



# IL-6 Directed Therapy in Transplantation

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## Abstract

**Purpose of Review** IL-6 is a pleiotropic, pro-inflammatory cytokine that plays an integral role in the development of acute and chronic rejection after solid organ transplantation. This article reviews the experimental evidence and current clinical application of IL-6/IL-6 receptor (IL-6R) signaling inhibition for the prevention and treatment of allograft injury.

**Recent Findings** There exists a robust body of evidence linking IL-6 to allograft injury mediated by acute inflammation, adaptive cellular/humoral responses, innate immunity, and fibrosis. IL-6 promotes the acute phase reaction, induces B cell maturation/antibody formation, directs cytotoxic T-cell differentiation, and inhibits regulatory T-cell development. Importantly, blockade of the IL-6/IL-6R signaling pathway has been shown to mitigate its harmful effects in experimental studies, particularly in models of kidney and heart transplant rejection. Currently, available agents for IL-6 signaling inhibition include monoclonal antibodies against IL-6 or IL-6R and janus kinase inhibitors. Recent clinical trials have investigated the use of tocilizumab, an anti-IL-6 mAb, for desensitization and treatment of antibody-mediated rejection (AMR) in kidney transplant recipients, with promising initial results. Further studies are underway investigating the use of alternative agents including clazakizumab, an anti-IL-6 mAb, and application of IL-6 signaling blockade to clinical cardiac transplantation.

**Summary** IL-6/IL-6R signaling inhibition provides a novel therapeutic option for the prevention and treatment of allograft injury. To date, evidence from clinical trials supports the use of IL-6 blockade for desensitization and treatment of AMR in kidney transplant recipients. Ongoing and future clinical trials will further elucidate the role of IL-6 signaling inhibition in other types of solid organ transplantation.

**Keywords** Transplantation · Allografts · Interleukin-6 · Rejection · Tocilizumab · Clazakizumab

## IL-6: A Pleiotropic Cytokine

Cytokines have been identified as key components of immune regulation and tissue homeostasis, and disruptions in cytokine activation pathways result in autoimmunity and tissue injury [1–3]. IL-6 is a pleiotropic cytokine that has been shown to cause deleterious inflammatory, immune, and fibrogenic responses. It was discovered by Kishimoto et al. in 1986 and identified as B-cell stimulating factor 2 (BSF-2) for its role in promoting immunoglobulin synthesis by activated B cells

[4–6]. IL-6 has since emerged as a master regulator of immune and physiologic processes involving multiple organ and cellular systems, including the acute phase reaction, innate and adaptive immunity, hematopoiesis, apoptosis, and cellular metabolism [1, 7, 8].

During physiologic inflammatory responses, IL-6 triggers the synthesis of acute phase proteins and facilitates the development of specific immunity. It modulates the activation, proliferation, and differentiation of T- and B-cells and induces cells of monocyte, endothelial, and stromal lineages to acquire a pro-inflammatory phenotype. Unlike the majority of other cytokines which have restricted cellular expression and signaling, IL-6 can be produced by most stromal and immune cells in the human body. These include a wide range of immune and non-immune cells, including T and B lymphocytes, monocytes, fibroblasts, endothelial cells, adipocytes, and smooth muscle cells [9, 10]. Under physiologic conditions, the level of IL-6 in peripheral blood/plasma is 0–6 pg/mL [7] with dramatic elevations after IL-6 activation/transcription; IL-6 levels in the microgram/

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milliliter range have been shown to correlate with increased risk of mortality [7, 11].

IL-6 production is induced in infection, cancer, and nearly all inflammatory conditions [2, 12]. Dysregulated IL-6 signaling has been implicated in autoimmunity (rheumatoid arthritis, Castleman's syndrome), chronic immune disorders (GVHD), cardiovascular disease, diabetes mellitus, neuroendocrine disorders, and tumorigenesis [1, 7, 13–15]. As such, IL-6 has become a key target for clinical intervention in a multitude of disease processes, including immune-mediated allograft injury. Here, we review the experimental evidence and current clinical application of IL-6/IL-6R signaling inhibition for the prevention and treatment of allograft injury after solid organ transplantation.

## Diverse IL-6 Signaling Pathways

IL-6 consists of 184 amino acids in addition to a 28 amino acid signal peptide [16]. It utilizes unique signaling mechanisms including classical, trans-signaling, and trans-presentation pathways [8, 17, 18]. The IL-6 receptor (IL-6R) forms a complex of molecules consisting of gp80 and gp130 components; the gp80 subunit directly binds to IL-6 and is generally identified as IL-6R and relies on the gp130 component for signal transduction. Notably, there exist two forms of IL-6R (gp80): a membrane-bound transmembrane protein and a soluble sIL-6R protein [1, 11]. The binding of IL-6 to gp80 causes gp130 on the cell surface to homodimerize, resulting in a formation of a functional IL-6/IL-6R/gp130 complex and activation of downstream signal transduction pathways leading to janus kinase (JAK)–dependent STAT3 signaling (as well as PI3K/AKT and RAS/MAPK pathways) [19]. The predominant target of IL-6 signaling is STAT3, which regulates genes involved in cellular proliferation (cyclin B1, cyclin D1), survival (B cells), angiogenesis (vascular endothelial growth factor), fibrosis, and immunosuppression (IL-10) [20–22].

The classical pathway (cis-signaling) occurs when IL-6 binds the membrane-bound heterodimer of the IL-6R and gp130 to activate downstream JAKs. The membrane-bound IL-6R is expressed on a small subset of cells including leukocytes, megakaryocytes, and hepatocytes, which enables the classical signaling pathway to regulate acute phase inflammation, hematopoiesis, and immune cell proliferation/differentiation [16].

Trans-signaling utilizes a soluble form of IL-6R (sIL-6R), which is produced by alternative gene splicing of IL-6R mRNA and cleavage by ADAM10 and ADAM17 from cell membranes. In this pathway, IL-6 binds sIL-6R in the extracellular space, and the complex then binds gp130 on any cell membrane to activate downstream signaling as in cis-signaling [23–26]. Trans-signaling dramatically expands the activation capacities and pathological effects of IL-6 by

enabling the transmission of IL-6R-initiated signals to cells that do not constitutively express the receptor. Indeed, sIL-6R and the widespread expression of gp130 enable IL-6 to activate nearly every cell in the body [27, 28]. Trans-signaling is regulated by a soluble form of gp130 (sgp130), which forms a complex with IL-6/sIL-6R and prevents its binding to membrane-bound gp130 [29].

Trans-presentation is a more recently identified IL-6 signaling pathway that occurs in the context of dendritic cells presenting to naïve CD4+ T-cells [30••]. IL-6 and IL-6R expressed in the cytoplasm of dendritic cells combine and are transported to the plasma membrane. There, the IL-6/IL-6R complex interacts with gp130 molecules expressed by CD4+ T cells, resulting in activation of JAK/STAT3 signaling and commitment of the T-cell to a tissue-destructive, pathogenic phenotype. Trans-presentation was discovered in mice and has not yet been confirmed in humans [2, 30••].

The diverse mechanisms of IL-6 signaling and ubiquitous ability of IL-6 to stimulate nearly every cell type provide a unique opportunity for therapeutic intervention in human disease, including the inflammatory and immune processes associated with solid organ transplant rejection.

## Integral Role of IL-6 in Inflammation/Immunity

IL-6/IL-6R signaling activates pathways involved in inflammation and ischemia reperfusion injury (IRI), adaptive cellular and humoral immunity, innate immunity, and fibrosis, all of which contribute to its role in promoting allograft injury.

### Inflammation

The deleterious impacts of IL-6 begin prior to organ procurement, with the promotion of a proinflammatory state due to IL-6 upregulation in the setting of brain death [31]. Following transplantation, IRI resulting from the use of cold, static preservation leads to further increases in intragraft IL-6 levels [32–34]. Elevated IL-6 in turn increases the level of adhesion molecules, inflammatory cytokines (IL-17, IFN- $\gamma$ ), and molecules that regulate migration, such as monocyte chemoattractant protein-1 (MCP-1) in endothelial cell [35]. Importantly, blocking IL-6 has been shown to mitigate the pro-inflammatory milieu associated with brain death and IRI [36–38].

### Adaptive Cellular Immunity

The involvement of IL-6 in adaptive cellular immunity results from its ability to expand the CD8+ T cell population and promote differentiation of naïve CD4+ T cells away from regulatory phenotypes. By augmenting the expression of IL-2 and receptor CD122/CD25, IL-6 expands the effector/

memory CD8<sup>+</sup> T cell population [39]. IL-6, along with TGF $\beta$ , is essential for the differentiation of naïve CD4<sup>+</sup> T cells towards the deleterious Th17 effector phenotype. The IL-17 produced by Th17 cells is responsible for neutrophil proliferation and migration, endothelial cell activation, and fibroblast activation and proliferation, all of which participate in the potent cytopathic responses implicated in acute and chronic allograft rejection [40, 41]. IL-17 also stimulates monocytes/macrophages, among other cell types (e.g., endothelium), to produce pro-inflammatory cytokines including IL-6 itself, thereby creating a positive feedback loop [42]. Blockade of this IL-6/IL-17 amplification circle is one purported mechanism by which IL-6 signaling inhibition exerts its beneficial effects [43–45]. Indeed, RNA profiling suggests that the IL-6 pathway is a promising target for preventing acute cellular rejection [46]. Moreover, since Th17 and regulatory T cells (Tregs; CD4<sup>+</sup>, CD25<sup>+</sup>, FoxP3<sup>+</sup>) share a reciprocal developmental origin, IL-6 inhibits TGF $\beta$ -induced Treg development [40]. IL-6 blockade thereby promotes Treg generation, which counterbalances the effects of alloreactive Th1 and Th17 lymphocytes [47]. IL-6R blockade has been shown to promote the development of CD39<sup>+</sup> Tregs in rheumatoid arthritis [48] and neutralize IL-6-induced arterial allograft rejection by promoting the emergence of Tregs [49]. This is of particular significance given the accumulating evidence suggesting that Foxp3<sup>+</sup> Tregs are critical for maintaining immune homeostasis and immune tolerance in transplantation [50, 51]. Lastly, amplification and expansion of the allogeneic T-cell response by graft-derived IL-6 have been shown to contribute to vascular rejection and allograft arteriosclerosis [52].

### Humoral Immunity

Development of humoral immunity requires IL-6, in conjunction with other cytokines, for normal antibody production [6]. Indeed, IL-6 is critical for the induction of follicular Th (T<sub>fh</sub>) cells as well as the production of IL-21, which regulates immunoglobulin synthesis [53, 54]. IL-6 is also crucial for B cell differentiation into plasmablasts and for enhancing plasmablast survival following differentiation [55, 56]. Thus, it is not surprising that blocking IL-6 signaling effectively reduces B cell activation, plasmablast differentiation, and antibody production (both primary and recall) [57–59••].

### Innate Immunity/Fibrosis

Innate immune signals via toll-like receptors (TLR), IL-1, or tumor necrosis factor (TNF) receptors can induce IL-6 in a variety of epithelial and endothelial cell types [60]. NK cells express the IL-6R and can be activated by IL-6 to induce cytotoxicity to endothelial cells in both mice and humans [61]. IL-6 appears to play an important role in activating NK cells in long-term cardiac allografts, as IL-6 deficiency in

mouse hearts has been shown to prevent NK-mediated cardiac allograft vasculopathy (CAV) [61]. IL-6 promotes collagen synthesis in fibroblasts, promotes their differentiation into myofibroblasts, and participates in vascular smooth muscle cell and endothelial cell proliferation/activation [10], all of which result in chronic allograft injury via fibrosis.

In summary, by altering upstream differentiation of alloreactive lymphocytes [43, 44, 47, 62], promoting the generation of Tregs [63], blocking immunoglobulin synthesis, and deamplifying downstream aspects of the inflammatory cascade [64], IL-6/IL-6R signaling inhibition provides a novel therapeutic option in preventing IRI, abrogating acute cellular rejection (ACR) and antibody-mediated rejection (AMR) and preventing fibrosis implicated in chronic allograft injury.

### IL-6 as a Critical Mediator of Allograft Injury

There are now considerable data from experimental and human studies linking IL-6 to allograft injury. Importantly, blockade of the IL-6/IL-6R signaling pathway has been shown to abrogate these effects. In a mouse skin transplantation model, IL-6 promoted T cell alloreactivity and impaired the ability of Tregs to suppress effector T cell alloresponses [65]. Inhibition of IL-6 signaling with anti-IL6R mAb attenuated de novo donor-specific antibody (DSA) production and alloantibody recall responses by modulating immune regulatory and effector cells [57, 66]. In murine models of solid organ transplantation, there are substantial and convincing data from many groups demonstrating that IL-6 plays a critical role in the pathogenesis of acute and chronic allograft rejection; moreover, blocking IL-6 reduces/prevents ACR, AMR, and effectively diminishes fibrosis [49, 57, 61, 67–79]. Studies in human recipients of different organ allografts consistently show that higher levels of IL-6 (gene and protein levels) are associated with worse outcomes (i.e., higher risk for acute rejection) [80–86]. Below, we review findings from important experimental and human studies on the role of IL-6 in kidney, liver, cardiac, and lung transplantation.

### Kidney Transplantation

The role of IL-6 in promoting acute and chronic kidney allograft rejection is well-established. In a murine model of kidney transplantation, renal expression of IL-6 was upregulated with decreased intragraft Foxp3<sup>+</sup> Tregs following allograft rejection [87]. Moreover, lack of graft-produced IL-6 prolonged renal allograft survival and was associated with decreased circulating anti-graft alloantibodies and increased intragraft Tregs, suggesting that IL-6 signaling inhibition may prevent both humoral and cellular rejection [76]. In an experimental model of chronic allograft nephropathy, interstitial fibrosis/tubular atrophy was shown to be mediated by

intra-graft B-cell secretion of chemokines and cytokines, including IL-6 [88]. B-cell depletion resulted in decreased intra-graft B cells, chemokines, and IL-6 levels as well as diminished allograft interstitial fibrosis and tubular atrophy, suggesting a potential role for IL-6 in mediating chronic allograft nephropathy.

In human renal transplant recipients, elevations of IL-6 in serum, urine, and biopsy tissue are observed during renal allograft rejection [89, 90], and levels correlate with the degree of inflammatory cell infiltration [36, 37]. Among renal allograft recipients undergoing tolerance induction using a mixed chimerism strategy, those who developed high serum IL-6 and IL-17 levels experienced rejection, while recipients without high IL-6/IL-17 survived long-term without rejection [91].

### Liver Transplantation

IL-6 is a key factor in promoting hepatocyte regeneration and maintaining liver homeostasis [92–94]; however, the role of IL-6 in liver transplantation is less clear. Data from a number of clinical and preclinical studies implicate IL-6 in acute liver rejection [95–99]. However, some rodent studies suggest that administration of IL-6 may provide hepatoprotective effects in the setting of transplantation [100, 101]. Higher levels of IL-6 are observed in human liver transplant recipients undergoing rejection as compared to recipients without rejection [95, 97]. In a nonhuman primate study evaluating serum IL-6 levels after orthotopic liver transplantation, animals who developed acute rejection experienced significantly increased IL-6 levels at 3–4 days post-transplant, which preceded biochemical abnormalities by 2–3 days [98]. Additional studies of IL-6 gene polymorphisms have been shown to be predictive of acute rejection following clinical liver transplantation [96, 99], with the high IL-6 producer genotype representing a risk factor for the development of acute rejection [99]. In contrast, *in-vitro* IL-6 treatment of steatotic liver allografts significantly reduced post-transplant mortality and protected against primary nonfunction after liver transplantation in a murine model [101]. Another rodent study showed that pretreatment of recipient rats with IL-6 *in vivo* 24 and 12 h before surgery promoted donor liver regeneration and improved the survival rate after partial liver transplantation [100].

### Heart Transplantation

Studies have consistently linked IL-6 with acute cardiac rejection. IL-6-deficient grafts survived approximately three times longer than wild-type controls, and graft-produced IL-6 promoted the activation of peripheral CD4<sup>+</sup> and CD8<sup>+</sup> T-cells in a mouse model [67]. Zhao et al. demonstrated that IL-6 and IFN gamma were the major cytokines upregulated during cardiac allograft rejection in mice and that the combination of costimulatory blockade with systemic absence of IL-6 leads

to tolerance by limiting effector T-cells and promoting Tregs [72]. In another study, neutralization of IL-6 in CD-8+ cell-dominant graft rejection delayed the onset of ACR and reduced graft T-cell infiltrates; in CD-4+ cell-mediated rejection, IL-6 neutralization prolonged graft survival, reduced serum DSA levels, and was associated with decreased graft infiltrate and altered Th1 responses [71]. The combination of these findings has established IL-6 as a critical mediator of both cellular and antibody-mediated rejection in cardiac transplantation. In human heart transplant recipients, myocardial biopsies and serum samples demonstrate increased transcription of IL-6 mRNA and IL-6 levels during acute rejection, which correlate with the severity of histologic cardiac allograft rejection [82, 83, 102–104].

It is now well-established that IL-6 plays an important role in chronic cardiac allograft rejection manifested as graft fibrosis, cardiomyocyte hypertrophy, and CAV [49, 69, 70, 75]. Neutralization of IL-6 in murine heart transplant recipients resulted in decreased cardiomyocyte hypertrophy and lessened cardiac allograft fibrosis [70]. In a human arterial allograft model, IL-6 signaling inhibition attenuated chronic rejection in the form of CAV via emergence of Tregs [49]. By studying IL-6 levels in human coronary artery segments grafted into immunodeficient mice, the authors concluded that IL-6 released from injured allograft vessels (specifically, endothelial cells) inhibited an increase in CD161+ Tregs, ultimately resulting in augmented T-cell infiltration and vasculopathy [49]. IL-6, together with IL-17, has even been implicated in disruption of established allograft tolerance in response to TLR signals [105].

### Lung Transplantation

Experimental murine and nonhuman primate models of lung transplantation have implicated IL-6 in both acute rejection and chronic lung allograft dysfunction (CLAD). Transplantation of incompatible lung allografts in rats resulted in elevated IL-6 mRNA levels in bronchoalveolar lavage (BAL) fluid of the transplanted lung on days one and six post-transplant, coinciding with histopathologic changes consistent with ACR [106]. Our group previously achieved long-term lung allograft tolerance for the first time in nonhuman primates by incorporating anti-IL-6R therapy (tocilizumab) in a mixed chimerism model [107]. In human lung transplant recipients, high levels of IL-6 and elevated IL-6/IL-10 ratios in donor's lungs were predictive of primary graft dysfunction and 30-day mortality [84, 108, 109]. In addition, IL-6 is upregulated in BAL fluid [85, 110], BAL-derived macrophages [111], and serum [86] of lung transplant recipients with ACR. Wheeler et al. demonstrated consistently elevated IL-6 and sIL-6R levels in BAL samples of human lung transplant recipients with CLAD and found that high BAL IL-6 levels were predictive of future CLAD development [68]. They also

demonstrated a > 50% reduction in allograft fibrosis in an IL-6 deficient murine orthotopic lung transplant model. The authors propose a synergistic relationship between infiltrating mononuclear cells and resident mesenchymal cells within the lung, which results in release of large quantities of IL-6 and sIL-6R and ultimately the development lung allograft fibrosis.

## Emerging Role of IL-6 Signaling Blockade in Clinical Transplantation

### Current Agents

Given the importance of IL-6 in mediating diverse inflammatory and immunomodulatory pathways, there exists a growing interest in the development of novel agents that interfere with dysfunctional IL-6/IL-6R signaling [2, 3]. These include agents that block the cytokine, its receptor, or intracellular kinases and transcription factors (Fig. 1). Agents that have been approved for clinical use or are in development include those that target IL-6 (clazakizumab, olokizumab, siltuximab, sirukumab), IL-6R (tocilizumab, sarilumab), the IL-6/sIL-6R complex (olamkicept), and downstream janus kinases (tofacitinib, baricitinib, ruxolitinib, filgotinib, upadacitinib) [2, 112]. Tocilizumab, a humanized monoclonal antibody against IL-6R, represents the first of these agents and was initially developed in 1997; it is currently approved in multiple countries for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, giant cell arteritis, Castleman disease, and cytokine release syndrome, with recent studies investigating its use in critically ill patients with COVID-19 [10, 16, 113, 114]. Application of IL-6/IL-6R signaling blockade in clinical transplantation has mainly focused on desensitization and prevention/treatment of antibody-mediated rejection in kidney transplant recipients, with the most-studied agents including tocilizumab and clazakizumab (Table 1).

### Tocilizumab

Tocilizumab has shown efficacy in single-arm, pilot trials aimed at reducing HLA antibody in highly sensitized patients awaiting kidney transplantation and those with AMR. One of the earliest studies was a single-center, phase I/II open-label study (NCT01594424) conducted by Vo et al. in 2015, in which 10 HLA-sensitized patients with end-stage renal disease who had failed desensitization with IVIg + rituximab +/- plasma exchange were treated with IVIg and monthly tocilizumab for 6 months [59••]. Serious adverse events (SAEs) occurred in 4 patients, with 5 of 7 SAEs likely related to tocilizumab treatment. Five patients underwent transplantation at a mean of 8 months post-treatment and 25 months post-initial treatment for desensitization. Overall, tocilizumab

therapy resulted in significantly reduced DSA levels, and there was no evidence of AMR on biopsies performed 6 months post-transplant. Importantly, when tocilizumab was discontinued, 2 patients developed mild AMR on biopsy at 1 year; the authors suggest that this may be due to rebound IL-6/IL-6R signaling from accumulation of serum IL-6, resulting in reinvasion of the alloimmune response.

A subsequent study by the same group evaluated tocilizumab as a “rescue” therapy for patients with DSA-positive cAMR and transplant glomerulopathy who had previously failed standard of care treatment with IVIg + rituximab +/- plasma exchange [115••]. Monthly tocilizumab treatment resulted in 80% graft survival at 6 years, significantly reduced DSA levels, and stabilized renal function without significant adverse events. Four of the 36 treated patients ultimately experienced graft loss due to cAMR; notably, all 4 patients had discontinued tocilizumab 6 months prior to graft loss for medical or financial reasons. This result further suggests that a rebound in IL-6/IL-6R signaling after cessation of tocilizumab may contribute to the initiation of alloimmune responses and ultimate allograft loss. More recently, tocilizumab has been investigated as a first-line therapy for cAMR in kidney transplantation. At a median follow up of 20 months, 15 patients treated for cAMR with monthly tocilizumab as the first line of therapy experienced stabilization of GFR and significant reduction in DSA, and biopsies at 6 months demonstrated improved pathology with reduced microvascular inflammation and no progression of transplant glomerulopathy, C4d deposition, or interstitial fibrosis/tubular atrophy [116].

Findings from clinical trials support the use of tocilizumab for not only chronic but also acute AMR. Reduction in DSA and stabilization/improvement of renal function was observed in 7 kidney transplant recipients who received at least one dose of tocilizumab in addition to conventional therapies for acute AMR [117]. In contrast, a single-center observational study found that tocilizumab did not alter the course of AMR in 9 kidney transplant recipients when compared to historical controls, making it clear that a randomized trial is needed to clarify the role of IL-6 signaling inhibition in AMR [125•]. Notably, a study investigating infectious complications associated with the use of tocilizumab in kidney transplant recipients with DSA and/or AMR demonstrated lower rates of infection in tocilizumab-treated patients compared to those receiving IVIg/rituximab, with no infection-related deaths in either group [126].

IL-6 signaling blockade may also represent a potential treatment option for regulating the T-cell alloimmune response in kidney transplantation, based on findings from a recent randomized-controlled trial (NCT02108600) [118]. In this study, 30 kidney transplant recipients with subclinical graft inflammation identified on biopsy within 1 year post-transplant were randomized to standard triple-drug

**Table 1** Clinical trials investigating IL-6/IL-6R signaling inhibition in solid organ transplantation

Author/trial name (NCT number)	Study design	Study population	Intervention	Endpoints/outcomes	Results
Tocilizumab Vo et al. [59••] (NCT01594424)	Single-center, phase I/II open-label study	- N = 10 highly HLA-sensitized patients (cPRA > 50%) w/ ESRD awaiting transplant who failed DES w/ IVIg + rituximab +/- plasma exchange	- IVIg 2 g/kg monthly for 2 doses + TCZ 8 mg/kg monthly for 6 months In transplanted patients: - IVIg 2 g/kg for 1 dose + TCZ 8 mg/kg monthly for 6 months post-transplant	- Rate of transplantation - DSA levels - SAEs and AEs In transplanted patients: - Time to transplant - Graft survival - Rate of AMR	- 50% transplantation rate - Decreased DSA - 40% of patients w/ SAEs; 5/7 total SAEs likely related to TCZ In transplanted patients: - Mean time to transplant 8 months post-TCZ (25 months after 1 <sup>st</sup> DES treatment) - No AMR on 6-month post-transplant biopsies - Stabilized renal function - Significantly reduced DSA - 80% graft survival, 91% patient survival 6 years post-cAMR diagnosis - Graft loss 2/2 cAMR in 4 patients - 13 patients w/ infectious AEs, no SAEs
Choi et al. [115••]	Single-center, open-label case study	- N = 36 kidney transplant recipients w/ cAMR, DSA+, TG who failed IVIg + rituximab +/- plasma exchange	- TCZ 8 mg/kg monthly for 6–25 months (max dose 800 mg)	- Renal function - DSA levels - Graft/patient survival - AEs and SAEs	- Renal function - DSA levels - Graft/patient survival - AEs
Lavacca et al. [116]	Single-center, open-label case study	- N = 15 kidney transplant recipients w/ previously untreated cAMR	- TCZ 8 mg/kg monthly (max dose 800 mg) for median 20 month follow up	- Renal function - DSA levels - Graft/patient survival - AEs	- Stabilized renal function - Significantly reduced DSA - Reduced microvascular inflammation on 6 month biopsies - Graft loss in 1 patient (6.7%), no patient deaths - 5 patients w/ infectious AEs, 6 w/ other AEs
Pottebaum et al. [117]	Single-center, observational study	- N = 7 kidney transplant recipients w/ acute AMR	- TCZ 8 mg/kg IV (max dose 800 mg) monthly for 1–6 months	- Renal function - DSA levels - AEs	- Stabilized/improved renal function - Reduced DSA - 1/7 patients w/ mixed rejection, 2/7 w/ ACR at 6–24 months post-TCZ therapy - 2 patients w/ AEs, unclear relation to TCZ
Chandran et al. [118] (NCT02108600)	Single-center, randomized-controlled study	- N = 30 kidney transplant recipients w/ graft inflammation on	- 1:1 randomization to standard triple-drug immunosuppression +/- TCZ 8 mg/kg IV monthly for 6 months	- Inflammation on 6 month biopsy (Banff ti-score) - De novo DSA formation - Development of AMR/ACR - AEs	In TCZ-treated group: - Significantly improved Banff ti-score - No de novo DSA formation - No AMR or ACR at 6 months - No graft loss or patient deaths

**Table 1** (continued)

Author/trial name (NCT number)	Study design	Study population	Intervention	Endpoints/outcomes	Results
Inflammation and Alloimmunity in Heart Transplant Recipients with Tocilizumab (ALL IN) [119] (NCT03644667) Clazakizumab Vo et al. [120] (NCT03380962)	Targeting Multicenter, phase II randomized-controlled trial	biopsy ≤ 1 year post-transplant  - N = 200 heart transplant recipients	- 1:1 randomization to standard triple-drug immunosuppression +/- TCZ 8 mg/kg IV monthly for 6 months	- Renal function - Graft/patient survival - Change in circulating immune profile  - <i>De novo</i> DSA - Development of AMR, ACR, hemodynamic compromise rejection - Graft/patient survival	- Stable renal function - No unexpected AEs Compared to control group: - Significantly increased Treg frequency - Blunted T-effector cytokine response - Not yet available
	Single-center, phase I/II trial	- N = 10 highly HLA-sensitized patients (GPR > 50%) w/ ESRD awaiting transplant	- DES w/ plasma exchange ×5 followed by IVig 2 g/kg ×1 dose - Then clazakizumab 25 mg SC monthly for 6 months In transplanted patients: - Clazakizumab 25 mg SC monthly for 12 months post-transplant	- Rate of transplantation - HLA MFI In transplanted patients: - Time to transplant - Presence of DSA - Graft survival	- 90% transplantation rate - Significantly reduced HLA MFI In transplanted patients: - Mean time to transplant 5.5 months post-clazakizumab - No detectable DSA at 6 months post-transplant - 2 patients with rejection from ACR/AMR and cAMR
Jordan et al. [121] (NCT03380377)	Single-center, phase I/II open-label study	- N = 10 DSA+ kidney transplant recipients w/ cAMR and TG	- Clazakizumab 25 mg SC monthly for 12 months - Then long-term extension w/ clazakizumab 25 mg SC every other month	- DSA levels - Renal function - Treg responses - SAEs	- Reduced DSA - Stable renal function - Increased Tregs - No clazakizumab-related SAEs
Dobeter et al. [122, 123] (NCT03444103)	Investigator-initiated, multicenter, phase II randomized-controlled trial	- N = 20 kidney transplant recipients w/ DSA+ cAMR > 1 year post-transplant	- 1:1 randomization to clazakizumab 25 mg SC monthly or placebo for 12 weeks - Then open-label extension w/ clazakizumab 25 mg SC monthly for 40 weeks in both groups	- DSA levels - Renal function - AEs - Rejection-related gene expression patterns	Compared to control group: - Significantly decreased DSA - Reduced decline in renal function In clazakizumab-treated group: - Infectious AEs/diverticulitis in 7 patients (35%) - On 1-year post-treatment biopsies: - Negative molecular AMR score in 7 patients (39%) - Disappearance of C4d in 5 patients (27.8%) - Resolution of morphologic AMR activity in 4 patients (22.2%)

**Table 1** (continued)

Author/trial name (NCT number)	Study design	Study population	Intervention	Endpoints/outcomes	Results
Clazakizumab for the Treatment of Chronic Active Antibody Mediated Rejection in Kidney Transplant Recipients (IMAGINE) [124] (NCT03744910)	Industry-sponsored, multicenter, randomized-controlled phase III trial	- N = 350 patients w/ DSA+ cAMR > 6 months post-kidney transplant	- Randomization to clazakizumab vs placebo for up to 5 years treatment	- DSA levels - Renal function - Graft/patient survival - Development of ACR/AMR	- Not yet available

Abbreviations: *TCZ*, tocilizumab; *cPRA*, calculated panel reactive antibody; *DES*, desensitization; *ESRD*, end-stage renal disease; *DSA*, donor-specific antibody; *AMR*, antibody-mediated rejection; *TG*, transplant glomerulopathy; *ACR*, acute cellular rejection; *AE*, adverse event; *SAE*, serious adverse event; *cAMR*, chronic antibody-mediated rejection; *Treg*, regulatory T-cell; *MFI*, mean fluorescence intensity

immunosuppression with or without 6 months of tocilizumab therapy. Compared to the control group, patients who received tocilizumab were found to have increased Treg frequency and a blunted Teff cytokine response, with no significant adverse effects related to tocilizumab therapy.

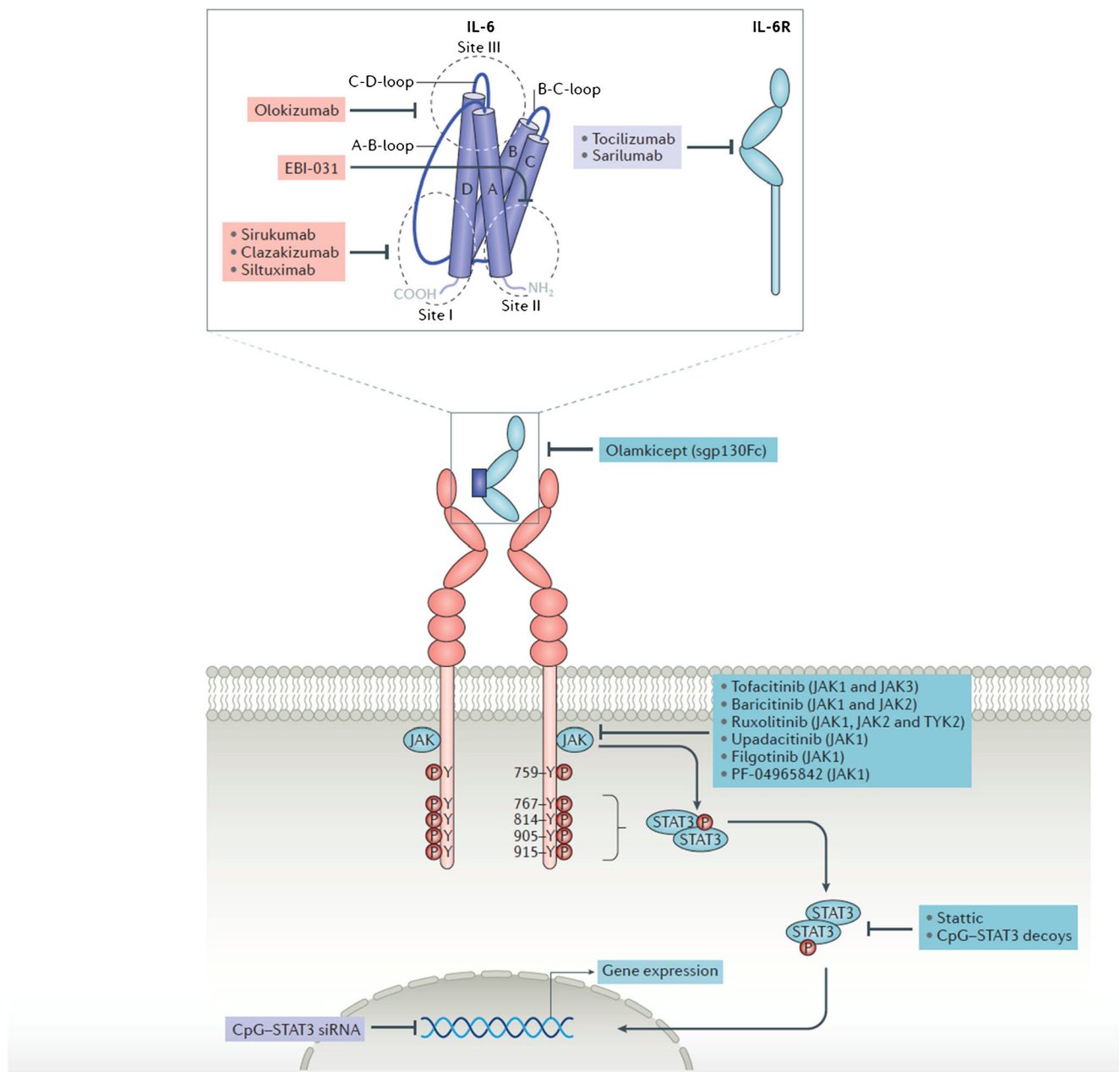
Based on experimental evidence supporting the crucial role of IL-6 in acute and chronic cardiac allograft rejection, a prospective, multicenter phase II clinical trial investigating the efficacy of tocilizumab in cardiac transplantation was initiated and is currently ongoing (NCT03644667; Targeting Inflammation and Alloimmunity in Heart Transplant Recipients with Tocilizumab (ALL IN)) [119]. In this NIAID/NIH-funded study, 200 heart transplant recipients are randomized to standard triple therapy maintenance immunosuppression with or without monthly tocilizumab for 6 months. Primary outcomes will be evaluated at 1 year post-transplant and defined by a composite endpoint including de novo DSA, biopsy-proven rejection (ACR, AMR), rejection resulting in hemodynamic compromise without biopsy/histologically-proven rejection, death, or re-transplantation.

### Clazakizumab

More recent trials investigating IL-6 signaling inhibition in clinical transplantation have utilized clazakizumab, an anti-IL-6 monoclonal antibody that has been evaluated extensively in RA but is not yet FDA approved [127••]. A potential benefit of direct IL-6 inhibition is the lack of possible rebound phenomenon resulting from the accumulation of serum IL-6. There are several ongoing studies evaluating the use of clazakizumab in highly sensitized patients awaiting transplantation and kidney transplant recipients with AMR. In a single-center, phase I/II trial (NCT03380962), highly HLA-sensitized patients received 6 doses of monthly clazakizumab therapy for desensitization with an additional 12 doses after transplantation [120•]. Clazakizumab desensitization significantly reduced HLA mean fluorescence intensity (MFI), enabling transplantation in 9/10 patients with no detectable DSA at 6 months post-transplant. A sub-analysis of these patients revealed a marked increase in FoxP3+ Tregs at 180 days post-transplant, suggesting that anti-IL-6 therapy with clazakizumab promotes differentiation of CD4+ T-cells towards a Treg phenotype [128].

A single-center, phase I/II investigator-initiated study (NCT03380377) aims to evaluate the safety and tolerability of monthly clazakizumab administration in 10 DSA-positive kidney transplant recipients with biopsy-proven cAMR and transplant glomerulopathy [121, 129]. At 18-month follow-up, there were sustained reductions in mean DSA relative intensity scores, stabilization of renal function, and increased Tregs, without drug-related serious





**Fig. 1** Agents currently approved or in development for inhibition of IL-6/IL-6R signaling. Adapted from [2]

adverse events. A similar prospective, randomized-controlled study (NCT03444103) included 20 kidney transplant recipients > 1 year post-transplant with DSA-positive cAMR randomized to 12 weeks of monthly clazakizumab or placebo, followed by a 40-week open-lab extension in which all patients received clazakizumab [122]. Clazakizumab treatment was associated with a significant decrease in DSA and reduced decline in renal function [123]. Eighteen patients underwent renal allograft biopsy at 1 year, with negative molecular AMR score in seven (39%), disappearance of C4d in five (27.8%), and resolution of morphologic AMR activity in four patients (22.2%). Seven patients developed infectious or

diverticulitis-related complications leading to withdrawal from the trial. A secondary endpoint analysis found increased serum levels of total but not unbound IL-6 in clazakizumab-treated patients, arguing against a potentially harmful rebound phenomenon from the accumulation of unbound IL-6 during treatment [130]. Currently, a large industry-sponsored, multi-center, randomized-controlled phase III trial (NCT03744910; Clazakizumab for the Treatment of Chronic Active Antibody-Mediated Rejection in Kidney Transplant Recipients [IMAGINE]) is underway to clarify the safety and efficacy of clazakizumab in cAMR after kidney transplantation [124]. The study aims to recruit 350 patients and will assess

the effect of up to 5 years of clazakizumab treatment on renal function and long-term graft survival.

## Future Directions/Conclusions

There exists a convincing role for IL-6 in innate immune responses and adaptive immunity, including those associated with cellular and antibody-mediated rejection after solid organ transplantation. Preclinical studies suggest that IL-6/IL-6R signaling blockade may be effective in modifying the T- and B-cell responses to allografts, as well as deamplifying downstream aspects of the inflammatory cascade. Recent clinical trials in kidney transplantation have focused on the use of IL-6 signaling inhibition with antibodies against IL-6 or IL-6R for desensitization and for the treatment of acute and chronic AMR, with promising initial results. Ongoing and future clinical trials should investigate the application of IL-6 signaling blockade for the prevention of allograft injury in other types of solid organ transplantation, including cardiac and lung transplantation.

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## Compliance with Ethical Standards

**Conflict of Interest** The authors declare no competing interests.

**Human and Animal Rights and Informed Consent** All procedures performed in studies involving animals were in accordance with the ethical standards of the institution at which the studies were conducted.

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