Taylor & Francis
Taylor & Francis Group

Expert Opinion on Investigational Drugs

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ieid20

Investigational drugs for the treatment of kidney transplant rejection

Lukas K van Vugt, Maaike R Schagen, Annelies de Weerd, Marlies EJ Reinders, Brenda CM de Winter & Dennis A Hesselink

To cite this article: Lukas K van Vugt, Maaike R Schagen, Annelies de Weerd, Marlies EJ Reinders, Brenda CM de Winter & Dennis A Hesselink (2022) Investigational drugs for the treatment of kidney transplant rejection, Expert Opinion on Investigational Drugs, 31:10, 1087-1100, DOI: 10.1080/13543784.2022.2130751

To link to this article: https://doi.org/10.1080/13543784.2022.2130751

Published online: 07 Oct 2022.

EXPERT OPINION ON INVESTIGATIONAL DRUGS
2022, VOL. 31, NO. 10, 1087–1100
https://doi.org/10.1080/13543784.2022.2130751

Taylor & Francis
Taylor & Francis Group

REVIEW

Investigational drugs for the treatment of kidney transplant rejection

Lukas K van Vugt[a,b#], Maaike R Schagen[a,b#], Annelies de Weerd[a,b], Marlies EJ Reinders[a,b], Brenda CM de Winter[c] and Dennis A Hesselink[a,b]

[a]Erasmus MC Transplant Institute, Rotterdam, the Netherlands; [b]Department of Internal Medicine, Division of Nephrology and Transplantation, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands; [c]Department of Hospital Pharmacy, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands

ABSTRACT

Introduction: Kidney transplant rejection remains an important clinical problem despite the development of effective immunosuppressive therapy. Two major types of rejection are recognized, T-cell-mediated rejection (TCMR) and antibody-mediated rejection (ABMR), which have a different pathophysiology and are treated differently. Unfortunately, long-term outcomes of both TCMR and ABMR remain unsatisfactory despite current therapy. Hence, alternative therapeutic drugs are urgently needed.

Areas covered: This review covers novel and investigational drugs for the pharmacological treatment of kidney transplant rejection. Potential therapeutic strategies and future directions are discussed.

Expert opinion: The development of alternative pharmacologic treatment of rejection has focused mostly on ABMR, since this is the leading cause of kidney allograft loss and currently lacks an effective, evidence-based therapy. At present, there is insufficient high-quality evidence for any of the covered investigational drugs to support their use in ABMR. However, with the emergence of targeted therapies, the potential arises for individualized treatment strategies. In order to generate more high-quality evidence for such strategies and overcome the obstacles of classic randomized controlled trials, we advocate the implementation of adaptive trial designs and surrogate clinical endpoints. We believe such adaptive trial designs could help to understand the risks and benefits of promising drugs such as tocilizumab, clazakizumab, belimumab, and imlifidase.

ARTICLE HISTORY
Received 26 April 2022
Accepted 27 September 2022

KEYWORDS
Adaptive trial design; Antibody-mediated rejection; Immunosuppressive drugs; Kidney transplantation; Rejection; Surrogate clinical endpoints; T-cell-mediated rejection

1. Introduction

Kidney transplant rejection remains an important clinical problem despite the development of effective immunosuppressive drug combination therapy. Incidence rates of kidney transplant rejection at six months post-transplant have stabilized at 10–20% in recent years [1]. The Banff 2019 classification divides kidney transplant rejection in different categories and grades based on histological and clinical features [2]. Two major types of rejection are discerned: T-cell-mediated rejection (TCMR) and antibody-mediated rejection (ABMR). In TCMR, kidney injury is caused directly by cytotoxic T lymphocytes and T-cell-mediated cytokine release, whereas in ABMR, kidney injury is caused by pathogenic antibodies [3]. These antibodies can be directed against blood-group antigens, human leukocyte antigens (HLA) and other antigens (non-HLA), such as the angiotensin type 1 receptor which is expressed on endothelial cells [3]. For both ABMR and TCMR, acute and chronic subtypes are distinguished based on histologic features and clinical course [2].

In general, patients with TCMR are treated with pulse high-dose glucocorticoids as first-line therapy [4]. Severe TCMR or glucocorticoid-resistant TCMR is treated with lymphocyte-depleting antibodies [4]. Rabbit anti-thymocyte globulin (rATG) is currently the only registered lymphocyte-depleting antibody for the treatment of acute kidney transplant rejection [5]. There is no generally accepted and evidence-based therapy for ABMR. In most centers, patients with ABMR are treated with pulse glucocorticoids (to suppress the inflammatory response), intravenous immunoglobulins (IVIG; to modulate the immune response), or plasma exchange (to remove the pathogenic antibodies from the blood) or a combination of these modalities [4].

TCMR generally responds well to glucocorticoid therapy or lymphocyte-depletion in short-term. However, long-term allograft survival is negatively affected by an episode of TCMR, with a fourfold increase in death-censored graft loss and a twofold increase of all-cause graft loss after a first episode of TCMR in a for-cause biopsy [6]. With regard to acute ABMR, short-term outcomes have improved with current treatment but long-term outcomes have remained poor [7]. Chronic ABMR typically does not respond to current treatment and is the most important cause of chronic allograft failure [7].

The unsatisfying long-term outcomes of both TCMR and ABMR and the lack of effective, evidence-based treatment for chronic ABMR, have instigated the search for alternative therapeutic drugs to treat rejection. These drugs, with various

CONTACT Lukas K van Vugt l.k.vanvugt@erasmusmc.nl Department of Internal Medicine, Division of Nephrology and Transplantation, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands
[#]Both authors contributed equally

Article highlights

- IL-6 plays a critical role in the pathophysiology of chronic ABMR and IL-6 directed therapy (tocilizumab and clazakizumab) holds potential for the treatment of chronic ABMR.
- Belimumab holds potential as B lymphocyte-targeted therapy, as it blocks the binding of BLyS to the B cell receptor, thereby preventing the survival of B lymphocytes and their differentiation into plasma cells, without causing general lymphocyte depletion.
- Cleavage of IgG-molecules and antigen-bound IgG by imlifidase could potentially replace plasma exchange in the treatment of ABMR.
- Complement inhibition is a potential, effector-mechanism targeted therapy for subtypes of ABMR characterized by high levels of complement activation.
- Implementation of adaptive trial designs and the use of surrogate clinical endpoints should be stimulated in kidney transplantation in order to facilitate more efficient data collection to enable rapid evaluation of new therapies of interest, and to develop individualized treatment strategies.

mechanisms of action such as depletion of immune cells, modulation of co-stimulatory signals, elimination of antibodies, and inhibition of effector mechanisms, are reviewed here.

2. Cellular-depleting therapies

2.1. Alemtuzumab

Alemtuzumab is a monoclonal antibody directed against the CD52 membrane protein. Its mechanism of action is to cause depletion of circulating CD52 positive cells by complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and induction of apoptosis (Figure 1) [8]. CD52 positive cells affected by alemtuzumab are B and T lymphocytes, natural killer (NK) cells, dendritic cells, and monocytes. The drug is registered for the treatment of relapsing-remitting multiple sclerosis [9] but has been used for many years for other indications, including transplantation.

In solid organ transplantation (SOT), alemtuzumab has been evaluated as an alternative to rATG, because of its apparent efficacy, easier mode of administration and superior tolerability [8]. In kidney transplantation, in addition to induction therapy, alemtuzumab has been used to treat severe or glucocorticoid-resistant acute rejection. Although alemtuzumab is not a novel therapy in kidney transplantation, recent publications and new insights regarding its pharmacokinetic and pharmacodynamic properties are reason to cover it in this review.

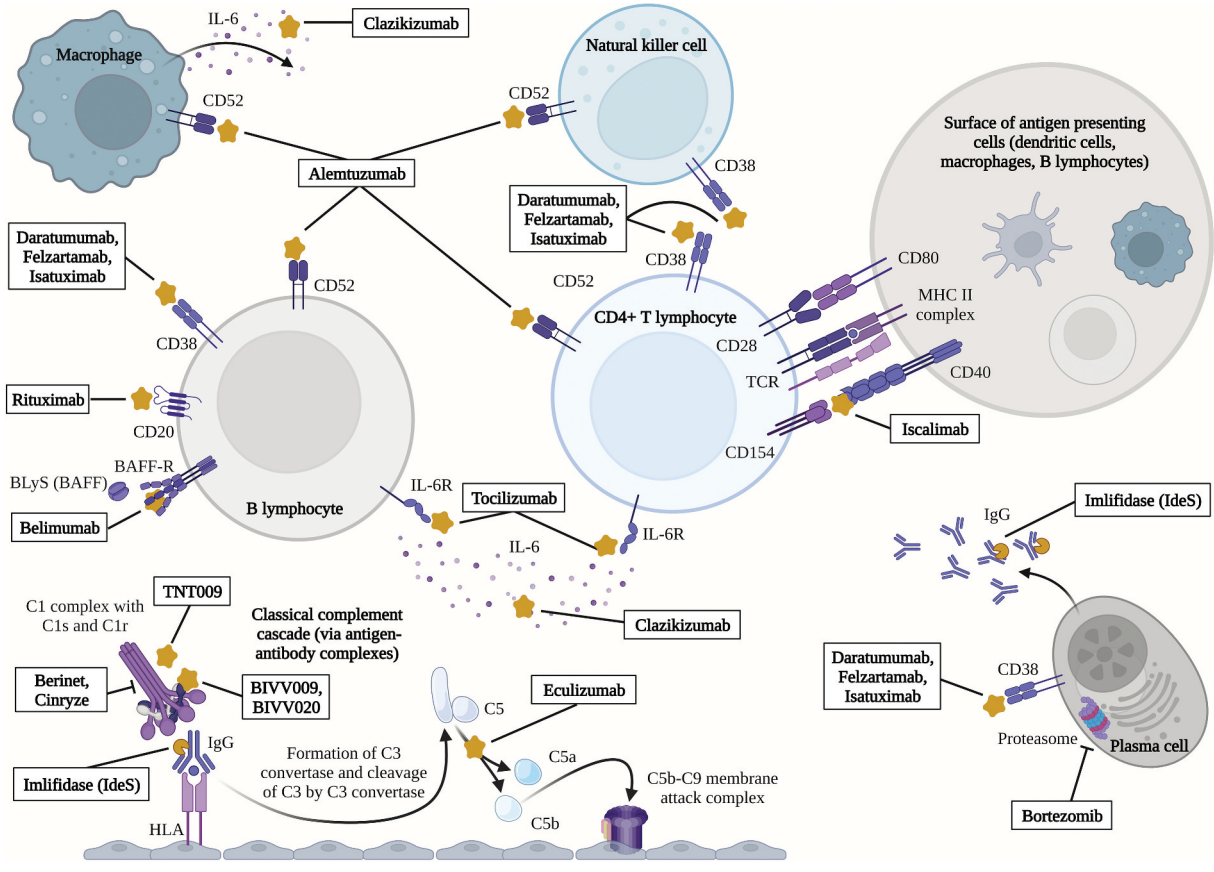

Figure 1. Schematic representation of investigational drugs for the treatment of kidney transplant rejection and their targets.

This figure presents a B- and T lymphocyte, macrophage, natural killer cell, plasma cell, and a cluster of antigen-presenting cells (dendritic cells, macrophages, B lymphocytes) with their surface receptors. Abbreviations: IL, interleukin; IL-6 R, interleukin-6 receptor; BAFF-R, B cell-activating factor-receptor; BLyS, B lymphocyte stimulator; BAFF, B cell-activating factor; IdeS, immunoglobulin-G-degrading enzyme of the human pathogen *Streptococcus pyogenes*; Ig, immunoglobulin; HLA, human leukocyte antigens; TCR, T cell receptor; MHC, major histocompatibility complex

No randomized controlled trial (RCT) comparing alemtuzumab with rATG head-to-head for the treatment of kidney allograft rejection has been conducted and it is unlikely that such a trial will ever be performed. A retrospective, propensity score-corrected comparison of alemtuzumab and rATG for severe or glucocorticoid-refractory rejection, which included n = 224 kidney transplant recipients, was reported by van der Zwan *et al*. [10]. This analysis demonstrated comparable patient and allograft survival but a superior infection-free survival for alemtuzumab compared to rATG [10]. Favorable results of alemtuzumab for the treatment of late ABMR (stabilization or improvement of renal function in 10 out of 12 patients) have been reported by others [11].

Compared with rATG, a slower lymphocyte reconstitution was observed after alemtuzumab. Only 55.7% of patients had a T cell count >200 × 10^6/L one year after treatment [10]. This prolonged lymphocyte depletion may in part explain the increased risk of infection, secondary auto-immunity and malignancy that have been associated with alemtuzumab [12]. Currently, alemtuzumab is most often prescribed as a fixed-dose of 30 mg. Plasma alemtuzumab concentrations have, however, shown substantial interpatient variability [13]. An individualized dose might lead to faster lymphocyte recovery and less adverse events. In kidney transplantation, weight-based dosing led to faster lymphocyte repopulation, less infection, and comparable rejection rates [14]. Furthermore, a lower dose (20 mg) was found to be effective [15]. These findings indicate that individualized alemtuzumab dosing may improve the balance between efficacy and toxicity. The use of a pharmacokinetic model, such as was recently developed for children who underwent stem cell transplantation [16], may allow for such individualized alemtuzumab dosing.

2.2. Rituximab

Rituximab is a monoclonal antibody directed at CD20, which is expressed on B lymphocytes and its precursor cells, but not on plasma cells. Its mechanism of action is to deplete B lymphocytes by various mechanisms (Figure 1) [17]. Rituximab is registered for the treatment of hematologic malignancies, rheumatoid arthritis, granulomatosis with polyangiitis, and microscopic polyangiitis. It has also been used off-label in a variety of other diseases characterized by pathogenic auto-antibody formation [18].

In transplant rejection, B lymphocytes play a versatile role. They can differentiate into (donor-specific) antibody-secreting plasma cells and influence the T lymphocyte response by acting as antigen presenting cells (APC) and through the production of cytokines [19]. Because of the central role of B lymphocytes and donor-specific anti-HLA antibodies (DSA) in ABMR, rituximab has been investigated extensively for this indication. In a murine transplantation model, repeated doses of rituximab reduced alloantibody formation against donor splenic cells and prolonged graft survival independent of antibody-secretion, suggesting rituximab inhibited both antibody-mediated and antibody-independent rejection mechanisms [20]. In human kidney transplantation, rituximab was effective in reducing blood group antibodies in blood group-incompatible transplantation and in reducing the concentration of DSA in highly immunized recipients [21]. However, rituximab was not effective in preventing TCMR when prescribed as an induction agent [22].

Although several retrospective case series and cohort studies reported favorable results of rituximab therapy for ABMR, this was not confirmed in RCTs [23]. In two recent RCTs, Moreso *et al*. (n = 25) and Shiu *et al*. (n = 23) compared rituximab with placebo for chronic ABMR in kidney transplantation [24,25]. They could not demonstrate a beneficial effect of rituximab on renal outcomes [24,25]. Additionally, no effects on DSA concentrations were observed [24]. Importantly, both trials were terminated prematurely due to low inclusion rates and were therefore underpowered.

Sautenet *et al*. conducted a RCT for active ABMR in which n = 38 patients were randomized to receive methylprednisolone, plasma exchange and high-dose IVIG or methylprednisolone, plasma exchange, high-dose IVIG plus rituximab. They found a comparable one-year graft survival between the two groups [26]. There was no significant difference in DSA concentrations [26]. Associated side effects of rituximab were infection-related: opportunistic infections occurred more frequently after rituximab (six *versus* one) [26]. A recently published, follow-up study of this cohort study reported equal long-term outcomes between the two therapies [27]. The modest sample size and high cross-over (8 out of 19 control patients received rituximab) should, however, be taken into account when these results are interpreted.

2.3. Bortezomib

Bortezomib is a proteasome inhibitor that is registered for the treatment of multiple myeloma [28]. Its mechanism of action is to inhibit the degradation of intracellular proteins, such as misfolded immunoglobulins, pro-apoptotic kinases, and protein inhibitors of cell survival pathways, which in the end causes apoptosis (Figure 1) [28]. Malignant and normal plasma cells are hypersensitive to bortezomib, possibly because of their extremely high protein synthesis [29]. In vitro, bortezomib caused human plasma cell apoptosis and prevented DSA production [30]. Therefore, bortezomib was suggested as a treatment option for ABMR [30,31].

Bortezomib as monotherapy for kidney transplant recipients suffering from late ABMR was investigated by Eskandary *et al*. [32]. They screened kidney transplant patients for the presence of DSA and performed a kidney biopsy in case of a positive DSA test result. Forty-four kidney transplant recipients with biopsy-proven ABMR were subsequently included and randomized to receive bortezomib (n = 21) or placebo (n = 23). After a follow-up of 24 months, no significant differences were observed between the two groups in estimated glomerular filtration rate (eGFR) slope, graft survival or rejection phenotype in follow-up biopsies [32]. Treatment with bortezomib was, however, associated with gastrointestinal and hematologic toxicity [32]. A RCT evaluating bortezomib for chronic, active ABMR has recently been completed (ClinicalTrials.gov identifier: NCT02201576). As opposed to the RCT of Eskandary *et al*., bortezomib was used as a supplement to plasma exchange, glucocorticoids, and IVIG. A total of 60 kidney transplant recipients were planned to be

recruited. No results have been published at time of writing this manuscript.

2.4. CD38-directed therapy

CD38 is a glycoprotein which is expressed on the surface of plasma cells, as well as NK cells, B- and T lymphocytes, and has an important function in cell adhesion and cell activation [33]. Therefore, CD38 is a promising therapeutic agent in ABMR.

Daratumumab is a monoclonal antibody directed against CD38. Like bortezomib, it is registered for the treatment of multiple myeloma [34]. Its mechanism of action is to deplete plasma cells and lymphocytes via complement-dependent cell lysis and antibody-dependent cytotoxicity (Figure 1). Daratumumab is proposed as ABMR therapy [33]. In macaques, treatment with daratumumab significantly reduced DSA concentrations and prolonged kidney graft survival. However, regulatory lymphocytes were also depleted after daratumumab, which could have contributed to the development of TCMR [35].

For the treatment of ABMR in kidney transplantation, daratumumab has only been described in three case reports [36–38]. Doberer *et al*. described a kidney transplant recipient with both smoldering myeloma and chronic, active ABMR in which graft function stabilized after a nine-month course of daratumumab. This was accompanied by improved histology on kidney biopsy (resolution of the microvascular inflammation) [36]. Jordan *et al*. reported a patient with severe ABMR that was resistant to plasma exchange, IVIG, rituximab, and complement-inhibition who was treated with four-weekly doses of daratumumab (16 mg/kg). After treatment, ABMR resolved but the patient developed severe TCMR. It was postulated that the depletion of regulatory B lymphocytes by daratumumab may have caused this TCMR [37]. Spica *et al*. presented a patient with ABMR due to anti-blood group antibodies. This patient did not respond to immunoadsorption, high-dose glucocorticoids, rATG and complement inhibition and was then treated with daratumumab because of persistent antibody formation. After daratumumab treatment, kidney function recovered and antibody titers decreased [38].

At present, there is too little evidence to recommend daratumumab for the treatment of ABMR. In fact, the possibility of adverse immunological effects like the development of TCMR which may have been caused by the depletion of regulatory B lymphocytes, is reason for concern [37]. These concerns were shared by others [35,36,38]. To our knowledge, no trials that evaluate daratumumab for the treatment of ABMR are currently planned.

Another CD38-directed drug is felzartamab. Its mechanism of action is to deplete plasma cells and NK cells trough antibody-dependent cellular cytotoxicity, but without complement activation (Figure 1) [39]. It has been deemed safe in a phase I–IIa trial in patients with refractory multiple myeloma [39], and is currently being evaluated for membranous nephropathy (ClinicalTrials.gov identifier: NCT04145440; NCT04733040). To our knowledge, no data about the use of felzartamab in ABMR is available at this point. However, a study protocol for a phase II trial to assess safety, tolerability, and efficacy of felzartamab in late ABMR has recently been published (ClinicalTrials.gov identifier: NCT05021484) [40].

Isatuximab is another CD38-specific monoclonal antibody developed for treatment of relapsed or refractory multiple myeloma [41]. Its mechanism of action is comparable to daratumumab and felzartamab (Figure 1). Although isatuximab has not yet been evaluated as ABMR therapy, it has recently been evaluated for desensitization in kidney transplantation (ClinicalTrials.gov identifier: NCT04294459). No results of this trial have been published at the time of this review. If isatuximab is well tolerated in kidney transplant recipients and shows effective DSA-reduction, isatuximab might be considered as a new therapeutic agent in ABMR.

3. Non-depleting antibodies

In contrast to the discussed cell-depleting therapies, non-depleting antibodies disturb pathways responsible for graft rejection without inducing cell lysis. Currently, two non-depleting antibodies are being evaluated, belimumab, and iscalimab.

3.1. Belimumab

Belimumab is a humanized, monoclonal, anti-B lymphocyte stimulator (BLyS) immunoglobulin (Ig) G1-antibody. Its mechanism of action is to bind members of the tumor necrosis factor (TNF) receptor superfamily, which prevents binding with BLyS (Figure 1). Three TNF receptors are identified as a binding site for BLyS: BAFF-R (BR3; B cell-activating factor-receptor), TACI (transmembrane activator and calcium modulator and cyclophilin ligand interactor) and BCMA (B-cell maturation antigen) [42,43]. BLyS (also known as BAFF; B-cell activating factor) is a cytokine of the TNF ligand family. BLyS is expressed in B cell lineage cells and on various other cell types (monocytes, dendritic cells, and bone marrow stromal cells) [44–46]. Binding of belimumab to the TNF receptor prevents the survival, maturation and activation of B lymphocytes and their differentiation into plasma cells. Moreover, it prevents stimulation of T lymphocyte-dependent and -independent antibody responses and T lymphocyte co-stimulation [47–50]. Belimumab is currently licensed for use in patients with systemic lupus erythematosus [51], where high circulating levels of BLyS result in an abnormally high pathogenic antibody production and autoimmune disease [52].

Over the last years, belimumab has been tested in kidney transplantation, since BLyS was found to be expressed in biopsies of rejecting kidney allografts [47]. Furthermore, higher levels of soluble BLyS are associated with a higher risk of DSA formation [49]. Experimental, non-human primate studies demonstrated that anti-BLyS therapy could prevent production of *de novo* DSAs and slightly extent allograft survival [53–55]. In contrast, anti-BLyS therapy was found to be ineffective in terms of meaningfully lowering DSA concentrations in highly sensitized patients with end-stage kidney disease [56,57].

Belimumab has been studied for the prevention of ABMR in one double-blind RCT, in which n = 28 kidney transplant

recipients were treated with belimumab for a total of seven doses during 20 weeks, followed by a six month follow-up without belimumab [58]. Patients received belimumab (10 mg/kg) intravenously (IV) (n = 14) or placebo (n = 14) on the day of kidney transplantation (day 0), day 14 and 28, followed by an infusion every four weeks. All patients received standard-of-care consisting of basiliximab, tacrolimus, mycophenolate mofetil, and glucocorticoids. Primary safety and efficacy endpoints were analyzed using the modified intention-to-treat population (n = 25), which consisted of participants who received at least one dose of belimumab (n = 12) or placebo (n = 13) on day 0 [58].

Safety analysis did not demonstrate a new safety signal. TCMR occurred in both groups (in one of eight (13%) and three of eight (38%) participants in the belimumab and placebo groups, respectively). During both treatment phases, no excess serious infections were observed. There was a similar frequency of BK virus and cytomegalovirus infection among participants in both groups [58].

Efficacy analysis, assessed by the change in concentration of naïve B lymphocytes from baseline to week 24, demonstrated that the total B lymphocyte concentrations in both groups were similar during the study period. Due to the small number of participants and since some participants only received one dose of belimumab, the sample size was not powered for clinical endpoints. However, data from exploratory endpoints revealed that the remaining B lymphocytes after treatment had a greater capacity to produce interleukin (IL)-10 compared with IL-6 [58]. This could be relevant for the treatment of rejection since IL-10 is an immunosuppressive cytokine with tolerogenic properties. In addition, activated memory B lymphocytes were significantly reduced and tissue-specific antibodies in serum were lowered [58].

To the best of our knowledge, no other studies are currently investigating the use of belimumab in kidney transplantation. An open-label, single-arm, pilot study evaluating the addition of belimumab to standard-of-care therapy in preventing *de novo* DSA was initiated (ClinicalTrials.gov identifier: NCT03591380). Unfortunately, this study has terminated due to recruitment complications caused by Coronavirus disease 2019 (COVID-19) (December 2021). The results of this study have not been published. Although belimumab is not currently being investigated for rejection, it is reviewed because it holds promise as treatment in kidney transplant rejection. B lymphocytes had a greater capacity to produce IL-10 compared with IL-6 after treatment with belimumab [58]. This might be of clinical relevance considering the role of IL-6 in kidney transplant rejection [59], which will be discussed in the section on IL-6 directed therapy.

3.2. Iscalimab

Iscalimab (CFZ533) is a non-B lymphocyte-depleting anti-CD40 monoclonal antibody [60]. Its mechanism of action is to bind the transmembrane glycoprotein CD40, which prevents binding with its ligand CD154 (CD40L) (Figure 1). CD40 belongs to the TNF receptor superfamily and is expressed on APCs and B lymphocytes [61–63]. CD154 is expressed on various cell types such as platelets, B lymphocytes, and activated T lymphocytes [63–65]. This CD40-CD154 costimulatory pathway has a function in the primary T lymphocyte-dependent antibody response: it generates germinal center formation, differentiation of memory B lymphocytes and Ig-isotype switching [66–68]. Stimulation of the CD40 pathway also induces the secretion of various cytokines and plays a role in dendritic cell maturation and macrophage survival [69,70]. The cascade of this immune response is known to contribute to lymphocyte activation in inflamed tissue and is involved in the pathology of some autoimmune diseases [71,72]. This cascade has been recognized as important in SOT rejection [73–78]. Available evidence of iscalimab is therefore discussed in this review, even though no evaluation of iscalimab as treatment for kidney transplant rejection has yet been undertaken.

Promising results from non-human primate [60,79] and *in vitro* [80] studies generated high expectations for iscalimab in kidney transplantation. The drug was found to be able to prolong survival of kidney allografts in the absence of B lymphocyte depletion, to completely inhibit primary and recall T lymphocyte-dependent antibody responses and to block germinal center formation, when administered as monotherapy in a non-human primate kidney transplantation model [60]. A following non-human primate study confirmed the ability of iscalimab to be immunosuppressive [79]. After stopping iscalimab treatment and soon after the serum iscalimab concentration dropped below the therapeutic level, the primates regained normal lymphatic tissue architecture and immune function [79]. Notably, *in vitro* and *in vivo* studies done by the same study group, demonstrated that iscalimab did not induce human platelet activation [80], where previous anti-CD154 monoclonal antibodies had an unacceptable incidence of thromboembolic events [74–76,81].

The study of Espie *et al*., was the first in-human RCT (n = 76), that tested different doses of iscalimab and compared it with placebo. Iscalimab was shown to be safe and well tolerated at single doses up to 30 mg/kg IV, with no increased risk of infection or thromboembolic events. Pharmacokinetic/pharmacodynamic studies confirmed complete CD40 receptor occupancy on whole-blood B lymphocytes when the therapeutic level of iscalimab was reached (>0.3–0.4 µg/L) [73].

Another multicenter, RCT (ClinicalTrials.gov identifier: NCT02217410), investigated iscalimab (10 mg/kg IV) with a tacrolimus-free immunosuppressive regimen (n = 33) and compared it with standard-of-care immunosuppression (tacrolimus, mycophenolate mofetil, and glucocorticoids) in *de novo* kidney transplant recipients (n = 18). Iscalimab was dosed every four weeks. All patients received basiliximab induction and glucocorticoids. Primary endpoints were the pharmacokinetics and efficacy of iscalimab, defined by the frequency and severity of treated biopsy-proven acute rejection, over a duration of 12 months. Preliminary data, presented as an abstract [82,83], showed non-inferiority in terms of acute rejection and a good safety profile. Allograft biopsies were performed in a subset of patients and demonstrated better kidney histology (chronic allograft damage index score <1) in patients treated with iscalimab (three out of five patients) compared to biopsies of patients who received the tacrolimus-

based regimen (none out of seven patients; $p < 0.01$) [82,83]. Although these results were promising, a full-length article was never published.

The partially blinded, multicenter, dose range-finding RCT (CIRRUS-I, ClinicalTrials.gov identifier: NCT03663335) investigated the ability of iscalimab to possibly replace calcineurin inhibitors. In n = 418 *de novo* and maintenance kidney transplant recipients, three different doses of iscalimab (with a tacrolimus-free regimen) were compared to standard-of-care (tacrolimus, mycophenolate mofetil, and glucocorticoids). The primary outcome was the proportion of patients reaching the composite endpoint (consisting of biopsy-proven acute rejection, graft loss, or death) over a duration of 12 months. However, the CIRRUS-I trial was recently discontinued following an interim analysis which demonstrated an unacceptably high incidence of rejection in the iscalimab treated group compared to the standard-of-care treated group (September 2021) [84]. Currently, the data from the CIRRUS-I trial is being reviewed and no final results have been published.

The manufacturer of iscalimab, Novartis Pharma, has announced that current and actively recruiting studies investigating the potential of iscalimab will continue. One of these studies is a multicenter, RCT evaluating iscalimab in *de novo* liver transplant recipients (CONTRAIL-I, ClinicalTrials.gov identifier: NCT03781414).

4. IL-6 directed therapy

IL-6 is a critical cytokine in inflammation. It stimulates the synthesis of acute-phase proteins, regulates the activation, proliferation, and differentiation of lymphocytes, stimulates antibody synthesis and induces a pro-inflammatory phenotype of monocytes and endothelial cells [59]. IL-6 exerts its inflammatory effects via different mechanisms. Classically, IL-6 binds to the membrane-bound IL-6 receptor (IL-6 R) which is expressed on lymphocytes, myeloid cells and hepatocytes, and induces intracellular signaling [59]. Alternatively, IL-6 is able to induce intra-cellular signaling by binding to soluble IL-6 R, which can interact with the membrane-bound glycoprotein 130 and activate downstream signaling pathways [59]. This 'trans-signaling' can occur on IL-6 R-negative cells, thereby significantly expanding the effector functions of IL-6 [59].

IL-6 is proposed to contribute to ABMR in SOT by promoting antibody synthesis and stimulating B lymphocyte differentiation into plasma cells [59]. Animal studies have demonstrated significant decreases in alloantibody production after anti-IL-6 treatment [85,86]. Proposed roles of IL-6 in TCMR are the promotion of the expansion of the $CD8^+$ T lymphocyte population and by promoting naïve $CD4^+$ T lymphocytes to differentiate to pro-inflammatory T helper lymphocytes [59]. Anti-IL-6 therapy was found to significantly reduce the number of pro-inflammatory T helper lymphocytes by 10% and increase regulatory T lymphocyte numbers by 10% in a murine skin transplantation model [85]. In a murine model using IL-6 deficient cardiac allografts, decreased activation of $CD4^+$ and $CD8^+$ T lymphocytes was observed resulting in increased allograft survival [87]. IL-6 directed therapy is a novel therapeutic approach for kidney transplant rejection. Currently, two drugs with anti-IL-6 activity have been approved for clinical use.

4.1. Tocilizumab

Tocilizumab is a recombinant, monoclonal antibody with specificity for both soluble and membrane-bound IL-6 R [88]. Its mechanism of action is to inhibit the effector functions of IL-6 by blocking the IL-6 R (Figure 1). It is currently registered for use in rheumatoid arthritis, systemic juvenile idiopathic arthritis, and polyarticular idiopathic arthritis [88]. Additionally, it has recently been recommended as treatment of severe COVID-19 infection by the World Health Organization [89].

Tocilizumab has shown promise as treatment for chronic ABMR after kidney transplantation. Choi *et al*. reported a six-year graft survival probability of 80% after the diagnosis of chronic ABMR when tocilizumab was used as rescue therapy (n = 36) [90]. Lavacca *et al*. treated n = 15 chronic ABMR patients with first-line tocilizumab monotherapy and observed a graft survival of 93% and stabilization of kidney function after a median follow-up of 21 months [91]. In both studies, patients had a relatively preserved kidney function at baseline [90,91]. Both studies lacked a control group and included low patient numbers. The most important side effect was increased susceptibility to bacterial infection, possibly due to associated neutropenia.

The only comparative study of tocilizumab in ABMR was performed by Massat *et al*., who published a retrospective, propensity score matched comparative study of n = nine patients who received rescue treatment with tocilizumab after treatment with rituximab, plasmapheresis, and IVIG and compared this with n = 37 patients who received rituximab, plasmapheresis, and IVIG only [92]. No differences were observed in one-year graft survival or kidney function decline [92]. It should be noted that the included patients suffered from both acute and chronic ABMR, as well as mixed-type rejection, which may have influenced the outcomes.

A large RCT evaluating tocilizumab for chronic ABMR is ongoing. (INTERCEPT-trial: ClinicalTrials.gov identifier: NCT04561986). INTERCEPT is a randomized, open-label study to evaluate the efficacy and toxicity of tocilizumab for chronic, active ABMR. Endpoints include change in kidney function and histologic changes (assessed in kidney transplant biopsies). The number of patients to be included is 50.

4.2. Clazakizumab

Clazakizumab is a humanized monoclonal antibody with a high affinity for the cytokine IL-6 (not its (soluble) receptor which is the target of tocilizumab) [93]. Its mechanism of action is to bind to IL-6 cytokines, which prevents association of IL-6 with IL-6 R and inhibits its effector functions (Figure 1). It is currently not registered for any specific condition but the drug has been evaluated for both psoriatic arthritis [93] and rheumatoid arthritis [94] and is under evaluation for severe COVID-19 (ClinicalTrials.gov identifier: NCT04494724; NCT04659772). Clazakizumab seems a promising therapy for

stabilizing kidney function in late, active and chronic, active ABMR.

Doberer *et al*. published a pilot RCT of clazakizumab as monotherapy for late, active and chronic, active ABMR [95]. Twenty patients were randomized to receive clazakizumab or placebo for 12 weeks. After a period of 12 weeks, less kidney function decline (measured as eGFR slope) was observed in the clazakizumab group [95]. Subsequently, all patients received clazakizumab for 40 weeks, which significantly improved the eGFR slope of the patients who were initially treated with placebo [95]. Overall, eGFR stabilized over the course of 40 weeks [95]. Median eGFR at baseline was 39 mL/min per 1.73 m^2 [95]. The response to therapy appeared smaller in patients who had a lower eGFR at baseline. Its use was associated with increased infection susceptibility and the occurrence of diverticulitis [95].

Jordan *et al*. recently published a prospective single cohort study (n = 10) of clazakizumab for therapy-resistant, chronic, active ABMR. They reported stabilization of previously deteriorating kidney function and reductions of ABMR-related features in kidney transplant biopsies after 12 months of clazakizumab therapy [96].

A large RCT evaluating clazakizumab for ABMR is ongoing (IMAGINE-trial: ClinicalTrials.gov identifier: NCT03744910). IMAGINE is a blinded, placebo-controlled RCT evaluating the efficacy of clazakizumab for chronic, active ABMR. Endpoints include allograft loss and kidney function. The number of patients to be included is 350.

5. Antibody targeted therapy

5.1. Imlifidase

Imlifidase is an IgG-degrading enzyme of the human pathogen *Streptococcus pyogenes* (IdeS). Its mechanism of action is IgG removal by cleaving of IgG in a two-step process. In a rapid first reaction, IgG is cleaved by the hinge region generating one F(ab') fragment and single cleaved IgG. In the second longer reaction, two F(ab') fragments and a fully separated Fc fragment are generated within hours (Figure 1) [97–101]. The cleaved IgG has lost its Fc-mediated activities, such as phagocytosis, antibody-dependent cell-mediated cytotoxicity, and complement activation [102–104], one of the major effector mechanism of ABMR in kidney transplantation [105–107].

In contrast to plasma exchange, imlifidase rapidly depletes IgG within hours and also cleaves extravascular IgG, when doses of 0.12 or 0.24 mg/kg bodyweight IV were administered in n = 29 healthy male subjects in a phase I study by Winstedt *et al*. [108]. However, imlifidase has a short-term effect since intact IgG returned within one week to two months [108]. Subjects all had detectable (IgG) anti-IdeS antibodies at baseline, with subsequent higher concentrations of these antibodies after imlifidase administration [108–110]. This phenomenon is likely to limit repeated imlifidase administration. Furthermore, B lymphocytes treated with imlifidase are unable to execute signaling through their B cell receptor, and memory B lymphocyte differentiation is inhibited, subsequently reducing the amount of IgG-producing cells. Imlifidase does not cleave IgA and IgM, and is restricted to (all four subclasses of) IgG [111]. Since then, imlifidase has been demonstrated to be efficient as a desensitization drug in highly sensitized patients awaiting kidney transplantation (n = 50). These four studies demonstrated disappearance of DSAs after treatment with imlifidase and successful kidney transplantation hereafter [109,112–114]. This has led to a conditional approval by the European Medicines Agency. Currently, a phase III RCT investigating the use of imlifidase as a desensitization drug in n = 64 kidney transplant recipients in comparison with standard-of-care desensitization drugs or plasma exchange is ongoing (ConfIdeS-trial: Clinicaltrials.gov identifier: NCT04935177).

Imlifidase is regarded to have potential in the treatment of ABMR, due to its properties to reduce the amount of DSAs. Recently, an multinational, open-label, phase II RCT completed the enrollment of n = 30 kidney transplant recipients with active or chronic ABMR according to Banff 2017 criteria and at least a 25% rise in serum creatinine compared with last measurement prior to the ABMR (Clinicaltrials.gov identifier: NCT03897205). Primary outcome is the maximum reduction in mean DSA level at any time point during the five days following the start of treatment with imlifidase compared to plasma exchange. Efficacy and safety is monitored over a six-month period post-treatment. Patients were treated with one dose of imlifidase IV (0.25 mg/kg) (n = 20) or five to ten sessions of plasma exchange (n = 10). All patients received standard-of-care consisting of pulse methylprednisolone for three days, started prior to first treatment, followed by a tapering schedule with prednisolone. Additionally, they received high dose IVIG three days after imlifidase infusion or directly after last plasma exchange, and a single dose of rituximab was given five days after completed IVIG infusion. Complete results are expected in March 2023.

6. Complement inhibition

The classical pathway of complement activation is a known effector of acute and chronic ABMR [115]. Inhibiting the classical pathway of complement activation or its effector mechanisms, are therefore interesting therapeutic strategies for ABMR [116,117]. *In vitro*, anti-complement antibody C1 TNT009 was shown to inhibit HLA antibody-triggered complement activation [118]. Anti-complement antibody C5 effectively prevented rejection of heart and skin grafts in sensitized mice [119–121]. Given these positive experimental results, several complement inhibitors have been evaluated in humans.

6.1. C1 esterase inhibitors

C1 esterase inhibitors are serine proteases isolated from human plasma. Their mechanism of action is to inactivate C1 esterase by binding to its reactive site, thus inhibiting the classical pathway of complement activation (Figure 1) [122]. Berinert® and Cinryze™ are currently on the market and are registered for the treatment of hereditary angio-edema [122].

In a comparative study in ABMR, the addition of a C1 esterase inhibitor to high-dose IVIG significantly improved

kidney function in late, active ABMR when it was compared to a historical cohort [123]. In a small randomized, placebo-controlled pilot study (n = 18) in acute ABMR, no effect on kidney function was observed after 30 days although less chronic endothelial injury in protocol biopsies occurred after eculizumab was added as co-treatment [124]. In both studies, C1 esterase inhibitors were well tolerated, although their use was associated with gastrointestinal toxicity [123,124].

6.2. Eculizumab

Eculizumab is a monoclonal antibody that targets C5. Its mechanism of action is to bind C5, inhibit cleavage of C5 into C5a and C5b and prevent the formation of the C5b-C9 membrane attack complex, which is the final common pathway effector of the complement system (Figure 1) [125]. It is currently registered for paroxysmal nocturnal hemoglobinuria, atypic hemolytic uremic syndrome, refractory generalized myasthenia gravis and neuromyelitis optica spectrum disorder [126]. Its use is, however, associated with increased susceptibility to meningococcal infection and with hepatotoxicity [126].

The evaluation of eculizumab as therapy for ABMR is hindered by the lack of adequately sized, controlled trials. Small patient series and retrospective, non-comparative studies have reported favorable kidney outcomes especially in (hyper) acute, severe ABMR when eculizumab treatment was started shortly after diagnosis [127–131]. However, these positive results were not confirmed in a retrospective comparative study [132]. The only prospective, pilot RCT included n = 15 patients who were at least six months after their first transplantation, had high *de novo* DSA-titers, a 20% reduction in eGFR during the previous year and antibody-mediated injury in kidney biopsies [133]. It showed no significant differences in kidney function or histology six months after eculizumab therapy [133].

6.3. Anti-C1s antibodies

Anti-C1s antibodies are monoclonal antibodies that specifically target the activated C1 protein of the complement system. Their mechanism of action is to bind and block activated C1 protein, thereby inhibiting the classical pathway of complement activation (Figure 1). Eskandary *et al*. evaluated an anti-C1s antibody (BIVV009) in a phase I trial (n = 8) [134]. They treated kidney transplant recipients with late, active ABMR with four weekly doses. BIVV009 was well tolerated and led to reduced or eliminated C4d-deposition in kidney biopsies after five weeks from the start of treatment [134].

Another anti-C1s antibody, BIVV020, is currently being evaluated for prevention of ABMR in sensitized recipients and treatment of patients with active ABMR (ClinicalTrials.gov identifier: NCT05156710). The study is expected to complete in 2025.

7. Conclusion

Treatment of kidney transplant rejection remains a challenging clinical problem and has prompted the search for alternative treatments. Many new drugs targeting different mechanisms in the pathogenesis of kidney transplant rejection are currently actively investigated. Unfortunately, for all discussed drugs there is yet no high-quality evidence demonstrating their efficacy in the treatment of kidney transplant rejection. The relatively small patient numbers in clinical trials, large heterogeneity in rejection subtypes and absence of validated, short-term outcome measures, all contribute to this sparsity of high-quality evidence.

8. Expert opinion

All kidney transplant recipients, with the exception of monozygotic twins, are at risk of developing graft rejection, which remains an important complication after kidney transplantation [3]. Improvements in the treatment of kidney transplant rejection will lead to longer graft and patient survival and better quality of life [135]. Furthermore, fewer re-transplantations will shorten the waiting list for patients with end-stage renal disease [135].

Improvement of rejection therapy has mainly focused on ABMR, since ABMR is the leading cause of graft loss and lacking an effective, evidence-based therapy [7]. As illustrated by this review, there are many investigational therapies available for ABMR with different mechanisms of action (Figure 1). Although there is no conclusive scientific evidence to support any of these therapies yet, future applicability of each treatment strategy can be discussed by taking the underling mechanisms of action and (dis)advantages into account (Table 1).

Depletion of lymphocytes or plasma cells is a rational treatment strategy to counter ABMR, when the central role of these immune cells in ABMR and the effectiveness of lymphocyte depletion in TCMR are considered. However, the potential risks of infection, malignancy, and recurrent rejections due to long-lasting cell depletion and subsequently altered immune reconstitution after cell depletion therapies are worrisome. Furthermore, some kidney allografts are lost despite intensive depletion therapy. This underlines the importance of a personalized approach for such therapies to optimize the risk–benefit ratio for individual patients. Prediction models, like a recently developed prediction model for alemtuzumab [136], could facilitate this personalized approach.

More specific targeted therapies, such as belimumab and iscalimab instead of all-or-nothing depletion therapies, could also help to optimize risk-benefit ratios for individual patients. Many potential therapies have been evaluated in recent years including non-depleting antibodies. Although the mechanism of action of non-depleting antibodies is promising, belimumab and iscalimab have not yet been evaluated for kidney transplant rejection. Especially belimumab, with its effect on IL-6 production, could be beneficial in treating chronic ABMR in the near future. However, this potential can be questioned, considering the ineffectiveness of anti-BLyS therapy in lowering DSAs in highly sensitized patients awaiting kidney transplantation [56,57]. Nevertheless, the availability of numerous other potential targets on B- and T lymphocytes, emphasize the high potential of non-depleting antibody treatment strategies in kidney transplant rejection in the near future.

Given the critical role of IL-6 in chronic ABMR [137], IL-6 directed therapies have high potential to counteract chronic

Table 1. Summary of investigational drugs for the treatment of kidney transplant rejection.

Type of immunosuppression	Mechanism of action	Therapeutic effect	Advantages	Disadvantages	Reference
Cellular-depleting therapies					
Alemtuzumab	B/T lymphocyte and NK cell depletion	In retrospective analysis, allograft survival comparable to rATG	Applicable in ABMR, TCMR and mixed rejection	Long-lasting lymphocyte depletion with risk of infection, malignancy, auto-immunity	[8]
Rituximab	B lymphocyte depletion	No clear evidence for beneficial effect in ABMR	Specifically targets B lymphocytes	Higher risk of infection, plasma cells unaffected	[26]
Bortezomib	Inhibits degradation intracellular protein	No conclusive evidence for beneficial effect in ABMR	Specifically targets plasma cells	High rate of gastro-intestinal and hematological toxicity	[32]
Daratumumab	Plasma cell, B/T lymphocyte and NK cell depletion	Anecdotal evidence only, regarding use in ABMR	Targets plasma cells and lymphocytes	Possibly increased rejection rate due to loss of regulatory cells	[36–38]
Non-depleting antibodies					
Belimumab	Blocks binding of BLyS to B cell receptor, preventing B lymphocyte survival and differentiation	No clear evidence for beneficial effect in ABMR. B lymphocytes possibly have greater capacity to produce IL-10 compared with IL-6 post-treatment	Specifically targets B lymphocytes	Ineffective in lowering DSAs	[58]
Iscalimab	Binds CD40, preventing activation of the CD40-CD154 costimulatory pathway	*In vitro* and non-human primate studies only. Clinical trial results awaited	B lymphocyte sparing, no platelet activation (in comparison to anti-CD154 antibodies)	Short-term effect, necessitating continued dosing.	[84]
Interleukin-6 directed therapy					
Tocilizumab	Blocks IL-6 R, thereby preventing effector functions of IL-6	No conclusive evidence for beneficial effect in chronic ABMR	Specifically targets IL-6, modulating immune responses without cellular depletion, potential co-treatment	Risk of neutropenia	[92]
Clazakizumab	Binds IL-6, thereby preventing effector functions of IL-6	Stabilization of kidney function in small numbers of patients with chronic ABMR	Specifically targets IL-6, modulating immune response without cellular depletion, potential co-treatment	Risk of gastro-intestinal adverse effects, most notably diverticulitis.	[95,96]
Antibody targeted therapy					
Imlifidase	Cleavage of IgG-molecules and antigen-bound IgG	Ongoing trial in ABMR (Clinicaltrials.gov identifier NCT03897205), registered as desensitization drug	Specifically targets IgG molecules resulting in rapid removal of circulating DSAs, so high potential in ABMR	Short-term effect (week-months) with possibility of rebound effect of DSAs	[108]
Complement inhibition					
C1 esterase inhibitors	Binding and inactivating C1 esterase	No conclusive evidence for beneficial effect acute and late, active ABMR	Specifically targets complement, modulating immune responses without cellular depletion	Gastro-intestinal toxicity	[124]
Eculizumab	Inhibits cleavage of C5 in active components	No conclusive evidence for beneficial effect in ABMR	Specifically targets complement, modulating immune responses without cellular depletion	Increased meningococcal infections and hepatotoxicity	[133]
Anti-C1s antibodies	Binds and blocks activated C1 protein	No conclusive evidence in ABMR, only phase I trials	Specifically targets complement, modulating immune responses without cellular depletion	Safety unclear. Safety data only available from small patient numbers	[134]

Abbreviations: NK, natural killer; rATG, rabbit anti-thymocyte globulin; ABMR, antibody-mediated rejection; TCMR, T-cell-mediated rejection; BLyS, B lymphocyte stimulator; IL, interleukin; DSA, donor-specific anti-human leukocyte antigens antibodies; Ig, immunoglobulin; IdeS, immunoglobulin-G-degrading enzyme of the human pathogen *Streptococcus pyogenes*; IL-6 R, interleukin-6 receptor

ABMR. This was reflected by the results from recent trials [91,92,95,96]. Furthermore, IL-6 directed therapies can be dosed repetitively over longer time-periods with acceptable toxicity. Since chronic ABMR is characterized by low-grade immune activation and an insidious course [137], it can be argued chronic ABMR needs such repetitive, long-term treatment strategies.

A different approach in treatment of ABMR is therapy which is targeted at the removal of DSAs. Imlifidase could hypothetically prevent further injury to the kidney graft in ABMR, by specifically cleaving IgG molecules with a rapid removal of circulating DSAs, much faster than plasma exchange in which multiple sessions are needed [138]. However, concern remains regarding its costs

and its short half-life with a rebound effect of DSAs and associated ABMR [109,112–114]. This suggests imlifidase might need to be dosed repetitively, which in turn can be complicated by the presence and rebound of anti-drug antibodies after imlifidase treatment. To evaluate the potential effectiveness and pitfalls of imlifidase in ABMR treatment, high-quality trials are necessary.

Complement inhibition is another interesting approach to the treatment of ABMR. It differs to other approaches, because it does not modulate the immune response but inhibits one of its effector mechanisms. The potential applicability of complement inhibitors in ABMR is hampered, however, because complement activation is not the only mechanism by which antibodies cause damage to the kidney allograft in ABMR [137]. Furthermore, the importance of complement activation in the pathophysiology of ABMR and potential treatment effects of complement inhibitors seem to differ between different subclasses of ABMR [137]. Thus, complement inhibition in particular holds potential as a personalized treatment strategy.

As discussed by Lefaucheur *et al*., rejection phenotypes and its outcomes are more complex in clinical practice than in theory [139]. Differences in immunological features of various rejection phenotypes may explain the discrepancy of treatment outcomes between them [137]. New cellular and molecular biotechnologies could lead to immunological subtyping of kidney transplant rejection and guide therapeutic strategies [140]. This could lead to personalized medicine and optimize treatment outcomes in kidney transplant rejection.

As illustrated in this review, the evaluation of alternative therapies for ABMR is hindered mainly by the lack of adequately powered, robust clinical trials. The RCT is currently the gold standard of clinical trials for determining the applicability of novel therapies. However, as discussed by other authors, the low number of eligible patients and the high number of potential therapies, complicate the design and execution of such RCTs in kidney transplant rejection [141]. To overcome these obstacles and in order to maximize the probability of promising experimental drugs reaching their potential in kidney transplant rejection, researchers should consider implementing adaptive trial designs and clinical research consortia. These are already relatively common in medical oncology [141]. Because adaptive trial designs incorporate flexibility in their designs, by allowing adaptation of the trial based on the outcomes of enrolled patients and the development of new therapeutic strategies, they facilitate more efficient data collection [141]. Importantly, adaptive trial designs work best with short-term outcomes, because rapid evaluation of the therapy of interest is necessary to timely adapt the trial [141,142]. Examples of these surrogate endpoints are eGFR slope over 12 months and a combination of functional, histological, and immunological prognostic risk factors called the iBox [142]. More validated surrogate clinical endpoints are necessary and advances in this field are underway [143].

Many promising drugs are currently under investigation for the treatment of kidney transplant rejection. With the implementation of alternative trial designs, the use of surrogate clinical endpoints, and the development of next-generation transplant diagnostics, high-quality evidence of these novel therapies will become available in the next few years and facilitate personalized treatment of rejection. Hopefully, this will significantly improve outcomes for kidney transplant recipients.

Funding

This paper was not funded.

Declaration of interest

AE de Weerd has received consultation fees from HANSA for the Expert Workshop about imlifidase. The fees have been transferred to the kidney transplantation fund of Erasmus MC.
D.A. Hesselink has received lecture fees and consulting fees from Astellas Pharma, Chiesi Pharma, Medincell, Novartis Pharma, Sangamo Therapeutics, and Vifor Pharma. He has received grant support from Astellas Pharma, Bristol-Myers Squibb, and Chiesi Pharma.
The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers

1. Registry AaNZDaT. Australia and New Zealand dialysis and transplant registry: 39th annual report, Chapter 8, transplantation. Adelaide, Australia, 2016.
2. Loupy A, Haas M, Roufosse C, et al., The banff 2019 kidney meeting report (I): updates on and clarification of criteria for T cell- and antibody-mediated rejection. Am J Transplant. 2020;20(9): 2318–2331.
3. Nankivell BJ, Alexander SI, Schwartz RS. Rejection of the kidney allograft. N Engl J Med. 2010;363(15):1451–1462.
4. Kasiske BL, Zeier MG, Chapman JR, et al. KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary. Kidney Int. 2010;77(4):299–311.
5. FDA. Thymoglobulin; 2018 . [updated 26th Febuary 2018; cited 2022 7th March]. [updated 26th Febuary 2018; cited 2022 7th March]: https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/thymoglobulin
6. Rampersad C, Balshaw R, Gibson IW, et al. The negative impact of T cell-mediated rejection on renal allograft survival in the modern era. Am J Transplant. 2022;22(3):761–771.
7. Loupy A, Lefaucheur C. Antibody-mediated rejection of solid-organ allografts. N Engl J Med. 2018;379(12):1150–1160.
8. van der Zwan M, Baan CC, van Gelder T, et al. Review of the clinical pharmacokinetics and pharmacodynamics of alemtuzumab and its use in kidney transplantation. Clin Pharmacokinet. 2018;57(2):191–207.
   • **Comprehensive review of the application of alemtuzumab in kidney transplantation.**
9. EMA. Lemtrada: European medicines agency; 2013. [updated 7-jan-2022; cited 2022 February 10th]. [updated 7-jan-2022; cited 2022 February 10th]: https://www.ema.europa.eu/en/medicines/human/EPAR/lemtrada
10. van der Zwan M, Groningen MC C-V, van den Hoogen MWF, et al. Comparison of alemtuzumab and anti-thymocyte globulin treatment for acute kidney allograft rejection. Front Immunol. 2020;11:1332.
11. Betjes MGH, Kho MML, Litjens NHR, et al. Alemtuzumab as second-line treatment for late antibody-mediated rejection of transplanted kidneys. Transplant Proc. 2021;53(7):2206–2211.

12. Guarnera C, Bramanti P, Mazzon E. Alemtuzumab: a review of efficacy and risks in the treatment of relapsing remitting multiple sclerosis. Ther Clin Risk Manag. 2017;13:871–879.
13. Bank JR, Heidt S, Moes DJ, et al. Alemtuzumab induction and delayed acute rejection in steroid-free simultaneous pancreas-kidney transplant recipients. Transplant Direct. 2017;3(1):e124.
14. Willicombe M, Goodall D, McLean AG, et al. Alemtuzumab dose adjusted for body weight is associated with earlier lymphocyte repletion and less infective episodes in the first year post renal transplantation - a retrospective study. Transpl Int. 2017;30 (11):1110–1118.
15. Guthoff M, Berger K, Althaus K, et al. Low-dose alemtuzumab induction in a tailored immunosuppression protocol for sensitized kidney transplant recipients. BMC Nephrol. 2020;21(1):178.
16. Willemsen L, Jol-van der Zijde CM, Admiraal R, et al. Impact of serotherapy on immune reconstitution and survival outcomes after stem cell transplantations in children: thymoglobulin versus alemtuzumab. Biol Blood Marrow Transplant. 2015;21(3):473–482.
17. Pavlasova G, Mraz M. The regulation and function of CD20: an "enigma" of B-cell biology and targeted therapy. Haematologica. 2020;105(6):1494–1506.
18. Delate T, Hansen ML, Gutierrez AC, et al. Indications for rituximab use in an integrated health care delivery system. J Manag Care Spec Pharm. 2020;267:832–838
19. Schmitz R, Fitch ZW, Schroder PM, et al. B cells in transplant tolerance and rejection: friends or foes? Transpl Int. 2020;33(1):30–40.
20. Laws LH, Parker CE, Cherala G, et al. Inflammation causes resistance to anti-CD20-mediated B cell depletion. Am J Transplant. 2016;16 (11):3139–3149.
21. Macklin PS, Morris PJ, Knight SR. A systematic review of the use of rituximab for desensitization in renal transplantation. Transplantation. 2014;98(8):794–805.
22. Macklin PS, Morris PJ, Knight SR. A systematic review of the use of rituximab as induction therapy in renal transplantation. Transplantation Rev. 2015;29(2):103–108.
23. Macklin PS, Morris PJ, Knight SR. A systematic review of the use of rituximab for the treatment of antibody-mediated renal transplant rejection. Transplant Rev (Orlando). 2017 Apr;31(2):87–95.
24. Moreso F, Crespo M, Ruiz JC, et al. Treatment of chronic antibody mediated rejection with intravenous immunoglobulins and rituximab: a multicenter, prospective, randomized, double-blind clinical trial. Am J Transplant. 2018;18(4):927–935.
25. Shiu KY, Stringer D, McLaughlin L, et al. Effect of optimized immunosuppression (including rituximab) on anti-donor alloresponses in patients with chronically rejecting renal allografts. Front Immunol. 2020;11:79.
26. Sautenet B, Blancho G, Büchler M, et al. One-year results of the effects of rituximab on acute antibody-mediated rejection in renal transplantation: RITUX ERAH, a multicenter double-blind randomized placebo-controlled trial. Transplantation. 2016;100(2):391–9.
    - **High quality, but underpowered RCT which showed no additional effect of rituximab as anti-rejection agent.**
27. Bailly E, Ville S, Blancho G, et al. An extension of the RITUX-ERAH study, multicenter randomized clinical trial comparing rituximab to placebo in acute antibody-mediated rejection after renal transplantation. Transpl Int. 2020;33(7):786–795.
28. Nunes AT, Annunziata CM. Proteasome inhibitors: structure and function. Semin Oncol. 2017 Dec;44(6):377–380.
29. Neubert K, Meister S, Moser K, et al. The proteasome inhibitor bortezomib depletes plasma cells and protects mice with lupus-like disease from nephritis. Nat Med. 2008;14(7):748–755.
30. Perry DK, Burns JM, Pollinger HS, et al. Proteasome inhibition causes apoptosis of normal human plasma cells preventing alloantibody production. Am J Transplant. 2009;9(1):201–209.
31. Choi AY, Manook M, Olaso D, et al. Emerging new approaches in desensitization: targeted therapies for HLA sensitization. Front Immunol. 2021;12:694763.
32. Eskandary F, Regele H, Baumann L, et al. A randomized trial of bortezomib in late antibody-mediated kidney transplant rejection. J Am Soc Nephrol. 2018;29(2):591–605.
33. Joher N, Matignon M, Grimbert P. HLA desensitization in solid organ transplantation: anti-CD38 to across the immunological barriers. Front Immunol. 2021;12:688301.
34. Offidani M, Corvatta L, Morè S, et al. Daratumumab for the management of newly diagnosed and relapsed/refractory multiple myeloma: current and emerging treatments [Review]. Front Oncol. 2021;2021:10.
35. Kwun J, Matignon M, Manook M, et al. Daratumumab in sensitized kidney transplantation: potentials and limitations of experimental and clinical use. J Am Soc Nephrol. 2019;30 (7):1206–1219.
36. Doberer K, Kläger J, Gualdoni GA, et al. CD38 antibody daratumumab for the treatment of chronic active antibody-mediated kidney allograft rejection. Transplantation. 2021;105(2):451–457.
37. Jordan S, Vescio R, Toyoda M, et al. Daratumumab for treatment of antibody-mediated rejection in a kidney transplant recipient. Am J Transplant. 2019;19(S3). Abstract.
38. Spica D, Junker T, Dickenmann M, et al. Daratumumab for treatment of antibody-mediated rejection after ABO-incompatible kidney transplantation. Case Rep Nephrol Dial. 2019;9(3):149–157.
39. Raab MS, Engelhardt M, Blank A, et al. MOR202, a novel anti-CD38 monoclonal antibody, in patients with relapsed or refractory multiple myeloma: a first-in-human, multicentre, phase 1–2a trial. Lancet Haematol. 2020;7(5):e381–e394.
40. Mayer KA, Budde K, Halloran PF, et al. Safety, tolerability, and efficacy of monoclonal CD38 antibody felzartamab in late antibody-mediated renal allograft rejection: study protocol for a phase 2 trial. Trials. 2022;23(1):270.
41. Frampton JE. Isatuximab: a review of its use in multiple myeloma. Target Oncol. 2021;16(5):675–686.
42. Mackay F, Schneider P. Cracking the BAFF code. Nat Rev Immunol. 2009 Jul;9(7):491–502.
43. Oren DA, Li Y, Volovik Y, et al. Structural basis of BLyS receptor recognition. Nat Struct Biol. 2002;9(4):288–292.
44. Schiemann B, Gommerman JL, Vora K, et al. An essential role for BAFF in the normal development of B cells through a BCMA-independent pathway. Science. 2001;293(5537):2111–2114.
45. Gross JA, Johnston J, Mudri S, et al. TACI and BCMA are receptors for a TNF homologue implicated in B-cell autoimmune disease. Nature. 2000;404(6781):995–999.
46. Schneider P, MacKay F, Steiner V, et al. BAFF, a novel ligand of the tumor necrosis factor family, stimulates B cell growth. J Exp Med. 1999;189(11):1747–1756.
47. Banham G, Prezzi D, Harford S, et al. Elevated pretransplantation soluble BAFF is associated with an increased risk of acute antibody-mediated rejection. Transplantation. 2013;96(4):413–420.
48. Wasowska BA. Mechanisms involved in antibody- and complement-mediated allograft rejection. Immunol Res. 2010 Jul;47(1–3):25–44.
49. Thibault-Espitia A, Foucher Y, Danger R, et al. BAFF and BAFF-R levels are associated with risk of long-term kidney graft dysfunction and development of donor-specific antibodies. Am J Transplant. 2012;12(10):2754–2762.
50. Schlößer HA, Thelen M, Dieplinger G, et al. Prospective analyses of circulating B cell subsets in ABO-compatible and ABO-incompatible kidney transplant recipients. Am J Transplant. 2017;17(2):542–550.
51. Navarra SV, Guzmán RM, Gallacher AE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet. 2011;377 (9767):721–731.
52. Steri M, Orrù V, Idda ML, et al. Overexpression of the cytokine BAFF and autoimmunity risk. N Engl J Med. 2017;376(17):1615–1626.
53. Bath NM, Ding X, Wilson NA, et al. Desensitization and treatment with April/BLyS blockade in rodent kidney transplant model. PLoS One. 2019;14(2):e0211865.
54. Kwun J, Page E, Hong JJ, et al. Neutralizing BAFF/April with atacicept prevents early DSA formation and AMR development in T cell depletion induced nonhuman primate AMR model. Am J Transplant. 2015;15(3):815–822.

55. Wilson NA, Bath NM, Verhoven BM, et al. April/BLyS blockade reduces donor-specific antibodies in allosensitized mice. Transplantation. 2019;103(7):1372–1384.
56. Mujtaba MA, Komocsar WJ, Nantz E, et al. Effect of treatment with tabalumab, a B cell-activating factor inhibitor, on highly sensitized patients with end-stage renal disease awaiting transplantation. Am J Transplant. 2016;16(4):1266–1275.
57. Agarwal D, Luning Prak ET, Bharani T, et al. BLyS neutralization results in selective anti-HLA alloantibody depletion without successful desensitization. Transpl Immunol. 2021;69:101465.
58. Banham GD, Flint SM, Torpey N, et al. Belimumab in kidney transplantation: an experimental medicine, randomised, placebo-controlled phase 2 trial. Lancet. 2018;391(10140):2619–2630.
- **High quality, but underpowered RCT which showed potential beneficial effects on humoral alloimmunity of belimumab immunosuppressive therapy.**
59. Miller CL, Madsen JC. IL-6 directed therapy in transplantation. Curr Transplant Rep. 2021 Jun;3:1–14.
60. Cordoba F, Wieczorek G, Audet M, et al. A novel, blocking, Fc-silent anti-CD40 monoclonal antibody prolongs nonhuman primate renal allograft survival in the absence of B cell depletion. Am J Transplant. 2015;15(11):2825–2836.
61. van Kooten C, Banchereau J. CD40-CD40 ligand. J Leukoc Biol. 2000 Jan;67(1):2–17.
62. Graham JP, Arcipowski KM, Bishop GA. Differential B-lymphocyte regulation by CD40 and its viral mimic, latent membrane protein 1. Immunol Rev. 2010 Sep;237(1):226–248.
63. Sayegh MH, Turka LA. The role of T-cell costimulatory activation pathways in transplant rejection. N Engl J Med. 1998;338(25):1813–1821.
64. Armitage RJ, Fanslow WC, Strockbine L, et al. Molecular and biological characterization of a murine ligand for CD40. Nature. 1992;357(6373):80–82.
65. Hollenbaugh D, Grosmaire LS, Kullas CD, et al. The human T cell antigen gp39, a member of the TNF gene family, is a ligand for the CD40 receptor: expression of a soluble form of gp39 with B cell co-stimulatory activity. Embo J. 1992;11(12):4313–4321.
66. Foy TM, Laman JD, Ledbetter JA, et al. gp39-CD40 interactions are essential for germinal center formation and the development of B cell memory. J Exp Med. 1994;180(1):157–163.
67. Kawabe T, Naka T, Yoshida K, et al. The immune responses in CD40-deficient mice: impaired immunoglobulin class switching and germinal center formation. Immunity. 1994;1(3):167–178.
68. Quezada SA, Jarvinen LZ, Lind EF, et al. CD40/CD154 interactions at the interface of tolerance and immunity. Annu Rev Immunol. 2004;22(1):307–328.
69. Alderson MR, Armitage RJ, Tough TW, et al. CD40 expression by human monocytes: regulation by cytokines and activation of monocytes by the ligand for CD40. J Exp Med. 1993;178(2):669–674.
70. Caux C, Massacrier C, Vanbervliet B, et al. Activation of human dendritic cells through CD40 cross-linking. J Exp Med. 1994;180(4):1263–1272.
71. Fisher BA, Szanto A, W-F N, et al. Assessment of the anti-CD40 antibody iscalimab in patients with primary Sjögren's syndrome: a multicentre, randomised, double-blind, placebo-controlled, proof-of-concept study. Lancet Rheumatol. 2020;2(3):e142–e152.
72. Mauri C, Mars LT, Londei M. Therapeutic activity of agonistic monoclonal antibodies against CD40 in a chronic autoimmune inflammatory process. Nat Med. 2000 Jun;6(6):673–679.
73. Espié P, He Y, Koo P, et al. First-in-human clinical trial to assess pharmacokinetics, pharmacodynamics, safety, and tolerability of iscalimab, an anti-CD40 monoclonal antibody. Am J Transplant. 2020;20(2):463–473.
74. Pearson TC, Trambley J, Odom K, et al. Anti-CD40 therapy extends renal allograft survival in rhesus macaques. Transplantation. 2002;74(7):933–940.
75. Schuler W, Bigaud M, Brinkmann V, et al. Efficacy and safety of ABI793, a novel human anti-human CD154 monoclonal antibody, in cynomolgus monkey renal allotransplantation. Transplantation. 2004;77(5):717–726.
76. Kanmaz T, Fechner JJ Jr., Torrealba J, et al. Monotherapy with the novel human anti-CD154 monoclonal antibody ABI793 in rhesus monkey renal transplantation model. Transplantation. 2004;77(6):914–920.
77. Imai A, Suzuki T, Sugitani A, et al. A novel fully human anti-CD40 monoclonal antibody, 4D11, for kidney transplantation in cynomolgus monkeys. Transplantation. 2007;84(8):1020–1028.
78. van der Zwan M, Hesselink DA, van den Hoogen MWF, et al. Costimulation blockade in kidney transplant recipients. Drugs. 2020;80(1):33–46.
79. Ulrich P, Flandre T, Espie P, et al. Nonclinical safety assessment of CFZ533, a Fc-silent anti-CD40 antibody, in cynomolgus monkeys. Toxicol Sci. 2018;166(1):192–202.
80. Ristov J, Espie P, Ulrich P, et al. Characterization of the in vitro and in vivo properties of CFZ533, a blocking and non-depleting anti-CD40 monoclonal antibody. Am J Transplant. 2018;18(12):2895–2904.
81. Kirk AD, Burkly LC, Batty DS, et al. Treatment with humanized monoclonal antibody against CD154 prevents acute renal allograft rejection in nonhuman primates. Nat Med. 1999;5(6):686–693.
82. Farkash EA. CNI-Free Therapy with Iscalimab (anti-CD40 mAb) preserves allograft histology compared to standard of care after kidney transplantation; 2019. [cited 2022 Apr 05]. Available from: https://atcmeetingabstracts.com/abstract/cni-free-therapy-with-iscalimab-anti-cd40-mab-preserves-allograft-histology-compared-to-standard-of-care-after-kidney-transplantation/
83. Nashan. CFZ533, a new anti-CD40 mAB demonstrates comparable efficacy and better renal function versus tacrolimus in De-Novo CNI-free kidney transplantation: American Transplant Congress; 2018 [updated 06-05-2018; cited 2022 05-04-2022]. Available from: https://atcmeetingabstracts.com/abstract/cfz533-a-new-anti-cd40-mab-demonstrates-comparable-efficacy-and-better-renal-function-versus-tacrolimus-in-de-novo-cni-free-kidney-transplantation/
84. Novartis announces discontinuation of CIRRUS-1 study of CFZ533 (iscalimab) in kidney transplant patients: novartis AG; 2021. [updated 03-09-2021; cited 2022 Feb 02]. Available from: https://www.novartis.com/news/novartis-announces-discontinuation-cirrus-1-study-cfz533-iscalimab-kidney-transplant-patients
85. Kim I, Wu G, Chai NN, et al. Anti-interleukin 6 receptor antibodies attenuate antibody recall responses in a mouse model of allosensitization. Transplantation. 2014;98(12):1262–1270.
86. Wu G, Chai N, Kim I, et al. Monoclonal anti-interleukin-6 receptor antibody attenuates donor-specific antibody responses in a mouse model of allosensitization. Transpl Immunol. 2013;28(2–3):138–143.
87. Liang Y, Christopher K, Finn PW, et al. Graft produced interleukin-6 functions as a danger signal and promotes rejection after transplantation. Transplantation. 2007;84(6):771–777.
88. Sheppard M, Laskou F, Stapleton PP, et al. Tocilizumab (Actemra). Hum Vaccin Immunother. 2017;13(9):1972–1988.
89. WHO. Therapeutics and COVID-19: living guideline. World Health Org. 2021. [cited 2021 Oct 18]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.3
90. Choi J, Aubert O, Vo A, et al. 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;17(9):2381–2389.
91. Lavacca A, Presta R, Gai C, et al. 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;34(8):e13908.
92. Massat M, Congy-Jolivet N, Hebral A-L, et al. 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;21(4):1641–1649.
93. Mease PJ, Gottlieb AB, Berman A, et al. The efficacy and safety of clazakizumab, an anti-interleukin-6 monoclonal antibody, in

a phase IIb study of adults with active psoriatic arthritis. Arthritis Rheumatol. 2016;68(9):2163–2173.
94. Weinblatt ME, Mease P, Mysler E, et al. The efficacy and safety of subcutaneous clazakizumab in patients with moderate-to-severe rheumatoid arthritis and an inadequate response to methotrexate: results from a multinational, phase IIb, randomized, double-blind, placebo/active-controlled, dose-ranging study. Arthritis Rheumatol. 2015;67(10):2591–2600.
95. Doberer K, Duerr M, Halloran PF, et al. A randomized clinical trial of anti-IL-6 antibody clazakizumab in late antibody-mediated kidney transplant rejection. J Am Soc Nephrol. 2021;32(3):708–722.
• **High quality, but small RCT which showed promising results of clazakizumab on ABMR activity and progression.**
96. 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.
97. Nandakumar KS, Johansson BP, Björck L, et al. Blocking of experimental arthritis by cleavage of IgG antibodies in vivo. Arthritis Rheum. 2007;56(10):3253–3260.
98. Johansson BP, Shannon O, Björck L. IdeS: a bacterial proteolytic enzyme with therapeutic potential. PLoS One. 2008;3(2):e1692.
99. Ryan MH, Petrone D, Nemeth JF, et al. Proteolysis of purified IgGs by human and bacterial enzymes in vitro and the detection of specific proteolytic fragments of endogenous IgG in rheumatoid synovial fluid. Mol Immunol. 2008;45(7):1837–1846.
100. Yang R, Otten MA, Hellmark T, et al. Successful treatment of experimental glomerulonephritis with IdeS and EndoS, IgG-degrading streptococcal enzymes. Nephrol Dial Transplant. 2010;25(8):2479–2486.
101. Tradtrantip L, Asavapanumas N, Verkman AS. Therapeutic cleavage of anti-aquaporin-4 autoantibody in neuromyelitis optica by an IgG-selective proteinase. Mol Pharmacol. 2013 Jun;83(6):1268–1275.
102. von Pawel-Rammingen U, Johansson BP, Björck L. IdeS, a novel streptococcal cysteine proteinase with unique specificity for immunoglobulin G. Embo J. 2002;21(7):1607–1615.
103. Vincents B, von Pawel-Rammingen U, Björck L, et al. Enzymatic characterization of the streptococcal endopeptidase, IdeS, reveals that it is a cysteine protease with strict specificity for IgG cleavage due to exosite binding. Biochemistry. 2004;43(49):15540–15549.
104. Wenig K, Chatwell L, von Pawel-Rammingen U, et al. Structure of the streptococcal endopeptidase IdeS, a cysteine proteinase with strict specificity for IgG. Proc Natl Acad Sci U S A. 2004;101(50):17371–17376.
105. Akiyoshi T, Hirohashi T, Alessandrini A, et al. Role of complement and NK cells in antibody mediated rejection. Hum Immunol. 2012;73(12):1226–1232.
106. Thomas KA, Valenzuela NM, Reed EF. The perfect storm: HLA antibodies, complement, FcγRs, and endothelium in transplant rejection. Trends Mol Med. 2015 May;21(5):319–329.
107. Ge S, Chu M, Choi J, et al. Imlifidase inhibits HLA antibody-mediated NK cell activation and antibody-dependent cell-mediated cytotoxicity (ADCC) In Vitro. Transplantation. 2020;104(8):1574–1579.
108. Winstedt L, Järnum S, Nordahl EA, et al. Complete removal of extracellular IgG antibodies in a randomized dose-escalation phase I study with the bacterial enzyme IdeS–A novel therapeutic opportunity. PLoS One. 2015;10(7):e0132011.
109. Lorant T, Bengtsson M, Eich T, et al. Safety, immunogenicity, pharmacokinetics, and efficacy of degradation of anti-HLA antibodies by IdeS (imlifidase) in chronic kidney disease patients. Am J Transplant. 2018;18(11):2752–2762.
• **Open-label ascending-dose study, which showed good biological effect and safety of imlifidase for antibody removal.**
110. Wahlberg J, Bengtsson M, Bergström C, et al. Impact of flow cytometry cross-matching results on the outcome of cadaveric kidney transplantation. Transplant Proc. 1994 Jun;26(3):1752–1753.
111. Järnum S, Bockermann R, Runström A, et al. The bacterial enzyme IdeS cleaves the IgG-type of B cell receptor (BCR), abolishes BCR-mediated cell signaling, and inhibits Memory B cell activation. J Immunol. 2015;195(12):5592–5601.
112. Jordan SC, Legendre C, Desai NM, et al. Imlifidase desensitization in crossmatch-positive, highly sensitized kidney transplant recipients: results of an international phase 2 trial (Highdes). Transplantation. 2021;105(8):1808–1817.
113. Jordan SC, Lorant T, Choi J, et al. IgG endopeptidase in highly sensitized patients undergoing transplantation. N Engl J Med. 2017;377(5):442–453.
114. Lonze BE, Tatapudi VS, Weldon EP, et al. IdeS (Imlifidase): a novel agent that cleaves human IgG and permits successful kidney transplantation across high-strength donor-specific antibody. Ann Surg. 2018;268(3):488–496.
115. Nauser CL, Farrar CA, Sacks SH. Complement recognition pathways in renal transplantation. J Am Soc Nephrol. 2017;28(9):2571–2578.
116. Stites E, Le Quintrec M, Thurman JM. The complement system and antibody-mediated transplant rejection. J Immunol. 2015;195(12):5525–5531.
117. Eskandary F, Wahrmann M, Mühlbacher J, et al. Complement inhibition as potential new therapy for antibody-mediated rejection. Transplant Int. 2016;29(4):392–402.
118. Wahrmann M, Mühlbacher J, Marinova L, et al. Effect of the anti-C1s humanized antibody TNT009 and its parental mouse variant TNT003 on HLA antibody-induced complement activation-A preclinical in vitro study. Am J Transplant. 2017;17(9):2300–2311.
119. Rother RP, Arp J, Jiang J, et al. C5 blockade with conventional immunosuppression induces long-term graft survival in presensitized recipients. Am J Transplant. 2008;8(6):1129–1142.
120. Wang H, Arp J, Liu W, et al. Inhibition of terminal complement components in presensitized transplant recipients prevents antibody-mediated rejection leading to long-term graft survival and accommodation. J Immunol. 2007;179(7):4451–4463.
121. Wang H, Jiang J, Liu W, et al. Prevention of acute vascular rejection by a functionally blocking anti-C5 monoclonal antibody combined with cyclosporine. Transplantation. 2005;79(9):1121–1127.
122. Chrvala CA, Caspi A. C1 esterase inhibitor (human). P&T. 2010;35(7 Section 2):2–3.
123. Viglietti D, Gosset C, Loupy A, et al. C1 inhibitor in acute antibody-mediated rejection nonresponsive to conventional therapy in kidney transplant recipients: a pilot study. Am J Transplant. 2016;16(5):1596–603.
• **Prospective study which showed positive effects on allograft function after adding C1 inhibitor in ABMR.**
124. Montgomery RA, Orandi BJ, Racusen L, et al. Plasma-derived C1 esterase inhibitor for acute antibody-mediated rejection following kidney transplantation: results of a randomized double-blind placebo-controlled pilot study. Am J Transplant. 2016;16(12):3468–3478.
125. Dubois EA, Cohen AF. Eculizumab. Br J Clin Pharmacol. 2009;68(3):318–319.
126. Wijnsma KL, Ter Heine R, Moes DJAR, et al. Pharmacology, pharmacokinetics and pharmacodynamics of eculizumab, and possibilities for an individualized approach to eculizumab. Clin Pharmacokinet. 2019;58(7):859–874.
127. González-Roncero F, Suñer M, Bernal G, et al. Eculizumab treatment of acute antibody-mediated rejection in renal transplantation: case reports. Transplant Proc. 2012;44(9):2690–2694.
128. Ikeda T, Okumi M, Unagami K, et al. Two cases of kidney transplantation-associated thrombotic microangiopathy successfully treated with eculizumab. Nephrology (Carlton). 2016;21 Suppl 1:35–40.
129. Smith B, Kumar V, Mompoint-Williams D, et al. Dosing eculizumab for antibody-mediated rejection in kidney transplantation: a case report. Transplant Proc. 2016;48(9):3099–3105.
130. Tan EK, Bentall A, Dean PG, et al. Use of eculizumab for active antibody-mediated rejection that occurs early post-kidney transplantation: a consecutive series of 15 cases. Transplantation. 2019;103(11):2397–2404.

131. Wongsaroj P, Choi J, Vo A, et al. Outcomes of eculizumab (ANTI-C5) therapy for treatment of refractory antibody-mediated rejection (ABMR) and thrombotic microangiopathy (TMA) [abstract]. Am J Transplant. 2015;15(suppl 3).
132. Orandi BJ, Zachary AA, Dagher NN, et al. Eculizumab and splenectomy as salvage therapy for severe antibody-mediated rejection after HLA-incompatible kidney transplantation. Transplantation. 2014;98(8):857–863.
133. Kulkarni S, Kirkiles-Smith NC, Deng YH, et al. Eculizumab therapy for chronic antibody-mediated injury in kidney transplant recipients: a pilot randomized controlled trial. Am J Transplant. 2017;17(3):682–691.
134. Eskandary F, Jilma B, Mühlbacher J, et al. Anti-C1s monoclonal antibody BIVV009 in late antibody-mediated kidney allograft rejection-results from a first-in-patient phase 1 trial. Am J Transplant. 2018;18(4):916–926.
135. Hariharan S, Israni AK, Danovitch G. Long-term survival after kidney transplantation. N Engl J Med. 2021;385(8):729–743.
136. Hullegie-Peelen DM, van der Zwan M, Clahsen-van Groningen MC, et al. Clinical and molecular profiling to develop a potential prediction model for the response to alemtuzumab therapy for acute kidney transplant rejection. Clin Pharmacol Ther. 2022;111(5):1155–1164.
137. Kim MY, Brennan DC. Therapies for Chronic Allograft Rejection. Front Pharmacol. 2021;12:651222.
138. Lonze BE. A review of imlifidase in solid organ transplantation. Expert Opin Biol Ther. 2021 Feb;21(2):135–143.
139. Lefaucheur C, Loupy A, Vernerey D, et al. Antibody-mediated vascular rejection of kidney allografts: a population-based study. Lancet. 2013;381(9863):313–319.
140. Lai X, Zheng X, Mathew JM, et al. Tackling chronic kidney transplant rejection: challenges and promises [Mini review]. Front Immunol. 2021;2021:12.
141. Stegall MD, Smith B, Bentall A, et al. The need for novel trial designs, master protocols, and research consortia in transplantation. Clin Transplant. 2020;34(1):e13759.
•• **Important narrative which clearly addresses the limitations of current research practice in transplantation medicine and provides suggestions of overcoming these issues with novel trial designs and research consortia.**
142. Anwar IJ, Srinivas TR, Gao Q, et al. Shifting clinical trial endpoints in kidney transplantation: the rise of composite endpoints and machine learning to refine prognostication. Transplantation. 2022;106(8):1558–1564.
143. Hilbrands L, Budde K, Bellini MI, et al. Allograft function as endpoint for clinical trials in kidney transplantation. Transpl Int. 2022;35:10139.