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Review

Treatment Strategies for Antibody-mediated Rejection in Kidney Transplantation and Its Prevention

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Abstract

This article reviews the current treatment strategies of antibody-mediated rejection in kidney transplantation, which is increasingly recognized as the leading immunological cause of graft failure. The pathophysiologic complexity of this condition poses significant challenges for its treatment; however, progress toward advancing our understanding of its pathogenesis and diagnosis will allow for identification of new therapeutic targets. Emphasis is also given to prevention, which is mainly based on careful assessment of the transplant candidate and immunological risk stratification.

Keywords

Sensitization; antibody mediated rejection; treatment; prevention

1. Introduction

Antibody-mediated rejection (AMR) is increasingly recognized as the leading immunological cause of graft failure after kidney transplantation [1, 2], with modern immunosuppression showing little protective role [1-4]. The incidence of AMR depends on the diagnostic criteria used, recipient sensitization status, and the immunosuppressive regimen adopted, and can range from 3.1% [5] to 40% [6-8]. Approximately 30% of patients on the transplant waiting list have evidence of sensitization in the form of alloantibodies, generated from exposure to previous transplants, blood transfusions, pregnancy, or other events [9]. The presence of a panel-reactive antibody level of at least 80% (i.e., a high level of sensitization) creates difficulty in finding matched kidneys from compatible donors, leading to low rates of transplantation in these patients [9, 10]. Despite the application of various desensitization protocols and immunological risk stratification, transplantation of highly sensitized patients is linked to an increased risk of AMR [9, 11]. AMR is also of significant concern in non-sensitized individuals, mostly in the setting of under-immunosuppression, with the development of de novo donor specific antibodies (DSAs) early or late after transplantation [12, 13]. By 10 years after kidney transplant, 25% of 189 non-sensitized patients in one cohort study were found to have de novo DSAs [14]. Early appearance of de novo DSAs weeks to months after transplantation may cause acute AMR and can be a significant contributor to premature graft failure. Antibody-mediated immunological injury was first hypothesized in 1971 [15] and many studies have since confirmed the role of DSAs in AMR [8, 16-27]. Furthermore, evidence of AMR in the form of DSAs is associated with a significant decrease in graft half-life and may even predict graft loss [11, 14]. In one study of 219 patients with biopsy-proven AMR, Orandi et al. found a 4.73-fold higher risk of graft loss in patients with AMR and HLA-compatible deceased donor grafts.

The Banff classification, a major advancement in the field of transplantation, has been used over the past 25 years to define and categorize AMR as a clinico-pathological entity [28-30]. However, the heterogeneity of the clinical presentation of AMR and wide spectrum of pathologies, ranging from abrupt allograft dysfunction in the early post-transplant period to insidious or subclinical presentations later [31-34], is a key limitation toward the effective treatment of AMR [35]. In this review, we discuss the main treatment modalities of the entire spectrum of AMR as well as emerging approaches to its prevention.

2. Treatment Modalities

The different clinical manifestations and the evolving clinico-pathological diagnosis reflect the complexity of the treatment of AMR. The current therapeutic strategy is to adopt a combination of modalities to address multiple pathophysiologic pathways [36]. A number of different approaches have been described in the literature, including: antibody removal with plasmapheresis (PLEX) or immunoadsorption (IA), intravenous immunoglobulin (IVIg), deletion of B cells with agents such as the anti-CD20 antibody rituximab, deletion of plasma cells with the proteasomal agent bortezomib, complement inhibitors, and several other interventions as detailed below in this review. As a consequence, treatments are rarely comparable and the available evidence on treatment effect is of low quality [37, 38]. Further complicating the analysis of the treatment effects is the fact that most studies are small retrospective trials of disparate patient populations [38]. The latter is an

important limitation given that numerous clinical factors are known to have significant impact on outcomes [39].

2.1 PLEX and IVIg

PLEX is the most common strategy for treatment of active AMR [40]. The rationale behind its widespread use lies in its endorsement by current guidelines and conclusions from consensus workshops [41, 42] despite the weakness of its efficacy and lack of Food and Drug Administration (FDA) approval [37, 38].

The mechanism of action of PLEX as well as IA, an alternative extracorporeal procedure based on affinity adsorption which is less common in the United States, is to remove DSAs directly from circulation. Desensitization studies have shown PLEX in particular is the fastest method to decrease DSAs [43]. PLEX is also the most frequent modality applied in the United States and generally involves 1.0–1.5 volume exchange using albumin or plasma as replacement. Commonly reported side effects (5-10%) include: allergic reactions that present as rigors and urticaria; symptoms of hypocalcemia such as paresthesia; and hypovolemia, which can manifest as muscle cramps and hypotension. Less frequent complications are related to the use of anticoagulants, the type of replacement fluid, and vascular access [44].

IVIg are derived from human plasma pooled from thousands of donors and is primarily composed of IgG with trace amounts of IgA and IgM. The dose of administration is variable with doses ranging from 100 mg/kg to 2 g/kg [35, 45]. The proposed mechanisms of immunomodulation by IVIg are complex and thought to involve multiple cell types, including monocytes, macrophages, and both B and T cells as well as the complement cascade [46-48]. Notably, although immunoglobulins classically activate the complement cascade, IgG fragments can inhibit complement activation by binding complement factors and removing them from circulation [49]. Additionally, high-dose IVIg delivers a lasting immunomodulatory effect on T cells and especially B cells, resulting in changes in the induction of B cell apoptosis and downstream modulation of B cell signaling [50-52]. According to a recent in vitro experimental study, IVIg also blocks NK cytotoxicity and antibody-dependent cellular cytotoxicity [53]. Another potential benefit of treatment with IVIg is the replacement of antibodies lost during PLEX [45]. In general, even high doses of IVIg are relatively safe. However, serious side effects have been reported, including acute renal dysfunction (likely related to high osmotic load), thrombotic events with rapid infusions, and aseptic meningitis [54].

In summary, while the combination of PLEX and IVIg is known to improve short-term outcomes, long-term results remain variable and generally less favorable [5, 37, 55-59]. In addition, there is a need to better define the duration of PLEX and dosing of IVIg, as this combination varies across different centers [40].

2.2 Anti-CD20: Rituximab

Rituximab is a chimeric monoclonal IgG antibody directed against the CD20 antigen expressed on the surface of both pre-B and mature B cells. Once bound to CD20, it causes B cell lysis via both complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity [60]. The use of this B-cell-depleting agent in the setting of active AMR is recommended as a treatment option by Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [41] and has been used in many institutions [56, 61]. However, based on the current literature, its efficacy is limited at best. One

systematic review and meta-analysis of 10 small retrospective or non-randomized trials evaluating the use of rituximab in AMR found that use of this agent is associated with improved graft outcome [62]. Two more recent systematic reviews and one meta-analysis was not able to show a clear benefit [38, 63]. A small multi-center, double-blind randomized controlled trial of 38 patients evaluated rituximab as an addition to standard of care for treatment of active AMR [64]. In this trial, standard of care consisted of six sessions of PLEX with IVIg at a dose of 100 mg/kg after each PLEX session, followed by 2 g/kg over 2 days at the end of the plasmapheresis cycle. At 1-year follow-up, the rituximab group did not show any difference from standard of care with respect to the primary endpoint, which was a composite of graft loss and early renal function [64]. Rituximab has a reasonable safety profile in transplant patients [60].

2.3 Proteasome Inhibitor: Bortezomib

Bortezomib is a proteasome inhibitor which disrupts the normal intracellular protein degradation process [65] and has been shown to induce plasma cell apoptosis and block anti‑HLA antibody production [66]. It is FDA-approved for use in multiple myeloma and mantle cell lymphoma. Studies in the transplant setting as a treatment modality for AMR have shown conflicting results. Small case series have noted beneficial effects when used in combination with plasmapheresis and IVIg or rituximab in the treatment of active AMR in kidney transplant recipients [67-69]. The only randomized controlled trial of bortezomib in late AMR failed to show improvement in transplant kidney function, incidence of histologic or molecular disease features, or reduction in DSAs [70]. Other studies have shown no improvement in glomerular filtration rate after bortezomib when used as add-on therapy with plasmapheresis and IVIg for chronic AMR [71]. Possible explanations for its lack of efficacy are the known increase in antibody production via germinal center B cell and follicular helper T cell expansion, a process triggered by the plasma cell depletion [72, 73], and the finding that bortezomib has little effect on HLA class II antibody production [74].

Bortezomib is associated with significant side effects, mostly GI and hematologic toxicity [65, 70]. There are no trials supporting its use in treating AMR.

2.4 Complement Inhibitors

Over the past decade, several studies have been conducted to evaluate the ability of complement inhibitors to prevent and treat AMR.

2.4.1 C5 Inhibition

Eculizumab is a humanized monoclonal IgG antibody that binds to complement protein C5, inhibiting its cleavage to C5a and C5b and blocking the generation of the terminal complement complex C5b-C9 [75]. It was approved by the FDA for use in the treatment of paroxysmal nocturnal hemoglobinuria and primary atypical hemolytic uremic syndrome. Eculizumab has been used off-label for antiphospholipid syndrome and the prevention and treatment of AMR in the kidney transplant population [7, 76-79]. Following the first successful case report on the use of eculizumab to treat early active AMR in combination with plasmapheresis and low-dose IVIg [80], a single-center small case series further showed that eculizumab is effective for the treatment of early active AMR occurring within the first month post-transplant [81]. Furthermore, 2 multicenter randomized Phase

II trials have suggested a protective effect for administering eculizumab prior to clinical evidence of AMR in positive crossmatch HLA-incompatible living and deceased donor populations [82, 83]. However, studies with longer follow-up failed to show a statistically significant reduction in the incidence of chronic AMR [84, 85], a finding likely related to the complexity of the pathophysiology of AMR.

2.4.2 C1 Inhibition

C1 inhibitor [C1-INH] is a serine protease inhibitor that inactivates both C1r and C1s, thus regulating proteases in both the classical and lectin complement pathways and resulting in major downstream effects on regulation of the coagulation and inflammation cascade [86, 87]. Two C1-INH products, Berinert® (CSL Behring, Kankakee, IL, USA) and Cinryze® (Shire ViroPharma Inc., Lexington, MA, USA) [87] are currently approved for use by the FDA in the treatment of hereditary angioedema [88].

Proximal complement inhibition with C1-INH has also been studied as a therapeutic target in kidney transplant recipients with AMR [89, 90]. In a single-arm pilot study, Viglietti et al. found that CI-INH (Berinert®) in combination with high-dose IVIg improved allograft function in kidney recipients with active AMR not responsive to conventional therapy [89]. This encouraging result has been reproduced in a randomized, double-blind, placebo-controlled, multicenter Phase IIb study which evaluated the safety and efficacy of another C1-INH (Cinryze®) for the treatment of active AMR [90]. A Phase III clinical trial is currently evaluating Cinryze® as an add-on therapy to standard-of-care PLEX and IVIg for treatment of active AMR in renal transplant recipients is ongoing (ClinicalTrials.gov identifier: NCT03221842).

2.5 Interleukin-6 Inhibitors

Tocilizumab is a humanized monoclonal antibody which binds to both soluble and membrane-bound forms of the interleukin-6 (IL-6) receptor [91, 92]. It is currently FDA-approved for the treatment of rheumatoid arthritis and juvenile idiopathic arthritis [91]. IL-6 is a key cytokine that regulates inflammation and the development, maturation, and activation of T cells, B cells, and plasma cells [91]. Based on the possible contributions of IL-6 signaling to AMR, Vo et al. conducted a small Phase I/II pilot study of tocilizumab and high-dose IVIg as a desensitization strategy in 10 patients who failed IVIg and Rituximab [93]. This trial found significantly reduced DSAs and improved transplantation rates with tocilizumab treatment [93]. Another study by Choi et al. was a single-center, non-randomized trial of tocilizumab as rescue therapy for chronic active AMR in 36 patients who failed IVIg plus rituximab. Patient and graft survival at 6 years was 91% and 80% respectively, which was superior to historical controls with significant reductions in DSAs and stabilization of renal function [94]. Last, a large multi-center randomized control trial is underway to evaluate clazakizumab, an investigational anti-IL-6 monoclonal antibody for the treatment of chronic active AMR [95] (ClinicalTrials.gov identifier: NCT03444103).

2.6 IgG-degrading Enzyme of Streptococcus Pyogenes (IdeS)

IgG-degrading enzyme of Streptococcus pyogenes (IdeS) is an enzyme which cleaves human IgG at a specific amino acid sequence [96] and can neutralize all IgG in the body within 4 hours of

administration. There is a period of about 7 days during which both soluble IgG and the B cell receptor are not detectable, with a rebound and full reconstitution within 2 weeks [96-98]. Clinical trials in transplant patients have shown its ability to eliminate DSA and, further, it has been used safely in highly-sensitized individuals for desensitization [99, 100]. Data on its use in the setting of AMR are lacking with the main obstacle being its immunogenicity: anti-IdeS antibodies usually appear after only one or two doses [101]. An interesting area for future work would be modulation of the immunogenicity of IdeS to allow for repeated dosing without production of anti-IdeS antibodies [102].

2.7 Splenectomy

There are several case series of surgical splenectomy, splenic embolization, and splenic radiation being used as a salvage procedure for severe early AMR [103, 104]. These procedures must be performed rapidly after the onset of early AMR to be effective. One potential mechanistic explanation for their success is the removal of antibody-producing plasmablasts and plasma cells that traffic to the spleen from regional lymphoid tissue. Orandi et al used this therapeutic modality as a salvage approach in the setting of early active AMR after HLA-incompatible living donor kidney transplantation [105]. The authors found that a combination of splenectomy with eculizumab as add-on therapy to PLEX with low-dose IVIg and rituximab resulted in the highest graft salvage rate and protection from transplant glomerulopathy when compared to splenectomy alone or eculizumab alone as an add-on therapy. Most of the case reports or studies in the literature are in the setting of early active AMR, characterized by profound graft dysfunction and a rapid rise in DSAs, usually from an anamnestic response. The interpretation of studies of splenectomy is complicated by the fact that those patients are known to be sensitized, exhibit pre-formed antibodies, and have already undergone desensitization therapy.

3. Prevention of Antibody Mediated Rejection

AMR will always be a consideration in allogeneic transplantation [35]. Its prevention starts with a careful assessment of the transplant candidate and immunological risk stratification. The initial assessment involves donor and recipient HLA typing, anti-HLA antibody screening, and obtaining a history of allosensitizing events, such as previous transplant, blood transfusion, or pregnancy [37, 41, 106]. For anti-HLA-sensitized recipients, a higher resolution of typing approaching or even reaching the allelic level, i.e., so-called “4-digit” typing, should be performed on the potential donor to match the resolution of recipient alloantibody identification assays [107-109]. The advantage of the 4-digit typing in recipients with HLA antibodies is that it increases the specificity in matching, allowing for a more precise risk stratification and a theoretical reduction in immunological risk of AMR [110]. The incidence of AMR can be greatly reduced by avoiding strong DSA [35]. Patients with no history of allosensitizing events and with negative anti-HLA antibody testing using single-antigen or multi-antigen bead solid-phase assays are at low risk for AMR [107, 109].

More than 20,000 patients awaiting kidney transplantation in the United States are sensitized to HLA class I or class II antibodies [9, 111]. Until recently, a common approach to AMR prevention has been to avoid transplanting highly sensitized patients. This approach results in prolonged waiting times for suitably HLA-matched organs and may negatively impact patient health, quality of life, and healthcare costs [112, 113]. With the advent of the virtual crossmatch [114, 115], kidney paired

donation, combined paired donation with desensitization, and the acceptable mismatch program, timely kidney transplantation has become a reality for many high-risk patients. These strategies yield reduced risk of AMR and its consequences [116-119].

There is growing evidence that non-HLA antigens are implicated in the humoral immune response to the renal allograft, substantiated by reports of AMR in HLA-identical siblings [120-122]. According to case reports and small case series, therapeutic success for AMR caused by non-HLA antibodies has been achieved with the treatment strategies previously described. To further complicate the picture, registry data suggest that non-HLA immunity could have a prominent role in chronic graft loss [123]. Further studies are needed to characterize alloantibodies targeting non-HLA immunogenic antigens.

A known risk factor for the development of AMR is reduction in maintenance immunosuppression, either as a result of non-adherence or under physician direction. This form of AMR is usually associated with the development of de novo DSAs [124-127]. Given the relationship between de novo DSAs, AMR, and graft loss, transplant patients with de novo DSAs should undergo close monitoring of allograft function in order to allow for timely intervention [14, 128, 129].

4. Conclusions

Prevention and treatment of AMR continues to represent a key aspect of the management of kidney transplant patient. Current treatment strategies are based largely on observational studies, expert opinion, and trials with low-level evidence. While significant progress has been made toward advancing our understanding of its pathogenesis, diagnosis, treatment, and prevention, future work should focus on identifying novel therapeutic targets [130]. The pathophysiologic complexity of AMR poses a significant challenge in the design of immunosuppressive protocols which both maximize the benefits to patients while accounting for the inherent risks of different treatment modalities.

Author Contributions

Pierpaolo Di Cocco - Drafting the article, data collection, critical revision of the article; Alberto Fratti - Drafting the article, data collection; Kerim B. Kaylan - Drafting the article, data collection; Ivo G. Tzvetanov- Critical revision of the article; Enrico Benedetti - Conception of the work, critical revision of the article, final approval of the version to be published.

Competing Interests

The authors have declared that no competing interests exist.

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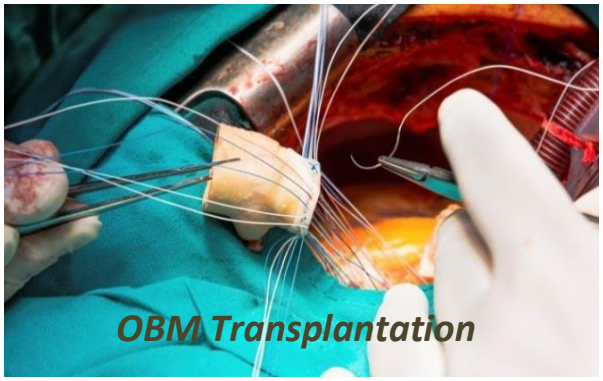

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