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Cytokine-targeted therapy for the management of solid organ transplant recipients

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ABSTRACT

Introduction: The number of solid organ transplants completed annually continues to trend upwards each year. Despite this, maintenance immunosuppression available on the market has remained relatively stagnant. Standard triple immunosuppression, composed typically of tacrolimus, mycophenolate, and steroids, lead to many side effects that limit the use of these medications. Tacrolimus, specifically, causes nephrotoxicity that can lead to renal dysfunction requiring a kidney transplant down the road. Alternative therapies for the management of immunosuppression need to be identified to try to mitigate these adverse effects.

Body: Cytokines are responsible for facilitating T cell differentiation and lead to the activation of inflammatory mediators that can contribute to graft damage and ultimately rejection. IL-4, IL-6, IL-12/23, and IL-15 are attractive targets for medications to try to ameliorate graft rejection. Various cytokine-targeted medications are currently available on the market for the treatment of inflammatory and autoimmune conditions such as rheumatoid arthritis, psoriatic arthritis, Crohn's, and multiple sclerosis.

Conclusion: This article reviews cytokine involvement in alloimmunity and the potential role cytokine-targeted therapy may play in prevention of allograft rejection in solid organ transplant recipients.

1. Introduction

The number of solid organ transplants performed annually continues to trend upwards by 4–5% [1]. However, introduction of new maintenance immunosuppression has been limited. Currently, the gold standard regimen for maintaining immunosuppression is composed of a calcineurin inhibitor, anti-proliferative agent, and corticosteroids. The main limitation with this regimen is the multitude of adverse effects that accompany these medications. [2] (Table 1) CNI minimization or withdrawal, corticosteroid withdrawal, and elimination of anti-proliferative agents are alternative methods studied for managing immunosuppression. No one strategy has been found to be effective [3–7]. This challenge highlights the need to identify new, alternative therapies for maintenance immunosuppression.

Targeting cytokine production and secretion to prevent activation of inflammatory mediators responsible for contributing to allograft rejection is a potential alternative for immunosuppression. Cytokines facilitate T cell differentiation into T helper 1 (T_H1), T helper 2 (T_H2), T helper 17 (T_H17), and T regulatory (T_{reg}) cells. T_H1 cells activate macrophages, the primary responders to infection, through the production of IFN-gamma (IFN-ɣ), IL-2, and TNF-beta (TNF-β) [7]. Through the activation of macrophages, T_H1 cells play a role with acute cellular rejection [7]. T_H2 cells are activated by IL-4 and secrete IL-4, IL-5, IL-10, and IL-13, which are cytokines that inhibit macrophage functions and activate eosinophils. Therefore, depending on presence of specific cytokines, naïve T_H cells can differentiate into a T_H1 response that will be driven by macrophage activation or a T_H2 response that will result in antibody production. T_H17 cells play a large role in

Abbreviations: APC, antigen presenting cell; CD, cluster of differentiation; CHO, Chinese hamster ovary; CNI, calcineurin inhibitor; CRP, C reactive protein; DC, dendritic cell; DSA, donor specific antibody; FDA, Food and Drug Administration; G-CSF, granulocyte colony-stimulating factor; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplant; IFN-ɣ, interferon-gamma; IgE, immunoglobulin E; IgG, immunoglobulin G; IL, interleukin; IL-R, interleukin-receptor; IP, interferon-inducible protein; JAK, janus kinase; KC, Kupffer cells; MAPK, mitogen-activated protein kinase; MCP, monocyte chemotactic protein; MFI, mean fluorescence intensity; MMP, matrix metalloproteinases; mTOR, mammalian target of rapamycin; NK, natural killer; SOT, solid organ transplant; STAT, signal transducer and activator of transcription; T_H1, T helper 1 cell; T_H2, T helper 2 cell; T_H17, T helper 17 cell; TNF-α, tumor-necrosis-factor alpha; T_{reg}, regulatory T cell; TGF-β, tumor-growth-factor beta; TYK, tyrosine kinase; US, United States

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Table 1
Maintenance Immunosuppression Agents and Adverse Effects.

Medication	Adverse Effects
Calcineurin inhibitors	
Tacrolimus, cyclosporine	Hypertension, hypercholesterolemia, hyperglycemia, hyperkalemia, hypomagnesemia, nephrotoxicity, neurotoxicity
Anti-proliferative	
Mycophenolate	Leukopenia, anemia, thrombocytopenia, diarrhea, nausea, vomiting, gastritis
Azathioprine	Leukopenia, thrombocytopenia, cholestatic hepatotoxicity, pancreatitis, stomatitis
Mammalian target of rapamycin inhibitors	
Sirolimus, everolimus	Hyperlipidemia, hypertriglyceridemia, impaired wound healing, mouth ulcers, proteinuria, lymphocele
Steroids	
Prednisone, methylprednisolone	Hypertension, hyperglycemia, peptic ulcer, osteoporosis, delayed wound healing, cataracts, psychosis, bruising
Co-stimulation blocker	
Belatacept	Increased risk for acute cellular rejection, post-transplant lymphoproliferative disease

*Infection and malignancy are risk factors for all immunosuppressive agents.

autoimmunity and T-cell mediated inflammation [8]. Because cytokines are involved in the acute rejection process, they can potentially be used as biomarkers for predicting when a patient is developing an acute rejection process. A paper recently published by Boix and colleagues reviewed the use of cytokines as surrogate biomarkers to monitor patients' immune function [9].

IFN-ɣ and IL-12 have been found to be predominantly responsible for T_H1 cell differentiation. The IL-12 receptor (IL-12R) consists of two subunits, β1 and β2, which are not expressed on resting T cells. However, when T cells become activated the β1 and β2 subunits are also activated. The effect of IL-12 is seen through janus kinase (JAK) 1 and tyrosine kinase (TYK) 2. It has been shown that mice deficient in IL-12 components have deficient T_H1 responses which confirm the importance of this cytokine in T_H1 differentiation [10,11]. IFN-ɣ activates JAK1 which upregulates STAT1 and as a result T-bet. T-bet is a transcription factor specific to T_H1 development and its overexpression leads to further differentiation of cells into T_H1 [12–14]. T_H1 differentiation plays a role in solid organ transplantation as these cells assist with intracellular pathogen elimination and organ-specific autoimmunity. This may help to prevent infections in solid organ transplant recipients. IFN-ɣ activates microglial cells and macrophages which lead to increased phagocytic activity. T_H1 cells also secrete IL-2 which increases the production of cytotoxic CD8+ T cells and increases the proliferation of CD8+ memory cells which leads to secondary immune responses [15].

The two main cytokines involved in T_H2 differentiation are IL-2 and IL-4 along with the transcription factors, STAT5, which is activated by IL-2, and STAT6, which is induced by IL-4 [15]. STAT6 is responsible for increasing the expression of GATA3, a master regulator binding protein. GATA3 plays a large role in the differentiation of T_H2 cells through interacting with T-bet and inhibiting T_H1 differentiation, recruiting Gfi-1 which leads to selective proliferation of Th2 cells, and increasing Th2 cytokine production. Mice deficient in GATA3 had more T_H1 differentiation and no T_H2 differentiation [16]. IL-6 plays a small role in T_H2 differentiation as it upregulates the nuclear factor of activated T cells (NFAT) which enhances IL-4 production by naïve CD4+ cells [15]. Further IL-4 production leads to further STAT6 production and GATA3 expression leading to continued T_H2 cell differentiation.

T_H17 cells are predominantly responsible for autoimmune diseases, inflammation, and profibrotic effects. T cells differentiate into T_H17 cells when tumor-growth-factor beta (TGF-β) and IL-21 binds to the IL-21R activating JAK1 and JAK3. T_H17 cells produce IL-17, which is where the cell name originates, IL-21, and IL-22. These cells help with fungal and staphylococcal pathogen clearance, especially those not cleared properly by T_H1 or T_H2 cells. Mouse models have shown that T_H17 cells reside in the allogeneic T cell compartment and when CD4+ T cells are mixed with MHC class II mismatched bone marrow DCs, a portion of the cells proliferate and produce IL-17 [17]. Kupffer cells (KC) are stimulated by IL-17 to produce IL-1β, IL-6, tumor necrosis factor alpha (TNF-α), and TGF-β1 which is a fibrogenic cytokine. Additionally, fibrogenic myofibroblasts are activated via STAT3 through IL-17 stimulation of HSCs leading to the expression of collagen type 1. Therefore, targeting and inhibiting IL-17 may be a potential therapeutic target for anti-fibrotic treatment [18].

T_{reg} cell production is stimulated predominantly by IL-2 and is responsible for self-tolerance. IL-2 binds to the IL-2 receptor which activates JAK1 and JAK3 and then activates STAT1, STAT3, and STAT5. As a result, IL-2 augments natural killer (NK) cell cytolytic activity, promotes production of B cells, contributes to T_{reg} development, and stimulates peripheral T cell tolerance [19].

Targeting cytokines may provide an alternative method for maintaining immunosuppression and ultimately preventing tissue injury and graft loss. The purpose of this article is to define the role of cytokines in transplantation and review the novel role of cytokine inhibitors for maintenance immunosuppression.

2. Role of cytokines

T_H17 cells, DCs, mast cells, NK cells, macrophages, and other specific cells of the immune system are responsible for the production of cytokines [20]. Inflammation and antibody production, factors responsible for playing a role in allograft damage and rejection in transplant recipients, are end results of cytokine production.

2.1. IL-17

The IL-17 family is primarily responsible for tissue inflammation and is comprised of six different cytokines (IL-17A through IL-17E) [21]. There are also five different IL-17 receptors (IL-17R) that each member of the IL-17 family binds to with varying affinities (IL-17RA through IL-17RE) [22]. IL-17RC is present on cells in the kidney, joints, liver, and thyroid [23]. When IL-17A, IL-17C, and IL-17F bind to their individual receptor, autoimmune and proinflammatory events occur. When IL-17E binds to its receptor, allergic reactions and T_H2 immune responses occur while T_H1 and T_H17 activity are inhibited [24]. The IL-17 family also activates mitogen-activated protein kinases (MAPKs) which leads to the stabilization of mRNA of proinflammatory cytokines and chemokines induced by TNF-α [21,22].

The most potent member of the IL-17 family is IL-17A and is predominantly produced by T_H17 cells [25]. Macrophages, NK cells, neutrophils, DCs, and mast cells also produce IL-17A [26]. IL-17A has a major role in stimulating host defense against extracellular pathogens. It is able to exert many different effects that ultimately lead to inflammation and destruction of foreign cells through cytokines, chemokines, and antimicrobial peptides. When IL-17 binds to the IL-17R, chemokines including CXCL1, CXCL2, CXCL5, CXCL8, CXCL10, CCL2,

and CCL20 are produced which leads to neutrophil recruitment from the circulation [27]. This may lead to neutrophil infiltration of sites of infection and inflammation such as the allograft [28]. The IL-17A/F subunit can stimulate macrophage production of IL-1β and TNF-α and production of matrix metalloproteinases (MMP). MMPs are inflammatory mediators that cause proteolytic degeneration of tissue collagen and proteoglycans [29]. When IL-17A/F binds to the IL-17R on antigen presenting cells, the T_H17 response is enhanced through the production of other cytokines and chemokines [30]. IL-17C, though less potent, acts similarly to IL-17A/F through triggering proinflammatory pathways including neutrophil recruitment and cytokine production [31].

The blockade of IL-17 in prevention of allograft rejection and prolongation of graft survival has been documented in various mice models [17,31,32]. Heidt and colleagues published an article demonstrating the blockade of IL-17 in humanized mice decreased graft expression of several cytokines impacting inflammatory response and preventing allograft rejection [17]. Antonysamy and colleagues similarly investigated the role of IL-17 in immune responses in a mice model and identified that IL-17 played a role in T cell proliferation through the maturation of DC progenitors suggesting IL-17 blockade may lead to prevention of allograft rejection [32]. Lastly, IL-17 expression has been demonstrated in biopsies from kidney transplant patients experiencing graft rejection while no expression has been identified in patients that did not experience rejection [33]. Therefore, IL-17 can act as a potential biomarker for predicting an episode of acute rejection [9].

2.2. IL-6

Cytokines, specifically IL-6 and TGF-β, have been shown to upregulate production of T_H17 cells which secrete IL-17. The IL-6 signaling system is made up of two receptor chains and downstream signaling molecules. Once IL-6 binds, the cytokine-receptor complex starts homodimerization of the IL-6R gp130 chain starting downstream signaling cascade involving activation of JAK-STAT3 and MAPK pathway [34]. IL-6 stimulates hepatocyte production of C-reactive protein and other acute phase proteins such as serum amyloid A, fibrinogen, and alpha 1-antitrypsin which initiates the emergency stress signal of host defense [35]. Finally, IL-6 also plays a role in the differentiation of activating B cells into plasma cells that produce immunoglobulins. In combination with TGF-β, IL-6 helps CD4+ T cells differentiate into T_H17 cells and inhibits the TGF-β development of T_{regs}.

2.3. IL-12

IL-12 is a pro-inflammatory cytokine that is produced by professional APCs such as DCs, macrophages, and monocytes in response to bacteria or intracellular parasites [15]. It primarily activates NK cells, cytokine production, enhances cytotoxicity, and stimulates the proliferation of IL-2. T cells, NK cells, and DCs express IL-12Rβ1 and IL-12Rβ2 subunits that IL-12 binds to, stimulating JAK2 and TYK2 activation which leads to STAT molecule phosphorylation [36]. STAT4 is the transcription factor responsible for inducing CD4+ T cell differentiation into T_H1 cells. IL-12 is also composed of p35 and p40 chains and the p40 chain can dimerize with p19 to give rise to IL-23, which is required for T_H17 differentiation and function [36].

2.4. IL-4

IL-4 exerts its effect on cell lines of mast cell, T cell, B cell, monocytic, and myeloid lineages [37]. IL-4 is produced by activated mast cells, basophils, and T cells and plays a role in B and T cell mediated immune responses. It is also important in the development of T_H2 cells which promote graft survival [38]. Finally, IL-4 is involved in allergic inflammation, secretion by B cells, and regulates cell proliferation, apoptosis, and expression of genes on macrophages, lymphocytes, and fibroblasts [39].

After reviewing various cytokines and their roles specific to the immune system, we will now discuss available cytokine targeted therapy available in the US market.

3. Available cytokine specific therapy

The majority of cytokine targeted therapies currently available are predominantly for the management of inflammatory and autoimmune conditions such as rheumatoid arthritis and multiple sclerosis. It is possible that these agents may also lead to prevention of allograft rejection through cytokine inhibition. Several studies have been published discussing the role cytokines play in other conditions in immunocompromised patients such as graft-versus-host disease (GVHD) [40–43].

A connection has been identified between IL and 6, IL-12, and GVHD severity and infection post-allogeneic hematopoietic stem cell transplant (HSCT) [40]. Certain pro-inflammatory cytokines can be potential biomarkers of acute GVHD as they have been shown to positively correlate with acute GVHD. Mouse models have demonstrated administration of an IL-6 receptor (IL-6R) antagonist during an acute GVHD episode leads to the induction of T_{regs} and decreased GHVD mortality [41,42]. Additionally, mouse models have shown IL-12 activating the innate and adaptive immune system during an episode of acute GVHD [43].

Below we will review several cytokine targeted therapies available on the market and the implications they may have in transplant recipients. Table 2 represents a compilation of dosing and pharmacokinetic parameters of the discussed biologics.

3.1. IL-17 antagonists

Secukinumab is a first in its class IL-17A receptor antagonist used for the management of psoriasis. It is a human IgG1 monoclonal antibody that binds to cytokine IL-17A, inhibiting it from interacting with the IL-17 receptor [44]. It demonstrates properties of an IgG1 antibody including a long half-life and slow serum clearance [45]. Given the role IL-17A plays, secukinumab may prevent allorecognition of the donor allograft as foreign and mounting an immune response against the allograft. It may lead to a reduced risk of inflammation and immune system activation, thereby preventing rejection.

Infections are a large concern in immunosuppressed patients. Published clinical trials investigating the role of secukinumab demonstrated a higher rate of infection in the secukinumab arm compared to the placebo arm. Higher rates of common infections such as nasopharyngitis, upper respiratory tract infections, herpes viral infections, staphylococcus skin infections, and mucocutaneous infections involving candida were seen [46,47]. The increase in infectious rates is likely due to the inhibition of IL-7 which plays a role in host defense against fungal and bacterial infections. Inhibition of IL-17 leads to the inability to mount a T_H17 response. Fungi such as *Candida albicans*, bacteria such as *Propionibacterium*, *Klebsiella pneumonia,* and *Bacteroides* lead to the activation of T_H17 responses and the inhibition of IL-17 can prevent the body from being able to mount an appropriate response. T cells that produce IL-17 populate the lung, preventing pneumonia and lung infections [48]. IL-17 leads to neutrophil recruitment at sites of infection, macrophage-inflammatory protein-2 in the lungs, and expression of granulocyte-stimulating colony factor. When IL-17 is inhibited, all of these functions are reduced increasing patients' susceptibility to bacterial infections [48]. IL-17 is also responsible for producing immune mediators that have fungicidal activity. Mice with IL-17R mutations have demonstrated increased fungal burden in tissues and reduced survival due to the inability to recruit peripheral neutrophils to infected tissues [49]. Neutropenia is another concern in the transplant population, however, neutropenia observed in clinical trials was both transient and reversible.

Ixekizumab is an IL-17A receptor antagonist, monoclonal antibody

Table 2
Cytokine-specific medications.

Agent	Cytokine Target	Dosing	Pharmacokinetics	Labeled Indications
Secukinumab	IL-17A	150 mg at weeks 0, 1, 2, 3, and 4 followed by 150–300 mg every 4 weeks depending upon clinical indication	Vd: 7.1–8.6 L Bioavailability: 55–77% T ½: 22–31 days Time to peak: 6 days Metabolism: degraded into small peptides similar to endogenous IgG Elimination: catabolism	Ankylosing spondylitis, plaque psoriasis, and psoriatic arthritis
Ixekizumab	IL-17A	160 mg SQ at week 0 followed by 80 mg at weeks 2, 4, 6, 8, 10, and Maintenance dose of 80 mg once every 4 weeks	Vd: 7.1: Bioavailability: 60–81% T ½: 13 days Time to peak: 4 days Metabolism: degraded into small peptides similar to endogenous IgG Elimination: catabolism	Plaque psoriasis, psoriatic arthritis
Brodalumab	IL-17A	210 mg SQ at week 0, 1, and 2 followed by 210 mg every 2 weeks	Vd: 8.9 ± 9.4 L Bioavailability: 55% T ½: N/A Time to peak: 3 days Metabolism: degraded into small peptides similar to endogenous IgG Elimination: catabolism	Plaque psoriasis
Dupilumab	IL-4	600 mg followed by 150 or 300 mg SQ weekly	Vd: 4.8 ± 1.3 Bioavailability: 64% T ½: N/A Time to peak: ~1 week Metabolism: degraded into small peptides similar to endogenous IgG Elimination: catabolism	Atopic dermatitis
Tocilizumab	IL-6	4 mg/kg IV every 4 weeks, may be increased to 8 mg/kg every 4 weeks (maximum 800 mg)	Vd: 6.4 L Bioavailability: 80% T ½: dose dependent (range 5–13 days) Time to peak: ~3 days Metabolism: no data Elimination: no data	Cytokine release syndrome (severe or life-threatening), giant cell arteritis, polyarticular juvenile idiopathic arthritis, rheumatoid arthritis, systemic juvenile idiopathic arthritis
Siltuximab	IL-6	11 mg/kg IV every 3 weeks	Vd: N/A Bioavailability: N/A T ½: ~21 days Time to peak: N/A Metabolism: no data Elimination: no data	Castleman disease
Ustekinumab	IL-12/IL-23	45 mg (≤100 kg) or 90 mg (> 100 kg) SQ at 0 and 4 weeks and then every 12 weeks thereafter	Vd = 2.74 L Bioavailability: N/A T ½: 10–126 days Time to peak: 45 mg 13.5 days, 90 mg 7 days Metabolism: degraded into small peptides similar to endogenous IgG Elimination: catabolism	Crohn's disease, plaque psoriasis, psoriatic arthritis

used in the treatment of psoriasis [50,51]. It is a humanized, IgG4 that is produced in Chinese hamster ovary (CHO) cells. It selectively binds and neutralizes IL-17 which blocks keratinocyte production of cytokines and chemokines [52]. Side effects observed in clinical trials included cardiovascular and cerebrovascular events, inflammatory bowel disease, malignancy, and neutropenia [50,51]. Similar to secukinumab, it is anticipated to prevent rejection through the inhibition of an immune response and as a result may lead to an increased risk for infection.

A review of seven uncontrolled and controlled ixekizumab psoriasis trials was performed to evaluate the incidence of infections [53]. The most commonly reported infections during the induction period of psoriasis management were upper respiratory tract infections including nasopharyngitis and urinary tract infections. During the maintenance phase, incidence rates of serious infections were similar among ixekizumab, placebo, and etanercept groups. Candida infections were numerically higher in the ixekizumab group during the induction period compared to placebo and etanercept. The mechanism behind the increased risk for fungal and bacterial infections is similar to secukinumab. Overall, ixekizumab had comparable adverse events and infection rates to that of placebo and etanercept [53].

Brodalumab is a fully human monoclonal IgG2 antibody also produced in CHO cells that antagonizes the IL-17A receptor and is approved for the treatment of psoriasis. The most common side effects include nasopharyngitis, headache, upper respiratory tract infection, and arthralgia. Suicidal ideations and completed suicides have been reported in clinical trials with brodalumab [53]. The mechanisms behind its effect and side effect profile are similar to what was discussed for secukinumab.

One concern across all IL-17 antagonists is neutropenia given IL-17A stimulates granulopoiesis and neutrophil trafficking. IL-17 causes the secretion of granulocyte colony-stimulating-factors (G-CSF) from epithelial cells, endothelial cells, synoviocytes, and rheumatoid synovial fibroblasts which maintain the proliferation of hematopoietic progenitor cells [54]. By inhibiting IL-17A through the use of IL-17 antagonists, there is a theoretical potential for increased leukopenia and neutropenia. While this was not reported as a significant side effect in most of the clinical trials, these studies did not evaluate the use of these

agents in solid organ transplant recipients who are on more intensive immunosuppressive regimens.

3.2. IL-4 antagonists

Dupilumab is a monoclonal antibody directed against the IL-4α-subunit with FDA approval for atopic dermatitis. Upon binding to the subunit, the release of pro-inflammatory cytokines, chemokines, and IgE are inhibited [55]. IL-4 regulates apoptosis, cell proliferation, and expression of genes on macrophages, lymphocytes, and fibroblasts. Through the inhibition of IL-4, the release of pro-inflammatory cytokines is inhibited and the production of antibodies through B cell activation may be limited. These effects may theoretically prevent rejection and contribute to graft survival.

The most common side effects include nasopharyngitis and headache. There has been no evidence of drug-related serious adverse events or organ toxicity. Similar to the IL-17 antagonists, there is a concern for immunogenicity with dupilumab. Approximately 7% of patients with atopic dermatitis developed anti-drug antibodies. Of the patients that developed anti-drug antibodies, 30% of them had neutralizing antibodies [56]. Therefore, this agent had relatively low immunogenic potential as well.

3.3. IL-6 antagonists

IL-6 is critical for the progression of naïve B cells transforming into plasmablasts and mature plasma cells as well as shaping T cell immunity. IL-6 is also responsible for activating the production of IL-17 signaling, inhibiting T_{reg} function, and tissue regeneration, homeostasis, and metabolism [57]. In GVHD, IL-6 has been shown to increase production of acute phase proteins such as C-reactive protein (CRP), fibrinogen, ferritin, and serum amyloid P. Tawara and colleagues demonstrated that a reduction in the secretion of IL-6 led to reduced incidence of GVHD in various mouse models. The researchers theorized this benefit was from reducing inflammation and cytopathic damage to tissues due to IL-6 [42]. This concept can be extrapolated to prevention of graft rejection through the neutralization of IL-6.

Tocilizumab is a monoclonal antibody directed against IL-6 receptor. It is currently FDA approved for the treatment of rheumatoid arthritis and juvenile idiopathic arthritis. Per the manufacturer labeling, dosing recommendations differ dependent upon indication [58]. Choi et al recently published an article evaluating the role of tocilizumab in the treatment of chronic antibody-mediated rejection in thirty-six renal transplant recipients [59]. Patients received tocilizumab 8 mg/kg (maximum 800 mg) monthly for 6–25 months along with immune globulin, rituximab, and plasmapheresis for chronic antibody-mediated rejection with donor specific antibodies (DSA). Four patients exhibited graft loss due to chronic antibody-mediated rejection (median follow-up 3.26 years, maximal follow-up 8 years). Patients receiving tocilizumab demonstrated graft survival probability of 77% at 6 years and patient survival probability of 91% at 6 years. Additionally, the immunodominant DSA showed a significant reduction at 24 months with a drop in mean fluorescence intensity (MFI) from ~12,000 to 7000. Out of thirty-six patients, thirteen demonstrated infection-related side effects. Five patients had cytomegalovirus infection, two patients had BK infections, and seven patients had bacterial infections. No patients required cessation of tocilizumab therapy due to infection concerns. Other side effects noted in this study were cardiovascular complications, primarily thought to be non-treatment related and hypogammaglobinemia [59].

Another IL-6 agent is siltuximab, a monoclonal antibody, which binds with high affinity and specificity to IL-6 preventing binding to both the soluble and membrane-bound IL-6 receptors. Currently, siltuximab is FDA approved for the treatment of multicentric Castleman disease [60]. In a phase 2 trial evaluating the role of silutximab in the management of relapsed or refractory multiple myeloma, neutropenia, anemia, and thrombocytopenia was seen. The most common non-hematologic side effects seen were fatigue, abnormal hepatic function, diarrhea, weight gain, and peripheral edema [61]. Approximately 57% of patients developed infections including upper respiratory infections, cellulitis, oral candidiasis, and pneumonia.

3.4. Other IL antagonists

Another IL responsible for stimulation of the immune system is IL-15, which stimulates the differentiation of immature NK cells and controls the development of NK cells from its precursors. IL-15 is also responsible for converting resting NK cells lacking cytolytic activity into effector NK cells with high cytolytic function. Finally, IL-15 promotes survival of mature NK cells in the peripheral lymphoid tissue through upregulation of the Mcl-1 [62]. Mortier and colleagues investigated the effect of a soluble IL-15Rα-chain and found that it displayed a high affinity for the IL-15R and acted as a potent and specific inhibitor of the IL-15R leading to reduced IL-15 cell proliferation [63]. Pavlakis and colleagues postulated that IL-15 plays a role in clinical rejection. The researchers extracted RNA from renal biopsies of patients that were actively rejecting. Out of 45 renal biopsies, all specimens contained increased number of IL-15 suggesting that IL-15 plays a role in T-cell mediated rejection. Additionally, there was a larger expression of IL-15 mRNA in the biopsies of grafts that were rejecting compared to grafts not rejecting [64]. The results of these two studies highlight a potential role for a therapeutic agent targeting IL-15 to prevent rejection in solid organ transplant recipients. A proof-of-concept study was published by Baslund and colleagues evaluating the ability of HuMax-IL15, a human IgG anti-IL-15 monoclonal antibody, to suppress IL-15 activity in rheumatoid arthritis patients [65]. No dose-limiting toxicities were identified in patients that received a single dose of HuMax-IL15. Patients that received multiple doses reported side effects including injection site reactions, upper respiratory tract infections which were treated with oral antibiotics, and influenza-like symptoms. Further studies need to be conducted with multiple doses and in solid organ transplant recipients, but IL-15 offers a novel therapeutic target for management of rejection in transplant recipients.

IL-12 and IL-23 are proinflammatory cytokines that have also been shown to play a role in allograft rejection. These cytokines are found in elevated levels in autoimmune and inflammatory conditions, activate NK cells, mediate T_H1 development, and play a role in T_H17 cell differentiation and IL-17 production by T cells. They are both secreted by activated APCs [66–68]. IL-12 is composed of a p35/p40 subunit and IL-23 is a composed of a p19/p40 subunit. Since both cytokines contain a p40 subunit and impact Th1 and Th17 cells, it is possible that targeting the p40 subunit will reduce the risk of graft rejection mediated by Th1 and Th17 cells. Ustekinumab is an IL-12/IL-23 inhibitor that disrupts expression of IL-8, interferon-inducible protein-10 (IP-10), TNF-α, and monocyte chemotactic protein-1 (MCP-1). Wang and colleagues published a paper investigating the ability of an IL-12/IL-23 antagonist to attenuate chronic cardiac allograft rejection in a murine model. Mice that received the IL-12/IL-23 antagonist had a significant inhibition of chronic allograft rejection and prolonged allograft survival. This was postulated to be due to inhibition of IFN-γ and IL-17 producing T cells [66]. Ustekinumab and briakinumab are two anti-p40 antibodies responsible for blocking IL-12 and IL-23 [69].

Ustekinumab has been studied for the treatment of moderate to severe plaque psoriasis in PHOENIX 1, PHOENIX 2, and the ACCEPT trials [70–72]. It was studied for the management of psoriatic arthritis in the PSUMMIT 1 and PSUMMIT 2 trials and for the treatment of Crohn's disease in the UNITI-1 and UNITI-2 trials [73–75]. From these trials, an increase in serious infections and cardiovascular-related events was seen in the ustekinumab arms. Given the concern for cardiovascular events associated with ustekinumab, the medication was prospectively followed for seven years in clinical practice and no additional increase or decrease in cardiovascular events was noted [76,77]. The most reported serious infection was cellulitis in the trials.

4. Potential place in therapy

Allograft rejection is due to various immune responses involving T_H cells and T_{regs}. Cytokines produced by these and other specific cells of the immune system lead to inflammation and antibody production which are known factors responsible for causing allograft damage and rejection in transplant recipients. Targeting and inhibiting cytokines may contribute to the production or stimulation of cytokines and may prevent allograft rejection and enhance allograft survival. An additional benefit to the use of cytokine-targeted therapy is the ability to minimize adverse effects caused by the current standard triple therapy composed of calcineurin inhibitors, anti-proliferatives, and steroids. Thus, cytokine specific therapies may be useful to replace components of triple therapy in an effort to minimize adverse events. While conventional immunomodulators have resulted in a reasonable early allograft survival, long term viability has not substantially improved. Targeting specific cytokine expression in SOT recipients may result in reductions in the incidence and progression of chronic allograft dysfunction in most patients with relevant RNA expression signatures. Selected cytokine specific therapies may prove helpful in patients with recurrent or refractory rejection in addition to conventional immunomodulating agents. Clearly, performing prospective studies to identify the role of cytokine specific therapy in SOT recipients, paired with further advanced precision medicine based mechanistic studies, and assessing the safety and tolerability of these agents is paramount.

Conflicts of interest

The authors do not have any conflicts of interest.

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