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REVIEW ARTICLE

The use of non-transplant biologics in solid organ transplant recipients: A practical review for the frontline clinician

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Abstract

Biologics have become the forefront of medicine for management of autoimmune conditions, leading to improved quality of life. Many autoimmune conditions occur in solid organ transplant (SOT) recipients and persist following transplant. However, the use of biologics in this patient population is not well studied, and questions arise related to risk of infection and adjustments to induction and maintenance immunosuppression. Guidelines have been published highlighting management strategies of biologics around the time of elective surgical procedures, but this is not always feasible in urgent situations, especially with deceased donor transplantation. The aim of this review is to summarize the current literature regarding the use of these agents in solid organ transplant recipients, and specifically address induction and maintenance immunosuppression, as well as the need for alternative infective prevention strategies to create

This paper represents the opinion of the Immunology/Transplantation Practice and Research Network of the American College of Clinical Pharmacy. It does not necessarily represent an official ACCP commentary, guideline, or statement of policy or position.

a practical reference for the frontline clinician, when faced with this complex clinical scenario.

KEYWORDS
biologics, immunosuppression, solid organ transplant

1 | INTRODUCTION

Biologic agents provide targeted therapy for autoimmune diseases and dramatically increase disease remission and improve patient quality of life. Many conditions managed with biologics will persist following solid organ transplantation (SOT), often requiring continued biologic therapy. However, the increased infection risk associated with biologics raises safety concerns for use in SOT recipients managed with immunosuppressive therapies required to prevent allograft rejection. As such, guidance for safe and effective use of biologics in SOT populations is important and necessary.

Available guidelines have addressed biologic therapy management at the time of non-SOT related surgical procedures for select autoimmune diseases, with the goal of decreasing infection risk without increasing the risk of disease flare.[1–3] Most of these guidelines recommend a case-by-case approach but state that it may be reasonable to discontinue therapy prior to surgery and schedule the surgery at the end of a dosing cycle. Additionally, these guidelines recommend waiting at least 2 weeks after surgery and ensuring the wound has healed properly, all sutures/staples have been removed, and no infections are present prior to re-initiation of the biologic. Translating this guidance to the perioperative period for SOT is challenging, particularly for deceased donation, as surgery typically occurs with very short notice. In these instances, holding biologic therapy prior to transplantation is not feasible and continuation of therapy is most practical. However, living donor transplantation scheduled sufficiently in advance would allow for a planned interruption of biologic therapy. These guidelines, however, do not specifically address patients receiving maintenance immunosuppression for SOT, which comes with its own infectious complications.

Currently, no published guidelines or consensus recommendations outlining the risk and benefit of biologic use in SOT recipients exist. This piece aims to summarize the current literature regarding the use of these agents in both the perioperative and post-transplant period, and specifically address induction and maintenance immunosuppression as well as the need for alternative infective prevention strategies to create a practical reference for the frontline clinician, when faced with this clinical scenario.

2 | METHODS

This review was completed by members of the Immunology/Transplantation Practice and Research Network of the American College of Clinical Pharmacy. PubMed, EMBASE, and the Cochrane Controlled Trials Register were reviewed for English language articles on biologics for autoimmune conditions and use in adult (age ≥ 18 years) SOT recipients. Additional studies were identified by searching abstracts presented at the American Transplant Congress. There were no restrictions on study design. Studies were identified using Medical Subject Headings. Keywords used for literature searches included: solid organ transplant, IL-12/IL-23, IL-6, IL-17, BLyS-specific inhibitors, complement inhibitors, CD antagonists, CD-80/86, check point inhibitors, and infection. Literature was evaluated to address the following clinical issues:

1) Potential need for pre-transplant washout
2) Indication for modification of induction/maintenance immunosuppression
3) Potential withholding of biologic in peri/post-transplant period
4) Assess if additional infection risk and need for alternative prophylaxis strategies

Biologic agents widely used in SOT for desensitization and antibody-mediated rejection, such as rituximab and tocilizumab, were omitted from this review. A summary of biologic agents by medication class addressing the above questions can be found in Table 1. A graphic highlighting the role each agent plays in overall immune regulation can be found in Figure 1.

The majority of literature identified consisted of case reports and case series or extrapolations from non-transplant populations. Therefore, because the quality of evidence supporting our recommendations is low, this document is designed to provide general guidance rather than firm recommendations. Additionally, there should be a multidisciplinary collaboration between the transplant team and biologic prescriber to discuss individual risk assessment and care planning. Patient specific factors such as extent of disease control and risk of relapse should factor into decision making.

3 | AGENTS

3.1 | T-cell co-stimulation blocker: CD-80/86

Abatacept is a fusion protein of an Fc of immunoglobulin (IgG) 1 and the extracellular domain of cytotoxic T lymphocyte protein 4 (CTLA4). It was the first agent developed to target the CD28-CD80/CD86

TABLE 1 Summary of biologic agents by medical class

Medication Class	Agents	Mechanism of Action	Pre-Transplant Washout	Use in Peri/ Post-Transplant	Induction IS Changes	Maintenance IS Changes	Infection Prophylaxis (PPx)	Article citations
T-Cell Costimulation Blocker	Abatacept	Binds to CD80/CD86 on antigen presenting cells which results in CD28 blockade and inhibition of T-lymphocyte activation	Not addressed in the literature	Continue therapy	No evidence to suggest adjustments are necessary	No evidence to suggest adjustments are necessary; could consider modified CNI goals	No additional PPx indicated. Additional surveillance for viral infection may be warranted	4–13
TNF-alpha antagonists	Adalimumab (recombinant monoclonal antibody) Certolizumab (pegylated humanized antibody) Etanercept (recombinant DNA-derived protein) Golimumab (human monoclonal antibody) Infliximab (chimeric monoclonal antibody)	Each agent interferes with the binding of human tumor necrosis factor alpha (TNF-α) to its receptor site and inhibit the inflammatory process driven by cytokines. (REF)	Consider holding IV TNF-alpha 4 weeks prior and SQ TNF-alpha 1 week prior to living donor transplantation	Consider holding as standard IS may be sufficient to control autoimmune disease. If patient develops recurrence of disease, resume TNF-alpha antagonist	If held prior to transplant, no change to induction IS. In patients who cannot stop TNF-alpha antagonists prior to transplant, a risk-benefit discussion should be made with the transplant team to evaluate the induction therapy utilized and consider less potent therapy	No evidence to suggest adjustments are necessary; May be reasonable to modify based on infectious risk	No additional PPx indicated. It is recommended to monitor patients for *Candida*, hepatitis B virus, BK, cytomegalovirus (CMV), and Epstein-Barr Virus (EBV) infections during treatment with anti-TNF-α.	14–31
IL-inhibitor	IL-4 [dupilumab] IL-17 [brodalumab, ixekizumab, secukinumab] IL-23 [guselkumab, risankizumab, ustekinumab, tildrakizumab]	Inhibit IL and therefore prevent cytokine driven inflammatory responses and reduce the production of acute phase reactants. (REF)	Insufficient evidence to say they must be held; Holding for one dosing interval may be a reasonable approach to reduce the risk of disease flares and need for rescue medications prior to surgery.	Consider holding as standard IS may be sufficient to control autoimmune disease. If IL-inhibitors are resumed, recommend waiting at last 2 weeks and ensuring proper wound healing	No evidence to suggest adjustments are necessary	No evidence to suggest adjustments are necessary	No additional PPx indicated. It is recommended to monitor patients for *Candida* infections during treatment with IL-17 inhibitors. Additional monitoring for tuberculosis and viral infections in patients receiving IL-inhibitors may be warranted.	32–57

(Continues)

TABLE 1 (Continued)

Medication Class	Agents	Mechanism of Action	Pre-Transplant Washout	Use in Peri/ Post-Transplant	Induction IS Changes	Maintenance IS Changes	Infection Prophylaxis (PPx)	Article citations
BLyS inhibitor	Belimumab	Prevent the binding of soluble human B lymphocyte stimulator protein (BLyS) to receptors on B lymphocytes preventing the survival of B lymphocytes	Insufficient evidence to say they must be held; Holding for one dosing interval may be a reasonable approach to reduce the risk of disease flares and need for rescue medications prior to surgery.	Consider holding as standard IS may be sufficient to control autoimmune disease. If patients experience a flare-up of their autoimmune disorder, they can re-initiate their BLyS inhibitor post-transplant without increased safety concerns.	No evidence to suggest adjustments are necessary	No evidence to suggest adjustments are necessary	No additional PPx indicated.	58–66
Complement inhibitors	Ravulizumab, Eculizumab	Inhibits the cleavage of C5 to C5a (a prothrombotic and proinflammatory molecule) and C5b (the initiating subunit of the terminal complement complex) resulting in inhibition of the terminal complement pathway.	Do not need to be held prior to transplant.	May be used immediately post-transplant if needed.	No evidence to suggest adjustments are necessary	No evidence to suggest adjustments are necessary	No additional PPx indicated. Meningococcal vaccines should ideally be administered at least 2 weeks prior to the first ravulizumab dose. Antibiotic prophylaxis should be taken for at least 2 weeks or the duration of ravilizumab	67–75

(Continues)

TABLE 1 (Continued)

Medication Class	Agents	Mechanism of Action	Pre-Transplant Washout	Use in Peri/ Post-Transplant	Induction IS Changes	Maintenance IS Changes	Infection Prophylaxis (PPx)	Article citations
Alpha-4/Alpha4Beta7 integrin inhibitor AKA Selective Adhesion Molecules	Natalizumab, Vedolizumab	Natalizumab prevents integrin association with vascular receptors which limits transmigration of leukocytes and adhesion. (REF) Vedolizumab prevents the migration of memory T lymphocytes to inflamed tissue. It also prevents alpha4beta7 integrin from interacting with mucosal addressing cell adhesion molecule-1 (MAdCAM-1). (REF)	Do not need to be held prior to transplant.	May be resumed immediately post-transplant.	No evidence to suggest adjustments are necessary	No evidence to suggest adjustments are necessary	No additional PPx indicated.	76–84
Check Point Inhibitors	atezolizumab avelumab Cemiplimab Dostarlimab Durvalumab Nivolumab Ipilimumab Pembrolizumab	T cell upregulation to facilitate anti-cancer activity via restoration of tumor immunogenicity Inhibition of PD1 ligands PD-L1 and PD-L2 results in reversal of T-cell suppression and induces antitumor responses (REF) Inhibition of CTLA4 results in enhanced activation and proliferation of T-cells.	Should be held for a minimum of 3 months prior to transplant	The use of CPI post-transplant should be considered on a case by case basis, with clear communication to the patient regarding risks and benefits balancing progressive malignancy with allograft rejection.	More potent induction may be required in patients receiving CPI prior to or after transplant.	More aggressive maintenance immunosuppression may be required in patients receiving CPI prior to transplant.	No additional PPx indicated.	85–100

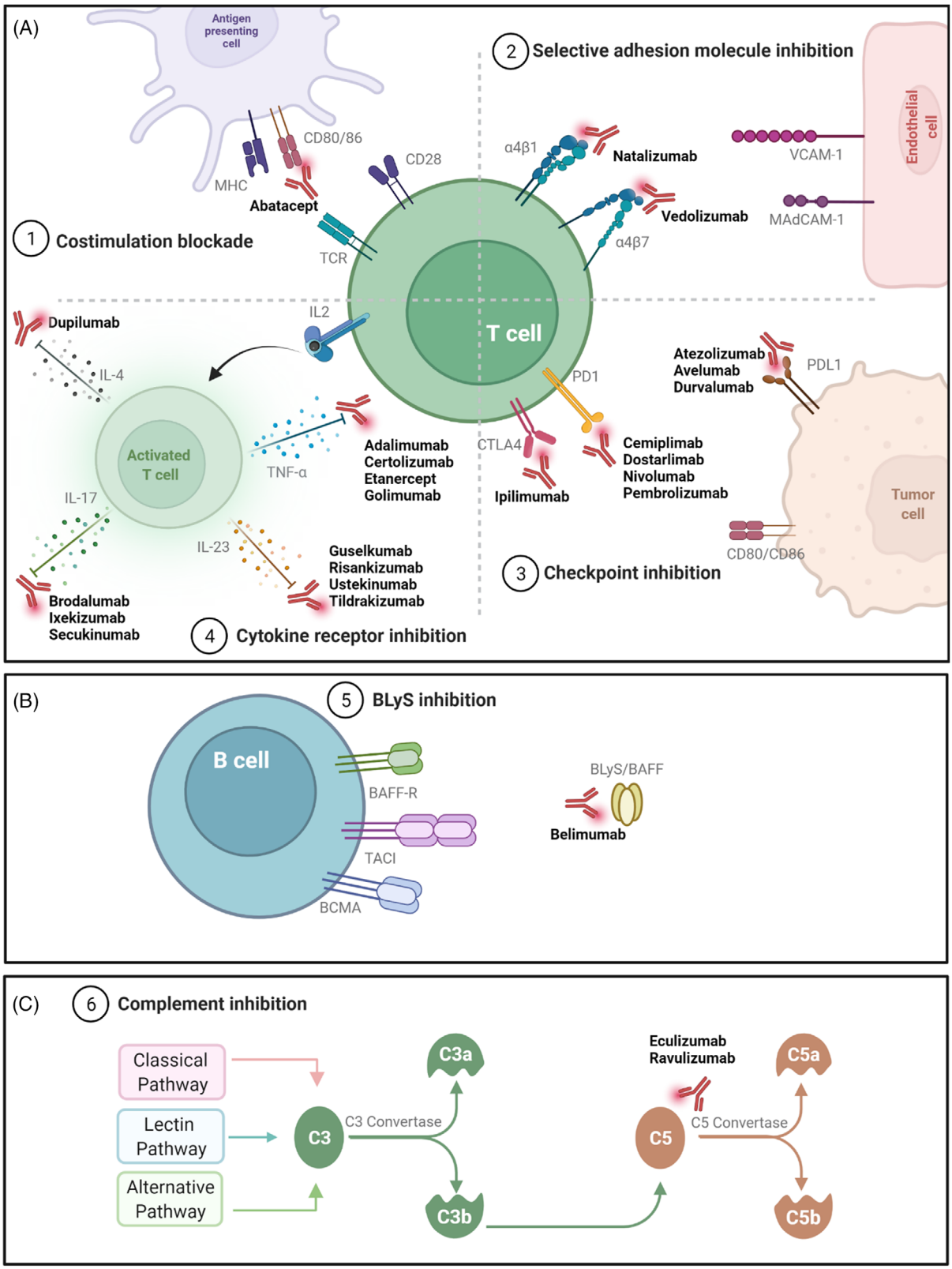

FIGURE 1 Site of action of non-transplant biologic agents for autoimmune conditions. For the therapeutics discussed in this review, panel A depicts site of action T cell-based agents, panel B displays B cell-based agents, and panel C complement-based site of action

superfamily.[4,5] However, it was found to have poor alloreactivity inhibition resulting in the development of belatacept, which has increased avidity for CD80 and CD86 and is widely used for maintenance immunosuppression in kidney transplant (KT) recipients.[6]

3.1.1 | Pre-transplant

The need for pre-transplant withholding and duration of withholding have not been addressed in the literature.

3.1.2 | Changes to induction and maintenance immunosuppression

There is no evidence to suggest modification of induction or maintenance immunosuppression is needed in patients using abatacept. Given drug class similarities, extrapolation from belatacept literature would suggest standard induction practices are appropriate, perhaps with modified calcineurin inhibitor (CNI) goals.[7,8]

A case series of nine KT recipients intolerant to CNI received abatacept as rescue therapy in the setting of belatacept unavailability. Abatacept was associated with no patient or allograft loss.[9] A single case report describes abatacept for *de novo* rheumatoid arthritis (RA) in a KT recipient more than 10 years post-transplant. This patient withdrew CNI therapy and was successfully maintained on abatacept, mycophenolate, and prednisone for 7 years with stable renal function and resolution of RA signs and symptoms.[10]

3.1.3 | Post-transplant

Based on a limited case series, abatacept can be used immediately postoperatively without negative consequences beyond what would be expected with belatacept.

A case series of three KT recipients with recurrent focal segmental glomerulosclerosis (FSGS) safely received abatacept within 3–60 days after transplant in addition to anti-thymocyte globulin induction and CNI-based immunosuppression.[11] All patients achieved complete remission of FSGS following treatment with abatacept.[11]

3.1.4 | Monitoring/safety considerations

Based on a single available case report, it does not appear that additional prophylaxis needs to be added for bacterial, fungal, or viral infections in patients on abatacept. However, additional surveillance for viral infection may be warranted.

In a case report of a 26-year-old KT recipient with recurrent FSGS after transplant, abatacept was given along with a reduction of mycophenolate from 1000 mg to 500 mg daily, followed by eight sessions of plasmapheresis and a second dose of abatacept. The patient developed BK and JC virus viremia, requiring discontinuation of mycophenolate and reduction in tacrolimus.[12] Given belatacept is associated with an increased risk of PTLD in patients that are Epstein-Barr Virus (EBV)-negative, there was concern regarding concomitant use of abatacept with tacrolimus and mycophenolate. In this case, the recipient's EBV serostatus was negative and the donor's was unknown. The authors monitored EBV DNA following administration and did not detect EBV DNA at any time point. Additionally, one study evaluated abatacept in patients with RA and no increased load of EBV was identified.[13] Given the lack of literature, EBV serostatus and PTLD risk should be discussed with the multi-disciplinary team prior to use.

3.2 | TNF-alpha antagonists

Adalimumab is a recombinant monoclonal antibody, certolizumab is a pegylated humanized antibody, etanercept is a recombinant DNA-derived protein, golimumab is a human monoclonal antibody, and infliximab is a chimeric monoclonal antibody. Each agent interferes with the binding of human tumor necrosis factor-alpha (TNF-α) to its receptor site and inhibits the inflammatory process driven by cytokines.[14–18]

3.2.1 | Pre-transplant

Based on limited data in abdominal transplant recipients, deceased donor transplantation should not be delayed or canceled due to recent anti-TNF-α therapy. For living donor transplantation, intravenous anti-TNF-α can be held 4 weeks prior to surgery (when dosed every 4–8 weeks) and subcutaneous therapy can be held 1 week prior (when dosed every 1–2 weeks).[19]

A systematic review assessing anti-TNF-α and postoperative complications in patients with Crohn's Disease (CD) receiving an abdominal transplant evaluated eight studies, including 1641 total patients.[20] This review found no difference in the rate of total complications (OR 1.72, 95% CI, .93–3.19), yet there was a higher rate of infectious complications (OR 1.50, 95% CI, 1.08–2.08), primarily driven by surgical site infection.

3.2.2 | Changes to induction and maintenance immunosuppression

It is recommended to hold anti-TNF-α agents prior to transplant and use induction therapy per protocol based on recipient and donor factors. However, in situations where anti-TNF-α cannot be held prior to transplant, a risk-benefit discussion should be made with the transplant team to evaluate the induction therapy utilized and consider less potent therapy.

Given the increased risk of infectious complications seen with anti-TNF-α agents (see Section 3.2.4), maintenance immunosuppression should be evaluated and reviewed in the context of risk versus benefit of rejection and infection.

3.2.3 | Post-transplant

It is recommended to hold anti-TNF-α following transplant, as maintenance immunosuppression may be sufficient to prevent primary disease recurrence. However, if a patient develops recurrence of disease despite maintenance immunosuppression, anti-TNF-α agents can be resumed post-transplant. Infliximab has been utilized in heart, simultaneous pancreas-kidney, and small bowel transplant patients without reported complications.[21–24]

A systematic review evaluated the safety of anti-TNF-α agents in liver transplant (LT) recipients. This study included eight papers comparing 53 post-transplant patients receiving anti-TNF-α and 23 patients that were not exposed. The researchers found no significant increase in serious infections in patients exposed to anti-TNF-α.[25] A review evaluated case reports and case series utilizing anti-TNF-α in LT patients with inflammatory bowel disease (IBD). Anti-TNF-α was safe in LT patients with most cases not reporting significant adverse effects, although some cases did highlight infections and malignancies. A nationwide case series evaluating the effectiveness and safety of anti-TNF-α therapy for 18 LT patients found that the use of anti-TNF-α agents appeared to be effective for treating IBD. However, there were increases in infection risk, with 33% of patients developing a severe infection and 17% of patients developing colorectal cancer.[26] The findings are similar for KT recipients. A case series evaluating 16 KT recipients treated with anti-TNF-α therapy found a clinical response rate of 81% to their autoimmune condition.[27] However, they reported that 50% of patients developed serious infections and 25% developed cancer (three patients developed solid tumors and one patient developed hematologic malignancy). Further analysis showed recipient age was associated with a higher increase in death ($P = .009$) and patient death occurred in older individuals (> 50 years of age). An additional case series evaluating anti-TNF-α after KT in 14 patients (seven patients resumed anti-TNF-α compared to seven patients that did not resume therapy) found no difference in time to first bacterial or fungal infection and no significant difference in malignancy ($P = .24$).[28]

3.2.4 | Monitoring/safety considerations

Patients receiving anti-TNF-α therapies are at higher risk of fungal, viral, and bacterial infections as well as colorectal cancer. At this time, there are no recommendations for initiating opportunistic infection or antibacterial prophylaxis in patients initiated on anti-TNF-α post-transplant. However, monitoring patients for Candida, hepatitis B virus, BK, cytomegalovirus (CMV), and EBV infections is recommended during treatment with anti-TNF-α. Per manufacturer recommendations, all patients should be evaluated for tuberculosis (TB) and hepatitis B infection prior to initiating treatment.

In a retrospective case series, there appeared to be higher infection rates due to CMV, *Clostridioides difficile*, Cryptosporidiosis and *Enterococcus faecalis*.[26] Additionally, case reports have found potential for exacerbation of BK viremia in KT recipients treated with adalimumab.[29] A case series evaluating anti-TNF-α agents in LT recipients found instances of oral candidiasis, *Clostridioides difficile* colitis, bacterial pneumonia, and cryptosporidiosis.[30] It was noted that one patient developed EBV-positive post-transplant lymphoproliferative disorder. A case report of etanercept used to treat graft versus host disease in a LT patient resulted in *Enterococcus faecium*, *Aspergillus fumigatus*, and CMV infection leading to death due to septic shock.[31] It is unclear if etanercept was solely the cause as the patient's overall immunosuppression was increased using higher doses of methylprednisolone and anti-thymocyte globulin in addition to etanercept.

3.3 | IL-inhibitors: IL-1, IL-4, IL-17, IL-23, IL-12/23

These agents include anakinra (IL-1), dupilumab (IL-4), brodalumab (IL-17), ixekizumab (IL-17), secukinumab (IL-17), guselkumab (IL-23), risankizumab (IL-23), tildrakizumab (IL-23), and ustekinumab (IL-12/IL-23). These agents inhibit various interleukins (IL) or interleukin receptors responsible for releasing proinflammatory cytokines, chemokines, nitric oxide, and IgE.

3.3.1 | Pre-transplant

There is insufficient evidence to state that interleukin (IL) antagonists should be held prior to transplant.

3.3.2 | Changes to induction and maintenance immunosuppression

Based on the limited published literature available, no adjustment to induction or maintenance immunosuppression is needed in patients receiving IL-inhibitors.

A case series was published describing the use of the IL-1 antagonist, anakinra, peri- and post-operatively in four KT recipients. All recipients received anakinra in combination with tacrolimus, mycophenolate, and prednisone and experienced no complications related to the anakinra post-operative.[32–34]

Several case reports have reported the safety and efficacy of utilizing the IL-4 inhibitor, dupilumab, to treat atopic dermatitis in patients post-transplant.[35–37] The case reports include renal, heart, and liver recipients who received dupilumab within the first year post-transplant for atopic dermatitis. All patients received tacrolimus, mycophenolate, and corticosteroids and they all experienced symptomatic improvement without any adverse effects.

There are three case reports of the use of IL-17 inhibitors in SOT recipients.[38–40] Di Altobrando et al. described a KT patient with psoriasis who received ixekizumab pre-transplant and continued immediately post-transplant. The patient received anti-thymoglobulin induction and tacrolimus, mycophenolate, and prednisone for maintenance and had no adverse events during a follow-up of 10 months post-transplant.[38] Lora et al. published a case report of a LT recipient who developed severe psoriasis 10 years post-transplant. The patient

was treated with ixekizumab for 1 year without adverse events while taking tacrolimus and mycophenolate for maintenance.[39] Singh et al. described a LT recipient who developed a psoriasis flare-up 1 year post-transplant treated with brodalumab, but immunosuppression detail was not included in the report.[40]

There is no published data on the use of IL-23 inhibitors guselkumab, risankizumab, or tildrakizumab in solid organ transplant recipients. Two case reports were published highlighting the use of ustekinumab (IL-12/IL-23 inhibitor): a LT recipient 4 years post-transplant on concomitant tacrolimus, azathioprine, and steroids and another LT recipient 16 years post-transplant on concomitant tacrolimus.[41,42] Neither patient had infectious or graft complications at 9 and 12 months following ustekinumab initiation, respectively.

3.3.3 | Post-transplant

There are some reports of using IL-inhibitors immediately post-transplant, but data is limited. IL-inhibitor use within the first few months post-transplant should be weighed against the risk of infection on a case-by-case basis.

3.3.4 | Monitoring/safety considerations

No additional bacterial, fungal or viral prophylaxis is needed when using IL-inhibitors post-transplant.[32–34,43–49] Most reported infections are bacterial and similar to those in recipients without therapy. Additional monitoring for tuberculosis and viral infections in patients receiving IL-inhibitors may be warranted. It is also recommended to monitor patients for *Candida* infections during treatment with IL-17 inhibitors.

Per manufacturer recommendations, all patients should be evaluated for TB infection prior to initiating treatment with IL-23 and IL-17 inhibitors, and treatment should be avoided during an active TB infection.[44,47,50–53] Treatment for latent TB should be initiated prior to starting therapy.

Based on clinical circumstance and theoretical concerns, consider Bacillus Calmette-Guerin vaccination and evaluation for infections caused by mycobacteria and salmonella in patients on ustekinumab. An increased risk of infection from these organisms has been observed in patients who are genetically deficient in IL-12/IL-23.

In randomized controlled trials for treatment of psoriasis/psoriatic arthritis, *Candida* infections were more common in patients treated with IL-17 inhibitors than comparator arms. A systematic review reported the overall incidences of *Candida* infections as 1.7–4%; the infections were mild to moderate in severity, did not interrupt treatment, and resolved with appropriate therapy.[54] In case reports of ixekizumab and brodalumab in SOT recipients, no infections were observed during the 6 months to 1 year follow-up.[38–40] The risk of serious infection associated with IL-17 inhibitors appears low. Other IL-inhibitors such as dupilumab have not demonstrated increased risks of infection in case reports of SOT patients.[35–37]

The risk of infection and cancer may be lower with ustekinumab compared to other historically used biologics in these disease states.[55–57]It should be noted that subjects with current infection, history of malignancy, on other biologics or conventional systemic psoriasis agents, low absolute neutrophil count and platelet counts were generally excluded from IL-23 inhibitor clinical trials, so it may be difficult to extrapolate these findings to the transplant population.[43–48] Therapy should be stopped if a serious infection develops.[44,50,51]

3.4 | BLyS inhibitor

Belimumab is an IgG1-lambda monoclonal antibody that prevents B lymphocyte survival through blocking the binding of soluble human B lymphocyte stimulator protein (BLyS) to receptors on B lymphocytes.

3.4.1 | Pre-transplant

Based on currently available literature, belimumab likely does not need to be held prior to transplantation.

Several cases of patients proceeding to KT while on belimumab report these patients continued belimumab up until the time of transplantation with no known postoperative complications.[58–60]

3.4.2 | Changes to induction and maintenance immunosuppression

Neither induction nor maintenance immunosuppression need to be adjusted in patients receiving belimumab.

A phase II clinical trial randomized 25 KT recipients to receive basiliximab induction, tacrolimus, mycophenolate, and prednisone plus belimumab or placebo for 6 months, followed by a 6-month monitoring phase.[60] Adverse events were similar between groups and included leukopenia, diarrhea, urinary tract infection, and anemia, demonstrating short-term safety of belimumab in combination with a common transplant immunosuppression regimen. A similar study using alemtuzumab along with belimumab in sensitized KT recipients is currently enrolling to evaluate the efficacy and safety of belimumab in preventing the production of de novo donor specific antibodies; however, no results have been reported.[61] Belimumab has been studied extensively in non-transplant patients with SLE along with concomitant mycophenolate, azathioprine, and steroids and revealed similar safety between those receiving steroids alone and steroids plus anti-malarials.[62] However, in a case report of a patient who continued pre-transplant belimumab along with belatacept after alemtuzumab induction complications including neutropenia, bronchitis, and grade 1a acute cellular rejection occurred.[60]

3.4.3 | Post-transplant

If patients experience a flare-up of their autoimmune disorder, they can re-initiate their BLyS inhibitor post-transplant without increased safety concerns.

Published reports describe belimumab continued through transplantation, restarted 6 months after transplant, and started *de novo* after transplant. Blew et al. described an 18-year old KT recipient receiving belimumab pre-transplant for SLE and continuing it post-transplant along with belatacept maintenance immunosuppression, with complications including neutropenia, bronchitis, and grade 1a acute cellular rejection.[60] Binda et al. published a case report of a 43-year-old woman who was on belimumab prior to transplant and resumed it 6 months post-transplant due to flares of arthralgia.[58] The patient was maintained on tacrolimus, mycophenolate, prednisone, hydroxychloroquine, and belimumab, with no safety concerns reported. Lastly, a clinical trial described starting belimumab *de novo* at the time of transplantation as part of induction immunosuppression, in combination with basiliximab, tacrolimus, mycophenolate, and prednisone, with no difference in safety events reported between belimumab and placebo groups.[63]

3.4.4 | Monitoring/safety considerations

Patients should be monitored and promptly treated for infections while taking belimumab. Opportunistic infection prophylaxis does not need to be altered, extended, or restarted when starting belimumab.

The European Alliance of Associations for Rheumatology (EULAR) recommendations for managing SLE do not recommend routine prophylaxis against opportunistic infections for patients taking medications for SLE, including belimumab.[64,65] However, the authors recommend protection with vaccinations against influenza, pneumococcal pneumonia, and herpes zoster, as well as timely recognition and treatment of infections. In a phase III clinical trial of belimumab for SLE, infection rates, including severe infections, were similar between belimumab and placebo groups.[66] The most common infectious complications in all groups were upper respiratory and urinary tract infections. One case of disseminated CMV was reported in a patient on belimumab and azathioprine, which resolved with antiviral therapy. In a post hoc analysis of patients receiving concomitant medications for SLE, the subgroup of patients receiving steroids, antimalarials, and immunosuppressants had similar rates of adverse events and infections. However, more patients in the belimumab experienced bronchitis (11% vs. 4%) and nasopharyngitis (23% vs. 12%).[62]

3.5 | Complement inhibitors

Ravulizumab is a humanized monoclonal antibody that targets the complement system, similar to eculizumab, by binding protein C5 with high affinity.[67]

3.5.1 | Pre-transplant

Data on the use of ravulizumab in SOT recipients is extremely limited. However, extrapolating from the eculizumab literature, which has a similar mechanism of action, ravulizumab likely does not need to be held prior to transplant.

Currently, only nine RT recipients treated with ravulizumab were identified in the literature.[68,69] However, due to its similarities with eculizumab, clinical data on the use of eculizumab in SOT recipients can be used to provide insight into considerations for the use of ravulizumab in transplant recipients. Ravulizumab was developed through amino acid modifications of eculizumab, aiming to improve its pharmacokinetic profile by extending its half-life and improving the efficiency of binding to complement factor C5.[70] In general, eculizumab is safe to use in the pre-and postoperative periods. More specifically related to transplant, eculizumab has been used at the time of transplant in highly sensitized KT patients.[71,72]

3.5.2 | Changes to induction and maintenance immunosuppression and post-transplant

No modifications to induction or maintenance immunosuppression are needed when using ravulizumab post-transplant, and it can be used at any time post-transplant. Based on the available eculizumab literature and limited ravulizumab literature, ravulizumab likely can be used at any time point post-transplant and in combination with typical induction and maintenance immunosuppression therapy.

Eculizumab has been used at the time of transplant in combination with rabbit anti-thymocyte globulin induction and triple maintenance immunosuppression.[71,72] In both articles, authors saw no difference between eculizumab and placebo-controlled groups in terms of severe adverse events or infection. Tan et al. published a case series of fifteen KT recipients experiencing antibody-mediated rejection (AMR) within the first 30 days post-transplant that were treated with plasmapheresis and eculizumab.[73]

3.5.3 | Monitoring/safety considerations

While the articles mentioned above demonstrated similar rates of infection between eculizumab and placebo controlled groups, it is worth noting initial reports on eculizumab as rescue AMR therapy resulted in death due to infection in some KT recipients.

Additional opportunistic infection prophylaxis for viral or fungal infections is not needed when administering complement inhibitors. However, both ravulizumab and eculizumab carry black box warnings for increased risk of life-threatening meningococcal infections when these agents are administered.[67,74] As a result, the meningococcal vaccines should ideally be administered at least 2 weeks prior to the first complement inhibitor dose. Antibiotic prophylaxis for meningococcal disease should be continued for 2–4 weeks after the last vaccination,

and some experts encourage continuing prophylaxis for meningococcal disease for the duration of complement inhibitor therapy in transplant recipients, even in the setting of immunization.[66,74,75]

3.6 | Alpha-4/Alpha4Beta7 integrin inhibitor AKA selective adhesion molecules

Natalizumab is a monoclonal antibody against the alpha-4 subunit of integrin molecules. Vedolizumab is a humanized monoclonal antibody that binds to alpha-4 beta-7 integrin and is designed to be a gut selective anti-integrin agent.[76,77] As a result, it is not considered to be systemically or minimally immunosuppressive. There is no literature on the use of natalizumab in transplant recipients. Therefore, the recommendations in this section are based on data pertaining to the utilization of vedolizumab.

3.6.1 | Pre-transplant

Based on limited literature, selective adhesion molecules do not need to be held prior to transplant.

Vedolizumab has been reported to be utilized prior to transplant for the management of IBD. Wright et al. published a case series reporting on their use of vedolizumab for the treatment of IBD. In the case series, three patients underwent LT while receiving vedolizumab; therapy was not interrupted for the surgery. None of the patients experienced post-transplant complications attributed to vedolizumab.[78] The most significant clinical consideration is increased risk for infection since 50% of all patients in this study ($n = 10$) experienced bacterial infection, with the predominant infection being *Clostridioides difficile*. No additional adverse events were noted in patients receiving vedolizumab therapy pre-transplant who also continued vedolizumab therapy after LT. Given the small sample size, it is difficult to extrapolate this information to all SOT recipients as only LT patients were included in this retrospective analysis. All patients who were receiving vedolizumab were also receiving IBD-related corticosteroid therapy.

3.6.2 | Changes to induction and maintenance immunosuppression and post-transplant

Based on the available case reports, no adjustments to induction or maintenance immunosuppression need to be made in patients receiving vedolizumab.

Meszaros et al. published a case report of a 40-year-old male who was diagnosed with ulcerative colitis (UC) and primary sclerosing cholangitis (PSC), status post LT, who experienced a UC flare-up followed by frequent relapses.[79] The patient underwent treatment with various biologics for several years and continued to relapse. Ultimately, he was transitioned to vedolizumab and remained in remission. The authors did not suggest adjusting maintenance immunosuppression post-LT in this case. Mumtaz et al. published a case report of a 22-year-old patient who underwent LT for PSC IBD.[80] The patient had an uncomplicated post-transplant course and was discharged home tacrolimus, azathioprine, and tapering prednisolone. Unfortunately, she experienced a relapse of her UC and ultimately was trialed on vedolizumab where she achieved clinical remission by the third dose. Like the previous case, there was no mention of adjusting maintenance immunosuppression, and no adverse events related to vedolizumab were reported. Wright et al. published a retrospective review of 10 adult LT recipients diagnosed with new-onset moderate to severe IBD treated with vedolizumab therapy and corticosteroids.[78] Nine out of 10 patients received tacrolimus-based maintenance immunosuppression while receiving vedolizumab. One patient received basiliximab induction at the time of LT while on concomitant vedolizumab therapy. All other patients received standard triple immunosuppression. Trentadue et al. published a case report of a 19-year-old female who was successfully treated with vedolizumab for acute cellular rejection after intestinal and abdominal wall transplant.[81] Maintenance immunosuppression therapy included tacrolimus and prednisone.

3.6.3 | Post-transplant

Vedolizumab can be resumed immediately post-transplant without adverse patient or allograft outcomes.

The use of vedolizumab has been evaluated in liver and intestinal transplantation.[78] The case reports previously discussed highlighted the use of vedolizumab in pre-, peri-, and post-transplant recipients. The risk of infection and adverse effects were similar between patients continuing vedolizumab post-transplant versus new starts post-transplant.[78–81]

3.6.4 | Monitoring/safety considerations

There is variable data on the risk of bacterial, fungal, and viral infection with the use of vedolizumab and natalizumab after transplantation with no consensus on the use of prophylaxis therapy at this time. There is an increased risk of progressive multifocal leukoencephalopathy (PML) with the use of anti-integrin agents.[76,77] Therefore, when considering use post-transplant, the risk of infection should be weighed on a patient case by case basis.

Solid organ transplant recipients are at risk of nervous system viral infections.[82] Treatment with natalizumab raises a significant concern for the risk of PML. Patients receiving natalizumab who are also seropositive for JC virus have a higher incidence of 1% for development of PML over a 2-year treatment period. Therefore, due to this risk, prescribing of natalizumab is restricted through the TOUCH prescribing program. Available real-world evidence suggests that vedolizumab does not carry the same risk of PML as natalizumab, but monitoring for concerning neurological signs or symptoms is still recommended in the package insert.[83] Additionally, there are some case reports and retrospective reviews discussing infectious complications associated with vedolizumab use after transplantation. One intestinal transplant

recipient receiving vedolizumab within three months of transplant for rejection developed astrovirus and CMV infections during treatment with vedolizumab but was able to clear both infections.[81] A published retrospective review of 10 adult LT recipients treated with vedolizumab therapy and corticosteroids reported a 50% incidence of infection, all bacterial, predominantly *Clostridioides difficile*. Additionally, the authors reported 11 infectious adverse events experienced by five patients: four cases of cholangitis, four episodes of CD colitis, two empyemas, and one case of pneumonia occurred. No recommendations for empiric prophylaxis were made.[78] A systematic review was conducted by Spadaccini et al. of eight studies (31 patients) who received vedolizumab after LT, and seven out of 31 patients experienced infection (mean follow-up 11.4 months, ranging 5–20 months). Again, no recommendations for initiation of empiric prophylaxis were made.[84]

3.7 | Checkpoint inhibitors

Immune checkpoint inhibitors (CPI) are a class of antineoplastic biologics. When used in combination ipilimumab and nivolumab have synergistic activity against several malignancies including metastatic melanoma and advanced renal cell carcinoma among others.[85–87]

3.7.1 | Pre-transplant

While prior receipt of CPI may not be an absolute contraindication to transplant, a washout period of a minimum of 3 months may be recommended, and patient-specific factors should be evaluated, including the risk of recurrent malignancy and rejection, especially considering the potential need for more potent induction in this setting.

Given that transplant waitlists typically exclude patients with active malignancy, the effects of CPI on immune function and allograft complications are not fully known. PD-1/PD-L1 agents have been approved to treat hepatocellular carcinoma (HCC), and therefore have been used in limited case series as a bridge to LT, with disparate results. In a case series of nine patients with HCC who received nivolumab 240 mg every 2 weeks with the last dose 4 weeks prior to transplantation, no severe rejection/graft loss, tumor recurrence, or death occurred at a median follow-up of 16 months. These patients were on an immunosuppressive maintenance regimen of mycophenolate, prednisone, and tacrolimus.[88] One patient did have a mild rejection in the setting of subtherapeutic tacrolimus. However, in a case report from another center, a patient who received pre-transplant bridging with nivolumab had subsequent fatal hepatic necrosis post-transplant, which was attributed to a profound immunogenic reaction, likely enhanced by nivolumab.[89] Additionally, a case series of five LT recipients evaluating the association between time from the last CPI and allograft outcomes was published. Two patients' last dose of nivolumab was less than 3 months from the time of transplant, and both experienced severe rejection and hepatic necrosis requiring re-transplant in one patient. The remaining three had a minimum of 3 month washout period and experienced stable graft function.[90] Half-life of these agents range from 6 to 27 days, so a long-lasting effect on immune regulation is anticipated. This has resulted in FDA warnings regarding the potential for fatal immune-mediated complications following allogeneic hematopoietic stem cell transplant when patients have been previously treated with PD-1 inhibitors.[91] However, more recent literature suggests that if more intense immunosuppressant therapy is used to prevent graft versus host disease, such as cyclophosphamide, the risk is reduced.[92]

3.7.2 | Changes to induction and maintenance immunosuppression and post-transplant

More potent induction and aggressive maintenance immunosuppression may be required in patients receiving CPI prior to transplant.

In the limited literature describing patients receiving perioperative CPI therapy as a bridge to LT in the setting of HCC, immune-mediated hepatic necrosis mirroring hyperacute rejection has been reported and attributed to recent pre-operative use of these agents.[89,90] In the more successful experience, patients were maintained on a fairly aggressive regimen after LT: tacrolimus trough levels of 10–12 ng/ml, 2000 mg of mycophenolate mofetil equivalents, and 10 mg of prednisone. Higher tacrolimus levels and lymphocyte depletion would be expected to reduce cell-mediated immune responses and negate some of the risk related to using these agents. However, this has not been quantified in the literature.[93]

3.7.3 | Post-transplant

The use of CPI post-transplant should be considered on a case by case basis, with clear communication to the patient regarding risks and benefits balancing progressive malignancy with allograft rejection.

When used in combination ipilimumab and nivolumab have synergistic activity against several malignancies including metastatic melanoma and advanced renal cell carcinoma among others.[85–87] PD1 and CTLA4 are important pathways for augmentation of allograft tolerance, so historically transplant recipients were purposely excluded from clinical trials of these agents due to concern for immune upregulation and resultant rejection. However, despite the increased risk of rejection/graft loss, mortality is more often attributed to malignancy progression.[94–96] In a retrospective study of 39 SOT patients receiving CPI for malignancy collected from medical records and systematic review of the literature, allograft rejection occurred in 41% of patients with a median time to rejection of 21 days from time of CPI initiation. Overall, there was no association between time since transplant and frequency of rejection. Graft loss occurred in 81% of patients; mortality in 46%.[96] In a systematic review of the literature analyzing 83 cases of cancer in SOT recipients treated with immune CPI, the rate of rejection was 39.8%, with organ failure in 71%. Median survival was 36 weeks, with most deaths attributed to cancer progression. Only 19.3% were alive without rejection or tumor progression at the end of the study.[95] In another systematic review of 57 SOT recipients receiving CPI post-transplant, 37% of patients experienced rejection, and 14% died of

graft loss. In this study, nivolumab was associated with the highest rate of rejection (52.2%) followed by pembrolizumab (26.7%) and ipilimumab (25%), although not significantly different ($P = .18$). Rejection rates were numerically higher in KT recipients (40%) followed by liver (35%) and heart (20%), although not significantly different ($P = .78$). Sixty-four percent of patients died due to progressive malignancy.[94] Therefore, the risk of rejection and benefit of preventing malignancy progression should be evaluated and discussed with the patient prior to initiating therapy with a CPI post-transplant.

3.7.4 | Monitoring/safety considerations

No specific modification of or additional antimicrobial prophylaxis is necessary due to CPI use alone; however, a careful history regarding treatment of CPI-associated immune-related adverse events that required immunosuppressive treatment is necessary to assess risk. Prophylaxis could be considered if the patient requires immunosuppressive therapy for immune-related adverse events. If immune-mediated enterocolitis develops, a thorough infectious work-up including CMV testing should be conducted.

A common toxicity of CPI is immune-related adverse events, which require withholding of immunotherapy and treatment with immunosuppressants. Prednisone at doses .5 mg/kg to 2 mg/kg/day can be used to treat these, based on the grade of toxicity. In steroid-refractory cases, infliximab 5 mg/kg is recommended.[97] In more severe immune-related adverse event manifestations, such as myositis, treatment can mirror cardiac allograft rejection therapy and include high dose steroids (methylprednisolone 1 g per day), mycophenolate, antithymocyte globulin, or abatacept.[98] In one study on the use of CPI for melanoma, serious infection occurred in 7.3% of cases and was more commonly noted in patients exposed to glucocorticoids or infliximab.[99] Additionally, immune-mediated enterocolitis due to CPI therapy has been associated with CMV reactivation.[100] Therefore, in patients with historical use of CPI prior to transplant, a careful history regarding the treatment of associated immune-related adverse events is suggested, as this could increase the net immunosuppressive burden and subsequent risk of opportunistic infection after transplant.

4 | CONCLUSION

In summary, there is limited literature assessing the role of biologics in SOT recipients. A care plan should be developed based on individual risk assessment in collaboration between the transplant team and the provider prescribing the biologic. The decision should factor in the patient's extent of disease control and risk of relapse. For the most part, biologics do not need to be held prior to transplant with the exception of the CPIs due to their risk of hepatic necrosis. If a biologic is to be held prior to transplant, one could consider delaying surgery until the end of one dosing cycle, although this may only be feasible in the cases of living donor transplantation. Based on the limited literature available, there were no increased risks or adverse allograft outcomes in patients without a washout period prior to transplant. The CPIs are one exception, and should be held for a minimum a 3-months before surgery. Additionally, increased maintenance immunosuppression may be needed in patients with any history of or concurrent CPI use due to the heightened rejection risk.

Standard induction and maintenance immunosuppression protocols should continue to be followed as data does not suggest the need for empiric adjustments. Biologics may carry an increased risk of bacterial, fungal, and viral infections. Patients should be monitored closely and counseled regarding the risk of infection. Based on current literature, no additional bacterial or opportunistic prophylaxis is needed outside of standard transplant prophylaxis. The exception to this statement is the complement inhibitors, ravulizumab and eculizumab, where meningococcal prophylaxis should be instituted following CDC recommendations.

This review highlights the paucity of data surrounding the use of non-transplant biologics during the peri-transplant period. We acknowledge that the majority of literature reviewed in this document consists of case reports and case series, so the strength of our recommendations is low. Because of this, variability from these recommendations in clinical practice is expected and appropriate. Future studies are needed to better determine the risks and benefits of these therapies after solid organ transplant.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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