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Antibody Mediated Rejection in Kidney Transplantation: Current Status and New Insights into Clinical Relevance and Therapeutic Approaches

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ABSTRACT

Long-term kidney allograft survival, even with notable improvement over last two decades, was still not satisfying. Antibody mediated rejection was currently considered among the most important barriers that limit long-term outcome. However, there still exit plenty of questions regarding the precision of diagnostic approaches and the efficacy of therapeutic strategies. With better understanding of the mechanisms of antibody mediated graft injury and the advance of detection technique, donor specific antibody was recognized as the most important risk factor and diagnosis biomarker of antibody mediated rejection. The definition of antibody mediated rejection has evolved over time and new phenotype of C4d negative was added in the most recent Banff classification. Therapeutic approaches to antibody mediated rejection focused on reducing the synthesis of DSA, removing DSA from the bloodstream and ameliorating its effect on the allograft. Plasmapheresis and intravenous immunoglobulin are still the main strategies. Some emerging immunosuppression for AMR showed better prospect to improve long-term graft

outcome, but randomized controlled trials are mandatory to validate these initial results and to ensure sustained effect on long-term graft survival.

Keywords: Kidney transplantation; Antibody mediated rejection; Long-term graft survival; Donor specific antibody; C4d; Therapeutic approaches

Abbreviations: Antibody Mediated Rejection (AMR); Human Leukocyte Antigen (HLA); Donor Specific Antibodies (DSA); Plasmapheresis (PP); Plasma Exchange (PE); Intravenous Immunoglobulin (IVIg); Complement Dependent Cytotoxicity (CDC); Solid-Phase Assay (SPA); Enzyme-Linked Immunosorbent Assay (ELISA); Mean Fluorescence Intensity (MFI); Immunoglobulin (Ig); Major Histologic Complex Class I Related Chain A Antigens (MICA); Anti-Endothelial Cell Antibodies (AECA); Anti-Angiotensin II Type 1 Receptor (AT1R); Peritubular Capillaries (PTC)

INTRODUCTION

With significant advances in histocompatibility and immunosuppressive agents, acute rejection rate post kidney transplantation has decreased dramatically over time, which has led to a substantial improvement in short-term kidney allograft survival [1,2]. However, long-term graft survival, even with notable improvement over last two decades, was still not satisfying [3]. A better understanding of the immune system has increasingly made people recognize that Antibody Mediated Rejection (AMR), besides T cell-mediated rejection, plays a major role in kidney allograft loss and is considered among the most important barriers that limit long-term outcomes [4]. The term 'AMR' defines all allograft rejections caused by antibodies directed against donor-specific Human Leukocyte Antigen (HLA), blood group antigen, or endothelial cell antigens. AMR occurs in up to 40-50% of all acute rejection episodes following kidney transplantation and can co-exist with cellular rejection [5,6]. The poor outcomes related to AMR have been widely confirmed. It is reported that 57-63% of recipients with late graft loss have evidence for AMR [7,8].

Despite the detrimental impact of AMR on graft function and survival has been clearly realized, its diagnosis and treatment remains a challenge. With better understanding of the mechanisms of antibody mediated graft injury, the criteria for the diagnosis of AMR has evolved but there still has controversy. AMR was redefined in the recent 2013 Banff classification [9].Three features are required which include histologic evidence of acute or chronic tissue injury, evidence of current/recent antibody interaction with vascular endothelium and serologic evidence of the presence of circulating Donor Specific Antibodies (DSA). Importantly, C4d staining is no longer a requirement for the diagnosis of AMR. Recognition of this new phenotype reveals AMR as the most common cause of late kidney transplant loss. The severity of AMR increases the need for a targeted therapy, focused on reducing the synthesis of DSA, removing DSA from the bloodstream and ameliorating its effect on the allograft. Plasmapheresis (PP) and intravenous immunoglobulin (IVIg) are still the main strategies. However, rituximab, bortezomib, eculizumab and other new therapeutic agents against AMR have shown better prospects to improve long-term outcome.

Here we will discuss the current status of the clinical relevance and therapeutic approaches of AMR, as well as the future directions needed to further improve the outcome of kidney allografts.

DSA AND ANTIBODY MEDIATED REJECTION

DSA generally represents antibody directed against HLA if there is no special specified. The presence of DSA is increasingly being recognized to play a major role in graft outcome [10]. The techniques to identify DSA have improved significantly from the so-called 'gold standard' Complement Dependent Cytotoxicity (CDC) antibody assay to Solid-Phase Assay (SPA) techniques [11]. The advent of solid-phase antibody assay has greatly enabled the characterization of DSA and has largely replaced cell-based antibody testing technique. Solid-phase antibody testing employs either an Enzyme-Linked Immunosorbent Assay (ELISA)-based system or a color-coded bead-based fluoro metric assay [12]. Moving from ELISA to flow cytometry and Luminex technology using single antigen beads has increased the ability to identify DSA with high sensitivity and specificity [13].

There is growing evidence supporting preformed and de novo DSA as independent risk factors for AMR and graft loss. DSA may pre-exist in allograft recipients before transplantation due to previous sensitization history, such as blood transfusion, transplantation or pregnancy [14]. A recent systematic review and meta-analysis by Mohan et al. pooled analysis of seven retrospective cohort studies comparing groups that were positive and negative for DSA in the setting of a negative CDC and negative flow cross match result [15]. The authors demonstrated a statistically significantly increased risk for biopsy-proven AMR and allograft failure in the DSA positive group, with nearly two-fold greater risk for AMR and a 76% greater risk of graft loss [16-22]. The meta-analysis also analyzed eight retrospective cohort studies (group 2) comparing DSA positive and negative patients by SPA in the setting of a negative CDC crossmatch result but with unknown results on flow cross match (because it was not performed) showed an even greater significant increase in the likelihood of developing a biopsy-proven AMR episode and allograft failure in the DSA positive group [23-30]. These findings suggest that preformed DSA are clinically significant even in the absence of a positive flow cytometery crossmatch and indicate immunologically higher-risk transplant recipients. As a result, these patients should be monitored closely for development of AMR and appear to be at risk for worse graft outcomes [15].

De novo DSA, as another important form of DSA, was found in 15–25% of patients post-transplant and the majority appeared within the first 6–12 months post-transplant [31]. Risk factors for the de novo development of DSA and subsequent occurrence of AMR are younger age, deceased donor kidney transplantation, previous transplants, nonadherence to immune suppression or insufficient immune suppression [32,33]. There are many reliable studies that have examined the impact of de novo DSA on kidney allograft survival. Hidalgo et al. found DSA in 37% of patients who had an indication biopsy, of which 60% represented de novo DSA. Microcirculation inflammation (glomerulitis, capillaritis) and damage (glomuerulopathy,

capillary basement membrane multilayering) were associated with de novo DSA [34]. De novo DSA correlated strongly with reduced graft survival: within 5 years from DSA detection, 50% of the patients in the study lost their grafts. Everly et al. found that 11% of the patients without detectable DSA at transplantation will have detectable DSA at 1 year, and over the next 4 years, the incidence of de novo DSA will increase to 20% [35]. After de novo DSA development, 24% of the patients will fail within 3 years. Wiebe et al. reported that de novo DSA developed in 15% of low-risk renal transplant recipients at a mean of 4.6 ± 3.0 years post-transplant. Even with weakly reactive, Luminex single antigen beads detected de novo DSA measured at the low positivity cut-off of 300 Mean Fluorescence Intensity (MFI), graft survival at 10 years was 40% lower in such patients than patients without de novo DSA [36]. Caner et al. also confirmed weak de novo DSA was associated with graft loss [37].

Although de novo DSA occurs against both class I and class II, it has been noted that majority of de novo DSA are class II, which is tend to occur late post-transplant. And even still not listed as a routine locus for kidney transplant HLA typing, antibody against DQ had been reported as the most common de novo DSA and was considered to be mainly responsible for rejection by recent observations [32]. Most authors believe that DSA against HLA class II confers a more increased risk for late graft loss than DSA against HLA class I. And series of studies that have attempted to define risk factors for de novo DSA development have consistently identified class II, but not HLA class I, antigen mismatches as univariate or multivariate predictors [35,36].

Among the isotypes of HLA-specific Immunoglobulin (Ig), IgG is considered to be the principal agent of AMR and is divided into four subclasses with varying capacity to activate complement. IgG3 is the strongest activator of complement, followed by IgG1 and IgG2. IgG4 has no detectable complement activity and is often linked with IgG2 as 'non-complement fixing'. Lefaucheur et al. enrolled 125 patients with DSA detected in the first year post-transplant [38]. The author's assessed DSA characteristics, including specificity, HLA class specificity and IgG subclass, and graft injury phenotype at the time of sera evaluation. They found the distribution of DSA IgG1–4 subclasses among the population was 75.2%, 44.0%, 28.0%, and 26.4%, respectively. In addition, DSA of the IgG3 subclass had the strongest association with acute AMR, while DSA of the IgG4 subclass was strongly associated with subclinical AMR. IgG3 DSA was associated with a shorter time to rejection, increased microcirculation injury, and C4d capillary deposition. IgG4 DSA was associated with later allograft injury with increased allograft glomerulopathy and interstitial fibrosis/tubular atrophy lesions. Using a Cox regression survival model, the authors revealed that IgG3 DSA and C1q-binding DSA were strongly associated with allograft failure.

It is important to note that not all DSA result in AMR. A critical issue for patient care is discerning which of the detected DSA is valuable for clinical decision making. The capacity of DSA to bind complement fraction C1q, which is the first step in the activation of the classic complement cascade, determines their cytotoxic potential. Thus assessment of the C1q fixing DSA has become of increasing interest. Loupy et al. reported a large study designed to determine whether

detection of C1q fixing DSA improves prediction of allograft loss and risk stratification [39].They found patients with C1q fixing DSA after kidney transplantation had the lowest 5-year rate of graft survival (54%), as compared with patients with non–C1q fixing DSA (93%) and patients without DSA (94%). The presence of C1q fixing DSA after transplantation was associated with a 4.78 fold adjusted increase in the risk of graft loss. These antibodies were also associated with an increased rate of AMR, a more severe graft histological injury pattern. Detection of C1q fixing DSA at 2 years post-transplantation has been associated with a worse 5-year graft failure risk compared with DSA-negative or non-C1q fixing DSA. Compared to C1q, the presence of C3d fixing DSA proves the efficient cleavage of C3 and is therefore more closely related to the pathogenic processes damaging the graft. Antoine et al. analyzed 69 cases of AMR and identified the presence of circulating C3d fixing DSA at the time of AMR is a strong independent predictor of allograft failure [40]. The presence of C3d fixing DSA was associated with a higher risk of graft loss, and exhibited a higher sensitivity than a C1q fixing DSA assay.

Endothelium of kidney allograft is the first barrier between recipients' immune system and transplanted grafts [41]. Antibodies mainly damage a graft by targeting the endothelium of the graft's microcirculation. Some of the non-HLA antigens expressed by endothelium cells are target of the antibody mediated response, such as the Major Histologic Complex Class I Related Chain A Antigens (MICA), the endothelial cell-restricted antigen and Angiotens in II type 1 receptor. MICA has proven to be the target of complement fixing alloantibody that can cause AMR [42]. The presence of anti-MICA DSA negatively impact short-term and long-term graft survival [43]. Anti-Endothelial Cell Antibodies (AECA) have been reported to mediate endothelial cell activation, apoptosis, and cell injury. In the sera of kidney transplant recipients AECAs were detected and they were associated with post-transplant donor specific HLA antibodies, AMR, and early transplant glomerulopathy [44, 45]. Dragun et al. linked the presence of Anti-Angiotensin II Type 1 Receptor (AT1R) antibody to AMR of non-AB0 incompatible allograft kidneys in 16 recipients without anti-HLA or anti-MICA DSA [46]. The authors provided evidence of the pathogenic role of anti-AT1R antibody as their removal with plasmapheresis and selective blockade of AT1R with losart an significantly improved graft survival. There are also some other non-HLA antibodies, such as viment in, collagen V and tubul in, indicating effect of diagnosing AMR and risk of deleterious graft outcome[47].

C4D AND ANTIBODY MEDIATED REJECTION

C4d, as an inactive split product of the complement cascade without a biological function, has been called 'a footprint' of antibody mediated tissue injury. In 2003, diffuse C4d deposition in the Peritubular Capillaries (PTC) became codified as a required diagnostic criterion for AMR in the Banff Classification of Renal Allograft Pathology [48]. PTC deposition of C4d is strongly associated with circulating DSA and is currently the best single marker of complement-fixing circulating antibodies to the endothelium and one of the core diagnostic tools to identify AMR [49, 50]. Feucht et al. firstly reported that patients with suspected antibody mediated injury in

the renal allograft had a linear C4d deposition in PTC, and the presence of C4d was associated with impaired graft outcome[51].Collins et al. demonstrated C4d deposition in PTC walls distinguished AMR from cellular mediated rejection[52]. The authors embodied the connection among the C4d staining, the presence of DSA and histom orphological features of AMR, which led to general acceptance of the usefulness of C4d in the identification of AMR. The introduction of C4d as a biomarker into daily clinical practice of renal transplant biopsies has provoked an enormous amount of insight into the role of antibodies. However, with the expanding use of C4d by transplant pathologists worldwide, several limitations of C4d were identified, such as its lack of utility for ABO incompatible allografts, the difficulties of interpreting focal staining patterns, and the relatively low sensitivity of C4d as a marker for AMR in late renal allograft biopsies[53]. It is reported that more than 70-80% of ABO incompatible kidney transplant allografts showed diffuse C4d deposition. As compared, there are only 30-40% diffuse C4d positives observed in the group of patients with a positive cross-match for anti-HLA antibodies [54, 55]. However, in contrast to conventional transplants where a diffuse C4d deposition is strongly associated with histological abnormalities, the ABO incompatible kidney allografts show diffuse C4d positivity without histological tissue injury, such as increased graft scarring, transplant glomerulopathy, or impaired graft outcome [56]. This phenomenon forces pathologists to apply other criteria to diagnose AMR in ABO incompatible grafts, as C4d staining in this group does not show useful relationship to rejection.

In addition, reports showedC4d deposition on for-cause biopsies, although very useful, was relatively insensitive for identifying patients with AMR and that those patients with C4d negative antibody mediated injury had reduced graft survival [57]. Recent molecular studies in kidney allograft tissues lead to discovery of a new AMR phenotype: 'C4d negative AMR'. Sis et al. performed a retrospective study of biopsies from 1320 transplanted patients and showed that only 36% of cases with alloantibody mediated injury were C4d positive, despite the fact that anti-HLA antibodies were detected in 70% of this group of patients [58].The updated Banff classification of renal allograft has included C4d negative AMR, in which C4d is not helpful as a diagnostic marker. Previous publication showed C4d negative AMR is twice as common as C4d positive AMR. C4d negative AMR is characterized by high intragraft endothelial gene expression, DSA, histologic evidence of AMR (chronic AMR in many cases), and poor outcomes.

Loupy et al. examined clinical relevance of subclinical AMR in a cohort of DSA positive kidney transplant recipients receiving a deceased donor [59]. The authors demonstrated a 49% prevalence of C4d negative subclinical AMR which biopsy showed glomerulitis, peritubular capillaritis and DSA but no C4d versus 31% for C4d positive subclinical AMR on the basis of 3-month protocol biopsies. C4d negative patients had a mean creatinine clearance and frequencies of interstitial fibrosis/tubular atrophy and transplant glomerulopathy intermediate between the no-AMR and C4d-positive subclinical AMR cohorts at 1 year post-transplantation. The substantial fluctuation of C4d status in the first year post-transplant reflected a dynamic humoral process.

However, C4d may not be a sufficiently sensitive indicator, such that microvascular inflammation and DSA (mostly class II) were more robust tools in predicting bad outcome related to chronic antibody graft damage. More recently, Orandi et al. quantified allograft loss risk in patients with consistently C4d negative AMR compared with C4d positive AMR patients [60]. There were no reliable clinical profiles distinguishing C4d negative from C4d positive AMR, since both groups appeared to be similar in terms of baseline characteristics, including immunologic risk factors (panel reactive antibody, prior transplant, HLA mismatch, donor type, DSA class, and anti-HLA/ABO-incompatibility). C4d positive AMR patients were significantly more likely to have a clinical presentation, and C4d negative AMR tended to present significantly later post-transplant and was more likely to be subclinical in its presentation. Both groups were associated with significantly worse graft survival compared with AMR-free patients. Graft outcomes were better for C4d negative AMR patients, but this did not reach statistical significance compared to C4d positive AMR patients. Both groups warrant close surveillance and consideration for intervention in preventing graft histologic injury and improving graft survival.

THERAPEUTIC APPROACHES TO ANTIBODY MEDIATED REJECTION

New knowledge of the humoral immunobiology in AMR has provided insights to therapeutic interventions. The main mechanism of injury involves the generation of DSA that binds to endothelium and subsequent cellular activation involving complement dependent and independent pathways. Currently our treatment options focus on reducing the synthesis of DSA, removing DSA from the bloodstream and ameliorating its effect on the allograft. Of note, most medications used for treating AMR were developed in different disciplines, and the transplant community has adopted them because of their effect on the humoral immune system. However, the US Food and Drug Administration has not recognized AMR as approvable indication, so no medications are licensed for use in the treatment of AMR.

PP with or without IVIg PP

PP with or without IVIg PP could effectively remove already formed alloantibodies from the circulation and is considered as a traditional therapy in most protocols developed for treating AMR. PP modalities include Plasma Exchange (PE), double filtration PP and immunoadsorption. PE is the preferred method in the United States because of the relatively low cost and ease of the procedure. Although PP is effective in reducing DSA from circulation, it does not suppress the synthesis and rebound of circulating DSA. Therefore PP is commonly followed by IVIg in most therapeutic protocols. IVIg is a commercially prepared product from pooled human plasma of 50,000-100,000 or more screened healthy donors [61]. The mechanism of action of IVIg is unclear. The proposed mechanisms of action include suppression of immunoglobulin synthesis, anti-idiotypic activity against DSA (with resultant neutralization of DSA), blockade of the Fc receptor, inhibition of complement activation, and anti-cytokine activity[61,62]. Yamada et al.

retrospectively investigated DSA reduction rate by HLA specificities and clinical outcome in kidney transplant recipients with AMR who underwent PE followed by low dose IVIg. They found six PE procedures decreased DSA more than three PE procedures, and reduction rate was lower by the second three PE procedures than the first three PE procedures [63]. DSA with HLA Class I specificity was reduced slightly more than Class II DSA, with least reduction rate of DSAs to DR51-53. Creatinine improvement rates were minimal with treatment. However, PE treatment may halt further functional deterioration in older grafts for at least 6 months. Orandi et al. reported subclinical AMR substantially increases graft loss, and treatment seems warranted [60]. In their study, subclinical AMR was independently associated with a 2.15-fold increased risk of graft loss compared to matched controls, but not different from clinical AMR. 53.2% of subclinical AMR patients were treated with PP within 3 days of their AMR defining biopsy. Treated subclinical AMR patients had no difference in graft loss compared to matched controls, but untreated subclinical AMR patients did show worse graft survival.

Rituximab

Rituximab is a chimeric monoclonal antibody against CD20, which is found on the surface of pre B cells, mature B cells, and memory B cells, but not on pro B cells or plasma cells. Rituximab could block B cells activation and differentiation into antibody secreting cells [64]. It was reported thatrituximab have some effect in the treatment of acute and chronic AMR, either in combination with other treatments or as an additional treatment once other treatments have been unsuccessful[65, 66]. The major drawback of rituximab is the risk of infections. Associated infections have been reported in up to 50% of patients and include cytomegalovirus, shingles, polyomavirus, and fungal infections. Fatal infection after the use of rituximab has also been reported, especially after concurrent use of antithymocyte globulin [67, 68].

Proteasome Inhibitor

Bortezomib is the first generation proteasome inhibitor that induces apoptosis of plasma cells and was used initially for treatment of multiple myeloma. By targeting plasmablasts and long-lived plasma cells, bortezomib may directly destroy the source of this damaging DSA in kidney transplant patients with AMR. In some small size of the cohort, bortezomib-based regimens have been shown a profound decrease of DSA titer and provided effective therapy for AMR [69-71]. However, some patients experienced a rebound of DSA during the observation period. Recent data demonstrated bortezomib does not significantly improve long-term kidney allograft outcome. There is evidence showing that bortezomib more effectively reduces Class I DSA with less efficacy in lowering Class II DSA titer [72]. Although bortezomib may eliminate plasma cells, it has a short half-life with mean inhibition of proteasome activity changing from greater than 90% after 5 min of administration to 22% to 48% within 48 hr [73].Therefore, rebound of DSA maybe the result of the generation of new plasma cells from activation of B cells. Of note, carfilzomib, a new proteasome inhibitor, was approved in 2012 for use in multiple myeloma. With irreversible inhibition to the proteasome, carfilzomib may have better clinical effect in AMR treatment [74].

Complement Inhibitor

As final step of the AMR development process, the complement activation is a major mechanism through which antibodies attack kidney allografts. There are two currently available complement inhibitors, a monoclonal antibody against C5 and a purified and recombinant C1 inhibitor. Eculizumab, as an anti-complement protein C5 monoclonal antibody, has been so far proved effective both for preventive and curative treatments of AMR in sensitized patients and patients diagnosed with severe AMR by reducing membrane attack complex formation and complement mediated injury [75,76]. Data from a placebo controlled trial of C1 inhibitor (Berinert) in kidney transplantation suggested a potential benefit in combining Berinert with antibody-reduction therapy for prevention of AMR [77]. However, the high cost, unclear effect on long-term graft survival, and a lack of prospective studies evaluating their efficacy and safety, limit routine application of complement inhibitors in the treatment of AMR in kidney transplant recipients.

CONCLUSION

AMR was currently considered among the most important barriers that limit long-term outcomes. With better understanding of the mechanisms of antibody mediated graft injury, we have made great progress in recognizing its associated clinical relevance. However, there still exit plenty of questions regarding the precision of diagnostic approaches and the efficacy of therapeutic strategies. Some emerging immunosuppressions for AMR are encouraging, but randomized controlled trials are mandatory to validate these initial results and to ensure sustained effect on long-term graft survival.

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