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Running head: Clinical study evaluating anakinra for gout flares

Title: A randomized, phase 2 study evaluating the efficacy and safety of anakinra in the treatment of gout flares

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ABSTRACT

Objective

To evaluate anakinra efficacy and safety compared to triamcinolone in the treatment of gout flares.

Methods

Patients unsuitable for NSAIDs and colchicine were enrolled in this multi-center, randomized, double-blind study lasting for up to 2 years (NCT03002974). The design was to show superiority of anakinra (100 or 200 mg/day for 5 days) over triamcinolone (40 mg single injection) for primary endpoint of changed patient-assessed pain intensity from baseline to 24–72 hours in the most affected joint measured on visual analogue scale (0–100). Secondary outcomes included: safety, immunogenicity, and patient's and physician's global response assessments.

Results

165 patients were randomized (110 to anakinra, 55 to triamcinolone). Median age was 55 (range 25–83) years, 87% were men, mean disease duration was 8.7 years, and mean number of self-reported flares during prior year was 4.5. In total, 301 flares were treated (214 anakinra; 87 triamcinolone). Both anakinra doses and triamcinolone provided clinically meaningful reduction in patient-assessed pain intensity in the 1st and subsequent flares. For the 1st flare, the mean pain intensity decline from baseline to 24–72 hours for total anakinra and triamcinolone was -41.2 and -39.4, respectively (p=0.688). Most secondary endpoints favored anakinra. No unexpected safety findings were identified. Presence of anti-drug antibodies was not associated with adverse events or altered pain reduction.

Conclusions

Anakinra was not superior to triamcinolone for the primary endpoint, but had comparable efficacy in pain reduction, and was favored for most secondary endpoints. Anakinra is an effective option for gout flares when conventional therapy is unsuitable.

Abbreviations: ADA, anti-drug antibodies; AE, adverse event; anaGO, anakinra in gout; BMI, body mass index; CRP, C-reactive protein; IL-1, interleukin-1; IL-1Ra, interleukin-1 receptor antagonist; MSU, monosodium urate; NAb, neutralizing anti-drug antibodies; NSAID, non-

steroidal anti-inflammatory drug; RA, rheumatoid arthritis; SAA, serum amyloid A; SAE, serious adverse event; ULT, urate-lowering therapy; VAS, visual analogue scale.

INTRODUCTION

Anti-inflammatory drugs used for treatment of gout flares include non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, and glucocorticoids [1, 2]. However, many patients with gout have underlying comorbidities, including hypertension, chronic kidney disease, heart disease, gastroesophageal disease and diabetes that render them unsuitable for one or more of these treatments [3-7]. Thus, there is an unmet need for effective gout flare treatment for patients who have contraindications to, do not tolerate, or are refractory to existing therapies.

Based on biological activities in gouty inflammation, and clinical data for the IL-1β-specific monoclonal antibody canakinumab [8-13] , IL-1β is an established target in the treatment of gout flares [1, 6, 7, 14-17]. That said, IL-1 inhibition according to EMA and ACR guidelines is clinically appropriate for only a small proportion of gout flares [18-19]. Anakinra is a recombinant form of the constitutively expressed soluble IL-1 receptor antagonist (IL-1Ra) that limits the activity of IL-1α and IL-1β by competitively inhibiting their binding to the IL-1 type I receptor, thereby suppressing inflammation. Efficacy of IL-1 inhibition with anakinra for gout flares is supported by a recent randomized, double-blind noninferiority trial compared to free choice of prednisone, naproxen, or colchicine [20], and multiple case series and retrospective studies, most commonly using 100 mg/day subcutaneously for 3 to 5 days. Most studies included patients with intolerance, or inadequate response to conventional anti-inflammatory therapies. In addition, the IL-1β and IL-1α inhibitory IgG1 Fc-linked fusion protein rilonacept, a soluble IL-1 receptor inhibitor effective in gout flare prophylaxis[21-24], was not associated with different pain relief, relative to indomethacin, over the first 72 hours of gout flares [25]. The current study investigated efficacy and safety of two doses of anakinra compared to the IM triamcinolone acetonide in treatment of gout flares in a randomized, blinded, controlled setting. We report on the first adequately powered randomized, controlled clinical trial evaluating anakinra, and additionally testing two anakinra dosing regimens. We tested the specific hypothesis that anakinra would be superior to IM triamcinolone for patient-assessed pain intensity in gout flare.

PATIENTS AND METHODS

Patients

Eligible patients were ≥18 years of age; had gout based on the American College of Rheumatology/European League Against Rheumatism 2015 classification criteria [26]; had ≥1 self-reported gout flare within 12 months prior to randomization; had onset of an ongoing flare within 4 days prior to randomization characterized by baseline pain intensity in the index joint of ≥50 on a 0–100 visual analogue scale (VAS), and defined by tenderness and swelling in the index joint of ≥1 on a 0 to 4-point Likert scale. Patients needed to have had ≥1 episode of intolerance or unresponsiveness to NSAIDs and colchicine or judged to be contraindicated or not appropriate for these treatments. Signs of unresponsiveness to NSAIDs and colchicine were pre-specified and included lost efficacy over time, failure to treat acute gout pain, inadequate/unsatisfactory pain relief, or incapacity to achieve/maintain adequate dose regimen of these agents. Patients using specified pain relief medications or biologics prior to randomization were excluded. Other exclusions were patients with a contraindication to triamcinolone or patients with rheumatoid arthritis (RA), polyarticular gouty arthritis (involving >4 joints), infectious/septic arthritis or any other acute inflammatory arthritis. Further details are provided in the study protocol (supplementary material).

Study design

The "anaGO" (anakinra in gout) study was a randomized, double-blind, double-dummy, active-control, multicenter study, designed to show superiority of anakinra over triamcinolone in patient-assessed pain intensity (NCT03002974). The study had three periods: a pre-screening period, a double-blind treatment period for the 1st flare in the study and an extension period for subsequent flares. Before treatment of the 1st flare, patients were randomized 1:1:1 to: anakinra 100 mg, anakinra 200 mg, or triamcinolone 40 mg (approved for treatment of gout flares) (Figure 1). An interactive web response system was used for the randomization. The randomization was stratified by urate-lowering therapy (ULT) use (yes/no) and body mass index (BMI) (<30.0 or ≥30.0 kg/m^2). Randomization was in blocks and equal numbers of patients were allocated to each group. Anakinra/placebo was

administered subcutaneously once-daily for 5 days and triamcinolone as a single intramuscular injection at Day 1. In accordance with the double dummy design the patients received one i.m. injection and 2 s.c injections on Day 1 and two s.c. injections Day 2-5. Treatments were initiated on the day of randomization (Visit 1) and were supervised or given by the investigator (or delegated study staff) at the out-patient clinic, emergency department (ED) or hospital. If a patient was treated at an outpatient clinic or was discharged from the hospital before the end of the 5-day drug administration period, the daily subcutaneous injections were administered at home by the patient themselves or a caregiver. The treatment and follow-up of the patients' flare was double-blinded i.e. blinded for the patients, the investigators and any other study personnel involved with the study conduct or evaluation at the investigational sites, contract research organization and sponsor.

The extension period continued until 52 weeks after randomization of the last patient, but no longer than 2 years for each patient. Protocolized treatment for subsequent flares was the same as for the 1st flare and the blinding was maintained for the patients, the investigational sites, and study personnel at the contract research organization until the final database lock.

Ethical approval was provided by the following institutional review boards: 'Western Institutional', 'University of Michigan Medical School', 'Duke Medicine Institutional Review Board for Clinical Investigations', 'Quorum Institutional' and 'Advarra' (acquired Quorum Review). The study was conducted in compliance with ICH-GCP and in accordance with the latest revision of the declaration of Helsinki. All patients provided informed consent prior to study admission.

Outcome measures

The primary endpoint was the change in patient-assessed pain intensity from baseline to 24–72 hours (average of assessments at 24, 48 and 72 hours) (Study objectives and endpoints are listed in Supplementary Table 1 and 2). Patients scored pain intensity in the joint most affected at baseline (the index joint) on a 0–100 VAS, ranging from no pain (0) to unbearable pain (100) using an e-diary. Allowed rescue medication was paracetamol/acetaminophen and/or codeine, short acting tramadol, and topical ice/cold packs. If insufficient relief,

prednisone or prednisolone was permitted. In addition, physician and patient assessment of global response to treatment, physician assessment of clinical signs (index joint tenderness, swelling and erythema), change in the serum concentration of the inflammatory biomarkers C-reactive protein (CRP) and serum amyloid A (SAA), safety variables, serum concentration of IL-1Ra and occurrence of anti-drug antibodies (ADA) and neutralizing antibodies (NAb) were assessed at baseline and after a flare.

Statistical methods

The population used for the primary analysis comprised all randomized patients grouped according to randomized treatment and stratum, regardless if any dose of study drug was administered or not.

Sample size calculation was based on the change in pain intensity on a VAS from baseline to 24–72 hours. A sample size of 106 patients receiving anakinra and 53 receiving triamcinolone ensured a power of 80% to reject the null hypothesis of no difference between anakinra and triamcinolone assuming a true difference of 12 on VAS mean change and a standard deviation of 25 when using a two-sided test with a significance level of 5%.

The main efficacy analyses were performed when all patients had completed Day 15 of the 1st flare. The primary endpoint was estimated using a mixed model repeated measures analysis with the measurements on the individual time points as responses and with treatment, ULT use, BMI, visit and treatment-visit-interaction as fixed effects, and center as a random effect.

Secondary time-to-event endpoints were analyzed using a stratified log-rank test, with ULT use and BMI as stratification factors. Secondary continuous endpoints were evaluated using an analysis of covariance including factors for treatment, ULT use, BMI and baseline value as covariate. Secondary binary endpoints were evaluated using a logistic regression model with treatment, ULT use, and BMI as explanatory variables.

Adverse events

Adverse events (AE) were reported from the first treatment to Day 28. In case of a subsequent flare, AE reporting started again. All AEs were followed up until resolution or until the patient's study participation ended. Serious adverse events (SAE) were reported

from the time of signing the informed consent to Week 12, thereafter only if a causal relationship to the treatment was suspected.

RESULTS

Patients characteristics

227 patients were screened and 165 patients were randomized to treatment; 110 to anakinra (56 to anakinra 100 mg and 54 to anakinra 200 mg) and 55 to triamcinolone. For 4 patients no data for the primary efficacy analysis were recorded; 3 patients (1 in the anakinra 200 mg group, 2 in the triamcinolone group) had missing pain (VAS) up to 72 hours due to technical issues with the diary device and 1 patient was randomized in error and did not receive anakinra 200 mg (Figure 2).

The median age (range) was 55 (25–83) years, 87% were men, 72% were white, mean (SD) disease duration was 8.7 (8.0) years and mean number (SD) of self-reported flares during the past year was 4.5 (2.5). Approximately 45% of the patients in both anakinra and triamcinolone groups used ULT at baseline. Almost half of the patients had more than 3 of the selected comorbidities at baseline (50.0% and 43.6% in the anakinra (total) and triamcinolone groups, respectively). Diabetes mellitus (type 2) was more common in the anakinra (total) group than in the triamcinolone group (32 [29.1 %] versus 9 [16.4 %], respectively), whereas obesity was comparable (76.4% of the patients in the triamcinolone group and 73.6% in the anakinra group had a BMI ≥30).

The patients included in the study were considered unsuitable for treatment with NSAIDs and colchicine as judged by the study investigators. The most common reason was lack of efficacy (Supplementary Table 3).

The study started in December 2016 and recruitment continued until May 2018. The patients were followed until August 2019 when the sudy ended. Patient demographics and baseline characteristics were similar between groups (Table 1).

Patient-assessed pain intensity

The mean change from baseline to 24–72 hours in patient-assessed pain intensity (VAS) for the 1st flare was -41.2 for total anakinra (95% CI: -46.3, -36.2) and -39.4 for triamcinolone

(95% CI: -46.8, -32.0). Similar change in pain intensity was demonstrated both in the anakinra 100 mg group, -41.8 (95% CI: -48.9, -34.8), and the anakinra 200 mg group, -40.7 (95% CI: -47.9, -33.4). The difference in mean change between the total anakinra and triamcinolone groups (-1.8; 95% CI: -10.8, 7.1), was not statistically significant (p=0.688) (Table 2).

Similar results were obtained for patient-assessed mean pain intensity measured by VAS and Likert scale at 6, 12, 18, 24, 36, 48 and 72 hours and Day 5, 6, 7 and 8 for the 1st flare in the anakinra and triamcinolone groups (Supplementary Figure 1).

The mean (SD) time from pain onset to treatment start for the first flare in the study was 2.0 (1.0) days for triamcinolone and 2.2 (0.9) days for anakinra.

Time to effect of treatment

The median time to pain resolution was 120.5 hours in the total anakinra group and 167.5 hours in the triamcinolone group (Hazard ratio 1.29 [95% CI: 0.9, 1.9]). The median time to response was 46.7 hours in the total anakinra group, and 47.6 hours in the triamcinolone group (Hazard ratio 1.19 [95% CI: 0.8, 1.7]). The median time to onset of effect for the 1st flare was 17.8 hours in the total anakinra group and 22.3 hours in the triamcinolone group (Hazard ratio 1.11 [95% CI: -0.8, 1.6]) (Supplementary Table 4). Differences between the treatment groups were not statistically significant. During the time interval between the first study drug administration and Day 15, 49 (44.5%) of patients in the total anakinra group and 26 (47.3%) in the triamcinolone group took rescue medication. Since fewer than 50% of the patients took rescue medication, the overall median time to first intake of rescue medication was not calculable.

Patient and physician assessments

The mean patient's assessment of global response to treatment was significantly better in the total anakinra group compared to the triamcinolone group, at Day 8 (-0.63; 95% CI: -1.03, -0.22) and Day 15 (-0.44; 95% CI: -0.86, -0.02). The mean physician's assessment of global response to treatment was also significantly better in anakinra-treated patients at Day 8 (-0.40; 95% CI: -0.78, -0.02). In addition, physician's assessments of tenderness and swelling were significantly better in the total anakinra group compared to the triamcinolone group at 72 hours for both tenderness (-0.47; 95% CI: -0.73, -0.20) and swelling (-0.31; 95%

CI: -0.56, -0.05), and at Day 8 for swelling (-0.33; 95% CI: -0.55, -0.11). Furthermore, significantly less presence of erythema was reported in the total anakinra group compared to the triamcinolone group at 72 hours (odds ratio 0.47; 95% CI: 0.23, 0.95). The differences between the treatment groups showed improvement in favor of anakinra for most of the secondary endpoints (Table 3).

CRP and SAA

Anakinra-treated patients had significantly reduced CRP levels at 72 hours and at Day 8, compared to those in the triamcinolone group, -0.93; 95% CI: -1.58, -0.29 and -0.55; 95% CI: -1.05, -0.04, respectively. However, at Day 15 CRP levels were significantly reduced in the triamcinolone group compared to the total anakinra group (0.78; 95% CI: 0.16, 1.40) (Supplementary Figure 2A).

Anakinra-treated patients had a significant reduction of SAA levels at 72 hours compared to those treated with triamcinolone (-60.65; 95% CI: -106.24, -15.06) and at Day 8 (-26.66; 95% CI: -49.72, -3.61), whereas no difference was found between the treatment groups on Day 15 (Supplementary Figure 2B).

Extension phase

The median (range) time of study participation was 62.4 (0.1–119.6) weeks for all patients, and was similar in each treatment group (Supplementary Table 5).

161 patients were treated for 1 flare (anakinra 100/200 mg, n=55/52; triamcinolone, n=54) and 61 for 2 flares (anakinra 100/200 mg, n=23/21; triamcinolone, n=17). More than twice as many patients were treated for 3 flares in the anakinra groups compared to the triamcinolone group (anakinra 100/200 mg, n=13/13; triamcinolone, n=5). One patient (anakinra group) was treated for 9 flares. Overall, 301 flares were treated in the study (214 anakinra, 87 triamcinolone).

Similar reduction in pain intensity for the 1st flare was demonstrated for the 2nd and 3rd flares. For the 2nd flare, the mean change in pain was -33.9 for anakinra and -31.1 for triamcinolone. For the 3rd flare the mean change in pain was -31.8 for anakinra and -51.2 for triamcinolone. The difference in the mean change for 2nd flare between anakinra and triamcinolone did not reach statistical significance (p=0.724) while the mean change in pain

intensity for the 3rd flare was significantly in favor of triamcinolone, although the number of subjects contributing to this finding was small (26 anakinra patients vs. 5 triamcinolone patients) (p=0.049) (Table 2). This difference was not due to NAbs to anakinra, since no patients in the anakinra-group had NAbs when experiencing the 3rd flare (Supplementary Figure 3). Changes in pain were not analyzed for 4th to 9th flares due to the low number of patients. Overall, anakinra showed numerically better improvement for most of the secondary endpoints (Table 3).

Safety

The incidence of treatment emergent AEs during all flares was similar in both treatment groups (Table 4). No unexpected safety findings were observed. Hypertriglyceridemia (5 patients), neutropenia (4 patients) and various types of injection site reactions (erythema, pruritus or swelling) were the most frequently reported AEs in the anakinra groups. When assessing all laboratory values, hypertriglyceridemia occurred in a similar frequency in all treatment groups and was assessed as related to the studied population. Headache (2 patients) was most common in the triamcinolone group. The majority of AEs were mild. In the anakinra group, severe AEs were observed in 8 patients (7.5%) whereas SAEs were reported by 5 patients (4.7%). SAEs in the anakinra group were: gastric ulcer, anemia, seizure, respiratory failure, cardiogenic shock, acute respiratory failure, coronary artery disease and sickle cell anemia. All SAEs were judged not causally related to anakinra. No severe AE or SAE were observed in the triamcinolone group. The pattern and frequency of AEs did not appear to change during treatment of repeated flares.

Immunogenicity

107 anakinra-treated patients were tested for ADAs; 19 (17.8%) had ADAs in low titers at some time point, and 4 (3.7%) had NAbs (Supplementary Figure 3). Seven (6.5%) patients tested positive for ADA already at baseline, which was similar to healthy individuals during method validation. Of the 12 (11.2%) anakinra treatment-induced ADA positive patients, 6 had repeated positive ADA at subsequent flares 2 to 8. Two triamcinolone-treated patients were positive for anakinra ADA at baseline. Of the 12 treatment-induced ADA positive patients, 7 (58.3%) tested positive for cross-reactivity with “endogenous-like” recombinant

IL-1Ra (IL-Ra ADA) and 3 (25.0%) were positive for NAbs. Incidence of NAbs was similar to that previously observed for other indications and treatment regimens with anakinra. Frequency of ADA occurrence did not appear to change across the repeated flares, with overall low ADA and NAbs titers. No ADA-associated AEs were observed and there was no apparent impact of ADA on anakinra serum exposure, serum levels of CRP, SAA or pain in the index joint up to Day 8.

DISCUSSION

This study evaluated efficacy, safety and dosing of anakinra for gout flares in patients unsuitable for conventional anti-inflammatory therapy. Anakinra was not superior to triamcinolone with regards to the primary outcome, but outperformed triamcinolone on most of the individual secondary outcomes. Anakinra dosed at 100 mg/day for 5 days was comparable to 200 mg/day, therefore the lower dose appears to be the clinically appropriate choice for treatment of a gout flare. Gout is a recurrent disease frequently requiring episodic re-treatment. Here, the study extension period added to background evidence that anakinra is safe for recurrent episodic use [1, 6, 7, 14-17].

The most common reason for inappropriateness for NSAID-treatment among the study participants was “lack of efficacy of NSAIDs”. Since NSAIDs typically are effective in the treatment of gout flares, it is conceivable that many patients were subject to relatively refractory gout. This notion was supported by resolution of pain in only 65.5% (triamcinolone) and 63.6% (anakinra) at Day 15 in this study.

Strengths of this study included a design that mimicked real-world treatment scenarios, which included patients with co-morbidities, and using ULT before or during the study. A superiority study design was selected to comply with USA regulatory agency guidance at the time, which specified that trials intending to provide evidence of efficacy for an analgesic should be designed as superiority trials and that the comparator could be a lower dose of the investigational drug, placebo, or an active comparator. However, for the purpose of fully informing clinicians, a non-inferiority design would have been more appropriate. A prime example is the randomized trial with a non-inferiority design that recently observed anakinra

to be non-inferior to the free choice of prednisone, naproxen, or colchicine treatment as usual for gout flares [20].

The use of biologics raises the issue of immunogenicity and the potential development of ADAs, the occurrence of which can be linked to altered pharmacokinetics, increased risk of AEs, and reduced efficacy. Previous immunogenicity data with anakinra in patients with severe cryopyrin-associated periodic syndrome (CAPS) or RA have not indicated ADAs to be associated with significant safety concern [27-29]. However, in CAPS and RA, anakinra was administered persistently, rather than intermittently as in this study. Overall, in this study the frequency of ADA-positive patients in the anakinra treatment groups was low and did not increase after repeated treatments. Furthermore, anakinra appeared to be generally well tolerated, with safety profile similar to previous observations in other indications and during post-marketing use.

The terminal half-life of anakinra ranges from 4 to 6 hrs, which is considerably shorter than that of triamcinolone. Moreover, the effect of triamcinolone can be much longer than the half-life in plasma would suggest (delayed effect) such that the extended effect is not directly linked to plasma half-life. As seen from the inflammatory biomarkers CRP and SAA, anakinra had a more immediate short-term onset of effect but shorter duration of effect compared to triamcinolone.

Although anakinra was not superior to triamcinolone, it may be an alternative therapy for patients who cannot tolerate the approved therapies, or who fail to respond to such therapies, as recommended by current American College of Rheumatology and European League Against Rheumatism guidelines. In contrast to glucocorticoids and/or NSAIDs, anakinra has not been reported to exacerbate diabetes, or promote hypertension, renal failure, sodium retention, gastric ulcerogenesis or myocardial infarction [30]. Morever, colchicine must be dosed with caution in patients with chronic kidney disease, those taking potent CYP3A4 or P-Gp inhibitors, or those on a sustained colchicine flare prophylaxis regimen, or who have recently used colchicine to treat a gout flare.

There were some limitations of this study. Since anakinra and triamcinolone reduced pain to similar extent in this trial, we speculate that a possible ceiling effect was reached for alleviation of gout flare-related pain by the anti-inflammatory agents. As such, pain response

as the primary endpoint might be seen as a limitation, particularly since secondary endpoints favored anakinra in this trial. Clearly, pain is an important and relevant endpoint in gout, and, unlike multiple other clinical response paramaters, is endorsed by OMERACT as a validated outcome measure for acute gout flare [31]. However, there has been recent attention to the need to better evaluate other clinical aspects of gout flares of importance to the patient such as tenderness, swelling, and immobility, including by a composite endpoint. One composite endpoint instrument in development, the Gout Attack Intensity Score, lacked floor or ceiling effect in using patient-reported symptoms for discriminating responders from non-responders [32], when analyzing data from the trial of anakinra compared to free choice usual care [20]. Finally, comparative effectiveness of anakinra and other IL-1 inhibitors for gout flare was beyond the scope of this study. Unlike 5-day dosing of anakinra in this study, a single 150 mg dose of canakinumab was superior to the same 40 mg IM triamcinolone acetonide comparator used here, by ~11 mm for pain relief at 72 hours on a 0-100 mm VAS in acute gout flare [9]. While it is inappropriate to directly compare studies post hoc, the study designs, study populations, and adherence to therapy appeared not to differ extensively and there is therefore no obvious explanation for the different results. It is not possible to perform a robust quantitative comparison of the primary outcome of VAS pain responses in our anaGO study compared to the IL-1β blocking trials with canakinumab for acute gout flares. Future head-to-head studies will be needed to directly test differences in the therapeutic effects for acute gout flare of distinct biologic IL-1 antagonists, and to discern the clinical immunopharmacologic bases for such differences.

In conclusion, anakinra was not superior to triamcinolone in this study but showed a substantial and similar reduction in patient-assessed pain, and most secondary outcomes favored anakinra. Consistent with current treatment guidelines, anakinra can be considered as an effective option in the treatment of gout flares when conventional therapy is unsuitable.

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FIGURE LEGENDS

Figure 1: The anaGO clinical study design.

anaGO study design. BL, baseline; D, day; EOS, end of study; FU, follow-up by phone; W, week; *Visits take place only if no subsequent flare has occurred; **Telephone call every 12 weeks after the latest flare has occurred and been treated with study drug.

Figure 2. Patient CONSORT flow diagram for the 1st flare of the study.

[a] Withdrawal by subject; [b] Randomized in error; [c] Withdrawal by subject (n=1) and Randomized in error (n=1); [d] Missing pain VAS up to 72 hours due to technical issues with the

diary device (n=2); [e] Randomized in error and did not receive IMP (n=1), Missing pain VAS up to 72 hours due to technical issues with the diary device (n=1).

Table 1: Demographics and baseline characteristics

		Triamcinolone N=55	**Total anakinra** N=110	**Anakinra 100 mg/day** N=56	**Anakinra 200 mg/day** N=54
Age (years)	Median (min, max)	56.0 (30, 83)	54.0 (25, 79)	53.5 (25, 79)	54.0 (27, 78)
Sex, n (%)	Male	48 (87.3)	95 (86.4)	48 (85.7)	47 (87.0)
Race, n (%)	White	39 (70.9)	80 (72.7)	38 (67.9)	42 (77.8)
	Black/African American	15 (27.3)	27 (24.5)	15 (26.8)	12 (22.2)
	Asian	1 (1.8)	3 (2.7)	3 (5.4)	0
eGFR (mL/min/1.73m^2), n(%)	≥90	9 (16.4)	34 (30.9)	22 (39.3)	12 (22.2)
	≥60-<90	31 (56.4)	54 (49.1)	23 (41.1)	31 (57.4)
	≥30-<60	11 (20.0)	15 (13.6)	7 (12.5)	8 (14.8)
	≥15-<30	1 (1.8)	0	0	0
	Missing	3 (5.5)	7 (6.4)	4 (7.1)	3 (5.6)
Disease duration (years), n (%)	Mean (SD)	7.7 (7.6)	9.2 (8.3)	9.7 (8.8)	8.6 (7.7)
No. of self-reported flares during the last year, n (%)	Mean (SD)	4.4 (2.0)	4.5 (2.7)	4.6 (3.4)	4.4 (1.7)
No. of affected joints at randomization, n (%)	1	46 (83.6)	82 (74.5)	43 (76.8)	39 (72.2)
	2 to 4	9 (16.4)	24 (21.8)	11 (19.6)	13 (24.1)
	Not reported	0	4 (3.6)	2 (3.6)	2 (3.7)
Tophi present, n (%)		21 (38.2)	38 (34.5)	17 (30.4)	21 (38.9)
ULT use at randomization, n (%)		23 (41.8)	50 (45.5)	28 (50.0)	22 (40.7)
No. of comorbidities	0	0	2 (1.8)	1 (1.8)	1 (1.9)
	1	2 (3.6)	9 (8.2)	7 (12.5)	2 (3.7)
	2	10 (18.2)	19 (17.3)	8 (14.3)	11 (20.4)
	3	16 (29.1)	19 (17.3)	13 (23.2)	6 (11.1)
	>3	24 (43.6)	55 (50.0)	25 (44.6)	30 (55.6)
	Not reported	3 (5.5)	6 (5.5)	2 (3.6)	4 (7.4)

BMI, body mass index; No., number; ULT, urate-lowering therapy

Table 2: Estimated change in patient-assessed pain intensity (VAS) in index joint from baseline to 24-72 hours, flare 1-3

	Total Triamcinolone (N=55)	Total Anakinra (N=110)	Anakinra 100 mg (N=56)	Anakinra 200 mg (N=54)
Flare 1 (n)	53	108	56	52
Baseline, mean (95% CI)	77.9 (73.0, 82.8)	75.5 (71.4, 79.5)	75.6 (70.9, 80.3)	75.4 (70.7, 80.0)
24-72 hours, mean (95% CI)	38.5 (30.6, 46.4)	34.2 (28.4, 40.1)	33.8 (26.2, 41.3)	34.7 (27.1, 42.3)
Mean change from baseline (95% CI)	-39.4 (-46.8, -32.0)	-41.2 (-46.3, -36.2)	-41.8 (-48.9, -34.8)	-40.7 (-47.9, -33.4)
Diff. vs triamcinolone (95% CI) in mean change	Ref.	-1.8 (-10.8, 7.1)	-2.4 (-12.6, 7.8)	-1.2 (-11.6, 9.1)
P-value		0.688	0.643	0.812
Flare 2 (n)	17	42	22	20
Baseline, mean (95% CI)	78.7 (69.2, 88.3)	74.8 (67.4, 82.2)	80.6 (71.8, 89.4)	69.0 (60.2, 77.8)
24-72 hours, mean (95% CI)	47.6 (35.1, 60.1)	40.9 (31.7, 50.1)	45.3 (34.3, 56.3)	36.5 (24.3, 48.7)
Mean change from baseline (95% CI)	-31.1 (-44.6, -17.6)	-33.9 (-42.5, -25.4)	-35.3 (-46.7, -23.9)	-32.5 (-45.3, -19.7)
Diff. vs triamcinolone (95% CI) in mean change	Ref.	-2.8 (-18.8, 13.2)	-4.2 (-21.9, 13.5)	-1.4 (-20.0, 17.2)
P-value		0.724	0.631	0.879
Flare 3 (n)	5	26	13	13
Baseline, mean (95% CI)	80.4 (67.5, 93.2)	76.6 (70.7, 82.4)	79.2 (71.7, 86.8)	73.9 (65.9, 81.9)
24-72 hours, mean (95% CI)	29.2 (11.2, 47.3)	44.8 (36.7, 53.0)	38.9 (28.1, 49.6)	50.8 (39.1, 62.4)
Mean change from baseline (95% CI)	-51.2 (-68.8, -33.5)	-31.8 (-39.7, -23.9)	-40.4 (-51.3, -29.5)	-23.1 (-34.6, -11.7)
Diff. vs triamcinolone (95% CI) in mean change	Ref.	19.4 (0.1, 38.7)	10.8 (-10.0, 31.5)	28.0 (7.0, 49.1)
P-value		0.049	0.297	0.011

CI, confidence interval; Diff., difference; VAS, visual analogue scale.

Table 3. Secondary endpoints, global assessments and signs of inflammation, anakinra versus triamcinolone

Secondary endpoints	Flare #	Day 4	Day 8	Day 15
Patient's assessment of global response to treatment	1	+	+	+
	2	+	+	+
	3	+	+	+
Physician's assessment of global response to treatment	1	+	+	+
	2	+	+	+
	3	+	+	+
Physician's assessment of tenderness	1	+	+	-
	2	+	-	+
	3	+	-	-

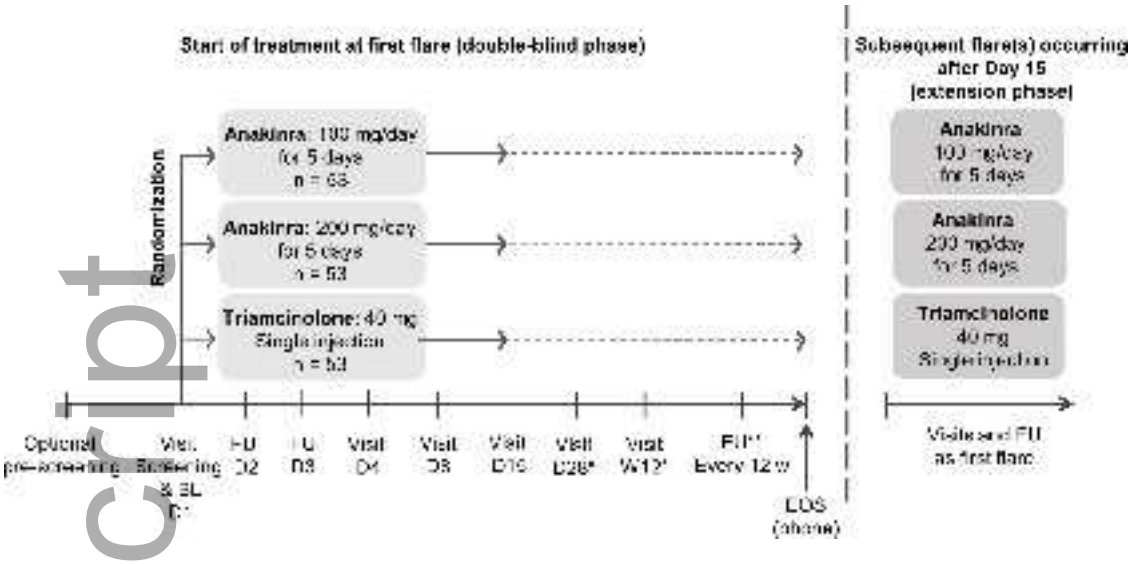
Physician's assessment of swelling	1	+	+	+
	2	+	-	-
	3	+	+	+
Physician's assessment of erythema	1	+	-	-
	2	+	-	+
	3	+	+	-

Notes: + indicates outcome in favor of anakinra; - indicates outcome in favor of triamcinolone; dark orange indicates statistically significant difference (statistical testing was only performed at flare 1); light orange color indicates numerical difference in favor of anakinra; white color indicates numerical difference in favor of triamcinolone.

Table 4: Overall summary of patients with treatment-emergent adverse events during the study

	Triamcinolone (N=54) n (%)	**Total anakinra (N=107) n (%)**	**Anakinra 100 mg/day (N=55) n (%)**	**Anakinra 200 mg/day (N=52) n (%)**
TEAE	22 (40.7)	50 (46.7)	21 (38.2)	29 (55.8)
Severe TEAE	0	8 (7.5)	5 (9.1)	3 (5.8)
Non-serious TEAE	22 (40.7)	48 (44.9)	19 (34.5)	29 (55.8)
Serious TEAE	0	5 (4.7)	4 (7.3)	1 (1.9)
Related TEAE	2 (3.7)	22 (20.6)	8 (14.5)	14 (26.9)
Fatal TEAE	0	0	0	0
TEAE leading to study withdrawal	2 (3.7)	1 (0.9)	0	1 (1.9)
TEAE leading to drug withdrawn	3 (5.6)	3 (2.8)	1 (1.8)	2 (3.8)

TEAE, treatment-emergent adverse event



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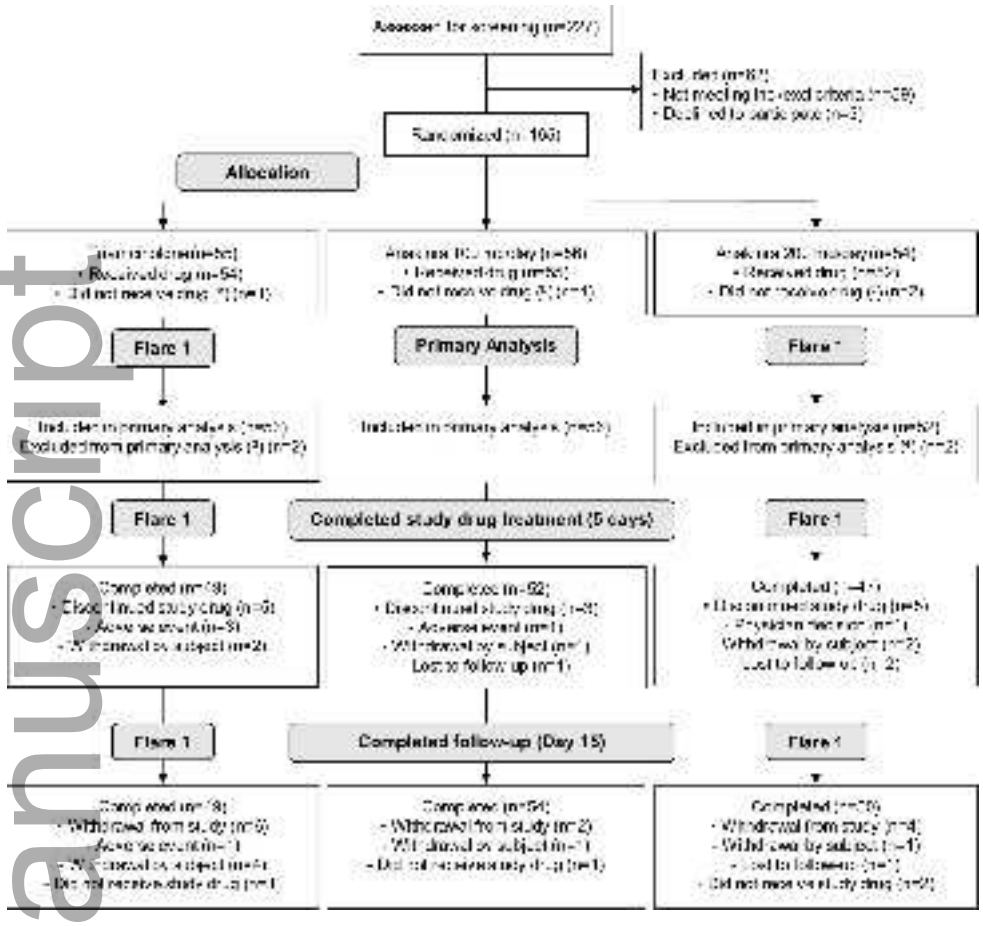

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