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Antibody-mediated rejection: prevention, monitoring and treatment dilemmas

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Purpose of review
Antibody-mediated rejection (AMR) has emerged as the leading cause of late graft loss in kidney transplant recipients. Donor-specific antibodies are an independent risk factor for AMR and graft loss. However, not all donor-specific antibodies are pathogenic. AMR treatment is heterogeneous due to the lack of robust trials to support clinical decisions. This review provides an overview and comments on practical but relevant dilemmas physicians experience in managing kidney transplant recipients with AMR.

Recent findings
Active AMR with donor-specific antibodies may be treated with plasmapheresis, intravenous immunoglobulin and corticosteroids with additional therapies considered on a case-by-case basis. On the contrary, no treatment has been shown to be effective against chronic active AMR. Various biomarkers and prediction models to assess the individual risk of graft failure and response to rejection treatment show promise.

Summary
The ability to personalize management for a given kidney transplant recipient and identify treatments that will improve their long-term outcome remains a critical unmet need. Earlier identification of AMR with noninvasive biomarkers and prediction models to assess the individual risk of graft failure should be considered. Enrolling patients with AMR in clinical trials to assess novel therapeutic agents is highly encouraged.

Keywords
antibody-mediated rejection, dilemma, donor-specific antibodies, kidney transplantation, treatment

INTRODUCTION

Antibody-mediated rejection (AMR) is the most common cause of late allograft loss after kidney transplantation [1–3]. Banff 2019 classification recognizes three diagnostic AMR categories: active AMR, chronic active AMR and chronic (inactive) AMR (Table 1) [4]. Active AMR requires three diagnostic criteria: histologic evidence of microvascular inflammation (MVI) (e.g. glomerulitis and peritubular capillaritis), evidence of current or recent antibody interaction with the endothelium (usually C4d-positive staining) and serologic evidence of donor-specific antibody (DSA), although C4d staining or validated endothelium transcripts may substitute for DSA [5]. Chronic active AMR has similar criteria but with histologic evidence of chronic MVI, such as transplant glomerulopathy. Chronic (inactive) AMR shows histologic evidence of chronic tissue injury, including basement membrane duplication, without MVI and without C4d deposition in peritubular capillaries [4]. Patients with active AMR are at an increased risk for subsequent rejection, chronic AMR and graft loss [2,5–7]. Similarly, those with chronic AMR have a higher risk for graft loss and patient death [1–3]. There are no FDA-approved treatments for AMR [8], resulting in significant heterogeneity in AMR treatment across the transplant centres.

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KEY POINTS

- Antibody-mediated rejection is the most common cause of late allograft failure after kidney transplantation.
- Risk factors for de-novo donor-specific antibody formation are nonadherence or reduced immunosuppression, higher eplet mismatch, younger age and preceding T-cell mediated rejection.
- Some characteristics of donor-specific antibodies associated with worse outcomes are certain IgG subclasses, higher titers and complement-binding ability.
- Active antibody-mediated rejection should be treated with plasmapheresis, intravenous immunoglobulins and corticosteroids with additional therapies considered on a case-by-case basis.
- Chronic active antibody-mediated rejection should be treated with optimization of maintenance immunosuppression and enrollment in clinical trials.
- Further validation of novel biomarkers to monitor AMR treatment response is needed.

In this review, we focus on specific clinical dilemmas encountered by physicians in preventing, monitoring and managing kidney transplantation recipients with AMR, including highlights about novel potential treatments in the pipeline.

WHAT IS THE BEST STRATEGY TO PREVENT THE DEVELOPMENT OF DE-NOVO DONOR-SPECIFIC ANTIBODIES?

Donor-specific antibody is an independent risk factor for active AMR and graft loss [9]. Given that most centres avoid preformed DSA by listing unacceptable donor human leukocyte antigen (HLA), the most prevalent form of AMR encountered in clinical practice today is associated with de-novo DSA (dnDSA) [2]. DnDSA develops in 15–25% of kidney transplantation recipients within the first 5 years posttransplant [10], with an incidence of 2% per year in adherent patients [11]. Risk factors for dnDSA formation are nonadherence or reduced immunosuppression, higher eplet mismatch, younger age and preceding T-cell mediated rejection (TCMR) [12–15].

Optimizing maintenance immunosuppression

Immunosuppressive medication nonadherence has emerged as the primary cause of dnDSA formation [11]. Maintaining adequate baseline immunosuppression, particularly a calcineurin inhibitor (CNI), is a key to preventing dnDSA formation [13,16,17]. When comparing CNIs, recipients treated with cyclosporin-based therapy have a 2.7-fold higher incidence of dnDSA development compared with tacrolimus-based therapy [13]. DnDSA may be prevented by maintaining tacrolimus trough levels (Tac C0) at least 7 ng/ml in the first year posttransplant [13] and at least 5 ng/ml beyond the first year posttransplant [13,18].

CNI withdrawal has been attempted in low-immunological risk patients who received T-cell depletion induction therapy. However, the rate of dnDSA was more than 40% within first-year posttransplant, leading to the early termination of the study [19]. Although T-cell depletion has a potent effect in lowering acute TCMR rates in high immunological risk patients, it can favour preferential expansion of T follicular helper (Tfh) cells and be associated with a higher risk of DSA generation [20▪]. Therefore, delaying initiation, dose minimization or withdrawal of CNI may favour the development of an antibody-mediated alloimmune response [21,22].

Alternatives to CNI-based therapy are being sought to eliminate its side effects for kidney transplantation recipients (e.g. nephrotoxicity and neurotoxicity). The alloimmune response requires signalling through the costimulatory pathway for optimal T cell activation and proliferation. Belatacept, a selective T cell costimulation blocker [23], has been FDA-approved based on noninferiority for biopsy-proven acute rejection relative to cyclosporine. Data from BENEFIT and BENEFIT-EXT trials showed significantly lower cumulative event rates for dnDSA development and better kidney function with belatacept-based vs. cyclosporine-based immunosuppression, at 7 years posttransplant [24,25]. A recent randomized control trial comparing belatacept with tacrolimus did not observe any difference in dnDSA formation or AMR rates at 1 year [26]. The estimated glomerular filtration rate (eGFR) was significantly higher with belatacept compared with tacrolimus, but so was the incidence of biopsy-proven TCMR [27▪]. However, the short-term follow-up may limit any conclusive interpretation with respect to dnDSA development or long-term outcomes [26,28–30] and follow-up of at least 5 years may be needed.

Why is the rate of dnDSA generation with belatacept lower compared with tacrolimus despite higher rates of TCMR? Tfh cells are a subset of specialized $CD4^+$ T cells that provide critical help to B cells through the costimulation pathway B7/CD28, enabling B cell activation and differentiation into memory B cells and plasma cells that secrete high-affinity antibodies [31]. Therefore, targeting

Table 1. Antibody-mediated rejection spectrum according to Banff 2019 Classification Report

	Active AMR	Chronic active AMR	Chronic (inactive) AMR
Histopathology[a]	Acute tissue injury, including one or more of the following: Microvascular inflammation (glomerulitis and/or peritubular capillaritis) in the absence of recurrent or de-novo glomerulonephritis Intimal or transmural arteritis Acute TMA, in the absence of any other apparent cause Acute tubular injury, in the absence of any other apparent cause	Chronic tissue injury, including one or more of the following: Transplant glomerulopathy (glomerular basement membrane duplication in the absence of subendothelial immune complex deposits) if no evidence of chronic TMA in the absence of recurrent or de-novo glomerulonephritis Severe peritubular capillary basement membrane multilayering (requires EM) Transplant arteriopathy (arterial intimal fibrosis of new onset) AND Mild to moderate acute tissue injury (microvascular inflammation)	Chronic tissue injury: Transplant glomerulopathy, and/or Severe peritubular capillary basement membrane multilayering (requires EM) Significant loss of peritubular capillaries (capillaries simply no longer exist to show capillaritis)
Evidence of antibody interaction with the endothelium[b]	C4d deposition in peritubular capillaries, OR At least moderate microvascular inflammation, OR Molecular markers of endothelial activation	C4d deposition in peritubular capillaries, OR At least moderate microvascular inflammation, OR Molecular markers of endothelial activation	C4d negative There may be prior evidence of antibody interaction with the endothelium
DSA[c,d]	Detectable serum anti-HLA DSA If anti-HLA DSA is undetectable, non-HLA antibody testing should be considered	Detectable serum anti-HLA DSA If anti-HLA DSA is undetectable, non-HLA antibody testing should be considered	Anti-HLA DSA may be undetectable However, there should be prior evidence of anti-HLA or non-HLA DSA
Clinical presentation	Acute kidney injury, hypertension ± proteinuria	Subacute. Commonly observed on for-cause biopsies in patients with deteriorating renal function and proteinuria, or on protocol biopsies from patients with normal graft function, with or without proteinuria, ranging from 3 months to 5 years posttransplant	Progressive kidney allograft dysfunction, progressive proteinuria, hypertension
Prognosis	It may respond to prompt therapy	Typically, more guarded prognosis	Poor prognosis with almost universal graft lost
Treatment	Under investigation in clinical trials Plasma exchange, intravenous immunoglobulin, and corticosteroids	Under investigation in clinical trials It is unclear how patients with microvascular inflammation, with or without early transplant glomerulopathy, should be treated	Optimization of baseline immunosuppression

At one end of the spectrum, active AMR is characterized by microvascular inflammation, endothelial injury and serological evidence of DSA, and may respond to current therapeutic strategies. At the other end of the spectrum, chronic AMR is characterized by transplant glomerulopathy, a form of advanced glomerular injury and remodelling, and is unlikely to be ameliorated by current therapies.
AMR, antibody-mediated rejection; DSA, donor-specific antibodies; EM, electron microscopy; TMA, thrombotic microangiopathy.
[a,b,c]All three criteria should be met for diagnosis of AMR.
[d]C4d staining and validated molecular assays could serve as potential alternatives to DSAs in the diagnosis of AMR.

Tfh–B cells costimulation signal by belatacept may prevent dnDSA and AMR [32]. Although Tfh cells are primarily located in secondary lymphoid organs, circulating Tfh cells may represent a biomarker of humoral alloreactivity [33]. In a retrospective study in kidney transplantation recipients, the expansion of the circulating Tfh cells was predictive of IgG3 DSA generation, more severe allograft injury and a higher rate of allograft loss [34]. Further studies are needed to investigate if monitoring Tfh cells may have a role in the early detection of AMR.

Greater human leukocyte antigen class II matching

Antibodies against HLA class II donor antigens are predominant in the posttransplant period [2]. Class II antibodies are more likely to persist compared with class I (HLA-DRβ3/4/5, HLA-DQα1β1 or HLA-DRβ1>Class I), which may explain the poor outcome observed in patients with class II antibodies [35]. Donor-recipient HLA-DQ and HLA-DR matching can potentially minimize the risk of dnDSA posttransplant [36–38]. HLA class II matching can

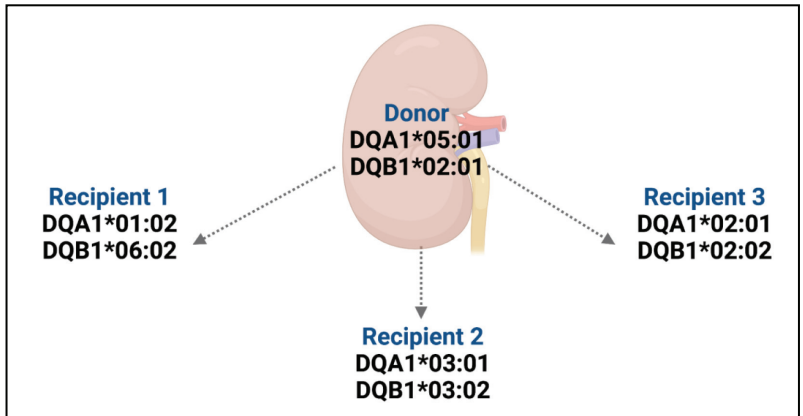
also decrease the risk for TCMR, AMR, transplant glomerulopathy and graft loss [10,12,13]. In retransplantation, class II repeat mismatches seem to increase the risk of graft loss [39]. Nonetheless, HLA class II matching on a large scale is currently challenging to implement in organ allocation algorithms due to the organ shortage and significant polymorphism of HLA class II antigens.

Decreasing human leukocyte antigen eplet mismatches

HLA antibodies recognize polymorphic, three-dimensional structures of the HLA antigen, called epitopes, rather than the complete antigen [40]. Each HLA antigen contains a unique set of epitopes (private epitopes) as well as epitopes that are present in other HLA antigens (shared/public epitopes). An eplet, or functional epitope, is a patch of amino acids within a 3 Å radius of polymorphic residues located on the surface of HLA molecules within the larger 15–22 amino acids of an HLA epitope that are recognized by anti-HLA antibodies. Scientific advances permit assessment of donor-recipient HLA mismatch at the eplet level [13,41,42]. The eplet-mismatch load is determined by counting the number of eplets that are mismatched between a recipient and the potential donor. Several observational studies have shown that a higher number of mismatched eplets is associated with a higher risk of developing DSA posttransplantation [10,43,44], transplant glomerulopathy [45] and graft loss [44]. Recipients of a low-risk HLA-DR/DQ molecular mismatch appear to tolerate lower CNI trough levels while maintaining minimal acute rejection rates and lower rates of dnDSA [19,46]. Nevertheless, universal CNI minimization based on low-risk eplet mismatch cannot be currently endorsed on a large scale in the absence of clinical trials supporting this strategy. Moreover, not all eplet mismatches result in the development of alloantibody responses. The immunogenicity of a donor HLA eplet is a consequence of several physicochemical factors (e.g. polarity, size, solubility, amino acid sequence). Thus, two donor-recipient combinations that have an identical eplet mismatch load may exhibit different immunogenicity (Fig. 1) [47]. HLA eplet mismatch calculation may represent a valuable tool for risk stratification at the population level, although prospective validation is needed [48].

Preventing T-cell mediated rejection

TCMR, dnDSA and AMR are on the continuum of the alloimmune response. TCMR frequently precedes the development of DSA [11]. Furthermore, reports have documented that dnDSA-associated AMR occurs later, has a higher rate of graft loss,



	Antigen MM	Eplet MM	Amino acid MM
D + R1	1	17	42
D + R2	1	13	23
D + R3	0	4	10

FIGURE 1. Antigen, eplet and amino acid mismatch loads for DQA1∗ DQB1∗ between a kidney donor and three potential recipients. Despite the kidney donor and potential recipients 1 and 2 exhibiting the same antigen mismatch load for DBA1-DQB1, they have different eplet mismatch loads (17 and 13, respectively). Furthermore, although the kidney donor and potential recipient 3 have no antigen mismatches, they exhibit 4 eplet mismatches and 10 amino acid mismatches. For this example, the donor and potential recipients are assumed to share one haplotype. www.epitopes.net and www.histocheck.org were used to estimate eplet and amino acid mismatches, respectively. D, donor; MM, mismatch; R, recipient.

and is frequently manifested as a mixed TCMR/AMR rejection, as compared to memory-associated AMR, which typically displays a pure AMR phenotype, occurs early posttransplant and is more responsive to therapy [17,49]. Thus, the alloimmune response cannot be separated into cellular or antibody-mediated, but should be considered a continuous process with the dominance of different components at various time-points posttransplant.

SHOULD ANTI-HUMAN LEUKOCYTE ANTIGEN ANTIBODIES BE MONITORED POST-TRANSPLANTATION?

There is controversy regarding the clinical utility of routine posttransplant DSA monitoring and management of patients with dnDSA, especially in the absence of allograft dysfunction. Monitoring for dnDSA is primarily recommended when immunosuppression reduction is advised by the physician (e.g. infection, cancer), known or suspected medication nonadherence, or at the time of a rejection episode [50]. Some transplant centres also perform annual anti-HLA testing as a monitoring strategy in stable patients. Patients with a pretransplant DSA undergo protocol kidney biopsies at months 3 and 12 posttransplant at some transplant centers or are followed by frequent DSA monitoring posttransplant (e.g. at 1 week, 2 weeks, 1, 3 and 6 months). If there is no concomitant rejection on biopsy at the onset of dnDSA, it appears that most centres would only optimize the maintenance immunosuppression [8]. A relevant question that remains unanswered is whether screening for dnDSA followed by an intervention (i.e. a kidney biopsy and treatment if subclinical rejection is identified) could minimize the subsequent development of chronic AMR and transplant glomerulopathy.

HOW SHOULD DE-NOVO DONOR-SPECIFIC ANTIBODIES BE MANAGED IN KIDNEY TRANSPLANT RECIPIENTS WITH STABLE GRAFT FUNCTION? IS DE-NOVO DONOR-SPECIFIC ANTIBODIES PATHOGENIC OR AN INNOCENT BYSTANDER?

Not all DSAs are pathogenic or associated with AMR [51,52]. Interestingly, 24–75% of kidney transplant recipients with dnDSA exhibit no evidence of clinical or subclinical rejection on biopsy [11,53,54]. This, together with the lack of demonstrated effect of antibody depletion on allograft rejection in preclinical models [55], brings into question DSA pathogenicity in at least a subset of cases with AMR. Several characteristics of DSA are associated with worse outcomes, such as certain IgG subclasses, higher titers and complement-binding ability [56,57]. In addition, antibody characteristics that are not routinely assessed could affect its pathogenicity, such as the antibody glycosylation pattern, its antigen affinity and the HLA antigen target expression on the donor kidney [58,59]. AMR in kidney transplant recipients with dnDSA is associated with higher levels of proteinuria, more transplant glomerulopathy lesions and worse eight-year allograft survival compared with kidney transplant recipients with AMR and pretransplant DSA [49]. Higher DSA mean fluorescent intensity (MFI) measured by single-antigen bead assay, IgG3 subclass of immunodominant DSA and C1q-binding ability of DSA have been associated with a higher risk of AMR and allograft loss [56]. DSA Fc glycosylation may modulate antibody pathogenicity and AMR risk through differential activation of Fc receptors on natural killer (NK) and myeloid cells [60], though further studies are needed to validate these findings. Despite these characteristics, there are no methods to reliably predict who will develop AMR in kidney transplant recipients with dnDSA and stable kidney function. As about half of the kidney transplant recipients with dnDSA and stable allograft function have subclinical AMR on allograft biopsy [54], we recommend performing a kidney allograft biopsy in patients with a significant rise in DSA or who develop a dnDSA to evaluate whether AMR is present.

WHAT IS THE BEST TREATMENT STRATEGY FOR PATIENTS WITH DONOR-SPECIFIC ANTIBODY POSITIVE ANTIBODY-MEDIATED REJECTION AND HOW SHOULD TREATMENT RESPONSE BE MEASURED?

There are several published randomized clinical trials evaluating treatment regimens in AMR in kidney transplant recipients [61–68]. However, most had small sample sizes and were underpowered to find differences between treatment regimens. As a result, there are no FDA-approved treatments for AMR in kidney transplant recipients. Current treatment strategies based on the understanding of AMR pathophysiology include a combination of antibody removal [61–65], glucocorticoids [61,64], intravenous immunoglobulins (IVIg) [69], anti-CD20 antibodies [66], proteasome inhibitors [67] and/or complement blockade [68]. Two clinical trials showed that adding antibody removal to AMR treatment was associated with an improvement in allograft survival [61,62], but other trials of antibody removal did not show a significant benefit [63,64]. Evidence for the combination of IVIg and

plasmapheresis to improve allograft outcomes in AMR only comes from observational studies [69]. Regarding anti-CD20 therapy, the largest randomized clinical trial showed that addition of a single dose of rituximab (375 mg/m^2) to glucocorticoids, plasma exchange and IVIg was not associated with improvement in allograft function or survival [66]. Remarkably, the coadministration of IVIg with rituximab can shorten the half-life of anti-CD20 mAb and lead to quicker recovery of B cells, potentially affecting anti-CD20 efficacy [70]. In terms of proteasome inhibitors, the largest randomized clinical trial of bortezomib in late AMR showed no improvement in allograft function [67]. Larger studies that are powered to detect differences between treatment groups and test new therapeutics for AMR in kidney transplant recipients are urgently needed. Given the lack of high-quality data, most recommendations are based on low-quality evidence and expert opinion [50].

We agree with the recommendations from the Transplantation Society that active AMR in the setting of pretransplant DSA should be treated with plasmapheresis, IVIg and corticosteroids with additional therapies considered on a case-by-case basis [50]. We are also in agreement that chronic active AMR in the setting of detectable DSA should be treated with optimization of maintenance immunosuppression [50]. Enrolling these patients in mechanistic studies to identify new therapeutic targets and in clinical trials evaluating novel treatments for chronic active AMR is highly encouraged.

AMR treatment responses can be monitored by evaluating changes in serum creatinine, proteinuria, DSA levels, histopathologic findings and other new potential approaches. Studies have shown that an improvement in serum creatinine to less than 1.5 mg/dl after treatment in kidney transplant recipients with rejection and allograft dysfunction is associated with better allograft survival. However, this should not be surprising as any improvement in function will portend better allograft survival regardless of the underlying cause of injury [71]. A decrease in the DSA MFI values after treatment, as measured by the semi-quantitative assay of Luminex, is associated with lower odds of allograft loss [17]. Nonetheless, experts caution against mistakenly concluding that the antibody removal treatment has been ineffective based on serial MFI alone [8], as anti-HLA antibodies are rarely eradicated [72], even in patients with clinical improvement [73]. Treating with incremental regimens for the goal of DSA elimination implies a significant risk of over-immunosuppression and toxicity. None of the non-invasive clinical assays are sensitive or specific enough to detect the resolution of injury in the allograft. A repeat kidney biopsy can be considered [74]. Potential novel approaches to assess response to AMR treatment include incorporating donor-derived cell-free DNA levels [75]. Deciding which patients to treat more aggressively could also be based on the use of novel allograft-failure prediction models, such as the iBox score [76] and the dynamic integrative system for predicting outcome (DISPO) [77▪]. DISPO is a risk prediction tool for death-censored allograft failure that includes eGFR, proteinuria, recipient's immunological profile and allograft biopsy findings. Longitudinal changes in DISPO scores were associated with risk of kidney allograft failure [77▪], making it an attractive tool to assess response to AMR treatment in kidney transplant recipients.

HOW SHOULD WE MANAGE PATIENTS WITH DONOR-SPECIFIC ANTIBODY NEGATIVE ANTIBODY-MEDIATED REJECTION?

The correlation between DSA and chronic AMR is poor, as chronic AMR frequently develops in individuals with no detectable DSA [58]. MVI in the kidney biopsy, suggestive of AMR but without DSA in serum, represents a challenge for diagnosis and patient management. This is a condition in which molecular diagnostics could be helpful. Treatment of such lesions could be recommended if the molecular scores were higher than a prespecified cut-off value [78]. An alternative explanation for such cases is the possible occurrence of non-HLA antibodies such as antiangiotensin II type 1 (AT1) receptor antibodies [79], anti-endothelial antibodies [80], perlecan fragment LG3 [81], anti-Ro/SS-A, anti-CENP-B [82▪] and several others. The prevalence of pretransplantation non-HLA antibodies is unknown, due to the use of distinct methods for non-HLA antibody detection [83]. In the absence of universally established and validated clinical assays to detect these antibodies, their overall prevalence and importance are difficult to study systematically. The immunosuppressive treatment of AMR in such patients is generally similar to that of patients with AMR and an anti-HLA DSA. Anti-AT1 receptor antibodies should be suspected in patients with severe hypertension and notable vascular lesions (e.g. endarteritis), with or without anti-HLA DSA [79]. Patients who are found to have an anti-AT1 receptor antibody should receive, in addition to immunosuppressive therapy, an angiotensin II receptor blocker, which inhibits AT1-receptor antibody-mediated effects [79,84].

Groups have reported that in the absence of preformed DSA, highly sensitized individuals have graft survival equivalent to unsensitized recipients

[85,86]. DSA-negative histologic AMR had an outcome equivalent to unsensitized patients without AMR as compared to DSA-positive AMR [87]. However, in a series of 180 kidney transplant recipients with moderate MVI with or without DSA, it was found that MVI, even in the absence of DSA, was associated with poor patient and graft survival compared to those with DSA-positive AMR [88]. Moreover, a recent study demonstrated that transcriptional changes in kidney allograft with histology of AMR showed overexpression of transcripts mostly related to IFNγ-induced pathways and activation of NK cells and endothelial cells irrespective of DSA status [89]. NK cells have been identified to play a central role in the pathophysiology and graft failure in AMR [90]. In sum, even in the absence of DSA, MVI should likely be treated as AMR to prevent chronic injury and graft function deterioration.

WHAT ARE THE NOVEL TREATMENTS FOR PATIENTS WITH REFRACTORY CHRONIC ANTIBODY-MEDIATED REJECTION?

Novel treatments for AMR include IgG endopeptidases (i.e. imilfidase) [91], newer generation anti-CD20 antibodies (e.g. obinutuzumab) [92], anti-CD38 antibodies [93], proteasome inhibitors [94], complement inhibitors [95], anti-IL-6/IL-6-receptor antibodies [96,97▪▪] and tyrosine kinase inhibitors [98] (Fig. 2). Many of these agents are being actively evaluated in ongoing clinical trials (Table 2). Given the complex pathophysiology of AMR that involves alloantibodies [99], the complement system [100] and multiple immune cell types [100–103], it is likely that a multitargeted treatment approach aimed at reducing antibody production by B and plasma cells, enhancing antibody removal and inhibiting the pathways underlying antibody-mediated allograft injury (e.g. complement-mediated

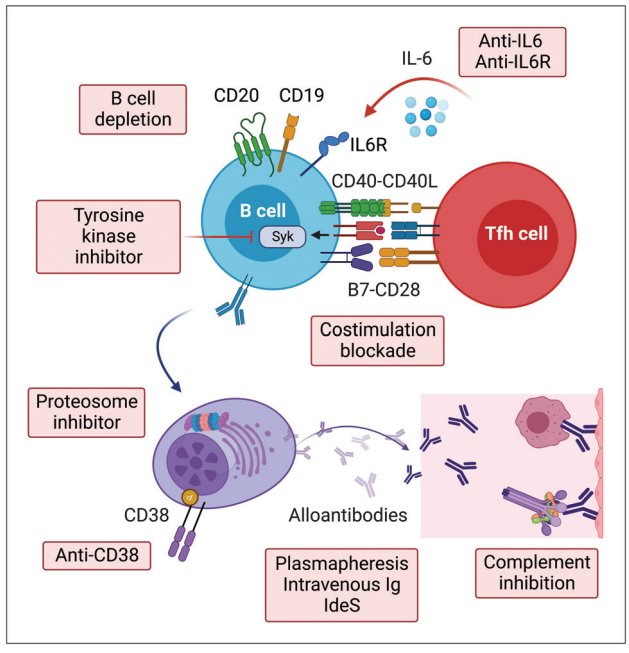


FIGURE 2. Currently used and investigational drugs for kidney transplant recipients with antibody-mediated rejection.

Table 2. Ongoing clinical trials for the treatment of antibody-mediated rejection

Trial ID number[a]	Intervention arm	Target/Mechanism	Control arm	AMR type	Phase
NCT03380377	Clazakizumab (anti-IL-6 antibody)	Plasma cells	N/A (single-arm study)	Chronic Active AMR	1/2
NCT03744910	Clazakizumab (anti-IL-6 antibody)	Plasma cells	Placebo	Chronic Active AMR	3
NCT04561986	Tocilizumab (anti-IL-6 receptor-α antibody)	Plasma cells	Placebo	Chronic Active AMR	3
NCT03737136	Bortezomib (proteasome inhibitor) in addition to PLEX, IVIg and rituximab	Plasma cells, antibody removal, immunomodulation, and B cells	PLEX, IVIg and rituximab	Chronic Active AMR	N/A
NCT05021484	Felzartamab (anti-CD38 antibody)	B cells and plasma cells	Placebo	Late AMR	2
NCT03994783	Rituximab (anti-CD20 antibody) in addition to PLEX, IVIg and corticosteroids	B cells, antibody removal, and immunomodulation	PLEX, IVIg and corticosteroids	Active AMR	3
NCT03991780	Fostamatinib (spleen tyrosine kinase inhibitor)	T and B cells	N/A (single-arm study)	Chronic Active AMR	1/2
NCT05156710	BIVV020 (anti-C1s antibody) in addition to PLEX, IVIg and corticosteroids	Proximal complement inhibition, antibody removal, immunomodulation	PLEX, IVIg and corticosteroids	Active AMR	2
NCT03897205	Imilfidase (IgG endopeptidase)	Antibody cleavage	PLEX or immunoadsorption	Active AMR	2

AMR, antibody-mediated rejection; IL, interleukin; IVIg, intravenous immunoglobulins; N/A, not available; PLEX, plasma exchange.
[a]Trials were identified from searching 'antibody-mediated rejection' in www.clinicaltrials.gov.

injury) is needed to effectively treat AMR. A multi-targeted approach has the potential to treat multiple components of the pathophysiology of the disease with additive and/or synergistic therapeutic actions, likely superior to a single-target approach [104].

CONCLUSION

AMR is the leading cause of kidney allograft failure. Despite a relatively large number of observational studies, it is unclear which combination therapy is the safest and most effective. In the context of a heterogeneous kidney transplant population, the challenge is to administer the right treatment to the right patient and personalize the degree of immunosuppression in proportion to the patient's alloimmune risk to minimize drug toxicity while maintaining therapeutic efficacy. In addition, to permit individualized treatment and immune monitoring strategies, an essential requirement is the availability of reliable prognostic or predictive biomarkers. Several potential therapeutic agents for AMR are currently being investigated in clinical trials. Similarly, diverse biomarkers and prediction models to assess the risk of individual graft failure and response to AMR treatment have shown promising findings. Efforts to phenotype kidney transplant patients better, identify new disease mechanisms and therapeutic targets, and evaluate them in clinical trials should lead to more successful prevention, monitoring and management of kidney transplant recipients with AMR.

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Conflicts of interest

L.V.R. had received research grant support from Bristoll-Meiers-Squibb, Caredx and Natera. For the remaining authors, there are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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