TREATMENT OF ANTIBODY-MEDIATED REJECTION IN KIDNEY TRANSPLANTATION

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ABSTRACT

Antibody-mediated rejection (AMR) is a relatively rare but severe complication in kidney transplantation associated with increased risk of graft loss. Diagnosis of acute and chronic AMR is based on typical histological hallmarks, deposition of C4d in peritubular capillaries and presence of donor-specific antibodies (DSA). Many novel and attractive treatment options have become available in recent years: antibody removal and production inhibition (plasmapheresis, IVIg), B cell depletion (rituximab), plasma cell depletion and apoptosis (bortezomib), and complement activation inhibition (eculizumab). Standard therapy is based on PP and IVIg. Preliminary results with new agents are encouraging but require randomised clinical trials and long-term follow-up.

Keywords: Kidney transplantation, antibody-mediated rejection, donor-specific antibodies, management of antibody-mediated rejection, IVIg, plasmapheresis, bortezomib, rituximab, eculizumab.

INTRODUCTION

The mechanism of organ transplant rejection may be cellular (T lymphocyte-mediated) or humoral – the latter being mediated by antibodies produced in response to donor-specific antigens exposed on endothelial cells of the allograft. For a long time, transplant specialists have focused on the diagnosis and treatment of cell-mediated reactions, even though the negative effects of alloantibodies in the transplanted organ have been identified by Patel and Terasaki as early as 1969.[1] However, it was only in the last two decades that the diagnosis of antibody-mediated rejection (AMR) was rendered possible by the introduction of sensitive methods of detection of anti-human leukocyte antigen (HLA) antibodies, and most importantly, of donor-specific antibodies, using synthetic antigen assays (Luminex) and C4d detection in graft tissue as a specific marker of complement activation. In 1991, Feucht et al.[2,3] described peritubular capillary C4d deposition in renal transplants, and in 1993 postulated the association of this finding with graft loss. In 1999, Collins et al.[4] reported a correlation between humoral rejection with peritubular capillary C4d deposition and the presence of circulating anti-donor antibodies in transplant recipients. C4d is a product of systemic breakdown of C4, a classic complement activation pathway component whose biological role is unclear. C4d has more stability than other complement components because it forms a covalent complex with the surface of the endothelium and the basement membrane; the time to breakdown is about 1-3 weeks. Identification of C4d deposition using immunofluorescence or immunoperoxidase assay marks a breakthrough in histopathologic diagnosis of kidney allografts, and peritubular capillary location of deposits is considered a highly specific marker of acute and chronic humoral rejection. C4d detection is currently a standard for histopathological diagnosis of kidney allografts.[5] In the Banff classification, the term 'acute antibody-mediated rejection' appeared for the first time in 2003, and 'chronic active antibody-mediated rejection' was introduced in 2005 due to growing evidence for the role of humoral mechanisms in allograft damage. The current Banff classification adopted in 2009 includes diagnostic criteria for acute and chronic antibody mediated rejection.[6]

THE ROLE OF ALLOANTIBODIES

Anti-HLA antibodies have been identified in 1% to 60% of recipients, depending on the tested population, time from transplantation, and to a significant extent, the sensitivity and specificity of detection methods. Donor-specific antibodies (DSA) developing *de novo* after transplantation are now considered as the principal factor in the pathogenesis of graft damage. *De novo* antibodies occur in the early post-transplantation period (within the first 3 months). They indicate a risk of acute or chronic AMR.[7,8] The development of alloantibodies precedes the appearance of morphological and functional abnormalities of the graft, therefore early identification of possible AMR warrants DSA monitoring every 3 months during the first-year post-transplantation, and once a year thereafter.

Acute AMR may occur in the absence of detectable antibodies, if the antibodies are bound in the organ transplant. The incidence of acute AMR among kidney transplant recipients ranges from about 5-7% to 40-90% in non-sensitised and sensitised subjects, respectively. Acute AMR occurs most commonly as part of mixed cellular-humoral rejection (25%) and is rarely an isolated phenomenon. Chronic kidney transplant rejection manifests as slowly progressing functional deterioration that may be seen over several months, or even years. Clinical manifestations include proteinuria, hypertension and slowly progressing loss of glomerular filtration. Histopathology shows evidence of chronic transplant glomerulopathy (TG). Chronic humoral rejection is seen in 5-15% of protocol biopsies, and the onset is usually subclinical. TG has been reported in more than 40% of recipients with a history of acute AMR. Chronic transplant glomerulopathy is associated with poor outcome, which is even worse than that of interstitial fibrosis (IF)/tubular atrophy (TA).[9,10]

It is now widely considered that the principal cause of kidney transplant loss is not nephropathy, but an ongoing immunological process that can be described as chronic antibody-mediated rejection. Furthermore, it has been emphasised that modern immunosuppression regimens, which tend to minimise or discontinue calcineurin inhibitor (CNI), or glucocorticosteroids may be responsible for the development of chronic AMR. Chronic graft rejection is known to result from inadequate immunosuppression. The role of chronic humoral response in the pathogenesis of late transplant loss was confirmed in a US multicentre study (DeKAF Study – Long-term Deterioration of Kidney Allograft Function). In 173 recipients with late graft dysfunction (average of 7 years post-transplantation) who underwent graft biopsy, AMR correlates, such as C4d deposits in biopsy samples or serum DSA, were found in 57% of cases. In 2 years, the poorest outcome in terms of graft survival was seen in those patients who had both C4d and DSA, and the best in those with negative humoral reaction correlates. Signs of nephrotoxicity, if present, had no significant effect on graft survival.[11]

TREATMENT

Treatment of humoral-mediated acute graft rejection differs from that of cell-mediated rejection; it involves the elimination of circulating antibodies and suppression of antibody production by B lymphocytes or plasma cells. To date, no formal standards for the management of humoral-mediated acute graft rejection have been developed. Knowledge in this area is growing rapidly, and recent reports in the literature continue to enrich and broaden its scope. The pathogenesis of AMR forms the basis of proposed therapeutic regimens. DSA are produced by plasma cells which may be present in the pre-transplantation period or develop after transplantation from B lymphocytes (memory or naïve). T lymphocytes are necessary to initiate primary B cell-mediated response, leading to the development of plasma cells.[12,13]

Treatment Modalities in AMR Include:

- Elimination of circulating antibodies
  - Plasmapheresis (PP)
  - Immunoadsorption
- Suppression of remaining antibodies
  - IV infusions of immunoglobulins - IVIg
  - Mycophenolate mofetil (MMF)
- Blocking antibody production, B lymphocyte depletion
  - Glucocorticosteroids (GS)
  - Anti-CD20 antibody - rituximab
  - Anti-thymocyte globulin
  - Splenectomy
- Suppression of T cell response
  - Anti-thymocyte globulin
  - Mycophenolate mofetil (MMF)
  - Calcineurin inhibitors (CNI)
- Plasmocyte depletion and apoptosis
  - Proteasome inhibitor - bortezomib
- Complement inhibition
  - Anti-C5 antibody - eculizumab
  - Recombinant C1 inhibitor

State-of-the-art, promising therapies target plasma cells or the complement. Typically the treatment consists in combining several therapeutic approaches.

Plasmapheresis

Plasmapheresis is the fastest and the most efficient way to eliminate DSA; 1 volume -1.5 volume of total plasma volume is exchanged using 5% albumin or fresh frozen plasma (FFP). Plasmapheresis is performed every other day until improvement in kidney function is obtained (usually five-seven procedures). Plasmapheresis has no inhibitory effect on antibody production, therefore it is usually combined with 100 mg/kg IVIg after each PP session (up to a total of 1 g/kg body weight) and 300-400 mg/kg body weight (bw) for 1-2 days following the last PP. A combination of plasmapheresis and rituximab has been reported. Tacrolimus and MMF are recommended for primary immunosuppression due to their inhibitory effect on DSA production.

Human Immunoglobulins

The immunomodulatory activity of IgG is unknown. They are known to affect cell-mediated (T and B) immune response.

Proposed mechanisms of action of immunoglobulin:

- Anti-idiotypic antibodies neutralise circulating alloantibodies
- IVIg blocks T lymphocyte activation by interacting with the Fc receptor on antigen-presenting cells
- IVIg inhibits the activity of complement factors C3b and C4b
- IVIg inhibits cytokine secretion and activity
- IVIg inhibits the proliferation and activation of T and B lymphocytes
- IVIg inhibits epithelial cell activation
- Increase B lymphocyte apoptosis

High dose (1-2 g/kg bw) IgG should be used to achieve the desired therapeutic outcome. Non-randomised studies based on small patient populations, show combination therapy with PP+IVIg+rituximab proved more effective than IVIg alone in the treatment of acute AMR.[14]

Anti-CD20

Rituximab is a murine/human chimera, directed against the CD20 molecule located on B lymphocytes. It causes B cell lysis via antibody-dependent cytotoxicity (ADCC) or complement dependent cytotoxicity (CDC), and prompts B cell apoptosis. The target protein for rituximab is the CD20 antigen located on immature pre-B cells and mature B lymphocytes, but not on plasma cells. Intravenous administration of rituximab leads to rapid and sustained depletion of circulating and tissue-based B lymphocytes. B lymphocyte recovery starts as late as approximately 6 months following termination of therapy, and the B cell counts return to normal within 9-12 months. Genberg et al.[15] investigated the effect of a single dose of rituximab on the B lymphocyte population in peripheral blood, kidney graft tissue and lymph nodes of 49 kidney transplant recipients. A single dose (375 mg/m^2) of rituximab was used in combination with standard triple agent immunosuppression. Total B cell depletion in peripheral blood was found in 78% of patients. At 15 months following administration of a single dose of rituximab, B lymphocytes were undetectable in peripheral blood and graft tissue (CD19 and CD20 less than 5 cells/μl). They could not be completely eliminated from the lymph nodes, but their number was significantly reduced. Rituximab is licensed for the treatment of non-Hodgkin lymphomas and post-transplant lymphoproliferative disease (PTLD). The efficacy of rituximab in the treatment of AMR was initially reported by Becker et al.,[16] who used a single dose of rituximab (375 mg/m^2) in renal transplant recipients and achieved remission in 24 patients. A number of reports in the literature support the efficacy of rituximab in the treatment of acute AMR, particularly in combination with plasmapheresis and glucocorticoid pulses. Kaposztas et al.[17] described a retrospective cohort of 54 graft recipients with AMR (the largest reported cohort to date), who were treated with a combination of PP and rituximab or PP alone. After 24 months, graft survival was significantly better in the rituximab group (90% vs. 60%). Lefaucher et al.[18] reported significantly better outcomes in terms of 36-month graft survival (92% vs. 50%) in 12 recipients treated with PP, IVIg and rituximab in comparison with a historical control group who received IVIg monotherapy [18]. The posology and duration of rituximab therapy in kidney transplant recipients have not been defined. Most reports used a single dose, but three to five doses have been described as well. Prospective randomised studies and follow-up results are lacking, and benefits of rituximab in the treatment of AMR cannot be evaluated unequivocally in the setting of concurrent polytherapies. Note should be taken of late onset, severe infectious events that may occur 3-4 months following administration of rituximab. It is recommended to take appropriate prophylactic

measures against *Pneumocystis* infection and monitor cytomegalovirus (CMV) and BK virus (BKV) replication, as well as signs of bacterial and fungal infections. The principal limitation of rituximab is the lack of effect on DSA-producing plasma cells.

Anti-Thymocyte Globulin

Anti-thymocyte globulin (ATG) is a polyclonal antibody. Its beneficial effects, in terms of suppressing AMR, involve the following mechanisms of action:

- Inhibition of T-helper lymphocytes which are necessary for B lymphocyte activation
- Complement-dependent lysis of B lymphocytes
- Suppression of B lymphocyte proliferation
- Induction of B lymphocyte apoptosis
- Inhibition of co-stimulation molecules and cytokine production

Since acute graft rejection frequently occurs via a mixed mechanism, with a predominant cellular component, ATG is often used to treat this type of rejection in combination with glucocorticosteroids (GS) and plasmapheresis.[19]

Glucocorticosteroids

Glucocorticosteroids are used as first-line therapy in acute graft rejection of any type. They are effective in T cell-mediated rejection, in mixed type rejection they act on the cell-mediated component, whereas in the humoral type they suppress B cell-mediated response by interacting with T-helper lymphocytes. Routine recommendations include pulses of methylprednisolone 250-500 mg for 3-5 days.

Mycophenolate Mofetil and Tacrolimus

MMF is an antiproliferative agent with an inhibitory effect on humoral response and antibody production. When used in combination with tacrolimus, MMF suppresses B cell-mediated response in AMR. In this context, MMF should not be co-administered with cyclosporine, as cyclosporine decreases exposure to MMF. Lederer et al.[20] showed that in kidney transplant recipients, MMF decreases the levels of anti-class I and II HLA antibodies and DSA, particularly in patients who started MMF therapy from the day of transplantation. In all cases of AMR, it is recommended to use primary immunosuppression regimens involving tacrolimus and MMF.[21]

Eculizumab

An interesting therapeutic option may consist in suppressing the complement system. Eculizumab is a humanised antibody directed against C5 complement protein, which inhibits the formation of the membrane attack complex (MAC, C5b-C9). MAC is a protein structure formed in terminal complement activation. Eculizumab induces accommodation of endothelial cells, reduces the formation of C5b-C9 (MAC) deposits in the transplanted kidney. Stegall et al.[22] reported the efficacy of eculizumab in 26 highly immunised patients with acute AMR. The incidence of AMR was significantly lower in the eculizumab group (7.7%) as compared to controls (41.2%); at 1 year, transplant glomerulopathy (TG) developed in 6.7% of patients receiving eculizumab vs. 35.7% of those who received no anti-C5 therapy. Eculizumab is not licensed for the treatment of AMR (indications include paroxysmal nocturnal haemoglobinuria and atypical haemolytic-uremic syndrome (HUS)). High cost (6,000 USD per one 300 mg vial) is another limitation for more widespread use.

Complement C1 Inhibitor

Another promising drug is the recombinant human complement C1 inhibitor (rhC1INH). It is presumed to inhibit the initial stage of complement activation via the classical pathway. The efficacy in preventing AMR has been demonstrated in chimpanzees. Phase I/II clinical trials are ongoing.[23]

Bortezomib

The largest number of recent literature reports concerning the treatment of AMR focus on bortezomib, a drug that targets plasma cells. Bortezomib is a small molecule, a tripeptide with an incorporated boron atom, which binds specifically to 26S proteasome. Bortezomib is a selective, reversible inhibitor of proteasome, an organelle containing proteases, whose role is the breakdown of proteins used throughout the cell's life cycle. Bortezomib inhibits the breakdown of pro-apoptotic factors and the cell is destroyed via the programmed cell death mechanism (apoptosis). The NFκB pathway plays a key role in the survival of memory B cells and long-lived plasma cells. NFκB pathway activation is controlled by the breakdown of its inhibitor (IκB) by the proteasome complex, and conversely, the suppression of NFκB is maintained by high levels of IκB induced by bortezomib. Bortezomib causes plasma cell depletion, thus decreasing the production of DSA. Bortezomib was

synthetised in 1995, and obtained FDA approval for the treatment of multiple myeloma in 2003. It is available as intravenous formulation. The product is 80% protein-bound, undergoes hepatic metabolism, with a half-life of 9-15 hours. The dosing is 1.3 mg/m^2/dose, four doses (day 1, 4, 7, 11). Major adverse effects include peripheral neuropathy (30% of patients), thrombocytopoenia and neutropoenia.[24] Everly et al.[25] demonstrated the efficacy of bortezomib in six kidney transplant recipients with recurrent AMR. Trivedi et al.[26] described the use of bortezomib in the protocol of tolerance induction in 11 living donor kidney graft recipients. Flechner et al.[27] used bortezomib (in combination with PP and IVIg) for the treatment of AMR in 20 recipients and obtained 85% graft survival after 10 months, 50% reduction in DSA, and significant effectiveness in the subgroup with better baseline kidney function (creatinine <30 mg/dL). Walsh et al.[28] showed better efficacy of bortezomib in early (<6 months) AMR in 13 kidney transplant recipients, as compared to 17 late AMR events; superiority manifested by a greater DSA reduction and improved morphological aspect of the graft. Waiser et al.[29] compared the outcomes of AMR therapy with bortezomib (1.3 mg/m^2 IV, day 1, 4, 8, 11) in 10 recipients with historical controls (9 patients who received a single dose of rituximab 500 mg) (all patients were given IVIg 30 g), and demonstrated a significantly higher efficacy of bortezomib at 18 months follow-up (graft loss 4/10 vs. 8/9). These preliminary results investigating the efficacy of bortezomib in the treatment of AMR are encouraging, but the outcomes of ongoing prospective randomised clinical trials are necessary to confirm them.

Splenectomy

The spleen is the largest lymphatic organ in humans and plays a major role in the production of alloantibodies. Splenectomy results in elimination of both precursor and mature DSA-producing plasma cells. The efficacy of splenectomy as rescue therapy for isolated cases of severe refractory AMR has been reported, however, due to the risk of infectious complications and the risk of surgery, it is not routinely recommended for the treatment of AMR.[30]

Chronic AMR

Risk factors for the development of chronic antibody-mediated rejection include acute AMR and pre-transplant immunisation. Hence, it is important to identify patients at high immunological risk, who are most likely to develop both acute and chronic antibody-mediated rejection. In chronic AMR, complement activation causes subclinical endothelial injury. However, slow immunological reaction leads inevitably to irreversible graft damage. Graft glomerulopathy being irreversible in the advanced stages, early detection of changes by DSA monitoring and protocol biopsies in high risk patients is justified. Theoretically, all acute AMR therapies could be useful in the treatment of chronic AMR, but there are practically no reports based on clinical trial evidence. IVIg, rituximab or bortezomib have been used in isolated cases. Therapies requiring continuous, repeated use, such as PP or eculizumab, are of limited value due to their high cost. Since TG-related changes are irreversible, the use of toxic therapies in chronic AMR cannot be justified as long as their efficacy is not confirmed in clinical trials. Preventing the development of AMR by adequate immunosuppression involving GS, tacrolimus and mycophenolate mofetil and monitoring of graft recipient is the key element.

CONCLUSION

To conclude, antibody-mediated rejection is relatively uncommon in kidney transplant recipients, but the risk of graft loss is high. Recently several promising therapies have emerged, most of them targeting B lymphocytes, plasma cells and complement (rituximab, bortezomib, eculizumab), but their efficacy should be confirmed in randomised clinical trials. Currently there is a risk of unjustified polypharmacy, severe infectious complications and high costs.[31] There is no single recommended regimen for the treatment of AMR. Many authors suggest to start with glucocorticoid pulses and primary immunosuppression involving prednisone, tacrolimus and MMF. First-line therapy consists in PP with IVIg 100 mg/kg bw (targeting 1 g/kg bw) after each PP session. If this proves ineffective, second-line therapy may involve rituximab (a single dose 375 mg/m^2) or bortezomib (four doses; 1.3 mg/m^2/dose), each dose preceded by plasmapheresis. Eculizumab or splenectomy may be considered as rescue therapy. DSA should be monitored weekly for 4-12 weeks, then once a month for 3 months. Increase in DSA levels is an indication for a repeat graft biopsy. Anti-thymocyte serum may prove effective in the presence of a steroid-resistant cellular rejection component.[32] These novel therapies cannot be used in Poland, as drugs such as eculizumab, bortezomib or rituximab are not licensed for use in transplantology.

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