Antibody-mediated rejection (ABMR) represents a major cause of late allograft loss in solid organ transplantation worldwide. This process is driven by donor-specific antibodies (DSA), which develop either de-novo or, in sensitized patients, are preformed at the time of transplantation. Effective targeting of ABMR has been hampered by a lack of robust randomized controlled trials (RCT), required for the regulatory approval of new therapeutics. In this review, we discuss the evidence behind the present “standard” of care and recent progress in the development of novel strategies targeting different aspects of the alloimmune humoral response, including naïve and memory B-cell activation, the germinal centre reaction, plasma cell survival and antibody effector functions. In particular, we focus on co-stimulation blockade and its combination with next-generation proteasome inhibitors, new depleting monoclonal antibodies (anti-CD19, anti-BCMA, anti-CD38, anti-CD138), interleukin-6 blockade, complement inhibition and DSA degradation. These treatment modalities, when used in the appropriate clinical context and combination, have the potential to finally improve long-term allograft survival.

**KEYWORDS**
alloantibody, antibody-mediated rejection, B cells, germinal centre, plasma cells, transplantation

This review was invited and edited by the Reviews Editor Katharina Fleischhauer.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2020 The Authors. HLA: Immune Response Genetics published by John Wiley & Sons Ltd
process can be hyperacute (minutes post-transplant) in the context of pre-formed DSAs (e.g., in AB0 blood group incompatibility), acute (the first 6 months post-transplant) or chronic (months to years post-transplant). Both acute and chronic ABMR may be mediated by memory responses in sensitized recipients, or by de-novo DSA generation in non-sensitized patients, for example, because of non-adherence and/or early T-cell mediated rejection. 

2 | B CELL BIOLOGY IN ALLOIMMUNE RESPONSES

De-novo complement-binding DSAs arise following activation of naïve B cells and their subsequent maturation into alloantigen-specific memory B cells and antibody-secreting cells (ASCs), including both short-lived plasmablasts and long-lived plasma cells. This process begins when alloantigen is delivered into secondary lymphoid organs (Figure 1). Donor-specific naïve B cells recognize antigen with their B-cell receptor (BCR), generating an activating signal (signal 1) that is modulated by BCR co-receptors such as activating CR2/CD21 or inhibitory CD22, CD72 and FcRRIIB. Activated B cells migrate from the follicle to the border of the T-cell zone, where they present alloantigen peptides in the context of MHCII to cognate T cells, and receive an activating signal through CD40/CD40L in return (signal 2). Alloreactive helper T cells are generated when engaging cognate antigen-MHCII complex on the surface of activated

FIGURE 1 Alloimmune humoral response and previous alloantigenic experience. In non-sensitized patients, alloantigens released from damaged allograft tissue (e.g., during complement-mediated ischaemia-reperfusion injury, IRI) activate antigen-presenting cells (APC) and alloreactive naïve B cells (via BCR). Both cells present alloantigen epitopes on their surface MHCII to cognate T cells. APCs activate alloantigen-specific naïve CD4+ T cells, which then as helper T cells (Th) provide co-stimulatory (second) signal to activated B cells. These B cells can have two possible fates—either extrafollicular development into a short-lived plasmablast secreting early DSAs, or a GC reaction (de-novo sensitized patients). Aided by follicular helper T cell (Tfh) co-stimulation (via CD40/CD40L) and cytokines (IL-21), GC B cells undergo somatic hypermutation (+/− class-switch recombination) leading to higher BCR affinity, and ultimately differentiate into either memory B cells or plasma cells (sensitized patients). Plasma cells migrate into their niches (e.g., bone marrow) where they receive essential survival signals from several other cell types, including stromal cells and granulocytes. DSAs generated by plasma cells bind to graft endothelium and trigger tissue-damaging complement activation and FcR-mediated cytotoxicity. Upon alloantigen encounter, memory B cells can either refine their BCR affinity through another GC reaction, or differentiate directly into plasma cells.
antigen-presenting cells with a co-stimulatory signal (CD28).

Within 5 days, activated alloreactive T and B cells clonally expand, with B cells differentiating into short-lived (extrafollicular) plasmablasts, or returning to the lymphoid follicle to establish a new germinal centre (GC). Although extrafollicular plasmablasts provide the first wave of antibodies, these are less mutated and with lower affinity. The GC is compartmentalized into a dark (DZ) and light (LZ) zone. The DZ contains intensely proliferating activated B cells (centroblasts), which undergo somatic hypermutation (SHM), changing the antigen-binding region of antibodies to improve affinity, a process known as affinity maturation. When SHM is finished, centroblasts become centrocytes and transit to the LZ. The LZ contains follicular helper and follicular regulatory T cells that orchestrate the positive selection of centrocytes via CD40-CD40L interaction and cytokines such as IL-4 and IL-21. Only centrocytes that find cognate T-cell help survive and either commit to another round of proliferation and SHM within the DZ, or exit the GC giving rise to long-lived memory B cells or plasma cells. Re-arrangement of heavy chain loci also enables mature B cells to express antibodies of non-IgM isotypes that differ in their effector functions.

Long-lived plasma cells migrate from their original GCs into specific niches enabling their survival and sustained antibody production (Figure 1). Bone marrow plasma cell niches consist of CXCL12+VCAM1+ stromal cells and a variety of hematopoietic cells that secrete survival factors such as APRIL, BAFF, and IL-6. More recently, plasma cell niches have also been observed in both inflamed and non-inflamed non-lymphoid organs (NLOs). Memory B cells recirculate in a similar manner to their naïve counterparts, but can become temporarily NLO-resident after encountering cognate antigen. In contrast to memory B cells, plasma cells lack CD20, with implications for their depletion. A recall alloantibody response in sensitized patients is initiated when alloreactive memory B cells are re-exposed to their cognate antigen and either directly or indirectly (via new GC reaction) differentiate into ASCs. Generally, memory B cells with high-affinity BCRs differentiate directly into ASCs while others enter GCs for further affinity maturation.

B cells may also participate in alloimmune responses via antibody-independent functions such as antigen presentation, production of pro-inflammatory cytokines (including TNFα, IL-6, and GM-CSF) and immune regulation via contact-dependent and -independent mechanisms (e.g., IL-10 or TGFβ secretion). Indeed, regulatory B cells have been implicated in the maintenance of transplant tolerance by several studies. Clatworthy et al reported a higher incidence of acute rejection in kidney transplant patients who received anti-CD20 therapy at induction compared to controls. Numerous groups have described a B-cell signature in peripheral blood (including an enrichment of transitional or naïve B cells) in operationally tolerant (OT) or rejection-free patients. The extent to which this finding reflects differences in maintenance immunosuppression has been questioned, but B cell genes remain in the consensus gene expression signature of OT, even after adjusting for differing immunosuppression.

3 PRINCIPLES OF B CELL TARGETING IN NON-SENSITIZED VERSUS SENSITIZED PATIENTS

The therapeutic goal in non-sensitized patients is the prevention of naïve alloreactive B cell activation, as well as subsequent plasmablast formation and GC response (Figure 1). In sensitized patients, the treatment target also includes alloreactive memory B cells and plasma cells. Notably, on-going exposure to alloantigen results in continued alloreactive B-cell activation with further refinement of existing DSA affinity in GCs and the generation of new DSA by bystander B cell activation and via epitope spreading as the allograft is progressively damaged (chronic ABMR). Hence, there is substantial overlap in the therapeutic targets in acute vs chronic ABMR.

Ideally, alloreactive B cells should be targeted selectively in antigen-specific manner, while sparing regulatory B cells and pathogen-protective B cells. Therapeutic expansion of regulatory B cells represents a promising indirect approach to this conundrum. Unfortunately, current treatments generically target B cells regardless of their function or specificity, with inevitable undesirable side effects.

4 SUMMARY OF HISTORIC AND MOST RECENT STRATEGIES

The lack of robust evidence for a standard of care in ABMR prompted The Transplantation Society to assemble an international working group to define consensus treatment recommendations, mostly based on expert opinion rather than evidence. This expert group suggested the combination of plasmapheresis (PLEX), IVIG and steroids for early (<30 days post-transplant) and late active AMBR in patients with preformed DSAs, and for chronic ABMR, optimization of maintenance immunotherapy (e.g., target trough tacrolimus level > 5 ng/mL). Adjunctive therapies such as rituximab, complement inhibition (e.g., eculizumab or C1 esterase inhibitors) or protease
inhibitors may be considered in patients at high risk of rapid allograft loss.\textsuperscript{43} In AMBR with \textit{de-novo} DSA, provision of sufficient maintenance immunosuppression was recommended along with concomitant treatment of TCMR (e.g., with anti-thymocyte globulin). The evidence for additional therapy in this context was viewed as inadequate.\textsuperscript{43}

The rationale for combining IVIG with PLEX is based not only on its ability to facilitate the removal of DSAs (by enhancing IgG turnover when occupying neonatal Fc receptors)\textsuperscript{44} but also on the modulatory effects of IVIG on immune cells (e.g., via binding surface inhibitory receptors such as Fc\textgamma{}RIIb or CD22).\textsuperscript{45} Despite varying protocols for these two treatment modalities, several studies have reported benefit for at least short-term outcomes in acute ABMR.\textsuperscript{46-49} There is a little convincing evidence of long-term benefit, possibly reflecting the limited effects of PLEX and IVIG on DSA-producing cells. Hence, B cell and plasma-cell depleting agents, such as rituximab or bortezomib, respectively, have been added to PLEX and IVIG.

Rituximab, a chimeric anti-CD20 depleting monoclonal antibody, has been successfully used for autoimmune and hematological conditions. However, in ABMR, a systematic review of rituximab utility could not draw any strong conclusions because of high heterogeneity and low power of available studies.\textsuperscript{50} Indeed, a recent multicentre RCT failed to show benefit for rituximab when added to standard of care in active ABMR and it was associated with more opportunistic infections.\textsuperscript{51} However, 8/19 patients in the control arm also received rituximab as “rescue therapy”, undermining any definitive conclusions. A similar outcome was reported in a Spanish multicentre RCT testing IVIG plus rituximab in chronic ABMR.\textsuperscript{52} Both studies were underpowered (N = 38 and N = 25, respectively) and weakened by a limited follow-up (up to 1 year).\textsuperscript{51,52} Two ongoing UK-based RTCs TAR:GET1 (NCT03994783) and MOT-AMR (NCT04496037) aiming to recruit 170 patients in total with a 4-year follow-up should enable robust conclusions. As noted previously, non-selective B-cell depletion with rituximab in ABMR may have counterproductive effects on regulatory B cells.

Bortezomib, a first-generation proteasome inhibitor (PI), has been used both in the context of acute ABMR and desensitization, with variable success. In uncontrolled studies, bortezomib combined with standard treatment modalities was associated with higher response in early compared with late acute ABMR (87.5% vs 53.8%; \textit{P} = .13), suggesting higher sensitivity of newly formed plasmablasts to PI therapy compared to long-lived niche-resident plasma cells.\textsuperscript{53} In a prospective iterative desensitization trial, bortezomib reduced HLA antibody levels in 38 out of 44 patients for up to 10 months.\textsuperscript{54} Although the reduction of immunodominant HLA antibodies was stronger with higher bortezomib dosing, this was limited by drug toxicity (mainly peripheral neuropathy).\textsuperscript{54,55} A similar desensitization trial with carfilzomib, a second-generation PI, showed a better safety profile, even at higher doses with a complete absence of neurotoxicity, and produced a more robust depletion of HLA antibodies both as monotherapy and in combination with PLEX.\textsuperscript{56} For late ABMR, a recently published RCT (BORTEJECT) comparing bortezomib monotherapy to placebo failed to show any impact on eGFR decline, DSA reduction or histological molecular signatures at 24 month follow-up, in spite of significant toxicity.\textsuperscript{57} However, the BORTEJECT study used only two cycles of bortezomib up to 3 months apart, and patient numbers were also relatively limited (only 18 patients completed both cycles of bortezomib).\textsuperscript{57}

\section*{5 \ NOVEL STRATEGIES TO TARGET B CELL ACTIVATION/GC RESPONSE}

As outlined previously, naïve alloimmune B cell activation is typically dependent on two signals - engagement of the BCR and its co-receptors (signal 1) and co-stimulation from helper T cells (signal 2), which is also essential for a successful GC reaction (Figure 2).

Co-stimulation blockade currently represents one of the most promising interventions in kidney transplantation. 7-year follow-up data from the phase 3 BENEFIT and BENEFIT-EXT RCTs showed better graft survival and lower \textit{de-novo} DSA formation in patients treated with belatacept (CTLA4-Ig fusion protein blocking CD28-CD80/86 co-stimulation) when compared with cyclosporine.\textsuperscript{58,59} Leibler et al showed that belatacept not only interferes with B cell—Tfh cell crosstalk but also has direct B-cell intrinsic (i.e., T cell-independent) effects, such as reduced plasmablast differentiation, BLIMP-1 expression and STAT3 activation.\textsuperscript{60} Subsequently, in the BELACOR trial, an open, multicentre, prospective pilot study with a retrospective control group, Leiber et al assessed kidney transplant outcomes and susceptibility to ABMR in patients with preformed DSAs treated with maintenance belatacept, or a CNI.\textsuperscript{61} The belatacept group (N = 49) had 0% ABMR incidence at 12 months compared to 5.81% (\textit{P} = .12) in controls (N = 73) and a significantly higher proportion of belatacept-treated patients had complete disappearance of class II DSAs (81\% vs 42\%, \textit{P} = .001). However, patients on belatacept had a more than four times higher frequency of acute TCMR (\textit{P} = .003) but similar median eGFR at 12 months.\textsuperscript{61} A significantly higher rate of acute TCMR in belatacept-treated patients was also reported in the BENEFIT trial and this likely reflects its limited action on
cytotoxic CD8+ T cells that lack CD28 expression. Hence, the combination of belatacept with a CNI, for early post-transplant period, has been suggested.

Co-stimulation blockade has also been combined with PI for desensitization. Kwun et al showed in a non-human primate model that although bortezomib monotherapy significantly depleted bone-marrow plasma cells, it failed to reduce DSAs and induced a rapid compensatory GC response in sensitized animals. In contrast, co-stimulatory blockade efficiently suppressed the GC reaction and de-novo DSA production in non-human primates. Hence, the combination of PI with belatacept and anti-CD40 mAb was tested in the same desensitization model and achieved both a significant reduction in pre-transplant DSA and prolonged graft survival, without ABMR. To reduce cumulative drug toxicity and the overall immunosuppressive burden, a follow-up study treated animals with a second-generation PI, carfilzomib, in combination with belatacept only. This produced similar graft survival but reduced viral infections. Aside from belatacept, anti-CD40 and anti-CD154 (ie, CD40L) monoclonal antibodies, alternative agents to target the immunological synapse (e.g., OX40 or ICOS) are yet to be tested in the context of solid organ transplantation.

The GC reaction is modulated by a plethora of locally secreted cytokines, including IL-21, IL-6, or B-cell survival factor BAFF. In mice, BAFF-deficiency was associated with prolonged heart allograft survival and BAFF blockade in combination with rapamycin induction resulted in long-term survival of islet allografts. We, and others, reported that elevated circulating BAFF was associated with both the development of DSA and an increased risk of ABMR in human kidney recipients. Subsequently, we showed in an experimental medicine, phase 2 RCT (N = 28) that belimumab (anti-BAFF mAb) added to the standard immunosuppression in the first 6 months post-kidney transplantation in non-sensitized recipients did not increase infection risk while reducing activated memory B cells and circulating plasmablasts, inhibiting de-novo IgG formation and increasing circulating regulatory B cells. The surrogate end-points in this study also raised the possibility that belimumab may have utility in sensitized patients and provided a solid foundation for a larger RCT in the future.

Several drugs have been developed to block B cell activation by disrupting BCR or its co-receptors, the signaling of which is essential for triggering memory B-cell recall responses. Imlifidase (IgG-degrading enzyme of Streptococcus pyogenes, IdeS), a highly specific protease cleaving human IgG at its hinge region, has been primarily trialed for DSAs degradation as part of desensitization protocols (see below). However, Järnum et al showed ex vivo that IdeS also cleaves BCRs on the surface of human memory B cells, temporarily inhibiting their activation and
subsequent differentiation into plasma cells.\textsuperscript{74} Epratuzumab, a humanized monoclonal antibody against CD22, an inhibitory BCR co-receptor, is able to terminate BCR activating signals, including via the recruitment of phosphatases and down-regulation of CD19.\textsuperscript{75,76} Although it does not induce complement- (CDC) or cellular-dependent cytotoxicity (ADCC), it leads to a significant reduction in peripheral B cells (in particular, naïve and transitional).\textsuperscript{77,78} A recent meta-analysis suggested epratuzumab as a safe treatment option for moderate-to-severe SLE, but its utility in solid organ transplantation is yet to be explored.\textsuperscript{79} Obexelimab (XmAb5871), an anti-CD19 humanized antibody that simultaneously engages FcγRIIB, is another promising agent harnessing inhibitory BCR co-receptor that could be of benefit in transplantation.\textsuperscript{80} Recent trials in autoimmune conditions such as SLE, rheumatoid arthritis and IgG4 disease suggest potential utility in reducing humoral responses.\textsuperscript{81-83}

The ultimate method to prevent activation of alloreactive naïve or memory B cells is their depletion, which has been traditionally achieved through the administration of polyclonal anti-thymocyte globulin (ATG), monoclonal alemtuzumab (anti-CD52, CAMPATH-1H) or rituximab (anti-CD20). One reason that rituximab has shown no substantial benefit in ABMR and desensitization (aside from under-powered RCTs) may be that B cell depletion is incomplete, particular within tissues.\textsuperscript{84,85} Obinutuzumab, a glycoengineered type 2 anti-CD20 humanized monoclonal antibody, was developed to supersede rituximab by enhancing the capacity for ADCC and B cell depletion, including in secondary lymphoid organs.\textsuperscript{86,87} NOBILITY, a phase 2 RCT trial, has recently showed efficacy and safety of obinutuzumab in proliferative lupus nephritis, which contrasts with the earlier results of EXPLORER and LUNAR trials that failed to show efficacy for rituximab in lupus.\textsuperscript{88-90} THEORY, a phase 1b open-label trial, showed good tolerability of obinutuzumab plus IVIG in highly sensitized patients with end-stage kidney disease and induced profound depletion of both circulating and lymph node B cells, but had limited effects on HLA antibodies.\textsuperscript{91} To extend B cell depletion to plasmablasts and potentially a substantial fraction of plasma cells, CD19 targeting therapies have been developed (Figure 3). In a phase 2/3 RCT, a humanized anti-CD19 monoclonal antibody, inebilizumab, significantly reduced autoantibodies and relapse rates in patients with neuromyelitis optica.\textsuperscript{92} Tolerability and safety of this drug is currently being evaluated in highly sensitized patients awaiting kidney transplantation (NCT04174677). Blinatumomab, a monoclonal CD19 bi-specific T-cell engager antibody capable of inducing cytolytic synapse between B cells and cytotoxic T cells has been used for acute lymphoblastic leukemia and may also have utility for B cell depletion in ABMR.\textsuperscript{93}

\textbf{FIGURE 3} Action sites of immunotherapeutics targeting plasma cells and alloantibody effector function. Left panel—numbers identify specific cellular/molecular target. Right panel—therapeutic agents for each cellular/molecular target.
chimeric antigen receptor (CAR) directed T cell therapy targeting CD19 represents potentially another attractive approach to B cell depletion in ABMR. Although it has revolutionized the treatment of B-cell malignancies, it is often associated with significant side-effects such as cytokine release syndrome and hypogammaglobulinaemia.94 Ultimately, a CAR could be designed to express a particular HLA antigen enabling selective binding to alloreactive B cells and their subsequent inhibition (by engaging Tregs) or death (via cytotoxic CD8+ T cells), while sparing bystander regulatory and protective B cells.95 Such a selective approach has been successfully applied to eliminate autoreactive B cells in experimental pemphigus.96

6 \ NOVEL STRATEGIES TO TARGET PLASMA CELLS

Current plasma cell therapies induce depletion either directly, by targeting surface molecules or proteasome activity, or indirectly, by disrupting their survival niches (Figure 3).

In addition to anti-CD19 antibodies, monoclonals directed against CD38, B-cell maturation antigen (BCMA) and CD138 have been also developed to deplete plasma cells. Daratumumab, a fully human anti-CD38 antibody, has shown treatment efficacy in multiple myeloma,97-99 eliminating plasma cells in bone marrow via CDC and ADCC, but it also reduced CD38+ regulatory T and B cells and myeloid-derived suppressor cells.100,101 This additional immuno-modulatory effect may limit its use in the context of ABMR or autoimmunity where induction of immune tolerance is desirable. Indeed, Kwun et al showed a significant DSA reduction and prolonged renal graft survival in sensitized rhesus macaques treated with daratumumab, but this was followed by a rebound in DSA and TCMR.102 Nevertheless, several dose-escalation studies are currently underway to test safety and efficacy of daratumumab (or chimeric mouse/human isatuximab) in sensitized patients awaiting kidney or heart transplantation (NCT04088903, NCT04204980, NCT04294459). Unlike CD38, BCMA is expressed only on late memory B cells and all plasma cells where it provides an essential survival signal after binding APRIL (and to a lesser extent BAFF).103 Currently, anti-BCMA targeting (including bispecific antibodies, CAR-T cells or antibody-drug conjugates) is driving a new era in the treatment of multiple myeloma with encouraging results from early phase trials and more than 70 other studies recruiting.104 Indatuximab ravtansine is an anti-CD138 antibody-drug conjugate that has showed promising results in inhibiting myeloma cell growth in relapsed or refractory disease.105 Targeting CD138 with a similar approach or using a bi-specific T cell engager is yet to be tested in solid organ transplantation.

As outlined already in previous chapters, PIs bortezomib and carfilzomib have been actively explored for desensitization strategies both in monotherapy and in combination with other modalities. Ixazomib is a new second-generation PI, that is, unlike its predecessors, administered orally and is currently being evaluated in IXADES phase 2 trial for its safety and efficacy in desensitization of kidney transplant candidates (NCT03213158). Apart from drug toxicity, PI therapy is also limited by the development of plasma-cell drug resistance through a compensatory overexpression of immunoproteasome, which is a specialized (structurally different) form of proteasome present in immune cells and inflamed tissues.106 Selective immunoproteasome inhibitors are an attractive alternative to traditional constitutive proteasome inhibitors because of their lower toxicity and additional immunomodulatory effects.107 Recently, Li et al showed that the selective immunoproteasome inhibitor ONX0914 prevented chronic allograft nephropathy in rats by eliminating plasma cells and reducing DSA. Interestingly, this inhibition did not only activate the unfolded protein response but also supressed plasma-cell survival factors in the bone marrow (e.g., IL-6 or APRIL).108,109

The plasma cell survival niche is a complex microenvironment providing essential cell-cell interactions (e.g., CXCR4-CXCL12) and secreted cytokines such as BAFF/APRIL and IL6). Plerixafor is a small-molecule reversible CXCR4 inhibitor that has been used for more than a decade as a bone-marrow stem cell mobilizer. Woodle et al recently reported preliminary data supporting plerixafor efficacy to mobilize plasma cells, leading to their apoptosis and enhanced effectiveness of bortezomib in highly sensitized patients.110,111 There has also been emerging interest in IL-6/IL-6 receptor blockade in ABMR. IL-6 is a pleiotropic cytokine that fuels various aspects of alloimmune humoral responses.112 IL-6 induces maturation of Tfh with subsequent differentiation of activated naïve B cells into plasma cells in the GC and also serves as a key survival factor for pre-existing long-lived DSA-producing cells.113-115 Moreover, in return, DSAs trigger IL-6 production in allograft endothelium, ultimately leading to obliterator vasculopathy and perpetuating the alloimmune reaction.116,117 Tocilizumab, a humanized anti-IL6 receptor-blocking antibody, provided a significant benefit in kidney graft survival at 6-years when given monthly to 65 patients with chronic refractory ABMR compared to a historic cohort of 39 controls receiving rituximab plus IVIG.118 Chandran et al reported the efficacy of tocilizumab in a prospective RCT to reduce subclinical kidney allograft inflammation while inducing circulating Tregs (N = 11 in both arms).119
Vo et al achieved a 50% transplant rate with tocilizumab, with no observed ABMR up to 6 months post-transplant in 10 patients unresponsive to standard desensitization protocols. While a larger RCT utilizing tocilizumab is still awaited, clazakizumab (anti-IL-6 IgG1 monoclonal antibody) is currently being tested in a multicentre placebo-controlled phase 3 RTC (IMAGINE) in chronic active ABMR (estimated completion in 2028, NCT03744910). This follows early-phase studies demonstrating safety and efficacy of clazakizumab to reduce DSAs and stabilize kidney allograft function. Finally, BAFF blockade was also trialed as monotherapy in sensitized patients but had no clinically meaningful efficacy. Kwon et al reported prevention of DSA formation and prolonged allograft survival in non-human primate model of ABMR treated with atacicept (a recombinant fusion protein containing soluble TACI receptor). However, interest in this treatment strategy has waned, after atacicept failed to show efficacy in several autoimmune conditions. APRIL/BAFF interact with three different receptors on plasma cells, and this requires consideration when attempting their blockade, which may necessitate combination with other anti-plasma cell therapies.

7 | NOVEL STRATEGIES TO TARGET ALLOANTIBODY EFFECOR FUNCTION

Alloantibody effector functions are derived from both their Fab (e.g., proliferation stimulus to allograft vasculature) and Fc region (complement activation and Fc-receptor-mediated modulation of immune cells activity, including phagocytosis and cytotoxicity) (Figure 3). Complement activation (predominantly via lectin and classical pathways) is a key player in allograft ischaemia-reperfusion injury (IRI) and ABMR. Recently, Cippa et al proposed a causal link between these two pathological states where IRI-driven tissue damage uncovers cryptic alloantigens and ultimately leads to alloreactive B-cell activation with de-novo DSAs production. Preventing IRI by therapeutic complement inhibition is being actively explored in solid organ transplantation. A phase 1/2 RCT (N = 70) reported a significant benefit of C1 esterase inhibitor (C1-INH) for 3.5-year allograft survival when given intraoperatively and 24 hours post-transplant. In contrast, a large multi-centre registration RCT (PROTECT, N = 288) did not meet its primary endpoint to justify perioperative administration of eculizumab (a C5 inhibitor) to prevent delayed graft function, although long-term follow data were not collected (NCT02145182). In a cohort of pediatric kidney transplant recipients, a single pre-transplant dose of eculizumab led to significantly better graft function up to 3 years later, but was associated with an unexpectedly high rate of early graft losses during a flu-like infection (all in non-vaccinated children).

Two small early-phase studies showed either histological or clinical improvement of kidney graft function 6 months after ABMR treatment with C1-INH either in addition to standard of care or in combination with IVIG, respectively. Two larger multicentre phase 3 RCTs testing C1-INH in acute ABMR are underway (NCT03221842, NCT02547220). Lefaucheur et al showed that ABMR driven by complement-binding DSAs had a specific histological and transcriptional signature and its incidence at 3 months could be reduced with prophylactic eculizumab, unlike AMBR in patients with non-complement binding DSAs. In parallel, Viglietti et al reported that the presence of complement-binding DSAs 3 months after standard ABMR treatment initiation (IVIG, PLEX and rituximab) was an independent predictor of poor allograft outcome, further justifying the role of complement blockade in AMBR treatment strategies. The efficacy and safety of eculizumab to prevent ABMR in sensitized kidney recipients was recently shown in an open-label single-arm phase 2 study (N = 80). A case series (N = 15) of early active ABMR treated with eculizumab plus PLEX as primary (rather than salvage) therapy also showed an impressive increase of median eGFR with no graft loss at minimum of 12-months follow-up. The development of complement-targeting therapies is a fast evolving field and there are many new agents, which will require rigorous testing in transplantation (e.g., ravulizumab or anti-C1s antibody BIVV009).

Although the current evidence suggests efficacy for complement inhibitors in the treatment of ABMR, combination with DSA-reducing strategies to mitigate other non-complement-related DSA effector functions will likely be required. Imlifidase (IdeS) cleaves IgG and eliminated all complement-binding DSAs (IgG only) within 1 hour of administration, with residual Fab fragments incapable of inducing CDC or ADCC. Two open-label phase 1/2 trials (in US and Sweden) reported successful HLA-incompatible kidney transplantation in 24 of 25 patients 4 to 6 hours after IdeS administration. In contrast to the Swedish group, the US patient cohort received IVIG plus rituximab 7 to 14 days after transplant, which prevented DSA rebound. Of note, imlifidase also cleaves IVIG or therapeutic monoclonal antibodies, the administration of which should therefore be delayed for at least for 5 days. Three cases of ABMR were reported in the Swedish cohort (N = 11) within a few weeks, and two in the US at 2 and 5 months. Allograft survival was 92% at 2 years, with only one new ABMR case despite several patients having high DSA.
Imlifidase (IdeS) is now approved by the European Medicine Agency (with accelerated FDA approval in process) for DSAs degradation in highly sensitized kidney transplant recipients. An open-label phase 2 RCT evaluating imlifidase for ABMR treatment in kidney transplantation is currently recruiting (NCT03897205).

8 | CONCLUSION

In recent years, there has been a considerable expansion of novel therapeutics (often repurposed from oncology or autoimmunity) that may target humoral alloimmune responses, now regarded as the leading cause of long-term allograft loss. Currently, rigorous evaluation of these agents in phase 3 RCTs is lacking, precluding regulatory approval. Innovative trial design, utilizing novel prognostic markers and surrogate end-points will be required to enable trials with a feasible size and duration to test these agents, providing hope that humoral alloimmunity will ultimately be better controlled.

ACKNOWLEDGMENTS

Ondrej Suchanek was funded by a Wellcome Clinical Training Fellowship (205250/Z/16/Z). Menna R. Clatworthy is supported by the National Institute of Health Research (NIHR) Cambridge Biomedical Research Centre, by a Medical Research Council New Investigator Research Grant (MR/N024907/1) and an NIHR Research Professorship (RP-2017-08-ST2-002). The Clatworthy Lab is also supported by the National Institute for Health Research Blood and Transplant Research Unit (NIHR BTRU) in Organ Donation and Transplantation at the University of Cambridge in collaboration with Newcastle University and in partnership with NHS Blood and Transplant (NHSBT). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, the Department of Health or NHSBT.

CONFLICT OF INTEREST

The authors have declared no conflicting interests.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

ORCID

Ondrej Suchanek https://orcid.org/0000-0003-1048-5251

REFERENCES

1. Hart A et al. OPTN/SRTR 2018 annual data report: kidney. *Am J Transplant*. 2020;20(Suppl s1):20-130.
2. Coemans M, Süssal C, Döhler B, et al. Analyses of the short- and long-term graft survival after kidney transplantation in Europe between 1986 and 2015. *Kidney Int*. 2018;94(5):964-973.
3. Halloran PF, Chang J, Famulski K, et al. Disappearance of T cell-mediated rejection despite continued antibody-mediated rejection in late kidney transplant recipients. *J Am Soc Nephrol*. 2015;26(7):1711-1720.
4. Loupy A, Lefaucheur C. Antibody-mediated rejection of solid-organ allografts. *N Engl J Med*. 2018;379(12):1150-1160.
5. Roufosse C, Simmonds N, Clahsen-van Groningen M, et al. A 2018 reference guide to the Banff classification of renal allograft pathology. *Transplantation*. 2018;102(11):1795-1814.
6. Wiebe C, Gibson IW, Blydt-Hansen TD, et al. Rates and determinants of progression to graft failure in kidney allograft recipients with de novo donor-specific antibody. *Am J Transplant*. 2015;15(11):2921-2930.
7. Rabant M, Gorbacheva V, Fan R, Yu H, Valujskikh A. CD40-independent help by memory CD4 T cells induces pathogenic alloantibody but does not lead to long-lasting humoral immunity. *Am J Transplant*. 2013;13(11):2831-2841.
8. Coffey F, Alabyev B, Manser T. Initial clonal expansion of germinal center B cells takes place at the perimeter of follicles. *Immunity*. 2009;30(4):599-609.
9. MacLennan IC et al. Extrafollicular antibody responses. *Immunol Rev*. 2003;194:8-18.
10. Bannard O, Horton RM, Allen CDC, An J, Nagasawa T, Cyster JG. Germinal center centroblasts transition to a centrocyte phenotype according to a timed program and depend on the dark zone for effective selection. *Immunity*. 2013;39(5):912-924.
11. Mesin L, Ersching J, Victora GD. Germinal center B cell dynamics. *Immunity*. 2016;45(3):471-482.
12. Nutt SL, Hodgkin PD, Tarlinton DM, Corcoran LM. The generation of antibody-secreting plasma cells. *Nat Rev Immunol*. 2015;15(3):160-171.
13. Espeli M, Bökers S, Giannico G, et al. Local renal autoantibody production in lupus nephritis. *J Am Soc Nephrol*. 2011;22(2):296-305.
14. Wilson RP, McGgettigan SE, Dang VD, et al. IgM plasma cells reside in healthy skin and accumulate with chronic inflammation. *J Invest Dermatol*. 2019;159(12):2477-2487.
15. Allie SR et al. Identification of antigen-specific, lung resident memory B cells after influenza infection. *J Immunol*. 2017;198 (1 Supplement):153.19.
16. Allie SR, Bradley JE, Mudunuru U, et al. The establishment of resident memory B cells in the lung requires local antigen encounter. *Nat Immunol*. 2019;20(1):97-108.
17. Garimilla S, Nguyen DC, Halliley JL, et al. Differential transcriptome and development of human peripheral plasma cell subsets. *JCI Insight*. 2019;4(9):e126732.
18. Groves CJ, Carroll J, Grady R, et al. CD19-positive antibody-secreting cells provide immune memory. *Blood Adv*. 2018;2(22):3163-3176.
19. Pape KA, Taylor JJ, Maul RW, Gearhart PJ, Jenkins MK. Different B cell populations mediate early and late memory during an endogenous immune response. *Science*. 2011;331 (6021):1203-1207.
20. McHeyzer-Williams LJ, Milpied PJ, Oikitsu SL, McHeyzer-Williams MG. Class-switched memory B cells remodel BCRs within secondary germinal centers. *Nat Immunol*. 2015;16(3):296-305.
21. Shlomchik MJ. Do Memory B Cells Form Secondary Germinal Centers?. Cold Spring Harbor Perspectives in Biology. 2018;10(1):a029405.

22. Crawford A, MacLeod M, Schumacher T, Corlett L, Gray D. Primary T cell expansion and differentiation in vivo requires antigen presentation by B cells. J Immunol. 2006;176(6):3498-3506.

23. Noonchashm H, Reed AJ, Rostami SY, et al. B cell-mediated antigen presentation is required for the pathogenesis of acute cardiac allograft rejection. J Immunol. 2006;177(11):7715-7722.

24. Rauch PJ, Chudnovskiy A, Robbins CS, et al. Inmate response activator B cells protect against microbial sepsis. Science. 2012;335(6068):597-601.

25. Menard LC, Minns LA, Darche S, et al. B cells amplify IFN-gamma production by T cells via a TNF-alpha-mediated mechanism. J Immunol. 2007;179(7):4857-4866.

26. Banham GD, Flint SM, Torpey N, et al. Belimumab in kidney transplantation: an experimental medicine, randomised, placebos-controlled phase 2 trial. Lancet. 2018;391(10410):2619-2630.

27. Fillatreau S, Sweeine CH, McGeeachy MJ, Gray D, Anderton SM. B cells regulate autoimmune by provision of IL-10. Nat Immunol. 2002;3(10):944-950.

28. Chesneaux M, Michel L, Dugast E, et al. Tolerant kidney transplant patients produce B cells with regulatory properties. J Am Soc Nephrol. 2015;26(10):2588-2598.

29. Clatworthy MR, Watson CJ, Plotnek G, et al. B-cell-depleting induction therapy and acute cellular rejection. N Engl J Med. 2009;360(25):2683-2685.

30. Asare A, Kanaparthi S, Lim N, et al. B cell receptor genes associated with tolerance identify a cohort of immunosuppressed patients with improved renal allograft graft function. Am J Transplant. 2017;17(10):2627-2639.

31. Newell KA, Asare A, Kirk AD, et al. Identification of a B cell signature associated with renal transplant tolerance in humans. J Clin Invest. 2010;120(6):1836-1847.

32. Newell KA, Asare A, Sanz I, et al. Longitudinal studies of a B cell-derived signature of tolerance in renal transplant recipients. Am J Transplant. 2015;15(11):2908-2920.

33. Shabir S, Girdlestone J, Briggs D, et al. Transitional B lymphocytes are associated with protection from kidney allograft rejection: a prospective study. Am J Transplant. 2015;15(5):1384-1391.

34. Viklicky O, Krystufkova E, Brabcova I, et al. B-cell-related biomarkers of tolerance are up-regulated in rejection-free kidney transplant recipients. Transplantation. 2013;95(1):148-154.

35. Bottomley MJ, Chen M, Fuggle S, Harden PN, Wood KJ. Application of operational tolerance signatures are limited by variability and type of immunosuppression in renal transplant recipients: a Cross-sectional study. Transplant Direct. 2017;3(1):e125.

36. Rebollo-Mesa I, Nova-Lamperti E, Mobillo P, et al. Biomarkers of tolerance in kidney transplantation: are we predicting tolerance or response to immunosuppressive treatment? Am J Transplant. 2016;16(12):3433-3437.

37. Tebbe B, Wilde B, Ye Z, et al. Renal transplant recipients treated with Calcineurin-inhibitors lack circulating immature transitional CD19+CD24hiCD38hi regulatory B-lymphocytes. PLoS One. 2016;11(4):e0153170.

38. Christakoudi S, Runglall M, Mobillo P, et al. Development and validation of the first consensus gene-expression signature of operational tolerance in kidney transplantation, incorporating adjustment for immunosuppressive drug therapy. EBioMedicine. 2020;58:102899.

39. Chhabra M et al. Germinal center alloantibody responses mediate progression of chronic allograft injury. Front Immunol. 2018;9:3038.

40. Eyer K, Doineau RCL, Castrillon CE, et al. Single-cell deep phenotyping of IgG-secreting cells for high-resolution immune monitoring. Nat Biotechnol. 2017;35(10):977-982.

41. Qureshi MS, Alsughayyir J, Chhabra M, et al. Germinal center humoral autoimmunity independently mediates progression of allograft vasculopathy. J Autoimmun. 2019;98:44-58.

42. Crippa PE et al. A late B lymphocyte action in dysfunctional tissue repair following kidney injury and transplantation. Nat Commun. 2019;10(1):1157.

43. Schinstock CA, Mannon RB, Buddle K, et al. Recommended treatment for antibody-mediated rejection after kidney transplantation: the 2019 expert consensus from the Transplant society working group. Transplantation. 2020;104(5):911-922.

44. Baldwin WM 3rd, Valujskikh A, Fairchild RL. The neonatal fc receptor: key to homeostastic control of IgG and IgG-related biopharmaceuticals. Am J Transplant. 2019;19(7):1881-1887.

45. Castro-Dopico T, Clatworthy MR. Fcgamma receptors in solid organ transplantation. Curr Transplant Rep. 2016;3(4):284-293.

46. Montgomery RA, Zachary AA, Racusen LC, et al. Plasmapheresis and intravenous immune globulin provides effective rescue therapy for refractory humoral rejection and allows kidneys to be successfully transplanted into cross-match-positive recipients. Transplantation. 2000;70(6):887-895.

47. Rocha PN, Butterfly DW, Greenberg A, et al. Beneficial effect of plasmapheresis and intravenous immunoglobulin on renal allograft survival of patients with acute humoral rejection. Transplantation. 2003;75(9):1490-1495.

48. Lefaucheur C, Nochy D, Andrade J, et al. Comparison of combination Plasmapheresis/IVIg/anti-CD20 versus high-dose IVIg in the treatment of antibody-mediated rejection. Am J Transplant. 2009;9(5):1099-1107.

49. Bohmig GA et al. Immunoabsorption in severe C4d-positive acute kidney allograft rejection: a randomized controlled trial. Am J Transplant. 2007;7(1):117-121.

50. 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;31(2):87-95.

51. Sautenet B, Blancho G, Büchler M, et al. One-year results of eculizumab treatment for refractory humoral rejection in renal transplantation: the 2019 expert consensus from the Transplantation society. Transplantation. 2020;100(2):391-399.

52. 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.

53. Walsh RC, Brailey P, Girnita A, et al. Early and late acute antibody-mediated rejection differ immunologically and in response to proteasome inhibition. Transplantation. 2011;91(11):1218-1226.
54. Woodle ES, Shields AR, Ezej NS, et al. Prospective iterative trial of proteasome inhibitor-based desensitization. *Am J Transplant*. 2015;15(1):101-118.

55. Moreno Gonzales MA, Gandhi MJ, Schin stock CA, et al. 32 doses of Bortezomib for desensitization is not well tolerated and is associated with only modest reductions in anti-HLA antibody. *Transplantation*. 2017;101(6):1222-1227.

56. Tremblay S, Driscoll JJ, Rike-Shields A, et al. A prospective, iterative, adaptive trial of carfilzomib-based desensitization. *Am J Transplant*. 2020;20(2):411-421.

57. 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.

58. Vincenti F, Rostaing L, Grinyo J, et al. Belatacept and long-term outcomes in kidney transplantation. *N Engl J Med*. 2016;374(4):333-343.

59. Durrbach A, Pestana JM, Florman S, et al. Long-term outcomes in Belatacept- versus cyclosporine-treated recipients of extended criteria donor kidneys: final results from BENEFIT-EXT, a phase III randomized study. *Am J Transplant*. 2016;16(11):3192-3201.

60. Leibler C, Thiolat A, Hénique C, et al. Control of Humoral response in renal transplantation by Belatacept depends on a direct effect on B cells and impaired T follicular helper-B cell crosstalk. *J Am Soc Nephrol*. 2018;29(3):1049-1062.

61. Leibler C, Matignon M, Moktefi A, et al. Belatacept in renal transplant recipient with mild immunologic risk factor: a pilot prospective study (BELACOR). *Am J Transplant*. 2019;19(3):894-906.

62. Adams AB, Goldstein J, Garrett C, et al. Belatacept combined with transient Calcineurin inhibitor therapy prevents rejection and promotes improved long-term renal allograft function. *Am J Transplant*. 2017;17(11):2922-2936.

63. Kwan J, Burghuber C, Manook M, et al. Humoral compensation after Bortezomib treatment of Allosensitized recipients. *J Am Soc Nephrol*. 2017;28(7):1991-1996.

64. Kim EJ, Kwun J, Gibby AC, et al. Costimulation blockade alters germinal center responses and prevents antibody-mediated rejection. *Am J Transplant*. 2014;14(1):59-69.

65. Burghuber CK, Manook M, Ezekian B, et al. Dual targeting: combining costimulation blockade and bortezomib to permit kidney transplantation in sensitized recipients. *Am J Transplant*. 2019;19(3):724-736.

66. Kwan J, Burghuber C, Manook M, et al. Successful desensitization with proteasome inhibition and costimulation blockade in sensitized nonhuman primates. *Blood Adv*. 2017;1(24):2115-2119.

67. Ezekian B, Schroder PM, Mulvihill MS, et al. Pretransplant desensitization with Costimulation blockade and proteasome inhibitor reduces DSA and delays antibody-mediated rejection in highly sensitized nonhuman primate kidney transplant recipients. *J Am Soc Nephrol*. 2019;30(12):2399-2411.

68. Eto D, Lao C, DiToro D, et al. IL-21 and IL-6 are critical for different aspects of B cell immunity and redundantly induce optimal follicular helper CD4 T cell (Tfh) differentiation. *PLoS One*. 2011;6(3):e17739.

69. Rahman ZS, Rao SP, Kalled SL, Manser T. Normal induction but attenuated progression of germinal center responses in BAFF and BAFF-R signaling-deficient mice. *J Exp Med*. 2003;198(8):1157-1169.

70. Ye Q, Wang L, Wells A D, et al. BAFF binding to T cell-expressed BAFF-R costimulates T cell proliferation and allogeneic responses. *Eur J Immunol*. 2004;34(10):2750-2759.

71. Parsons RF, Yu M, Vivek K, et al. Murine islet allograft tolerance upon blockade of the B-lymphocyte stimulator, BLyS/BAFF. *Transplantation*. 2012;93(7):676-685.

72. 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.

73. 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.

74. Järnum S, Bockermann R, Runström A, Winstedt L, Kjellman C. 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.

75. Rossi EA, Goldenberg DM, Michel R, Rossi DL, Wallace DJ, Chang CH. Trogocytosis of multiple B-cell surface markers by CD22 targeting with epratuzumab. *Blood*. 2013;122(17):3020-3029.

76. Lumb S, Fleischer SJ, Wiedemann A, et al. Engagement of CD22 on B cells with the monoclonal antibody epratuzumab stimulates the phosphorylation of upstream inhibitory signals of the B cell receptor. *J Cell Commun Signal*. 2016;10(2):143-151.

77. Srinivasan L, Sasaki Y, Calado DP, et al. PI3 kinase signals BCR-dependent mature B cell survival. *Cell*. 2009;139(3):573-586.

78. Dörner T, Shock A, Goldenberg DM, Lipsky PE. The mechanistic impact of CD22 engagement with epratuzumab on B cell function: implications for the treatment of systemic lupus erythematosus. *Autoimmune Rev*. 2015;14(12):1079-1086.

79. Li J, Wei MM, Song Q, Guo XH, Shao L, Liu Y. Anti-CD22 epratuzumab for systemic lupus erythematosus: a systematic review and meta-analysis of randomized controlled trials. *Exp Ther Med*. 2019;18(2):1500-1506.

80. Szili D, Cserhalmi M, Bankó Z, Nagy G, Szymkowski DE, Sármay G. Suppression of innate and adaptive B cell activation pathways by antibody coengagement of FcyRIIB and CD19. *MAbs*. 2014;6(4):991-999.

81. Chu SY, Yeter K, Kotha R, et al. Suppression of rheumatoid arthritis B cells by XmAb5871, an anti-CD19 antibody that coengages B cell antigen receptor complex and Fcγ receptor IIb inhibitory receptor. *Arthritis Rheumatol*. 2014;66(5):1153-1164.

82. Merrill JT, June J, Koupouras F, et al. Top-line results of a phase 2, double-blind, randomized, placebo-controlled study of a reversible B cell inhibitor, XmAb5871, in systemic lupus Erythematosus (SLE). *Arthritis Rheumatol*. 2018;70(suppl 10).

83. Stone JH, Wallace ZS, Perugino CA, Fernandes AD, Foster PA, Zack DJ. A Trial of XmAb5871, a reversible inhibitor of CD19+ cells, in IgG4-related disease. *Arthritis Rheumatol*. 2016;68(suppl 10).
84. Kamburova EG, Koenen HJPM, Borgman KJE, ten Berge JJ, Joosten I, Hilbrands LB. A single dose of rituximab does not deplete B cells in secondary lymphoid organs but alters phenotype and function. *Am J Transplant.* 2013;13(6):1503-1511.

85. Wallin EF, Jolly EC, Suchánek O, et al. Human T-follicular helper and T-follicular regulatory cell maintenance is independent of germinal centers. *Blood.* 2014;124(17):2666-2674.

86. Horer S, Herting F, Mundigl O, et al. Preclinical activity of the type II CD20 antibody GA101 (obinutuzumab) compared with rituximab and ofatumumab in vitro and in xenograft models. *Mol Cancer Ther.* 2013;12(10):2031-2042.

87. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med.* 2014;370(12):1101-1110.

88. Furie R, Aroca G, Alvarez A, et al. A phase II randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of Obinutuzumab or Placebo in combination with mycophenolate mofetil in patients with active class III or IV Lupus Nephritis. *Arthritis Rheumatol.* 2019;71(suppl 10).

89. Rovin BH, Furie R, Latinis K, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the lupus nephritis assessment with rituximab study. *Arthritis Rheum.* 2012;64(11):1215-1226.

90. Merrill JT, Neuwelt CM, Wallace DJ, et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. *Arthritis Rheum.* 2010;62(1):222-233.

91. Redfield RR, Jordan SC, Busque S, et al. Safety, pharmacokinetics, and pharmacodynamic activity of obinutuzumab, a type 2 anti-CD20 monoclonal antibody for the desensitization of candidates for renal transplant. *Am J Transplant.* 2019;19(11):3035-3045.

92. Cree BAC, Bennett JL, Kim HJ, et al. Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo-controlled phase 2/3 trial. *Lancet.* 2019;394(10206):1352-1363.

93. Zhao J, Song Y, Liu D. Recent advances on blinatumomab for acute lymphoblastic leukemia. *Exp Hematol Oncol.* 2019;8:28.

94. Shah NN, Maatman T, Hari P, Johnson B. Multi targeted CAR T cell therapies for B-cell malignancies. *Front Oncol.* 2019;9:146.

95. Kitching AR, Jaw J. Chimeric antigen receptor T (CAR T) cells: another cancer therapy with potential applications in kidney disease and transplantation? *Kidney Int.* 2018;94(1):4-6.

96. Ellebrecht CT, Bhoj VG, Nace A, et al. Reengineering chimeric antigen receptor T cells for targeted therapy of autoimmune disease. *Science.* 2016;353(6295):179-184.

97. Facon T, Kumar S, Pleasner T, et al. Daratumumab plus Lenalidomide and dexamethasone for untreated myeloma. *N Engl J Med.* 2019;380(22):2104-2115.

98. Lonial S, Weiss BM, Usmani SZ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. *Lancet.* 2016;387(10027):1551-1560.

99. Mateos MV, Dimopoulos MA, Cavo M, et al. Daratumumab plus Bortezomib, Melphalan, and prednisone for untreated myeloma. *N Engl J Med.* 2018;378(6):518-528.

100. Krejci J, Casneuf T, Nijhof IS, et al. Daratumumab depletes CD38+ immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. *Blood.* 2016;128(3):384-394.

101. van de Donk N. Reprint of “Immunomodulatory effects of CD38-targeting antibodies”. *Immunol Lett.* 2019;205:71-77.

102. 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.

103. O’Connor BP et al. BCMA is essential for the survival of long-lived bone marrow plasma cells. *J Exp Med.* 2004;199(1):91-98.

104. Cho SF, Lin L, Xing L, et al. BCMA-Targeting Therapy: Driving a New Era of Immunotherapy in Multiple Myeloma. *Cancers.* 2020;12(6):1473.

105. Jagannath S, Heffner LT Jr, Ailawadhi S, et al. Indatuximab Ravidansine (BT062) Monotherapy in patients with relapsed and/or refractory multiple myeloma. *Clin Lymphoma Myeloma Leuk.* 2019;19(6):372-380.

106. Woodle ES, Tremblay S, Brailey P, et al. Proteasomal adaptations underlying carfilzomib-resistance in human bone marrow plasma cells. *Am J Transplant.* 2020;20(2):399-410.

107. Eskandari SK, Seelen MAJ, Lin G, Azzi JR. The immunoproteasome: An old player with a novel and emerging role in alloimmunity. *Am J Transplant.* 2017;17(12):3033-3039.

108. Li J, Basler M, Alvarez G, Brunner T, Kirk CJ, Groettrup M. Immunoproteasome inhibition prevents chronic antibody-mediated allograft rejection in renal transplantation. *Kidney Int.* 2018;93(3):670-680.

109. Li J, Koerner J, Basler M, Brunner T, Kirk CJ, Groettrup M. Immunoproteasome inhibition induces plasma cell apoptosis and preserves kidney allografts by activating the unfolded protein response and suppressing plasma cell survival factors. *Kidney Int.* 2019;95(3):611-625.

110. Tremblay S, Castro-Rojas C, Driscoll J, et al. Pilot study of plasma cell niche-targeted therapy for enhancement of proteasome inhibitor effectiveness. *Am J Transplant.* 2017;17(suppl 3).

111. Woodle E, Tremblay S, Castro-Rojas C, et al. In vivo Administration of Plerixafor in humans mobilizes bone marrow resident plasma cells that demonstrate apoptosis in both bone marrow and peripheral blood. *Am J Transplant.* 2017;17(suppl 3).

112. Jordan SC, Choi J, Kim I, et al. Interleukin-6, a cytokine critical to mediation of inflammation, autoimmunity and allograft rejection: therapeutic implications of IL-6 receptor blockade. *Transplantation.* 2017;101(1):32-44.

113. Jourdan M, Cren M, Robert N, et al. IL-6 supports the generation of human long-lived plasma cells in combination with either APRIL or stromal cell-soluble factors. *Leukemia.* 2014;28(8):1647-1656.

114. Muraguchi A, Hirano T, Tang B, et al. The essential role of B cell stimulatory factor 2 (BSF-2/IL-6) for the terminal differentiation of B cells. *J Exp Med.* 1988;167(2):332-344.
115. Papillion A, Powell MD, Chisolm DA, et al. Inhibition of IL-2 responsiveness by IL-6 is required for the generation of GC-TFH cells. Science Immunology. 2019;4(39):eaww7636.

116. Lion J, Taflin C, Cross AR, et al. HLA class II antibody activation of endothelial cells promotes Th17 and disrupts regulatory T lymphocyte expansion. Am J Transplant. 2016;16(5):1408-1420.

117. Lion JPK, Chong E, Glotz D, Mooney NA. Clazakizumab acts on endothelial cells to limit antibody mediated damage. Am J Transplant. 2019;19(suppl 3).

118. Choi JAO, Louie S, Ammerman N, et al. Plasma-derived C1 inhibitor in acute antibody-mediated rejection: a prospective randomized controlled trial. Am J Transplant. 2017;17(suppl 3).

119. Jordan SC, Ammerman N, Toyoda M, et al. Clazakizumab as an agent to reduce donor specific HLA antibodies and improve outcomes in patients with chronic & active antibody-mediated rejection post-kidney transplantation. Am J Transplant. 2019;19(suppl 3).

120. Vo AA, Choi J, Kim I, et al. A phase I/II trial of the Interleukin-6 receptor-specific humanized monoclonal (Tocilizumab) + intravenous immunoglobulin in difficult to desensitize patients. Transplantation. 2015;99(11):2356-2363.

121. Muhammad 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.

122. Kwan 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.

123. Kaelgi C et al. Systematic review of safety and efficacy of Atacicept in treating immune-mediated disorders. Front Immunol. 2020;11(433).

124. Hickey MJ, Valenzuela NM, Reed EF. Alloantibody generation and effector function following sensitization to human leukocyte antigen. Front Immunol. 2016;7:30.

125. Chun N, Fairchild RL, Li Y, et al. Complement dependence of murine Costimulatory blockade-resistant cellular cardiac allograft rejection. Am J Transplant. 2017;17(11):2810-2819.

126. Farrar CA, Tran D, Li K, et al. Collectin-11 detects stress-induced L-fucose pattern to trigger renal epithelial injury. J Clin Invest. 2016;126(5):1911-1925.

127. Loupy A, Lefaucheur C, Vernerey D, et al. Complement-binding anti-HLA antibodies and kidney-allograft survival. N Engl J Med. 2013;369(13):1215-1226.

128. Huang E, Vo A, Choi J, et al. Three-year outcomes of a randomized, double-blind, placebo-controlled study assessing safety and efficacy of C1 esterase inhibitor for prevention of delayed graft function in deceased donor kidney transplant recipients. Clin J Am Soc Nephrol. 2020;15(1):109-116.

129. Jordan SC, Choi J, Aubert O, et al. A phase I/II, double-blind, placebo-controlled study assessing safety and efficacy of C1 esterase inhibitor for prevention of delayed graft function in deceased donor kidney transplant recipients. Am J Transplant. 2018;18(12):2955-2964.

130. Kaabak M, Babenko N, Shapiro R, Zokoyev A, Dymova O, Kim E. A prospective randomized, controlled trial of eculizumab to prevent ischemia-reperfusion injury in pediatric kidney transplantation. Pediatric Transplantation. 2018;22(2):e13129.

131. 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.

132. 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):1596-1603.

133. Lefaucheur C, Viglietti D, Hidalgo LG, et al. Complement-activating anti-HLA antibodies in kidney transplantation: allograft gene expression profiling and response to treatment. J Am Soc Nephrol. 2018;29(6):620-635.

134. Viglietti D, Bouatou Y, Kheav VD, et al. Complement-binding anti-HLA antibodies are independent predictors of response to treatment in kidney recipients with antibody-mediated rejection. Kidney Int. 2018;94(4):773-787.

135. Glotz D, Russ G, Rostaing L, et al. Safety and efficacy of eculizumab for the prevention of antibody-mediated rejection after deceased-donor kidney transplantation in patients with preformed donor-specific antibodies. Am J Transplant. 2019;19(10):2865-2875.

136. Tan EK, Bentall A, Dean PG, Shaheen MF, Stegall MD, Schinstock CA. 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.

137. Eskandary F, Jilma B, Mühlbacher J, et al. Anti-C1s monoclonal antibody BIVV009 in late antibody-mediated kidney allo rejection-results from a first-in-patient phase 1 trial. Am J Transplant. 2018;18(4):916-926.

138. Kulasekararaj AG, Hill A, Rottinghaus ST, et al. Ravalizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. Blood. 2019;133(6):540-549.

139. 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. 2019; Publish Ahead of Print. https://doi.org/10.1097/TP.0000000000003023.

140. 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.

143. 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.

144. Jordan SC, Montgomery RA, Lundgren T, et al. Follow up of Imlifidase (IdeS) desensitized kidney transplant recipients. *Am J Transplant*. 2020;20(suppl 3).

**AUTHOR BIOGRAPHIES**

**Ondrej Suchanek**, Specialty Registrar in Nephrology, Addenbrooke’s Hospital, Cambridge, UK. Clinical Research Fellow, University of Cambridge, UK. Ondrej Suchanek obtained his MD with summa cum laude and Dean’s Award from Charles University in Prague. He subsequently won several competitive scholarships to complete MSc in Integrated Immunology (University of Oxford) and MPhil in Translational Medicine & Therapeutics (University of Cambridge) focusing on B cells and their patient-stratification potential in autoimmunity or immunodeficiency. His recent PhD work (University of Cambridge), investigating phenotype and function of tissue-resident B cells in both mouse and human non-lymphoid organs, has been awarded both nationally and internationally. He is currently working as a Specialty Registrar in Nephrology at Addenbrooke’s Hospital in Cambridge with a special interest in transplantation and autoimmunity.

**Menna R. Clatworthy**, Professor of Translational Immunology. University of Cambridge, UK. Honorary Consultant Nephrologist. Addenbrooke’s Hospital, Cambridge, UK. NIHR Research Professor, Fellow and Director of Studies, Clinical Medicine. Pembroke College, Cambridge. Associate Faculty, Cellular Genetics, Wellcome Sanger Institute. Menna Clatworthy read Medicine at Cardiff, completed her professional training in nephrology at Cambridge, and undertook a PhD at the University of Cambridge investigating the role of IgG antibodies in autoimmunity and infection. She was awarded the British Renal Association Raine Award and the Academy of Medical Sciences/Medical Research Society Young Investigator Award for this work. She subsequently completed a Wellcome Trust Intermediate Fellowship at Cambridge and the National Institutes of Health, Bethesda, USA. She is currently the Professor of Translational Immunology at the University of Cambridge Department of Medicine. She also works clinically as an Honorary Consultant Nephrologist and holds an Associate Faculty position in Cellular Genetics at the Wellcome Sanger Institute. Her research is focused on understanding the regulation of antibody generation and effector function, novel methods of targeting humoral immunity in transplantation and autoimmunity and the role of tissue-environment in shaping resident immune cell activation and function, particularly in the kidney. She is also an active participant in the Human Cell Atlas Project (https://www.humancellatlas.org), utilizing single cell technologies to better understand the cellular landscape of the human kidney.

**How to cite this article**: Suchanek O, Clatworthy MR. Novel strategies to target the humoral alloimmune response. *HLA*. 2020;96:667–680. [https://doi.org/10.1111/tan.14092](https://doi.org/10.1111/tan.14092)