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REVIEW

Antibody-mediated kidney allograft rejection: therapeutic options and their experimental rationale

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Summary

With the advent of novel therapies to directly intervene with B cell immunity and complement activation, antibody-mediated kidney allograft rejection (AMR) has come into the focus of transplant immunologists. Intravenous immunoglobulin, rituximab, bortezomib, and eculizumab have been used to treat patients with acute AMR, apart from the standard treatment of antibody removal with plasma exchange or immunoadsorption and steroid pulses. This article describes the experimental rationale and summarizes the still limited clinical experience with these novel therapies in the transplant setting. Results with the standard treatment for acute AMR, including intense plasmapheresis, intravenous immunoglobulins, and steroids are good with a graft survival of 80% at 18 months. In contrast, patients suffering from chronic AMR have significant irreversible damage in their grafts with substantially impaired graft survival. Thus, the authors propose a step-wise escalation of therapy in refractory cases of acute AMR and advocate an urgent need for controlled therapeutic trials for acute and chronic AMR not to inflict unnecessary harm on our patients by uncontrolled polypragmasy.

Introduction

Three major factors limit the success of kidney transplantation as the preferred therapy for end stage renal failure: (i) acute and chronic rejection as a manifestation of underimmunosuppression, (ii) direct allograft toxicity, infections, and tumors as a consequence of overimmunosuppression, and (iii) death of the patient with a functioning graft mainly as a result of cardiovascular complications caused by either the underlying disease and/or side effects of immunosuppressants [1]. Recently, major efforts have been undertaken to limit long-term complications through immunosuppression minimization trials. However, most of them have been associated with more frequent rejection episodes [2]. In parallel, it has been increasingly recognized that alloimmunity plays a critical role for many of the chronic lesions previously called ''chronic allograft nephropathy'' [3], and the development of *de novo* donor-specific anti-HLA antibodies (DSA) is associated with reduced graft survival [4]. Thus, caring for a kidney allograft recipient often feels like traveling on the boat with Odysseus – a famous hero of the Trojan war described in Greek mythology – through the passage of Messina trying to avoid the two monsters Scylla as the devouring and destructive alloimmune response and Charybdis representing the threats of overimmunosuppression (Fig. 1).

With the advent of more sensitive techniques to measure DSA and demonstrate antibody deposition in allograft biopsies via C4d staining, it has been possible to more reliably define the novel entities of acute and chronic antibody-mediated rejection (AMR; [5]). The definite diagnosis of AMR relies on three facts: (i) presence of DSA, (ii) deposition of C4d in peritubular capillaries, together with other typical histological hallmarks, and (iii) allograft dysfunction manifested by declining GFR, rising proteinuria or both. If all three criteria are present, diagnosis of AMR can be made with high certainty. However, in clinical

Figure 1 Odysseus between Scylla and Charybdis (1794/96). Painting by Johann Heinrich Füssli, Oil on canvas. Art Museum in Aarau, Switzerland (Inventory 884).

practice often only one or two of these criteria are present, which hampers the design of good clinical trials to study novel therapies for these conditions.

When planning treatment of AMR, several options exist to interfere with the cascade of B cell immunity (Fig. 2). B cells develop into plasma cells, which then produce antibodies that bind to the target tissue and activate complement. Complement can directly destroy target tissues via its membrane attack complex (consisting of components C5-9), and it releases chemotactic fragments (such as C5a), which attract inflammatory cells to the allograft. There are now options to therapeutically intervene on every level of this cascade. In this review, we briefly discuss each of these options together with their experimental rationale and the current clinical experience. One has to bear in mind that isolated AMR does not exist outside the rare clinical situation of hyperacute rejection, where preformed antibodies destroy the allograft within hours. In all other situations, AMR is associated with T cell-mediated rejection (TMR), as a sensitized T-cell response is a prerequisite for the formation of DSA of IgG isotype. Thus, preformed anti-HLA antibodies also serve as a risk marker for TMR [6], and treatment of AMR should always include an element of T-cell immunosuppression.

Targeted therapy in acute AMR

Acute AMR is characterized by the presence of DSA, acute allograft dysfunction often associated with impaired urine output, C4d deposition in peritubular capillaries and morphologic evidence of acute tissue injury. Alloantibodies preferentially attack the endothelium of peritubular and glomerular capillaries. The histological hallmarks are acute tubular necrosis, glomerulitis or capillaritis with neutrophils and mononuclear cells, capillary thrombosis, transmural arteritis, or fibrinoid necrosis of arteries (Fig. 3; [5]). The classical approach to treatment of acute AMR includes antibody removal combined with intravenous immunoglobulins (IVIG). Newer therapies, which mainly target the B cell cascade, will be discussed individually in the following paragraphs.

Antibody removal – plasma exchange or immunoadsorption

Circulating DSA deposited in the kidney and activating complement are the pathogenetic hallmark of AMR.

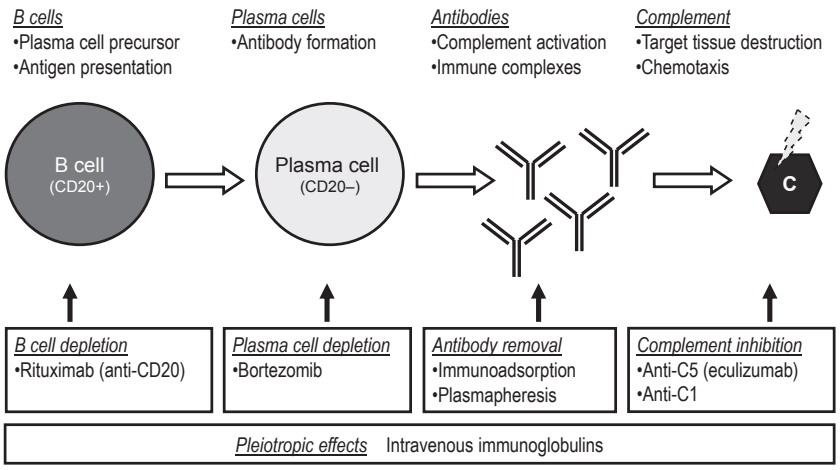

Figure 2 Cascade of B cell immunity. Schematic representation of the cascade of B-cell immunity from the mature B cell to complement activation, and available options to therapeutically intervene on each level (bottom part of the figure).

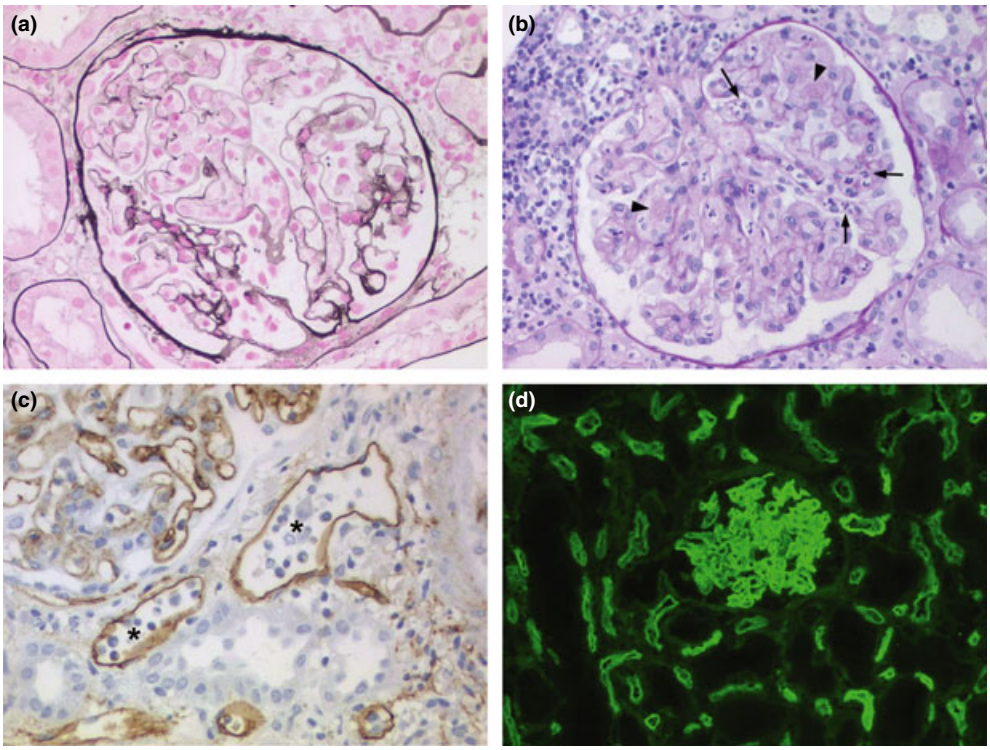

Figure 3 Histological hallmarks of acute AMR. (a) Transplant glomerulitis with increased mononuclear cells in glomerular capillary loops (silver methenamine stain, original magnification 160×). (b) Glomerulitis with neutrophils (arrows) and fibrin (arrowheads) in capillary loops (periodic acid-Schiff stain, original magnification 160×). (c) Capillaritis with dilated peritubular capillaries and accumulation of mononuclear cells (asterix; immunohistochemistry for CD31, original magnification 250×). (d) Diffuse bright linear positivity for C4d in peritubular capillaries and glomerular capillaries (immunofluorescence stain, original magnification 100×).

Thus, antibody removal has been a mainstay of treatment in most centers, since all other treatments do not allow to lower antibody titers fast enough, as it is required in acute AMR. We are aware of only two randomized controlled trials evaluating this treatment. An earlier study performed by Soulillou *et al.* in 1983 showed no benefit of early and extensive plasma exchange compared with conventional therapy [7]. However, AMR therapy at that time was otherwise limited to steroid pulses, and maintenance immunosuppression consisted only of azathioprine and prednisone. As mentioned above, AMR almost never occurs isolated, but is always associated with a component of TMR, which was not affected by plasma exchange and low-dose double immunosuppression.

In the late 90s, the first uncontrolled series of patients were reported, in whom acute AMR was successfully reversed using plasma exchange with [8] or without IVIG [9] in combination with tacrolimus, and mycophenolate mofetil. The only randomized controlled study in recent time was performed by Böhmig *et al.* and compared two patient groups receiving either steroid pulses + conversion to tacrolimus/mycophenolate mofetil or the same plus additional immunoadsorption (IADS) using protein A columns [10]. This trial was stopped after 10 patients, as four of the five patients lost their graft in the control group compared with no graft loss in the IADS group. One patient in the latter group died as a result of a non-treatment-related cause (aspiration).

IADS using protein A- or sheep-anti-human Ig-coated columns has theoretical advantages over plasma exchange, as higher volumes of plasma can be treated, immunoglobulin G is removed almost completely (>95% after two treatments [11]), and no disturbances of coagulation factors occur. However, both treatment modalities lead to significant IgG depletion and may require IVIG substitution to prevent infections in the context of otherwise intense immunosuppression, although this risk has to be balanced by the potential side effects of IVIG application [11]. There are no reported studies directly comparing plasma exchange with IADS in terms of efficacy and safety for treatment of AMR, but both seem to be effective.

Pleiotropic immunomodulation by IVIG

Intravenous immunoglobulin is widely used for treatment of autoimmune diseases, and it is used as an element of

desensitizing protocols for ABO- and HLA-incompatible renal transplantation [12,13]. A lot has been speculated on how it exerts its immunomodulatory effects. In the context of AMR therapy, the effects of IVIG on the B cell cascade are of particular interest. Ravetch *et al.* showed that inhibitory FcγIIB receptors expressed on B cells modulate their activation [14]. Later, the same group demonstrated that the anti-inflammatory properties of IVIG are indeed mediated through the Fc portion of the immunoglobulin molecule and depend on differential sialylation of the Fc core polysaccharide [15]. They could be reproduced by recombinant isolated and appropriately sialylated Fc molecules [16]. Seite *et al.* reported that sialylated IVIG binds to CD22 and induces apoptosis in mature human B cells [17]. Furthermore, sialylated Fc molecules suppress inflammation through a novel T(h)2 pathway by triggering IL-33 secretion in macrophages and dendritic cells [18].

Apart from its effects on B cells and antigen-presenting cells, IVIG also functions as a scavenger of activated complement, as shown by *in vitro* studies [19] as well as in sera from patients treated with high-dose IVIG for acute AMR [20].

For treatment of acute AMR in kidney and heart allografts by high-dose IVIG, a first uncontrolled series was published by the Jordan group showing successful reversal of this condition in 10 patients, four of which had clear evidence of high level DSA [21]. So far there is only one randomized-controlled trial comparing IVIG (7×500 mg/kg/d) to OKT3 [22]. In this study, IVIG was equally effective in terms of graft and patient survival in 30 patients suffering from steroid-resistant acute rejection. However, at the time of the study (1995–97) no strict definition of AMR based on highly sensitive detection of DSA and C4d staining was available yet, so most probably a mix of acute AMR and TMR was included. Further evidence comes from a number of observational studies summarized in a recent review [23]. These authors recommend the use of IVIG in combination with antibody removal (but *not* alone), and this is in fact what most centers are doing according to a recent meta-analysis [24]. It also corresponds to the most recent recommendations in the KDIGO guidelines for the management of kidney allograft recipients [25].

B cell depletion – rituximab (anti-CD20)

Rituximab is a chimeric antibody recognizing the cell surface marker CD20, which is expressed on most stages of B cell development except the very early stages and the plasma cell [26]. It is widely established for treatment of lymphoma, but has only recently found its way into transplantation medicine, where it has found a firm place as induction agent for ABO blood group incompatible kidney transplantation [27].

Experimental evidence for the treatment of acute AMR came from a study by Wu *et al.*, who used HLA-A2 transgenic mice as donors for skin grafts on conventional C57BL6 mice [28]. These mice developed cytotoxic anti-A2 antibodies. After treatment with a murine anti-CD20 antibody, a drop in cytotoxic antibody titers and subsequently prolonged survival of secondary A2-positive grafts were observed.

The first clinical experiences were reported in two pilot studies with eight and seven patients, respectively. The first study by Faguer *et al.* reported graft survival after a mean follow-up of 10 months in six of the eight patients treated with 3–5 doses of 375 mg/m^2 rituximab given in weekly intervals [29], whereas the second study by Muller *et al.* observed 100% graft survival in seven patients treated with a single dose of 500 mg/m^2 rituximab [30]. These patients showed a mean drop of creatinine from 559 to 171 μmol/l. A limitation of the first study was the doubtful inclusion criteria (e.g. two patients had neither DSA nor C4d positivity). Furthermore, in both of these studies significant infectious complications in up to 50% of patients occurred (cytomegalovirus, shingles, polyomavirus nephropathy, and fungal infection). A higher risk of infection-associated death was confirmed in a separate retrospective analysis performed by Kamar *et al.* on rituximab-treated patients after kidney transplantation, but this risk was particularly high when rituximab and anti-thymocyte globulin (ATG) were combined [31]. Reports on increased incidence of infectious complications after rituximab therapy outside of the field of transplantation (e.g. progressive multifocal encephalopathy associated with JC virus, liver failure-associated with Hepatitis B reactivation) are also disturbing [32].

Two studies evaluated rituximab as part of a combination treatment approach. Lefaucheur *et al.* compared 12 patients receiving a combination treatment with rituximab, plasmapheresis and IVIG with a historic control group of 12 patients receiving only high-dose IVIG. Graft survival was improved from 50% to 92% in the combination treatment group [33]. However, as rituximab and plasmpheresis were added to the treatment in the combination group, the separate impact of these two components could not be assessed. Knowing that a rigorous plasma exchange/IVIG protocol achieves a success rate of around 80% graft survival [24], it is likely that the addition of plasma exchange had a more important impact than rituximab. A high level of DSA and the failure to decrease them by treatment were significant predictors of graft loss in this study, a finding independently confirmed by others [34].

So far the largest rituximab study included 54 patients and compared a historical group treated with plasma exchange and IVIG with a later group receiving a single dose of 500 mg/m^2 rituximab in addition [35]. In this study, the use of rituximab was associated with a 90% 2-year graft survival, compared with 60% in the control group. However, the study was limited by its retrospective design, even if the benefit associated with the use of rituximab remained significant in multivariate analysis. Recently, a retrospective study comparing a historic rituximab-based with a recent bortezomib-based regimen showed only one of the nine grafts surviving at 18 months in the rituximab group [36].

Taken together, the benefit of adding rituximab to established treatment protocols for acute AMR remains doubtful given the fact, that the benefit is small in the published patient series, and a positive publication bias seems likely. One reason may be that acute AMR is usually a rapidly occurring event, and potential positive effects of rituximab treatment may just be too slow to take place, before the allograft is lost. Furthermore, the use of rituximab in this context may be associated with a significantly higher risk of infection [31].

Plasma cell depletion/proteasome inhibition – bortezomib

Bortezomib is a proteasome inhibitor widely used for the treatment of plasma cell dyscrasias. In contrast to rituximab, which does not affect the antibody-forming cell pool, bortezomib selectively induces apoptosis among plasma cells in whole bone marrow cell cultures [37]. By doing so it also reduces secretion of alloantibodies in bone marrow cultures *in vitro*. In the same study, bortezomib treatment *in vivo* was able to block anti-HLA antibody production in a patient providing three bone marrow aspirates before transplantation, at the time of AMR and 1 week after bortezomib treatment.

Clinical experience with this compound in the context of acute AMR is still limited. A first series of six patients was reported in 2008 by Everly *et al.*, who showed reversal of combined AMR and TMR associated with a significant decline of DSA in all patients [38]. This result was even more impressive in the light, that these patients were refractory to ''standard treatment,'' such as plasma exchange, IVIG and ATG, or rituximab.

The largest series of 20 patients was reported recently by Flechner *et al.* [39]. These patients also received bortezomib according to a myeloma schedule (4 doses at 1.3 mg/m^2 at days 1, 4, 7, and 11, each time preceded by a plasma exchange session). With this treatment regimen a graft survival rate of 85% at 10 months post-transplant was achieved. When performing subgroup analysis, the authors showed that the benefit of this treatment was largely limited to patients with still reasonable graft function (creatinine <3 mg/dl, proteinuria <1 g/d), whereas 50% of patients with a creatinine >3 g/dl at the time of treatment initiation lost their grafts. The mean decrease of the dominant DSA in MFI values was 50%. However, the side effects of treatment were considerable with 7/20 being hospitalized for a variety of symptoms (diarrhea with dehydration, edema, nausea, and vomiting, infection).

The most recent study compared 10 bortezomib-treated with a historical group of 9 rituximab-treated patients and achieved a graft survival of 60% with bortezomib compared to only 11% with rituximab at 18 months post-transplant [36].

Taken together, these preliminary results for bortezomib in acute AMR are very promising, but carefully performed controlled studies are necessary to prove its benefit and assess its side effect risk.

Complement inhibition – eculizumab (anti-C5) and C1 inhibitor

Alloantibodies exert their detrimental effect on allografts by intra-graft activation of complement, subsequent tissue destruction, and attraction of inflammatory cells to the graft. Thus, blocking complement activation as the last step in this cascade seems to be a very attractive concept. Experimentally, blockade of C5 with an anti-C5 monoclonal antibody was able to prolong survival of fully MHC-mismatched skin allografts in sensitized mice over 100 days, when used in combination with double immunosuppression consisting of cyclosporine, and leflunomide [40]. In parallel, C1 blockade prevented acute AMR of kidney allografts in allosensitized baboons [41].

So far there are only three case reports in the literature for the use of eculizumab in therapy-refractory AMR in humans [42–44]. The first case was a patient with DSA, who was desensitized with plasma exchange and CMV-Ig and who developed treatment refractory AMR despite ongoing plasmapheresis treatment 5 days after transplantation [42]. Eculizumab, a humanized anti-C5 monoclonal antibody approved for the treatment of paroxysmal nocturnal hemoglobinuria, was successfully used as a salvage treatment. As also rituximab and high-dose IVIG were given to this patient, this effect could not be solely attributed to eculizumab with certainty. However, complement C5-9 deposition was demonstrated by immunofluorescence in the graft at the time of AMR and was successfully reversed by eculizumab treatment in a follow-up biopsy. A similar effect on C5-9 activation was seen with an intentional ABO-incompatible combined kidney-pancreas transplant [44]. This patient had already received rituximab as an induction treatment and

subsequently developed an IADS-resistant AMR, which promptly responded to eculizumab treatment.

Very recently Stegall *et al.* presented a study using preemptive eculizumab as part of a desensitizing protocol and could demonstrate an impressive reduction of the incidence of acute AMR from 41% in a historic control group desensitized with plasma exchange/IVIG to 7.7% in the experimental group receiving additional eculizumab post-transplant. The treatment schedule was a modified protocol according to the treatment of patients with paroxysmal nocturnal hemoglobinuria. Patients received weekly doses of eculizumab up to week 5 (initial dose 1200 mg, then 600 mg) with bi-weekly doses of 1200 mg thereafter. Importantly, the two patients developing AMR despite preemptive eculizumab still responded to classical AMR therapy with plasma exchange and IVIG [45].

C1-inhibition has not been tested in clinical transplantation yet, but as a C1 inhibitor for treatment of patients with hereditary angioedema is already available [46], it may be a future treatment option for refractory AMR. This is further supported by the fact that C1q binding of anti-HLA antibodies was found to be predictive for the success of platelet transfusions [47]. A phase I/II trial testing the C1 inhibitor Berinert® (CSL Behring, Marburg, Germany) was initiated in fall 2011 (ClinicalTrials.gov number: NCT01134510).

Rescue splenectomy

There are desperate cases of acute AMR, which do not respond to any of the classical treatments described elsewhere in the text. One last option to salvage such a kidney relies on rescue splenectomy, which has been reported in the literature by at least three groups [48–50]. Splenectomy leads to an immediate and substantial reduction of the B cell and plasma cell pool, and subsequently to a drop of antibody titers [49]. How this leads to the immediate restoration of urine output and rapid improvement of kidney function with 1–2 days, as described in the reported cases, remains unclear. The authors have experience with rescue splencectomy in one case of a patient with acute AMR leading to oliguric allograft dysfunction in the context of ABO incompatibility and additional DSA. This patient's rejection was resistant to treatment with steroids, plasma exchange, protein A immunoadsorption and rituximab and promptly restored allograft function after rescue splenectomy and has stable graft function at a level of 35 ml/min eGFR 18 months thereafter (Fehr *et al.*, manuscript in prep.).

Most patients in the literature underwent this operation before the advent of eculizumab, and it may be well that in the future for many of these patients splenectomy might be avoided by using eculizumab instead [42]. The authors recommend splenectomy as a last escalation of therapy in resistant cases of AMR, in which bortezomib or eculizumab already failed (Table 1).

Treatment of chronic AMR

Chronic AMR is characterized by the presence of DSA, chronic allograft dysfunction manifesting itself by slowly creeping creatinine and often significant amount of proteinuria, C4d deposition in peritubular capillaries and morphological features, such as transplant glomerulopathy, peritubular capillary basement membrane multilayering, interstitial fibrosis and tubular atrophy, and fibrous intimal thickening in arteries without duplication of the internal elastica (Fig. 4; [51]). In theory, every option

Table 1. Step-wise treatment approach to the patient with acute AMR.

STEP 1	**Acute allograft dysfunction**	
	Allograft biopsy: acute AMR ± TMR	
	Treatment of AMR component	Treatment of TMR component
	Steroid pulses	Steroid pulses
	Antibody removal (plasma exchange or immunoadsorption)	Switch to tacrolimus/mycophenolate mofetil
	IVIG	
STEP 2	**Persistent allograft dysfunction**	
	Allograft biopsy: persistent/progressive acute AMR ± TMR	
	Treatment of AMR component	Treatment of TMR component
	Bortezomib	ATG
	Rituximab	
STEP 3	**Persistent allograft dysfunction**	
	Allograft biopsy: persistent/progressive acute AMR ± TMR	
	Treatment of AMR component	Treatment of TMR component
	Eculizumab	Anti-CD3 monoclonal antibody (OKT3)
	Rescue splenectomy	

AMR, antibody-mediated rejection; TMR, T cell-mediated rejection; ATG, anti-thymocyte globulin.

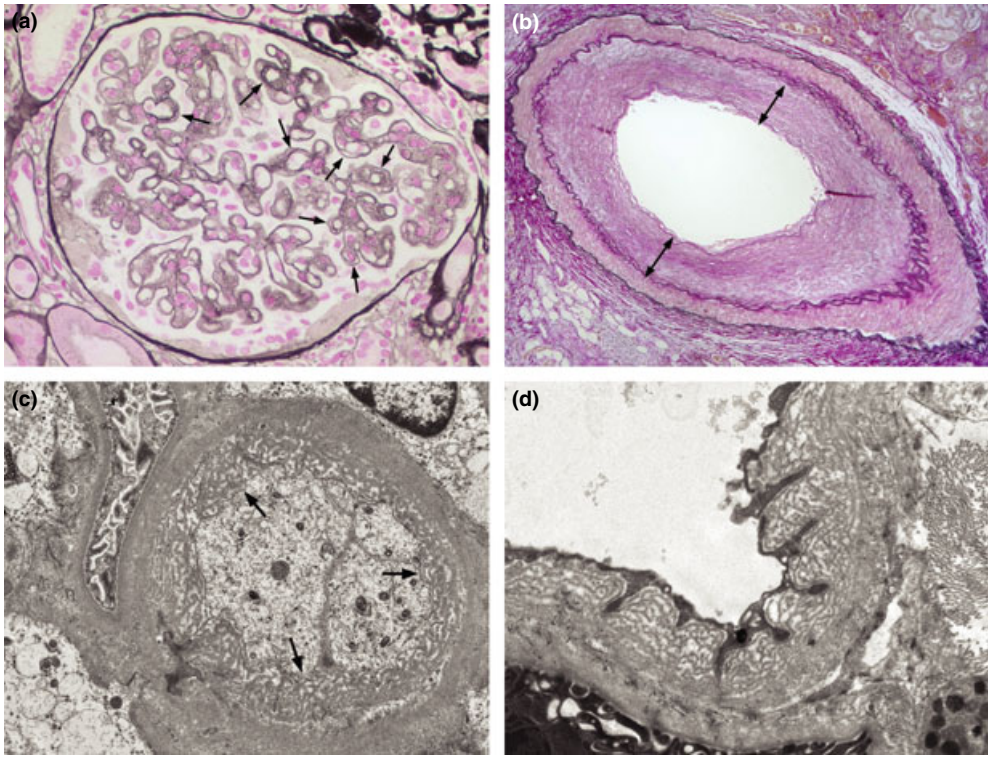

Figure 4 Histological hallmarks of chronic AMR. (a) Transplant glomerulopathy showing double contours (arrows) of the glomerular basement membranes (silver methenamine stain, original magnification 160×). (b) Fibrous intimal thickening (arrows) in an artery without duplication of the internal elastica (Elastica-van Gieson stain, original magnification 50×). (c) Transplant glomerulopathy with multilamellation (arrows) of the glomerular basement membrane (electron microscopy, original magnification 6800×). (d) Multilayering of the peritubular capillary basement membrane (electron microscopy, original magnification 7900×).

available to treat acute AMR could also be applied to chronic AMR. However, there are no controlled trials for treatment of chronic AMR reported in the literature. In addition, some of the treatment options for acute AMR are difficult to use in the setting of chronic AMR because of the high burden and cost required for continuous treatment (e.g., for continued plasma exchange or repeated application of eculizumab).

The only treatment option with some reported benefit is the combination of rituximab and IVIG. This combination has been successfully used for desensitization of broadly HLA-sensitized patients to bring them to transplantation [12]. In addition, this strategy was used for induction therapy in patients with pretransplant DSA to prevent chronic AMR and transplant glomerulopathy [52]. For treatment of established chronic AMR, there are only two case series with six pediatric and our own four adult patients in the literature [53,54]. In both series, some improvement of graft function was observed. DSA went down in only a part of these patients, which may indicate, that targeting the B cell compartment as a major pool of antigen-presenting cells is as important as the influence on DSA levels. In our own series, one of the four patients lost his graft around 1 year after rituximab treatment, whereas the other three grafts are still functioning now. Currently, several clinical trials are actively recruiting patients for evaluation of rituximab in the treatment of chronic AMR (ClinicalTrials.gov number: NCT00476164 in the UK, NCT00565331 in the Netherlands and an NIH-sponsored trial NCT00307125 in the US), the results of which should be awaited until drawing more definite conclusions on the efficacy of this treatment on the outcome of chronic AMR.

Very few patients received bortezomib as a rescue treatment for chronic AMR and proteinuria with mixed results: some patients showed a significant drop in DSA, others not – and the same was true for proteinuria [55,56]. This result was reminiscent of pilot series of four patients, in whom 1 cycle of bortezomib (4 doses à 1.3 mg/m^2) was used for the purpose of desensitization. In none of these patients, a drop of antibody titers was observed [57]. Taken together, these preliminary results temper the enthusiasm of using bortezomib in the context of chronic AMR. However, if multiple cycles of bortezo-

mib (as used for myeloma treatment) or the combination of bortezomib with other compounds would be more effective, cannot be answered at this stage.

As for complement inhibition, no data are available at the moment for the treatment of chronic AMR. However, one clinical trial evaluating eculizumab for the treatment of chronic complement-mediated injury in kidney transplantation is currently recruiting patients (NCT01327573).

Taken together, patients with chronic AMR already have a significant amount of irreversible damage in their grafts, and if C4d+ transplant glomerulopathy is present, graft survival is drastically impaired [58]. Thus, any treatment to intervene at this stage using drugs with potentially high toxicity should only be performed in the context of a well-controlled trial. Such a trial should ideally attempt to identify patients at risk at an earlier stage, before they develop transplant glomerulopathy as a probably irreversible lesion. One possible approach could be to install a systematic monitoring of DSA post-transplant, to perform protocol biopsies in patients developing *de novo* DSA or failing to clear pretransplant DSA and design an immunological intervention at the time, when early changes of chronic AMR are visible in protocol biopsies. Such a trial would certainly require a multicentric design and a long enough follow-up to yield conclusive results.

Conclusions and future directions

Acute AMR after kidney transplantation is a relatively rare, but usually dramatic event, and this has hampered the development of rational and controlled treatment strategies. Many novel and attractive treatment options have become available in recent years, and this has led to a polypragmasy of using anything possible in these urgent situations. In this context, it is important to know that with the use of antibody removal (plasmapheresis or immunoadsorption) and IVIG, the outcome of this previously dismal condition has massively improved. According to a recent meta-analysis, an overall patient survival was 99% and graft survival 80% at a mean follow-up of 18 months post-transplant can be expected [24]. Thus, any new addition to this standard treatment (be it rituximab, bortezomib, eculizumab, or other compounds) must show additional benefit compared to a rigorous plasmapheresis/IVIG regimen. The need for randomized controlled trials in this field is urgent, and such trials should include a thorough cost-effectiveness analysis including not only the cost of the treatment itself, but also those of treatment-related complications (mainly infectious complications), and comparing those to potential cost-savings of avoiding dialysis and retransplantation. Until such studies are available, these expensive drugs with a substantial side effect profile should only be used as rescue treatments in nonresponder patients. Importantly, transplant physicians should remind that AMR is almost never an isolated condition, but mostly combined with TMR in an HLA-sensitized patient, and treatment of refractory cases should also envisage this fact. Therefore, the authors suggest a step-wise and biopsy-based escalation of therapy in patients with acute AMR (see Table 1), always bearing in mind that fighting Scylla too aggressively may drive you too close to Charybdis (Fig. 1), and you risk losing your graft to polyomavirus or your patient to a severe infectious complication caused by overimmunosuppression.

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