Management of Antibody-Mediated Rejection in Transplantation

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KEYWORDS

• Antibody-mediated rejection • Kidney transplantation • Donor-specific antibodies • Plasma cell

KEY POINTS

- Development of donor-specific anti-HLA antibodies following transplantation is associated with reduced allograft survival.
- To date, there are no immunosuppressive agents approved by the Food and Drug Administration to treat acute antibody-mediated rejection (AMR).
- AMR is generally less responsive then acute cellular rejection (ACR) to antirejection therapy.
- AMR is associated with lower long-term graft survival than ACR.
- Late AMR is associated with lower long-term graft survival than early AMR.
- Emerging therapies including bortezomib and eculizumab are providing promising data for managing transplant recipients who present with AMR.

INTRODUCTION

Renal allograft rejection may be T-cell mediated (acute cellular rejection [ACR]), B-cell mediated (antibody-mediated rejection [AMR]), or mixed (mixed acute rejection [MAR]). Recent studies have demonstrated that development of donor-specific anti–human leukocyte antigen (HLA) antibodies (DSA) is associated with reduced long-term graft function and survival,[1,2] and is associated with 20% to 30% of acute rejection episodes

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in kidney transplant recipients.[3,4] Despite intensive traditional immunosuppressive therapy, rates of graft loss have approximated 15% to 20% at 1 year following AMR.[3,5–7] Therefore, the development of antihumoral therapies that provide prompt elimination of DSA and improve allograft survival is an important goal.[8]

To date, there are no immunosuppressive agents approved by the Food and Drug Administration (FDA) for antibody-mediated rejection (AMR) treatment. Traditional treatment modalities for AMR include intravenous immunoglobulin (IVIg), plasmapheresis (PP), rituximab, and rabbit antithymocyte globulin (rATG). However, these agents deplete B-cell populations but not the cell at the source of antibody production, namely the mature plasma cell.[9,10] This situation has led to development of plasma cell–targeted therapies using proteasome inhibition (PI) as a novel approach for treating AMR.[11,12] This review discusses current and emerging treatment modalities used for AMR in solid organ transplantation.

DIAGNOSIS AND CLASSIFICATION OF AMR

Acute AMR diagnosis after kidney transplantation continues to undergo modifications as knowledge accumulates. The Banff '07 update remains a cornerstone for diagnosing acute AMR and includes 3 cardinal features[5,13]:

- Morphologic evidence, such as: (1) acute tissue injury and/or presence of neutrophils and/or mononuclear cells in peritubular capillaries (PTC) and/or glomeruli, (2) acute tubular injury or capillary thrombosis, and (3) intimal arteritis/fibrinoid necrosis/intramural or transmural inflammation in arteries
- Immunopathologic evidence of antibody presence, such as: (1) C4d and/or immunoglobulin in PTC or (2) immunoglobulin and complement in arterial fibrinoid necrosis
- Serologic evidence of circulating antibodies to donor HLA or DSA

Presence of C4d deposition in PTC plus 1 of the 2 criteria above leads to the diagnosis of AMR.[13]

Recently, considerable attention has focused on a variant of AMR known as C4d-negative AMR, as Halloran and colleagues[14] have emphasized the prominent importance of microcirculatory inflammation (MI). This evidence highlights the limitations of C4d, thereby suggesting that MI is likely superior to C4d as an AMR criterion.

AMR may also be classified into 3 groups based on timing: (1) hyperacute AMR, (2) acute AMR, and (3) chronic AMR.

Hyperacute AMR typically occurs within minutes to hours after allograft reperfusion and is associated with the presence of preformed antibodies against donor histocompatibility antigens. Histologic findings include neutrophil and platelet margination in glomerular and peritubular capillaritis, hemorrhagic cortical necrosis, acute tubular injury, and thrombosis and fibrin deposition within the microvasculature.

Acute AMR presents with allograft dysfunction within the first few weeks after transplantation. Major histologic findings associated with acute AMR include MI: neutrophils or mononuclear cells in the PTC or glomeruli with C4d deposition. Based on the current Banff criteria, acute AMR is classified into 3 types: type I (acute tubular necrosis), type II (glomerular type resembling thrombotic microangiopathy), and type III (vascular type with arterial inflammation). Type I represents less than 10% of patients, with only morphologic evidence of acute tubular injury with minimal tubulointerstitial neutrophil infiltrates. Type II includes peritubular capillaritis with or without glomerulitis, and type III acute AMR includes arterial inflammation with or without fibrinoid changes.