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Full Reviews

Better understanding of transplant glomerulopathy secondary to chronic antibody-mediated rejection

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ABSTRACT

Transplant glomerulopathy (TG) is generally accepted to result from repeated episodes of endothelial activation, injury and repair, leading to pathological abnormalities of double contouring or multi-layering of the glomerular basement membrane. TG is a major sequel of chronic active antibody-mediated rejection (cABMR), from pre-existing or *de novo* anti-HLA antibodies. Hepatitis C infection, thrombotic microangiopathy or other factors may also contribute to TG development. TG prevalence is 5–20% in most series, reaching 55%, in some high-risk cohorts, and is associated with worse allograft outcomes. Despite its prevalence and clinical significance, few well-studied treatment options have been proposed. Similar to desensitization protocols, plasmapheresis with or without immunoabsorption, high-dose intravenous immunoglobulin, rituximab, bortezomib and eculizumab have been proposed in the treatment of TG due to cABMR individually or in various combinations. Robust clinical trials are urgently needed to address this major cause of allograft loss. This review summarizes the current knowledge of the epidemiology, etiology, pathology, and the preventive and treatment options for TG secondary to cABMR.

Keywords: chronic active antibody-mediated rejection, kidney transplantation, pathology, transplant glomerulopathy, treatment

Transplant glomerulopathy (TG) was traditionally described as a unique glomerular duplication of the glomerular basement membrane [1]. TG has evolved to be recognized as one histological feature of chronic antibody-mediated rejection (cABMR) and is identified in many cases presenting with nephrotic-range proteinuria during late allograft dysfunction. Fifteen years ago, the concept of 'chronic allograft nephropathy' induced by calcineurin inhibitor (CNI) nephrotoxicity was considered the main etiology of death-censored graft loss based on protocol biopsy studies [2] and was supported by the observation that long-term graft survival improvements had not mirrored the marked reduction in acute rejection attributed to CNI [3]. It became clear in the last decade that cABMR is the major cause of late allograft loss outside of death with functioning graft [4].

Peritubular capillary deposition of C4d, as an inactive by-product of classical complement pathway activation, was recognized as a marker of antibody-mediated graft injury and subsequently as a predictor of both rejection and long-term graft outcome [5]. Additionally, this confirmation of alloantibody binding was a critical first step in understanding and documenting the inadequacies of traditional immunosuppression on alloreactive humoral immunity and has resulted in the introduction of the term of acute and chronic active antibody-mediated rejection (ABMR) [6–10].

Concurrent improvements in HLA antibody detection methods (solid-phase assays in particular single antigen bead platforms—SAB) have permitted extensive investigation into the clinical significance of donor-specific HLA antibodies (DSA). Recent analyses have confirmed the strong association of DSA and antibody-mediated graft injury with death-censored graft loss [11–13]. In combination with increasingly accurate and detailed histopathologic evaluation of renal allograft biopsies, TG is now clearly classified as one of the final pathways of chronic active antibody-mediated rejection

(cABMR) with incorporation into the Banff classification [13–17].

This review will summarize current knowledge in epidemiology, etiology and pathology of TG secondary to cABMR and detail prevention and treatment options. Other causes, such as hepatitis C virus (HCV) infection and thrombotic microangiopathy, are not within the scope of in this review, but they have been recently discussed elsewhere [18].

EPIDEMIOLOGY OF TG SECONDARY TO cABMR

The prevalence of TG secondary to cABMR is poorly described in the literature. Analysis of one Italian center's 666 graft biopsies data (collected between 1983 and 2000) demonstrated TG in 5.6% [19]. A higher incidence (12%) was reported from the Mayo Clinic group during 4.5 years of follow-up [20]. The same group reported in a 582 patient cohort, a cumulative incidence of 20% at 5 years [15] in patients with negative pre-transplant T-cell complement-dependent cytotoxicity cross-match (CDCXM) compared with 54.5% in a different desensitized positive CDCXM cohort [21]. Development of TG is strongly associated with both pre-existing or *de novo* DSA [22–24]. With improved sensitivity, negative flow cytometry cross-match (FCXM) patients have improved outcomes compared with FCXM-positive recipients [25].

TG independently impacts on graft survival; however, other factors (presence of proteinuria, C4d positivity, class type of DSA) can modify outcomes. TG patients with significant proteinuria (>2.5 g/day) reported much worse graft survival outcomes (92 versus 33%, $P < 0.001$) compared with those with less proteinuria [19]. In a Mayo Clinic trial of 102 CDCXM positive subjects with 204 age- and sex-matched negative cross-match (XM) counterparts, graft survival was significantly worse in patients with Class II DSA (alone or with Class I) in comparison to Class I DSA alone (63 versus 85%, $P = 0.05$). Those without Class II DSA had similar survival to negative XM recipients (85 versus 88%, $P = 0.64$) [21]. Buob *et al.* compared 20 TG patients without C4d positivity or morphologic evidence of rejection with 44 recipients without TG or rejection histopathology. At 3 years, renal function, acute rejection and development of HLA antibodies were not significantly different between the two groups [26].

PATHOLOGY OF TG SECONDARY TO cABMR

According to the Banff 2013 classification, the biopsy diagnosis of cABMR should meet three criteria [13]:

(1) Presence of donor-specific alloantibodies,

(2) Demonstration of alloantibody interaction with vascular endothelium: complement 4d-positivity in peritubular capillaries and/or at least moderate microvascular inflammation (MVI) and/or increased gene expression of endothelial activation and injury transcripts (ENDATs),

(3) Morphologic signs of alloantibody-induced chronic vascular injury: TG and/or severe peritubular capillary basement membrane multi-layering and/or new onset arterial intimal fibrosis.

One of the most specific histologic phenotypes of cABMR is TG (Figure 1) [18]. Pathogenetically, persisting or *de novo* anti-endothelial DSA, particularly to HLA antigen Class II alloantigens [15, 27], activate and cause sublytic injury to the glomerular capillary endothelial cells [28]. The subsequent repair process produces a new basement membrane layer. Repeated episodes of endothelial activation, injury and repair result in the deposition of several basement membrane layers involving the entire capillary circumference. The new layer(s) are recognized as double contouring or multi-layering of the glomerular basement membranes (GBMs) on tissue sections stained with periodic acid-Schiff or methenamine silver stain that highlight the GBM. A similar pathological multi-layering feature can be seen in the peritubular capillary basement membrane. Since the peritubular capillary basement membranes are much thinner than the GBMs, the gold standard in the assessment of peritubular capillary lamination is the ultrastructural evaluation of the peritubular capillary basement membranes [29].

Overt TG is now characterized histologically by GBM duplication in ≥1 of the capillary loops (as opposed to the previous criterion of >10% of capillary loops), mesangial expansion with or without mesangial hypercellularity and mesangial cell interposition; glomerulitis can accompany these lesions [13]. The immunostaining for C4d discloses diffuse or focal linear C4d along peritubular capillaries (C4d-positive, antibody-mediated rejection) or the C4d staining is negative (C4d-negative, antibody-mediated rejection). Thus, glomerulitis and/or C4d deposition and the presence of DSA indicate the ongoing active nature of the rejection process. The immunostaining for immunoglobulin G (IgG), IgA and C1q is negative; IgM and C3 can be mildly or moderately positive in the mesangium and along the capillary loops. Electron microscopy reveals multilayering of GBMs in several loops with or without signs of endothelial activation. In some analyses, DSA and peritubular C4d were absent, indicating such an antibody-mediated rejection independent form, but these cases may also represent a temporary inactive cABMR period based on the similar outcome results with the full cABMR cohort [30]. Overt TG is regularly accompanied by chronic damage to the allograft parenchyma: fibrous intimal thickening of arteries, arteriolar hyalinosis, segmental and/or global glomerulosclerosis, interstitial fibrosis, tubular atrophy, circumferential multi-layering of peritubular capillary basement membranes and sometimes loss of peritubular capillaries. Significant proteinuria, hypertension and slowly worsening graft function are observed clinically.

The differential diagnosis of TG includes diseases that lead to GBM duplication: membranoproliferative glomerulonephritis, lupus glomerulonephritis, HCV infection-related glomerulonephritis and smoldering thrombotic microangiopathy. The diagnosis is usually straightforward if immunofluorescent and ultrastructural examination of the renal biopsy sample is performed. Hemolytic-uremic syndrome or anti-phospholipid,

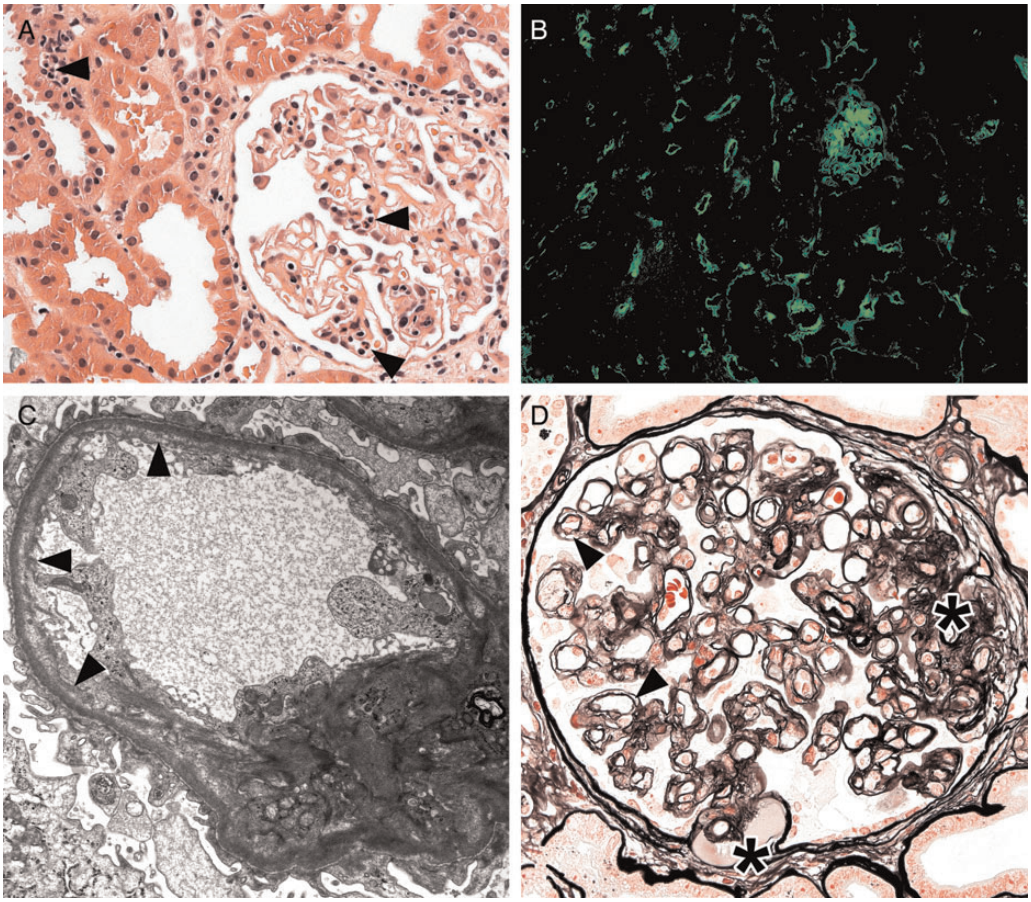

FIGURE 1: Early transplant glomerulopathy was diagnosed using electron microscopy in a 6-month protocol biopsy. (**A**) Light microscopy revealed leukocyte accumulation (arrowheads) in the glomerular and peritubular capillaries (glomerulitis and peritubular capillaritis, respectively); double contoured glomerular capillary walls were not observed (hematoxylin–eosin stain; original magnification, ×400). (**B**) Immunofluorescence demonstrated C4d positivity in peritubular capillaries (C4d stain; frozen section, original magnification, ×200). (**C**) Electron microscopy of glomerular capillaries revealed subendothelial widening, focal loss of endothelial cell fenestrations and the duplication of glomerular basement membrane along the entire capillary circumference (arrowhead) in three loops (uranyl acetate and lead citrate stain, original magnification, ×7000). Several peritubular capillaries displayed 3–4 circumferential basement membrane layers. Serology confirmed the presence of *de novo* donor-specific alloantibodies. (**D**) Well-developed transplant glomerulopathy is characterized light microscopically by widespread double contours of capillary loops (arrowheads). Asterisks indicate segmental sclerosis (methenamine silver, original magnification, ×400).

antibody-induced chronic thrombotic microangiopathy can, however, cause difficulties in the differentiation from TG if the C4d staining is negative. Based on previous data and one series of indication biopsies of a cyclosporine–azathioprine–corticosteroid-treated renal transplant cohort, an overlapping pathway of cABMR, thrombotic microangiopathy and HCV infection-associated glomerulopathy, was hypothesized [15, 31].

Chronic ABMR lesions are irreversible and worsen with time and, therefore, the early biopsy diagnosis of TG would facilitate the development of treatment options. The features of early TG have been observed in protocol biopsies and include glomerulitis and no double contours (Banff cg score 0). The C4d immunostaining reveals either diffuse or focal linear C4d deposition along peritubular capillaries or is negative; the staining for immunoglobulins and early complement components are negative. The ultrastructural investigation demonstrates signs of endothelial activation, i.e. hypertrophy/swelling of the cell bodies, disappearance of fenestrations and widening of the subendothelial space [32–35]. A new, continuous basement membrane layer along the entire capillary circumference can be observed in a few loops (Banff cg score 1a). Focal fibrin and platelet microthrombi are additional ultrastructural signs of active injury. It should be emphasized that the ultrastructural alterations *per se* are not specific for early TG, and all findings observed by light microscopy, immunohistochemistry and electron microscopy, together with the presence of DSA point to early cABMR. The lesions of early TG are usually associated with mild proteinuria and/or unexplained mild deterioration in allograft function [15].

The alloreactive immune response of the host is a continuous process, underlying the nature of the pathological findings. The rigorous, binary distinction between 'acute' or 'chronic' antibody-mediated rejection is necessary for a descriptive diagnosis, but over time, the full spectrum of humoral immunity may result in tissue injury and repair in the biopsy specimens. TG indicates a late and generally non-reversible manifestation of this process and is viewed as an 'end-product' of the antibody-mediated pathophysiological process.

PATHOPHYSIOLOGY OF TG SECONDARY TO cABMR

Recurrent alloantibody-mediated (HLA antigen or non-HLA antigen) endothelial injury is the major factor of development of TG secondary to cABMR, and several distinct patterns of pathophysiological process have emerged even though our current knowledge on the intra-graft events is particular. Alloantibody binding to endothelial surface antigens may induce different intracellular signaling leading to endothelial activation, recruitment of natural killer (NK) cells, monocytes and lesser T-lymphocytes and neutrophil granulocytes. Recent studies have shown that alloantibody-dependent cellular cytotoxicity is triggered by interaction of Fc-γ RIII on NK cells turning to expression to T-bet and IFN-γ production and increased levels of NK transcripts might have been detected during cABMR [36, 37]. Related to MVI, there is evidence that ENDATs and DSA-dependent transcripts are indicators of ongoing ABMR and their identification in C4d-negative renal biopsy specimens have established significance [38]. The presence of complement activation and C4d deposition is more characteristic to acute ABMR (aABMR) but in the case of complement-activating IgG_1 and IgG_3 DSAs, a fluctuating C4d status may accompany the process of cABMR and subsequent graft loss. Urine and/or plasma mRNAs, chemokines and other potential biomarkers to identify either TCMR or ABMR are under current investigations and have been recently discussed elsewhere [39, 40].

Growing evidence has been emerged in the last years on the effect of non-HLA antibodies on short- and long-term outcome. In the database of Collaborative Transplant Study, the pre-transplant presence of antibodies targeted to major histocompatibility complex (MHC) Class I-related chain A (MICA) antigens was associated with poorer outcome even in the case of good HLA matching [41]. However, it is important to note that in this cohort anti-HLA DSA was poorly characterized and most cases where MICA is positive also have HLA antibodies as well [41]. Additionally, angiotensin II receptor type 1 activating autoantibody (AT1R Ab) has been confirmed behind graft loss [42–45]. Again, it is important to note that majority of patients did not have anti-HLA antibody tested on the same sera with AT1R Ab, which is not the same as not having anti-HLA antibody. A better observation is that in some patients the impact of anti-HLA antibody and AT1R Ab was additive [46]. *De novo* anti-endothelial cell antibodies (EACAs) rather than pre-existing EACAs were also independently associated with glomerulitis and peritubular capillaritis [47]. Although their utility has yet to be demonstrated in a broader clinical setting, these early investigations are clearly supportive of a broader consideration of agents of antibody-mediated graft injury beyond HLA DSA-associated mechanisms.

CLINICAL AND IMMUNOLOGICAL RISK FACTORS OF TG SECONDARY TO cABMR

The evolution of the Banff classification [13] makes it difficult to compare different immunosuppressive protocol impact on the natural history of TG or cABMR. In the cyclosporine era and before the introduction of mycophenolic acid, TG had been identified in 5.6% of cases of for-cause biopsies in a large Italian patient cohort with 10-year graft survival of 48 compared with 88% in controls [19]. With the introduction of tacrolimus, a case–control study was performed to compare the results of protocol graft biopsies in tacrolimus- versus cyclosporine-treated recipients, otherwise receiving corticosteroids and mycophenolic acid, and found significantly lower Banff cg score for tacrolimus-treated patients [48]. Suboptimal drug exposure is now widely accepted in the etiology of dnDSA appearance, aABMR late chronic AMR and subsequent graft loss. Non-adherence of recipients is one of the major causes of ineffective immunosuppression and late graft loss as well as physician-recommended modification in the immunosuppression therapy [12, 49]. A recent analysis showed a reduction in immunosuppression leading to late ABMR in 17% of patients [50]. Furthermore, CNI minimization or other withdrawal strategies might further increase the risk of dnDSA development and late acute or chronic ABMR [51, 52].

Pre-transplant/pre-existing high-titer, donor-specific IgG anti-HLA antibodies detected by CDCXM and resulting in hyperacute rejection were considered a contraindication to transplant [53]. FCXM and SAB detection of low-titer DSA, undetectable by CDCXM, have improved identification of sensitized kidney transplant recipients [54]. Mohan *et al.* performed a systematic review and meta-analysis of rejection rates and graft outcomes for renal transplant recipients with preformed low-titer DSA, defined by positive SAB but negative CDCXM and FCXM. SAB identified DSA with negative CDCXM, nearly doubles the risk for AMR and increases risk for graft failure by 76% [55]. Moreover, increased risk was also found in the case of DSA-positive/FCXM-negative recipients [56]. These results are not universal and many patients with only SAB assay-positive DSA have achieved good long-term renal graft function [57]. Identification of antibody strength in studies using mean fluorescence intensity (MFI) in the SAB assay is common, but this is a semi-quantitative test [58, 59]. The FCXM assay is similarly not standardized [60]. Studies reporting MFI and rejection outcomes must be interpreted in this context. A consensus conference guidelines on HLA and non-HLA antibodies in transplantation recommends that in renal transplantation, if DSA is present but the CDCXM against donor T and B cells is negative, this should be regarded as an increased risk but not necessarily a contraindication to transplantation, especially after elimination of DSA by desensitization [57]. Persistence of pre-existing Class I DSA post-transplant is highly correlated to the emergence of early acute ABMR and should be recognized as a risk factor of TG development [22, 61].

Late aABMR (which frequently has histopathologic features of acuity and chronicity) and cABMR/TG are strongly related to the *de novo* appearance of donor-specific IgG HLA antibodies (dnDSA). During long-term follow-up, 15–29% of recipients develop *de novo*, predominantly Class II DSA frequently to HLA-DQ antigens [22–24]. In a study of 315 kidney transplant recipients without pre-transplant DSA, 15% of the cohort has developed dnDSA, mainly secondary to non-adherence,

during a 6.3-year mean follow-up time, and 61% of them have shown signs of acute or indolent ABMR on indication or surveillance biopsy. The median 10-year graft survival for the dnDSA patient group was significantly, 40%, lower than non-DSA patient group [49]. In a recent study of 245 kidney transplant recipients without pre-existing DSA at 12 months, 8.2% of them had dnDSA and those who had an MFI value of 3000 or greater had almost 11-fold higher risk for aABMR [hazard ratio (HR): 10.6, 95% confidence interval (CI): 2.27–49.5], but indicating the late onset in non-immunized recipients, TG has not occurred in any cases at 12-month surveillance biopsies [62]. The harmful effect of dnDSA is not proven for all cases, but the presence of complement-binding IgG_1 and IgG_3 dnDSA generally negatively impacts long-term outcome and may be associated with 30% lower 5-year graft survival [63]. Analyzing a large kidney transplant population, from 316 DSA-positive patients, 77 patients had C1q-binding DSA. Additionally, the presence of C1q-binding, post-transplant DSA was associated with the increased risk of graft loss (HR: 4.78, 95% CI: 2.69–8.49) after adjustment for several immunological, histological and clinical factors [64].

The development of desensitization protocols in the last 15 years has permitted a greater number of kidney transplants across DSA, positive cross-match barriers and ABO incompatibility offering the possibility of successful transplantation to highly sensitized recipients otherwise unlikely to receive a kidney graft on the waiting list. Even if achieving a pre-transplant negative CDCXM, these recipients remain immunologically high risk with high incidence of ABMR, due to memory responses that cannot be completely abrogated with desensitization. In the pilot trial of the Mayo Clinic comparing the results of 12-month post-transplant protocol biopsies, TG was diagnosed in 22% of the previously positive cross-match (+XM) group versus 8% of conventional patients [65]. In further analysis, the strength of pre-transplant DSA was loosely correlated with the increased risk of early aABMR but not with TG, beyond the presence of DSA alone [66]. Five-year outcomes of this +XM patient cohort have shown inferior death-censored graft survival compared with conventional renal transplant recipients (70.7 versus 88%; $P < 0.01$) and consistent with this association, TG was present in 54.5% of surviving grafts and equally common in Class I and Class II DSA subgroup [21]. In the +XM renal transplant program of Johns Hopkins University, the occurrence of TG was 25% at 1-year protocol biopsy histology and resulted in worse graft survival compared with control XM-negative patients (66.7 versus 96.6%; $P < 0.001$) during a 42-month median follow-up [67]. During the entire study comprising 129 +XM recipients with 745 graft biopsies, TG developed in 47% of patients as early as 3 months. In recipients having glomerulitis in the specimens of first 3 months, TG developed in 61% within an average of 15 months [68]. Despite a high proportion of patients having antibody-mediated renal graft injury, live donor kidney transplantation and desensitization protocols have provided an increased survival benefit compared with sensitized patients on maintenance dialysis [69].

The outcome results of ABO-incompatible renal transplantation after the 15th postoperative day are similar to ABO compatible ones [65]. Later, the rates of chronic antibody-mediated graft injury and the occurrence of TG were similar in ABO incompatible renal grafts and ABO compatible grafts [65]. The special histological feature of ABO incompatible grafts is the very common C4d deposition at peritubular capillaries without an inflammatory response or pathological injury [70, 71]. The phenomenon of accommodation is under extensive investigations for understanding its potential therapeutic potential.

PREVENTION OF TG SECONDARY TO cABMR

The most important primary prevention of TG secondary to cABMR is to perform transplantation without pre-existing DSA. Compelling evidence exists to show that pre-existing DSA has a major impact on TG and long-term graft survival [27]. An other primary prevention method is to avoid transplantation with HLA mismatches, especially Class II HLA mismatches, which has been shown as strong predictor of the presence of DSA [72]. Moreover, Sapir-Pichhadze [73] elegantly demonstrated a Class II EPLET mismatch as an independent predictor of TG in a nested case–control study.

As both pre-transplant and *de novo* donor-specific IgG anti-HLA antibodies play the most significant role in the development of cABMR/TG, any secondary prevention, which can eliminate these antibodies, can reduce the probability of development of TG. Three major desensitization protocols in use today are plasmapheresis (PLEX) with or without immunoabsorption (IA), high-dose intravenous immunoglobulin (IVIG) and PLEX combined with low-dose IVIG and rituximab [74]. In the mid-90s, Alarabi *et al.* treated 23 sensitized (PRA>50%) waitlisted patients with 12 sessions of PLEX and cyclophosphamide and prednisolone. Although a majority of patients' PRA decreased significantly, most of these patients lost their graft secondary to rejection [75]. Later, Gloor *et al.* introduced a complex protocol that includes PLEX (4–5 sessions), low-dose IVIG, rituximab and splenectomy combined with thymoglobulin induction and tacrolimus/MMF/prednisolone maintenance treatment. They reported excellent graft and patient survival with very low rejection rate (14% clinical and 29% subclinical) [76]. Similar to PLEX, the more expensive IA (using protein A column) can also effectively reduce the DSAs; however, this effect is mostly temporary [77].

Almost all desensitization protocols include a high dose (2 g/kg) or low dose (100 mg/kg)—always linked with PLEX–IVIG treatment. High-dose IVIG was able to reduce PRA and DSAs in most of the studies [74]; however, IVIG failed to lower the strength of DSAs in at least two previous trials [78, 79]. In the last decade, rituximab (1 g twice), an anti-CD20 monoclonal antibody, was also given with IVIG as desensitization treatment. Vo *et al.* [80] reported a significant decrease in PRA (from 77 ± 19 to $44 \pm 30\%$) and excellent patient and graft survival in 16 highly sensitized patients. After this landmark trial, PLEX with IVIG and rituximab were the backbones of most of these protocols and experienced excellent (0–55%) rate of ABMR and patients' and graft survival [74].

Table 1. Efficacy and side effects of interventions for the prevention or treatment of antibody-mediated graft injury

	Desensitization protocols	Acute ABMR treatment	Chronic ABMR treatment	Potential adverse events	Cost
1. PLEX	+	+	±	Hypotension, bleeding, hypovolemia	+
2. IVIG	+	+	±	Allergy, headache, myalgia, fever	+
3. Rituximab (Rx)	++	++	+ ?	Infections, neutropenia, infusion reactions	++
4. Bortezomib (Bx)	ND	+++	+ ?	Myelosuppression, neuropathy GI toxicity	++
5. Eculizumab (Ex)	NA	++	+ ?	Meningococcal infection, hypertension	+++
6. Splenectomy (Sx)	++	++	+ ?	Infections, thrombocytosis	+
7. PLEX + IVIG	++	++	±	Additive	Additive
8. IVIG + Rx	++	++	+		
9. PLEX + IVIG + Rx	+++	+++	NA		
10. PLEX + IVIG + Sx	+++	+++	+ ?		
11. PLEX + IVIG + Rx + Bx	ND	+++	+		
12. PLEX + IVIG + Rx + Ex	NA	++++	ND		

ND, no data; NA, not applicable; ±, occasional; ?, few data, not exactly known.

Recently, the protocols described above have been augmented with new therapeutic agents. Two of these, in wide use, are bortezomib, a proteasome inhibitor that leads to apoptosis of plasma cells, and eculizumab, a humanized antibody specific for the C5 component of complement that prevents formation of the membrane attack complex (MAC) [74]. The efficacy and side effects of interventions for the prevention/treatment of TG secondary to cABMR are summarized in Table 1.

FULL REVIEW

TREATMENT OF TG SECONDARY TO cABMR

The treatment of aABMR does not differ substantially from desensitization protocols. However, all treatments are supposed to be given early before chronic changes have already been developed. The combinations of IVIG, PLEX/IA, rituximab and new agent, bortezomib, are widely accepted in post-transplant care with the additional administration of eculizumab in some studies [81–83]. Recent reviews summarize the development in this field in contrary to the very scarce case series-based literature results of the identical protocols used in the setting of cABMR [84, 85]. In a prospective pediatric study of aABMR and cABMR, four weekly doses of IVIG (1.0 g/kg body weight at each session) followed by a single dose of rituximab decreased the progressive loss or stabilized transplant kidney function during a 24-month observation period in 5 of 11 patients with TG. Only 9 of 20 patients had a follow-up biopsy without detailed data regarding cABMR histological outcome [86]. In a recent study, high-dose IVIG alone has been proven to be unfavorable for the treatment of cABMR. Nine of 20 treated patients had a follow-up biopsy and only 4 had no histological progression [87]. Based on the favorable results of the use of bortezomib in late aABMR, a patient cohort comprising nine patients with cABMR, and seven of them having TG, was treated effectively with PLEX, low-dose IVIG, rituximab and bortezomib combination, and 22 of 23 patients underwent follow-up biopsy. Lack of a histologic response was associated with older patients [odds ratio (OR) = 3.17], the presence of cytotoxic DSA at the time of diagnosis (OR = 200) and severe chronic vasculopathy (cv > 2) on index biopsy (OR = 50) [50]. However, such an improvement could not be achieved in other series [88, 89]. The advantage of addition of eculizumab to these protocols remains to be elucidated further [90]. Multicenter clinical trials of bortezomib, rituximab, eculizumab and cyclophosphamide for the treatment of cABMR are ongoing or recruiting patients [18, 22, 91, 92].

In the current era of immunosuppressive drugs, splenectomy takes back seat in the treatment options of cABMR; nevertheless, its usefulness as a rescue therapy has been published [93, 94] and shown to be more efficient in combination with eculizumab in the clinical setting of +XM transplantation [95]. Out of the 24 patients, there was more chronic glomerulopathy in the splenectomy-alone and eculizumab-alone groups at 1 year, whereas splenectomy + eculizumab patients ($n = 5$) had almost no TG. Splenectomy is likely to remain controversial in the setting of financially strongly supported transplant programs in developed countries but may provide a solution for transplant programs having more unassertive financial circumstances.

Much effort is being made to develop and investigate new therapeutic options for the prevention and treatment of acute and chronic ABMR. Newer maintenance immunotherapies with the co-stimulatory pathway blocking belatacept may provide additional inhibition of donor-specific B cells, and potential benefit to prevent cABMR is supported by the 3- and 5-year outcome results of belatacept studies [96, 97]. They are currently investigating B-cell-depleting therapies in systemic lupus erythematosus (SLE) as anti-CD20 antibody ocrelizumab and anti-CD22 antibody epratuzumab may be an interesting area of research in renal transplantation [98]. The controlling of anti-apoptotic survival factors critical for the maturation of the B-cell lineage is also a promising target for therapeutic interventions. The humanized monoclonal anti-BlyS antibody belimumab is under current investigation in Phase III SLE trial, and recruitment of patients into a Phase-II study of both APRIL and BlyS ligand inhibiting immunoglobulin fusion protein atacicept is currently ongoing [99].

Understanding the pathophysiological process leading to TG potentially explains its therapeutic resistance. Whereas the treatment options are very scarce, awareness of patient non-adherence and the avoidance of suboptimal maintenance immunosuppression is currently the best way to prevent the

occurrence of cABMR and TG to provide good long-term transplanted kidney survival results.

EPILOGUE

TG secondary to cABMR is one of the most annoying problems that transplant nephrologists have to face in 2014. Despite this fact, we have succeeded in better understanding of pathophysiology of these diseases; the effective and safe treatment is still unknown. In the near future, the transplant community needs to perform well-designed clinical trials in a well-defined recipient population.

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CONFLICT OF INTEREST STATEMENT

None declared.

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FULL REVIEW

Nephrosclerosis: update on a centenarian

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ABSTRACT

Nephrosclerosis is an umbrella term defining changes in all compartments of the kidney, changes caused by hypertension and by ageing. Among other lesions, arteriolosclerosis and arteriolohyalinosis play a major role in inducing glomerular ischaemic shrinking and sclerosis along with glomerulomegaly and focal-segmental glomerulosclerosis (FSGS). These lesions are accompanied by tubulointerstitial inflammation and fibrosis that predict the decline of renal function. Nephrosclerosis is a major cause of renal insufficiency in blacks of African descent with a severe, early form of renovasculopathy and a rapid course to renal failure with predominant lesions of FSGS. It seems that in blacks, separate genetic factors independently lead to vascular lesions and to hypertension with a different time-scale of their onset and of their progression, nephroangiosclerosis preceding the onset of hypertension. Conversely, true and histologically identified nephrosclerosis in white Europeans rarely leads to end-stage renal disease in the absence of malignant hypertension. Various animal models demonstrate that renal vascular lesions may exist in the absence of hypertension. These experiments also point to a major role of angiotensin II and of a number of independent and overlapping cellular and molecular pathways in a cascade of inflammatory events that end in renal fibrosis. Two pathophysiologic mechanisms are at work in inducing glomerular lesions and tubulointerstitial fibrosis: a loss of autoregulation of the renal blood flow caused by an arteriolohyalinosis of the glomerular afferent arteriole and ischaemia that fosters the generation of hypoxia inducible-fibrosing factors. Not all antihypertensive drugs equally