ultrasound capsular width and MRI assessed amount of synovitis was moderate both at the subcondylar and condylar level, spearmans rho 0.483, p <0.001 and 0.347, p<0.001 respectively. The ROC curve indicated the best discriminatory ability at the subcondylar level with an area under the curve of 0.77 (95% CI 0.69-0.85) and a cut off of 1.2 mm (sensitivity 72%, specificity 70%) for the capsular width.
4111, El-Miedany, 2001 [14]	Cohort		38 patients with JIA and clinical signs of knee joint involvement and 10 healthy controls	All patients underwent plain radiography, US and MRI examinations before and after contrast administration	Acute synovitis in at least one knee joint was present in 15/38 (39.5%) of patients while chronic synovitis was evident in the rest of the patients, 23/38 (60.5%). On radiographs, joint effusion was suspected in 6 out of 29 joints (21%). On MRI, joint effusions were seen as areas of decreased signal intensity on T1W1 in 29 out of 38 joints (76%) before and after enhancement with Gd-DTPA. Compared to control, sonographic examination was found to be of great value for evaluating joint effusion, popliteal cysts, lymph nodes, and to

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					a lesser extent, the degree of affection of the articular cartilage. MRI was superior in evaluating the extent of synovial proliferation, thinning out and erosions of articular cartilage, loculated effusions as well as hypoplastic menisci and ligaments, especially after contrast enhancement.
2383, Malattia, 2008 [15]	Cross sectional study	June 2006 to March 2007	26 JIA patients	The clinically more affected wrist was studied for erosions with MRI, radiography, and ultrasound coupled with standard clinical assessment and biochemical analysis	Of 26 JIA patients, 25 (96.1%) had 1 or more erosions as detected by MRI whereas conventional radiography and US revealed erosions in 13 (50%) and 12 (50%) of 24 patients, respectively. MRI detected erosive changes more compared to conventional radiography (p=0.002 with Bonferroni correction and US (pb= 0.0002) in the group of patients with less than 3 years disease duration. US and radiography were of equivalent value for the detection of destructive changes. Wrist MRI score correlated highly with radiographic erosion score (r=0.82) and with wrist limited range of motion score (r=0.69).
3636 Rydholm 1986 [16]	Single Arm Cohort		14 patients with JCA (16 hips examined)	Hips examined clinically, radiographically, and by US prior to joint pressure measurement and arthroscopy	Capsular distention correlated with stage of synovitis, r=0.7, p<0.01. Stage of synovitis correlated with intracapsular pressure, r=0.6, p<0.05. Stage of synovitis correlated with stage of cartilage damage, r=0.5, p<0.05. Stage of cartilage destruction correlate with radiographic score, r=0.7, p<0.01. No correlation with capsular distention and intracapsular pressure.
802 Lerkvaleekul 2017 [17]	Cross sectional	1 year	46 JIA patients Inactive group (16 patients with prior wrist arthritis now inactive on	Wrist joints examined by infrared thermography, PE, and US	T_{mean} and T_{max} were higher in arthritis group compared to inactive and healthy (p<0.05). area under the ROC curve was 0.93, and $T_{mean} \geqslant 31$ °C was used as a cut-off point between healthy controls and the moderate to severe arthritis group, sensitivity 85.7% and specificity 80.0%. $T_{max} \geqslant 32.3$ °C cut-off point between healthy controls and the moderate to severe arthritis group, area under the ROC curve 0.91, sensitivity and specificity of 71.4% and 93.3% respectively.

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			clinical exam) Arthritis group (30 patients with active wrist arthritis) Healthy Controls (15 patients with no arthritis)		correlation coefficients between T_{mean} and T_{max} with the wrist examination were 0.36 (P = 0.01) and 0.31 (P = 0.04) respectively. Of 46 JIA patients, 28 (60%) had abnormal findings in US, 28 (60%) had abnormal findings in GSUS, and 14 (30%) had abnormal findings in PDUS In inactive group, 3 abnormal GSUS, 1 abnormal PDUS. US score $\geqslant$ 1 was used as a cut-off point between the inactive group and arthritis group, the area under the ROC curve was 0.87 with sensitivity and specificity of 83.3% and 81.3% respectively The correlation coefficient between US score and wrist examination was 0.67, $p < 0.01$ if using either abnormal findings in GSUS or PDUS as a definition of arthritis
3099 Pedersen, 2008 [18]	Case-control study	N/A	15 JIA patients with TMJ involvement and 10 healthy children	Clinical examination, MRI-scanning, and orthopantomograms (OPG)	There was no correlation between tenderness on palpation and MRI variables or radiographic findings. Decreased translation of the condylar head was correlated to reduced mouth opening capacity. The opening capacity and condylar resorption were significantly related, as shown on MRI and OPG. MRI was superior to OPG in following changes of the condyle over time, and inflammation was detected in nearly all joints.
2554 Malattia, 2012 Malattia, 2013 [19]	Single-arm study	1 year	40 JIA patients on DMARD or biologics	Pediatric (ACRp) response criteria and conventional radiography versus MRI	MRI synovitis score (0-3): at baseline 4.0 (3.0; 6.0); at 1 year 3.0 (2.0; 3.0). The MRI synovitis score was able to discriminate between different levels of ACRp response. Relative efficiency (RE) score showing a higher responsiveness to change: RE of Physician's Global Assessment 6.7; MRI 1.8; number of active joints 1.3; ESR 1.3; limited joint count 1.2; swollen joint count 1.2; tender joint count 1.2; CHAQ 0.7; patient global assessment 0.7. RE values of the pediatric and the RAMRIS bone erosion scores in relation to the adapted Sharp/van der Heijde score were <1, indicating that MRI is less efficient than conventional radiography in detecting destructive changes over 1 year.

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790, Pradsgaard et al., 2019 [20]	Cross-sectional	N/A (cross-sectional)	74 patients with JIA (n = 10 systemic JIA, 4 RF+ poly, 17 RF- poly, 15 extended oligo, 28 persistent oligo	X-ray, ultrasound	US measurements of cartilage thickness correlated well with radiographic joint space width (JSW) at proximal sites - MCP: ICC 0.806 and 0.863 for right and left MCP, respectively - PIP: ICC 0.411 and 0.392 for right and left PIP, respectively - Knee: ICC 0.629, 0.458, 0.721, 0.534 for right knee medial condyle, lateral condyle, and left knee medial condyle and lateral condyle, respectively No significant differences in joint space width (JSW) or cartilage thickness between finger joints without or with previous arthritis with either US or radiography Cartilage thickness measured by US smaller in knees with previous arthritis compared to knees without previous arthritis, but not statistically significant Radiographic JSW significantly less at right medial condyle in knees with previous arthritis compared to knees without previous arthritis (p = 0.04) Cartilage thickness or JSW decreased significantly with increasing age Limitations: 1 examiner (separate examiner for US and radiograph), unable to test intra-reader or inter-reader reliability
835, Hemke, 2017 [21]	Prospective, single arm, cohort study	1 year	85 patients with JIA (using ILAR criteria) and knee involvement ;	Patients underwent a clinical assessment and pixel by pixel DCE-MRI time intensity curve (TIC) shape analysis method (Type 1: no enhancement, Type 2: slow enhancement, Type 3: fast enhancement,	Poor correlation observed between the relative number of TIC-shape 3 and the JAMRIS synovial hypertrophy score (R=0.328, P=0.0002). No significant correlation observed btwn the relative number of TIC-shape 2, 4 and 5 and the JAMRIS score.

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			consecutively included	Type 4: fast enhancement followed by washout, Type 5: fast enhancement followed by gradual enhancement increase, type 6: arterial enhancement); grade of synovitis was scored on conventional MR images using the JAMRIS system	Significant correlation between the JAMRIS synovial hypertrophy score and the descriptive parameters of maximal enhancement (R=0.658, p< 0.001), enhancing volume (R=0.618, p< 0.001) and initial area under the curve (R=0.639, p< 0.001). The maximal initial slope correlated moderately with the synovial hypertrophy score (r=0.453, p< 0.001). Overall concluded that the pixel by pixel DCE-MRI parameters correlated moderately to significantly with conventional MRI scores for synovitis.
4095 Fedrizzi 1997 [**Error! Reference source not found.**]	Controlled cohort	August - December 1993	Hip joints of 53 patients with JRA; SoJIA n=9, poly n=18, oligo n=26	Ultrasound and X-ray	-21 asymptomatic joints (19.8%) had abnormal findings on ultrasound -all cases where XR was abnormal also showed abnormality on US - 26 cases with normal XR were found to have abnormalities on US - 9 pts presented with initial normal radiographs but abnormalities on US had repeat US an average of 28 months later, which showed 3 of whom to have severe radiographic abnormalities, 2 had clinical alterations initially, 3 had changes on US, and 4 still had abnormal US but normal XR - mean UJS 0.8 cm (0.7-0.9) in SoJIA; increased from expended normal in 2/2 - mean UJS 0.7 cm (0.5-1.4 cm) in poly; increased from expected normal (0.5 cm +/- 0.05 cm) in 16 (64%) - mean UJS 0.6 cm (0.4-1.0 cm) in oligo; increased from expected normal (0.5 cm +/- 0.05 cm) in 7 (27%) - in total there were abnormalities in widening with UJS >0.6 cm in 46/106 hip joints
4469 Zwir, 2020	Case-series	N/A	92 JIA patients	US and MRI examinations of the TMJs	MRI detected inflammation in 119 (64.7%) of the joints, power Doppler US did not detect inflammation in any of the JIA patients.

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[**Error! Reference source not found.**]			with TMJ involvement		US sensitivity was 0%, specificity 36.4%, PPV 0%, NPV 100%, when compared with MRI as the reference standard.
4479 Barendregt, 2020 [**Error! Reference source not found.**]	Single arm study	N/A	45 Patients with JIA or suspected JIA	Pre- and postcontrast 3.0-T MRI of the knee with an additional Diffusion-weighted imaging (DWI) sequence. For the clinical reference standard, a multidisciplinary team determined the presence or absence of arthritis on the basis of clinical, laboratory, and imaging findings (excluding DWI).	Detection of arthritis: Sensitivity DWI was 93% (13 of the 14 participants; 95% CI: 64%, 100%) Specificity was 81% (25 of 31; 95% CI: 62%, 92%). Scores for synovial inflammation: DWI and contrast-enhanced MRI agreed in 37 of 45 participants (82%), resulting in a sensitivity of 92% (12 of 13 participants; 95% CI: 62%, 100%) and specificity of 78% (25 of 32 participants; 95% CI: 60%, 90%) with DWI, with contrast-enhanced MRI as the reference standard.

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References:

1. C. Malattia, M. B. Damasio, A. Pistorio, M. Ioseliani, I. Vilca, M. Valle, N. Ruperto, S. Viola, A. Buoncompagni, G. M. Magnano, A. Ravelli, P. Toma, A. Martini. Development and preliminary validation of a paediatric-targeted MRI scoring system for the assessment of disease activity and damage in juvenile idiopathic arthritis. Ann Rheum Dis. 2011. 70:440-6
2. B. Oren, H. Oren, E. Osma, N. Cevik. Juvenile rheumatoid arthritis: cervical spine involvement and MRI in early diagnosis. Turk J Pediatr. 1996. 38:189-94
3. G. F. Eich, F. Halle, J. Hodler, R. Seger, U. V. Willi. Juvenile chronic arthritis: imaging of the knees and hips before and after intraarticular steroid injection. Pediatr Radiol. 1994. 24:558-63
4. B. Koos, N. Tzaribachev, S. Bott, R. Ciesielski, A. Godt. Classification of temporomandibular joint erosion, arthritis, and inflammation in patients with juvenile idiopathic arthritis. J Orofac Orthop. 2013. 74:506-19
5. A. Kuseler, T. K. Pedersen, T. Herlin, J. Gelineck. Contrast enhanced magnetic resonance imaging as a method to diagnose early inflammatory changes in the temporomandibular joint in children with juvenile chronic arthritis. J Rheumatol. 1998. 25:1406-12

6. V. M. Gylys-Morin, T. B. Graham, J. S. Blebea, B. J. Dardzinski, T. Laor, N. D. Johnson, A. E. Oestreich, M. H. Passo. Knee in early juvenile rheumatoid arthritis: MR imaging findings. Radiology. 2001. 220:696-706
7. M. O. Senac, D. Deutsch, B. H. Bernstein, P. Stanley, J. V. Crues, D. W. Stoller, J. Mink. MR imaging in juvenile rheumatoid arthritis. AJR Am J Roentgenol. 1988. 150:873-8
8. A. M. Barendregt, E. C. van Gulik, C. Lavini, C. M. Nusman, J. M. van den Berg, D. Schonenberg-Meinema, K. M. Dolman, T. W. Kuijpers, R. Hemke, M. Maas. Diffusion-weighted imaging for assessment of synovial inflammation in juvenile idiopathic arthritis: a promising imaging biomarker as an alternative to gadolinium-based contrast agents. Eur Radiol. 2017. 27:4889-4899
9. D. O. Pradsgaard, B. Fiirgaard, A. H. Spannow, C. Heuck, T. Herlin. Cartilage thickness of the knee joint in juvenile idiopathic arthritis: comparative assessment by ultrasonography and magnetic resonance imaging. J Rheumatol. 2015. 42:534-40
10. L. Laurell, M. Court-Payen, S. Nielsen, M. Zak, M. Boesen, A. Fasth. Comparison of ultrasonography with Doppler and MRI for assessment of disease activity in juvenile idiopathic arthritis: a pilot study. Pediatr Rheumatol Online J. 2012. 10:23
11. L. Muller, C. J. Kellenberger, E. Cannizzaro, D. Ettlin, T. Schraner, I. B. Bolt, T. Peltomaki, R. K. Saurenmann. Early diagnosis of temporomandibular joint involvement in juvenile idiopathic arthritis: a pilot study comparing clinical examination and ultrasound to magnetic resonance imaging. Rheumatology (Oxford). 2009. 48:680-5
12. P. F. Weiss, B. Arabshahi, A. Johnson, L. T. Bilaniuk, D. Zarnow, A. M. Cahill, C. Feudtner, R. Q. Cron. High prevalence of temporomandibular joint arthritis at disease onset in children with juvenile idiopathic arthritis, as detected by magnetic resonance imaging but not by ultrasound. Arthritis Rheum. 2008. 58:1189-96
13. E. Kirkhus, R. B. Gunderson, H. J. Smith, B. Flato, S. O. Hetlevik, T. A. Larheim, L. Z. Arvidsson. Temporomandibular joint involvement in childhood arthritis: comparison of ultrasonography-assessed capsular width and MRI-assessed synovitis. Dentomaxillofac Radiol. 2016. 45:20160195
14. Y. M. El-Miedany, I. H. Housny, H. M. Mansour, H. G. Mourad, A. M. Mehanna, M. A. Megeed. Ultrasound versus MRI in the evaluation of juvenile idiopathic arthritis of the knee. Joint Bone Spine. 2001. 68:222-30
15. C. Malattia, M. B. Damasio, F. Magnaguagno, A. Pistorio, M. Valle, C. Martinoli, S. Viola, A. Buoncompagni, A. Loy, A. Ravelli, P. Toma, A. Martini. Magnetic resonance imaging, ultrasonography, and conventional radiography in the assessment of bone erosions in juvenile idiopathic arthritis. Arthritis Rheum. 2008. 59:1764-72
16. U. Rydholm, H. Wingstrand, N. Egund, R. Elborg, L. Forsberg, L. Lidgren. Sonography, arthroscopy, and intracapsular pressure in juvenile chronic arthritis of the hip. Acta Orthop Scand. 1986. 57:295-8
17. B. Lerkvaleekul, S. Jaovisidha, W. Sungkarat, N. Chitrapazt, P. Fuangfa, T. Ruangchaijatuporn, S. Vilaiyuk. The comparisons between thermography and ultrasonography with physical examination for wrist joint assessment in juvenile idiopathic arthritis. Physiol Meas. 2017. 38:691-700

For Peer Review Only

18. T. K. Pedersen, A. Kuseler, J. Gelineck, T. Herlin. A prospective study of magnetic resonance and radiographic imaging in relation to symptoms and clinical findings of the temporomandibular joint in children with juvenile idiopathic arthritis. J Rheumatol. 2008. 35:1668-75
19. C. Malattia, A. Consolaro, S. Pederzoli, A. Madeo, A. Pistorio, M. Mazzoni, C. Mattiuz, G. M. Magnano, S. Viola, A. Buoncompagni, E. Palmisani, R. Hasija, N. Ruperto, A. Ravelli, A. Martini. MRI versus conventional measures of disease activity and structural damage in evaluating treatment efficacy in juvenile idiopathic arthritis. Ann Rheum Dis. 2013. 72:363-8
20. D. O. Pradsgaard, A. Horlyck, A. H. Spannow, C. Heuck, T. Herlin. A Comparison of Radiographic Joint Space Width Measurements Versus Ultrasonographic Assessment of Cartilage Thickness in Children with Juvenile Idiopathic Arthritis. J Rheumatol. 2019. 46:301-308
21. Hemke, R., Nusman, C. M., Berg, J. M. v. d., Lavini, C., Schonenberg-Meinema, D., Dolman, K. M., . . . Maas, M. (2017). Construct validity of pixel-by-pixel DCE-MRI: Correlation with conventional MRI scores in juvenile idiopathic arthritis. Eur J Radiol, 94, 1-5. doi:10.1016/j.ejrad.2017.07.00310.1016/j.ejrad.2017.07.003. Epub 2017 Jul 14.
22. Fedrizzi, M. S., Ronchezel, M. V., Hilario, M. O., Lederman, H. M., Sawaya, S., Goldenberg, J., & Sole, D. (1997). Ultrasonography in the early diagnosis of hip joint involvement in juvenile rheumatoid arthritis. J Rheumatol, 24(9), 1820-1825.
23. Zwir, L. F., Terreri, M. T., do Amaral e Castro, A., Rodrigues, W. D. R., & Fernandes, A. R. C. (2020). Is power Doppler ultrasound useful to evaluate temporomandibular joint inflammatory activity in juvenile idiopathic arthritis? Clin Rheumatol, 39(4), 1237-1240. doi:10.1007/s10067-019-04731-x
24. Barendregt, A. M., Mazzoli, V., Gulik, E. C. v., Schonenberg-Meinema, D., Rashid, A. N.-S. a., Nusman, C. M., . . . Hemke, R. (2020). Juvenile Idiopathic Arthritis: Diffusion-weighted MRI in the Assessment of Arthritis in the Knee. Radiology, 295(2), 373-380. doi:10.1148/radiol.2020191685.

Indirect evidence

Summary: There are 116 indirect studies that may address this PICO question with varying results. These studies either presented outcomes for only one type of imaging technology or compared an imaging technology to clinical examination.

Ultrasound: Forty-six studies evaluated ultrasound (US) for JIA joint assessment. In comparison with clinical examination, one study [1] reported US performance for predicting risk of clinical flare in patients with inactive JIA as follows: US accuracy 64.8% (57/88), CI 54.4-73.9%; US sensitivity: 36.6% (15/41), CI 23.6-51.9%; US specificity: 89.4% (42/47), CI 77.4-95.4%; US positive predictive value: 75.0% (15/20), CI 53.1-88.8%; US Negative predictive value: 61.8% (42/68), CI 49.9-72.4%. Another study reported US sensitivity 52%, specificity 99% in detecting synovitis out of all swollen joints [2]. In assessment of US of subtalar joint compared to clinical assessment as a reference test, the sensitivity was 71% and specificity was 62% [3]. In assessment of physical examination (PE) of the knee joint and ankle with US as a reference test, the sensitivity of PE was 64%, and specificity was 86% [14], while in other study sensitivity was 60.7%, and specificity was 99.5% [26]. The sensitivity, specificity and

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positive predictive value for both clinical examination and US were 34.5%; 100%, and 1 for clinical, and 45.7%, 100%, and 1 for US, respectively [20]. The ROC curve analysis of PDUS score<2 versus mild disease activity (DAS28-CRP=2.3–2.69) had 100% sensitivity and 75% specificity; the ROC curve analysis of synovial hyperplasia score <3 versus mild disease activity had 87.6% sensitivity and 65.6% specificity; the ROC curve analysis of total US score <3 versus mild disease activity had 75% sensitivity and 90.6% specificity [36]. Another study reported sensitivity of PDUS 0.904 (95% CI 0.7-0.98), specificity 0.895 (0.67-0.98), PPV 0.90 (0.67-0.98), NPV 0.89 (0.67-0.98) [37]. There is a variation of both sensitivity and specificity depending on the joints, as reported by a study, where pooled sensitivity for all joints was 48%, highest for the knee (69%) and lowest for the carpal and tarsal joints, and the small joints of fingers and toes, the specificity varied between 92% and 100% [38]. One study concluded that a subclinical synovitis detected by MSUS proved not to be a predictor of flares [6], while in other study the risk of flare was 5 times higher in patients with positive PD signal and 14 times higher in patients in remission on medication [27]. The correlation between total clinical score and total US score was higher for clinically active patients than for clinically inactive patients [7, 12]; US synovitis was associated with the presence of synovial fluid and artilage vascularization [10], the US variables were moderately correlated with clinical measures of joint swelling, but poorly correlated with those of joint tenderness/pain on motion and restricted motion [11]. There was a positive correlation between limitation of range of motion and US joint space in the children with JRA, but this was not consistent in every child [43]. In one study the subclinical synovitis was detected in 42% patients by US [16], in other studies subclinical disease was around 35% [5, **Error! Reference source not found.**]. Tenosynovitis was present in the absence of tibiotalar disease [4]. The agreement for each clinical and US interaction was consistently less than moderate (k<0.4) [18, **Error! Reference source not found.**], about 23% of joints were clinically inactive but were active by US [19]. The concordance rate of US with clinical examination was 89.4% [42]. Clinical tenderness and/or swelling were significantly associated with US-PD enthesitis and was strongly associated with grade 3 vascularization by US-PD; the kappa coefficients for concordance with US-PD enthesitis were 0.35 for clinical tenderness and 0.50 for clinical swelling; and of the 20 sites with US-PD enthesitis, 50% were normal by physical examination [39]. One study reported that US showed changes under the treatment [21]. Patients with hip arthritis who had IA Triamcinolone Hexacetonide and did not respond sonographically to the injection had long duration of disease and coxitis [44]. Synovial effusion detected in the knee joints at baseline was in 29(80.5%) joints after 1 month and 22(61.1%) after 2 months of intra-articular steroid injection [28].The US of TMJ had no correlation with ESR, CRP or ANA [33] or with peripheral joint count and disc-dislocation in closed mouth position, but had correlation with peripheral joint count and disc dislocation in max open mouth position [34]. The cartilage in OJIA patients was thicker than in polyarticular JIA patients and was decreased in the knee, wrist, and second PIP joint in children with JIA compared with the healthy cohort [13, 30], but no statistically significant difference was found by other study [25] in cartilage thickness of the knee between JIA patients and healthy controls. There was no significant difference between groups for PDUS VI, SMI VI, or max synovial membrane thickness, and no correlation observed between SMI or PDUS and the ESR, CRP, disease duration, age of the patients, sex, and JADAS-27 [9], but positive correlation was found between US and CRP, ESR, and number of joints in patients with active disease [**Error! Reference source not found.**]. 28.6% of ACR90 responders did not display complete resolution of synovial abnormalities, 29% of patients in clinical remission by cJADAS-10 at follow up had persistence of GSUS abnormalities [29]. In other study, the discrepancy between clinically active and US active: 8.8% clinically inactive joints were active by MSUS, 2.8% clinically active joints were inactive by MSUS, and 21.3% both clinically and MSUS active [31].

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Quality of evidence across all clinical outcomes: Very low

Table 2. Studies of Ultrasound

Ref ID, Author, year	Study type	Duration	Population Description	Assessment given to relevant population	Results
390 De Lucia, 2018 [1]	Case-control study	4 years	88 inactive patients with JIA and 30 healthy children	Ultrasonography and clinical examination	Abnormal US in 20/88 (22.7%) patients and in 38/3872 (0.98%) joints. Among patients with inactive disease (n=47), 42 (89%) US-negative and 5 (11%) US-positive. Among patients with synovitis flare (n=41), 26 (63%) US-negative, and 15 (37%) US-positive. Remission probability at 1 year: US(+) 55%; US(-) 94%; at 2 years US(+) 30%; US(-) 71%; at 3 years US(+) 63%; US(-) 25%; at 4 years US(+) 62%; US(-) 25%. US performance for predicting risk of clinical flare in patients with inactive JIA: US Accuracy: 64.8% (57/88), CI 54.4-73.9% US Sensitivity: 36.6% (15/41), CI 23.6-51.9% US Specificity: 89.4% (42/47), CI 77.4-95.4% US Positive predictive value: 75.0% (15/20), CI 53.1-88.8% US Negative predictive value: 61.8% (42/68), CI 49.9-72.4%
4098 Filippou 2011 [2]	Single arm cohort	June - December 2009	31 children with suspected JIA, 42 joints with suspected arthritis	Ultrasound	-42/1302 joints were found to have synovitis or effusion with US - of 27 joints clinically assessed as swollen, only 14 had had synovitis on US - of 1195 joints that were clinically assessed as having no disease, 12 had synovitis on US - no difference in sensitivity noted between age groups - US findings resulted in diagnosis of arthritis in 2 cases and reclassification of subtype in a third case
949 Lanni, 2016 [3]	Case-control	N/A	50 patients with clinically active JIA and 10 controls	Clinical versus US assessment of the subtalar joint	Detected synovitis by Clinical evaluations in 24 of 50 (48.0%) and US in 27 of 50 (54.0%) of STJs. US detected synovitis in 10 of 26 STJs (38.5%) recorded as normal on clinical evaluation, but was negative in 7 of 24 STJs (29.2%) diagnosed as having involvement on clinical examination.

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205 Rooney, 2008 [4]	Singe-arm study	N/A	34 JIA patients with 49 clinically swollen ankles	Ultrasound examination to assess the prevalence of synovitis and tenosynovitis	Tibiotalar synovitis in 30 (61%) joints. Tibiotalar disease without tendon involvement in 14 joints (29%). Tenosynovitis in 35 ankles (71%). In 19 of these (39%), tenosynovitis was present in the absence of tibiotalar disease.
323 Silva, 2013 [5]	Single-arm study	N/A	92 patients with JIA	Ultrasonographic findings in the hips	29 (32%) patients had abnormal findings. Out of those 29, 10 (34.5%) had subclinical synovitis, and 19 (65.5%) had clinical synovitis. Clinical synovitis was associated with the polyarticular subtypes and the active disease, whereas subclinical synovitis bore no correlation with the disease activity.
514 Nieto-González, 2019 [6]	Single-arm study	12 months	56 JIA patients in stable remission undergoing TNFi therapy tapered at baseline and in some cases at 6 months	MSUS to detect subclinical synovitis.	B-Mode synovitis any grade in 47 (83.9%) patients and 147 joints (10.1%), grades 2 or 3 in 19 (1.3%) of the 1456 joints. Doppler mode (PD) synovitis in 5 (8.9%) patients and in 5 (0.3%) different joints, and none of the patients had flares during follow-up. Authors concluded that a subclinical synovitis, as detected by MSUS, proved not to be a predictor of flares.
655 Kakati, 2007 [7]	Case - control study	6 months	30 patients with pauciarticular JRA who received naproxen (15-20 mg/Kg/day) for a period of six months	Clinical assessment and ultrasound	At follow-up: Spearman's correlation coefficient (R) between total clinical score and total US score were 0.6213 for group A (clinically active patients) and 0.1716 for group B (clinically inactive patients) joints, reaching statistical significance only in group A (p<.001). On initial exam, Synovial thickening in 14 joints (93.33%) of group A (mild 5, moderate 7, severe 2) and 15 joints (48.37%) of group B (mild 8, moderate 5, severe 2) Ta follow-up, Synovial thickening in 5 joints [29.46% (mild 3, moderate 1, severe 1)] in group A and 4 joints in group B [16.66% (mild 2, moderate 2)]
732 Algergawy, 2011 [8]	Cross-sectional study	N/A	20 with JIA and 20 healthy controls.	Clinical assessment and ultrasound of knee joints	Correlation coefficients between clinical and laboratory variables of JIA patients in relation to their ultrasonographic findings: AI score: synovial thickness 0.74, effusion volume 0.64 VAS (cm): synovial thickness 0.21, effusion volume 0.41

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					DAS score: synovial thickness 0.73, effusion volume 0.83 JAFAR score: synovial thickness 0.13, effusion volume 0.37 Clinical knee score: synovial thickness 0.71, effusion volume 0.85 Clinical hip score: synovial thickness 0.23, effusion volume 0.15 Hb level (gm/dL): synovial thickness −0.31, effusion volume −0.81 ESR level (mm first hour): synovial thickness 0.61, effusion volume 0.44 CRP level (mg/L): synovial thickness 0.51, effusion volume 0.45
3713 Alis 2019 [9]	Cross sectional	1 year	34 Patients with JIA who have at least one knee with active arthritis by clinical exam, 68 knees	Clinical and lab exam followed by MSUS including PDUS and SMI (superb microvascular imaging)	45/68 knees with positive clinical exam findings. 4/45 (8.8%) with normal US findings (excluded). 14 contralateral (clinically negative) knees with US findings of pathologic changes, synovial hypertrophy with effusion. 41 knees with positive clinical and US findings = Group A 14 knees with negative clinical and positive US findings = Group B No significant difference between groups for PDUS VI, SMI VI, or max synovial membrane thickness (p>0.05 for all). Maximum effusion thickness higher in Group A than B (p=0.005). No correlation observed between SMI or PDUS and the ESR, CRP, disease duration, age of the patients, sex, and JADAS-27 (p > .05).
781 Breton, 2011 [10]	Cross-sectional	N/A	31 JIA patients and 41 healthy volunteers	The physical and US assessments done for 558 joints in the JIA group.	Of 558 peripheral joints in JIA patients, 69 (12.5%) had US synovitis and 83 (15%) had abnormal physical findings. All the physical abnormalities were significantly associated with US synovitis (P < 0.0001) but agreement was low between US and physical findings. US synovitis was most common at the feet (59.4%), where it was detected clinically in only 25% of cases. US synovitis was associated with the presence of synovial fluid. Cartilage vascularization was significantly associated with US synovitis but was found in 1% of joints that had no other US abnormalities.

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782 Magni-Manzoni, 2009 [11]	Clinical and imaging assessment	N/A	32 JIA patients	1,664 joints assessed both clinically and with US.	A total of 104 (6.3%) and 167 (10%) joints had clinical and US synovitis, respectively. Of the 1,560 clinically normal joints, 86 (5.5%) had subclinical synovitis. US variables were moderately correlated with clinical measures of joint swelling, but poorly correlated with those of joint tenderness/pain on motion and restricted motion.
859 Cellerini, 1999 [12]	Case-control	Two assessments with 7 months interval	49 patients with pauci-articular JIA: 46 with active disease and 28 with quiescent disease	US and clinical assessment	Inflammatory signs of knee joint, Mean ± SD: in patients with active disease US score 3.7 ± 1.5; Clinical score 3.7 ± 1 0; in patients with quiescent disease US score 1.4 ± 1.7; clinical score 0.5 ± 0.5. Correlation between clinical and US findings was significant in patients with active disease, and not significant in patients with quiescent disease.
932 Pradsgaard, 2013 [13]	Case-control	N/A	95 patients with JIA 394 healthy children	Ultrasound	Joint cartilage thickness was decreased in the knee, wrist, and second PIP joint in children with JIA compared with the healthy cohort ($p < 0.001$ for all). Patients with oligoarticular JIA had thicker cartilage than patients with polyarticular and systemic JIA.
960 Janow, 2011 [14]	Single arm study	6 months	19 JIA patients	Physical examination (PE) and ultrasound (US) of knee and ankle	On PE, 46 (60.5%) joints were inactive and 30 (39.5%) were active. Of the clinically active joints, 6 (20%) had non-bony swelling alone, 4 (13%) had limitation with either POM or tenderness alone, and 20 (66.6%) met both criteria. On sonography, 37 (48.7%) joints were inactive and 39 (51.3%) were active. 14 (35.9%) of the sonographically active joints had synovial thickening, 21 (53.8%) had joint fluid, and 27 (69.2%) had hyperemia. Agreement between US and PE in 75% of cases. PE was 64% sensitive and 86% specific for identifying active arthritis. PE was 100% specific if 1) the patient was positive for both PE criteria or 2) if arthritis was present on PE in the knees. When the PE was negative and the US was positive, 21.4% developed active disease on PE within 6 months.
963 Collado,	Cross-sectional study	N/A	34 JIA patients with inactive disease (ID) on	All patients had ultrasound (US) and clinical examination,	Of the 13/34 (38.2%) patients with synovial abnormalities, US detected joint involvement (detection of synovitis) – in inactive disease off medication group: 12 joints in 8 patients;

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2014 [15]			and off medication	21 patients had radiographic assessment	in inactive disease on medication group: 25 joints in 5 patients. Patients without US findings (21 patients) achieved longer ID states than did patients with findings (13 patients); median [IQR] months was 10 [3-30] and 8 [6-15], respectively. Radiography showed abnormality in 1 out 21 patients. No erosions were detected.
1086 Silva, 2014 [16]	Cross-sectional study	N/A	36 JIA patients and 36 healthy controls	US for assessment of subclinical synovitis	Subclinical synovitis was detected in 15 (41.7%) patients (38/1,224 (3.1 %) joints) and 4 (11.1%) controls (8/1,224 (0.6 %) joints).
1389 Ranjan, 2013 [17]	Cross-sectional study	16 months	JIA patients and healthy controls	Power Color Doppler and Spectral Doppler Ultrasonography	Color fraction, Pooled joint: JIA patients 0.28 (±0.01); controls 0.015604 (±0.00112) Resistive index, pooled joint: JIA patients 0.61 (±0.01); controls 0.80783 (±0.007749).
1515 Hendry, 2011 [18]	Case-series	N/A	30 JIA patients	US examination of articular and periarticular foot disease (24 foot joints, 10 tendons, and 6 periarticular soft tissues).	Clinically detected synovitis, tenderness, and swelling were recorded in 42 (5.8%), 78 (10.8%), and 73 joints (10.1%), respectively. US-detected effusions, synovial hypertrophy, and PD signal were recorded in 88 (12.2%), 47 (6.5%), and 12 joints (1.7%), respectively. Subclinical foot disease was found in 52 joints (7.2%), 5 tendons (1.6%), and 4 soft tissue sites (2.2%). Agreement was consistently less than moderate (k<0.4) for each clinical and US interaction.
1666 Hassan, 2014 [19]	Case-series	N/A	20 oligoarticular JIA patients	High frequency power Doppler ultrasonography	Out of 57 joints, 44 were clinically active and 13 (23%) were clinically inactive but were active by US.
1823 Darwish, 2016 [20]	Cross-sectional	6 months	40 JIA patients and 20 controls	Clinical examination vs US	At follow-up, patients with clinical synovitis n = 30; Patients with US synovitis n = 38. N. of joints with US synovitis at baseline: Joints with clinical Synovitis 79/79 (100%); Clinically asymptomatic joints 44/321 (13.7%). N. of joints with US synovitis at follow-up: Joints with clinical synovitis 138 (100%); Clinically asymptomatic joints 45/262 (17.17%). Sensitivity: clinical 34.5%; US 45.7%

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					Specificity: clinical 100%; US 100% Positive predictive value: clinical 1; US 1
1964 Vidovic, 2018 [21]	Before and after single arm study	18 months	30 JIA patients	Doppler US before and after intraarticular infliximab	B mode score fell from 2.379 down to 1.17 at 1 month, 0.82 at 2 months, and 0.66 at 3 months. PD grade fell from 2.037 down to 0.86 at 1 month, 0.62 at 2 months, and 1.10 at 3 months. JADAS changed from 17.6 down to 8.8 at 1 month, 5.68 at 2 months, and to 9.52 at 3 months.
2002 Thieman n, 1994 [22]	Case series	N/A	69 JIA patients	US to measure bone density	In 10/69 (14.5%) patients the bone density measured by speed of sound (SOS) was below normal range
2018 Assaf, 2012 [23]	Case-series	16 months	20 JIA patients	High-resolution ultrasonography for the detection of TMJ changes	287 changes (35.9%) were detected by using high-resolution US. Among those, condylar erosions on 124 images (77.5%); synovial thickness abnormality on 55 images (34.4%); higher thickness of the condylar disc on 48 images (30%); irregularities of the bony surface on 40 images (25%); and joint effusion on 20 images (12.5%).
2176 Doria, 2001 [24]	Case-control		31 JIA patients divided by 3 groups: Group A – active disease, Group B – quiescent disease with lab levels of active disease, Group C – remission	Contrast-enhanced color doppler US.	Enhancement ratios, mean (SD): group A – 702% (402); Group B – 731 (703); group C – 314% (263) Mean number of pixels (range): group A 1417 (271-3252); group B 905 (0-2566); group C 176 (0-582); control group 66 (0-265). The maximum synovial membrane thickness, Mean (SD): group A: 5.6 (2.6); group B: 2.8 (1.2); group C: 1.7 (0.6); controls: 1.4 (0.3). Joint effusion: group A: 7 joints (77.8%); group B: 3 (25%); group C: 2(20%)
2177 Sureda, 1994 [25]	Cross-sectional	N/A	56 with JIA of the knee and 30 healthy children	US	Synovial proliferation in 52(93%) of JIA patients with active disease, 17(35%) in JIA patients in remission. Mean synovial thickness ± SD: 5.2mm ± 2.5 in JIA patients with active disease, 4.5mm ± 1.6 in JIA patients in remission, and 2.7mm ± 0.8 in healthy controls.

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					Joint effusion: 37 (55%) in JIA patients with active disease, 10 (21%) in JIA patients in remission, and none in healthy controls. No statistically significant difference was found in cartilage thickness between JIA patients and healthy controls.
2574 Dev, 2019 [26]	Cross-sectional	1 year	108 JIA patients with 864 joints examined	US vs clinical examination	Synovitis detected, # of joints: clinical examination 305, US 502. Discrepancy: 20 (19%) patients who were initially thought to be oligoarticular by clinical examination were later classified to polyarticular subtype on the basis of US findings. Sensitivity of clinical examination: 60.7%; specificity 99.48%
2828 Silva, [27]	Case-control	30 months	35 JIA patients in clinical remission	US	24 (68.6%) patients had subclinical synovitis (9 with positive PD signal), and 7 had erosion in at least 1 joint. The risk of flare was 5 times higher in patients with positive PD signal and 14 times higher in patients in remission on medication. After 6 months and 12 months of US evaluation, 70/3162 (2.2%) joints and 80/2108 (3.8%) joints flared. 25/2108 (1.2%) joints showed erosion at 12 months.
2973 Baikar, 2017 [28]	Case-control	2 months	27 JIA patients and 27 healthy controls	US indices (Color Fraction and Resistive Index) in assessing the effect of intra-articular steroid (IAS) injection on synovial inflammation in knee joints.	Synovial thickness, synovial effusion and CF decreased by 51.78%, 64.17% and 49.35% respectively and range of motion and RI increased by 166% and 31.94% respectively at second follow-up. CF and RI showed a significant correlation with active joint count. Synovial effusion detected in the joints at baseline was in 29(80.5%) joints after 1 month and 22(61.1%) after 2 months of intra-articular steroid injection.
4101 Lanni 2018 [29]	Single arm cohort	November 2013-November 2014	83 joints belonging to 33 newly diagnosed pts	Ultrasound	-83 joints were noted to have arthritis at the beginning of the study and at follow up after intervention there was remission in 63 on US with no notable synovial abnormalities - of note, 70 joints were in clinical remission - remission noted in 17/22 tibiotalar joints, 25/33 knees, 5/9 subtalar joints, and 8/10 wrists - residual synovial abnormalities were noted at 6 mos in 13/70 joints judged to be in remission on clinical examination in 11

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					patients - joint effusion noted in the knee in 32/33 (97%) pts at baseline, 19/22 (86.4) tibiotalar joints, 7/9 (77.8) subtalar joints, 6/10 (60) wrists, and 7/9 (77.8) elbows - synovial hypertrophy noted baseline in 32/33 (97%) knees, 21/22 (95.5) tibiotalar joints, 9/9 (100) subtalar joints, 9/10 (90) wrists, and 9/9 (100) elbows - power doppler abnormalities noted at baseline in 22/32 (66.7%) knees, 14/22 (63.6) tibiotalar joints, 8/9 (88.9) subtalar joints, 8/10 (80) wrists, and 5/9 (55.6%) elbows - at follow up there were joint effusions noted in 6/33 (18.2%) knees, 2/22 (9.1) tibiotalar joints, 1/9 (11.1) subtalar joints, no wrists, and 1/9 (11.1) elbows - synovial hypertrophy was noted at follow up in 5/32 (15.2%) of wrists, 4/22 (18.2) tibiotalar joints, 4/9 (44.4) subtalar joints, 2/10 (20) wrists, and 1/9 (11.1) elbows - power doppler abnormalities at follow up were present in 1/33 (3%) of knees, 0 tibiotalar joints, 2/9 (22.2) subtalar joints, 0 wrists and 0 elbows - decrease in grey scale US (GSUS) score and in power doppler US (PDUS) score in 16/20 (80%) - median GSUS decreased from 2.0 to 0, p<0.001 - median PDUS diminished from 2.0 to 0, p<0.001 - 21/33 (63.6%) of pts were ACR90 responders, but 6 (28.6) did not display complete resolution of synovial abnormalities -17/3 pts were in clinical remission by cJADAS-10 at follow up, but in 7 joints of 5 pts there was persistence of GSUS abnormalities
4102 Mitra 2019 [30]	Cross sectional study	June 2013-May 2014	27 JIA pts; poly n = 17, oligo n = 8, ERA n = 1, SoJIA n = 1,	Ultrasound	-median cartilage thickness with (IQR) in the wrist, knee and ankle joints of the cases (n = 27) were compared re- spectively with the control group (n = 54) by Mann-Whitney U test; statistically significant reduction in joint cartilage thickness in all the three joints (P < 0.01 in wrist, knee and ankle joints) - affected joints (n = 130) compared with unaffected joints (n = 32) of JIA patients without any previous history of arthritis

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					by paired t test; mean cartilage thickness in the affected wrist (n = 44), knee (n = 42) and ankle (n = 44) joints were significantly decreased (P < 0.05) in comparison to the unaffected joints -significant difference in median cartilage thickness of the knee joint between oligoarticular versus polyarticular subtypes of JIA (right knee P = 0.028, left knee P < 0.01) except in wrist and ankle joints where no statistically significant difference in median cartilage thickness was elucidated (P > 0.05) -oligo and poly were associated with decreased median cartilage thickness in all the three joints when compared with the age- and sex-matched healthy cohort (P < 0.05) - mean cartilage thicknesses of wrist, knee and ankle joints were less in boys than in girls suffering from JIA, although statistically significant thinning was found only in knee joints (P = 0.01) - no statistically significant difference between right and left sides of wrist, knee and ankle joints in cases by Wilcoxon's matched paired signed rank test (P = 0.02) - negative Spearman's coefficient of rank correlation of joint cartilage width with body weight in diseased children and it was statistically significant in the wrist, knee and ankle joints (P < 0.05)
3442 El-Banna 2019 [31]	Single Arm Cohort	Cross sectional	40 children with (30) oJIA or (10) pJIA	20 joints in each patient (knees, wrists, 2-5 MCP, 2-5 PIP)	Discrepancy between clinically active and US active (p<0.001); 70 (8.8%) clinically inactive joints were active by MSUS, 22 (2.8%) clinically active joints were inactive by MSUS, 170 (21.3%) clinically and MSUS active.
3444 Shanmugavel 2008 [32]	Single Arm Cohort	6 months	30 children with JIA and knee involvement: Group A – active	Bilateral knees on same day as clinical assessment, end of 2nd month, end of 6th month	End of month 6: Group A – 1 active joint clinically, 1 effusion US, 16 synovial thickening, 16 PDS hyperemia. Group B – 0 active joints clinically, 1 effusion US, 0 synovial thickening, 3 PDS hyperemia. All clinically assessed effusions detected on US.

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			Group B – inactive by clinical assessment (score)		
3633 Melchiorre 2010 [33]	Single Arm Cohort		68 children with JIA, never receiving treatment	US of bilateral TMJ in static and dynamic phase	46/68 (68%) with joint effusion (16 bilateral, 35%). 2/46 (4.3%) were symptomatic 62/68 (91.2%) with condylar remodeling (unilateral in 17, bilateral in 37). 18/124 (14.5%) TMJs with cortical "break" – erosion. 14/124 (11.3%) with osteophytes No disk alterations. No correlation with ESR, CRP, or ANA.
3634 Jank 2007 [34]	Single Arm Cohort		48 patients with JIA	US TMJ in closed and maximal open-mouthed position	53 (55.2%) patients with destructive changes. 41 (42.7%) disk dislocation in closed mouth position, not present in open-mouth position in 17 (17.7%). Correlation with ≥5 peripheral joints and TMJ destruction, p=0.002 No correlation with peripheral joint count and disc-dislocation in closed mouth position, p=0.144. Correlation with peripheral joint count and disc dislocation in max open mouth position, p=0.021. Duration of JIA >23 months associated with disc dislocation and TMJ destruction, p<0.0001 for both. Duration of JIA >60 months associated with TMJ destruction, p<0.0001, but not disc dislocation in open or closed position, p=0.070 and p=0.059.
962 Haslam 2009 [**Error! Reference source not found.**]	Cross sectional		17 children with oJIA <12 months and DMARD/systemic steroid naive (40 joints each)	Clinical history, physical exam, US	23/680 joints with clinical synovitis, 17 of these with US synovitis. 15/657 joints with US detected synovitis, clinically inactive. Subclinical disease was detected by US in 6/17 children assessed. US changed the joint count in 9/17 of patients assessed, with 5/17 having an increased joint count on US assessment.

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3429 Lofty 2018 [36]	Single arm cohort	3 years	40 patients with JIA	Clinical and lab assessment at enrollment, gray scale US and power doppler US for 28 joints	On clinical examination, 182 joints (16.3%) were swollen, 139 joints (12.4%) were tender, and 196 joints (17.5%) had clinical synovitis in the form of (swelling and/or tenderness). On US evaluation, 210 joints (18.8% of the total number of examined joints) were sonographically affected, including 192 joints (17.1% of total) with synovial hyperplasia, and 39 joints (3.5% of total) with joint effusion 142 joints (12.7% of total number of examined joints) had power Doppler (PD)signals. US of the clinically asymptomatic joints (82.5% of total number examined) had US signs of synovitis in 32 joints (3.5% of the clinically normal joints). 18 joints with clinical synovitis were normal on US. US positive predictive value is 84.7% & negative predictive value is 98%. US documented Power Doppler signals in (68.4%) of joints with clinical synovitis, (69.2%) of swollen joint, and (86.3%) of tender joints. kappa values for agreement between swollen joints and US =0.84 for swelling versus synovial hyperplasia, 0.74 for swelling versus power Doppler US, and 0.39 for swelling versus joint effusion. ROC curve analysis of PDUS score≤2 versus mild disease activity (DAS28-CRP=2.3–2.69) = 100% sensitivity and 75% specificity. ROC curve analysis of synovial hyperplasia score ≤3 versus mild disease activity (DAS28-CRP=2.3–2.69) = 87.6% sensitivity and 65.6% specificity. ROC curve analysis of total US score ≤3 versus mild disease activity (DAS28-CRP=2.3–2.69) = 75% sensitivity and 90.6% specificity.
3445 Sparchez 2010 [37]	Single Arm Cohort	1 year	32 patients with JIA	Clinical and lab evaluation, US performed on all clinically active joints (current or prior) with PDUS	2 clinically inactive joints with US synovitis. Compared to clinical exam: Sensitivity of PDUS 0.904 (95% CI 0.7-0.98), specificity 0.895 (0.67-0.98), PPV 0.90 (0.67-0.98), NPV 0.89 (0.67-0.98)

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					PD signal grade 1 predicted 85.6% but grade 2 and 3 predicted 100% of active visits. Fisher's Exact Test demonstrated a significant association between PhGA and PDUS score (F=26.169, p 0.00<<0.05).
4086 Nielsen 2013 [38]	Single Arm Cohort	7 years	62 newly diagnosed JIA patients	First clinical and US exam, monitored for 6 months after 4464 joints examined clinically, 1064 examined by US, mean of 17 joints per child	35/62 children with US synovitis and no clinical findings, total 80 joints, 23 of these developed arthritis in the next 6 months (29%). In these 35 children of 847 joints clinically and US normal, 9 joints developed clinical arthritis in 6 months (1%). pooled sensitivity for all joints is 48%, highest for the knee (69%) and lowest for the carpal and tarsal joints, and the small joints of fingers and toes The specificity varied between 92% and 100%. The differences of specificity between individual joints were not statistically significant.
4091 Jousse-Joulin 2011 [39]	Cross sectional		26 JIA (213 entheses) and 41 healthy volunteers (410 entheses)	Standardized clinical and PDUS exam of 5 entheseal sites bilaterally	In the JIA group, 27 entheseal sites (12.5%) were abnormal by physical examination. Among them, 23 (85%) were tender, 1 (4%) was swollen, and 3 (11%) were both. No clinical abnormalities found in healthy controls. 20/213 (9.4%) JIA sites with PD signal at enthesis -- 14 (70%) were in patients with ERA, 4 in oligoarthritis and 2 in polyarthritis. 7 JIA sites with erosions (4 with US enthesitis). No erosions in control group. Clinical tenderness and/or swelling were significantly associated with US-PD enthesitis (P < 0.0001). Clinical tenderness was strongly associated with grade 3 vascularization by US-PD (P < 0.0001). The kappa coefficients for concordance with US-PD enthesitis were 0.35 for clinical tenderness and 0.50 for clinical swelling. Of the 20 sites with US-PD enthesitis, 10 (50%) were normal by physical examination.
4088 , Laurell et al.,	Single arm cohort	Clinical and US assessment	30 patients with JIA and clinically active	US with and without color Doppler	US examination details: - Following joints and tendon sheaths examined: anterior, anteromedial and anterolateral talo-crural

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2011 [40]		before injection and at 4 weeks after steroid injection	ankle arthritis (n = 11 polyarticular JIA, 19 oligoarticular JIA)	US-guided injections triamcinolone acetonide 40 mg/mL	joint (anterior, anteromedial and anterolateral recesses), posterior subtalar joint (lateral recess), anterior subtalar joint (dorsal and medial recesses), tibialis posterior, flexor digitorum longus, flexor hallucis longus, peroneus, tibialis anterior, extensor hallucis longus, and extensor digitorum longus - Assessed for synovial hypertrophy, joint effusion, synovial hyperemia via color Doppler **Imaging outcomes** 121 compartments with active disease (joints, tendon sheaths, 1 ganglion cyst) based on synovial hypertrophy, effusion, and/or hyperemia 80% of ankle regions had multiple compartments involved - 78%: talo-crural - 65% posterior subtalar - 30% midfoot - 55% tendon sheaths 50 active tendon sheaths **Joint injection outcomes (US-guided):** - Accurate placement of corticosteroid in all 85 injected compartments - 4.7% rate of subcutaneous atrophy (4/85) - Normalization or regression of synovial hypertrophy in 89% of compartments (87% talo-crural, 95% post-subtalar, 91% midfoot, 86% tendons, 100% para-articular cyst) - Normalization of synovial hyperemia in 89% (86% talo-crural, 95% post-subtalar, 80% midfoot, 90% tendons, 100% para-articular) - Clinical resolution of active arthritis in 72%
4089, Laurell et	Case series	Prior to joint injection	11 patients with JIA and	US and color Doppler	US technique

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al., 2012 [41]		and 4 weeks after	clinically active wrist arthritis (n = 5 oligoarticular JIA, 2 polyarticular JIA, 2 undifferentiated, 1 ERA, 1 systemic JIA)	US-guided injection with triamcinolone acetonide (10-40 mg per joint and tendon sheath)	- Radiologist specialized in musculoskeletal US using Logiq 9 scanner - Dorsal and palmar views - Color doppler for hyperemia US results - Synovial hypertrophy in 26 compartments, hyperemia in 23 (radio-carpal, midcarpal, tendon sheaths) - Effusion in 2/21 inflamed joint compartments and 5/20 diseased tendon sheaths - Multiple compartments involved in 10/15 wrists - 5/15 wrists with isolated radio-carpal involvement - Synovitis in 13/15 radio-carpal joints (87%) and 8/15 midcarpal joints (53%) - Tenosynovitis in 5/15 wrists (33%) - 20/135 tendon sheaths (15%) with synovial hypertrophy, 16/135 (12%) with hyperemia - All patients with tenosynovitis also had radio-carpal or midcarpal involvement **US-guided injection results** - US-guided steroid injection in 21/26 diseased compartments - 4 of diseased tendon sheaths injected - 30 minute procedure time including general anesthesia (5-15 minutes for steroid injection) - Quick and effective placement of needle tip and steroid in all compartments - 1 week post-injection: normalization of synovial hypertrophy in 57%, normalization of hyperemia in 86%; 8/15 wrists (53.3%) clinically inactive arthritis - 4 week post-injection: normalization of synovial hypertrophy in 86%, normalization of hyperemia in 91%; 12/15 wrists (80%) clinically inactive arthritis - 1 relapse in oligo JIA patient 7 months after steroid injection

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					Complications: local subcutaneous atrophy in 1 patient at radio-carpal joint (4.8%)
3637 Shenoy, 2016 [42]	Cross-sectional study	N/A	30 JIA-ERA patients with 360 enthesital sites and 10 healthy children	US and clinical examination	Ultrasound enthesitis was seen in 25 of 30 (83%) patients, clinical enthesitis was present in 15 of 30 (50%) patients. USG picked up 20 (47 vs. 27) more sites of enthesitis as compared to clinical examination. The concordance rate was 89.4%. 25 of 47 sites (53%) with US changes) had acute changes only, 6 of 47 sites (13%) had chronic changes only and 16 of 47 sites (34%) had features chronicity associated with active acute lesions.
4097 Friedman, 2002 [43]	Cross-sectional Study	N/A	24 JIA patients and 24 healthy children	US of hip joint space	JIA group, mean ± SD: 0.60cm ± 0.16 cm (range 0.39–1.32 cm). Control group, mean ± SD: 0.43cm ± 0.08 cm (range 0.27–0.55 cm). There was a positive correlation between limitation of range of motion and US joint space in the children with JRA, but this was not consistent in every child.
1963 Boehnke, 1994 [44]	Case series	24 months	26 JIA patients	US of hip joint before and after IA Triamcinolone Hexacetonide	8 of 25 hips were in sonographic remission after 18 months. Patients who did not respond sonographically to the injection had long duration of disease and coxitis.
4375 Lanni, 2020 [**Error! Reference source not found.**]	Case-series	N/A	163 joints in 89 ankles in JIA patients	Joint and tendon disease on ultrasound (US) and clinical examination (CE)	Tenosynovitis was found on US in 70.5%, on CE in 32.4%. Agreement between US and CE for detection of active synovitis and tenosynovitis k<0.4. No correlation between any feature of active disease recorded on CE (joint swelling, tenderness/pain on motion and restricted motion) and active synovitis on US in the TTJ, STJ and ITJ.
4391 Zhu, 2019 [**Error! Reference source**	Case-series	24 weeks	82 JIA patients	US and clinical exam before and after treatment with ETN	Of 2296 scanned joints, 608 (26.5%) joints presented US synovitis, 513 (22.3%) joints with clinical synovitis. The mean number of joints showing synovitis on US was 7.42±3.35, the mean number of joints showing clinical synovitis (6.26±2.70) at baseline.

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Ref ID, Author, year	Study type	Duration	Population Description	Assessment given to relevant population	Results
not found.]					The number of joints showing synovitis on US at baseline was positively correlated with CRP, ESR, number of joints with active disease. No correlation with age (P=0.929), gender (P=0.204), height (P=0.874), weight (P=0.806), or disease duration (P=0.664) was observed. US synovitis correlated with increased disease activity in JIA patients. The number of joints showing synovitis on US at baseline was greater in response patients compared to non-response patients, suggesting that US synovitis had potential to predict clinical response to ETN.

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References:

1. Lucia, O. D., et al. (2018). "Baseline ultrasound examination as possible predictor of relapse in patients affected by juvenile idiopathic arthritis (JIA)." Ann Rheum Dis **77**(10): 1426-1431.
2. Filippou, G., et al. (2011). "Ultrasonography vs. clinical examination in children with suspected arthritis. Does it make sense to use poliarticular ultrasonographic screening?" Clin Exp Rheumatol **29**(2): 345-350.
3. Lanni, S., et al. (2016). "Delineating the Application of Ultrasound in Detecting Synovial Abnormalities of the Subtalar Joint in Juvenile Idiopathic Arthritis." Arthritis Care Res (Hoboken) **68**(9): 1346-1353.
4. Rooney, M. E., et al. (2009). "Ankle disease in juvenile idiopathic arthritis: ultrasound findings in clinically swollen ankles." J Rheumatol 36(8): 1725-1729.
5. Silva, V. B., et al. (2013). "Association between the ultrasonographic and clinical findings in the hips of patients with juvenile idiopathic arthritis." Rev Bras Reumatol 53(4): 322-327.
6. Nieto-Gonzalez, J. C., et al. (2019). "Can ultrasound-detected subclinical synovitis be an indicator of flare recurrence in juvenile idiopathic arthritis remission patients on tapered TNFi?" Clin Exp Rheumatol **37**(4): 705-712.
7. Kakati, P., et al. (2007). "Clinical and ultrasound assessment of the knee in children with juvenile rheumatoid arthritis." Indian J Pediatr **74**(9): 831-836.
8. Algergawy, S., et al. (2011). "Clinical, laboratory, and ultrasound assessment of the knee in juvenile rheumatoid arthritis." Clin Med Insights Arthritis Musculoskelet Disord 4: 21-27.
9. Alis, D., et al. (2019). "Superb Microvascular Imaging Compared With Power Doppler Ultrasound in Assessing Synovitis of the Knee in Juvenile Idiopathic Arthritis: A Preliminary Study." J Ultrasound Med.
10. Breton, S., et al. (2011). "Comparison of clinical and ultrasonographic evaluations for peripheral synovitis in juvenile idiopathic arthritis."

Semin Arthritis Rheum **41**(2): 272-278.
11. Magni-Manzoni, S., et al. (2009). "Comparison of clinical versus ultrasound-determined synovitis in juvenile idiopathic arthritis." Arthritis Rheum **61**(11): 1497-1504.
12. Cellerini, M., et al. (1999). "Correlation between clinical and ultrasound assessment of the knee in children with mono-articular or pauci-articular juvenile rheumatoid arthritis." Pediatr Radiol **29**(2): 117-123.
13. Pradsgaard, D. O., et al. (2013). "Decreased cartilage thickness in juvenile idiopathic arthritis assessed by ultrasonography." J Rheumatol **40**(9): 1596-1603.
14. Janow, G. L., et al. (2011). "Detection of active disease in juvenile idiopathic arthritis: sensitivity and specificity of the physical examination vs ultrasound." J Rheumatol **38**(12): 2671-2674.
15. Collado, P., et al. (2014). "Detection of synovitis by ultrasonography in clinically inactive juvenile idiopathic arthritis on and off medication." Clin Exp Rheumatol 32(4): 597-603.
16. Silva, V. B. M. e., et al. (2013). "Do patients with juvenile idiopathic arthritis in remission exhibit active synovitis on joint ultrasound?" Rheumatol Int **34**(7): 937-945.
17. Ranjan, S., et al. (2013). "Evaluation of synovial inflammation in juvenile idiopathic arthritis by power color Doppler and Spectral Doppler ultrasonography." Indian J Pediatr 81(1): 29-35.
18. Hendry, G. J., et al. (2011). "Frequent discordance between clinical and musculoskeletal ultrasound examinations of foot disease in juvenile idiopathic arthritis." Arthritis Care Res (Hoboken) **64**(3): 441-447.
19. Hassan, H. A. E. S., et al. (2015). "High frequency power doppler ultrasonography in oligoarticular juvenile idiopathic arthritis: Correlation with disease severity." Egyptian Rheumatologist **37**(3): 125-131.
20. Darwish, A. F., et al. (2016). "Implementation of musculoskeletal ultrasonography in detection of early juvenile idiopathic arthritis." Eur J Radiol Open **3**: 264-271.
21. Vidovic, M., et al. (2018). "Intraarticular infliximab therapy in patients with juvenile idiopathic arthritis: the role of musculoskeletal ultrasound and disease activity scores in monitoring therapy response." Clin Exp Rheumatol **36**(4): 676-682.
22. Thiemann, H. H., et al. (1994). "Investigations of bone density in patients with juvenile chronic arthritis by a sonographie method." Acta Univ Carol Med (Praha) 40(1-4): 37-41.
23. Assaf, A. T., et al. (2013). "Is high-resolution ultrasonography suitable for the detection of temporomandibular joint involvement in children with juvenile idiopathic arthritis?" Dentomaxillofac Radiol 42(3): 20110379.
24. Doria, A. S., et al. (2001). "Juvenile rheumatoid arthritis of the knee: evaluation with contrast-enhanced color Doppler ultrasound." Pediatr Radiol 31(7): 524-531.
25. Sureda, D., et al. (1994). "Juvenile rheumatoid arthritis of the knee: evaluation with US." Radiology **190**(2): 403-406.
26. Dev, S., et al. (2019). "Musculoskeletal Ultrasonography in Detecting Disease Activity in Patients of Juvenile Idiopathic Arthritis: A Cross-Sectional Study." Indian Journal of Rheumatology **14**(2): 104-108.
27. Miotto e Silva V. B., et al. (2017). "Patients with juvenile idiopathic arthritis in clinical remission with positive power Doppler signal in joint ultrasonography have an increased rate of clinical flare: a prospective study." Pediatr Rheumatol Online J **15**(1): 80.

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28. Baikar, T., et al. (2017). "Power Color Doppler and Spectral Doppler Ultrasonography to Evaluate Response to Intra-articular Steroid Injection in Knee Joints in Juvenile Idiopathic Arthritis." Indian J Pediatr **84**(11): 826-832.
29. Lanni, S., et al. (2017). "Ultrasound changes in synovial abnormalities induced by treatment in juvenile idiopathic arthritis." Clin Exp Rheumatol **36**(2): 329-334.
30. Mitra, S., et al. (2019). "Ultrasound detected changes in joint cartilage thickness in juvenile idiopathic arthritis." Int J Rheum Dis **22**(7): 1263-1270.
31. El-Banna, H. S., et al. (2019). "Role of musculoskeletal ultrasonography in the detection of subclinical synovitis in oligo and polyarticular juvenile idiopathic arthritis children." Egyptian Rheumatologist **41**(2): 151-155.
32. Shanmugavel, C., et al. (2007). "Role of power Doppler sonography in evaluation of therapeutic response of the knee in juvenile rheumatoid arthritis." Rheumatol Int 28(6): 573-578.
33. Melchiorre, D., et al. (2010). "Sonographic evaluation of the temporomandibular joints in juvenile idiopathic arthritis." J Ultrasound **13**(1): 34-37.
34. Jank, S., et al. (2007). "Sonographic investigation of the temporomandibular joint in patients with juvenile idiopathic arthritis: a pilot study." Arthritis Rheum **57**(2): 213-218.
35. Haslam, K. E., et al. (2009). "The detection of subclinical synovitis by ultrasound in oligoarticular juvenile idiopathic arthritis: a pilot study." Rheumatology (Oxford) 49(1): 123-127.
36. Lotfy, H. M., et al. (2018). "The role of Doppler Ultrasonography in evaluating disease activity in a group of juvenile idiopathic arthritis patients." Egyptian Journal of Radiology and Nuclear Medicine **49**(4): 1036-1042.
37. Sparchez, M., et al. (2010). "The role of Power Doppler ultrasonography in comparison with biological markers in the evaluation of disease activity in Juvenile Idiopathic Arthritis." Med Ultrason **12**(2): 97-103.
38. Nielsen, H. E., et al. (2013). "Ultrasonographic examination in juvenile idiopathic arthritis is better than clinical examination for identification of intraarticular disease." Dan Med J **60**(8): A4669.
39. Jousse-Joulin, S., et al. (2011). "Ultrasonography for detecting enthesitis in juvenile idiopathic arthritis." Arthritis Care Res (Hoboken) **63**(6): 849-855.
40. Laurell, L., et al. (2011). "Ultrasonography and color Doppler in juvenile idiopathic arthritis: diagnosis and follow-up of ultrasound-guided steroid injection in the ankle region. A descriptive interventional study." Pediatr Rheumatol Online J 9(1): 4.
41. Laurell, L., et al. (2012). "Ultrasonography and color Doppler in juvenile idiopathic arthritis: diagnosis and follow-up of ultrasound-guided steroid injection in the wrist region. A descriptive interventional study." Pediatr Rheumatol Online J 10: 11.
42. Shenoy, S. and A. Aggarwal (2016). "Sonologic enthesitis in children with enthesitis-related arthritis." Clin Exp Rheumatol **34**(1): 143-147.
43. Friedman, S. and M. A. Gruber (2002). "Ultrasonography of the hip in the evaluation of children with seronegative juvenile rheumatoid arthritis." J Rheumatol **29**(3): 629-632.
44. Boehnke, M., et al. (1994). "Intraarticular hip treatment with triamcinolonehexacetonide in juvenile chronic arthritis." Acta Univ Carol Med (Praha) **40**(1-4): 123-126.
45. Lanni, S., Marafon, D. P., Civino, A., Alongi, A., Proverbio, E., Agostoni, C., . . . Filocamo, G. Comparison between clinical and ultrasound

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assessment of the ankle region in juvenile idiopathic arthritis. Arthritis Care Res (Hoboken), n/a(n/a). doi:10.1002/acr.24241.
46. Zhou, L., & Gu, X. (2019). Correlation of ultrasonography synovitis with disease activity and clinical response to etanercept treatment in juvenile idiopathic arthritis patients. Brazilian Journal of Medical and Biological Research, 52.

MRI: Fifty studies evaluated MRI for assessment of patients with JIA. In a study comparing MRI with clinical assessment, the clinical assessment had a sensitivity of 25.7% and specificity of 91% for detecting MRI diagnosed arthritis; the agreement between MRI activity and clinical assessment was fair in cases with arthritis less than 4 years from diagnosis (k score 0.38, P = 0.045); there was no agreement in longer standing disease (k score 0.02, P = 0.62), and concordance between clinician and MRI result was highest in undamaged hips with agreement in 61% of cases [1]. In another study, the combined clinical exam in comparison with MRI had sensitivity 85%, specificity 54%; the combined clinical exam's false-positive rate was 0.46 and the false-negative rate was 0.15 [2]. Synovial hypertrophy on MRI was correlated moderately with physician global score (r_s=0.410) [3]. 36% of active JIA patients had no synovial thickening on MRI (JAMRIS score 0) [5], and 23.6% of patients with clinical evidence of knee arthritis and 16.3% with clinical wrist arthritis had no abnormalities on MRI [6]. However, in other studies 33% to 63% of patients in clinical remission had an abnormality on MRI [7, 8, 16, 19]. In unaffected knees of JIA patients with monoarthritis, MRI detected abnormalities in 50% of the knees [25]. The rate of early enhancement (REE) in wrist enhancement was highly correlated with wrist swelling (r_s=0.72, p<0.02) and moderately correlated with pain intensity (r_s=0.63, p<0.05) and CHAQ (r_s=0.6, p<0.05). The agreement between the automated estimation of normalized synovial volume (NSV) and the manual measurements was high (intraclass correlation coefficient 0.93 (95% CI 0.79-0.98) [32]. In hip arthritis maximal absolute enhancement (ME) was correlated with limitation of motion (rs=0.69, p<0.05), in wrist arthritis, rate of early enhancement highly correlatted with wrist swelling (Rs =0.72) and moderately correlated with pain intensity (Rs=0.6) [9], and the presence of MRI-based synovitis was independently and significantly associated with onset of JIA (RR 3.16, 95%CI 1.56-6.39) [4].

In TMJ assessment, MRI abnormalities revealed significant association with clinical signs of TMJ examination but not with symptoms [18], no association found between pain on TMJ palpation or crepitation and intense contrast enhancement of TMJ, with the latter being associated with disease activity [11, 30, 49]; and the maximal incisal opening (MIO) and deviation on opening were the only physical findings significantly associated with synovitis on MRI [33]. An enhancement ratio threshold of 1.55 had 91% sensitivity and 96% specificity for detecting synovitis by MRI of TMJ [34]. 25% of patients without clinical signs on TMJ examination had MRI abnormalities [38]. The MRI of TMJ's SI ratio of 0.9 was the best discriminating threshold, which, however, corresponded only to a moderate specificity of 0.70 and a sensitivity of 0.77 [13]. In diagnostic assessment of the early TMJ arthritis, the contrast-enhanced MRI is a more reliable method [17]. The analysis of MRI TMJ with contrast revealed that for abnormal condyle and flattened articular eminence, independent predictors were type of JIA, age at onset, and duration of disease activity. Pannus was present with probability >0.5 when the disease started before 4 years of age [40]. Inclusion of MCP joints produced better inter-reader agreement for the extended score (ICC 0.86) and accurate assessment of disease activity and treatment efficacy [14]. A preliminary scoring system weighted for degree of acute and chronic TMJ arthritis MRI findings was found to have substantial inter- and intra-reader reliability [15]. In MRI assessment of the hip VAS, PGA and ESR were significantly correlated with MRI score [37].

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Changes of MRI of the knee during follow up in synovial hypertrophy scores correlated moderately with changes observed in the PGA of overall disease activity score (Rs = 0.45) [35]. The correlation coefficients of clinical and 3D MRI scores of the knee were found to be 0.50 at 1-3 months and 0.70 at 3-6 months [39]. In assessment of pre and post contrast Knee MRI synovial hypertrophy, specificity of unenhanced MRI (−Gd) was high (0.97), but the sensitivity of was low 0.62 [42]. In one study, the sensitivity and specificity of MRI of the knee were 93.5% and 92.5%, respectively [44]. Positive clinical examination was associated with higher MR grades, negative clinical examination was associated with lower MR grades [46]. The MRI without contrast in assessment of synovial proliferation enhancement of knee joints underestimates cartilage thickness, loculation of effusion and pannus as compared to MRI with contrast [20]. In MRI of the knee, the ICC inter-reader realiability was best for synovial thickening, joint effusion, synovial enhancement, and bone marrow changes, moderate for cartilage lesions and bone erosions, and low for enthesopathy [22]. In assessment of early sacroilitis, MRI had higher sensitivity and lower specificity detecting inflammation, and low sensitivity and high specificity in detection of structural damage [50].

Quality of evidence across all critical outcomes: Very low

Table 3. Studies of MRI

Ref ID, Author, year	Study type	Duration	Population Description	Assessment given to relevant population	Results
663 Nistala, 2006 [1]	Single-arm study	N/A	34 JIA patients with established disease	clinical assessment vs magnetic resonance imaging (MRI)	Clinical assessment had a sensitivity of 25.7% and specificity of 91% for detecting MRI diagnosed arthritis. Agreement between MRI activity and clinical assessment was fair in cases with arthritis less than 4 years from diagnosis (k score 0.38, P = 0.045). There was no agreement in longer standing disease (k score 0.02, P = 0.62). Concordance between clinician and MRI result was highest in undamaged hips with agreement in 11 out of 18 cases. This worsened with increasing damage score (chi^2 trend = 5.18, 1 df, P = 0.023) and in hips with a damage score of 3, there was agreement in only 4 of 16 cases.
3303 Koos, 2014 [2]	Cross-sectional study	3 months	134 JIA patients	Clinical and gadolinium-enhanced-MRI examinations of TMJ	TMJ arthritis was diagnosed by Gd-MRI in 80% of the 134 patients with JIA, with 25% exhibiting symptoms of unilateral and 55% bilateral TMJ arthritis. Cohen's κ for the interrater reliability of the MRI-based diagnosis of TMJ arthritis was 0.74.

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					Combined clinical exam had sensitivity 0.85, specificity 0.54. Combined clinical exam's false-positive rate was 0.46, false-negative rate was 0.15.
840, Hemke, 2013 [3]	Prospective observational	n/a	146 JIA patients with current or history of knee involvement	Contrast-enhanced knee MRI obtained with open bore 1T scanner, knee coil scored using JAMRIS (juvenile arthritis MRI scoring) system.	Synovial hypertrophy score differed significantly between clinically active and inactive patients (p=0.016). Synovial hypertrophy correlated moderately with physician global score (r_s=0.410, p<0.001) No significant differences in bone marrow changes, cartilage lesions or bone erosions between clinically active and inactive patients. **Synovial hypertrophy was present in 14/39 (35.9%) clinically inactive patients.
841, Hemke, 2015 [4]	Prospective observational	n/a	80 treatment-naïve patients with clinically suspected JIA and active arthritis of at least one knee. 44 (55%) were ultimately diagnosed with JIA.	Contrast-enhanced knee MRI obtained with open bore 1T scanner, knee coil, scored using JAMRIS (juvenile arthritis MRI scoring) system.	Synovial hypertrophy was present in 61.4% of JIA patients and 19.4% of non-JIA patients (p<0.001). Synovitis on MRI was one of five factors identified by univariate analysis as potentially associated with onset of JIA (OR 6.58, 95%CI 2.36-18.33) (other factors clinical or laboratory). Multivariate analysis showed the presence of MRI-based synovitis to be independently and significantly associated with onset of JIA (RR 3.16, 95%CI 1.56-6.39)
842, Nusman, 2015 [5]	Prospective observational	n/a	25 children with clinically active JIA and 25 age/sex matched IBD patients without history of joint symptoms or	Contrast-enhanced knee MRI, scored using JAMRIS (juvenile arthritis MRI scoring) system.	Enhanced thickening (at least 2 mm) of the synovium on at least 1 of the defined JIA-associated JAMRIS locations was present in 64% of JIA pts and 52% of controls. 36% of active JIA patients had no synovial thickening on MRI (JAMRIS score 0).

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Ref ID, Author, year	Study type	Duration	Population Description	Assessment given to relevant population	Results
			clinical evidence of joint inflammation		JAMRIS score differed significantly at 2 locations between active JIA and control patients: infrapatellar (p=0.011) and cruciate ligaments (p=0.007)
1082, Nusman, 2014 [6]	Cross sectional cohort	n/a	153 clinically active JIA patients	Contrast-enhanced MRI of the knee or wrist performed using open-bore 1.5T scanner. Images were scored using the JAMRIS system.	23.6% of patients with clinical evidence of knee arthritis and 16.3% with clinical wrist arthritis had no abnormalities on MRI.
1085, Brown, 2012 [7]	Cross sectional cohort	n/a	11 JIA patients with previous hand/wrist involvement in clinical remission for at least 6 months.	Contrast-enhanced MRI of the hand/wrist performed on 3T scanner. Images were scored using a modified RAMRIS system.	63% of patients in clinical remission had an abnormality on MRI: synovitis (5), bone marrow lesions (3), tenosynovitis (6), some with multiple findings.
1113, Nusman 2017 [8]	Prospective observational	2 years	32 JIA patients with clinically inactive disease	Contrast-enhanced knee MRI performed on open-bore 1T scanner with dynamic contrast enhanced (DCE) sequences. Images scored using JAMRIS system.	<u>Findings in clinically inactive patients:</u> 39.4% had synovial hypertrophy score ≥1, 30.3% bone marrow changes score ≥1, 6.1% cartilage lesions score ≥1, 3% bone erosion score ≥1. <u>MRI predictors of flare:</u> - 12/32 (37.5%) flared, at a median time of 0.68 mos. - None of the JAMRIS features (synovial hypertrophy, bone marrow edema, cartilage lesions, bone erosions) were significantly different in patients who flared than those who did not (p=0.2-0.87) - Maximum enhancement (ME) on DCE-MRI was significantly different between the 2 groups (P=0.05), though this did not meet significance when corrected for multiple testing.
1114, Malattia, 2009 [9]	Cross-sectional cohort	n/a	22 JIA patients with active wrist (12) or hip (10) arthritis	Contrast-enhanced wrist or hip MRI performed on 1.5T scanner, with 3D FFE dynamic sequences acquired before	<u>Assessment of DCE-MRI measurements as markers of disease activity:</u> - In wrist arthritis, rate of early enhancement (REE) highly correlated with wrist swelling (r_s=0.72, p<0.02) and

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				and after contrast administration.	moderately correlated with pain intensity (r_s=0.63, p<0.05) and CHAQ (r_s=0.6, p<0.05). - In hip arthritis, maximal absolute enhancement (ME) correlated with limitation of motion (r_s=0.69, p<0.05). - Semiquantitative synovial enhancement score from static MRI images correlated with maximum rate of enhancement (MV) in wrist arthritis (r_s=0.63, p<0.05) and ME in hip arthritis (r_s=0.68, p<0.05).
644, Koos, 2013 [10]	Retrospective cohort study	Unclear	23 patients with JIA, 23 matched controls	Underwent contrast enhanced MRI or cone beam CT scan (CBCT)	78% of TMJs in control group were considered normal; 83% of the TMJs in the JIA group showed severe changes; difference between TMJ arthritis in control and JIA group was highly significant p<0.0001 Paper devises a scoring method for assessing TMJ arthritis that can be used with MRI and CBCT but does not compare them head to head
268, Zwir, 2015 [11]	Prospective single arm cohort study	1 year	75 patients with JIA per ILAR criteria who completed the study; 39 oligoJIA, 31 poly JIA, 5 sJIA patients divided into active disease (33 patients at 1st eval, 21 at 2nd) vs clinical remission on meds (21 patients at 1st eval, 28 at 2nd) vs clinical remission off of medication (21	Patients examined at outset (1st eval) and 1 year later (2nd eval) Gadolinium enhanced MRI (enhancement quantified as mild, moderate or intense; intense defined as enhancement surrounding the mandibular condyle of more than 180 degrees in the sagittal or coronal plane) and clinical exam by pediatric rheumatologist and dentist; underwent 2 evaluations	At 1st eval, 28 (37.3%) of patients reported symptoms, at 2nd eval 11 (14.7%) reported symptoms. Synovial enhancement was present in 70 (93.3%) of patients at 1st eval compared with 65 (86.7%) at 2nd eval. Synovial enhancement was significantly associated with altered condylar shape at both evaluations (p=0.007 and p=0.003). When synovial enhancement quantified, intense enhancement was present in 26 (34.7%) at 1st eval and 25 (33.3%) at the 2nd eval. It was also significantly associated with disease activity at the 1st eval (p=0.0008) and with the poly/systemic subtypes at both evaluations (p=0.028, p=0.049). When synovial enhancement quantified, intense enhancement was significantly associated with the presence of erosions at both evaluations (p=0.0001 and p< 0.0001) and

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			patients at 1st eval, 26 at 2nd)		with altered condylar shape at the second evaluation (p=0.0005). No association found between pain on TMJ palpation or crepitation and intense contrast enhancement. A significant association was found with a mouth opening < 40 mm and intense enhancement at both the 1st and 2nd eval (p=0.013 and p=0.0017). Intense contrast enhancement of the TMJ was significantly associated with disease activity (p< 0.001).
1115 Nusman et.al. 2016 [12]	Prospective, cohort	March 2012-July 2013,	32 children with JIA Age 8.2-17.9. 6 (19%) persistent OJIA, 4 (13%) extended OJIA, 15 (47%) polyarthritis RF (-), 2 (6%) polyarticular RF(+), 2 (6%) PsA, 2 (6%) enthesitis-related arthritis 1 (3%) undifferentiated arthritis.	Wrist MRI: All patients either had current wrist involvement (clinically active) or previous wrist involvement (clinically inactive).	The conventional descriptive measure maximum enhancement differed significantly between clinically active and inactive disease (P = 0.019), whereas time-intensity-curve shape analysis showed no differences. Juvenile Arthritis Disease Activity Score correlated moderately with enhancing volume (P= 0.484).
1124, von Kalle et.al. 2014 [13]	Retrospective review	In January 2011, so exams from 12/2005-1/2011	50 patients with JIA (40 females, 10 males) referred for MRI of TMJ	MRI of TMJ	Degree of contrast enhancement alone did not allow a clear differentiation between joints with and without inflammation in dynamic contrast-enhanced MR

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			(if multiple MRIs included the initial one) 100 dynamic contrast-enhanced MRI studies of 46 children (non-inflammatory) controls		Mean values and the number of abnormally high SI ratios of morphologically normal and abnormal joints of JIA patients were, at 6 min post-contrast, significantly higher than in the reference cohort. only 10 of the 39 (26%) joints with abnormally thick or irregular contrast enhancement had an SI ratio above 1.23, which is an enhancement above 2 SD of the reference group. 74% of the TMJs with signs of thickening of the joint tissue SI ratios remained within the range of the reference group. The ROC curve indicated the SI ratio of 0.9 as the best discriminating threshold, which, however, corresponded only to a moderate specificity of 0.70 and a sensitivity of 0.77. Signal intensity ratios of morphologically normal joints of patients with JIA were most variable. Their reference interval widely overlapped with the SI ratios of both the normal and the arthritic joints
1184 van Dijkhuizen et.al. 2018 [14]	Retrospective review	MRI examinations were performed between June 2006 and June 2008.	Seventy patients with JIA who had previously participated in observational studies. MRI after a median of 1.2 years follow-up was available for 38 patients.	Wrist MRI of 70 patients with JIA were scored by 3 independent readers and an extended score including the MCP joints	The inter-reader agreement was moderate for the original score (ICC 0.77; 95% CI 0.68–0.84) and good for the extended score (ICC 0.86; 95% CI 0.80–0.91). Using 95% LOA, the aggregate score variability was less favorable with relatively wide LOA. Weighted Cohen's k of the individual joints indicated good agreement for the original score and good to excellent agreement for the extended score. Correlations with clinical variables reflecting disease activity improved for the extended score and its SRM was higher compared to that of the original score. Inclusion of MCP joints should be considered for a more accurate assessment of disease activity and treatment efficacy in JIA.

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1767 Vaid et.al. 2014 [15]	Retrospective review	N/A	TMJ MRIs representative of acute and chronic TMJ arthritis in JIA (>500 TMJ MRI studies annually at Children's of Alabama). Computed tomography scans depicting select bony changes (osteophyte formation, micrognathia).	Evaluation of MRI/CT of TMJs	Compiled an atlas of radiographic images of the temporomandibular joint (TMJ) in children with juvenile idiopathic arthritis (JIA). A preliminary scoring system weighted for degree of acute and chronic TMJ arthritis MRI findings was found to have substantial inter- and intra-reader reliability.
1853 Hemke et.al. 2012 [16]	Prospective observational	11/2007-10/2008	47 children: 94 sets of MR images from 47 children with JIA Group 1 (active JIA) 58 knees Group 2 (inactive JIA) 36 knees	MRI of knees without contrast	Reproducibility of scoring method: Cohen kappa **Synovial hypertrophy 0.76** Cartilage lesions 0.73 Bone erosions 0.92 Bone marrow changes 0.80 **Infrapatellar fat pad heterogeneity 0.75** – Water 0.96 – Scar tissue 0.83 Effusion 0.85 Tendinopathy/internal derangement 0.49 Popliteal lymph nodes 0.85 **MRI showed synovial hypertrophy suggestive of inflammation in 33% of the children with clinically inactive JIA**
2017 Keller et. al.	Prospective cohort	March 2006 and October 2008	76 JIA pts	I-MRI of the TMJs reviewed by two paediatric radiologists II. Rheum exams by peds rheum	Clinical findings in affected TMJs are correlated with structural damage only. Clinical assessment of TMJs does not allow accurate diagnosis of early arthritis and will still depend on contrast-enhanced MRI.

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2015 [17]				III.Orthodontic examination by an orthodontist	
2094 Mohammed et. al. 2012 [18]	Case control (please check this – not sure)	N/A	40 pts with JIA: oligo, poly, SJIA,26 girls/14 boys). Age 8.5 to 17. 10 control subjects	clinical and post contrast magnetic resonance imaging (MRI) examinations for TMJs.	The clinical symptoms and signs of TMJ arthritis were detected in 35% and 62.5% of JIA cases, respectively. TMJ disease was observed in 80% of patients using contrast-enhanced MRI. The mean total MRI score was significantly higher in patients with active disease compared to those without activity. Patients with systemic and polyarticular JIA showed significant increase in the mean of synovial enhancement, effusion and total MRI scores compared to those with the oligoarticular type. MRI abnormalities revealed significant association with clinical signs of TMJ examination but not with symptoms. Synovial enhancement score showed significant positive correlation with disease activity score and C-reactive protein as a marker of inflammation.
2125 Van Gulik et. al. 2018 [19]	Prospective cohort	12/2008-12/2014	52 clinically inactive JIA patients (median age 13.3 years, 63.5% girls) who underwent MRI of the knee 2 groups based on MRI: 1-w/synovial thickening on MRI; 2-no synovial thickening on MRI.	MRI of knee with contrast	Synovial thickening on MRI was present in 18 clinically inactive patients (group 1, 34.6%). The age was significantly lower for the patients in group 1 (median 10.7 versus 14.4, P=0.008). No significant differences were observed in any of the other patient characteristics nor the disease activity parameters tested. In more than one-third of children with clinically inactive disease: MRI of the knee showed synovial thickening.

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2178 Herve-Somma et. al. 1992 [20]	Prospective cohort	Can't tell, published 1992	24 knees in 24 pts with "JRA" 17 female, 7 male 3-18 years	MRI with and without contrast	Enhancement of synovial proliferation was present in 23/24 knee with contrast versus without contrast where cartilage thickness, loculation of effusion and pannus were underestimated
2190 Yulish et. al. 1987 [21]	prospective cohort	Can't tell, published 1987	15 children with "JRA", 10 girls, 5 boys, 6-18 yo (pauci, poly, systemic). 33 joints examined: 19 knees, 3 wrists, 6 hips,4 ankles, 1 elbow	MRI T1/T2 Xray of multiple different joints	Synovial hypertrophy in 13 joints, probable abnml articular cartilage in10 joints, MR showed epiphyseal overgrowth, bone erosions, joint effusions, joint narrowing
2369 Hemke, 2017 [22]	Cohort Study	Not clearly stated	25 Juvenile Idiopathic Arthritis pts with knee involvement	4 radiology readers scored MRI's of the Knee	ICC inter-reader reliability ranged from 0.33 (95% CI 0.12–0.52, SDD = 0.29) for enthesopathy up to 0.95 (95% CI 0.92–0.97, SDD = 3.19) for synovial thickening. Good inter-reader reliability found for joint effusion (ICC 0.93, 95% CI 0.89–0.95, SDD = 0.51), synovial enhancement (ICC 0.90, 95% CI 0.85–0.94, SDD = 9.85), and bone marrow changes (ICC 0.87, 95% CI 0.80–0.92, SDD = 10.94). Moderate to substantial reliability was found concerning cartilage lesions and bone erosions (ICC 0.55–0.72, SDD 1.41–13.65).
2371 Lochbuhler, 2015 [23]	Cohort Study	5 years	33 pts with Juvenile Idiopathic Arthritis with TMJ involvement	MRI Assessment of Temporomandibular Joint Involvement and Mandibular Growth Following triamcinolone hexacetonide Injection: 156 injections, up to 3 times per joint	Repetitive corticosteroid injection to the TMJ decreased bone marrow edema, synovial hyperplasia, and contrast enhancement but does not prevent progressive osseous deformation or normalize mandibular ramus growth.
2374 Stoll,	Cohort Study	1 year	33 JIA pts with refractory TMJ arthritis (oligo,	MRI Findings following Intraarticular Infliximab	Per MRI scoring system 17 subjects had worsening of acute findings compared with 3 net unchanged and 13

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2015 [24]			poly RF+ and RF-, psoriatic, and ERA)	Therapy into the Temporomandibular Joint	improved. For chronic findings: 24 worsened, 4 unchanged, and 5 improved. In 10/66 TMJ, there were no chronic changes at baseline; of those, 7 were absent of chronic changes at follow up. The remaining 3 TMJ had active arthritis in the interim.
2375 Gardner-Medwin, 2006 [25]	Case series	3.8 years	10 JIA pts with monoarthritis and 1 unaffected knee	MRI in clinically unaffected knees done to evaluate for subclinical arthritis in children with monoarthritis	5/10 had abnormal knee MRI's and normal clinical exams at start. 3/10 developed clinical features in the previously normal knee 4–11 months after MRI identified small joint effusions, synovial hypertrophy, and lymph node enhancement.
2380 Abramowicz, 2011 [26]	Cohort study	4 years	48 JIA (poly, oligo, psoriatic) patients	MRI of temporomandibular joints in children with JIA	48 patients (96 joints) with MRI scans, 2 (4 joints) had normal MRI findings and 46 (92 joints) had abnormal MRI findings. Of these 46 patients, 13 had abnormal findings for 1 of their TMJs and 33 had bilateral abnormal findings. Bilateral synovial enhancement and bilateral condylar head articular surface flattening were more common in oligo and poly JIA than in juvenile psoriatic arthritis.
2535 Taylor, 1993 [27]	Cohort study	Unclear	15 JRA (pauci, poly, and systemic) pts	MRI evaluation of the temporomandibular joint in juvenile rheumatoid arthritis	Abnormalities were found in 21 joints: articular disc thinning, flattening, abnormal signal, perforation, anterior dislocation, Thinning was the most common finding (18), while abnormal ROM was found in 21/27 joints. 20 joints had reduced ROM-3 of those were locked.
2546 Davis, 2011 [28]	Cohort study	Unclear	26 Pts with JRA	MRI evaluation of the temporomandibular joints in juvenile rheumatoid arthritis	Abnormal condyles in 49%. Abnormal translation was seen in 71% and pannus in 49%. Erosions were seen in 37%, effusions in 24% and contrast enhancement in 50%. 3/5 asymptomatic patients had abnormal translation. 15 patients with joint asymmetry on clinical examination showed abnormal translation on MRI.
2551 Ording Muller, 2013 [29]	Cohort study	Unclear	85 healthy children were compared with 68 Pts with JIA	MRI of the wrist in juvenile idiopathic arthritis compared with healthy children	The wrist was significantly smaller in children with JIA ($P < 0.001$), but otherwise no significant difference in the number of bony depressions in the carpal bones between groups.

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2553 Ma, 2015 [30]	Cohort study	N/A	67 Pts with JIA (oligo, poly, systemic, psoriatic, ERA) compared against 24 non-rheumatologic children	MRI features compared between normal and mild temporomandibular joint involvement in juvenile idiopathic arthritis	Mean enhancement ratio values were highest in the moderate/severe group (P < 0.0001)-significantly different between the TMJs without active disease and those with mild and moderate/severe synovial enhancement. Similar findings were seen for condylar enhancement with P < 0.005. Relative signal intensity change was unable to differentiate TMJs with mild synovitis from the two controls (P > 0.10). 27/60 (45 %) TMJs without active disease had osteochondral changes. 8/40 (20 %) TMJs in the mild group did not demonstrate any synovial thickening.
2649 van Gulik et al. 2018 [31]	Cohort, single arm study	N/A	72 clinically active JIA, two groups based on presence or absence of synovial thickening on MRI: Group 1: 47 patients (65.3%) with a JAMRIS synovial hypertrophy score of ≥1 and Group 2: 25 patients (34.7%) with a JAMRIS synovial hypertrophy score of 0.	Contrast enhanced MRI of the knee	Group 2 (MRI inactive): older at the date of examination (median age of 13.2 IQR 11.3–15.6 vs median age 10.9 IQR 8.6–13.7) and at the moment of disease onset (median age 10.0 IQR 3.5–12.0 vs 8.0 IQR 3.0–10.0). Group 2 had significantly fewer patients with an oligoarticular JIA (34% vs. 72%, p = 0.001) and significantly more patients with a polyarticular subtype (p = 0.003). Between both groups, no significant difference (p = 0.783) found in the number of patients who were treatment-naïve (14 vs. 6 in group 1 and 2 respectively) or had relapse/smoldering disease (33 vs. 19 in group 1 and 2 respectively). Time between clinical assessment and MRI and other clinical parameters were not significantly different between both groups.
2652 Malattia et al. 2012 [32]	Cross sectional	N/A	78 JIA with active wrist arthritis	Wrist MRI – testing MRI automated method [normalized synovial volume (NSV)] for JIA monitoring	The agreement between the automated estimation of NSV and the manual measurements was excellent (intraclass correlation coefficient 0.93, 95% confidence interval 0.79-0.98). NSV showed a strong responsiveness to clinical change (standardized response mean values >1) and satisfactory

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					discriminant validity. ACR Pedi 70 responders showed a significantly higher decrease in NSV compared to patients who met the ACR Pedi 30 and 50 criteria (P 0.02) and compared to non-responders (P 0.002). The RAMRIS synovitis score did not discriminate among different ACR Pedi categories Predictive value. High baseline NSV (>4.6) had high predictive value (100%) with respect to erosive progression.
2918 Abramowicz et al. 2013 [33]	Cross sectional	N/A	51 JIA, 43 included, 27 dx with TMJ arthritis	MRI TMJ with contrast	The age-adjusted limited maximal incisal opening (MIO) and deviation on opening were the only physical findings significantly associated with synovitis on MRI (P = .003 and P = .043, respectively) Limited MIO and deviation on opening had a high specificity (86% and 94%, respectively). Patients with a limited MIO were 6.7 times more likely to have synovitis than those with a normal MIO. All patients with a limited MIO and deviation on opening had TMJ synovitis on the MRI scan.
3156 Resnick et al. 2016 [34]	Case-control	N/A	187 JIA TMJ, 142 control TMJ	MRI TMJ with contrast An enhancement ratio (ER) was calculated according to the following equation: ER = Average TMJ synovial pixel intensity/Longus capitis pixel intensity	The mean ER in the JIA group was 2.52 ± 0.79, and that in the control group was 1.28 ± 0.16 (P <0.001). Males in the JIA group had a higher ER than females (P = 0.045). An ER threshold of 1.55 had a sensitivity and specificity for detecting synovitis of 91% and 96%, respectively.
2702 Hemke et al. 2013 [35]	Cohort	2 years (duration of study) Follow up period 1.3 years	40 JIA 13 (32.5%) newly diagnosed with JIA and 27 (67.5%) with relapsing or unremitting disease	MRI Knee contrast enhanced	Clinically improved patients with JIA showed statistically significant changes in synovial hypertrophy scores as compared with the clinically unimproved patients (–1.52 vs 1.67, respectively; p = 0.004). No statistically significant differences were observed regarding changes in bone marrow, cartilage lesion, and bone erosion scores between clinically improved and unimproved patients

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			11 (27.5%) persistent oligoarthritis, 8 (20.0%) extended oligoarthritis, 17 (42.5%) rheumatoid factor (RF)-negative polyarthritis		Change or intensification of treatment after the first MRI was observed in 85.2% (23/27) of the clinically improved patients (ACR-Ped50) Changes during follow up in synovial hypertrophy scores correlated moderately with changes observed in the PGA of overall disease activity score (Rs = 0.45, p = 0.002).
3160 Workie et al. 2007 [36]	cohort	12 months	17 JIA patients	dynamic contrast-enhanced MRI (DCE-MRI) of Knee	All of the clinical and laboratory measures (median values) showed a significant decrease during the study period (P<0.05), except CHAQ-DI and CRP at 3 months. The PK parameters, synovial volumes, and clinical and laboratory measures decreased from enrollment to 3 months and to 12 months in the majority of children The following parameters were correlated between baseline and 12 months: Ktrans':PGA (rho=0.80, P=0.003), Ktrans':TAJ (rho=0.76, P=0.006), kep:PGA (rho=0.72, P=0.012), and synovial volume:TAJ (rho=−0.51, P=0.04).
3440 El-Azeem et al. 2012 [37]	cohort	2 years (duration of study)	30 JIA patients	MRI Hips bilateral with contrast	MRI of hips was abnormal in 12/30 (40%) patients: 2/8 (25%) of oligoarticular group, 4/13 (30.8%) of polyarticular group, 5/7 (71.4%) of systemic onset group and 1/2(50%) of enthesitis related group. Comparing mean values of MR score of the four clinical subsets showed significant difference (p < 0.001). Patients with active disease showed higher MR score (3.7 ± 1.5) than those with inactive disease (2.1 ± .9) [p < 0.002]. Presence of effusion and gadolinium enhancement were significantly higher in active hips (p < 0.01 and p < 0.001 respectively). VAS– PGA and ESR were significantly correlated with MRI score (p < 0.02 and <0.05 respectively).
3580	Case-control	N/A	20 JIA (80 % had TMJ	TMJ MRI and serum S100A12 level	Contrast enhanced MRI was done for 20 patients (40 TMJs): 16 patients (80%) showed MRI abnormalities while 4 patients

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Abdul-Aziez et al. 2010 [38]			arthritis), 10 healthy controls JIA: 3 (15%) with SoJIA ; 3 (15%) oligo-JIA and 14 (70%) poly- JIA.		had no MRI findings. The mean total score for MRI among JIA patients was 5.05±4.21. Synovial enhancement was detected in 16 patients (80%), 31 TMJs (77.5%) with a mean score 2.60±1.60; joint effusion was present in 13 patients (65%), 19 TMJs (47.5%) with a mean score 1.40±1.46. mean value of Maximal Interincisal Opening was significantly decreased in patients versus controls. mean serum levels of S100A12 showed significant increase among JIA patients compared to controls (p<0.001). Serum levels of S100A12 showed a significant positive correlation with disease activity score, pain score, ESR, CRP serum levels, synovial enhancement score and total MRI score.
3595 Cakmakci et al. 2001 [39]	Longitudinal cohort	6 months	JIA 42 knees of 21 patients	Fat-Sat 3D MRI Knee	Correlation coefficients according to progression, improvement and equivalent findings of months 1-3 and months 3-6 comparison of clinical and MRI scores were found to be 0.50 and 0.70, respectively. Synovial hypertrophy was found to be the main determinant of pain on first- and third-month evaluations (r=o.68 and 0.74 respectively)
3838 Argyropoulou et al. 2008 [40]	Cohort	N/A	46 JIA (88 TMJ) 18 oligo JIA, 17 poly JIA; 11 SoJIA with polyarticular course	MRI TMJ with contrast (contrast given for all except for 1 patient with contrast allergy)	Abnormal condyle in 32%, flattened articular eminence in 27%, flattened articular disk in 17%, intra-articular fluid in 10%, enhancing pannus in 45% restricted condylar motion in 9%. Logistic regression analysis revealed that for abnormal condyle and flattened articular eminence, independent predictors were type of JIA (P < 0.015), age at onset (P < 0.038), and duration of disease activity (P < 0.001). Pannus was present with probability >0.5 when the disease started before 4 years of age
3842	Case - control	N/A	18 adolescents (15 females,	contrast enhanced TMJ MRI	In the ADD group, 31 of 36 disks were displaced. In total, 28 of 31 displaced disks showed thickening of the bilaminar zone.

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Kellenberger et al. 2018 [41]			mean age 15.1 ± 1.9 years) with ADD and age- and gender-matched patients with JIA		In JIA patients, the disks were mainly flattened (19/36), centrally perforated (12/36) and/or anteriorly displaced (2/36). 19 of 31 TMJs with ADD showed various degrees of inflammation, with joint effusion, synovial thickening and joint enhancement not significantly different from JIA patients. Osseous deformity was present in 27 of 31 TMJs with ADD, with frequent erosions in both groups (ADD 25/31; JIA 32/36, P = 0.55) but lower grades of condylar and temporal bone flattening than in JIA (P ≤ 0.001). Glenoid fossa depth was preserved in 28 of 31 joints with ADD and decreased in 26 of 36 joints with JIA (P < 0.0001). Mandibular ramus height was decreased in both groups.
1013 Hemke et al. 2013 [42]	Single arm cohort	2 years	73 JIA patients: 17 (23.3 %) persistent OJIA, 13 (17.8 %) extended OJIA, 27 (37.0 %) RF- polyarthritis, 1 (1.4 %) RF+ polyarthritis, 1 (1.4 %) SJIA, 2 (2.7 %) PsA, 10 (13.7 %) enthesitis-related arthritis and 2 (2.7 %) undifferentiated JIA	Pre and post contrast Knee MRI	Agreement between Gd-enhanced (+Gd) and Gd-Unenhanced (−Gd) MRI scores of bone marrow changes, cartilage lesions and bone erosions were good concerning sensitivity, specificity, negative predictive value and positive predictive value. Inter-observer agreement was good for both −Gd and +Gd scores (ICC=0.91–1.00, 0.93–1.00, respectively). Regarding the assessment of synovial hypertrophy, specificity of −Gd was high (0.97), but the sensitivity of unenhanced MRI was only 0.62. Inter-reader agreement for +Gd MRI was ICC=0.94; however, omitting post-Gd acquisitions increased inter-reader variation (ICC=0.86) Omitting intravenous contrast medium decreases the reliability of synovial hypertrophy scores.
1129 Johnson et al.	Single arm cohort	N/A	11 JIA	MRI knee (contrast enhanced in 9 patients) Obtained mean 2 months after disease onset	Synovial hypertrophy, joint effusions, popliteal lymph nodes and soft tissue swelling were present in all patients. Gadolinium DTPA enhancement improved the detection of synovial hyperplasia.

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2002 [43]					Metaphyseal splaying and condylar overgrowth were seen in five cases (41%) Edema of the lateral collateral ligament in two cases (18%) and superficial cartilage thinning in one case. Bony erosions and deep cartilage destruction were not demonstrated.
2209 Uhl et al. 2001 [44]	Case-control	N/A	40 JIA 40 control painful knee joints (MR diagnosis: bone bruise of the knee (7), normal knee joint (12), osteomyelitis (6), septic arthritis (2), bone tumor (7) and misc bone lesions (6)	Knee MRI: 1.5 T Receiver operating characteristic (ROC) curves evaluation was conducted by 5 independent radiologists.	The positive criteria for diagnosing JIA were joint effusions (n=.40), contrast-enhancing synovitis (n=39), cartilage lesions (n=15), subchondral erosions and bony destruction (n=1). Sensitivity and specificity were 93.5% and 92.5%, respectively. Two cases of septic arthritis were misdiagnosed as JIA by all radiologists.
2422 Rieter et al. 2016 [45]	Single arm cohort	N/A	34 children, 20 (58.8%) had oligo-arthritis, 9 (26.5%) had polyarthritis and 5 (14.7%) had systemic arthritis.	Wrist MRI with contrast	Pathological contrast enhancement was seen in 100/170 (58.8%) in early postcontrast images vs. 131/170 (77.1%) based on late postcontrast images. 52/170 locations (30.6%) received a higher synovial enhancement-score based on the late post-contrast images as compared to the early post-contrast images. 60/170 (35.3%) locations received a higher total inflammation score based on the late post-contrast images. The mean scores of synovial enhancement and total inflammation were significantly higher when based on the late postcontrast images as compared to the early contrast images

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3441 Argyropoulou et al. 2002 [46]	Single arm cohort	N/A	28 JIA (mean age 12.5 years) (oligoarthritis 8, polyarthritis 13, systemic arthritis 7)	MRI hip plain and contrast enhanced MR grading score: grade 1=no contrast enhancement; grade 2=focal synovial contrast enhancement; grade 3=diffuse synovial contrast enhancement; grade 4=grade 3+diffuse synovial thickening; grade 5=grade 4+villonodular synovial thickening; and grade 6=grade 5+cartilage and subchondral bone erosions.	MRI was abnormal in 57.1% of cases (25% of oligoarthritis, 53.8% of polyarthritis and 100% of systemic arthritis). Clinical examination was positive in 32.1% of cases and was associated with higher MR grades (mean 4.6, SD 1.34) Negative clinical examination was associated with lower MR grades (mean 1.78, SD 1.13) (p,0.001). Patients with active disease (mean grade 3.9, SD 2) had higher MR grades than those with inactive disease (mean grade 2.1, SD 1.4) (p,0.01). The MR grades were different in the three clinical subtypes: oligoarticular (mean 1.5, SD 1.06); polyarticular (mean 2.38, SD 1.55); and systemic (mean 4.85, SD 1.21) (F:12.3, p,0.001), with a significant difference between systemic arthritis and oligoarthritis, and between systemic arthritis and polyarthritis (p,0.001).
4634 Barendregt, 2020 [**Error! Reference source not found.**]	Case series	N/A	13 children with JIA or suspected JIA.	3-tesla (T) knee MRI that included conventional sequences and a T1ρ sequence.	No structural cartilage damage and no differences in T(1ρ) between children with (n=7) and without (n=6) inflamed knees (37.8 ms vs. 31.7 ms, P=0.20). A moderate correlation between T(1ρ) values and the juvenile arthritis MRI synovitis score (r=0.59, P=0.04).
4578 Bernini, 2020 [47]	Case series	N/A	76 JIA patients with TMJ involvement	Facial asymmetry determined clinically or by morphometric analysis of three-dimensional (3D) photographs	Among 49/76 (64.5%) patients with negative asymmetrical osseous destruction on MRI, 26 (53%) had clinical gonion asymmetry, 11 (22%) had clinical chin assymetry, 16 (31%) had digital chin assymetry. Clinical gonion assymetry: sensitivity 70%, specificity 47%, PPV 42%, NPV 74%. Clinical chin assymetry: sensitivity 48%, specificity 78%, PPV 54%, NPV 73%. Digital chin assymetry: sensitivity 63%, specificity 67%, PPV 52%, NPV 77%.

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4500 Bollhalder, 2020 [**Error! Reference source not found.**]	Case series	3.6 years	38 patients with JIA with TMJ involvement	Clinical and MRI findings	Presence of TMJ pain did not correlate with MRI grades of inflammation or deformity. Both absolute values and centiles of MOC showed no correlation with MRI grades of inflammation or deformity.
4672 Weiss, 2020 [**Error! Reference source not found.**]	Case-series	N/A	120 JIA patients with sacroilitis	MRI in the assessment of early sacroiliitis	Local reports for inflammation: Sensitivity, 93.5% (95% CI: 78.6-99.2%), and specificity, 69.7% (95% CI: 59.0-79.0%), PPV 51.8% (95% CI: 38.0-65.3%). Local reports detecting structural damage: Sensitivity 45.7% (95% CI: 28.8-63.4%), specificity, 88.2% (95% CI: 79.4-94.2%); PPV 61.5% (95% CI: 40.6-79.8%).

References:

1. Nistala, K., Babar, J., Johnson, K., Campbell-Stokes, P., Foster, K., Ryder, C., & McDonagh, J. E. (2006). Clinical assessment and core outcome variables are poor predictors of hip arthritis diagnosed by MRI in juvenile idiopathic arthritis. Rheumatology (Oxford), 46(4), 699-702. doi:10.1093/rheumatology/kel401
2. Koos, B., Twilt, M., Kyank, U., Fischer-Brandies, H., Gassling, V., & Tzaribachev, N. (2014). Reliability of clinical symptoms in diagnosing temporomandibular joint arthritis in juvenile idiopathic arthritis. J Rheumatol, 41(9), 1871-1877. doi:10.3899/jrheum.131337
3. Hemke, R., Maas, M., Veenendaal, M. v., Dolman, K. M., Rossum, M. A. v., Berg, J. M. v. d., & Kuijpers, T. W. (2013). Contrast-enhanced MRI compared with the physical examination in the evaluation of disease activity in juvenile idiopathic arthritis. Eur Radiol, 24(2), 327-334. doi:10.1007/s00330-013-3036-2
4. Hemke, R., Kuijpers, T. W., Nusman, C. M., Schonenberg-Meinema, D., Rossum, M. A. v., Dolman, K. M., . . . Maas, M. (2015). Contrast-enhanced MRI features in the early diagnosis of Juvenile Idiopathic Arthritis. Eur Radiol, 25(11), 3222-3229. doi:10.1007/s00330-015-3752-x

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5. Nusman, C. M., Hemke, R., Benninga, M. A., Schonenberg-Meinema, D., Kindermann, A., Rossum, M. A. v., . . . Kuijpers, T. W. (2015). Contrast-enhanced MRI of the knee in children unaffected by clinical arthritis compared to clinically active juvenile idiopathic arthritis patients. Eur Radiol, 26(4), 1141-1148. doi:10.1007/s00330-015-3912-z
6. Nusman, C. M., Hemke, R., Schonenberg, D., Dolman, K. M., Rossum, M. A. v., Berg, J. M. v. d., . . . Maas, M. (2014). Distribution pattern of MRI abnormalities within the knee and wrist of juvenile idiopathic arthritis patients: signature of disease activity. AJR Am J Roentgenol, 202(5), W439-446. doi:10.2214/ajr.13.11314
7. Brown, A., Hirsch, R., Laor, T., Hannon, M. J., Levesque, M. C., Starz, T., . . . Kwoh, C. K. (2012). Do patients with juvenile idiopathic arthritis in clinical remission have evidence of persistent inflammation on 3T magnetic resonance imaging? Arthritis Care Res (Hoboken), 64(12), 1846-1854. doi:10.1002/acr.21774
8. Nusman, C. M., Hemke, R., Lavini, C., Schonenberg-Meinema, D., Rossum, M. A. v., Dolman, K. M., . . . Kuijpers, T. W. (2017). Dynamic contrast-enhanced magnetic resonance imaging can play a role in predicting flare in juvenile idiopathic arthritis. Eur J Radiol, 88, 77-81. doi:10.1016/j.ejrad.2017.01.003
9. Malattia, C., Damasio, M. B., Basso, C., Verri, A., Magnaguagno, F., Viola, S., . . . Martini, A. (2009). Dynamic contrast-enhanced magnetic resonance imaging in the assessment of disease activity in patients with juvenile idiopathic arthritis. Rheumatology (Oxford), 49(1), 178-185. doi:10.1093/rheumatology/kep343
10. Koos, B., Tzaribachev, N., Bott, S., Ciesielski, R., & Godt, A. (2013). Classification of temporomandibular joint erosion, arthritis, and inflammation in patients with juvenile idiopathic arthritis. J Orofac Orthop, 74(6), 506-519. doi:10.1007/s00056-013-0166-8
11. Zwir, L. M., Terreri, M. T., Sousa, S. A., Fernandes, A. R., Guimaraes, A. S., & Hilario, M. O. (2015). Are temporomandibular joint signs and symptoms associated with magnetic resonance imaging findings in juvenile idiopathic arthritis patients? A longitudinal study. Clin Rheumatol, 34(12), 2057-2063. doi:10.1007/s10067-015-2925-y
12. Nusman, C. M., Lavini, C., Hemke, R., Caan, M. W., Schonenberg-Meinema, D., Dolman, K. M., . . . Maas, M. (2016). Dynamic contrast-enhanced magnetic resonance imaging of the wrist in children with juvenile idiopathic arthritis. Pediatr Radiol, 47(2), 205-213. doi:10.1007/s00247-016-3736-2
13. Kalle, T. v., Stuber, T., Winkler, P., Maier, J., & Hospach, T. (2014). Early detection of temporomandibular joint arthritis in children with juvenile idiopathic arthritis - the role of contrast-enhanced MRI. Pediatr Radiol, 45(3), 402-410. doi:10.1007/s00247-014-3143-5
14. Dijkhuizen, E. H. P. v., Vanoni, F., Magnano, G. M., Magnaguagno, F., Rosendahl, K., Rossum, M. A. v., . . . Malattia, C. (2018). Effect of the Inclusion of the Metacarpophalangeal Joints on the Wrist Magnetic Resonance Imaging Scoring System in Juvenile Idiopathic Arthritis. J Rheumatol, 45(11), 1581-1587. doi:10.3899/jrheum.171246
15. Vaid, Y. N., Dunnavant, F. D., Royal, S. A., Beukelman, T., Stoll, M. L., & Cron, R. Q. (2013). Imaging of the temporomandibular joint in juvenile idiopathic arthritis. Arthritis Care Res (Hoboken), 66(1), 47-54. doi:10.1002/acr.22177
16. Hemke, R., Veenendaal, M. v., Kuijpers, T. W., Rossum, M. A. v., & Maas, M. (2012). Increasing feasibility and patient comfort of MRI in children with juvenile idiopathic arthritis. Pediatr Radiol, 42(4), 440-448. doi:10.1007/s00247-011-2306-x

For Peer Review Only

17. Keller, H., Muller, L. M., Markic, G., Schraner, T., Kellenberger, C. J., & Saurenmann, R. K. (2015). Is early TMJ involvement in children with juvenile idiopathic arthritis clinically detectable? Clinical examination of the TMJ in comparison with contrast enhanced MRI in patients with juvenile idiopathic arthritis. Pediatr Rheumatol Online J, 13, 56. doi:10.1186/s12969-015-0056-2
18. Mohammed, Y., Saeed, O., Zaghloul, N., Samer, S., Mahmud, S., & Abdulah, A. (2012). Juvenile idiopathic arthritis and the temporomandibular joint. Alexandria Journal of Medicine, 48(2), 123-129. doi:http://dx.doi.org/10.1016/j.ajme.2011.11.004
19. Gulik, E. C. v., Welsink-Karssies, M. M., Berg, J. M. v. d., Schonenberg-Meinema, D., Dolman, K. M., Barendregt, A. M., . . . Hemke, R. (2018). Juvenile idiopathic arthritis: magnetic resonance imaging of the clinically unaffected knee. Pediatr Radiol, 48(3), 333-340. doi:10.1007/s00247-017-4059-7
20. Herve-Somma, C. M., Sebag, G. H., Prieur, A. M., Bonnerot, V., & Lallemand, D. P. (1992). Juvenile rheumatoid arthritis of the knee: MR evaluation with Gd-DOTA. Radiology, 182(1), 93-98. doi:10.1148/radiology.182.1.1727317
21. Yulish, B. S., Lieberman, J. M., Newman, A. J., Bryan, P. J., Mulopulos, G. P., & Modic, M. T. (1987). Juvenile rheumatoid arthritis: assessment with MR imaging. Radiology, 165(1), 149-152. doi:10.1148/radiology.165.1.3628761
22. Hemke, R., Tzaribachev, N., Nusman, C. M., Rossum, M. A. J. v., Maas, M., & Doria, A. S. (2017). Magnetic Resonance Imaging (MRI) of the Knee as an Outcome Measure in Juvenile Idiopathic Arthritis: An OMERACT Reliability Study on MRI Scales. J Rheumatol, 44(8), 1224-1230. doi:10.3899/jrheum.160821
23. Lochbuhler, N., Saurenmann, R. K., Muller, L., & Kellenberger, C. J. (2015). Magnetic Resonance Imaging Assessment of Temporomandibular Joint Involvement and Mandibular Growth Following Corticosteroid Injection in Juvenile Idiopathic Arthritis. J Rheumatol, 42(8), 1514-1522. doi:10.3899/jrheum.141502
24. Stoll, M. L., Vaid, Y. N., Guleria, S., Beukelman, T., Waite, P. D., & Cron, R. Q. (2015). Magnetic Resonance Imaging Findings following Intraarticular Infliximab Therapy for Refractory Temporomandibular Joint Arthritis among Children with Juvenile Idiopathic Arthritis. J Rheumatol, 42(11), 2155-2159. doi:10.3899/jrheum.150308
25. Gardner-Medwin, J. M., Killeen, O. G., Ryder, C. A., Bradshaw, K., & Johnson, K. (2006). Magnetic resonance imaging identifies features in clinically unaffected knees predicting extension of arthritis in children with monoarthritis. J Rheumatol, 33(11), 2337-2343.
26. Abramowicz, S., Cheon, J. E., Kim, S., Bacic, J., & Lee, E. Y. (2011). Magnetic resonance imaging of temporomandibular joints in children with arthritis. J Oral Maxillofac Surg, 69(9), 2321-2328. doi:10.1016/j.joms.2010.12.058
27. Taylor, D. B., Babyn, P., Blaser, S., Smith, S., Shore, A., Silverman, E. D., . . . Laxer, R. M. (1993). MR evaluation of the temporomandibular joint in juvenile rheumatoid arthritis. J Comput Assist Tomogr, 17(3), 449-454.
28. Davis, M. A., & Castillo, M. (2011). MRI evaluation of the temporomandibular joints in juvenile rheumatoid arthritis: a retrospective review. Neuroradiol J, 24(6), 928-932. doi:10.1177/197140091102400618
29. Muller, L. S. O., Boavida, P., Avenarius, D., Damasio, B., Eldevik, O. P., Malattia, C., . . . Rosendahl, K. (2013). MRI of the wrist in juvenile idiopathic arthritis: erosions or normal variants? A prospective case-control study. Pediatr Radiol, 43(7), 785-795. doi:10.1007/s00247-012-2575-z

For Peer Review Only

30. Ma, G. M., Amirabadi, A., Inarejos, E., Tolend, M., Stimec, J., Moineddin, R., . . . Doria, A. S. (2015). MRI thresholds for discrimination between normal and mild temporomandibular joint involvement in juvenile idiopathic arthritis. Pediatr Rheumatol Online J, 13, 53. doi:10.1186/s12969-015-0051-7
31. Gulik, E. C. v., Hemke, R., Welsink-Karssies, M. M., Schonenberg-Meinema, D., Dolman, K. M., Barendregt, A. M., . . . Berg, J. M. v. d. (2018). Normal MRI findings of the knee in patients with clinically active juvenile idiopathic arthritis. Eur J Radiol, 102, 36-40. doi:10.1016/j.ejrad.2018.02.027
32. Malattia, C., Damasio, M. B., Basso, C., Santoro, M., Verri, A., Pederzoli, S., . . . Martini, A. (2012). Novel automated system for magnetic resonance imaging quantification of the inflamed synovial membrane volume in patients with juvenile idiopathic arthritis. Arthritis Care Res (Hoboken), 64(11), 1657-1664. doi:10.1002/acr.21739
33. Abramowicz, S., Susarla, H. K., Kim, S., & Kaban, L. B. (2013). Physical findings associated with active temporomandibular joint inflammation in children with juvenile idiopathic arthritis. J Oral Maxillofac Surg, 71(10), 1683-1687. doi:10.1016/j.joms.2013.04.009
34. Resnick, C. M., Vakilian, P. M., Breen, M., Zurakowski, D., Caruso, P., Henderson, L., . . . Peacock, Z. S. (2016). Quantifying Temporomandibular Joint Synovitis in Children With Juvenile Idiopathic Arthritis. Arthritis Care Res (Hoboken), 68(12), 1795-1802. doi:10.1002/acr.22911
35. Hemke, R., Veenendaal, M. v., Berg, J. M. v. d., Dolman, K. M., Rossum, M. A. v., Maas, M., & Kuijpers, T. W. (2013). One-year followup study on clinical findings and changes in magnetic resonance imaging-based disease activity scores in juvenile idiopathic arthritis. J Rheumatol, 41(1), 119-127. doi:10.3899/jrheum.130235
36. Workie, D. W., Graham, T. B., Laor, T., Rajagopal, A., Brien, K. J. O., Bommer, W. A., . . . Dardzinski, B. J. (2007). Quantitative MR characterization of disease activity in the knee in children with juvenile idiopathic arthritis: a longitudinal pilot study. Pediatr Radiol, 37(6), 535-543. doi:10.1007/s00247-007-0449-6
37. El-Azeem, M. I. A., Taha, H. A., & El-Sherif, A. M. (2012). Role of MRI in evaluation of hip joint involvement in juvenile idiopathic arthritis. Egyptian Rheumatologist, 34(2), 75-82. doi:http://dx.doi.org/10.1016/j.ejr.2012.03.001
38. Abdul-Aziez, O. A., Saber, N. Z., El-Bakry, S. A., Mohammad, A. A., Abdel-Maksud, S. S., & Ali, Y. (2010). Serum S100A12 and temporomandibular joint magnetic resonance imaging in juvenile idiopathic arthritis Egyptian patients: a case control study. Pak J Biol Sci, 13(3), 101-113.
39. Cakmakci, H., Kovanlikaya, A., & Unsal, E. (2001). Short-term follow-up of the juvenile rheumatoid knee with fat-saturated 3D MRI. Pediatr Radiol, 31(3), 189-195. doi:10.1007/s002470000371
40. Argyropoulou, M. I., Margariti, P. N., Karali, A., Astrakas, L., Alfandaki, S., Kosta, P., & Siamopoulou, A. (2008). Temporomandibular joint involvement in juvenile idiopathic arthritis: clinical predictors of magnetic resonance imaging signs. Eur Radiol, 19(3), 693-700. doi:10.1007/s00330-008-1196-2

For Peer Review Only

41. Kellenberger, C. J., Bucheli, J., Schroeder-Kohler, S., Saurenmann, R. K., Colombo, V., & Ettlin, D. A. (2018). Temporomandibular joint magnetic resonance imaging findings in adolescents with anterior disk displacement compared to those with juvenile idiopathic arthritis. J Oral Rehabil, 46(1), 14-22. doi:10.1111/joor.12720
42. Hemke, R., Kuijpers, T. W., Berg, J. M. v. d., Veenendaal, M. v., Dolman, K. M., Rossum, M. A. v., & Maas, M. (2013). The diagnostic accuracy of unenhanced MRI in the assessment of joint abnormalities in juvenile idiopathic arthritis. Eur Radiol, 23(7), 1998-2004. doi:10.1007/s00330-013-2770-9
43. Johnson, K., Wittkop, B., Haigh, F., Ryder, C., & Gardner-Medwin, J. M. (2002). The early magnetic resonance imaging features of the knee in juvenile idiopathic arthritis. Clin Radiol, 57(6), 466-471. doi:10.1053/crad.2001.0876
44. Uhl, M., Krauss, M., Kern, S., Herget, G., Hauer, M. P., Altehoefer, C., . . . Langer, M. (2001). The knee joint in early juvenile idiopathic arthritis. An ROC study for evaluating the diagnostic accuracy of contrast-enhanced MR imaging. Acta Radiol, 42(1), 6-9.
45. Rieter, J. F., Horatio, L. T. d., Nusman, C. M., Muller, L. S., Hemke, R., Avenarius, D. F., . . . Rosendahl, K. (2016). The many shades of enhancement: timing of post-gadolinium images strongly influences the scoring of juvenile idiopathic arthritis wrist involvement on MRI. Pediatr Radiol, 46(11), 1562-1567. doi:10.1007/s00247-016-3657-0
46. Argyropoulou, M. I., Fanis, S. L., Xenakis, T., Efremidis, S. C., & Siamopoulou, A. (2002). The role of MRI in the evaluation of hip joint disease in clinical subtypes of juvenile idiopathic arthritis. Br J Radiol, 75(891), 229-233. doi:10.1259/bjr.75.891.750229
47. Barendregt, A. M., Mazzoli, V., van den Berg, J. M., Kuijpers, T. W., Maas, M., Nederveen, A. J., & Hemke, R. (2020). T1ρ-mapping for assessing knee joint cartilage in children with juvenile idiopathic arthritis — feasibility and repeatability. Pediatr Radiol, 50(3), 371-379. doi:10.1007/s00247-019-04557-4
48. Bernini, J. M., Kellenberger, C. J., Eichenberger, M., Eliades, T., Papageorgiou, S. N., & Patcas, R. (2020). Quantitative analysis of facial asymmetry based on three-dimensional photography: a valuable indicator for asymmetrical temporomandibular joint affection in juvenile idiopathic arthritis patients? Pediatric rheumatology, 18(1), 10. doi:10.1186/s12969-020-0401-y
49. Bollhalder, A., Patcas, R., Eichenberger, M., Müller, L., Schroeder-Kohler, S., Saurenmann, R. K., & Kellenberger, C. J. (2020). Magnetic Resonance Imaging Followup of Temporomandibular Joint Inflammation, Deformation, and Mandibular Growth in Juvenile Idiopathic Arthritis Patients Receiving Systemic Treatment. J Rheumatol, 47(6), 909-916. doi:10.3899/jrheum.190168
50. Weiss, P., Brandon, T., Bohnsack, J., Heshin-Bekenstein, M., Francavilla, M., Jaremko, J., . . . Chauvin, N. Variability in magnetic resonance imaging interpretation of the pediatric sacroiliac joint. Arthritis Care Res (Hoboken), n/a(n/a). doi:10.1002/acr.24206

X-ray. Seventeen studies evaluated X-ray for JIA joint assessments. In X-ray and clinical assessment of TMJ dysfunctions and disorders, a negative correlation was found between ANB angle (retrognatia) and maximal mouth opening [1]. Clinical exam (stiffness at mouth opening), as compared to X-ray, sensitivity: 37%; specificity 98%, PPV 94%; NPV 71%; Maximal Voluntary Mouth opening sensitivity 61%, specificity 95%; PPV 89%, NPV 79%; Postnormal occlusion sensitivity 34%, specificity 92%; PPV 74%, NPV 69%; Anterior open bite sensitivity 24%, specificity 98%; PPV

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91%, NPV 67%; Mandibular retrognathia sensitivity sensitivity 37%, specificity 97%; PPV 88%, NPV 70% [2]. In a study that compared Sharp, Larsen and Poznanski methods of radiograph scoring, the correlation from baseline to the final visit and the corresponding score values at the final visit were in the moderate-to-high range for all methods (rs 0.75 for total Sharp score, 0.83 for Larsen score, 0.87 for Poznanski score, and 0.63 for radiologist score) [3]. Positive hip exam and X-ray in patients age < 6 were similar: 38% and 37%, while in patients age > 6 positive findings were 53% by hip exam and 26% by X-ray [4]. Less than 40% of the patients with affected mandibular condyles on X-ray displayed clinical symptoms [5]. By JIA subtype, 41%-57% of oligoarticular and 49%-77% of polyarticular cases exhibited condylar erosion [6, 7, 10]. Radiographic progression occurred in 38%; predictors of progression: joints with swelling/osteoporosis on X-ray, young age, and a large number of mobility-restricted joints at baseline [11]. Among JIA patients, 13%-55% had clinical TMJ disease, while 20%-78% had changes on X-ray [12, 13, 14].

Quality of evidence across all critical outcomes: Very low

Table 4. Studies of X-ray

Ref ID, Author, year	Study type	Duration	Population Description	Assessment given to relevant population	Results
3824 Gorska, 2014 [1]	Single-arm study	N/A	46 patients with JIA with low and moderate disease activity	Clinical and radiological assessment of TMJ dysfunctions and disorders	A significant negative correlation between the ANB angle (retrognathia) and maximal mouth opening (statistical power = 0.69) 2 out of 15 (13%) patients with TMJ dysfunction had no changes in the mandibular condyle and articular surface.
3807 Svensson, 2000 [2]	Single-arm study	N/A	105 JIA patients and TMJ involvement	Clinical exam vs X-ray (mandibular condylar lesions)	Clinical exam (stiffness at mouth opening) sensitivity: 37%; specificity 98%. Positive Predictive Value 94%; Negative Predictive Value 71%. Maximal Voluntary Mouth opening sensitivity 61%, specificity 95%; PPV 89%, NPV 79%. Postnormal occlusion sensitivity 34%, specificity 92%; PPV 74%, NPV 69%. Anterior open bite sensitivity 24%, specificity 98%; PPV 91%, NPV 67%. Mandibular retrognathia sensitivity sensitivity 37%, specificity 97%; PPV 88%, NPV 70%.
4203, Rossi et al., 2006 [3]	Case Series	4-5 years (baseline radiograph then annual radiographs)	25 patients with JIA (n = 12 systemic JIA, n = 8 polyarticular, n	X-ray, compared Sharp, Larsen and Poznanski methods of radiograph scoring	**Results for validity of scoring measures:** ICC for Sharp and Larsen methods of radiograph scoring good (> 0.9)

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Ref ID, Author, year	Study type	Duration	Population Description	Assessment given to relevant population	Results
			= 5 extended oligoarticular)		Median normalized values of Sharp and Larsen scores steadily increased during study period, most significant during first year of follow up Sharp joint space narrowing (JSN) scores increased more rapidly and remained consistently higher over time than erosion scores. Poznanski score (measure of cartilage loss) captured more damage at baseline than other methods, but then became very close to Sharp JSN score Spearman correlation = 0.96 between Sharp and Larsen scores, 0.91 between Larsen score and Sharp erosion score, and 0.94 between Sharp JSN and erosion score **Correlation between score changes and clinical variables:** Total Sharp, Larsen, and Poznanski score changes moderately to highly correlated with number of joints with active arthritis (r_s = 0.63, 0.63, and -0.41, respectively) and restricted motion (r_s = 0.57, 0.61, and -0.40, respectively) and with the CHAQ score (r_s = 0.80, 0.70, and -0.68, respectively). Poor correlation with ESR (r_s = 0.23, 0.24, and -0.36, respectively) Radiologist score had poor correlation with all variables (r_s = 0.02-0.12) Correlations between the score changes from baseline to the final visit and the corresponding score values at the final visit were in the moderate-to-high range for all methods (r_s 0.75 for total Sharp score, 0.83 for Larsen score, 0.87 for Poznanski score, and 0.63 for radiologist score).
1684 Jacobsen, 1992 [4]	Single-arm study	N/A	386 JIA patients	Clinical exam and x-ray of the hip	Positive hip exam in patients age < 6: 73/190 (38%) Positive hip x-ray in patients age < 6: 40/107 (37%) Positive hip exam in patients age > 6: 104/196 (53%) Positive hip x-ray in patients age > 6: 33/129 (26%)

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Ref ID, Author, year	Study type	Duration	Population Description	Assessment given to relevant population	Results
2009 Ronning, 1974 [5]	Cross-sectional	N/A	249 JIA patients and 2244 healthy controls	Clinical exam and x-ray of TMJ	X-ray found 72/249 (29%) JIA patients had condylar lesions. Less than 40% of the patients with affected mandibular condyles on x-ray displayed clinical symptoms.
2087 Mandall, 2010 [6]	Cross-sectional	1 timepoint	68 JIA patients (33 oligoarticular and 35 polyarticular)	X-ray	Clinical TMJ involvement in 20%, but crepitus and click in 24-40%. X-ray: 57% of oligoarticular and 77% of polyarticular cases exhibited condylar erosion, but only 1 patient with sclerosis and only 1 patient with osteophyte formation.
2417 Sidiropoulou-Chatzigiannni, 2008 [7]	Cross-sectional	1 timepoint	66 JIA patients (30 oligoarticular and 36 polyarticular)	Panoramic radiographs	50% showed some form of condylar destruction (35% B/L and 15% unilateral); 41% of oligo and 75% of poly's. 56% of girls affected, 41% of boys.
1175, Ince et al., 2000 [8]	Cross-sectional	N/A (cross-sectional)	45 patients with JIA (40% oligoarticular, 60% polyarticular) 18 with MTX exposure, 27 without MTX exposure	XR (panoramic radiograph), CT (panoral and individually corrected axial tomograms)	TMJ involvement on tomography in 63% of patients (at least grade 1 involvement) - 33% in oligoarticular group - 80% in polyarticular group 75% with vertical height asymmetry and symphysis deviation, 70% with smaller mandibular length, 60% with shorter ramus height, and 75% ANB angles greater than normative values **Clinical outcomes** Non-MTX group with less dysfunction index (DI) value than MTX group (mean 0.12 vs. 0.21, $p = 0.02$) **Radiographic outcomes** Significant difference in right condylar involvement in polyarticular JIA group (K-W 4.7, $p < 0.05$) Moderately strong correlation between craniomandibular index (CMI) and right and left condylar lesions (0.36)

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Ref ID, Author, year	Study type	Duration	Population Description	Assessment given to relevant population	Results
					Moderate to strong correlation between tomographic TMJ data and lateral cephalometric measurements (0.3 to 0.6) and between tomographic TMJ findings and asymmetry of lower face (0.5).
3346 Vilalyuk, 2016 [9]	Single-arm study	The median follow-up duration was 3.1 years (range 0.5–15).	158 JIA patients	Radiography	14 patients from the total (8.9%) had disease onset before biologic agents became available; 5/14 who delayed in receiving biologic treatment resulted in severe bone erosion and bone deformity. 2 patients (1.2%) under long-term corticosteroid treatment for refractory SJIA had spinal fractures.
3803 Cedstromer, 2014 [10]	Retrospective cohort study	Not reported	158 JIA patients (4 sJIA, 74 oligoarticular, 53 polyarticular, 17 psoriatic, 2 ERA, and 8 other)	Panoramic X-ray	Condylar alterations were found in 43% (0% of sJIA and ERA, 42% of oligoarticular, 49% of polyarticular, and 56% of psoriatic). Patients with condylar alterations were more extensively treated over time than those without. High disease activity and intensive medication at any time was associated with increased risk of alteration.
3165 Selvaag, 2006 [11]	Cohort study	3 years	197 JIA patients (111 oligoarticular, 60 polyarticular, 14 sJIA, 7 ERA, and 5 psoriatic)	X-ray	Radiographic abnormalities found in 88% at baseline and in 81% after 3 years (most in RF- polyarthritis) Frequency of swelling/osteoporosis decreased, and frequency of abnormal growth increased from baseline to followup (increased most in oligo and sJIA), increased erosions in all subtypes but not SS. Knees, hands, and wrists had most frequent radiographic abnormalities. Radiographic progression occurred in 38%; predictors of progression: joints with swelling/osteoporosis on XR, young age, and a large number of mobility-restricted joints at baseline. Radiographic progression in 27% of the patients in remission and 42% of the patients with persistent disease.
3828 Larheim,	Cohort study	Unclear	100 JIA patients (64 oligoarticular,	X-ray	24/100 patients had clinical TMJ disease. Definite x-ray changes found in 41 patients, possible changes in an additional 11 (definite changes B/L in 59%); clinical

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Ref ID, Author, year	Study type	Duration	Population Description	Assessment given to relevant population	Results
1982 [12]			22 polyarticular, 14 sJIA)		findings in 16/41 patients with definite changes, 1/11 with possible, and 7 of those without x-ray changes.
1590 Sairanen, 1966 [13]	Cohort study	Unclear	24 JIA patients and 55 healthy controls	Orthopantomography	TMJ involvement: Clinically -- 3/24 JIA patients; Imaging -- 5/24 JIA patients (2 of those with clinical TMJ involvement). Imaging WNL in all healthy controls.
3815 Billiau, 2007 [14]	Cohort study	1 timepoint	46 JIA patients, sex and age-matched healthy controls	Orthopantomogram and lateral cephalogram (XRs)	55% of patients with JIA had clinical TMJ arthritis, but 78% had radiographic condylar lesions; presence of condylar damage was not related to clinical orthodontic findings, JIA subtype, disease activity, severity, or duration. Patients with JIA had many changes on XR compared to controls, thought to be related to condylar damage.
3898 Klenke, 2018 [15]	Cohort study	1 timepoint	46 JIA patients	Orthopantomogram (XR)	59% were WNL, 12% were scored 1 (+erosions), 14% showed flattening of the condyles (score 2), 12% were scored 3, and 3% were scored 4. This enabled the patients to be classified into slightly affected (Group I: n = 36) or severely affected (Group II: n = 10); disease duration was significantly longer in Group II (8.9 ± 5.2 years) vs. Group I (4.6 ± 4.7 years).
4383 Cedströmer, 2020 [16]	cross-sectional study	N/A	65 children with JIA with TMJ involvement	Lateral head cephalometric radiographs to measure facial growth and relate the findings to temporomandibular joint (TMJ) condylar changes on panoramic radiographs	On panoramic radiographs no condylar alterations were seen in 27 and condylar alterations were seen in 38 of the 65 children.
4524 Muller, 2019 [17]	RCT	40 months	60 patients with the recent-inset JIA	X-ray Poznanski measurements to determine the RM/M2 score in 3 treatment arms: MTX+SSZ, MTX+Prednisone, MTX+ETN	No significant change in Poznanski-score, unadjusted nor after adjusting for age and symptom duration, compared to baseline, was observed, and there were no differences between the 3 arms.

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References:

1. Gorska, A., Przystupa, W., Rutkowska-Sak, L., Kwiatkowska, M., Chlabicz, S., & Szarmach, I. (2014). Temporomandibular joint dysfunction and disorders in the development of the mandible in patients with juvenile idiopathic arthritis - preliminary study. Adv Clin Exp Med, 23(5), 797-804.
2. Svensson, B., Adell, R., & Kopp, S. (2000). Temporomandibular disorders in juvenile chronic arthritis patients. A clinical study. Swed Dent J, 24(3), 83-92.
3. Rossi, F., Dia, F. D., Galipo, O., Pistorio, A., Valle, M., Magni-Manzoni, S., . . . Ravelli, A. (2006). Use of the Sharp and Larsen scoring methods in the assessment of radiographic progression in juvenile idiopathic arthritis. Arthritis Rheum, 55(5), 717-723. doi:10.1002/art.22246
4. Jacobsen, F. S., Crawford, A. H., & Broste, S. (1992). Hip involvement in juvenile rheumatoid arthritis. J Pediatr Orthop, 12(1), 45-53.
5. Ronning, O., Valiaho, M. L., & Laaksonen, A. L. (1974). The involvement of the temporomandibular joint in juvenile rheumatoid arthritis. Scand J Rheumatol, 3(2), 89-96.
6. Mandall, N. A., Gray, R., Brien, K. D. O., Baildam, E., Macfarlane, T. V., Davidson, J., . . . Ward, S. (2010). Juvenile idiopathic arthritis (JIA): a screening study to measure class II skeletal pattern, TMJ PDS and use of systemic corticosteroids. J Orthod, 37(1), 6-15. doi:10.1179/14653121042831
7. Sidiropoulou-Chatzigianni, S., Papadopoulos, M. A., & Kolokithas, G. (2008). Mandibular condyle lesions in children with juvenile idiopathic arthritis. Cleft Palate Craniofac J, 45(1), 57-62. doi:10.1597/07-014.1
8. Ince, D. O., Ince, A., & Moore, T. L. (2000). Effect of methotrexate on the temporomandibular joint and facial morphology in juvenile rheumatoid arthritis patients. Am J Orthod Dentofacial Orthop, 118(1), 75-83. doi:10.1067/mod.2000.104953
9. Vilaiyuk, S., Soponkanaporn, S., Jaovisidha, S., Benjaponpitak, S., & Manuyakorn, W. (2015). A retrospective study on 158 Thai patients with juvenile idiopathic arthritis followed in a single center over a 15-year period. Int J Rheum Dis, 19(12), 1342-1350. doi:10.1111/1756-185x.12637
10. Cedstromer, A. L., Ahlqwist, M., Andlin-Sobocki, A., Berntson, L., Hedenberg-Magnusson, B., & Dahlstrom, L. (2014). Temporomandibular condylar alterations in juvenile idiopathic arthritis most common in longitudinally severe disease despite medical treatment. Pediatr Rheumatol Online J, 12, 43. doi:10.1186/1546-0096-12-43
11. Selvaag, A. M., Flato, B., Dale, K., Lien, G., Vinje, O., Smerdel-Ramoya, A., & Forre, O. (2006). Radiographic and clinical outcome in early juvenile rheumatoid arthritis and juvenile spondyloarthropathy: a 3-year prospective study. J Rheumatol, 33(7), 1382-1391.
12. Larheim, T. A., Hoyeraal, H. M., Stabrun, A. E., & Haanaes, H. R. (1982). The temporomandibular joint in juvenile rheumatoid arthritis. Radiographic changes related to clinical and laboratory parameters in 100 children. Scand J Rheumatol, 11(1), 5-12.
13. Sairanen, E., & Helminen-Pakkala, E. (1966). Growth disturbance of the mandible in juvenile rheumatoid arthritis. Acta Radiol Ther Phys Biol, 4(2), 86-90.

For Peer Review Only

14. Billiau, A. D., Hu, Y., Verdonck, A., Carels, C., & Wouters, C. (2007). Temporomandibular joint arthritis in juvenile idiopathic arthritis: prevalence, clinical and radiological signs, and relation to dentofacial morphology. J Rheumatol, 34(9), 1925-1933.
15. Klenke, D., Quast, A., Prelog, M., Holl-Wieden, A., Riekert, M., Stellzig-Eisenhauer, A., & Meyer-Marcotty, P. (2018). TMJ pathomorphology in patients with JIA-radiographic parameters for early diagnosis. Head Face Med, 14(1), 15. doi:10.1186/s13005-018-0173-5
16. Cedströmer, A.-L., Andlin-Sobocki, A., Abbu, N., Hedenberg-Magnusson, B., Dahlström, L., & Berntson, L. (2020). Condylar alterations and facial growth in children with juvenile idiopathic arthritis. Journal of Orofacial Orthopedics / Fortschritte der Kieferorthopädie, 81(3), 163-171. doi:10.1007/s00056-020-00216-8.
17. Hissink Muller, P. C. E., van Braak, W. G., Schreurs, D., Nusman, C. M., Bergstra, S. A., Hemke, R., . . . Maas, M. (2019). No radiographic wrist damage after treatment to target in recent-onset juvenile idiopathic arthritis. Pediatric rheumatology, 17(1), 62. doi:10.1186/s12969-019-0362-1.

CT: Eight studies evaluated CT for assessment of JIA. One study reported muscle cross sectional area (CSA) median Z-score: onset -1.94; follow-up -1.10; Cortical thickness: onset -1.55; follow-up -0.97; Marrow area: onset 0.96; follow-up 1.05; Cortical density: onset 0.34; follow-up 0.69; Trabecular density: onset -0.75; follow-up -0.36; Strength–strain index (SSI) onset -0.79; follow-up -0.13 [1]. There was moderate to strong correlation between tomographic TMJ data and lateral cephalometric measurements (0.3 to 0.6) and between tomographic TMJ findings and asymmetry of lower face (0.5) [2]. On peripheral quantitative computed tomography (PQCT) of radial diaphysis total cross-sectional area and BMC were decreased somewhat less in the oligoarticular than in the other groups, total bone mineral density was reduced in the polyarticular and systemic JIA population and normal in oligoarticular and connective tissue disease populations, muscle cross sectional area was decreased in all groups [3]. In spite of the articular alterations having been frequent in the TMJs evaluated by means of cone beam CBCT in 25 patients, only 5 ATMs presented a clinical diagnosis that could lead to suspecting some articular bone alteration, thereby perhaps confirming the risk of diagnostic underestimation [4]. On high resolution CT, TMJ lesions were more prevalent in those with polyarticular disease, and the largest AP measurements of the mandibular condyle depth were found in those with severe TMJ lesions (9.1 +/- 1) without statistically significant differences among patients with mild lesions (8.4+/- 0.9) and without TMJ lesions (7.9 +/- 1.2 mm) [5]. In other study, 62% of patients had morphologic evidence of TMJ involvement on CT, with a correlation between the craniomandibular index value and the pathosis index for the left joint as 0.376, and correlation between the vertical difference in mandibular angle regions and the average grade of TMJ as 0.303 [6].

Quality of evidence across all critical outcomes: Very low

Table 5. Studies of Computed Tomography (CT)

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Ref ID, Author, year	Study type	Duration	Population Description	Assessment given to relevant population	Results
2568 Roth, 2007 [1]	Single-arm study	Median 48 months	25 JIA patients	Peripheral quantitative computed tomography to measure geometric parameters of bone and density.	Muscle cross sectional area (CSA) median Z-score: onset -1.94; follow-up -1.10. Cortical thickness: onset -1.55; follow-up -0.97 Marrow area: onset 0.96; follow-up 1.05. Cortical density: onset 0.34; follow-up 0.69 Trabecular density: onset -0.75; follow-up -0.36. Strength–strain index (SSI) onset -0.79; follow-up -0.13.
1175, Ince et al., 2000 [2]	Cross-sectional	N/A (cross-sectional)	45 patients with JIA (40% oligoarticular, 60% polyarticular) 18 with MTX exposure, 27 without MTX exposure	XR (panoramic radiograph), CT (panoral and individually corrected axial tomograms)	TMJ involvement on tomography in 63% of patients (at least grade 1 involvement) - 33% in oligoarticular group - 80% in polyarticular group 75% with vertical height asymmetry and symphysis deviation, 70% with smaller mandibular length, 60% with shorter ramus height, and 75% ANB angles greater than normative values **Clinical outcomes** Non-MTX group with less dysfunction index (DI) value than MTX group (mean 0.12 vs. 0.21, $p = 0.02$) Radiographic outcomes Significant difference in right condylar involvement in polyarticular JIA group (K-W 4.7, $p < 0.05$) Moderately strong correlation between craniomandibular index (CMI) and right and left condylar lesions (0.36) Moderate to strong correlation between tomographic TMJ data and lateral cephalometric measurements (0.3 to 0.6) and between tomographic TMJ findings and asymmetry of lower face (0.5).
2571, Bechthold, 2005 [3]	Prospective cohort	Unclear	94 patients with JIA (OJIA (n=31), polyarticular	Anthropometric data was obtained; Patients also underwent peripheral quantitative computed	No significant differences in anthroprometric data. PQCT of radial metaphysis: Total metaphyseal cross-sectional area of the radius was reduced in all groups compared to a

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Ref ID, Author, year	Study type	Duration	Population Description	Assessment given to relevant population	Results
			(n=27), SJIA (n=20) and connective tissue disease (CTD) (n=16)) Anthropometric data were compared with the longitudinal growth data of the 'Swiss study'. The pQCT results were compared to those in a German reference population using identical methodology. These were participants of the DONALD study.	tomography (PQCT) at 2 sites on non-dominant radius, distal metaphysis and proximal diaphysis as a measure of bone stability.	healthy reference population. BMC (mg/mm) was also significantly decreased in all groups (P< 0.05). PQCT of radial diaphysis: Total cross-sectional area and BMC were decreased in all patients, somewhat less in the oligoarticular than in the other groups (P<0.001). Total bone mineral density was reduced in the polyarticular and systemic JIA population (P< 0.05) and normal in oligoarticular and connective tissue disease populations. Muscle cross sectional area was also decreased in all groups (P< 0.01). The higher the functional disability of the patient, the lower was the cortical thickness, the cortical CSA and the muscle CSA (r= -0.50, r= -0.51 and r= -0.42, P <0.01). After correction for height only the metaphyseal Strength/Strain Index and the diaphyseal total CSA were significantly reduced.
3805, Ferraz, 2012 [4]	Prospective, cross-sectional cohort study	Unclear	15 patients diagnosed with JIA (diagnosis occurred in past as age range was 6-28 yrs); 30 TMJs evaluated	Performed clinical chart review and then patients underwent cone beam CT (CBCT) scanning	Of the 30 TMJs studied, 25 (83.3%) were clinically diagnosed as having disease. In spite of the articular alterations having been frequent in the TMJs evaluated by means of CBCT (83.3% of TMJs), only 5 ATMs (3 with osteoarthritis and 2 with osteoarthrosis) presented a clinical diagnosis that could lead to suspecting some articular bone alteration, thereby perhaps confirming the risk of diagnostic underestimation. The mean time from onset of symptoms for the patients who had the presence of condyle flattening was approximately 8 years; for patients who did not have condyle flattening in their

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Ref ID, Author, year	Study type	Duration	Population Description	Assessment given to relevant population	Results
					TMJ, it was 3 years, these data were not statistically significant (P .334). There was a statistically significant correlation between the sides, demonstrating that a higher number of tomographic alterations on one side would be correlated with a higher number on the opposite side (P=0.047). When comparing JIA patients that had been diagnosed up to 3 years before to those diagnosed for 3+ years, there was a statistically significant difference in the temporomandibular disorders identified on CBCT (p=0.024). When comparing JIA patients on treatment for less than 3 years to those on treatment for 3+ years, there was a statistically significant difference in the temporomandibular disorders identified n CBCT (p=0.024).
3811, Ronchezel, 1995 [5]	Controlled Prospective cohort study	2 years	26 patients with JRA using the ACR criteria; randomly selected; control group of 10 children w/ dental malocclusion and no other abnormalities	Clinical evaluation, high resolution computer tomography, orthodontic evaluation	Tomographic evaluation demonstrated alterations in 13 of those with JRA (50%). TMJ lesions were more prevalent in those with polyarticular disease (71.4%). Measurement of mandibular condyle depth (measured in AP) showed higher values (mean +/- SD) in the polyarticular group (8.7 +/- 0.9 mm) than pauciarticular (7.7 +/- 1.1) and control groups (7.7 +/- 1 mm) (apparently statistically significant though no p value reported). The largest AP measurements of the mandibular condyle depth were found in those with severe TMJ lesions (9.1 +/- 1) without statistically significant differences among patients with mild lesions (8.4+/- 0.9) and without TMJ lesions (7.9 +/- 1.2 mm).

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Ref ID, Author, year	Study type	Duration	Population Description	Assessment given to relevant population	Results
3829, Hu, 1996 [6]	Controlled prospective cohort	Unclear	37 consecutive patients with JRA (8 pauciarticular, 23 polyarticular, 6 systemic); published norms for mandibular dimensions and for prevalences of symptoms and signs of TMJ disorders served as control data	Clinical exam, standardized photographs, cephalometric analysis (mandibular length, ramus height), axial CT for TMJ morphology (pathosis score assigned based on qualitative evaluation of the axial CT images/ largest condylar dimension/ condylar angulation/ constructed joint space/ condylar cross-sectional area measured)	CT: 62% had morphologic evidence of TMJ involvement on CT. Significant correlation noted between the craniomandibular index value and the pathosis index for the left joint (=0.376, P< 0.05). Significant correlation between the vertical difference in mandibular angle regions and the average grade of TMJ (=0.303, P< 0.05). No statistically significant differences when comparing the different JRA groups and their craniomandibular index, opening, pain or joint noise. Cephalometric analysis: Using cephalometric analysis, smaller mandibular lengths were observed in the JRA sample compared to controls though none of the mean differences attained statistical significance. There was also no statistical significance reached when the three JRA groups were investigated indenpendently. Ramus height was was 'considerably smaller' in the polyarticular group than in the other two groups. Statistically significant inverse relationships found between average grade of TMJ and the mandibular length as well as ramus height in the pauciarticular and polyarticular groups (=-0.694, P< 0.05). Standardized measures (age-adjusted) of mandibular length and ramus height were also significantly negatively correlated with the average grades of TMJ lesions (=-0.505, P< 0.005; =-0.329, P< 0.05). Those with the most severe joint

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Ref ID, Author, year	Study type	Duration	Population Description	Assessment given to relevant population	Results
					abnormalities tended to have the shortest mandibular lengths. Duration of JRA was negatively correlated with the standardized mandibular length (r=-0.361, P< 0.028). No associations seen between RF or ANA and the indicators of mandibular growth (absolute or standardized mandibular length and ramus height).
644, Koos, 2013 [7]	Retrospective cohort study	Unclear	23 patients with JIA, 23 matched controls	Underwent contrast enhanced MRI or cone beam CT scan (CBCT)	78% of TMJs in control group were considered normal; 83% of the TMJs in the JIA group showed severe changes; difference between TMJ arthritis in control and JIA group was highly significant p<0.0001 Paper devises a scoring method for assessing TMJ arthritis that can be used with MRI and CBCT but does not compare them head to head
580, Farronato, 2010 [8]	Prospective cohort	Unclear	34 children with TMJ involvement of their JIA	Patients had clinical exam consisting of facial observation, intraoral obs and TMJ functional analysis They also underwent cone beam CT scan (CBCT) of the TMJ	There was a very significant difference in volume between the healthy and affected condyles (P< 0.001). The volumes of the hemimandible (p=0.03), ramus (p= 0.01) and hemisymphysis (p=0.02) also differed significantly. There was no significant difference between the affected and healthy hemibody. *4 children excluded d/t radiographic noise

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References:

1. Roth, J., Linge, M., Tzaribachev, N., Schweizer, R., & Kuemmerle-Deschner, J. (2007). Musculoskeletal abnormalities in juvenile idiopathic arthritis--a 4-year longitudinal study. Rheumatology (Oxford), 46(7), 1180-1184. doi:10.1093/rheumatology/kem100
2. Ince, D. O., Ince, A., & Moore, T. L. (2000). Effect of methotrexate on the temporomandibular joint and facial morphology in juvenile rheumatoid arthritis patients. Am J Orthod Dentofacial Orthop, 118(1), 75-83. doi:10.1067/mod.2000.104953
3. Bechthold, S., Ripperger, P., Ruder, H., Truckenbrodt, H., Schwarz, H. P., & Butenandt, O. (1998). Growth hormone therapy in patients with chronic juvenile arthritis: effect on growth after 1 year's therapie. Monatsschrift fur kinderheilkunde, 146(Suppl 2), S124.

4. Ferraz, A. M., Devito, K. L., & Guimaraes, J. P. (2012). Temporomandibular disorder in patients with juvenile idiopathic arthritis: clinical evaluation and correlation with the findings of cone beam computed tomography. Oral Surg Oral Med Oral Pathol Oral Radiol, 114(3), e51-57. doi:10.1016/j.oooo.2012.02.010
5. Ronchezel, M. V., Hilario, M. O., Goldenberg, J., Lederman, H. M., Faltin, K., Azevedo, M. F. d., & Naspitz, C. K. (1995). Temporomandibular joint and mandibular growth alterations in patients with juvenile rheumatoid arthritis. J Rheumatol, 22(10), 1956-1961.
6. Hu, Y. S., & Schneiderman, E. D. (1995). The temporomandibular joint in juvenile rheumatoid arthritis: I. Computed tomographic findings. Pediatr Dent, 17(1), 46-53.
7. Koos, B., Tzaribachev, N., Bott, S., Ciesielski, R., & Godt, A. (2013). Classification of temporomandibular joint erosion, arthritis, and inflammation in patients with juvenile idiopathic arthritis. J Orofac Orthop, 74(6), 506-519. doi:10.1007/s00056-013-0166-8
8. Farronato, G., Garagiola, U., Carletti, V., Cressoni, P., Mercatali, L., & Farronato, D. (2010). Change in condylar and mandibular morphology in juvenile idiopathic arthritis: Cone Beam volumetric imaging. Minerva Stomatol, 59(10), 519-534.

18F-FDG: Three studies evaluated 18F-FDG. There was a significant association between the degree of 18F-FDG uptake and typical clinical, radiographic and biochemical findings in JIA [1]. Correlation of 18F-FDG PET/CT with clinical disease activity of AOSD: Visual grade of lymph node with the systemic score of AOSD (r = 0.664). SUV intensity of lymph node with the systemic score (r = 0.601). Visual grade of spleen with the systemic score (r =0.771), ESR (r = 0.617), and ferritin (r =0.557). SUV intensity of spleen with the systemic score (r = 0.676). Visual grade of bone marrow with the systemic score (r = 0.734), ESR (r = 0.761), leukocyte (r = 0.775), and neutrophil (r =0.711). SUV intensity of bone marrow with the systemic score (r = 0.57), ESR (r = 0.612), leukocyte (r = 0.773), and neutrophil (r = 0.725) [2]. FDG-PET showed a diffuse distribution pattern in inflamed joints. There was no accumulation in the bone marrow. In 12 sJIA patients it was found either in all vertebral bodies, pelvis, and around large joints. Accumulation was not in synovia but in the bone itself or at the end of long bones and thought to be in the bone marrow. There was greater accumulation in the spleen compared to the liver; 3 out of these 12 patients developed MAS. In 8 cases of sJIA, there was diffuse accumulation in inflamed joints, no bone marrow involvement, no significant difference between liver and spleen, and none of these patients had MAS. [3]

Quality of evidence across all critical outcomes: Very low

Table 6. Studies of 18F-FDG

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Ref ID, Author, year	Study type	Duration	Population Description	Assessment given to relevant population	Results
2873 Tateishi, 2010 [1]	Single-arm study	N/A	560 joints in 28 JIA patients	18F-FDG PET, clinical, radiographic examination performed with interval mean, 2.6 weeks; range, 0–5 weeks.	There was a significant association between the degree of 18F-FDG uptake and typical clinical, radiographic and biochemical findings in JIA. In multivariate analysis, factors associated with increased maximum standardized uptake value (SUVmax) of the joint included erosion (OR, 6.17; 95% confidence interval (CI), 2.60–14.66; P<0.0001), tenderness (OR, 5.22; 95%CI, 2.85–9.57; P<0.0001), soft-tissue swelling (OR, 3.77; 95%CI, 2.22–6.41; P<0.0001), the presence of multiple major joints involvement (OR, 3.50; 95%CI, 2.10–5.83; P<0.0001), and CRP (OR, 1.81; 95%CI, 1.09– 3.02; P=0.022).
3420 An, 2015 [2]	Single-arm study	N/A	13 adult-onset Still's disease (AOSD) patients	18F-FDG PET/CT vs clinical examination	Increased 18F-FDG uptake in 10 (90%) of clinically active AOSD patients. Correlation of 18F-FDG PET/CT with clinical disease activity of AOSD: Visual grade of lymph node with the systemic score of AOSD (r = 0.664, p = 0.013). SUV intensity of lymph node with the systemic score (r = 0.601, p = 0.03). Visual grade of spleen with the systemic score (r =0.771, p = 0.002), ESR (r = 0.617, p = 0.025), and ferritin (r =0.557, p = 0.048). SUV intensity of spleen with the systemic score (r = 0.676, p = 0.011). Visual grade of bone marrow with the systemic score (r = 0.734, p = 0.004), ESR (r = 0.761, p =0.003), leukocyte (r = 0.775, p = 0.002), and neutrophil (r =0.711, p = 0.006). SUV intensity of bone marrow with the systemic score (r = 0.57, p = 0.042), ESR (r = 0.612, p = 0.026), leukocyte (r = 0.773, p = 0.002), and neutrophil (r = 0.725, p = 0.005).
597, Kanetaka , 2015 [3]	Retrospective single arm cohort	9 years	68 children (59 with systemic JIA, 9 with polyarticular JIA per ILAR criteria); used 1 case of fibromyalgia as a 'normal' comparator as	FDG PET	In children without inflammation, accumulation in the brain, heart, bladder and joints at the growth stage can be observed. In 11 cases with poly JIA, FDG PET showed a diffuse distribution pattern in inflamed joints. There was no accumulation in the bone marrow. There were 2 characteristic patterns of FDG accumulation in sJIA patients.

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Ref ID, Author, year	Study type	Duration	Population Description	Assessment given to relevant population	Results
			well as 23 juvenile SLE, 20 JDM, 10 MCTD, 8 systemic sclerosis and 10 Kawasaki positive controls		-Type I: 12 cases, found in all vertebral bodies, pelvis, around large joints; accumulation was not in synovia but in the bone itself or at the end of long bones; thought to be in the bone marrow; greater accumulation in the spleen compared to liver; 3 of these patients developed MAS -Type II: 8 cases, Similar to poly JIA, diffuse accumulation in inflamed joints; no bone marrow involvement; no significant difference between liver and spleen; none of these patients had MAS. Inflammation markers (WBC, CRP, ESR, ferritin, IL18, GCSF) were significantly higher in type I (P< 0.005). No significant difference between type I and II in terms of SAA, IL-6. Synovitis marker (MMP-3) was significantly higher in type II. Overall, noticeable uptake in the bone marrow of sJIA patients which may indicate inflammatory focus of the disease.

References:

1. Tateishi, U., Imagawa, T., Kanezawa, N., Okabe, T., Shizukuishi, K., Inoue, T., & Yokota, S. (2010). PET assessment of disease activity in children with juvenile idiopathic arthritis. Pediatr Radiol, 40(11), 1781-1788. doi:10.1007/s00247-010-1716-5
2. An, Y. S., Suh, C. H., Jung, J. Y., Cho, H., & Kim, H. A. (2016). The role of 18F-fluorodeoxyglucose positron emission tomography in the assessment of disease activity of adult-onset Still's disease. Korean J Intern Med, 32(6), 1082-1089. doi:10.3904/kjim.2015.322
3. Kanetaka, T., Mori, M., Nishimura, K., Nozawa, T., Kikuchi, M., Sakurai, N., . . . Yokota, S. (2015). Characteristics of FDG-PET findings in the diagnosis of systemic juvenile idiopathic arthritis. Mod Rheumatol, 26(3), 362-367. doi:10.3109/14397595.2015.1082686

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PICO 56: In children with JIA who require IA corticosteroid (IAC) injections, should injections be done with imaging guidance?

Summary. The literature search identified 12 studies that addressed this question in patients with JIA. Studies included two controlled cohort studies, with the rest being single-arm cohort studies and case series. Interventions included: IAC injections with no guidance (one study), Ultrasound (US) guidance, and CT guided injections. Six observational studies addressed IAC guided injections in different joints including a mix of peripheral joints and TMJ [1, 2, 3, 4, 5, 6], while six studies addressed IAC guidance for TMJ steroid injections[7, 8, 9, 10, 11, 12] (Table 1).

IAC injections – non-TMJ studies

Cunha et al.[1] published a cohort study evaluating US-guided intra-articular corticosteroid injections in 16 patients (with a longer disease duration and previous injections) and compared them to non-US guided IAC injections (n=149). US-guided injections showed poor response to IAC (p = 0.02) and associated with higher CHAQ values (p = 0.03), higher number of injections with poor response (p = 0.01) and a shorter time to relapse (p = 0.02) compared to patients submitted to blindly performed procedures. This study highlights a selection bias for the US guided group likely had a more severe disease process which may have led to worse outcomes.

Young et al.[3] examined 241 US-guided 1444 corticosteroid injections (1340 joints, 104 tendon sheaths), 414 of which were repeat injections. Reported complications were minimal and included subcutaneous tissue atrophy (29 injections, 2.1%), skin hypopigmentation (4 injections, 0.3%), erythema and pruritis (2 injections, 0.1%), soft tissue atrophy + skin hypopigmentation (2 injections, 0.1%), 2 patients had avascular necrosis (AVN) (hip, tibiotalar) but attributed to long-term systemic steroid therapy. Young et al., further examined US guided IAC in 2015.[2] This observational study investigated US-guided subtalar corticosteroid injections in 122 patients. Injections were complicated in 9/241 (3.7) % with atrophy of or skin hypopigmentation, isolated atrophy of subcutaneous soft tissues occurred in 5/241 (2.1%), skin hypopigmentation and subcutaneous atrophy in 3/241 (1.2%), and one patient had low-grade fever (n = 1).

Laurell et al. published a case series[4] and cohort study[5] with focus on US-guided IAC injections in patients with JIA. The authors report accurate placement of corticosteroid in all injected compartments. In their cohort study there was reported Clinical resolution of active arthritis in 72% of the cases and in the case series, they reported 4-week post-injection normalization of synovial hypertrophy in 86%, normalization of hyperemia in 91%; 12/15 wrists (80%) clinically inactive arthritis. They reported 1 relapse in a patient with oligo JIA 7 months after steroid injection. The authors reported 4.7% rate of subcutaneous atrophy.

A cohort study by Tynjala et al.[6] examined hip US-guided injections in 20 affected hips. They measured treatment response by absence of clinical signs and symptoms and no effusion on US. Following injections, mean duration of efficacy 8.3 months (median 11.5 months), 14 (70%) of hip joints had normal clinical examination and ultrasound at 3 months, 14 (70%) at 6 months and 10 (50%) of hip joints at 12 months without synovitis. No side effects were observed for 12 months follow up period.

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TMJ guided IAC injections:

A retrospective cohort study by Resnick et al.[7] compared Image-guided [CT or Ultrasound] TMJ IAC injections. The authors observed no differences in resolution of pain (p = 1.00), increase in maximal incisal opening (MIO) (p = 0.975), or decrease in synovial enhancement ratio (ER) (p = 0.492) between landmark and image guided injections. A statistically significant longer average procedure time was observed in image-guided group (p < 0.008).

Parra et al.[8] investigated US guidance in total of 180 TMJ injections, 127 injections (70%) needle placement confirmed with CT (limited focused CT protocol). Needle placement was acceptable in 115/127 joints (91%) of those confirmed with CT with major readjustment required in 12/127 joints (9%). As for the outcomes, 80/99 (81%) good response at follow up visit. Observed complications of US guided IAC in this study included skin atrophy in 1 patient and transient early swelling and pain in 10 patients. In contrast, Habibi et al.[9] performed 63 US-guided steroid injections and reported efficacy of IAC and symptom resolution in 58/63 (92.06%); 1 child developed scar at site of injection. A retrospective review by Cahill et.al.[10] where 27 CT guided intraarticular TMJ steroid injections were performed concluded that intraarticular TMJ injection of a long-acting steroid in children is a safe procedure even in patients with joint space deformities, with reduction in acute and subacute inflammatory changes noted on MRI. Arabshahi et al.[11] reported that CT-guided TMJ IAC injections alleviated pain in more than two-thirds of symptomatic patients; one-third of these patients had persistence of effusions on follow up MRI (77 % of 13 patients with pre-injection pain had pain resolution; P 0.05). Presence of jaw pain did not significantly correlate with the presence of effusions on MRI (P=0.96). Side effects reported in this study included facial swelling in 2 patients consistent with Cushing 'syndrome, lasting 2 days in 1 patient and 2 weeks in the other. In contrast, a retrospective chart review by Ringold et al.[12] TMJ IAS injections were done under general anesthesia but without imaging guidance, outcomes of this study showed that there was a mean increase in MIO of 3.8 mm following each IAS injection (p = 0.003; 95% CI 1.4, 6.2). Patients who underwent multiple IAS injections had a mean increase in MIO after first injection of 6.6 mm (p < 0.001; 95% CI 4.1, 9.1); however, the mean increase in MIO after subsequent injections was 0.4 mm (p = 0.8; 95% CI –3.5, 4.4). Authors reported complications that were more or less similar to imaging guided studies. One patient developed subcutaneous atrophy at the injection site, two patients developed small, asymptomatic intraarticular calcifications. No additional adverse events were reported.

Quality of evidence across all critical outcomes: Very low

Table 1. Data from Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Intervention given to relevant population	Results
Non-TMJ injection studies					

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Ref ID, Author, year	Study type	Duration	Population Description	Intervention given to relevant population	Results
1965, Cunha et al., 2016 [1]	Single-arm cohort	6 month follow-up period	88 patients with JIA (35.2% oligoarticular JIA) Total of 165 intra-articular corticosteroid injections	Triamcinolone hexacetonide (1-2 mg/kg for large joints, 0.5-1 mg/kg for medium joints, 4-10 mg for small joints; maximum dose 100 mg) 16 patients with US-guided injections	US-guided injections: - 16 patients - 37.5% with good response* vs. 62.5% with poor response**, p = 0.02) - Compared to non-US guided injections, higher values of CHAQ (mean 1.6 vs. 0.3; p = 0.03), higher number of injections with poor response (p = 0.01) and shorter time to relapse (p = 0.02) Major limitation/source of confounding: Guided injections were performed on joints that had already showed a poor response to blindly conducted IAC injection * all injected joints remained inactive for at least six months or some of injected joints remained inactive for at least six months ** all infiltrated joints remained active or exhibited reactivation within a period under six months after IAC injection
4113, Young et al., 2015 [2]	Single-arm cohort	Follow up period not reported	122 patients with JIA, 241 total subtalar corticosteroid injections	US-guided subtalar corticosteroid injection (triamcinolone acetonide or triamcinolone hexacetonide) Average triamcinolone acetonide dose 10.4 mg; triamcinolone hexacetonide 10.0 mg Lateral approach	26 of 122 patients had repeat injections for recurrent symptoms (68 total repeat injections) - Average interval between injections 24.8 months (range 2.2-130.7, median 14.2 months) Complications - 9/241 (3.7)% of injections with atrophy of or skin hypopigmentation - Isolated atrophy of subcutaneous soft tissues in 5/241 (2.1%) - Skin hypopigmentation and subcutaneous atrophy in 3/241 (1.2%) - Low-grade fever (n = 1)
4114, Young et	Single-arm cohort	1-week rheumatology follow-up	198 patients with JIA	US-guided injection	1444 corticosteroid injections (1340 joints, 104 tendon sheaths) - 497 upper extremity - 837 lower extremity

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Ref ID, Author, year	Study type	Duration	Population Description	Intervention given to relevant population	Results
al., 2012 [3]		phone call, clinical evaluation 1–3 months following injection therapy		Triamcinolone hexacetonide most common, some injections with triamcinolone acetonide Age-weight-joint-based dose protocol used	- 6 TMJs 414 repeat injections - Average time interval of 17.7 months (range 0.5-101.5 months) between intra-articular injections and 12.7 months (range 5.6-16.9 months) between tendon sheath injections - 140 upper extremity joints, 267 lower extremity joints, 7 tendon sheaths Complications - 2.6% overall - Subcutaneous tissue atrophy (29 injections, 2.1%) - Skin hypopigmentation (4 injections, 0.3%) - Erythema and pruritis (2 injections, 0.1%) - Soft tissue atrophy + skin hypopigmentation (2 injections, 0.1%) - Evenly distributed between injection sites - 2 patients with AVN (hip, tibiotalar) but attributed to long-term systemic steroid therapy
4089, Laurell et al., 2012 [4]	Case series	Prior to joint injection and 4 weeks after	11 patients with JIA and clinically active wrist arthritis (n = 5 oligoarticular JIA, 2 polyarticular JIA, 2 undifferentiated, 1 ERA, 1 systemic JIA)	US and color Doppler US-guided injection with triamcinolone acetonide (10-40 mg per joint and tendon sheath)	US technique - Radiologist specialized in musculoskeletal US using Logiq 9 scanner - Dorsal and palmar views - Color doppler for hyperemia US results - Synovial hypertrophy in 26 compartments, hyperemia in 23 (radio-carpal, midcarpal, tendon sheaths) - Effusion in 2/21 inflamed joint compartments and 5/20 diseased tendon sheaths - Multiple compartments involved in 10/15 wrists - 5/15 wrists with isolated radio-carpal involvement - Synovitis in 13/15 radio-carpal joints (87%) and 8/15 midcarpal joints (53%) - Tenosynovitis in 5/15 wrists (33%)

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Ref ID, Author, year	Study type	Duration	Population Description	Intervention given to relevant population	Results
					- 20/135 tendon sheaths (15%) with synovial hypertrophy, 16/135 (12%) with hyperemia - All patients with tenosynovitis also had radio-carpal or midcarpal involvement US-guided injection results - US-guided steroid injection in 21/26 diseased compartments - 4 of diseased tendon sheaths injected - 30 minute procedure time including general anesthesia (5-15 minutes for steroid injection) - Quick and effective placement of needle tip and steroid in all compartments - 1 week post-injection: normalization of synovial hypertrophy in 57%, normalization of hyperemia in 86%; 8/15 wrists (53.3%) clinically inactive arthritis - 4 week post-injection: normalization of synovial hypertrophy in 86%, normalization of hyperemia in 91%; 12/15 wrists (80%) clinically inactive arthritis - 1 relapse in oligo JIA patient 7 months after steroid injection Complications: local subcutaneous atrophy in 1 patient at radio-carpal joint (4.8%)
4088, Laurell et al., 2011 [5]	Single arm cohort	Clinical and US assessment before injection and at 4 weeks after steroid injection	30 patients with JIA (n = 11 polyarticular JIA, 19 oligoarticular JIA)	US with and without color Doppler US-guided injections triamcinolone acetonide 40 mg/mL	US examination details: - Following joints and tendon sheaths examined: anterior, anteromedial and anterolateral talo-crural joint (anterior, anteromedial and anterolateral recesses), posterior subtalar joint (lateral recess), anterior subtalar joint (dorsal and medial recesses), tibialis posterior, flexor digitorum longus, flexor hallucis longus, peroneus, tibialis anterior, extensor hallucis longus, and extensor digitorum longus - Assessed for synovial hypertrophy, joint effusion, synovial hyperemia via color Doppler

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Ref ID, Author, year	Study type	Duration	Population Description	Intervention given to relevant population	Results
					Imaging outcomes: 121 compartments with active disease (joints, tendon sheaths, 1 ganglion cyst) based on synovial hypertrophy, effusion, and/or hyperemia 80% of ankle regions had multiple compartments involved - 78%: talo-crural - 65% posterior subtalar - 30% midfoot - 55% tendon sheaths 50 active tendon sheaths Joint injection outcomes (US-guided): - Accurate placement of corticosteroid in all 85 injected compartments - 4.7% rate of subcutaneous atrophy (4/85) - Normalization or regression of synovial hypertrophy in 89% of compartments (87% talo-crural, 95% post-subtalar, 91% midfoot, 86% tendons, 100% para-articular cyst) - Normalization of synovial hyperemia in 89% (86% talo-crural, 95% post-subtalar, 80% midfoot, 90% tendons, 100% para-articular) - Clinical resolution of active arthritis in 72%
1971, Tynjala et al., 2004 [6]	Cohort study	12-month post-injection follow up	32 patients with JIA: 19 patients with 22 swollen ankles/feet (ankle, hindfoot, midfoot) and 13 patients with synovitis in 20 hip joints	Ultrasound for all JIA patients suspected of having hip synovitis MR with gadolinium-enhancement for all ankles/feet with swelling and/or limited range of motion and pain or tenderness	Tarsal intra-articular steroid results (unclear if US-guidance used; not explicitly stated in article) - Duration of treatment response varied from 0.5 months to 12 months (mean 5.5 months, median 3.5 months) - Positive clinical response in 18/22 (82%) of cases at 1 month, 13 (59%) at 3 months, 9 (41%) at 6 months and 7 (32%) at 12 months - No side effects during 12-month follow up time Hip intra-articular steroid results (US-guidance used) - Treatment response = absence of clinical signs and symptoms and no effusion on US - Mean duration of efficacy 8.3 months (median 11.5 months)

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Ref ID, Author, year	Study type	Duration	Population Description	Intervention given to relevant population	Results
				US-guidance for hip intra-articular injection; does not explicitly state if used for ankle injections, but seems to infer ultrasound-guidance Triamcinolone hexacetonide used for hip injections, methyl-prednisolone used for ankle injections	- 14 (70%) of hip joints had normal clinical examination and ultrasound at 3 months - 14 (70%) at 6 months and 10 (50%) of hip joints at 12 months without synovitis No side effects for the 12 months follow up period.
TMJ injection studies					
2021, Resnick et al, 2017 [7]	Retrospective controlled cohort	N/A	45 patients with JIA who received intra-articular steroid injections (IASI) of TMJ	• Ultrasound guided • Fluoroscopy/CT • No image guidance Image-guided injections performed by board-certified IR. US examination used for all patients. Fluoroscopy or CT was used If severe arthritic deformity precluded visualization	45 patients with 71 injected TMJs included - Landmark group (no image guidance) 22 patients with 36 injected TMJs - Image-guided (US and CT) 23 patients with 35 injected TMJs No differences in age, gender, family history of rheumatologic disease, or disease subtype between groups No differences in resolution of pain (75% vs 74% decrease, p = 1.00), increase in maximal incisal opening (MIO) (5.1 +/- 2.5 vs. 5.0 +/- 2.0, p = 0.975), or decrease in synovial enhancement ratio (ER) (-1.16 +/- 0.26 vs -0.96 +/- 0.7, p = 0.492) between landmark and image guided injections Average procedure time 49 minutes longer for image-guided group (p < 0.008).

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Ref ID, Author, year	Study type	Duration	Population Description	Intervention given to relevant population	Results
4164, Parra et al., 2010 [8]	Single-arm cohort	Post-injection follow up clinic visit (available for 85% encounters)	83 children with TMJ arthritis (180 injections) 3% systemic JIA, 18% persistent oligo, 23% extended oligo, 21% RF- poly, 14% RF+ poly, 8% psoriatic, 7% ERA, 6% other (3 IBD-related arthritis, 1 pseudo-rheumatoid dysplasia, 1 inflammatory linear verrucous epidermal nevus syndrome)	US guided (CT confirmed) TMJ injection in coronal plane Triamcinolone hexacetonide in 92% injections, triamcinolone acetonide in 8%	Total of 180 TMJ injections in 83 children (116 separate encounters) 127 injections (70%) US needle placement was confirmed with CT (limited focused CT protocol) Needle placement acceptable in 115/127 joints (91%) of those confirmed with CT - Major readjustment required in 12/127 joints (9%) 80/99 (81%) good response at follow up visit, 10/99 (10%) partial response, 9/99 (9%) poor response. Complications: - Skin atrophy in 1 patient - Transient early swelling and pain in 10 patients
3491 Habibi 2012 [9]	Single Arm Cohort	2 years	39 children with JIA who had TMJ injection (63 joints injected)	Triamcinalone hexacetonide injection (10mg for 10-20kg, 15mg for 20-40kg, 20mg >40kg BW) US-guided needle placement and visualization of injectant into TMJ joints.	Efficacy of CS injection (symptom resolution and PE) 58/63 (92.06%) 1 child developed scar at site of injection.

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Ref ID, Author, year	Study type	Duration	Population Description	Intervention given to relevant population	Results
				Efficacy assessed at clinical visit 6-8 weeks later.	
901, Cahill et.al., 2007 [10]	Retrospective review	From October 2002 to February 2004,	14 girls/1 boy JIA: 9 oligo 4 poly 1 sJIA 1 pJIA	Pre-procedure MRI showed signs of inflammatory arthropathy in all 27 joints considered for treatment 27 CT guided intraarticular TMJ steroid injections were performed	Results support intraarticular CT-guided TMJ injection of a long-acting steroid in children is a safe procedure even in patients with joint space deformities. Many patients w/improved clinical symptoms: Reduction in acute and subacute inflammatory changes on MRI.
4219 Arabshahi et al. 2005 [11]	Cohort study	13 patients were Monitored 6-12 months	23 children ages 4-16 years with JIA and MRI evidence of TMJ inflammation	CT-guided TMJ injections of corticosteroid (triamcinolone acetonide [n = 16] or triamcinolone hexacetonide [n = 7]	Corticosteroid injections alleviated pain in more than two-thirds of symptomatic patients, one-third of these patients had persistence of effusions on follow up MRI. (77 % of 13 patients with pre-injection pain had pain resolution; P 0.05). Presence of jaw pain did not significantly correlate with the presence of effusions on MRI (P=0.96). Side effects: 2 patients developed facial swelling consistent with Cushing 'syndrome, lasting 2 days in 1 patient and 2 weeks in the other.
1954, Ringold et.al., 2008 [12]	Retrospective chart review	January 2000-January 2006	Twenty-five patients, 21F/4M 14ANA+ 5HLA B27 The mean age at dx 8.9 years (range 1–16 yrs, median 8.4). The mean duration of time from initial	TMJ IAS injections by OMF surgeon with GA/no imaging. Each TMJ was injected with 0.5–1 ml triamcinolone acetonide (40 mg/ml) or triamcinolone hexacetonide (20 mg/ml)	When baseline MIO (maximal incisal opening) measurements were compared to the last MIO measurements of the study period, there was a mean increase in MIO of 6.9 mm (p = 0.002; 95% CI 3, 10.7). There was a mean increase in MIO of 3.8 mm following each IAS injection (p = 0.003; 95% CI 1.4, 6.2). Patients who underwent multiple IAS injections had a mean increase in MIO after first injection of 6.6 mm (p < 0.001; 95% CI 4.1, 9.1); however, the mean increase in MIO after subsequent injections was 0.4 mm (p = 0.8; 95% CI –3.5, 4.4). One patient developed subcutaneous atrophy at the injection site. Two patients developed small, asymptomatic intraarticular calcifications. No additional adverse events were reported.

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Ref ID, Author, year	Study type	Duration	Population Description	Intervention given to relevant population	Results
			diagnosis of JIA to the onset of TMJ symptoms or suspected TMJ arthritis was 11 months (range 0–55 mo, median 2). Ten patients (40%) had TMJ complaints or suspected TMJ arthritis at their first visit.		Done without imaging guidance.

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References:

1. Cunha, A. L. G., Silva, V. B. M. e., Osaku, F. M., Niemxeski, L. B., Furtado, R. N. V., Natour, J., & Terreri, M. T. d. S. e. L. R. A. (2016). Intra-articular injection in patients with juvenile idiopathic arthritis: factors associated with a good response. Rev Bras Reumatol, 56, 490-496.
2. Young, C. M., Horst, D. M., Murakami, J. W., & Shiels, W. E., 2nd. (2015). Ultrasound-guided corticosteroid injection of the subtalar joint for treatment of juvenile idiopathic arthritis. Pediatr Radiol, 45(8), 1212-1217. doi:10.1007/s00247-015-3291-2
3. Young, C. M., Shiels, W. E., 2nd, Coley, B. D., Hogan, M. J., Murakami, J. W., Jones, K., . . . Rennebohm, R. M. (2012). Ultrasound-guided corticosteroid injection therapy for juvenile idiopathic arthritis: 12-year care experience. Pediatr Radiol, 42(12), 1481-1489. doi:10.1007/s00247-012-2487-y
4. Laurell, L., Court-Payen, M., Nielsen, S., Zak, M., & Fasth, A. (2012). Ultrasonography and color Doppler in juvenile idiopathic arthritis: diagnosis and follow-up of ultrasound-guided steroid injection in the wrist region. A descriptive interventional study. Pediatr Rheumatol Online J, 10, 11. doi:10.1186/1546-0096-10-11
5. Laurell, L., Court-Payen, M., Nielsen, S., Zak, M., Boesen, M., & Fasth, A. (2011). Ultrasonography and color Doppler in juvenile idiopathic arthritis: diagnosis and follow-up of ultrasound-guided steroid injection in the ankle region. A descriptive interventional study. Pediatr Rheumatol Online J, 9(1), 4. doi:10.1186/1546-0096-9-4

6. Tynjälä, P., Honkanen, V., & Lahdenne, P. (2004). Intra-articular steroids in radiologically confirmed tarsal and hip synovitis of juvenile idiopathic arthritis. Clin Exp Rheumatol, 22(5), 643-648.
7. Resnick, C. M., Vakilian, P. M., Kaban, L. B., & Peacock, Z. S. (2017). Is Intra-Articular Steroid Injection to the Temporomandibular Joint for Juvenile Idiopathic Arthritis More Effective and Efficient When Performed With Image Guidance? J Oral Maxillofac Surg, 75(4), 694-700. doi:10.1016/j.joms.2016.09.045
8. Parra, D. A., Chan, M., Krishnamurthy, G., Spiegel, L., Amaral, J. G., Temple, M. J., . . . Connolly, B. L. (2010). Use and accuracy of US guidance for image-guided injections of the temporomandibular joints in children with arthritis. Pediatr Radiol, 40(9), 1498-1504. doi:10.1007/s00247-010-1581-2
9. Habibi, S., Ellis, J., Strike, H., & Ramanan, A. (2012). Safety and efficacy of US-guided CS injection into temporomandibular joints in children with active JIA. Rheumatology, 51 5, 874-877.
10. Cahill, A. M., Baskin, K. M., Kaye, R. D., Arabshahi, B., Cron, R. Q., Dewitt, E. M., . . . Towbin, R. B. (2007). CT-Guided Percutaneous Steroid Injection for Management of Inflammatory Arthropathy of the Temporomandibular Joint in Children. American Journal of Roentgenology, 188(1), 182-186. doi:10.2214/AJR.04.1103
11. Arabshahi, B., Dewitt, E. M., Cahill, A. M., Kaye, R. D., Baskin, K. M., Towbin, R. B., & Cron, R. Q. (2005). Utility of corticosteroid injection for temporomandibular arthritis in children with juvenile idiopathic arthritis. Arthritis Rheum, 52(11), 3563-3569. doi:10.1002/art.21384
12. Ringold, S., Torgerson, T. R., Egbert, M. A., & Wallace, C. A. (2008). Intraarticular corticosteroid injections of the temporomandibular joint in juvenile idiopathic arthritis. J Rheumatol, 35(6), 1157-1164.

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SUPPLEMENTARY APPENDIX 3: List of Outcomes

2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis (JIA): Recommendations for Non-Pharmacologic Therapies, Medication Monitoring, Immunizations, and Imaging

Critical Outcomes:

- Quality of life (QOL) (e.g., PedsQL, CHQ, PROMIS)
- Disease activity (including active joint count, patient/parent global, MD global, ESR/CRP) as measured by the individual variables and/or composite disease activity measure (e.g., Pediatric ACR response, JADAS)
- ACR provisional criteria for clinical inactive disease
- Functional ability (e.g., CHAQ/PROMIS)
- Joint damage requiring surgical intervention
- Significant limb length discrepancy
- Significant or life-threatening adverse events (e.g., hospitalization, infection, malignancy)

Important Outcomes:

- Arthritis-related pain
- Preservation of normal growth and development
- Fatigue
- Joint damage
- Significant medication side effects leading to medication discontinuation

Risk Factors:

- Signs of joint damage
- Presence of RF or CCP antibodies
- Severe functional impairment

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SUPPLEMENTARY APPENDIX 4: Panel Teams

2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis (JIA): Recommendations for Non-Pharmacologic Therapies, Medication Monitoring, Immunizations, and Imaging

Core Leadership Team

- **Karen B. Onel**, MD, Hospital for Special Surgery, New York, NY, project PI (pediatric rheumatologist)
- **James T. Reston**, PhD, ECRI Institute, Plymouth Meeting, PA, literature review leader (methodologist)
- **Daniel B. Horton**, MD, MSCE, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ (pediatric rheumatologist)
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- **Carlos A. Cuello**, MD, PhD ,McMaster University, Hamilton, Ontario, Canada (GRADE consultant)
- **Amy S. Turner**, American College of Rheumatology, Atlanta, GA (ACR staff lead)

Voting Panel

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- Jennifer Horonjeff, PhD, Columbia University Medical Center, New York, NY (patient)
- Yukiko Kimura, MD, Joseph M. Sanzari Children's Hospital, Hackensack Meridian School of Medicine, Hackensack, NJ (pediatric rheumatologist)
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Patient Panel

- Jacob Anderson
- Leah Nicholson Bush
- Molly Dickerson
- Jennifer Horonjeff
- Stephanie Dodunski Hudgins
- Sophie Meuch
- Katherine Murphy
- Chelsea Campbell O'Donnell
- Carolina Mejia Peña
- Tammy Qualls
- Nicole Reitz
- Jennifer Rollins
- Grayson Schultz
- Sophia Sherman
- Judith Skidmore

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SUPPLEMENTARY APPENDIX 1: Methods

2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis (JIA): Recommendations for Non-Pharmacologic Therapies, Medication Monitoring, Immunizations, and Imaging

Methodology Overview

This guideline was developed following the American College of Rheumatology (ACR) guideline development process (https://www.rheumatology.org/Portals/0/Files/ACR%20Guideline%20Manual_Appendices_updated%202015.pdf). This process includes the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology (www.gradeworkinggroup.org) (1-3).

Teams Involved

A Core Leadership Team (6 members) supervised the project and was responsible for defining the scope, drafting the clinical (Patient/Intervention/Comparator/Outcomes – PICO) questions, coordinating with the Literature Review Team, overseeing the voting process, and drafting the manuscript. The Core Team, together with the Literature Review Team, was comprised of individuals with content and methodological expertise, and included a GRADE methodologist who advised on the process of developing and presenting the evidence and provided input on the quality assessment of evidence and summary of findings (SoF) tables (provided in Supplementary Appendix 2).

The Literature Review Team (15 members) conducted a systematic search, screened papers for relevance, assessed study quality, extracted data, computed pooled estimates of outcomes, graded the quality of evidence, generated the SoF tables, and compiled an evidence report.

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The Voting Panel included 15 pediatric rheumatologists and 2 patients who were diagnosed with JIA in childhood. The role of the Voting Panel was to participate in the development of the scope and PICO questions, including making judgments regarding the relative importance of the outcomes, and vote on the final recommendations, keeping the evidence report, their expertise and experience, and patient values and preferences in mind.

A Patient and Parent Panel was convened virtually to discuss patient values and preferences related to treatment options, outcomes and evidence. The two patients on the Voting Panel also participated in the Patient and Parent Panel discussions. The Voting Panel used the input from the patient meeting to help guide their votes in balancing tradeoffs between the harms and benefits of the alternative management strategies.

The ACR provided training for everyone involved in the development of this guideline, which included sessions on the ACR guideline process and GRADE methodology. See Supplementary Appendix 4 for team/panel rosters.

Patient and Parent Panel

The Patient and Parent Panel, consisting of 9 adults with juvenile idiopathic arthritis (JIA) and 6 parents of children with JIA, was convened by webinar on September 16, 2020. Ten of the 11 patients/parents were female. Dr. Karen Onel, Principal Investigator (PI) of the guideline project, and 2 ACR staff members facilitated the 5-hour webinar discussion.

The participants were first presented with the background and scope of the guideline project. They were then specifically queried on the relative importance of beneficial and adverse events of drugs and drug classes, including but not limited to efficacy, route of administration, and side effects, with particular attention paid to how values and preferences might differ in a pediatric population. The Patient and Parent Panel reviewed the evidence synthesized by the Literature Review Team as several PICO questions were discussed. The

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participants were encouraged to consider their personal experiences relevant to the questions and judge the importance of the outcomes accordingly. The two patients on the Voting Panel, who had been at the patient meeting, presented the values and preferences of the patient panel and the voting results to the Voting Panel during the two-day Voting Panel meeting held by webinar October 1-2, 2020.

Disclosures and Management of Conflicts of Interest

Per ACR policy, everyone who was intellectually involved in the project (i.e., considered for guideline authorship) disclosed all relationships (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Juvenile-Idiopathic-Arthritis). Disclosures were compared against a previously drafted list of "affected companies" (i.e., companies or organizations that were considered reasonably likely to be positively or negatively affected by care delivered in accordance with the guideline) to determine which relationships were considered potential conflicts of interest for purposes of this project. Individuals were also asked to explicitly highlight relationships with any companies *not* on the affected companies list that related to the topic of the guideline. Individuals whose primary employment (> 51% of work time/effort) was with a company that manufactured or sold therapeutics or diagnostics were not eligible to participate.

The project's principal investigator (PI), the literature review leader, and the majority of the guideline development team members had no relevant conflicts of interest for the full 12 months before this project began, through the duration of the project. However, approximately one-third of team members did have some conflicts (the ACR allows up to 49%). A participant who had any relationship with an affected company was counted as conflicted (i.e., toward the allowed threshold) regardless of the type or subject of the relationship.

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Intellectual conflicts, such as a prior publication or scientific presentation on JIA therapy, were recognized as important and were required to be disclosed, but because they were ubiquitous, intellectual conflicts were not counted as conflicted toward the allowed threshold.

Participant disclosures were included in the project plan that was posted online for public comment (see description below). In addition, disclosures of all participants were shared, in writing, with each project participant, including just before the Voting Panel meeting. Updated participant disclosures are included online with this manuscript. Finally, author disclosures are also included in this paper.

Scope and Target Audience

The scope of this project included both pharmacologic and non-pharmacologic treatment of patients with JIA, covering topics that were not covered in the ACR-Arthritis Foundation 2019 JIA and uveitis guidelines, including recommendations for the use of glucocorticoids, non-biologic, and biologic disease-modifying antirheumatic drugs (DMARDs) for the treatment of individuals with oligoarticular JIA arthritis, TMJ arthritis, and systemic JIA; screening recommendations for the use of conventional and biologic DMARDs for individuals with JIA; and guidance for the use of immunizations and imaging for individuals with JIA. The target audience for this guideline includes health care providers and patients with JIA (and/or their parents). The ACR plans to develop derivative products to facilitate implementation of this guideline.

Establishing Key Principles and PICO Development

The Core Leadership Team collaborated with the Voting Panel members to develop the initial set of PICO-formatted clinical questions for the guideline. The critical outcomes varied, depending on what the focus of the PICO question was. For PICOs relating to treatment, physical function, radiographic progression, quality of life, other patient-reported outcome

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measures, and adverse events were defined as important outcomes. Toxicity of medications, inconvenience and company input were evaluated to make guidance regarding medication monitoring. Immunizations were evaluated while considering safety, risk of flare and ability to respond. (See Supplemental Appendix 3 for a summary list of outcomes evaluated.)

The Core Leadership Team held weekly conference calls, convened an initial meeting of the Core Leadership Team, Literature Review Team and Voting Panel in which the scope of the guideline was determined, and then developed the PICO questions. The PICO questions were posted for 30 days on the ACR website for public comment and revised accordingly. Final PICO questions are included within the evidence report, in Supplemental Appendix 2 (at the top of each evidence summary that relates to a particular PICO).

Framework for the JIA Guideline Development

During initial scoping, it was agreed that the scope of the populations to be addressed would include individuals with JIA with the phenotypes of oligoarticular JIA arthritis, TMJ arthritis, and systemic JIA, with additional guidance for immunizations and imaging use for JIA patients.

After defining population groups, interventions and comparators were specified for each PICO question. The Core Leadership Team agreed that the guideline should include both pharmacologic and non-pharmacologic treatment approaches and elected to include the following interventions: NSAIDS; glucocorticoids (oral and intra-articular injections); non-biologic disease modifying anti-rheumatic drugs (nbDMARDs), including methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, and calcineurin inhibitors; biologic disease modifying anti-rheumatic drugs (bDMARDs), including TNF inhibitors (adalimumab, etanercept, infliximab, golimumab, and certilizumab pegol), IL-1 inhibitors (anakinra,

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canakinumab and rilonacept), tocilizumab, and abatacept; as well as immunizations, physical therapy, occupational therapy, diet and supplement use.

Systematic Synthesis of the Literature

Literature Searches

To identify relevant evidence for the PICO questions, a medical librarian, in collaboration with the Literature Review Team, performed systematic searches of the published English language literature. OVID Medline, PubMed, Embase, and the Cochrane Library (including Cochrane Database of Systematic Reviews; Database of Abstracts of Reviews of Effects (DARE); Cochrane Central Register of Controlled Trials (CENTRAL); and Health Technology Assessments (HTA)) were searched. Medline (PubMed) and Cochrane searches were originally run from the beginning of each database through August 3, 2019 and were updated on July 8, 2020. Embase searches were originally run from database inception through August 5, 2019 and were updated on July 8, 2020. See Supplementary Appendix 7 for detailed search strategies.

Study Selection

DistillerSR software (https://distillercer.com/products/distillers-systematic-review-software) was used to aid screening the literature search results. Teams of two independent reviewers performed duplicate screening of each title and abstract with articles identified as potentially eligible passing to review of full text. Eligible articles underwent full-text screening by two independent reviewers. Selected manuscripts were then matched to PICO questions. RCTs were preferred, when available, but in clinical scenarios not addressed by RCT data, data from observational cohort studies was used to estimate relative effects. See Supplementary Appendix 6 for details related to the study selection process.

Data Extraction and Analysis

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Data from RCTs for each PICO question was extracted into RevMan software (http://tech.cochrane.org/revman). Risk of bias of each primary study was assessed using the Cochrane risk of bias tool (http://handbook.cochrane.org/). Certain critical/important outcomes selected for this guideline were binary, and if meta-analysis was appropriate, they were analyzed using the Mantel-Haenszel method in a random effects model and reported as relative risks or odds ratios with 95% confidence intervals. Critical/important continuous outcomes and binary outcomes not combinable in a meta-analysis were tabled as reported in the individual studies.

Evidence Report Formulation

RevMan files were exported into GRADEpro software to formulate a GRADE Summary of Findings (SoF) table for each PICO question (4). The quality of evidence for each outcome was evaluated in duplicate by two independent reviewers using GRADE quality assessment criteria (1) with discordance resolved by discussion. The resulting SoF tables were compiled in an evidence report (Supplementary Appendix 2). The Core Team reviewed the evidence report and addressed possible evidence gaps prior to presentation to the Voting Panel.

Moving from Evidence to Recommendations

GRADE methodology specifies that panels make recommendations based on a consideration of the balance of benefits and harms of the treatment options under consideration, the quality of the evidence (i.e., confidence in the effect estimates), and patients' values and preferences. Key to the recommendation is the trade-off between desirable and undesirable outcomes; recommendations require estimating the relative value patients place on the outcomes.

A recommendation could be either in favor of or against the proposed intervention and either strong or conditional. According to GRADE, a recommendation is categorized as strong if

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the panel is very confident that the benefits of an intervention clearly outweigh the harms (or vice versa); a conditional recommendation denotes uncertainty regarding the balance of benefits and harms, such as when the evidence quality is low or very low, or when the decision is sensitive to individual patient preferences, or when costs are expected to impact the decision. Thus, conditional recommendations refer to decisions in which incorporation of patient preferences is a particularly essential element of decision making.

Judgments are based on the experience of the clinician panel members in shared decision making with their patients, on the experience and perspectives of the two patient members of the Voting Panel, and, to a considerable extent, on the results of discussion with the Patient Panel.

Consensus Building

The Voting Panel received the evidence report for review before it met to discuss and decide on the final recommendations. During a two-day, virtual meeting held October 1-2, 2020, the Voting Panel, for each PICO question, reviewed the evidence and feedback from the Patient Panel, and provided votes on the direction and strength of the recommendations. The virtual voting process was conducted using Poll Everywhere software (http://www.polleverywhere.com/). A 70% consensus was used as the threshold for a recommendation; if 70% consensus was not achieved during an initial vote, panel members held additional discussions before re-voting until at least 70% consensus was achieved.

Consistent with GRADE guidance, in some instances, the Voting Panel chose to provide a strong recommendation despite a low or very low quality rating of evidence (3). In such cases, a written explanation is provided describing the reasons behind this decision with reference to GRADE guidance on the matter (3).

Final Review and Approval of the Manuscript by the ACR

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In addition to journal peer reviews, the manuscript was reviewed by the following committees and subcommittees of the ACR: ACR Guideline Subcommittee; ACR Quality of Care Committee; and ACR Board of Directors. These ACR oversight groups did not mandate that certain recommendations be made within the guideline, but rather, served as peer reviewers.

Moving from Recommendations to Practice

These recommendations are designed to support health care providers who work with patients and parents in selecting therapies. Health care providers, patients and parents must take into consideration not only clinical phenotype and level of disease activity, but also comorbidities, response and tolerance of prior therapies, a patient's values and preferences, and a patient's functional status and functional goals in choosing the optimal therapy for an individual patient at the given point in treatment.

REFERENCES

1. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6.
2. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol. 2013;66(7):719-25.
3. Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013;66(7):726-35.

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4. Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. J Clin Epidemiol 2011;64:395-400.

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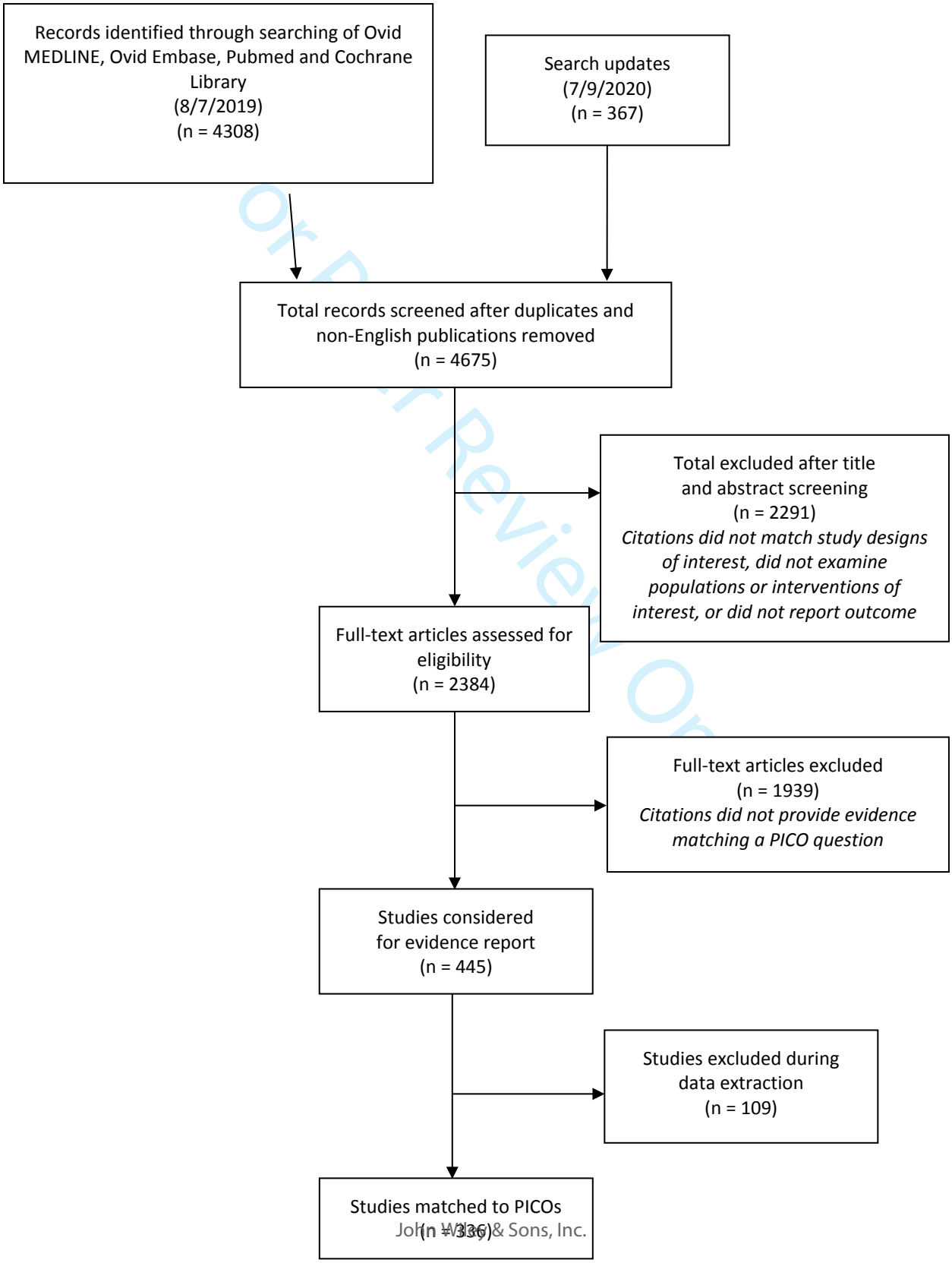
SUPPLEMENTARY APPENDIX 5: Flowchart of the Study Selection Process

2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis (JIA): Recommendations for Non-Pharmacologic Therapies, Medication Monitoring, Immunizations, and Imaging



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Supplementary Appendix 6: Research Agenda

2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis (JIA): Recommendations for Non-Pharmacologic Therapies, Medication Monitoring, Immunizations, and Imaging

These recommendations in conjunction with those published in 2019 were intended to be a "complete" coverage of the treatment of management of persons with JIA. During the writing of these recommendations, several areas for exploration were noted by patients/parents and investigators. In addition, the low level of evidence clearly pointed to necessary studies for the future.

1. Filling in evidentiary gap
2. Head to head trials of nb and bDMARDs within and across class of medication
3. bDMARD vs. nbDMARD for TMJ arthritis
4. Frequency and type of screening for mental health issues in JIA patients
5. Approach to tapering medications in remission: All subtypes
6. Diet: Role in treatment
7. Supplements: Role in treatment
8. Biosimilars:Use and monitoring
9. Exercise safety
10. Immunization safety: Clarity of risk of live virus vaccine by type of immunization

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