REVIEW

The therapeutic challenge of late antibody-mediated kidney allograft rejection

Georg A. Böhmig[1], Farsad Eskandary[1], Konstantin Doberer[1] & Philip F. Halloran[2]

1 Division of Nephrology and Dialysis, Department of Medicine III, Medical University of Vienna, Vienna, Austria
2 Alberta Transplant Applied Genomics Centre (ATAGC), University of Alberta, Edmonton, AB, Canada

Correspondence
Georg A. Böhmig MD, Division of Nephrology and Dialysis, Department of Medicine III, Medical University of Vienna, Währinger Gürtel 18-20, A-1090 Vienna, Austria.
Tel.: +43 40400 43630;
fax: +43 40400 39302;
e-mail:
georg.boehmig@meduniwien.ac.at

SUMMARY

Late antibody-mediated rejection (ABMR) is a cardinal cause of kidney allograft failure, manifesting as a continuous and, in contrast with early rejection, often clinically silent alloimmune process. While significant progress has been made towards an improved understanding of its molecular mechanisms and the definition of diagnostic criteria, there is still no approved effective treatment. In recent small randomized controlled trials, therapeutic strategies with promising results in observational studies, such as proteasome inhibitor bortezomib, anti-C5 antibody eculizumab, or high dose intravenous immunoglobulin plus rituximab, had no significant impact in late and/or chronic ABMR. Such disappointing results reinforce a need of new innovative treatment strategies. Potential candidates may be the interference with interleukin-6 to modulate B cell alloimmunity, or innovative compounds that specifically target antibody-producing plasma cells, such as antibodies against CD38. Given the phenotypic heterogeneity of ABMR, the design of adequate systematic trials to assess the safety and efficiency of such therapies, however, is challenging. Several trials are currently being conducted, and new developments will hopefully provide us with effective ways to counteract the deleterious impact of antibody-mediated graft injury. Meanwhile, the weight of evidence would suggest that, when approaching using existing treatments for established antibody-mediated rejection, "less may be more".

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General considerations

Late antibody-mediated rejection (ABMR) is well-established to be a major determinant of allograft outcome [1]. Nevertheless, in contrast with early acute ABMR, there is still no treatment proven to modify its natural course [2]. There is a need of new innovative therapeutic approaches, which will have to be evaluated for their safety and efficiency in adequately designed intervention trials. Our increasing understanding of the pathophysiology of ABMR, its natural course and diagnosis, including its different subphenotypes, may provide a valuable basis for a robust study design. In search of new treatment concepts, transplant medicine may learn substantially from other medical disciplines, such as rheumatology or haematology, where numerous new developments have enabled considerable success in the treatment of B cell- and plasma cell-driven diseases.

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However, we are still lacking in our understanding of the natural history of ABMR, a point that must be remembered when evaluating any study that does not have a randomized control design.

Pathogenesis of ABMR

Key elements of ABMR pathogenesis as well as potential treatments and their targets are illustrated in Fig. 1. A major trigger of ABMR is the formation of donor-specific antibodies (DSA) against mismatched HLA class I and, particularly in chronic rejection, HLA class II antigens [1]. Upon binding to the endothelium, DSA may initiate a cascade of molecular events that result in endothelial activation and inflammation in the microcirculation, ultimately culminating in irreversible tissue injury. A driving force of HLA antibody formation is the extent of tissue incompatibility between recipient and donor, suggesting that a precise definition of immunogenic HLA mismatches may significantly contribute to alloimmune risk stratification to accurately predict the risk of *de novo* DSA formation [3–5]. Major approaches in this context – not the primary topic of this review – may be the implementation of novel allocation strategies to improve the precision of traditional HLA antigen mismatching and/or the use of immunosuppressive regimens, such as costimulation inhibitors, that *a priori* prevent the formation of deleterious DSA and the subsequent development of rejection [5,6].

As illustrated in Fig. 1, DSA may trigger a sequence of different events that may contribute to tissue injury, including possible direct signalling via HLA molecules (although this has only been demonstrable in *in vitro* systems), induction of Fc gamma receptor-dependent cellular effects, and/or activation of the complement cascade, primarily via the classical pathway (CP) [7]. In this context, also natural killer (NK) cells have recently gained attention. Studies support an involvement of transcripts related to Fc gamma receptor IIIA-mediated NK cell activation [8,9]. In addition, morphological and molecular evidence of NK cell infiltration was associated with ABMR and inferior graft survival [10]. DSA-triggered CP activation and the subsequent release of anaphylatoxins, the recruitment of inflammatory cells with complement receptors and the formation of the membrane attack complex may contribute to tissue injury [11,12]. However, the frequent finding of C4d-negative rejection [13] and the limited success of complement inhibitory treatment (see also below) [14–17] have questioned the dominant importance of complement cascade activation in late ABMR.

ABMR diagnosis and subphenotypes

Since its first description as a separate entity, the diagnosis of ABMR has been refined in subsequent amendments of the Banff classification [18–20]. Diagnostic criteria are the detection of typical morphological lesions in the microcirculation, which include glomerulitis (g), peritubular capillaritis (ptc), transplant glomerulopathy (cg), serological evidence of circulating DSA and/or the finding of C4d as a specific marker of DSA-triggered complement activation in the microvasculature. The phenotypic presentation of ABMR is heterogenous, and, according to recent updates of the Banff scheme, not all criteria need to be fulfilled for its diagnosis. For example, ABMR is often C4d-negative, or under certain conditions (e.g. positive C4d staining reflecting recent/current antibody interaction with vascular endothelium), this type of rejection may be diagnosed without serological DSA detection. In addition, the innovative diagnostic tool of gene expression analysis using validated platforms, such as the Molecular Microscope Diagnostic system (MMDx) [21,22], has been in included in the Banff scheme to further increase diagnostic precision [20].

Antibody-mediated rejection can occur at any time, but is most frequent in the late phase after transplantation [22–24]. According to its timing, many authors distinguish between early and late ABMR, the latter being commonly defined by its diagnosis beyond 6 months post-transplantation, often associated with anti-HLA DSA, sometimes in the context of underimmunosuppression ("minimization") or nonadherence. In addition, ABMR may present with different subphenotypes, classified according to morphological, molecular and/or serological characteristics.

The Banff 2017 scheme defines two major variants, that are, (i) active (formerly 'acute active' ABMR) and (ii) chronic active ABMR, based on the absence or presence of time-dependent "stage" lesions: cg or the ultrastructural finding of capillary basement membrane multilayering [20]. These two phenotypes may occur at any time, with active ABMR, without any chronic lesions being occasionally found even many years post-transplantation [25]. At the same time, gene expression analysis, e.g. using the innovative principle of unsupervised archetypal analysis, may allow for an alternative classification of rejection subphenotypes that differ substantially with respect to timing, intensity and prognostic impact (early stage versus fully developed versus late-stage ABMR) [22]. Late ABMR is commonly associated with *de novo* DSA (also referred to as type 2

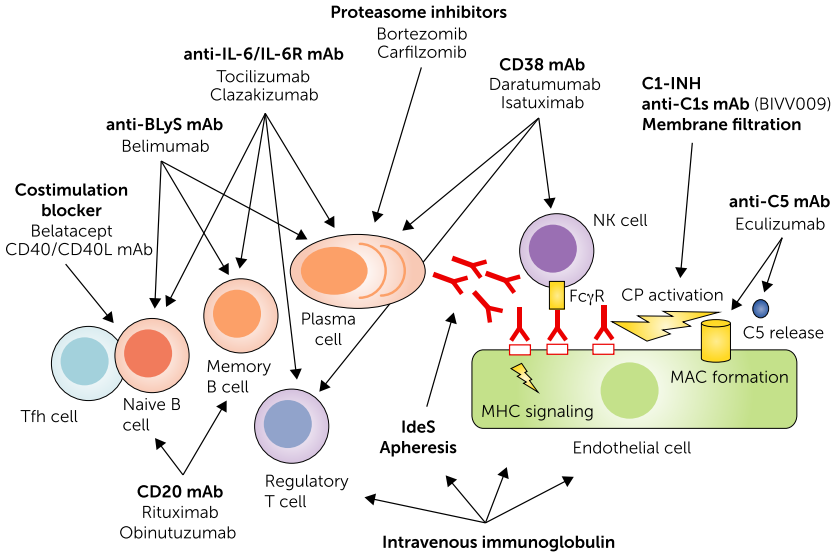

Figure 1 Pathogenesis of antibody-mediated rejection and potential therapeutic targets. A primary trigger of B cell alloimmunity may be the interaction of follicular T helper cells with naive B cells. This leads to B cell proliferation and differentiation, and the generation of B memory cells and antibody-producing plasma cells. Binding of alloantibodies to the endothelium may trigger direct signalling, induce Fc gamma receptor (FcγR) dependent cellular effects, such as natural killer (NK) cell (and macrophage) activation, and trigger complement activation via the classical pathway (CP). Costimulation blockers, monoclonal antibodies (mAb) that target the interleukin-6 (IL-6)/IL-6 receptor (IL-6R) axis, or B lymphocyte stimulator may prevent proper B cell activation/differentiation and affect the generation or integrity of plasma cells. IL-6 antagonists may also enhance the formation of regulatory T cells. Proteasome inhibitors and CD38 mAb may deplete alloantibody-producing plasma cells, the latter affecting also NK cells and regulatory T cells. Complement inhibitors and membrane filtration target the C1 complex, a key component of the CP, or by interference with the terminal component C5 (eculizumab), the formation of the membrane attack complex and anaphylatoxin C5a. The mode of action of intravenous immunoglobulin is multifaceted and may include interference with B and T cell activation, antibody formation and recycling, as well as complement activation.

rejection [26]), but in this respect, transplant centres may differ substantially: series including a high proportion of high immunological risk patients subjected to desensitization at the time of transplantation have also shown an accumulation of late ABMR cases among patients with preformed DSA [25].

Of particular relevance for the design and interpretation of intervention trials is that the individual screening strategies applied to identify ABMR may critically influence rates and phenotypes detected in distinct patient cohorts (e.g. prospective protocol biopsies versus indication biopsies; longitudinal versus cross-sectional DSA screening). For example, in a recently published cross-sectional evaluation (BORTEJECT trial) of 741 kidney transplant recipients in outpatient care >6 months after transplantation (estimated glomerular filtration rate (eGFR) > 20 ml/min/1.73 m^2), 111 DSA-positive recipients were identified (15%), and 86 of these patients were subjected to protocol biopsies. ABMR was diagnosed in 44 recipients, at the median time of 5 years after transplantation (6% of the screened population) [25]. Every second ABMR patient had a history of presensitization, which was more frequent than expected. Moreover, there was a marked heterogeneity of morphological subphenotypes, a case mix of active and chronic active (C4d-positive or C4d-negative) ABMR cases [25]. In another cohort, prospective serial DSA monitoring in nonsensitized patients without preformed DSA revealed an initially low but steadily increasing incidence of *de novo* DSA, with rates of 2%, 10% and 19% after 1, 5 and 10 years, respectively [27]. In this study, 76% of the recipients who underwent DSA-triggered protocol biopsies showed active ABMR [27].

Clinical impact of ABMR

Antibody-mediated rejection diagnosis is commonly associated with progressive deterioration of graft function and premature allograft failure. The cardinal impact of ABMR as a trigger of transplant failure may have major implications for patient survival, given the well-documented increased risk in death following allograft loss [28]. In a large cohort of 885 kidney transplant recipients who underwent biopsies for graft dysfunction, ABMR morphology was shown to be

tightly associated with adverse graft survival [29]. Eight-year graft survival was 53% in C4d-positive and 66% in C4d-negative ABMR, as compared with 81% in patients without any rejection features. In mixed models, the calculated annual slope of eGFR among C4d-positive recipients or patients with histomorphological evidence of ABMR was between −8 and −9 ml/min/1.73 m^2 [29].

In a cohort of 508 nonsensitized renal allograft recipients *de novo* DSA formation was associated with an eGFR slope of −3.63, compared with −0.65 ml/min/1.73 m^2 per year in DSA-negative patients [27]. Among DSA-positive subjects, those with graft dysfunction at the time of antibody detection had a steeper annual eGFR decline (mean −5.61 ml/min/1.73 m^2) than subclinical cases (mean −3.15 ml/min/1.73 m^2). Outcome analysis revealed a tight relationship between eGFR slope and graft survival, showing a highly significant increase (by 6%) in the risk of graft loss for each 1 ml/min/1.73 m^2 decease in eGFR at 3 years postsubclinical *de novo* DSA onset [27].

The clinical course of ABMR may vary substantially between individuals, and may critically depend on varying characteristics, such as the extent of graft dysfunction at baseline [27], capillary C4d staining, the complement-fixing capability of detected DSA (which may correlate mainly with antibody levels in the circulation and the amount of antibody bound in solid phase assays) [30,31], and the presence or absence of chronic microcirculation injury (cg) [32].

Treatment of late ABMR – concepts evaluated in RCTs

Potential anti-rejection therapies and their targets in ABMR are illustrated in Fig. 1. Numerous therapeutic concepts, amongst them apheresis (plasmapheresis, immunoadsorption), intravenous immunoglobulin (IVIG), CD20 antibody rituximab, proteasome inhibitor bortezomib, and anti-C5 antibody eculizumab have been evaluated in the treatment of ABMR. Levels of evidence, however, have remained low [33]. Only three distinct therapies – IVIG/rituximab, bortezomib and eculizumab – have now been tested systematically in the specific context of late/chronic ABMR, but results of RCTs are disappointing (Table 1) [16,34,35].

IVIG plus rituximab

Many authors promote the use of high dose IVIG combined with rituximab as a treatment of ABMR. For late/chronic ABMR, however, treatment efficiency is still controversial.

Observational studies suggesting treatment efficiency

In a small observational study (four patients with chronic ABMR) by Fehr *et al.* [36], IVIG/rituximab was associated with a reduction in DSA levels over time and improved graft function. These results were supported by a series from Heidelberg (six paediatric recipients), which showed improved renal function 12 months after treatment [37]. Four years later, the same group reported on an extended cohort of 20 paediatric recipients followed for 2 years [38]. Again, combined treatment was associated with a decline in the mean fluorescence intensity (MFI) of detected DSA and, in parallel, improved renal function and follow-up biopsy results (less C4d staining), whereby response rates were higher among patients without features of chronic injury (100% vs. 45% in patients with chronic lesions) [38].

In a recent single-centre observational study of the Wisconsin group, Parajuli *et al.* [39] evaluated outcomes among 78 kidney transplant recipients with late acute or chronic active ABMR subjected to high dose steroids and IVIG or steroids and IVIG/rituximab (one dose of 375 mg/m^2). Treatment was associated with a significant decline in DSA-MFI and microvascular inflammation in follow-up biopsies performed within 6 weeks. The authors reported that patients who received rituximab less often experienced graft failure (15% graft loss at 1 year vs. 32% in patients who did not receive rituximab, $P = 0.02$). This outcome effect was independent in multivariate analysis. In contrast with the results of the Heidelberg study, the extent of chronic injury had no significant clinical impact [39].

Finally, Redfield *et al.* [40] reported on a large observational series of 123 consecutive kidney transplant recipients diagnosed with chronic ABMR. Ninety-three percent of the patients received anti-rejection treatment, including steroids (93%), steroids/IVIG (87%), rituximab (30%), plasmapheresis (13%) and anti-thymocyte globulin (ATG) (10%). Overall, the median graft survival after diagnosis of rejection was only 1.9 years. Retrospective analysis revealed that the use of steroids/IVIG, as compared with no treatment, was associated with a reduced risk of graft loss. Patients treated with additional rituximab or ATG showed superior survival rates, however, observed differences did not achieve statistical significance. Discussing their results, the authors pointed out that the ability to detect differences was

Table 1. Randomized controlled trials in late and/or chronic ABMR after kidney transplantation.

Author, year	Trial design	Inclusion criteria	Treatment	Patients	Immunosuppression	Follow-up	Major EP	Major results
Kulkarni, 2017 [16]	Single centre nonblinded RCT	HLA-DSA+, 20% eGFR decline upon 12 months	Eculizumab, 600 mg/week for 4 weeks; 900 mg every 2 weeks for 26 weeks	Treatment: $n = 10$ Control: $n = 5$	Not specified	1 year	Primary EP: eGFR decline Secondary EP: acute rejection; treatment failure (death, graft loss, loss to follow-up or withdrawal from trial); biopsies at 3, 6 and 12 months, DSA MFI and C1q fixation	Marginal improvement of eGFR trajectory ($P = 0.09$); no effect on morphological and molecular biopsy results
Moreso, 2018 [35]	Multicentre placebo-controlled RCT*	HLA-DSA+, chronic ABMR (cg > 0)	IVIGx4 (0.5 g/kg) every 3 weeks RTX (375 mg/m^2) 1 week after the last IVIG infusion	Treatment: $n = 13$ Placebo: $n = 12$	Tac/MMF Tac C0: 5–10 ng/ml	1 year	Primary EP: eGFR decline Secondary EP: proteinuria, biopsies at 12 months, DSA MFI	No effect on eGFR decline, biopsy results and DSA-MFI; no differences in adverse events
Eskandary, 2018 [34]	Single centre placebo-controlled RCT	HLA-DSA+, late ABMR after >180 days	Bortezomib (two cycles; each four injections, 1.3 mg/m^2; 3-month interval)	Treatment: $n = 21$ Placebo: $n = 23$	Triple immunosuppression Tac C0: 7–10 ng/ml CyA C0: 80–120 ng/ml	2 years	Primary EP: eGFR slope Secondary EP: proteinuria; biopsies at 24 months, DSA MFI	No effect on eGFR decline, biopsy results and DSA MFI Higher rate of SAEs

ABMR, antibody-mediated rejection; DSA, donor-specific antibody; eGFR, estimated glomerular filtration rate; EP, endpoint; MMF, mycophenolate mofetil; MFI, mean fluorescence intensity; RCT, randomized controlled trial; SAE, severe adverse event; Tac, tacrolimus.

*Planned sample size: 25 patients per group (not achieved because of budgetary constraints and slow patient recruitment).

limited by an inherent selection bias and a small number of cases [40].

Observational studies suggesting no treatment efficiency

Bachelet *et al.* [41] reported on a series of 21 patients with transplant glomerulopathy who received four doses of IVIG and two doses of rituximab. Results were compared with those obtained in a control group of 10 patients. 24-month graft survival was similar in both groups, and there was only a marginal difference in DSA-MFI. The number of adverse events, however, was higher in the treatment group [41]. More recently, Pineiro *et al.* [42] evaluated a cohort of 62 patients with chronic active ABMR, of whom 23 received treatment with IVIG/rituximab together with plasmapheresis (PP). The other 39 recipients (control group) did not receive any therapy. Combined treatment had no effect on eGFR decline and graft survival, but was associated with significantly higher infection rates [42].

TRITON trial

This multicentre (six transplant units in Spain) randomized controlled double-blinded trial was designed to evaluate the effect of IVIG plus rituximab in patients with chronic ABMR [35]. The study included subjects with transplant glomerulopathy (cg score > 0) and anti-HLA DSA (predominance of HLA class II antibodies), but stable graft function between the index biopsy and trial inclusion. Patients with an eGFR below 20 ml/min/1.73 m^2 and severe IFTA were excluded. Treatment consisted of four doses of 0.5 g/kg IVIG and rituximab at 375 mg/m^2. The study was powered to detect a 10 ± 10 ml/min/1.73 m^2 inter-group difference in eGFR decline over 1 year. The calculated sample size was 25 subjects per group, but because of financial constraints and a low case number, patient recruitment was prematurely stopped, and only 25 subjects were enrolled. One major result was that there was no significant difference in the eGFR decline within the first year (-4.2 ± 14.4 vs. -6.6 ± 12.0 ml/min/1.73 m^2 in the treatment versus placebo group). Moreover, treatment did not affect renal lesions in follow-up biopsies, the course of proteinuria, or DSA-MFI. Graft loss rates were low, with one loss in each group. Treatment was well-tolerated, and there were no differences regarding adverse events and hospitalization rates, respectively. Although underpowered to provide definitive answers, this trial may argue against a relevant therapeutic effect of IVIG/rituximab [35].

Proteasome inhibition

Inhibition of the 26S proteasome in myeloma is well-established to prevent the proper degradation of misfolded proteins, a trigger of endoplasmatic reticulum stress and a proapoptotic condition promoting the death of malignant plasma cells. In the last decade, the use of proteasome inhibitors to affect the integrity of nonmalignant plasma cells has gained increasing interest in transplant medicine [43,44].

Uncontrolled studies

In early studies, treatment of kidney transplant recipients with the first-generation proteasome inhibitor bortezomib was shown to trigger apoptosis of alloantibody-producing bone marrow plasma cells [45]. Since then, this agent has been broadly used for recipient pretransplant desensitization or ABMR treatment, commonly in combination with other therapies [46–50]. A large number of case series was thereby supportive of a treatment effect, even though interpretation of results was complicated by considerable therapeutic polypragmasia (i.e. administering of multiple drugs) and the lack of robust RCTs. In an observational cohort study, Walsh *et al.* [48] reported therapeutic efficiency of bortezomib in combination with PP, IVIG and rituximab in early ABMR. This was supported by a marked improvement of eGFR and a considerable morphological response. However, in the same study, patients with late ABMR were less responsive, suggesting limited treatment efficacy in this indication. As in many other observational studies, the concomitant use of "standard of care" treatment (PP, IVIG), however, complicated a valid interpretation of results [48].

BORTEJECT trial

Very recently, Eskandary *et al.* [34] reported a double-blinded single centre RCT evaluating bortezomib as the sole treatment of late ABMR. Forty-four recipients with late ABMR were randomized to receive either two cycles of bortezomib or placebo. The primary endpoint was the course of eGFR over 2 years as a surrogate endpoint predicting long-term graft survival, whereby, anticipating an eGFR slope of about -9 ml/min/1.73 m^2 per year, the study was powered to detect an annual 5 ml/min/1.73 m^2 difference in the eGFR slope. A key finding in this study was that groups did not differ with respect to kidney function, both showing an eGFR slope of approximately -5 ml/min/1.73 m^2 per year. Notably, the eGFR

Table 2. Planned and ongoing, trials evaluating new therapies in late and/or chronic ABMR after kidney transplantation.

Treatment	Participating centres	Design; interventions	ClinicalTrials.gov
Anti-IL-6 antibody	Los Angeles, CA (USA) [70]	Single arm trial (n = 10): clazakizumab (6 months)	NCT03380377
Anti-IL-6 antibody	Vienna (Austria); Berlin (Germany) [68,69]	RCT (n = 20): clazakizumab vs. placebo (part A month 0–3); clazakizumab (open-label part B: month 4–12)	NCT03444103
Anti-IL-6 antibody	USA, Europe, Australia [71] (IMAGINE trial)	RCT (IMAGINE trial; n = 350): clazakizumab versus placebo (260 weeks)	NCT03744910
DFPP	Genoble (France) [83]	Open-label RCT (n = 16): PP + RTX vs. DFPP + RTX (11 days treatment course; 1 year follow-up)	NCT03436134
Bortezomib – combined regimen	France [53] (TRIBUTE trial)	RCT (n = 100): bortezomib + PP + IVIG + dexamethasone vs. PP + IVIG + dexamethasone	NCT02201576
Bortezomib – combined regimen	Tehran (Iran) [54]	RCT (n = 20): bortezomib + PP + IVIG + RTX vs. PP + IVIG + RTX	NCT03737136
Corticotropin	Birmingham, Alabama (USA), Baltimore, Maryland (USA) [89]	Single-arm trial (n = 20): corticotropin (24 weeks) in addition to centre-specific standard therapy	NCT02546492
Mesenchymal stem cells	Ljubljana (Slovenia) [90]	Single-arm (n = 10): mesenchymal stem cells + PP, IVIG and steroids	NCT03585855

DFPP, double filtration plasmapheresis; IL-6, interleukin-6; IVIG, intravenous immunoglobulin; PP, plasmapheresis; RCT, randomized controlled trial; RTX, rituximab.

decline in the control arm was less pronounced than expected, and the study was not powered to detect smaller changes in kidney function. There was, however, no effect of bortezomib on other secondary outcomes, including the course of DSA-MFI and the morphological and molecular results of 24-month follow-up biopsies. Bortezomib, however, was associated with a trend towards more severe adverse events, in particular, gastrointestinal side effects and haematological toxicity [34]. A recent nonhuman primate model has provided possible explanations for the disappointing results of the BORTEJECT trial [51]. In this study, animals were sensitized by incompatible skin allografts. Treatment with bortezomib led to a transient decrease in antibody-secreting cells, however, was followed by an immediate increase in germinal centre T cells and reconstitution of B cells as well as antibody secreting cells [51].

New concepts

Experimental data suggest that the rebound of humoral alloimmunity may be overcome by the combination of bortezomib with costimulation blockers. In a study by Burghuber *et al.* [52], in a sensitized nonhuman primate transplant model, such combined treatment was found to effectively prevent sensitization and transplant rejection. However, in this experimental study considerable rates of severe infections and deaths were reported [52]. As shown in Table 2, there are currently two ongoing registered trials where bortezomib (two cycles) is applied as an add-on to other treatments, such as PP, steroids, rituximab and/or IVIG [53,54]. Finally, a potentially interesting concept may also be the use of alternative proteasome inhibitors, such as carfilzomib, which in contrast with bortezomib is an irreversible proteasome inhibitor with a favourable toxicity profile. This compound was recently evaluated in an observational study including 14 lung transplant recipients believed to have acute ABMR [55]. In this study, carfilzomib was used in addition to PP and IVIG. The authors reported on 10 responders in whom treatment led to a decrease in DSA levels and C1q fixation, which was associated with less chronic graft dysfunction and ABMR progression [55].

Complement blockade

Anti-C5 antibody eculizumab

In a study from the Mayo clinic, C5 blockade using the monoclonal antibody was suggested to prevent acute

ABMR in flow crossmatch-positive kidney transplant recipients (comparator: historical control group), even though long-term treatment failed to counteract the development of chronic ABMR [14,15,56]. In a subsequent (still unpublished) RCT, eculizumab has failed to prevent acute ABMR in sensitized live donor kidney transplant recipients [57]. In the setting of chronic ABMR there is one small nonblinded RCT available [16]. In this study, 15 patients were included to receive either eculizumab ($n = 10$) or no such treatment ($n = 5$). There was no effect on gene expression patterns in follow-up biopsies. However, the authors noted a marginal effect on the course of allograft function (trajectories of eGFR). The study was limited by its small sample size, which complicated interpretation of results [16].

Anti-C1s antibody BIVV009

There is evidence of limited efficacy of C5 blockade in late ABMR, and one may argue that terminal complement inhibition does not preclude earlier key steps of DSA-triggered complement activation, such as C3 cleavage and the release of the anaphylatoxin C3a. In this respect, early blockade of complement at the level of key component C1 may be of interest. One compound of interest is the C1s monoclonal antibody BIVV009 (former term TNT009) which allows for a selective blockade of the CP. In a phase 1 study, this antibody was shown to abrogate CP activity in healthy volunteers [58], and in a subsequent uncontrolled pilot trial, the antibody was tested in patients with late ABMR associated with features of complement activation (C4d staining and/or complement fixation to microbeads) [17]. Patients received four doses of BIVV009, which led to complete CP blockade in peripheral blood for at least 5 weeks. A major finding was that in follow-up biopsies C4d staining was markedly reduced, suggesting that CP was also effectively inhibited at tissue level. Nevertheless, treatment failed to affect gene expression patterns in biopsies performed after 5 weeks. In parallel, there was no significant effect on features of microcirculation inflammation (glomerulitis or peritubular capillaritis scores) [17].

C1 esterase inhibitor

Another approach is the use of purified C1 esterase inhibitor (C1-INH), which might have a variety of relevant pharmacological actions beyond the dissociation/inactivation of C1, including interference with the lectin pathway, the alternative pathway, coagulation and the kallikrein-kinin system [59]. In a randomized controlled two-centre study by Montgomery *et al.* [60], C1-INH was suggested to prevent the development of chronic injury. However, no significant effect was seen in early follow-up biopsies (the primary endpoint), but in a subset of patients with late biopsies, there was less development of cg. At the same time, the authors reported a trend towards an improved graft function. These data may be in line with an uncontrolled study evaluating patients with refractory ABMR [61]. Comparison with a historical control group revealed some benefit, including improved kidney function and regression of ABMR features in follow-up biopsies [61]. Currently, a large multicentre study evaluating C1-INH as add-on to standard treatment in acute ABMR, which plans to enroll 90 patients, is underway [62].

Treatment of late ABMR – concepts in the pipeline

IL-6/IL-6R interference

IL-6 is a pleotropic cytokine involved in many facets of innate and adaptive immunity. Blockade of the Il-6/IL-6R axis, a concept well-established for the treatment of rheumatoid arthritis [63], was discussed to slow ABMR progression because of its effects on B cell immunity, including the generation and integrity of antibody-producing plasma cells [64]. Moreover, a beneficial mode of action may be an altered balance between effector and regulatory T cells [64].

Recently, Choi *et al.* [65] reported on a series of 36 paediatric and adult kidney transplant recipients with chronic ABMR refractory to IVIG/rituximab plus/minus PP, who all underwent monthly treatment with anti-IL-6R monoclonal antibody tocilizumab. The authors reported an acceptable safety profile, favourable graft survival rates (80% at 6 years, a significant reduction in DSA levels over time, stabilization of renal function, and a reduction in microcirculation inflammation and C4d staining in follow-up biopsies [65]. These data support a therapeutic impact of tocilizumab in ABMR. However, interpreting these data, concerns about the varying natural history of rejection need to be considered, and the true safety and efficacy of IL-6(IL-6R) antagonists will need to be clarified in a systematic trial with rigorous controls.

An interesting approach in this respect may be the use of clazakizumab, a genetically engineered anti-IL6

monoclonal antibody that has earlier been shown to be highly effective in rheumatoid arthritis and psoriasis arthritis [66,67]. As shown in Table 2, two pilot trials evaluating clazakizumab in late/chronic ABMR are currently underway [68–70], and, very recently, a large multicentre trial has been registered in the NIH database [71]. One concern about these biologicals is what toxicities will be incurred in fully immunosuppressed kidney transplant recipients: it is likely to be higher than the toxicity in rheumatoid patients, who are not on full immunosuppression.

Targeting B-lymphocyte stimulator

Another interesting strategy to modulate B cell alloimmunity may be targeting B-lymphocyte stimulator (BLyS), a cytokine that enhances B cell survival and proliferation and significantly contributes to the plasma cell niche [72]. Belimumab, a humanized anti-BLyS antibody was shown to be effective in the treatment of systemic lupus erythematosus [73] and has now entered clinical research in transplantation. In a phase 2 randomized double-blind trial, belimumab was evaluated as an induction treatment in 28 kidney transplant recipients [74]. There was no significant effect on the primary endpoint, naïve B cell counts in peripheral blood from baseline to week 24. However, the IL-10/IL-6 ratio of the B cell profile was skewed towards a more regulatory profile, and activated memory B cells and plasmablasts were significantly reduced. In parallel, tissue-specific antibodies in serum were lowered. Gene expression analysis in peripheral blood suggested attenuation of genes coding for immunoglobulin G (IgG), and at the same time markers of T cell proliferation were reduced [74]. Of course, the study was too small to be powered for detection of clinical outcome differences, but some of the preliminary results of this trial may be of interest for the context of ABMR treatment. Currently, there is a study underway, where belimumab – combined with bortezomib, PP and rituximab – is evaluated as a pretransplant desensitization therapy [75] (Table 2).

Targeting CD38

Another target of potential interest may be the transmembrane protein CD38, which is expressed at high levels in plasma cells. Daratumumab, a humanized monoclonal anti-CD38 antibody, has now been approved for the treatment of relapsed or refractory myeloma [76,77]. Its mode of action includes the induction of complement-dependent cytotoxicity and apoptotic signalling in CD38-expressing cells. One may argue that this antibody also depletes alloantibody-producing plasma cells, perhaps being an effective way to counteract alloantibody production. In addition, an interesting mode of action may be the induction of fratricide of CD38-expressing NK cells [78]. Considering the discussed pathogenetic role of NK cells in rejection, one may argue that this effect could be beneficial in ABMR treatment. In support of effective interference with humoral alloimmunity, Chapuy *et al.* [79] reported on the successful use of daratumumab for red cell repletion in a case of ABO-incompatible allogeneic stem-cell transplantation, presumably the result of a marked effect on ABO antibody production. One concern using this antibody in transplant patients may be the earlier shown reduction of CD38-expressing regulatory T cells, an effect that may be advantageous in the context of cancer treatment, as it promotes host-antitumor immune responses [77]. To our knowledge there are no published studies that have evaluated the use of daratumumab or other CD38 antibodies, such as isatuximab [80] in organ transplant rejection. Nevertheless, the unique mode of action may be of interest for the prevention and treatment of ABMR.

Apheresis

Apheresis (PP, immunoadsorption) to deplete circulating alloantibodies is broadly used in the treatment and prevention of acute ABMR. Even in this setting, however, evidence levels are low, and only few small RCTs are available [33,81]. Some authors have promoted the use of apheresis, combined with other treatments, for use in late or chronic ABMR [42]. However, given the lack of randomized studies, the true efficiency of extracorporeal antibody depletion in this specific context remains unclear. Different techniques may vary considerably in their treatment efficacy. This may include the depletion of DSA as well as other components that potentially contribute to injury, such as complement proteins. For example, the combined use of a porous membrane filter and conventional immunoadsorption, the latter to eliminate IgG, was recently shown to markedly enhance the depletion of macromolecules, including IgM and CP key component C1q [82]. Currently, a controlled trial is underway, where double filtration plasmapheresis to selectively remove macromolecular plasma components versus conventional PP, both in combination with rituximab, are evaluated in chronic ABMR [83].

Immunoglobulin G–degrading enzyme of *Streptococcus pyogenes*

There is now increasing interest in the use of immunoglobulin G–degrading enzyme of *Streptococcus pyogenes* (IdeS) for enzymatic degradation of alloantibodies [84]. Recent studies have shown that, upon virtually complete elimination of intact IgG, IdeS creates a window of opportunity allowing for transplantation across major HLA antibody barriers [85,86]. A caveat is its short half-life and a rapid neutralizing anti-IdeS antibody response that impedes repeated administration [87]. Moreover, transient cleavage of the IgG type of B cell receptor resulting in a profound inhibition of receptor signalling and memory B cell activation [88] may not be able to considerably affect rebound antibody responses: first studies on the use of IdeS as a pretransplant desensitization treatment have shown that, despite effective IgG elimination, a significant proportion of treated patients developed rejection, which was attributed to a rapid rebound of antibody [85,86]. It was suggested that the type of adjunctive immunomodulatory treatment might be decisive in preventing this phenomenon. In this respect, however, a major challenge is that IdeS also inactivates therapeutic antibodies (e.g. IVIG, rituximab or rabbit ATG). IdeS has to our best knowledge so far not been tested in late (chronic) ABMR. Given its short half-life and the transient effect on IgG integrity, respectively, one may argue that IdeS would have limited therapeutic efficiency in this specific context.

Alternative strategies studied in ongoing trials

Other new strategies tested in ongoing registered trials are corticotropin [89] and the use of mesenchymal stem cell transplantation [90], both as an add-on to centre-specific standard treatment, in an effort to modulate alloimmunity in chronic rejection.

The challenge of trial design

There is a need for robust interventional trials to clarify the efficiency of innovative treatment concepts in ABMR. However, the design of a high standard trial in late ABMR, given the variation in natural history, must use the gold-standard of a randomized placebo-controlled design, which represents a unique challenge. Several important aspects, such as adequate case selection, stratification for stage and the choice of an appropriate primary endpoint that precisely predicts long-term allograft survival, need to be considered. This also includes the definition of a proper sample size to meet the goal of detecting meaningful outcome differences.

The use of hard clinical endpoints, in particular, graft survival, would require the recruitment of hundreds of patients and, given rather low overall event rates, prolonged observation periods. Early alternative outcome parameters that are able to reliably predict the long-term fate of allografts may be an effective strategy to substantially reduce sample size requirements. One useful surrogate endpoint may be the slope of eGFR, which in the context of *de novo* DSA was shown to be tightly associated with long-term renal allograft survival [27]. However, to detect meaningful slope differences, still a considerable number of patients need to be included, which supports the choice of a multicentric approach. In this respect, much has been learned from the BORTEJECT trial, where a power analysis based on registry data (average eGFR decline and its variation in an Austrian transplant population) revealed the need of a comparatively small sample size (44 patients) to establish an annual slope difference of 5 ml/min/1.73 m^2 between study groups [91]. This difference was chosen on the basis of retrospective data that suggested an eGFR slope of -8 ml/min/1.73 m^2 per year for patients with late C4d-positive ABMR, and the assumption that bortezomib would approximate the course of eGFR to that of nonrejecting patients. At the end, deterioration of graft function in the BORTEJECT trial, however, was far less pronounced than expected, likely because many cases were subclinical at ABMR diagnosis. Placebo (and bortezomib) patients had an annual eGFR decline of approximately -5 ml/min/m^2. Thus, reaching the endpoint would have required a slope reduction to zero in patients receiving treatment, which is unrealistic and highlights the importance of a careful sample size calculation adjusted to the studied patient population, and of course the critical importance of controls [34].

Another (invasive) surrogate endpoint may be the read-out of systematic follow-up biopsies. Lesions reflecting microcirculation inflammation are well-known to be associated with the development of chronic lesions, such as transplant glomerulopathy or basement membrane multilayering in peritubular capillaries [92], and chronic microcirculation injury has shown to be a strong predictor of graft survival [32]. In addition, one may argue that detecting patterns of transcript expression that specifically reflect the extent of rejection and injury may help to dissect treatment responsiveness (or nonresponsiveness) early after initiation of a given intervention. Gene expression analysis using the MMDx

platform has been used as a secondary endpoint in two prospective intervention trials conducted in late ABMR, the BORTEJECT study and a trial evaluating C1s inhibitor BIVV009 [17,34]. The result of absent changes in gene expression patterns thereby paralleled the lack of any relevant treatment effect on transplant outcomes [17,34].

Again, a major point is that enhanced immunosuppression to counteract rejection confers a risk of increased toxicity. Besides substance-specific patterns of toxicity, compounds that effectively target critical key steps of B cell immunity and/or affect plasma cell integrity, can be expected to confer a substantial risk of over-immunosuppression and associated adverse events, in particular, infections. This may be of particular relevance for the transplant setting, where most treated patients are already on multi-compound baseline immunosuppression, with a history of prior anti-rejection treatments in many cases. In this specific context, the choice of appropriate medication dosage, paired with careful patient monitoring and adjustment of baseline immunosuppression, needs to be considered.

Planning a systematic evaluation of new therapeutic concepts, one attractive strategy may be the design of one or more (controlled or uncontrolled) pilot trials conducted in advance of a larger RCT adequately powered to detect relevant outcome differences. Pilot studies may provide first insights on the safety and efficacy of a given treatment, supporting the appropriate design of a subsequent pivotal trial. A representative example is the current multi-step approach for the evaluation of IL-6 monoclonal antibody clazakizumab in late ABMR. This compound, which has been successfully tested in patients with autoimmune disease, is now being evaluated in the context of late and/or chronic ABMR. Two small independent investigator-initiated short-term pilot trials are currently underway, primarily to explore the safety and tolerability of clazakizumab in patients on standard immunosuppression [68–70]. Moreover, in both studies an array of efficacy endpoints including protocol biopsies will be evaluated. Preliminary results can be expected to provide a valuable foundation for the design of a large multicentre RCT (IMAGINE trial) which is planned to include more than 300 recipients with an extended follow-up of 5 years to detect meaningful differences in eGFR slope and graft survival, respectively [71].

Conclusion

Currently, there is no treatment proven to be effective in late and/or chronic ABMR. For sole treatment with bortezomib, and the combined use of high dose IVIG plus rituximab, double-blind RCTs have failed to demonstrate a meaningful short-term effect on ABMR progression. Complement inhibitors may have limited efficacy, as small studies – including one controlled pilot trial – revealed no or only marginal clinical effects. However, there are several promising new treatment concepts in the pipeline, which require careful evaluation in robust intervention trials before they can be introduced into broad clinical practice.

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