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The Role of Tocilizumab in Kidney Transplantation: A Narrative Review on Desensitization and Antibody-Mediated Rejection Treatment

In depth review

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ABSTRACT
Kidney transplantation is generally considered as the best therapeutic approach for patients with end-stage kidney disease. A considerable proportion of patients on the transplant waiting list, nearly one-third, present anti-Human Leukocyte Antigen donor-specific antibodies, a condition that tends to reduce the chances of receiving a transplant and increases the risk of immunological complications after transplantation. Among the different factors influencing graft survival, the immune response remains central in determining long-term outcomes. Antibody-mediated rejection remains a significant clinical challenge, as it contributes to both acute damage and progressive graft deterioration, ultimately affecting its survival. Interleukin-6 has been implicated in several inflammatory and immune regulatory pathways. In kidney transplantation, it is thought to participate in the mechanisms that favor the persistence of plasma cells and the interaction between T and B lymphocytes, thereby sustaining antibody production. By modulating Interleukin-6 signaling, it may be possible to interfere with these processes and limit the extent of alloimmune injury. Tocilizumab, an Interleukin-6 receptor antagonist originally developed for autoimmune conditions, has recently been investigated in the kidney transplant field. Preliminary reports suggest that it could play a role both in desensitization strategies for highly sensitized patients and in the management of antibody-mediated rejection, supporting its potential as an additional option in kidney transplantation.

KEYWORDS: interleukin-6, desensitization, chronic antibody-mediated rejection, kidney transplantation, tocilizumab

Introduction

Kidney transplantation (KT) remains the gold standard treatment for end-stage kidney disease (ESKD), providing superior survival, quality of life, and cost-effectiveness compared to dialysis [1, 2]. Approximately 30% of patients on the kidney transplant waiting list are sensitized, as indicated by panel reactive antibody (PRA) levels greater than 0%, and nearly 15% are classified as highly sensitized (HS), with PRA levels exceeding 80%. Pre-formed anti-donor specific antibodies (DSAs) constitute a major immunological barrier, often preventing transplantation and prolonging dialysis dependence in HS patients [3, 4]. The presence of DSAs cannot only limit access to KT but also increase the risk of antibody-mediated rejection (AMR) after transplantation, adversely affecting both short- and long-term graft survival rates [3, 5]. Morever, post-transplant development of de novo DSAs can occur, exerting a detrimental effect on graft survival comparable to that of preformed DSAs [6]. These antibodies can lead to AMR, a significant complication that occurs in approximately 1-10% of kidney transplant recipients overall and in nearly 30% of KT recipients with pre-formed DSAs desensitized before transplantation. AMR represents a major cause of progressive and irreversible graft dysfunction, and it poses a significant therapeutic challenge [7].

Attempts to inhibit the DSA production, to remove or reduce the serum levels, to decrease their strength, or, at last, to modify their activity are therefore important. New desensitization (DES) protocols have been developed in the latest years, usually applied before KT (or rarely in the early post-transplant period) in HS patients, intending to make possible the access to transplantation [8–11], and different scheme therapies have been used to treat AMR episodes in the post-transplant period [12–15].

The most common strategies of desensitization and AMR treatment protocols include the use of low or high doses of intravenous Immunoglobulins (IVIg), and anti-CD20 monoclonal antibody-Rituximab (RTX) alone or combined with plasmapheresis (PLEX), which are considered the current standard of care (SC) [16, 17]. These approaches aim to down-regulate B cell activity, reduce antibody production, and promote antibody removal with the aim of facilitating transplantation in HS patients and managing AMR in post-transplant period. However, despite their widespread use, these strategies remain largely empirical and not supported by standardized protocols or high-level evidence. In approximately 25-30% of patients, the antibody cannot be effectively eliminated prior to KT [18, 19], and clinical outcomes following AMR treatment remain suboptimal.

Recent studies have failed to demonstrate a clear beneficial effect of SC in AMR management [20–22], and a multicenter randomized trial comparing PLEX/IVIg with or without RTX showed no significant improvement in chronic AMR outcomes [23]. Similarly, other therapy options, such as Bortezomib or Eculizumab, did not achieve nephroprotective endpoint in KT [24, 25]. These limitations highlight a major unmet need for more effective and targeted therapies to improve graft outcomes in this high-risk population.

Alternative therapies targeting cytokine immune pathways have gained attention in KT treatment protocols. Of relevant interest was Interlukin 6 (IL-6), which is known to have a deleterious impact on inflammatory and immune response [26]. In KT, IL-6 can promote antibody production, acute and/or chronic rejection in solid organ transplantation [27]. Recently, IL-6 has become a therapeutic target in KT.

Tocilizumab (TCZ), the first-in-class humanized monoclonal antibody targeting the IL-6 receptor, can bind to both soluble and membrane-bound forms of the IL-6 receptor, thereby blocking IL-6 activity [28]. The efficacy of TCZ was confirmed in a clinical trial involving patients with Castelman disease; it is now approved for the treatment of several autoimmune-mediated diseases [29]. Starting from these data, many authors have analyzed the role, the impact, and the space that TCZ can have in KT.

Another IL-6 targeting agent has also been evaluated in small clinical studies, Clazakizumab – a monoclonal antibody that directly binds IL-6 rather than the IL-6 receptor – has shown encouraging preliminary results in desensitization and AMR treatment in HS patients [30–32].

This narrative review article gives an overview of the molecular mechanisms of IL-6 blockade that provide the rationale for the use of TCZ in KT. In addition, we aimed to summarize the limited clinical evidence on this topic, particularly regarding the use of TCZ for desensitization of anti-HLA-immunized kidney transplant candidates on the WL, and for patients who have developed AMR after transplantation. These emerging therapies further support the pivotal role of IL-6 signaling in modulating alloimmune responses and provide a broader therapeutic context in which TCZ should be considered.

Methodology

For this narrative review, a literature search was performed using PubMed, Web of Science, and the Cochrane Library. The search employed the keywords: “kidney transplantation”, “interleukin-6”, “desensitization”, “antibody-mediated rejection”, “chronic active antibody-mediated rejection”, and “tocilizumab”, and covered the period between January 2015 and January 2024. We considered all relevant articles published in English up to the time of writing, focusing on the clinical use, recent advances, and safety profile of TCZ in desensitization DES protocols and treatment of antibody-mediated rejection in KT. The population studied consisted of HS patients on the transplant waiting list and KT patients who manifest biopsy-proven AMR.

In all the studies the intervention involved the use of TCZ at a dosage of 8 mg/kg, up to a maximum of 800 mg monthly in monotherapy or combined with standard of care (SC) therapy for at least 6 months of treatment. The expected outcomes for studies where TCZ was used in DES protocol were made by reduction rate of DSAs serum levels, the degree of B and T cells maturation, and access to transplantation after 6 months of treatment. Whereas the expected outcomes for studies where TCZ was used to treat AMR were to be compared to baseline data, with outcomes assessed by comparing the initial and final kidney graft function (eGFR and proteinuria), DSAs levels expressed as mean fluorescence intensity (MFI) and histological changes. Assessment of patient and graft survival rates was included in the outcomes of AMR treatment studies.

Exclusion criteria comprised follow-up periods of less than six months, studies that included pediatric patients and animals, single case reports, SC different from RTX + PLEX + IVIg, TCZ used in KT with graft dysfunction with other indication rather than AMR, and research published in languages other than English.

We identified 22 studies where TCZ was used in the setting of KT. We excluded studies that did not meet our inclusion criteria, as shown in the flow Diagram 1.

We would like to point out that this study did not adhere to PRISMA guidelines and was not registered in PROSPERO, as a full systematic review was beyond the scope and objectives of the article.

Donor-specific antibody

Sensitization is defined by the presence of anti-Human Leukocyte Antigen (HLA) antibodies and is quantified using panel reactive antibody (PRA), a measure that reflects the risk of a positive crossmatch [33]. Preformed DSAs arise from prior exposure to HLA antigens via transplantation, pregnancy, or transfusion, and can impact transplant eligibility [34]. De novo DSAs develop in 13-30% of previously non-sensitized recipients, typically within the first year. Risk factors include high HLA mismatches (especially DQ), insufficient immunosuppression, nonadherence, and graft inflammation due to infection, ischemia, and rejection [35, 36].

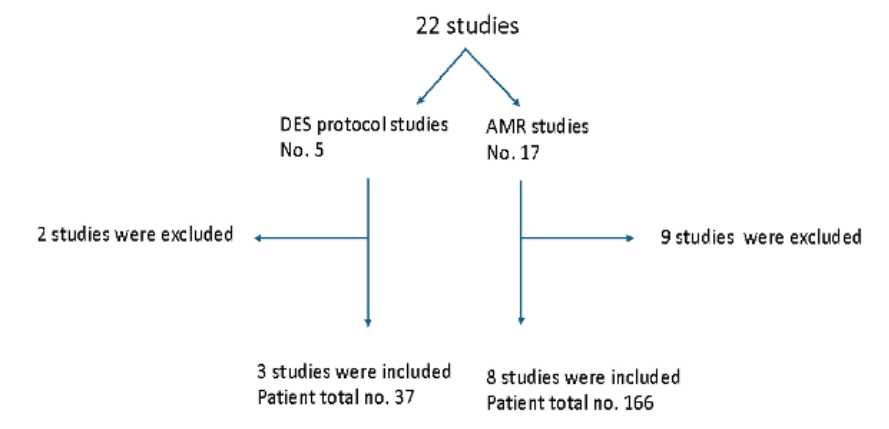

Diagram 1. Flow diagram of study selection.

Detection relies on Luminex single antigen bead assays. Clinically significant DSAs are usually defined by mean fluorescence intensity (MFI) thresholds of ≥3000 for class I and ≥5000 for class II of HLA [3, 37].

Antibody-mediated rejection

AMR results from antibody-driven injury to the microvascular endothelium, primarily driven by DSAs. The diagnosis of AMR in KT relies on a multimodal approach that integrates clinical, serological, and histopathological data, as well as molecular data when available. Clinically, AMR typically presents with graft dysfunction, such as rising serum creatinine, new-onset or worsening proteinuria, or hypertension. These signs are nonspecific and may overlap with other causes of allograft injury, including T cell-mediated rejection, calcineurin inhibitor nephrotoxicity, or recurrent primary disease. Therefore, kidney allograft biopsy remains the gold standard for the definitive diagnosis of AMR.

Histopathological assessment is guided by the Banff 2022 [38] classification, which provides standardized criteria for the diagnosis and reporting of AMR.

Diagnosis is based on the integration of three main categories of evidence:

- *Histologic evidence of acute or chronic tissue injury:* Microvascular inflammation (MVI), with glomerulitis (g > 0) and/or peritubular capillaritis (ptc > 0), in the absence of recurrent or de novo glomerulonephritis.
  Intimal or transmural arteritis (v > 0). Thrombotic microangiopathy (TMA) not attributable to other causes and/or acute tubular injury without alternative explanation.
- *Evidence of antibody–endothelial interaction*, demonstrated by at least one of the following: linear C4d deposition in peritubular capillaries, detected by immunohistochemistry or immunofluorescence; moderate or severe microvascular inflammation, defined as a combined score of glomerulitis and peritubular capillaritis (MVI = g + ptc) ≥ 2; increased expression of validated gene transcripts in the biopsy, strongly associated with AMR, as assessed by molecular diagnostics.
- *Serologic evidence of circulating DSAs*: detection of circulating DSA remains a central criterion. In the absence of detectable DSA, positive C4d staining in peritubular capillaries and/or detection of validated gene expression consistent with antibody-mediated injury may provide supportive evidence.

The Banff 2022 introduced two additional diagnostic categories to better capture the spectrum of antibody-mediated injury:

Probable AMR:

Defined as cases with incomplete fulfillment of classic AMR criteria – typically positive DSA with sub-threshold histologic findings, or ambiguous molecular signals – where antibody-mediated injury is suspected but not fully confirmed.

MVI, DSA-negative and C4d-negative:

Refers to cases with significant MVI in the absence of DSA or C4d. These are not classified as classical AMR but are recognized as clinically relevant and require careful clinicopathologic correlation.

Furthermore, acute tubular injury is no longer considered sufficient for AMR diagnosis in isolation. Likewise, arterial intimal fibrosis is no longer accepted as evidence of active antibody-mediated injury without additional supportive findings.

Chronic active AMR is characterized by persistent or recurrent microvascular injury, most notably glomerulitis (g) and peritubular capillaritis (ptc), reflecting inflammation of glomerular and peritubular capillary compartments. These lesions are semiquantitatively scored, and a combined MVI score (g + ptc) ≥ 2 strengthens the suspicion for AMR.

Additional histological features may include intimal or transmural arteritis, TMA, or acute tubular injury, not attributable to other causes. Chronic injury markers – such as transplant glomerulopathy and interstitial fibrosis/tubular atrophy – often coexist and influence prognosis [39].

Role of IL-6 in Kidney Transplantation

In 1986, Kishimoto et al. identified IL-6 as B-cell stimulating factor 2 (BSF-2) and its role in the promotion of immunoglobulin synthesis by activated B cells [40]. Aberrant IL-6 production and signaling contribute to chronic immune, cardiovascular, neuroendocrine, and metabolic disorders, as well as tumorigenesis [41]. It is a pleiotropic cytokine and is implicated in innate and adaptive immunity response, cellular and humoral response, determining itself the main factor of graft damage in KT [27] (Figure 1).

An increase of IL-6 in serum, urine, and biopsy tissue is observed during kidney allograft rejection, and levels correlate with the degree of inflammatory cell infiltration in human KT recipients [41]. Moreover, in the setting of a brain death donor, the pro-inflammatory process mediated by IL-6 starts before organ procurement [42]. Additionally, the kidney cold static preservation promotes the upregulation of intra-graft IL-6 production after the organ transplantation. This process promotes the pro-inflammatory cells' recall, cytokine production, and up-regulation of adhesion molecules, which lead to graft damage/injury. IL-6 promotes the CD8+ T cell memory expansion and CD4+ T cell differentiation to Th17, which are implicated in acute and chronic graft rejection [43]. In a murine model of KT, following the graft rejection, intra-graft expression of IL-6 was upregulated and Foxp3+ Tregs were decreased [44]. Foxp3+ Tregs are critical for maintaining immune homeostasis and immune tolerance in transplantation [45]. IL-6 is a main growth factor involved in the differentiation of B cells to IgG-secreting plasmablasts and plasma cells, so the upregulation of antibody production in KT can lead to AMR [27, 46]. Morever, IL-6 is implicated in innate immunity by binding Natural Killer (NK) cells, subsequently, it induces cytotoxicity to endothelial cells and promotes collagen synthesis by fibroblast and endothelial cell activation, which results in chronic graft injury [27]. This theory was also confirmed in the experimental model of chronic allograft nephropathy, in which interstitial fibrosis/tubular atrophy (IFTA) was shown to be mediated by the presence of chemokines and cytokines, including IL-6 produced by B cells [47]. Due to its pleiotropic activity, IL-6 has become a therapeutic target; it was supposed that inhibiting IL-6 signaling effectively reduces B cell

activation, plasmablast differentiation, and antibody production (both primary and recall). B-cell depletion resulted in decreased intra-graft B cells, chemokines, and IL-6 levels, limiting in this way the allograft interstitial fibrosis and tubular atrophy, leading to better tolerance and graft survival rates [48]. IL-6 inhibition can also promote regulatory T cells (T-reg) generation, which counterbalances the effects of alloreactive Th17 lymphocytes [49]. Indeed, Chandran et al. showed that KT recipients with biopsy-proven intra-graft inflammation treated with IL-6 inhibitor developed significantly higher proportions of Treg as well as substantially lower proportions of T effector cells as compared to control patients, indicating that IL-6 inhibition shifts T cell maturation towards Tregs in the absence of IL-6 signaling [50].

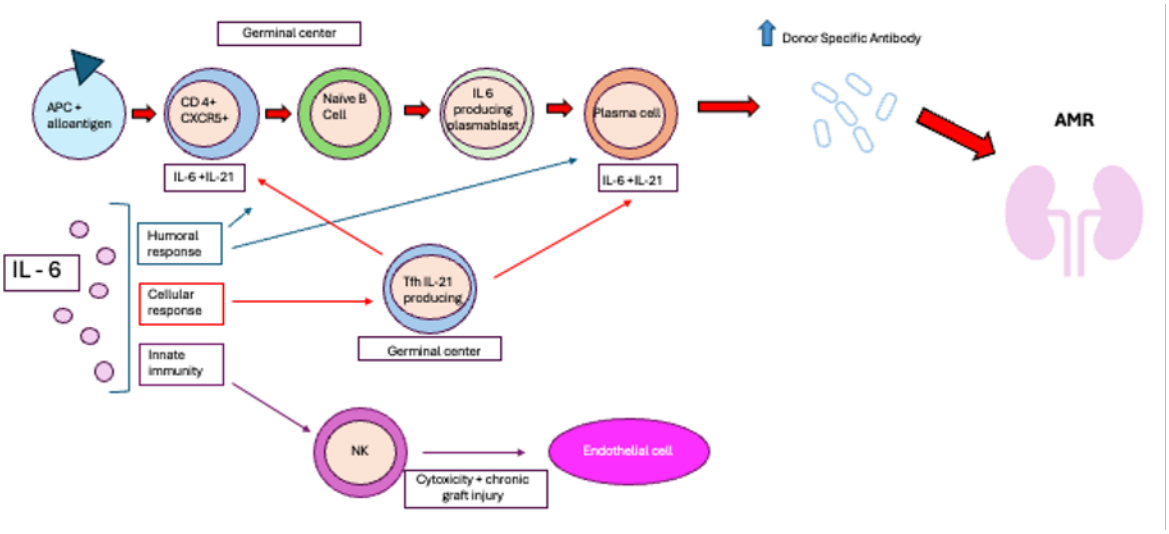

Figure 1. Role of IL-6 in immunity. IL-6 involvement in humoral, cellular and innate immune responses. IL-6 production by APCs is an important stimulus for IL-21 production by naive T cells which mature toward the Tfh phenotype expressing CXCR5 and IL-21. Naive B cells migrate to the germinal centers in response to CXCR5+ Th cells. This activates B cell maturation to memory B cells and IL-6 producing plasmablasts that further promote germinal center formation and progression to antibody-producing plasma cells driving pathogenic antibody production and tissue injury. Impact of anti–IL-6/IL-6R therapy on reducing Tfh activation and subsequent plasmablast and plasma cell development with reductions in pathogenic antibody production and tissue injury. IL-6 by binding NK cells can induce cytotoxicity toward endothelial cells and promotes collagen synthesis by fibroblast and endothelial cell activation, which results in chronic graft injury. AMR: antibody-mediated rejection; APC: antigen-presenting cell; DSA: donor-specific HLA antibody; IL: interleukin; Tfh: T-follicular helper cells; NK: natural killer.

Role of Tocilizumab in Kidney Transplantation

TCZ is a humanized monoclonal antibody (IgG1 subclass) that binds IL-6 Receptor (IL-6R). It has been approved for the treatment of moderate to severe rheumatoid arthritis and idiopathic juvenile arthritis [51]. Many studies have shown that using TCZ as an add-on therapy induced an intense relative reduction of DSAs in terms of MFI; although the reduction was not clinically significant, it was a tendency to induce lower post-transplantation antibody rebound [52]. Moreover, TCZ appears to be a safe and feasible strategy for managing AMR in sensitized kidney transplant recipients [53].

The mechanism of action of TCZ is illustrated in Figure 2.

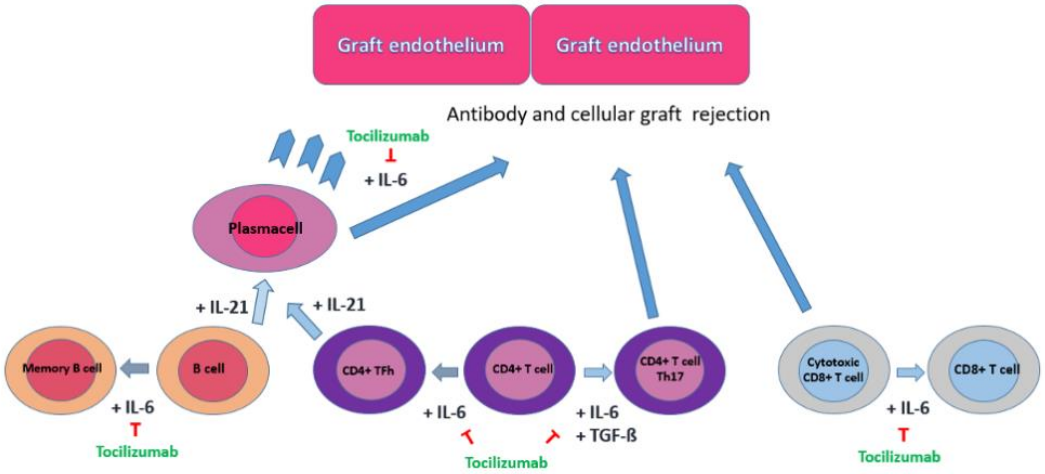

Figure 2. IL-6 receptor targets of Tocilizumab in the development of AMR. Impact of Tocilizumab inhibiting IL-6 pathway can reduce Tfh activation and subsequent plasmablast and plasma cell development with reductions in pathogenic antibody production and tissue injury. In addition, anti–IL-6 therapy inhibits T effector cell function and enhances Treg cell/Breg cell differentiation which likely inhibits DSA formation and allograft injury. AMR: antibody-mediated rejection; IL-6: interleukin-6; IL-21: interleukin-21; Tfh: T-follicular helper cell.

Efficacy of Tocilizumab in Desensitization Protocols for Highly Sensitized Kidney Transplant Candidates

The use of TCZ in desensitization protocols for HS kidney transplant candidates remains an area of emerging investigation. Preclinical data derived from an HLA-incompatible skin graft mouse model suggest that TCZ not only reduces circulating anti-HLA antibody levels but also significantly decreases the frequency of antibody-secreting plasma cells in both the bone marrow and spleen, supporting its potential role in modulating humoral alloimmune responses [54].

In clinical settings, TCZ has been evaluated both as monotherapy and as part of combination regimens. The following is a synthesis of three principal studies investigating the efficacy of TCZ in HS patients, with specific focus on changes in DSA levels, lymphocyte subset dynamics, access to transplantation, and posttransplant outcomes.

A summary of the findings is presented in Table 1.

Vo et al. evaluated the efficacy of TCZ in a cohort of 10 HS kidney transplant candidates who had previously failed standard desensitization (SC) protocols involving IVIG and RTX. Patients received IVIG (2 g/kg on days 0 and 30) and TCZ (8 mg/kg on day 15), followed by monthly TCZ infusions for six months. TCZ enabled transplantation in 50% of participants. A statistically significant reduction in DSA MFI was observed ($p = 0.03$), and no episodes of AMR were detected in posttransplant surveillance biopsies. The treatment was well tolerated, suggesting that TCZ may represent a valuable adjunct in desensitization protocols for HS patients unresponsive to conventional therapy [55].

Daligault et al. investigated TCZ monotherapy in 14 HS patients on the transplant waitlist, all with anti-HLA DSAs exhibiting MFI ≥10,000. Patients received monthly TCZ infusions (8 mg/kg). The therapeutic goal was to reduce DSA MFI values below the 10,000 thresholds. While a modest reduction in both the number and intensity of DSAs was achieved, the response was insufficient to enable clinically meaningful desensitization. Only one patient proceeded to transplantation after TCZ monotherapy, whereas 11 required subsequent SC therapy, which allowed successful transplantation in eight cases. The authors concluded that TCZ monotherapy provides limited benefit in treatment-naïve HS patients, due to its modest and narrow impact on DSA reduction [56].

In a third prospective single-center study conducted by Jouve et al., TCZ monotherapy was assessed in 13 naïve HS patients with DSAs >10,000 MFI. Patients received 8 mg/kg every four weeks for six months. Immunologic endpoints included quantitative and qualitative changes in anti-HLA DSAs (MFI, panel reactive antibody [PRA] levels), as well as phenotyping of T and B cell subsets, including follicular helper T cells (Tfh), regulatory T cells (Tregs), and circulating cytokine/chemokine profiles (IL-6, IL-6R, IL-21, CXCL10, CXCL13). After six months, DSA MFI values showed only marginal changes without statistical significance, and no variation in PRA levels was detected. TCZ had negligible effects on CD3+ T cell and B cell compartments, except for a significant increase in naïve B cells ($p = 0.020$) and a decrease in post-germinal center B cells. No significant changes were observed in Th cells, Tregs, or circulating cytokine/chemokine levels. None of the patients achieved transplant eligibility following TCZ monotherapy. However, seven eventually underwent successful KT after receiving adjunctive SC therapy. The authors concluded that TCZ monotherapy had limited efficacy as a standalone desensitization strategy, though its effect on B-cell maturation may support its use in preventing post-transplant humoral rebound [57].

As summarized in Table 1, two of the three reviewed studies demonstrated that TCZ monotherapy exerts only modest effects on DSA reduction and access to transplantation in HS patients. In contrast, when combined with SC protocols, TCZ appears to enhance transplant eligibility and may contribute to reducing the risk of post-transplant AMR. These findings suggest that the primary role of TCZ may lie not in its desensitizing capacity per se, but rather in its ability to modulate long-term humoral alloimmune responses and prevent post-transplant DSA rebound, thereby potentially improving graft survival rates.

Encouraging and similar data have also been recorded in studies conducted in other types of solid organ transplantation. Sommer et al. examined the effect of TCZ in cardiac transplant patients who had pre-transplant pre-formed DSA and received TCZ in the context of desensitization protocols. Post-transplant rejection rates were significantly lower than those of controls, and no graft failures were reported. This suggests TCZ's potential in reducing DSA rebound and preventing graft rejection, though the benefits likely stemmed from its use in a multi-drug combo therapy regimen [58].

Efficacy of Tocilizumab in Antibody-Mediated Rejection in Kidney Transplant Patients

This section summarizes evidence from eight clinical studies assessing the efficacy of TCZ in the treatment of AMR with particular focus on its effects on renal allograft histopathology, graft function over time, DSA trends, graft and patient survival, and safety profile.

All key findings of those studies are presented in Table 2.

Efficacy of Tocilizumab in Acute Antibody-Mediated Rejection in Kidney Transplant Patients

In a single-center retrospective observational study, Potteboun et al. [59] studied the efficacy of TCZ as an adjunct to SC therapy in seven KT recipients with biopsy-proven acute antibody-mediated rejection (a-AMR). DSAs levels were measured at the time of diagnosis and monitored longitudinally over a 24-month follow-up period. This study provides novel insights into the therapeutic potential of IL-6 blockade in the setting of a-AMR, a condition associated with a high risk of progression to chronic AMR and subsequent graft dysfunction or loss. Given the central pathogenic role of DSAs in AMR, therapeutic strategies aimed at depleting circulating antibodies or suppressing their production are of critical importance. While SC therapy-PLEX, IVIg, and RTX-typically result in a modest reduction of DSA levels (approximately 15-35%, depending on the specificity of anti-HLA antibodies and the intensity of PLEX), the authors identified a 50% reduction in DSA MFI as a clinically relevant threshold, reflective of a meaningful immunologic response with potential impact on graft survival. In this case series, the addition of TCZ to SC therapy was associated with stabilization or improvement of renal function in all patients, along with a notable reduction in DSA levels in most

cases. These findings suggest that TCZ may enhance the efficacy of conventional immunomodulatory strategies in patients with a-AMR and could play a role in delaying or preventing the progression of alloimmune-mediated graft injury. However, the limited sample size and retrospective design underscore the need for prospective controlled trials to validate these preliminary observations.

Study	Design / Setting	Population	Intervention	Outcomes	Main results			
					Outcomes on DSAs	Transplantation Rate	Immunological Findings	Key Conclusions
Vo et al. Transplantation 2015 [55]	Phase I/II uncontrolled, single-center	10 HS patients refractory to IVIG + RTX +/- PLEX	IVIG (2 g/kg on days 0 & 30) + TCZ (8 mg/kg on day 15) monthly × 6 months + IVIG at D0 and D30	Efficacy – % of patients receiving Kidney transplant – rejection at 6 months biopsy – DSAs at 6 months	Significant DSA MFI reduction (p = 0.03) No DSAs at M6	5/10 (50%) transplanted	No AMR in post-transplant biopsies M6 1 AMR at M12, no graft loss	TCZ effective as adjunct in SC-refractory patients
Daligault et al. Transplantation Direct 2021 [56]	Phase II uncontrolled, single center	14 naïve HS patients with DSA ≥10,000 MFI First DES attempt	TCZ monotherapy (8 mg/kg every 4 weeks x 6 months) No other prior or DES therapies	Efficacy – MFI of anti-HLA immunodominant Ab – Number of anti-HLA Ab with MFI>10000 – % of patients received transplant	Modest DSA decline, insufficient for clinical DES	1/14 transplanted with TCZ; 8/11 transplanted after rescue SC	No AMR data	TCZ monotherapy has limited efficacy in naïve HS patients
Jouve et al. AJT 2021 [57]	Controlled non-randomized, single-center	13 naïve HS patients with DSA >10,000 MFI Control group: HS patients remaining in dialysis without DES attempt; healthy subjects	TCZ monotherapy (8 mg/kg every 4 weeks × 6 months) No other prior or DES therapies	Rates evolution of: Tfh 1, 2, and 17 Treg; plasmablasts, plasma-cells, B memory cells; evolution of anti HLA Ab MFI	Marginal MFI reduction; no significant PRA change T population: no significant changes in Tfh 1, 2, 17 Treg B population: blocking post germinal B cells, plasmablasts, plasma-cells	0/13 transplanted with TCZ; 7 transplanted after SC	No AMR data	TCZ monotherapy has limited efficacy in naïve HS patients

Table 1. Tocilizumab for Desensitization in Highly Sensitized Kidney Transplant Candidates. Abbreviations: Ab, antibody; AMR, antibody-mediated rejection; DES, desensitization; IVIG, intravenous immunoglobulin; HS, highly sensitized; MFI, mean fluorescence intensity; SC, standard of care; DSA, donor-specific antibodies; KT, kidney transplant; TCZ, tocilizumab; RTX, rituximab; T fh, T follicular helper cells; T reg, T regulatory cells.

Study (Year)	Design / Sample	Type of AMR	Baseline data	TCZ Use	Histological Outcomes	Renal Function (eGFR and/or proteinuria)	DSA Response	Key Notes
Choi et al. Am J Transplant 2017 [60]	Open-label case study, n=36	Chronic active	Mean eGFR 48.4 ml/min/1.73m2 DSAs + 91,7% Mean DSAs 1.91	Rescue therapy 6–36 months	↓ g + ptc (p=0.0175), ↓ C4d (p=0.0318)	Stable eGFR at 36 months (38.8 ± 10.4 ml/min/1.73 m2 in adults) over 3.26 years	↓ DSA (p=0.043 at 24 months)	First report; abrupt TCZ withdrawal led to graft loss
Lavacca et al. Clin Transplant 2020 [62]	open-label case study n=15	Chronic active	Mean eGFR 45.1 ml/min/1.73m2 Mean of proteinuria 1.1 g/day DSA + 100%	First-line monotherapy	↓ g+ ptc at 6 months (p=0.014). no changes in C4d deposition or chronic lesions (cg and IFTA) (p= 0.206, p= 0.180, p= 0.608 respectively)	Stable eGFR and proteinuria eGFR decline 4.4 mL/ min/1.73 m2 after 12 months of treatment vs 10.5 ml/min/ min/1.73m2/year baseline 1.1 before treatment and 1 g/day after treatment	↓ DSA 22600, pre-TCZ and 18200 post-TCZ	First-line TCZ effective in active inflammation
Potteboun et al. Transplant Direct 2020 [59]	Retrospective, single-center n=7	Acute	DSAs + 100%%	Adjunct to SC	Not reported	Improved/stabilized in all patients	↓ DSA in 4/6 patients (reduction of 50%)	Acute AMR setting; TCZ enhanced DSA reduction
Kummar et al. Kidney360 2020 [63]	Observational single-center cohort study n=10	Chronic active	DSA+ 80%	Adjunct, to SC Belatacept in 7 patients	↓ g+ptc and C4d at 12 months (4.8 ± 1.4 to 4.2 ± 2.0; p = 0.39)	eGFR: 42 ± 18 to 37±24 ml/min/1.73 m2; P = .27), and the slope of eGFR decline remained unchanged (−0.14 ± 0.9 to −0.33 ± 1.1; p = 0.25).	↓ DSA (NS) (p=0.629)	Combined with Belatacept; 47.3% discontinued TCZ
Massat et.al. Am J Transplant 2021 [64]	Retrospective, single-center n=46 9/46 Control group 37/46	Chronic active and mixed	DSAs were present in 66,7% of patients Mean eGFR 40ml/min/1.73m2 Mean g + ptc 3.0+/-0.82	9/46 Rescue 12 months	↓ g + ptc ↓ t (0.07)	No differences between groups (↓ eGFR by – 4 ml/min/1.73m2/year)	↓ DSA In MFI at 12 months (−48 ± 44%)	TCZ rescue therapy provide significant DSAs reduction
Noble et al. Front Med 2021 [65]	Retrospective, single-center n=40	Chronic active	Mean e-GFR 43 ± 17 ml/min/1.73m2 Mean proteinuria 1± 0.9 g/L DSAs + 55%	7/40 TCZ in monotherapy; 33 /40 TCZ + SC	No change in g+ptc	Stable (e-GFR p=0.12 and proteinuria p=0.95 at 6 month and p=0.28 at 12 months)	Not assessed	Baseline severity predicted graft loss
Khairallah et al. Clin Transplant 2023 [66]	Retrospective, single-center n=38	Chronic active	Mean e-GFR 41±17 ml/min/1.73m2, mean proteinuria 0.6 ± 0.5g DSAs + 82%	35/38 rescue 3/38 first line	↓ interstitial inflammation (p=0.03), no change in others	↓ slope of eGFR decline (p=0.002) 34 ± 15 ml/min/1.73 m2 at 3 months 36 ± 15 ml/min/1.73 m2 by 6 months no significant change in terms of proteinuria (p=0.07	No change MFI of DSA Baseline 3450 At 6months 4000	DSA unchanged despite functional stabilization
Boonpheng et al. Clin Transplant 2023 [67]	Retrospective, single-center n=11	Chronic active	64% DD-Cf-DNA mean proteinuria 1.19 g/g	Mixed (6 rescue, 5 first-line)	Limited data (2 biopsies) ↓ g+ptc	Stable eGFR, ↓ proteinuria (NS, p=0.7) eGFR of 57 ± 18 ml/min/1.73 m2 pretreatment eGFR of 56 ± 17 ml/min/1.73 m2 at 6 months and 60 ± 24 ml/min/1.73 m2 at 12 months proteinuria baseline 1.19g/g and 0.97g/g at 12 months	↓ dd-cfDNA (p=0.01 ant 6 moths), ↓ DSA (p=0.047 at 12 months)	First to monitor dd-cfDNA; potential biomarker use

Table 2. Tocilizumab for the treatment of AMR in kidney transplantation. Abbreviations: NA, not assessed; SC, standard of care; TCZ, tocilizumab; e-GFR, estimated glomerular filtration rate; AMR, chronic antibody-mediated rejection; DSAs, donor-specific antibodies; ptc, peritubular capillaritis; g, glomerulitis; cg, chronic glomerulopathy; IFTA, interstitial fibrosis and tubular atrophy; DD-Cf-DNA, Donor Derived Cell free DNA; NS, not significant.

Efficacy of Tocilizumab in Chronic Active Antibody-Mediated Rejection in Kidney Transplant Patients

The first clinical investigation into the use of TCZ in chronic active AMR (ca-AMR) was conducted by Choi et al. [60], who evaluated 36 kidney transplant recipients with biopsy-proven, SC-resistant ca-AMR. Patients received monthly intravenous infusions of TCZ at 8 mg/kg (maximum dose: 800 mg) for a treatment duration ranging from 6 to 36 months. Baseline histological assessments revealed high Banff scores [61] for microvascular inflammation, including glomerulitis and peritubular capillaritis, along with C4d deposition hallmarks of active AMR. After 12 months of TCZ treatment, follow-up biopsies performed in nine patients demonstrated a significant reduction in glomerulitis ($p = 0.0175$), peritubular capillaritis, and C4d staining ($p = 0.0318$). These changes reflect an attenuation of the immunologic injury. Glomerulitis and peritubular capillaritis are typically associated with poor long-term graft prognosis. DSA levels were monitored quarterly, while renal function was assessed via estimated eGFR, and was evaluated monthly throughout the study period. A sustained decline in DSA levels was observed, particularly for immunodominant specificities, with a statistically significant reduction noted at 24 months of therapy ($p = 0.043$). At six years post-ca-AMR diagnosis, graft and patient survival rates were 80% and 91%, respectively. Treatment discontinuation in four patients due to financial constraints ($n = 3$) or clinical indications ($n = 1$) was associated with subsequent graft loss. The authors hypothesized that abrupt cessation of TCZ may have triggered an IL-6 rebound effect, exacerbated by IL-6 accumulation during prolonged receptor blockade. Notably, all four patients experiencing graft failure harbored class II DSAs (HLA-DQ or HLA-DR). Among patients who remained on therapy, renal function was stable, with no significant decline in eGFR at 36 months. Lavacca et al. evaluated the efficacy and safety of TCZ as a first-line therapeutic approach in KT recipients with biopsy-proven ca-AMR. In this open-label, prospective study conducted between 2016 and 2018, 15 patients meeting Banff criteria for ca-AMR [38, 61] were enrolled. None of the participants had received prior targeted anti-rejection therapy. TCZ was administered intravenously at a dose of 8 mg/kg (maximum 800 mg) every four weeks. One patient with advanced graft dysfunction was converted to Belatacept-based maintenance immunosuppression prior TCZ initiation. Patients were followed for a median duration of 20.7 months. Outcome measures included graft function (assessed by eGFR rate and proteinuria), patient survival, serum levels of DSAs and anti-angiotensin II type 1 receptor antibodies (AT1R-Abs), histopathological changes, and adverse events. Protocol biopsies were performed at 6 months post-treatment initiation to assess early histological response. TCZ treatment was associated with stabilization of eGFR and proteinuria, along with a significant reduction in circulating DSA levels ($p = 0.002$). Histological analysis demonstrated a reduction in microvascular inflammation, particularly in glomerulitis and peritubular capillaritis scores. However, no significant improvements were observed in chronic injury markers, including interstitial fibrosis/tubular atrophy and C4d deposition. These findings suggest that TCZ, when used as first-line therapy in ca-AMR, may contribute to the attenuation of active alloimmune injury and stabilization of graft function, although its impact on chronic injury progression remains limited. eGFR and 24-hour proteinuria showed stabilization at the 12-month follow-up. eGFR declined by 10.5 mL/min/1.73 m^2 (median) in the 12 months before ca-AMR diagnosis compared with 4.4 mL/ min/1.73 m^2 the first year after diagnosis. Median proteinuria at diagnosis and at the 12-month follow-up were 1.1 and 1 g/day, respectively. Mean MFI values significantly declined after TCZ treatment (22600 pre-TCZ and 18200 post-TCZ with complete negativization in one patient). This trend was also confirmed for AT1R-Ab [62].

A retrospective study conducted by Kumar et al. evaluated the efficacy of TCZ in 10 kidney transplant recipients with biopsy-proven ca-AMR refractory to SC therapy. Notably, seven of these patients were maintained on Belatacept-based immunosuppression. Serial graft biopsies were performed at baseline and one year following initiation of TCZ therapy. At 6 months post-treatment initiation, there was an improvement in the mean of eGFR, but not statistically significant, while proteinuria levels remained unchanged throughout follow-up. A reduction in DSA MFI was also observed at 6 months, although this did not reach statistical significance ($p = 0.5$). Histological analysis demonstrated a reduction in microvascular inflammation following 12 months of TCZ therapy, mirroring the findings reported by Choi et al. [60]. Specifically, reductions in glomerulitis, peritubular capillaritis, and C4d deposition were noted, as detailed in Table 2. TCZ was discontinued in 47.3% of patients (18/38 in the overall cohort), after a median treatment duration of 10.4 months. In three cases, the decision to withdraw TCZ was made upon stabilization of graft function, highlighting the ongoing uncertainty regarding optimal treatment duration. Discontinuation was also necessitated by the development of HPV-positive tonsillar carcinoma in one patient, and by infectious complications in four others. Collectively, the studies by Choi et al. and Kumar et al. demonstrate consistent histological improvements in patients with refractory ca-AMR treated with TCZ, particularly in the reduction of MVI ($p = 0.0175$) and C4d deposition ($p = 0.0318$), suggesting a potential disease-modifying role for IL-6 blockade in this setting [63].

A retrospective study investigated the efficacy of TCZ as adjunctive SC in nine kidney transplant recipients with biopsy-proven graft rejection. Of these, six patients were diagnosed with ca-AMR, while the remaining three exhibited mixed rejection characterized by features of both AMR and T cell-mediated rejection. All patients had detectable circulating DSAs at the time of diagnosis and had demonstrated resistance to prior SC therapies. TCZ was administered intravenously at a dose of 8 mg/kg (maximum 800 mg) monthly. Outcomes were compared to those of a control group comprising 37 patients with AMR who had received SC therapy alone. At 12-month follow-up, the TCZ-treated group exhibited a significant reduction in the MFI of DSAs across both HLA class I and class II antigens ($p = 0.01$). Despite this immunological response, there were no statistically significant differences between the TCZ and control groups in terms of graft survival or decline in renal function over the same period. Histopathological evaluation revealed a modest improvement in inflammatory indices, including a reduction in tubulitis scores, following TCZ treatment. However, the progression of AMR-related lesions and chronic glomerulopathy remained largely comparable between the two cohorts. The incidence of infections did not differ significantly between TCZ-treated patients and those receiving SC alone [64].

Noble et al. [65] recently published a single-center retrospective study evaluating the efficacy of TCZ in 40 KT recipients with biopsy-proven ca-AMR. TCZ was administered intravenously at a dose of 8 mg/kg (maximum 800 mg) every four weeks. Seven patients received TCZ as first-line monotherapy, whereas the remaining patients were treated with TCZ in combination with other immunosuppressive agents, including corticosteroids (52.5%), RTX (40%), PLEX (20%), and anti-thymocyte globulin (5%). One patient had received Belatacept prior TCZ initiation, and 18 additional patients were converted to Belatacept-based maintenance immunosuppression following the diagnosis of AMR and the initiation of TCZ. The primary endpoints were changes in graft function, assessed by eGFR rate and proteinuria, and histological progression at one year. Compared with baseline values, no statistically significant differences were observed in eGFR decline ($p = 0.102$) or proteinuria ($p = 0.28$) after 12 months of TCZ therapy. Likewise, histopathological assessment revealed no significant changes in Banff lesion scores after one year of treatment. During follow-up, six patients (15%) experienced graft loss. These patients had more severe baseline clinical and histological parameters compared with the rest of the cohort, including lower baseline eGFR (24.5 ± 16 mL/min/1.73 m^2), higher levels of proteinuria (1.8 ± 1.0 g/L), and more advanced chronic injury

on biopsy, with significantly higher scores of tubular atrophy (ct; p = 0.007), interstitial fibrosis (ci; p = 0.002), and intimal arteritis (v; p = 0.001). The study did not include longitudinal monitoring of donor-specific antibodies (DSAs) or systematically report adverse events related to TCZ, thus limiting the interpretation of immunological efficacy and safety outcomes.

Khairallah et al. [66] conducted a retrospective study to evaluate the impact of TCZ on allograft function and histopathological features in 38 kidney transplant recipients with biopsy-proven ca-AMR. Among the included patients, 35 had previously failed SC therapies, while TCZ was administered as first-line therapy in the remaining three. At the time of TCZ initiation, 15 patients had detectable DSAs. TCZ was administered intravenously at a dose of 8 mg/kg monthly. Follow-up biopsies were performed in approximately half of the cohort after a median of 5.1 months from treatment initiation. Histological analysis revealed a significant reduction in interstitial inflammation scores (p = 0.03), while other Banff parameters such as glomerulitis, tubulitis, peritubular capillaritis, arteritis, glomerulosclerosis, and C4d deposition-remained unchanged. No significant variation in DSA levels was observed following TCZ treatment (p = 0.5). Graft function remained stable during the six months following TCZ initiation. A significant deceleration in the rate of eGFR decline was observed, with a difference in slope of 2.6 mL/min/1.73 m^2 per month before and after treatment initiation (p = 0.002). Proteinuria did not change significantly over the observation period (p = 0.07).

Boonpheng et al. conducted a study involving 11 kidney transplant recipients with biopsy-proven ca-AMR treated with TCZ. DSAs and donor-derived cell-free DNA (dd-cfDNA) were serially monitored to assess immunologic activity and allograft injury during follow-up. In six patients, TCZ was initiated following failure of SC therapy, while in the remaining five patients was used as a first-line treatment. At six months, a significant reduction in dd-cfDNA levels was observed (p = 0.01), suggesting a potential attenuation of alloimmune-mediated graft injury. Among the six patients who completed 12 months of treatment, ddcfDNA levels remained significantly reduced compared to baseline at both six and twelve months (p = 0.05 and p = 0.04, respectively). The authors also reported a decline in the MFI of immunodominant DSAs over time. While the reduction did not reach statistical significance at six months (p = 0.13), it became significant at twelve months (p = 0.047), indicating a potential immunomodulatory effect of IL-6 inhibition on humoral alloimmunity. Graft function remained stable during TCZ treatment. The eGFR rate at six months did not differ significantly from baseline (p = 0.25), and in the subgroup of patients treated for at least 12 months, eGFR remained unchanged at six and twelve months (p = 0.29 and p = 0.48, respectively). Proteinuria showed a decreasing trend, but the differences were not statistically significant; mean proteinuria declined from 1.19 g/g at baseline to 0.97 g/g at twelve months (p = 0.70). Only two patients underwent follow-up biopsies after 16 months of treatment, which revealed modest improvements in microvascular inflammation [67].

Tocilizumab safety profile

Adverse events are summarized in Table 3. Across published studies, the safety profile of TCZ in KT recipients has been overall acceptable and comparable to that observed in other clinical settings. The most frequently reported adverse events were infectious complications, particularly bacterial and viral infections, consistent with the immunomodulatory effects of IL-6 blockade.

In the largest available series, Choi et al. [60] reported infectious events in approximately 25–30% of patients treated for ca-AMR, while Lavacca et al. [62] documented infections in one-third of their cohort, mainly urinary and respiratory tract infections and cytomegalovirus (CMV) viremia. Similarly, Kumar et al. [63] observed infections in 50% of patients, including opportunistic infections, and in several cases, this led to treatment discontinuation. In other retrospective cohorts [64–66], the incidence of infections ranged from 20% to 30%, without a statistically significant difference

compared to SC therapy. Boonpheng et al. [67] reported three non-severe events (uncomplicated diverticulitis, localized herpes zoster, and mild COVID-19), and Potteboun et al. [59] observed no serious adverse events in acute AMR patients. In the desensitization setting, TCZ was very well tolerated across three studies [55–57], with no severe infections reported.

The most common infectious events included urinary tract infections, respiratory infections, CMV reactivation, herpes zoster, and, less frequently, gastrointestinal infections. No invasive fungal infections were documented.

Non-infectious adverse events were uncommon. One case of HPV-positive tonsillar carcinoma was reported during prolonged TCZ treatment; the event was not directly TCZ-related [63], and a single episode of diverticulitis [67]. Mild, transient laboratory abnormalities (e.g., elevated transaminases) were occasionally described but were not clinically significant. Only one study reported a cardiovascular event in two patients: non-ST-segment elevated myocardial infarctions and one stroke. However, the causal relationship with TCZ therapy is not clear. There were no reports of TCZ-related nephrotoxicity. Importantly, several studies reported no significant increase in infection rates compared with SC alone [64], suggesting that TCZ does not substantially increase the infectious burden when used in experienced transplant centers with appropriate prophylaxis and monitoring. TCZ infusion was overall well tolerated across the included studies.

Overall, TCZ demonstrates a favorable and manageable safety profile in kidney transplant recipients. Infectious events remain the main clinical concern but are generally controllable. The drug is well tolerated both as adjunctive therapy for AMR and as part of desensitization strategies, supporting its use in selected high-risk populations under close clinical surveillance.

Critical Comparison and Limitations of Studies Evaluating Tocilizumab in AMR

Across the current body of literature, TCZ has emerged as a potentially effective therapeutic agent for the management of AMR, particularly in patients who are refractory to SC therapies. Although most available studies are single-center, retrospective, and non-randomized, with limited sample sizes (ranging from 7 to 40 patients per study) and often lacking adequately matched control groups, they consistently demonstrate a significant attenuation of microvascular inflammation, including reductions in glomerulitis and peritubular capillaritis scores, accompanied by stabilization of renal allograft function.

In the pivotal study by Choi et al. [60], TCZ administered as rescue therapy was associated histological improvements and sustained reductions in DSA levels over a long-term follow-up, supporting its disease-modifying potential in ca-AMR. Similarly, Kumar et al. [63] and Lavacca et al. [62] reported concordant findings, with significant reductions in microvascular inflammation and stabilization of e-GFR, although DSA declines were more variable and not consistently statistically significant across all patients. By contrast, the study by Noble et al. [65], which included a larger and more heterogeneous cohort of patients treated with TCZ in combination with other immunomodulatory agents, did not show significant changes in either histological lesions or functional parameters after one year of therapy. This discrepancy may be attributable to more advanced chronic injury at baseline, differences in treatment timing and duration, and the absence of standardized immunological monitoring protocols. Importantly, heterogeneity in treatment duration – ranging from a few months to three years –, timing of TCZ administration (first-line vs rescue therapy), and baseline histopathological severity likely influenced clinical and immunological outcomes. Furthermore, the use of TCZ as monotherapy versus combination therapy represents an additional source of variability. While some studies suggested promising effects of TCZ monotherapy in mitigating microvascular inflammation, most cohorts received combination regimens, making it challenging to isolate the specific contribution of IL-6 blockade.

Study	Infection	Others
Vo et al. Transplantation 2015 [55]	1 episode of colonic diverticulitis with perforation (possible correlation with TCZ)	Anemia and hypertension during time of treatment. 1 episode of acute pulmonary edema unrelated to TCZ and
Daligault et al. Transplantation Direct 2021 [56]	1 episode of Spondylodiscitis	Hypogammaglobulinemia
Jouve et al. AJT 2021 [57]	1 episode of spondilodiscitis	hypogammaglobulinemia
Choi et al. Am J Transplant. 2017 [60]	13/36 5 CMV viremia 3 BKV viremia 7 bacterial infections	3/36 1 stroke 2 NSTEMI 1/36 transient visual disturbance 8/36 hypogammaglobulinemia
Lavacca et al. Clin Transplant. 2020 [62]	5/15 bacterial Infection 4/5 UTI 1/5 low respiratory tract infection 1/15 encephalitis of undefined origin 2/15 interstitial lung disease infection	4/15 hypogammaglobulinemia 3/15 asymptomatic mild alterations in liver enzymes
Pottebaum et al. Transplant Direct. 2020 [59]	1/7 CMV esophagitis	1 potential hypersensitivity reaction
Kummar et al. Kidney360. 2020 [63]	3/ 19 bacterial infections 1/10 viral with HSV	5/10 leukopenia 1/19 severe diarrhea
Massat et al Am J Transplant. 2021. [64]	6/9 (SC+TCZ) * 2 bacterial infections 2 viral infections 2 fungal infections	NA
Noble et al. Front Med. 2021 [65]	NA	NA
Khairallah et al. Clin Transplant. 2023 [66]	3/38 CMV viremia 3/3 BKV viremia 1/3 EBV viremia 1/38 pneumonia 1/38 cellulitis 3/38 pyelonephritis	15/3 leucopenia 16/38 thrombocytopenia 7/38 asymptomatic mild alterations in liver enzymes
Boonpheng at al. Clin Transplant. 2023 [67]	1/11 VZV 1/11 uncomplicated diverticulitis 1/11 mild covid 19 infection 1/11 clostridium difficile colitis	NA

Table 3. Tocilizumab Adverse effects. NA, not assessed. CMV: cytomegalovirus; BKV: poliomavirus BK; EBV: Epstein-Barr virus; VZV: varicella zoster virus; HSV: herpes simplex virus; NSTEMI: non–ST-segment elevation myocardial infarction; UTI: urinary tract infection; TCZ: tocilizumab. *There were no significant differences between the SC group and the SC+TCZ group.

The timing of intervention and extent of baseline histological injury also appear to modulate therapeutic response. In acute AMR, early initiation of TCZ (Potteboun et al.) was associated with stabilization of graft function and significant reductions in DSA levels, suggesting a beneficial effect on ongoing alloimmune injury. In contrast, in ca-AMR, TCZ consistently reduced microvascular inflammation and C4d deposition but exhibited limited effects on chronic injury parameters such as IFTA, transplant glomerulopathy, and intimal arteritis, particularly in patients with advanced structural damage at baseline (e.g., Noble et al.). These findings support the hypothesis that IL-6 blockade may exert its maximal therapeutic effect when introduced in earlier phases of the disease, before the establishment of irreversible chronic allograft injury.

Additional mechanistic insights were provided by Khairallah et al. [66] and Boonpheng et al. [67], who explored eGFR slope dynamics and donor-derived cell-free DNA (dd-cfDNA), respectively, as surrogate markers of graft injury and immunological activity. Khairallah et al. observed a significant deceleration in the rate of eGFR decline following TCZ initiation, even in the absence of significant DSA changes, suggesting an anti-inflammatory effect independent of antibody clearance. Boonpheng et al. demonstrated both dd-cfDNA and DSA reductions over 12 months, indicating a dual anti-inflammatory and immunomodulatory mechanism of IL-6 blockade. Importantly, the

therapeutic benefit of TCZ appeared more pronounced in early or moderate ca-AMR, whereas its impact in advanced stages with extensive fibrosis and glomerulopathy remained limited.

By targeting IL-6 signaling, TCZ can reduce DSA levels, suppress their production, and mitigate histological damage in both the short and long term.

Given the lack of standardized treatment algorithms for AMR, accumulating evidence supports a potential role for TCZ as an adjunctive therapy, particularly in patients with inadequate responses to SC. By targeting the IL-6 signaling pathway, TCZ has the capacity to modulate both humoral and inflammatory components of the alloimmune response, reduce DSA production, and attenuate histological injury in both the short and long term.

Within this therapeutic landscape, Belatacept, a fusion protein that selectively inhibits CD28-mediated T-cell co-stimulation, may represent a synergistic partner for TCZ. Its calcineurin inhibitor-sparing properties and capacity to suppress T-cell activation make it an attractive strategy for high-immunological-risk recipients. Data from randomized phase 3 trials (BENEFIT and BENEFIT-EXT) have shown reduced DSA production with Belatacept, supporting the rationale for dual targeting of both T- and B-cell compartments to achieve more effective immunological control, reduce microvascular inflammation, and prevent DSA rebound [68, 69]. Consequently, the combination of TCZ and Belatacept represents a promising and biologically rational therapeutic approach that warrants further evaluation in prospective clinical trials, particularly in patients with high immunological risk or resistance to conventional therapies.

Alternatives in IL-6 pathway inhibition – Clazakizumab

Clazakizumab is a humanized monoclonal IgG1 antibody that bind with high affinity and neutralizes human IL-6. In 2016 it was used to treat 10 patients with chronic AMR. Findings from this study demonstrating a stabilization of eGFR after initiation of clazakizumab therapy (eGFR −24 months [52], 0 month [38], +12 months [41], and +24 months [38]), reductions in DSA levels and Banff scores for C4d and g + ptc scores. The authors noted a trend to reductions in total IgG levels and an increase in Treg cells at 24 months post treatment [30]. In a randomized, double-blind, placebo-controlled, parallel-group phase II pilot trial conducted and published in 2021, that included 20 KT patients with DSA-positive AMR after a median of 10.6 years post-transplantation. KT patients were randomly assigned to receive Clazakizumab or a placebo to assess safety, tolerability, and efficacy of the molecule. Within 12 weeks of therapy DSA MFI decreased by 77%, without significant differences in AMR and T-cell–mediated rejection between the two groups. The key results of the secondary endpoint analysis were a slowed decline in eGFR and, after extended treatment, modulation of rejection-associated gene expression patterns, reduction of C4d scores, and, in some patients, resolution of AMR activity. These results were promising [31].

In addition to TCZ, Clazakizumab has been investigated in early-phase studies involving 20 HS kidney transplant candidates. Clazakizumab desensitization protocols, after PLEX + IVIg, appear safe with significant reductions in HLA class I and II antibodies. The treatment allowed 18 of 20 patients to receive transplantation with no de novo DSA generation [32].

The data suggest that Clazakizumab can reduce circulating DSA levels and modulate humoral alloimmune responses, potentially facilitating access to transplantation in difficult-to-match patients. Compared with TCZ, Clazakizumab may provide a more complete and sustained blockade of IL-6 signaling, although evidence remains limited and mostly derived from small, non-randomized cohorts. Ongoing randomized trials, including the IMAGINE trial (NCT03744910), will be crucial to clarify the role of IL-6 inhibition in kidney transplantation.

Comparative Therapeutic Landscape of AMR: IL-6 Blockade, CD38 Targeting, and Complement Inhibition

Over the past decade, increasing understanding of the complex immunopathology of antibody- AMR has prompted the development of several novel therapeutic strategies beyond conventional ones. So, IL-6 blockade with tocilizumab and Clazakizumab, CD38-targeting monoclonal antibodies, proteasome inhibition, and complement inhibition represent the most promising emerging approaches. Each of these strategies acts on distinct – but potentially complementary – pathogenic pathways of AMR, and their comparison provides important insights into future treatment algorithms.

CD38-targeting monoclonal antibodies, including Daratumumab and Felzartamab, have recently emerged as a promising class of agents with a distinct and potentially more rapid mechanism of action. CD38 is highly expressed on plasma cells and NK cells, two key effector populations in AMR pathogenesis. By targeting CD38, these agents deplete both DSA-producing plasma cells and Fc receptor–expressing NK cells, thus intervening at multiple levels of the alloimmune cascade. Felzartamab, evaluated in a randomized, placebo-controlled phase 2 trial in late AMR, demonstrated histologic resolution of AMR activity in over 80% of patients after six months of therapy, with a marked reduction in MVI scores and AMR transcriptomic activity, along with significant depletion of circulating NK cells. These effects occurred despite minimal changes in immunodominant DSA levels, supporting the hypothesis that targeting effector mechanisms downstream of DSA may be sufficient to attenuate graft injury. Importantly, dd-cfDNA levels – a biomarker of active allograft injury – declined rapidly during treatment, although recurrence of molecular and histologic activity was observed after therapy cessation, indicating that prolonged or combination regimens may be required [70].

Daratumumab, an anti-CD38 antibody with a well-established safety profile in hematology, has been used off-label in several case reports and small series involving both early and late AMR. These studies consistently showed reduction in DSA mean fluorescence intensity, NK cell depletion, attenuation of MVI, and stabilization or improvement of graft function. In some cases, significant dd-cfDNA reduction paralleled these effects, further supporting its immunomodulatory potential [71–74]. Notably, sequential or combination strategies, such as Daratumumab followed by TCZ, have been associated with enhanced and more sustained immunologic responses, suggesting a synergistic effect between plasma cell depletion and IL-6 blockade [75].

Similarly, complement inhibition, particularly with anti-C5 (eculizumab), has shown promise in acute AMR by attenuating complement-mediated endothelial injury and reducing C4d deposition, but its effect on long-term graft survival remains uncertain, and its use is currently limited to selected high-risk cases or rescue therapy [25].

Taken together, these findings underscore the heterogeneity and complementarity of available immunomodulatory strategies. While IL-6 blockade primarily targets upstream inflammatory and B cell–mediated pathways, CD38-targeting antibodies intervene at both the level of antibody production and effector mechanisms, resulting in rapid attenuation of rejection activity even in late stages. Proteasome and complement inhibition offer additional therapeutic angles, targeting upstream plasma cell survival and downstream complement-mediated injury, respectively. In this context, rational combinatorial or sequential approaches may offer the most effective strategy for patients with refractory or advanced AMR. Ongoing phase 3 trials with Felzartamab (TRANSCEND) and Daratumumab (DARTABMR)-based regimens are expected to define their position in the therapeutic armamentarium, and their potential integration with IL-6 blockade or other targeted therapies may further improve allograft outcomes in high immunological risk populations.

Conclusions

The current evidence on the use of TCZ for the treatment of AMR and for desensitization in HS kidney transplant candidates is promising but remains limited. Most available studies are retrospective, include small patient cohorts, and lack randomized controlled trials (RCTs), which hinders the ability to draw definitive conclusions regarding the efficacy of TCZ either as monotherapy or in combination with standard therapies. Larger, prospective, randomized studies are needed to better define the role of TCZ in these contexts and to optimize treatment protocols. TCZ has shown encouraging results in attenuating microvascular inflammation, stabilizing graft function, and reducing DSA levels, particularly when used as rescue therapy in patients with AMR refractory to SC. Its continuation after transplantation in patients undergoing desensitization may be justified, as it could help prevent DSA rebound and reduce the risk of post-transplant humoral rejection, especially in highly sensitized recipients. These findings suggest that TCZ could be strategically positioned as both an adjunctive therapy and a maintenance option in selected high-risk patients.

In summary, IL-6 pathway inhibition represents a promising and biologically targeted strategy in the management of AMR and desensitization in kidney transplantation. However, further high-quality studies are required to determine the optimal timing, duration, and combination strategies for IL-6 blockade.

BIBLIOGRAPHY

1. Schold JD, Buccini LD, Goldfarb DA, Flechner SM, Poggio ED, Sehgal AR. Association between kidney transplant center performance and the survival benefit of transplantation versus dialysis. Clin J Am Soc Nephrol. 2014 Oct 7;9(10):1773-80. https://doi.org/10.2215/cjn.02380314.
2. Laupacis A, Keown P, Pus N, Krueger H, Ferguson B, Wong C, Muirhead N. A study of the quality of life and cost-utility of renal transplantation. Kidney Int. 1996 Jul;50(1):235-42. https://doi.org/10.1038/ki.1996.307.
3. Lefaucheur C, Loupy A, Hill GS, Andrade J, Nochy D, Antoine C, Gautreau C, Charron D, Glotz D, Suberbielle-Boissel C. Preexisting donor-specific HLA antibodies predict outcome in kidney transplantation. J Am Soc Nephrol. 2010 Aug;21(8):1398-406. https://doi.org/10.1681/asn.2009101065.
4. Collins AJ, Foley RN, Chavers B, et al. US Renal Data System 2013 Annual Data Report. Am J Kidney Dis. 2014 Jan;63(1 Suppl):A7. https://doi.org/10.1053/j.ajkd.2013.11.001.
5. David-Neto E, Souza PS, Panajotopoulos N, Rodrigues H, Ventura CG, David DS, Lemos FB, Agena F, Nahas WC, Kalil JE, Castro MC. The impact of pretransplant donor-specific antibodies on graft outcome in renal transplantation: a six-year follow-up study. Clinics (Sao Paulo). 2012;67(4):355-61. https://doi.org/10.6061/clinics/2012(04)09.
6. Wan SS, Chadban SJ, Watson N, Wyburn K. Development and outcomes of de novo donor-specific antibodies in low, moderate, and high immunological risk kidney transplant recipients. Am J Transplant. 2020 May;20(5):1351-1364. https://doi.org/10.1111/ajt.15754.
7. Loupy A, Hill GS, Jordan SC. The impact of donor-specific anti-HLA antibodies on late kidney allograft failure. Nat Rev Nephrol. 2012 Apr 17;8(6):348-57. https://doi.org/10.1038/nrneph.2012.81.
8. Vo AA, Choi J, Cisneros K, Reinsmoen N, et al. Benefits of rituximab combined with intravenous immunoglobulin for desensitization in kidney transplant recipients. Transplantation. 2014 Aug 15;98(3):312-9. https://doi.org/10.1097/tp.0000000000000064.
9. Marfo K, Lu A, Ling M, Akalin E. Desensitization protocols and their outcome. Clin J Am Soc Nephrol. 2011 Apr;6(4):922-36. https://doi.org/10.2215/cjn.08140910.
10. Montgomery RA, Loupy A, Segev DL. Antibody-mediated rejection: New approaches in prevention and management. Am J Transplant. 2018 Jan;18 Suppl 3:3-17. Erratum in: Am J Transplant. 2018 Jun;18(6):1579. https://doi.org/10.1111/ajt.14584.
11. Malvezzi P, Jouve T, Noble J, Rostaing L. Desensitization in the Setting of HLA-Incompatible Kidney Transplant. Exp Clin Transplant. 2018 Aug;16(4):367-375. https://doi.org/10.6002/ect.2017.0355.
12. Billing H, Rieger S, Ovens J, Süsal C, Melk A, Waldherr R, Opelz G, Tönshoff B. Successful treatment of chronic antibody-mediated rejection with IVIG and rituximab in pediatric renal transplant recipients. Transplantation. 2008 Nov 15;86(9):1214-21. https://doi.org/10.1097/tp.0b013e3181880b35.
13. Fehr T, Rüsi B, Fischer A, Hopfer H, Wüthrich RP, Gaspert A. Rituximab and intravenous immunoglobulin treatment of chronic antibody-mediated kidney allograft rejection. Transplantation. 2009 Jun 27;87(12):1837-41. https://doi.org/10.1097/tp.0b013e3181a6bac5.
14. Hong YA, Kim HG, Choi SR, Sun IO, Park HS, Chung BH, Choi BS, Park CW, Kim YS, Yang CW. Effectiveness of rituximab and intravenous immunoglobulin therapy in renal transplant recipients with chronic active antibody-mediated rejection. Transplant Proc. 2012 Jan;44(1):182-4. https://doi.org/10.1016/j.transproceed.2011.12.006.
15. Noble J, Metzger A, Naciri Bennani H, et al. Apheresis Efficacy and Tolerance in the Setting of HLA-Incompatible Kidney Transplantation. J Clin Med. 2021 Mar 23;10(6):1316. https://doi.org/10.3390/jcm10061316.
16. Wan SS, Ying TD, Wyburn K, Roberts DM, Wyld M, Chadban SJ. The Treatment of Antibody-Mediated Rejection in Kidney Transplantation: An Updated Systematic Review and Meta-Analysis. Transplantation. 2018 Apr;102(4):557-568. https://doi.org/10.1097/tp.0000000000002049.
17. Schinstock C.A, Mannon R.B, Budde K, et al. Recommended Treatment for Antibody-mediated Rejection After Kidney Transplantation: The 2019 Expert Consensus From the Transplantion Society Working Group. Transplantation. 2020, 104:911-922. https://doi.org/10.1097/tp.0000000000003095.
18. Manook M, Koeser L, Ahmed Z, Robb M, Johnson R, Shaw O, Kessaris N, Dorling A, Mamode N. Post-listing survival for highly sensitised patients on the UK kidney transplant waiting list: a matched cohort analysis. Lancet. 2017 Feb 18;389(10070):727-734. doi: 10.1016/S0140-6736(16)31595-1. Epub 2017 Jan 6. Erratum in: Lancet. 2017 Feb 18;389(10070):700. https://doi.org/10.1016/s0140-6736(16)31595-1.
19. Vo AA, Lukovsky M, Toyoda M, Wang J, Reinsmoen NL, Lai CH, Peng A, Villicana R, Jordan SC. Rituximab and intravenous immune globulin for desensitization during renal transplantation. N Engl J Med. 2008 Jul 17;359(3):242-51. https://doi.org/10.1056/nejmoa0707894.
20. Smith RN, Malik F, Goes N, Farris AB, Zorn E, Saidman S, Tolkoff-Rubin N, Puri S, Wong W.

Partial therapeutic response to Rituximab for the treatment of chronic alloantibody mediated rejection of kidney allografts. Transpl Immunol. 2012 Oct;27(2-3):107-13. https://doi.org/10.1016/j.trim.2012.08.005.
21. Muller YD, Ghaleb N, Rotman S, Vionnet J, Halfon M, Catana E, Golshayan D, Venetz JP, Aubert V, Pascual M. Rituximab as monotherapy for the treatment of chronic active antibody-mediated rejection after kidney transplantation. Transpl Int. 2018 Apr;31(4):451-455. https://doi.org/10.1111/tri.13111.
22. Mella A, Gallo E, Messina M, Caorsi C, Amoroso A, Gontero P, Verri A, Maletta F, Barreca A, Fop F, Biancone L. Treatment with plasmapheresis, immunoglobulins and rituximab for chronic-active antibody-mediated rejection in kidney transplantation: Clinical, immunological and pathological results. World J Transplant. 2018 Sep 10;8(5):178-187. https://doi.org/10.5500/wjt.v8.i5.178.
23. Moreso F, Crespo M, Ruiz JC, Torres A, Gutierrez-Dalmau A, Osuna A, Perelló M, Pascual J, Torres IB, Redondo-Pachón D, Rodrigo E, Lopez-Hoyos M, Seron D. Treatment of chronic antibody mediated rejection with intravenous immunoglobulins and rituximab: A multicenter, prospective, randomized, double-blind clinical trial. Am J Transplant. 2018 Apr;18(4):927-935. https://doi.org/10.1111/ajt.14520.
24. Eskandary F, Regele H, Baumann L, Bond G, et al. A Randomized Trial of Bortezomib in Late Antibody-Mediated Kidney Transplant Rejection. J Am Soc Nephrol. 2018 Feb;29(2):591-605. https://doi.org/10.1681/asn.2017070818.
25. Kulkarni S, Kirkiles-Smith NC, Deng YH, Formica RN, Moeckel G, Broecker V, Bow L, Tomlin R, Pober JS. Eculizumab Therapy for Chronic Antibody-Mediated Injury in Kidney Transplant Recipients: A Pilot Randomized Controlled Trial. Am J Transplant. 2017 Mar;17(3):682-691. https://doi.org/10.1111/ajt.14001.
26. Akira S, Taga T, Kishimoto T. Interleukin-6 in biology and medicine. Adv Immunol. 1993;54:1-78. https://doi.org/10.1016/s0065-2776(08)60532-5.
27. Miller CL, Madsen JC. IL-6 Directed Therapy in Transplantation. Curr Transplant Rep. 2021;8(3):191-204. https://doi.org/10.1007/s40472-021-00331-4.
28. Mihara M, Kasutani K, Okazaki M, Nakamura A, Kawai S, Sugimoto M, Matsumoto Y, Ohsugi Y. Tocilizumab inhibits signal transduction mediated by both mIL-6R and sIL-6R, but not by the receptors of other members of IL-6 cytokine family. Int Immunopharmacol. 2005 Nov;5(12):1731-40. https://doi.org/10.1016/j.intimp.2005.05.010.
29. Nishimoto N, Terao K, Mima T, Nakahara H, Takagi N, Kakehi T. Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease. Blood. 2008 Nov 15;112(10):3959-64. https://doi.org/10.1182/blood-2008-05-155846.
30. Jordan SC, Ammerman N, Choi J, et al. Evaluation of Clazakizumab (anti-Interleukin-6) in patients with treatment-resistant chronic active antibody-mediated rejection of kidney allografts. Kidney Int Rep. 2022;7(4):720-731. https://doi.org/10.1016/j.ekir.2022.01.1074.
31. Doberer K, Duerr M, Halloran PF, Eskandary F, et al. A Randomized Clinical Trial of Anti-IL-6 Antibody Clazakizumab in Late Antibody-Mediated Kidney Transplant Rejection. J Am Soc Nephrol. 2021 Mar;32(3):708-722. https://doi.org/10.1681/ASN.2020071106. Epub 2020 Dec 18. PMID: 33443079; PMCID: PMC7920172
32. Vo AA, Huang E, Ammerman N, Toyoda M, et al. Clazakizumab for desensitization in highly sensitized patients awaiting transplantation. Am J Transplant. 2022 Apr;22(4):1133-1144. https://doi.org/10.1111/ajt.16926. Epub 2021 Dec 30. PMID: 34910841.
33. Sautner T, Gnant M, Banhegyi C, Wamser P, Götzinger P, Steininger R, Mühlbacher F. Risk factors for development of panel reactive antibodies and their impact on kidney transplantation outcome. Transpl Int. 1992;5 Suppl 1:S116-20. https://doi.org/10.1007/978-3-642-77423-2_38.
34. Yeung MY. Pre-formed DSA and kidney allograft outcomes. J Bras Nefrol. 2020 Jun 1;42(2):136-137. https://doi.org/10.1590/2175-8239-jbn-2020-0043.
35. Park WY, Kim Y, Paek JH, Jin K, Han S. Clinical Significance of De Novo Donor Specific Antibody Based on the Type of Kidney Transplantation. Transplant Proc. 2022 Mar;54(2):335-340. https://doi.org/10.1016/j.transproceed.2022.01.001.
36. Bhutani S, Harris S, Carr M, Russell-Lowe M, Worthington J, Wu HHL, Chinnadurai R, Poulton K. Evaluating the Clinical Relevance of Antibodies against Non-Human Leukocyte Antigen in Kidney Transplantation. Antibodies (Basel). 2024 Jun 6;13(2):44. https://doi.org/10.3390/antib13020044.
37. Zhang R. Donor-Specific Antibodies in Kidney Transplant Recipients. Clin J Am Soc Nephrol. 2018 Jan 6;13(1):182-192. https://doi.org/10.2215/cjn.00700117
38. Naesens M, Roufosse C, Haas M, et al. The Banff 2022 Kidney Meeting Report: Reappraisal of microvascular inflammation and the role of biopsy-based transcript diagnostics. Am J Transplant. 2024 Mar;24(3):338-349. https://doi.org/10.1016/j.ajt.2023.10.016. Epub 2023 Oct 28. PMID: 38032300.

39. Mauiyyedi S, Pelle PD, Saidman S, Collins AB, Pascual M, Tolkoff-Rubin NE, Williams WW, Cosimi AB, Schneeberger EE, Colvin RB. Chronic humoral rejection: identification of antibody-mediated chronic renal allograft rejection by C4d deposits in peritubular capillaries. J Am Soc Nephrol. 2001 Mar;12(3):574-582. https://doi.org/10.1681/asn.v123574.
40. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. Cold Spring Harb Perspect Biol. 2014 Sep 4;6(10):a016295. https://doi.org/10.1101/cshperspect.a016295.
41. Van Oers MH, Van der Heyden AA, Aarden LA. Interleukin 6 (IL-6) in serum and urine of renal transplant recipients. Clin Exp Immunol. 1988 Feb;71(2):314-9. https://pmc.ncbi.nlm.nih.gov/articles/PMC1541438/.
42. Watts RP, Thom O, Fraser JF. Inflammatory signalling associated with brain dead organ donation: from brain injury to brain stem death and posttransplant ischaemia reperfusion injury. J Transplant. 2013;2013:521369. https://doi.org/10.1155/2013/521369.
43. Bettelli E, Carrier Y, Gao W, Korn T, Strom TB, Oukka M, Weiner HL, Kuchroo VK. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Nature. 2006 May 11;441(7090):235-8. https://doi.org/10.1038/nature04753.
44. Wang S, Jiang J, Guan Q, Lan Z, Wang H, Nguan CY, Jevnikar AM, Du C. Reduction of Foxp3-expressing regulatory T cell infiltrates during the progression of renal allograft rejection in a mouse model. Transpl Immunol. 2008 May;19(2):93-102. https://doi.org/10.1016/j.trim.2008.03.004.
45. Campbell DJ, Koch MA. Phenotypical and functional specialization of FOXP3+ regulatory T cells. Nat Rev Immunol. 2011 Feb;11(2):119-30. https://doi.org/10.1038/nri2916.
46. Matthes T, Manfroi B, Zeller A, Dunand-Sauthier I, Bogen B, Huard B. Autocrine amplification of immature myeloid cells by IL-6 in multiple myeloma-infiltrated bone marrow. Leukemia. 2015 Sep;29(9):1882-90. https://doi.org/10.1038/leu.2015.145.
47. Kang S, Tanaka T, Kishimoto T. Therapeutic uses of anti-interleukin-6 receptor antibody. Int Immunol. 2015 Jan;27(1):21-9. https://doi.org/10.1093/intimm/dxu081.
48. Tse GH, Johnston CJ, Kluth D, Gray M, Gray D, Hughes J, Marson LP. Intrarenal B Cell Cytokines Promote Transplant Fibrosis and Tubular Atrophy. Am J Transplant. 2015 Dec;15(12):3067-80. https://doi.org/10.1111/ajt.13393.
49. Wu G, Chai N, Kim I, Klein AS, Jordan SC. Monoclonal anti-interleukin-6 receptor antibody attenuates donor-specific antibody responses in a mouse model of allosensitization. Transpl Immunol. 2013 Mar;28(2-3):138-43. https://doi.org/10.1016/j.trim.2013.03.003.
50. Chandran S, Leung J, Hu C, Laszik ZG, Tang Q, Vincenti FG. Interleukin-6 blockade with tocilizumab increases Tregs and reduces T effector cytokines in renal graft inflammation: A randomized controlled trial. Am J Transplant. 2021 Jul;21(7):2543-2554. https://doi.org/10.1111/ajt.16459.
51. Choy EH, Isenberg DA, Garrood T, Farrow S, et al. Therapeutic benefit of blocking interleukin-6 activity with an anti-interleukin-6 receptor monoclonal antibody in rheumatoid arthritis: a randomized, double-blind, placebo-controlled, dose-escalation trial. Arthritis Rheum. 2002 Dec;46(12):3143-50. https://doi.org/10.1002/art.10623.
52. Jouve T, Daligault M, Noble J, Terrec F, Imerzoukene F, Dard C, Bardy B, Malvezzi P, Rostaing L. Tocilizumab Evaluation in HLA-Desensitization before Kidney Transplantation as an Add-On Therapy to Apheresis: The TETRA Study. J Clin Med. 2023 Jan 4;12(2):424. https://doi.org/10.3390/jcm12020424.
53. Cabezas L, Jouve T, Malvezzi P, Janbon B, Giovannini D, Rostaing L, Noble J. Tocilizumab and Active Antibody-Mediated Rejection in Kidney Transplantation: A Literature Review. Front Immunol. 2022 Apr 14;13:839380. https://doi.org/10.3389/fimmu.2022.839380.
54. Kim I, Wu G, Chai NN, Klein AS, Jordan S. Anti-interleukin 6 receptor antibodies attenuate antibody recall responses in a mouse model of allosensitization. Transplantation. 2014 Dec 27;98(12):1262-70. https://doi.org/10.1097/tp.0000000000000437.
55. Vo AA, Choi J, Kim I, Louie S, Cisneros K, Kahwaji J, Toyoda M, Ge S, Haas M, Puliyanda D, Reinsmoen N, Peng A, Villicana R, Jordan SC. A Phase I/II Trial of the Interleukin-6 Receptor-Specific Humanized Monoclonal (Tocilizumab) + Intravenous Immunoglobulin in Difficult to Desensitize Patients. Transplantation. 2015 Nov;99(11):2356-63. https://doi.org/10.1097/tp.0000000000000741.
56. Daligault M, Bardy B, Noble J, Bourdin A, Masson D, Naciri Bennani H, Bugnazet M, Malvezzi P, Rostaing L, Jouve T. Marginal Impact of Tocilizumab Monotherapy on Anti-HLA Alloantibodies in Highly Sensitized Kidney Transplant Candidates. Transplant Direct. 2021 Apr 22;7(5):e690. https://doi.org/10.1097/txd.0000000000001139.
57. Jouve T, Laheurte C, Noble J, Weinhard J, et al. Immune responses following tocilizumab therapy to desensitize HLA-sensitized kidney transplant candidates. Am J Transplant. 2022 Jan;22(1):71-84. https://doi.org/10.1111/ajt.16709.
58. Sommer W, Avsar M, Aburahma K, et al. Heart transplantation across preformed donor-specific antibody barriers using a perioperative

desensitization protocol. Am J Transplant. 2022 Aug;22(8):2064-2076. https://doi.org/10.1111/ajt.17060.
59. Pottebaum AA, Venkatachalam K, Liu C, Brennan DC, Murad H, Malone AF, Alhamad T. Efficacy and Safety of Tocilizumab in the Treatment of Acute Active Antibody-mediated Rejection in Kidney Transplant Recipients. Transplant Direct. 2020 Mar 13;6(4):e543. https://doi.org/10.1097/txd.0000000000000988.
60. Choi J, Aubert O, Vo A, Loupy A, Haas M, Puliyanda D, Kim I, Louie S, Kang A, Peng A, Kahwaji J, Reinsmoen N, Toyoda M, Jordan SC. Assessment of Tocilizumab (Anti-Interleukin-6 Receptor Monoclonal) as a Potential Treatment for Chronic Antibody-Mediated Rejection and Transplant Glomerulopathy in HLA-Sensitized Renal Allograft Recipients. Am J Transplant. 2017 Sep;17(9):2381-2389. https://doi.org/10.1111/ajt.14228.
61. De Serres SA, Noël R, Côté I, Lapointe I, Wagner E, Riopel J, Latulippe E, Agharazii M, Houde I. 2013 Banff Criteria for Chronic Active Antibody-Mediated Rejection: Assessment in a Real-Life Setting. Am J Transplant. 2016 May;16(5):1516-25. https://doi.org/10.1111/ajt.13624.
62. Lavacca A, Presta R, Gai C, Mella A, Gallo E, Camussi G, Abbasciano I, Barreca A, Caorsi C, Fop F, Messina M, Rossetti M, Biancone L. Early effects of first-line treatment with anti-interleukin-6 receptor antibody tocilizumab for chronic active antibody-mediated rejection in kidney transplantation. Clin Transplant. 2020 Aug;34(8):e13908. https://doi.org/10.1111/ctr.13908.
63. Kumar D, Yakubu I, Safavi F, Levy M, Moinuddin I, Kimball P, Kamal L, King A, Massey D, Halloran P, Gupta G. Lack of Histological and Molecular Signature Response to Tocilizumab in Kidney Transplants with Chronic Active Antibody Mediated Rejection: A Case Series. Kidney360. 2020 Apr 27;1(7):663-670. https://doi.org/10.34067/kid.0000182019.
64. Massat M, Congy-Jolivet N, Hebral AL, et al. Toulouse Acquired Immune Deficiency, Infection (TAIDI) Study Group. Do anti-IL-6R blockers have a beneficial effect in the treatment of antibody-mediated rejection resistant to standard therapy after kidney transplantation? Am J Transplant. 2021 Apr;21(4):1641-1649. https://doi.org/10.1111/ajt.16391.
65. Noble J, Giovannini D, Laamech R, Imerzoukene F, Janbon B, Marchesi L, Malvezzi P, Jouve T, Rostaing L. Tocilizumab in the Treatment of Chronic Antibody-Mediated Rejection Post Kidney Transplantation: Clinical and Histological Monitoring. Front Med (Lausanne). 2021 Dec 24;8:790547. https://doi.org/10.3389/fmed.2021.790547.
66. Khairallah P, Robbins-Juarez S, Patel S, Shah V, Toma K, Fernandez H, Dube GK, King K, Mohan S, Husain SA, Morris H, Crew RJ. Tocilizumab for the treatment of chronic antibody mediated rejection in kidney transplant recipients. Clin Transplant. 2023 Jan;37(1):e14853. https://doi.org/10.1111/ctr.14853.
67. Boonpheng B, De Castro ICC, Ng YH, Blosser C, Bakthavatsalam R, Gimferrer I, Smith K, Leca N. Tocilizumab for treatment of chronic active antibody-mediated rejection in kidney transplant recipients. Clin Transplant. 2023 May;37(5):e14936. https://doi.org/10.1111/ctr.14936.
68. Durrbach A, Pestana JM, Pearson T, Vincenti F, Garcia VD, Campistol J, Rial Mdel C, Florman S, Block A, Di Russo G, Xing J, Garg P, Grinyó J. A phase III study of belatacept versus cyclosporine in kidney transplants from extended criteria donors (BENEFIT-EXT study). Am J Transplant. 2010 Mar;10(3):547-57. https://doi.org/10.1111/j.1600-6143.2010.03016.x.
69. Vincenti F, Charpentier B, Vanrenterghem Y, et al. A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study). Am J Transplant. 2010 Mar;10(3):535-46. https://doi.org/10.1111/j.1600-6143.2009.03005.x.
70. Mayer KA, Schrezenmeier E, Diebold M, et al. A Randomized Phase 2 Trial of Felzartamab in Antibody-Mediated Rejection. N Engl J Med. 2024 Jul 11;391(2):122-132. https://doi.org/10.1056/NEJMoa2400763. Epub 2024 May 25. PMID: 38804514.
71. Jordan S, Vescio R, Toyota M, et al. Daratumumab for treatment of antibody-mediated rejection in a kidney transplant recipient. Am J Transplant. 2019;19, 1062-1062. https://doi.org/10.1159/000503951.
72. Doberer K, Klager J, Gualdoni GA, et al. CD38 antibody dar- atumumab for the treatment of chronic active antibody- mediated kidney allograft rejection. Transplantation. 2021;105:451–457. https://doi.org/10.1097/TP.0000000000003247.
73. De Nattes T, Kaveri R, Farce F, et al. Daratumumab for antibody-mediated rejection: is it time to target the real culprit? Am J Transplant. 2023;23:1990–1994. https://doi.org/10.1016/j.ajt.2023.06.018.
74. Van Vugt LK, Schagen MR, de Weerd A, Reinders ME, De Winter BC, Hesselink DA. Investigational drugs for the treat- ment of kidney transplant rejection. Expert Opin Investig Drugs. 2022;31:1087–1100. https://doi.org/10.1080/13543784.2022.2130751.
75. Guo Z, Sa R, Zhao D, Li S, Guo H, Zhu L, Chen G. Daratumumab followed by tocilizumab for treatment of late antibody-mediated rejection in renal transplant recipients with high or moderate levels of de novo donor-specific antibodies: a pilot study. BMC Nephrol. 2025 Jan 11;26(1):19. https://doi.org/10.1186/s12882-025-03951-5.