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Minireview

Treatment Options for Pediatric Renal Transplant Recipients with Acute Antibody-Mediated Rejection

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Abstract

Antibody mediated rejection is increasingly being recognized as a significant player in contributing to long term graft injury and loss in renal transplant recipients. Due to the paucity to large and robust trials, much of what we know about this entity is based on small case series and reports. Our review discusses the importance of antibody mediated rejection in children with renal transplants and provides an overview of the diagnostic and therapeutic options available to clinicians caring for these children.

ABBREVIATIONS

ABMR: Antibody-Mediated Rejection; CDC: Complement-Dependent Lymphocytotoxicity; DSA: Donor Specific anti-HLA Antibody; FDA: Food and Drug Administration; HLA: Anti-Human Leukocyte Antigen; IVIg: Intravenous Immunoglobulin; PP: Plasmapheresis.

INTRODUCTION

Renal transplantation remains the preferred treatment of choice for pediatric patients with advanced chronic kidney disease due to better patient survival, growth, and quality of life compared to chronic dialysis [1-3]. Despite improvements in the prevention and treatment of T-cell mediated rejection, long-term graft loss in renal transplant recipients remains high. Recent insights and discoveries are changing the paradigm on how rejection is viewed, from the previous belief that rejection is primarily a T-cell mediated process to the more contemporary recognition of a significant humoral component of the immune system as a contributor to graft dysfunction and loss [4-6].

BACKGROUND

The donor graft endothelium of the peritubular and glomerular capillaries displays Major Histocompatibility Complex molecules which are the targets of antibody mediated injury [7]. Endothelial damage leads to an inflammatory response, leukocyte adhesion from cytokines, and complement activation. The membrane attack complex is assembled as a result of complement activation and causes necrosis and endothelial cell detachment from the basement membrane, characteristic histological features of antibody-mediated rejection (ABMR). Progression of the insult may lead to a thrombotic microangiopathy with arterial wall necrosis.

Several significant discoveries have aided in the identification of ABMR. First and foremost was the discovery that peritubular capillary deposition of C4d, a product of complement activation, was associated with graft loss and seen most often in sensitized transplant recipients [8,9]. C4d, a cleavage product of complement C4, becomes covalently bound to tissue at the site of C4 activation, and can be detected using immunohistologic staining by IF or immunoperoxidase. Currently C4d staining is scored based on the percent of peritubular capillaries that stain positive in the biopsy tissue [10]. There are some limitations to the use of C4d staining as a marker for ABMR, since inter-institutional reproducibility is low and techniques may differ from one center to another [11]. In the future, gene transcripts may become available and might be better markers for ABMR, compared to C4d staining [12,13].

Secondly, the development of assays for detecting anti-human leukocyte antigen (HLA) antibodies has improved our understanding of ABMR. Donor-specific HLA antibodies (DSAs) can exist prior to transplant or develop *de novo* at any time after transplant. HLA antibodies increase the risk of ABMR with highly sensitized patients being at even greater risk [14]. As many as 30% of transplant recipients develop *de novo* DSA; they can do so after T-cell rejection [15] or following a period of non-adherence [16]. *De novo* DSA also predict late graft loss in children [17]. *De novo* DSA are mainly directed against class II HLA, and are associated with worse prognosis than class I HLA DSA. DSA assays use either cell-based or solid phase tests. The cell-based tests include the complement-dependent lymphocytotoxicity (CDC)

and the flow cytometric crossmatch assay. The solid phase tests include enzyme-linked immunosorbent assays and multianalyte bead test by flow cytometry (Luminex technology). Only the CDC and solid phase tests have been approved by the US Food and Drug Administration (FDA) for detection of HLA antibodies as qualitative assays [18]. These assays use arbitrary units to quantify HLA antibodies, the mean channel shift for cell based flow cytometry cross-matches and the mean fluorescent intensity for the Luminex assay. While often used in studies as quantitative assays, many technical problems still limit their reliability, such as lack of standardization of solid phase assays and variations in laboratory protocols and handling [19]. Hopefully new consensus guidelines on DSA testing will help to improve test performance [20].

DIAGNOSIS

The clinical presentation of ABMR can range from acute clinical deterioration in graft function to a more indolent course with little change in graft function and minimal pathologic changes on biopsy. The definition of ABMR has undergone several iterations over the past decade [10, 21-23] . Morphology is still crucial for diagnosis; classically, acute ABMR is diagnosed in the setting of serologic evidence of DSAs, immunohistologic evidence of C4d staining, and morphological evidence of tissue injury. The features of tissue injury on biopsy include acute tubular necrosis, peritubular capillaritis, glomerulitis, thrombosis, intimal arteritis and/or arterial fibrinoid necrosis with lymphocytic infiltrate. The absence of graft dysfunction differentiates subclinical ABMR from clinical ABMR. However, much like with acute clinical ABMR, patients with subclinical ABMR are at risk of developing progression of histologic changes such as interstitial fibrosis, tubular atrophy and transplant glomerulopathy with accompanying deterioration of graft function [13,24].

While the Banff consensus criteria require C4d staining for a definitive diagnosis of ABMR, there is increasing recognition of the entity of C4d-negative ABMR. C4d staining positivity is more likely seen in early AMR, within the first 3 months after transplantation, but is more often negative in late rejection episodes [4]. This may indicate that there is a different mechanism of graft injury in these 2 groups, as early acute ABMR is more likely to be seen in highly sensitized patients while late ABMR more commonly occurs in the setting of non-adherence with immunosuppression and with the appearance of *de novo* DSA [25].

TREATMENT

Most treatment protocols in current use are derived from the clinical experience obtained from the treatment of patients sensitized prior to transplantation. Therapies have been focused on depletion of B-cells and/or preformed antibodies, and on complement inhibition or inactivation. These therapies include intravenous immunoglobulin (IVIg), plasmapheresis (PP), rituximab, bortezomib, and eculizumab. While there are no clear consensus guidelines for treatment of ABMR, there have been some proposals on adopting a standard of care approach for future clinical trials, and considering this standard to be IVIg and PP [18].

Based on case series and anecdotal reports, it appears quite clear that combinations of treatments are more effective than any one therapy alone, as discussed below. PP removes plasma and thereby antibodies from circulation. IVIg is thought to have anti-inflammatory properties, inducing apoptosis of mature B cells, and in combination with PP is used to neutralize antibodies and block complement activation. PP and IVIg either alone or, more commonly, used together, have been shown to reverse acute ABMR [26-29]. Typically each PP session uses 1-1.5x full blood volume exchange with 5% albumin replacement fluid daily or every other day for 4-7 sessions. Rebound synthesis of DSA can occur after PP is stopped. IVIg when used alone is given at a higher dose (2g/kg) once or up to 3 doses on a monthly basis [29]. When given in conjunction with PP, the IVIg dose is usually much lower (100mg/kg) and is given after each PP session or sometimes a slightly higher dose (300-400mg/kg) is administered for 1-2 days after the last PP session, for a cumulative dose of 1g/kg [7]. Alternatively 1-3 doses of IVIg (2g/kg) can be given at the end of the PP session. As stated earlier, PP with or without low dose IVIG and high-dose IVIg alone have been proposed as standard of care for treatment of ABMR. However, there is no consensus on the number of PP sessions, the amount of blood volume exchange, or type of replacement fluid proposed, as the gold standard. Serious adverse reactions are rare but include aseptic meningitis, renal failure, thrombotic events, and anaphylaxis. Common adverse reactions include headache, fever, chills, myalgia, and hyper- or hypo-tension.

Rituximab is a chimeric anti-CD 20 monoclonal antibody that is currently FDA approved for the treatment of patients with non-Hodgkin's Lymphoma, Wegener's granulomatosis and rheumatoid arthritis. Rituximab binds to the CD20 antigen found on the surface of B-cells, thereby activating antibody-dependent cell mediated cytotoxicity, complement-mediated cell death, and natural killer cell interaction leading to cell death. There is a rapid depletion of the B-cell population over 1-2 days after rituximab, with complete B cell depletion seen within 1-6 weeks; the B-cell populations remains suppressed for up to a year in renal transplant recipients [30]. There is more experience using rituximab for ABO incompatible renal transplants and for desensitization prior to transplant [31]. To date most reports on rituximab for treatment of acute ABMR have been case reports and case series; significant variations exist in the reported doses of rituximab used in the reports, ranging from 375mg/m^2 for 1-4 doses to a single 500mg dose. In all of these reports, patients also received other therapies for the treatment of acute ABMR in addition to rituximab, most commonly PP and IVIg. Graft survival after this combination is reported to be between 50-100% in the larger case series. There is only one randomized control trial using rituximab for rejection with B cell infiltrates on biopsy in pediatric renal transplant recipients. This study compared usual care (pulse doses of steroids ± thymoglobulin) versus the combination of usual care and rituximab [32]. While the group that received rituximab appeared to have worse rejection to begin with, after treatment this group had better graft function and follow-up biopsy scores compared to the 'usual care' cohort. High dose IVIG and rituximab have also been proposed as a possible treatment for chronic ABMR [33,34]. Adverse reactions include infusion reactions due to cytokine release syndrome, thrombocytopenia, and neutropenia. The 3-year follow-up data

from a randomized controlled trial of rituximab for induction therapy for renal transplantation showed a significantly increased risk of cardiovascular death [35]. Patients treated with rituximab are also at increased risk of serious infections and reactivation of latent infections. There have been reported cases of death from progressive multifocal leukoencephalopathy caused by reactivated JC virus in patients with systemic lupus erythematosus receiving rituximab [36]. More recently the FDA has added a black box warning for Hepatitis B reactivation with rituximab.

CD 20 is expressed early in the B-cell cycle but is lost on mature plasma cells, which is a limiting factor of rituximab. Bortezomib, a proteasome inhibitor, causes apoptosis of mature plasma cells to decrease antibody production, overcoming the aforementioned drawback with rituximab. Bortezomib has been shown in case reports and case series of adult transplant recipients to lead to a rapid depletion of DSA and effective treatment of refractory ABMR [37] and even as a first line treatment for ABMR [38]. Patients with early (within 6 months) post-transplant ABMR have been noted to have a better response to therapy with bortezomib [39]. There are only 2 published reports on the use of bortezomib in treating ABMR in pediatric renal transplant recipients with mixed results [40, 41]. Bortezomib is most often given in 4 doses (bortezomib 1.3 mg/m^2/dose) with some combination of steroids, IVIg, PP, and rituximab. Bortezomib use in adults with cancer and with renal transplants has been associated with a variety of infectious, hematologic, neurologic and gastrointestinal toxicities [42].

Eculizumab, a monoclonal antibody directed against complement C5, inhibits the production of the terminal complement components C5a and the membrane attack complex C5b-9. Currently it is FDA approved for the treatment of paroxysmal nocturnal hemoglobinuria and atypical Hemolytic Uremic Syndrome. Eculizumab appears to prevent ABMR in sensitized transplant recipients and has been shown to decrease the incidence of transplant glomerulopathy at 1 year follow-up [43]. Several case reports have been published on the use of eculizumab for ABMR, also with mixed results [44]. In one pediatric case report, ABMR resistant to steroids, thymoglobulin and PP was successfully treated with eculizumab though interestingly the patient was found to have a deficiency in complement Factor H-related protein 3/1, a plasma protein that regulates the complement cascade at the level of C5 conversion [45]. Eculizumab dosing and protocols have been highly variable; however, all the reports mentioned use some combination of steroids, IVIg, PP, bortezomib and rituximab. Adverse effects include increased risk of infection with encapsulated bacteria, namely meningococcus and pneumococcus. Vaccinations for these should be given. In addition, prophylactic antibiotics are also recommended as not all bacterial serotypes are covered by the current vaccines [46].

Splenectomy has been proposed as a final treatment option to be used in a treatment escalation protocol for refractory ABMR when all else has failed [47]. The mechanism of how splenectomy may help in ABMR is not entirely clear although there is some evidence that the spleen may be a repository for direct antibody-secreting cells and hence removing it would reduce the production of new antibodies [48]. Adult case reports using splenectomy for refractory cases of ABMR have shown significant success after failure to respond to different combinations of PP, IVIg, thymoglobulin, and rituximab [48-51]. There is one pediatric case report on a child who was successfully treated with splenectomy for refractory ABMR that had not improved despite steroids, IVIg, PP, and thymoglobulin [52]. Adverse effects include long term risk of infection with encapsulated bacteria.

CONCLUSION

In conclusion, much remains to be established with respect to the optimal surveillance, diagnosis and management of children and adults with ABMR. Clinicians taking care of this vulnerable population need to be aware of the implications of ABMR and consider using a multi-disciplinary approach to plan the management of patients diagnosed with ABMR, since existing therapies can be quite invasive and not without significant risk. The future will likely bring some clarity on best practices for diagnosis and management; until then, an individualized approach, incorporating the team's experience, the patient/family needs, and the unique circumstances of the situation will need to be employed to facilitate the best possible long-term outcome.

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