Chapter 11

Humoral Rejection in Cardiac Transplantation: Management of Antibody-Mediated Rejection

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Abstract

After a successful heart transplantation, fundamental keys to achieve good results in the long term are to establish immunosuppressive therapy in the postoperative period in an appropriate manner and to ensure continuity of follow-ups. Despite the fact that these stages are maintained perfectly, patients may face one or more rejection episodes. T-cell-mediated acute cellular rejection of the cardiac allograft has well-established treatment algorithms, whereas antibody-mediated rejection (AMR) is challenging to diagnose, and its treatment varies between centers. Investigators reported that AMR is among the most important factors to improving long-term outcomes. Improved understanding of the roles of acute and chronic AMR has evolved in recent years following a major progress in the technical ability to detect and quantify recipient antihuman leukocyte antigen (HLA) antibody production. Recently, a study of the immunobiology of B cells and plasma cells that pertains to allograft rejection and tolerance has emerged. There are some questions regarding the classification of AMR, the diagnostic approaches, and the treatment strategies for managing. In this chapter, we are discuss the effector mechanisms that are used by antibodies to eliminate antigens and clinical experience about AMR and its treatment with a discussion about the latest articles.

Keywords: heart transplantation, rejection, humoral, plasmapheresis, rituximab

1. Introduction

Orthotopic heart transplantation (OHT) is still the gold standard of treatment among end-stage heart failure. Worldwide, about 3500 heart transplantations are performed annually [1]. However, shortage of donors and allograft dysfunction are the most common problems cardiac surgeons have to cope with. Rejection is the most common reason for allograft dysfunction and

is responsible for 25% of postoperative deaths [2]. Episodes of rejection may emerge at any time after transplantation as acute or chronic cellular rejection (CR), humoral rejection (=antibody-mediated = vascular rejection (AMR)), or mixed rejection. Despite AMR that is known to be rare, it is potentially lethal due to the capillary vasculopathy caused by neutrophil and macrophage infiltration in endothelial cells [3, 4]. Today, treatment of rejection episodes is directed mostly to cellular response. Each center sets the treatment in the light of their experience. In this chapter, we will discuss the effector mechanisms that are used by antibodies to eliminate antigens and clinical experience about AMR and its treatment with discussing the latest articles.

2. Overview of humoral immunity

Antibodies are accumulated by the immune system to identify and neutralize foreign objects. They were the first specific product of the adaptive immune response to be identified and are found in the plasma, in the blood, and in extracellular fluids. Immunity mediated by antibodies is known as humoral immunity because of body fluids that were once known as humors [4]. The humoral immune response begins with the recognition of antigens by native B cells. These cells then undergo a process of clonal expansion and differentiation. In this way, the B cell matures into antibody-secreting plasma cells, which secrete antibodies. The activation of B cells and their differentiation into antibody-secreting plasma cells is triggered by antigen and usually requires helper T cells. The term "helper T cell" is often used to mean a cell from the TH2 class of CD4 T cells, but a subset of TH1 cells can also help in B-cell activation [5]. B cells can receive help from helper T cells when antigen bound by surface immunoglobulin is internalized and returned to the cell surface as peptides bound to major histocompatibility complex (MHC) class II molecules. MHC then delivers activating signals to the B cell. Thus, protein antigens binding to B cells both provide a specific signal to the B cell by cross-linking its antigen receptors and allow the B cell to attract antigen-specific T-cell help. These antigens are unable to induce antibody responses in animals or humans who lack T cells, and they are therefore known as thymus-dependent antigens [5]. The first signal required for B-cell activation is delivered through its antigen receptor. For thymus-dependent antigens, the second signal is delivered by a helper T cell that recognizes degraded fragments of the antigen as peptides bound to MHC class II molecules on the B-cell surface; the interaction between CD40 ligand on the T cell and CD40 on the B cell contributes an essential part of this second signal [5]. For thymus-independent antigens, the second signal can be delivered by the antigen itself or by non-thymus-derived accessory cells. The B-cell co-receptor complex of CD19:CD21:CD81 can greatly enhance B-cell responsiveness to antigen. CD21 (=complement receptor 2) is a receptor for the complement fragment C3d. Whether binding of CD21 enhances B-cell responsiveness by increasing B-cell signaling, by inducing co-stimulatory molecules on the B cell, or by increasing the receptor-mediated uptake of antigen is not yet known [5]. Antibodies are the effector products of humoral immunity. Finally, as this response declines, a pool of memory cells remains behind. If the body is reexposed to the antigen, these memory cells will recognize the antigen and respond much more quickly and effectively [6]. There are two purposes of antibodies. The first purpose is to neutralize the target threat, and the second purpose is to recruit other cells or proteins to an antigen so that those cells or proteins can

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eliminate the antigen [6]. AMR develops when recipient antibody is directed against donor human leukocyte antigens (HLA) on the endothelial layer of the allograft. Antibodies induce fixation and activation of the complement cascade, resulting in tissue injury. Complement and immunoglobulin are deposited within the allograft microvasculature, which results in an inflammatory process that is characterized by endothelial cell activation, upregulation of cytokines, infiltration of macrophages, increased vascular permeability, and microvascular thrombosis. This process ultimately manifests as allograft dysfunction [6].

3. Humoral rejection (=antibody-mediated = vascular rejection (AMR))

AMR is mediated by donor-specific antibodies and is histologically defined by linear deposits of immunoglobulin (Ig) and complement in the myocardial capillaries [7]. Herskowitz et al. [8] described AMR for the first time in 1987 as an arteriolar vasculitis with poor outcome. Hammond et al. [9] firstly demonstrated that vascular rejection is associated with deposits of antibodies and complement activation. AMR incidence is reported between 8 and 15% [10–12], and it has been reported concurrent with CR in up to 24% of cases. Approximately 50% of heart transplant recipients who develop rejection >7 years after transplantation have evidence of AMR [12]. AMR was described as an acute phenomenon seen in weeks to months just after OHT. However, in recent years, studies have been reported that it also occurs in the longer term [9, 13, 14]. Rejection can be hyperacute (occurring within minutes after the vascular anastomosis (0–7 days)) in patients who are sensitized to donor HLA antigens and acute (occurring days to weeks after transplantation) because of the development of de novo donor-specific antibody (DSA) and preexisting DSA. Early AMR tends to be associated with a higher prevalence of allograft dysfunction and hemodynamic compromise. Late (occurring 3 months after transplantation) or chronic rejection most likely because of heightened recognition (occurring months to years after transplantation) [15]. Risk factors include young age, female gender, high levels of pretransplant panel-reactive antibodies (PRAs), positive donor-specific crossmatch, cytomegalovirus infection, prior OKT3 use, and artificial heart devices [10, 13]. Olsen et al. [16] stated that 23% of patients had AMR episodes for the second time resulting in graft loss in two-thirds due to the continuous complement activation and production of donor-reactive antibodies that cause graft dysfunction by sensitized memory B cells. As the definition of AMR has evolved and more sensitive diagnostic modalities have become available, there is increasing evidence that AMR is a spectrum of immunologic injury that ranges from subclinical, histological, immunologic, and/or serological findings without graft dysfunction (i.e., subclinical AMR) to overt AMR with hemodynamic compromise.

3.1. Diagnosis

The first description of humoral rejection was included in the 1990 International Society of Heart and Lung Transplantation (ISHLT) criteria defined as positive immunofluorescence, vasculitis, or severe edema in the absence of cellular infiltrate [14, 17]. The classification AMR 0 was assigned in the absence of histological or immunopathologic features. Confirmation of

AMR or AMR 1 was defined as histological evidence with identification of antibodies (CD68, CD31, C4d) and serum presence of DSA [14]. ISHLT Immunopathology Task Force provided an expanded description of the histological evidence of acute capillary injury, the minimum requirement for immunopathologic evidence of antibody-mediated injury, and an improved definition of serological evidence of circulating antibodies in 2006 [18]. The persistent variations in the diagnosis and treatment of AMR were addressed in the Heart Session of the Tenth Banff Conference on Allograft Pathology (2009) and the ISHLT Consensus Conference on AMR (2010) conferences. The most important issues included the need for a clinical definition of AMR, the significance of asymptomatic patient without cardiac dysfunction biopsy-proven AMR, and the recognition that AMR may be caused by DSA as well as antibodies to non-HLA antigens. Although AMR would be a pathological diagnosis, it was strongly recommended that at the time of suspected AMR, blood can be drawn at biopsy and tested for the presence of donor-specific anti-HLA class I and class II antibodies [14]. On the basis of the initial Banff criteria, a definitive diagnosis of AMR required morphologic evidence (primarily microvascular inflammation), immunohistological (C4d staining), and serologic criteria (presence of circulating DSA). These criteria were modified to address the current evidence of the existence of C4d-negative AMR and lesions of intimal arteritis secondary to the action of the antibodies at the Banff Consensus in 2013 [19]. The myocardial capillaries, arterioles, and venules are readily sampled at biopsy. The vascular endothelium is the point of the first contact for anti-donor antibody in the allograft and the primary locus of activity in AMR. The appearance of vasculitis or leukocytes infiltrating through the endothelium into the vessel wall demonstrates active humoral immunity with antibody-dependent cytotoxicity, cytokine, and circulating monocyte recruitment [20, 21]. Mechanisms of immune complex-mediated neutrophil recruitment and tissue injury. Antibodies induce fixation and activation of the complement cascade, resulting in tissue injury. Complement activation, a key contributor to the pathogenesis of AMR, results in activation of the innate and adaptive immune responses. Complement and immunoglobulin are deposited within the allograft microvasculature, which results in an inflammatory process that is characterized by endothelial cell activation, upregulation of cytokines, infiltration of macrophages, increased vascular permeability, and microvascular thrombosis. Interstitial edema and hemorrhage are also seen. Capillary changes indicative of AMR include endothelial cell swelling and intravascular macrophage accumulation coincident with pericapillary neutrophils. The role of immunoglobulins, complement activation, and coagulation cascade in AMR is under constant study as diagnostic methods increase in sensitivity and specificity [14, 22]. It has been suggested that AMR is a clinical pathological continuum that begins with a latent humoral response of circulating antibodies and then progresses through a silent phase of circulating antibodies with C4d deposition without clinical or histological alterations, to a subclinical stage, to symptomatic AMR [14]. Mauiyyedi et al. described the correlation between DSAs and diffuse C4d deposition (>50%) as diagnostic markers for AMR [23]. C4d deposition may be earlier than 3 months, as may be after 160 months [7, 10, 24]. The complement components C3 and C1q have been demonstrated in kidney AMR; however, their detection is limited by a short half-life in vivo and consequently a short window of detection during a rejection episode [25]. The protein C4d is a complement split product that binds covalently to the endothelium at the site of complement activation and persists longer than C3 or C1q [14]. C4d and C3d detection predicts graft dysfunction and mortality better than C4d alone [14, 26]. Haas et al. reported that biopsies positive for C4d (C4d+) and C3d (C3d+) are strongly associated with DSA and allograft dysfunction, while cases with episodes that are

only positive for C4d are mostly subclinical [19]. Berry et al. published working formulation by pathologists to diagnose "pathological AMR (pAMR)" without the requirement of clinical dysfunction or positive DSA (**Table 1**) [27, 28]. CD59 and CD55 (decay-accelerating factors) are used in conjunction with C4d and C3d to indicate aborted complement activation. Lengthy incubation times and a granular staining pattern render these assays impractical for clinical use [26]. The macrophage antigen CD68 allows identification of subtle accumulations of macrophages within vessels, which helps to differentiate intravascular/perivascular macrophages from lymphocytes, thereby excluding ACR. Because interstitial macrophages are commonly found in allograft myocardium in a variety of settings, including AMR, ACR, and ischemic injury, investigators agree that only macrophages within capillaries and small venules are to be considered [29]. The term "intravascular macrophage" was replaced by "activated mononuclear cells" because it was clear that without immunostaining with CD68, intravascular T lymphocytes and activated endothelial cells could be misinterpreted as macrophages at the 2012 ISHLT workshop [28]. Endothelial cell markers CD34 and CD31 can be used to ascertain the intravascular location of macrophages/mononuclear cells [30]. Immunopathologic features of AMR were summarized in **Table 2**. Using criteria that included prominent endothelial cell swelling and/or vasculitis and the vascular deposition of immunoglobulin and complement, it was first defined by Hammond and co-workers [9]. The clinic spectrum of AMR ranges from latent AMR to silent AMR, to subclinical AMR, and to clinical AMR. Pathologic evidence of AMR appears in silent AMR as C4d deposition in capillaries of an otherwise normal myocardium and progresses to subclinical AMR showing myocardial alterations in the setting of C4d deposition but the absence of organ dysfunction. The onset of allograft dysfunction is the hallmark of clinical AMR [28, 31].

3.1.1. Surveillance and frequency of immunopathologic assessment

Kfoury et al. recommended that immunostaining for C4d be avoided in the first 2 weeks after transplant because a number of perioperative issues can confound staining and interpretation [32]. Center-specific approaches to the issue of surveillance vary widely, ranging from none to every biopsy. The other question is follow-up of positive immunostaining after therapy of AMR. The ISHLT pathology group recommended that subsequent biopsies should be studied

Category	Description
pAMR 0: negative for pathological AMR	Both histological and immunopathologic studies are negative
pAMR 1 (H+): histopathologic AMR alone	Histological findings positive and immunopathologic findings negative
pAMR1 (I+): immunopathologic AMR alone	Histological findings negative and immunopathologic findings positive
pAMR 2: pathological AMR	Both histological and immunopathologic findings are present
pAMR 3: severe pathological AMR	Severe AMR with histopathologic findings of interstitial hemorrhage, capillary fragmentation, mixed inflammatory infiltrates, endothelial cell pyknosis and/or karyorrhexis, and marked edema

AMR, antibody-mediated rejection; pAMR, pathological AMR (Source: [28]).

Table 1. The 2013 ISHLT working formulation for pathologic diagnosis of cardiac antibody-mediated rejection.

	Interpretation	AMR limitations
IgG/IgM	Immunoglobulin binding	+ Easily dissociated, short half-life, interobserver variability
C3, C1q	Complement activation	+ Short half-life
C3d/C4d	Complement activation	+ Combination more predictive of AMR than C4d alone, long half-life
HLA-DR	Endothelial integrity	+ Staining always present, but "frayed" pattern indicates capillary injury
Fibrin	Thrombotic environment	+ Interstitial extravasation suggests more severe AMR episode
CD55, CD59	Complement inhibitor	− Long incubation and granular staining pattern, difficult to be interpreted
CD31, CD34, CD68	Intravascular macrophages	+ CD68 confirms macrophage lineage of mononuclear cells, CD31 and CD34 are endothelial markers which differentiate macrophages from endothelial cells and delineate intravascular localization

AMR, antibody-mediated rejection; HLA, human leukocyte antigens (Source: [14]).

Table 2. Immunopathologic features of antibody-mediated rejection.

by immunostaining until a negative result is achieved in 2011. However, investigators reported that capillary staining of C3d cleared within 2 weeks to 1 month, while capillary staining of C4d cleared within 1–2 months [26].

3.2. Treatment

Investigators have since reported on its incidence, histopathological features, clinical outcome, and treatment. However, clinical series are few and sparse, and the incidence of HR and the method of choice for its management remain uncertain and may differ among different centers [33]. All transplantation centers often prefer pulse steroid as an initial therapy in combination with plasmapheresis. Otherwise, intravenous cyclophosphamide (0.5 to 1 gm/m^2, every 3 weeks for 4–6 months) may be added to treatment regimen according to the clinical experience and preferences. In case of recurrent AMR exacerbations, cyclophosphamide and IVIg (250 mg/kg/day, 4 days, 4–6 months repeated every 3 weeks) followed by plasmapheresis (5–6 sessions, 10–14 days) have been suggested. After 2002, rituximab (375 mg/m^2, once a week, four dose infusions) after plasmapheresis is added to treatment regimen [34].

Plasmapheresis is the cornerstone in the treatment of AMR. Exchange method and double-filtration technique are among the most used plasmapheresis methods. Both techniques are nonselective and eliminate immunoglobulins nonspecifically. Immunoadsorption plasmapheresis method using adsorbent membrane is more specific to the removal of antibodies; however, it is expensive. Each type of plasmapheresis involves risks such as hypovolemia and infection [4, 35, 36].

Plasmapheresis has been always reported in combination with other immunosuppressive agents; there is always a possibility of AMR recurrence as a monotherapy. In this context, other therapies are to be combined in order to prevent recurrence.

Another issue which is also controversial regarding plasmapheresis is about the number of sessions of plasmapheresis to be made and at what intervals. General practice is three to five

sessions every other day. However, Crespo-Leiro et al. [33] reported that they use plasmapheresis every day until the recovery of the clinical status. The author who reported this period may extend to the nineteenth day. We perform plasmapheresis every other day for three sessions, and if there is no clinical improvement, we extend it up to five sessions in our general practice. Cytolytic therapy would be useful especially for those who need inotropics or mechanical circulatory support [13, 16]. Cytolytic therapy may indirectly suppress B lymphocyte activation, whereas antithymocyte globulin may directly suppress B-cell function [37, 38].

CD20 protein is a molecule present on the surface of B lymphocytes. Rituximab is a chimeric monoclonal antibody raised against the CD20 protein. Combination of rituximab with plasmapheresis, IVIg, or steroids was found to increase the success of treatment [39, 40]. Complement blockade would be an important strategy for prevention and treatment of AMR. Agents targeting C5 and C1 esterase have been evaluated in clinical trials. Eculizumab binds to complement protein C5 and inhibits complement. It prevents the breakdown of C5 and formation of MAC. Since eculizumab cannot decrease the levels of donor-specific antigen, antibody-lowering therapy should be added. Although early studies on the effects of eculizumab are promising, the use of eculizumab is limited due to the cost and lack of coverage by most insurers [41, 42]. Plasma-derived human C1-inhibitor (20UI/kg/twice weekly), an inhibitor which targets the classical complement pathway, was successfully administered for caAMR prevention in highly sensitized patients [43, 44]. Two C1-INH products that are approved for use by the FDA in the treatment of hereditary angioedema have been evaluated in small pilot studies for AMR: Berinert® (CSL Behring, Kankakee, IL, USA) and Cinryze® (Shire ViroPharma Inc., Lexington, MA, USA) [45, 46, 47]. A potential limitation of available therapies for AMR is the lack of direct effect on the major alloantibody-producing plasma cell. In recent years, studies regarding bortezomib, a reversible 26S proteasome inhibitor used in the treatment of multiple myeloma, have been reported [48, 49]. These studies rather relate to the treatment of AMR in kidney transplantation. Woodle et al. reported promising results in this regard [49, 50]. This molecule has been used as a rescue therapy in combination with other immunotherapies for refractory AMR. Everly et al. treated refractory mixed AMR and ACR with kidney transplant recipients. They used a single cycle of bortezomib: 1.3–1.5 mg/m^2 × 4 doses over 11 days (days 1, 4, 8, and 11) [51, 52]. Alemtuzumab is a monoclonal antibody that binds to CD52 on the surface of B and T lymphocytes. It depletes mature lymphocytes without myeloablation [53]. Woodside et al. reported reversal of recurrent severe cardiac rejection [54].

A humanized monoclonal antibody against the IL-6R (tocilizumab) has been used in phase I/phase II studies for the treatment of chronic active AMR unresponsive with high-dose IVIg for patients who are difficult to desensitize. Choi et al. reported that AMR patients who had failed high-dose IVIg, rituximab, and plasmapheresis received monthly doses of tocilizumab for 6 to 18 months and they found to have good outcomes [55, 56].

Antithymocyte globulins (ATG) are antibodies directed at T-cell lymphocyte. This class of drugs is used for active treatment of ACR; thus, they are adapted for AMR treatment, but there are few data on their effect. Although there have been patients with AMR treated successfully with ATG in combination with other drugs, ATG requires more analysis as part of a randomized trial [14, 57]. Furthermore, total lymphocyte radiation is used to treat acute rejection but is risky due to its reported effects increasing hematologic malignancies [58].

Our opinion is that pAMR should be considered important due to the long-term survival of patients. If patient has pAMR, we perform plasmapheresis every other day for three sessions.

There are limited studies about treatment of subclinical AMR. Patients with subclinical AMR are not generally treated, because more data regarding the significance of a positive biopsy in the absence of symptoms are needed. Wu et al. reported that 5-year actuarial survival rates for the subclinical AMR (86%), treated AMR (68%), and control groups (79%) were not significantly different; however, patients with subclinical AMR were more likely to develop cardiac allograft vasculopathy than the control group and even tended to do worse than patients with treated symptomatic AMR [59]. The incidence of CAV or death in the patients with AMR was twice that of the control subjects [13].

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References

[1] Stehlik J, Edwards LB, Kucheryavaya AY, et al. The registry of the International Society for Heart and Lung Transplantation: Twenty-Seventh Official Adult Heart Transplant Report-2010. The Journal of Heart and Lung Transplantation. 2010;**29**:1089-1103

[2] Boucek MM, Novick RJ, Bennett LE, Fiol B, Keck BM, Hosenpud JD. The registry of the International Society of Heart and Lung Transplantation: First Official Pediatric Report-1997. The Journal of Heart and Lung Transplantation. 1997;**16**:1189-1206

[3] Chou HW, Chi NH, Lin MH, et al. Steroid pulse therapy combined with plasmapheresis for clinically compromised patients after heart transplantation. Transplantation Proceedings. 2012;**44**(4):900-902

[4] Chaplin DD. Overview of the immune response. The Journal of Allergy and Clinical Immunology. 2010;**125**(2 Suppl. 2):S3-S23

[5] Wilson IA, Cresswell P, Davis MM, Allen PM, Trowsdale J. The humoral immune response. In: Janeway AC, Travers P, Walport M, Shlomchik, editors. Immunobiology: The Immune System in Health and Disease. 5th ed. New York: Garland Publishing; 2001. pp. 401-454

[6] Abbas AK, Lichtman AH, Pillai S. Effector mechanisms of humoral immunity. In: Cellular and Molecular Immunology. 9th ed. Philadelphia, PA: Elsevier; 2018. pp. 275-298

[7] Aranda JM Jr, Scornik JC, Normann SJ, et al. Anti-CD20 monoclonal antibody (rituximab) therapy for acute cardiac humoral rejection: A case report. Transplantation. 2002;**73**(6): 907-910

[8] Herskowitz A, Soule LM, Ueda K, et al. Arteriolar vasculitis on endomyocardial biopsy: A histologic predictor of poor outcome in cyclosporine-treated heart transplant recipients. The Journal of Heart Transplantation. 1987;**6**(3):127-136

[9] Hammond EH, Yowell RL, Nunoda S, et al. Vascular (humoral) rejection in heart transplantation: Pathologic observations and clinical implications. The Journal of Heart Transplantation. 1989;**8**(6):430-443

[10] Uber WE, Self SE, Van Bakel AB, Pereira NL. Acute antibody-mediated rejection following heart transplantation. American Journal of Transplantation. 2007;**7**(9):2064-2074

[11] McNamara D, Di Salvo T, Mathier M, et al. Left ventricular dysfunction after heart transplantation: Incidence and role of enhanced immunosuppression. The Journal of Heart and Lung Transplantation. 1996;**15**:506-515

[12] Loupy A, Cazes A, Guillemain R, et al. Very late heart transplant rejection is associated with microvascular injury, complement deposition and progression to cardiac allograft vasculopathy. American Journal of Transplantation. 2011;**11**:1478-1487

[13] Michaels PJ, Espejo ML, Kobashigawa J, et al. Humoral rejection in cardiac transplantation: Risk factors, hemodynamic consequences and relationship to transplant coronary artery disease. The Journal of Heart and Lung Transplantation. 2003;**22**:58-69

[14] Colvin MM, Cook JL, Chang P, et al. Antibody-mediated rejection in cardiac transplantation: Emerging knowledge in diagnosis and management: A scientific statement from the American Heart Association. Circulation. 2015;**131**(18):1608-1639

[15] Garces JC, Giusti S, Staffeld-Coit C, Bohorquez H, Cohen AJ, Loss GE. Antibody-mediated rejection: A review. The Ochsner Journal. 2017;**17**(1):46-55

[16] Olsen SL, Wagoner LE, Hammond EH, et al. Vascular rejection in heart transplantation: Clinical correlation, treatment options, and future considerations. The Journal of Heart and Lung Transplantation. 1993;**12**:135-142

[17] Billingham ME, Cary NR, Hammond ME, et al. A working formulation for the standardization of nomenclature in the diagnosis of heart and lung rejection: Heart Rejection Study Group: The International Society for Heart Transplantation. The Journal of Heart Transplantation. 1990;**9**:587-593

[18] Reed EF, Demetris AJ, Hammond E, Itescu S, Kobashigawa JA, Reinsmoen NL, Rodriguez ER, Rose M, Stewart S, Suciu-Foca N, Zeevi A, Fishbein MC, International Society for Heart and Lung Transplantation. Acute anti- body-mediated rejection of cardiac transplants. The Journal of Heart and Lung Transplantation. 2006;**25**:153-159

[19] Haas M, Sis B, Racusen LC, et al. Banff 2013 meeting report: Inclusion of c4d-negative antibody-mediated rejection and antibody-associated arterial lesions. American Journal of Transplantation. 2014;**14**(2):272-283

[20] Mayadas TN, Tsokos GC, Tsuboi N. Mechanisms of immune complex-mediated neutrophil recruitment and tissue injury. Circulation. 2009;**120**(20):2012-2024

[21] Bruckheimer EM, Fazenbaker CA, Gallagher S, et al. Antibody-dependent cell-mediated cytotoxicity effector-enhanced EphA2 agonist monoclonal antibody demonstrates potent activity against human tumors. Neoplasia. 2009;**11**(6):509-517

[22] Brasile L, Zerbe T, Rabin B, Clarke J, Abrams A, Cerilli J. Identification of the antibody to vascular endothelial cells in patients undergoing cardiac transplantation. Transplantation. 1985;**40**:672-675

[23] Mauiyyedi S, Pelle PD, Saidman S, et al. Chronic humoral rejection: Identification of antibody-mediated chronic renal allograft rejection by C4d deposits in peritubular capillaries. Journal of the American Society of Nephrology. 2001;**12**:574-582

[24] Brandle D, Joergensen J, Zenke G, Burki K, Hof RP. Contribution of donor-specific antibodies to acute allograft rejection: Evidence from B cell-deficient mice. Transplantation. 1998;**65**(11):1489-1493

[25] Baldwin WM 3rd, Samaniego-Picota M, Kasper EK, et al. Complement deposi- tion in early cardiac transplant biopsies is associated with ischemic injury and subsequent rejection episodes. Transplantation. 1999;**68**:894-900

[26] Tan CD, Sokos GG, Pidwell DJ, et al. Correlation of donor-specific antibodies, complement and its regulators with graft dysfunction in cardiac antibody-mediated rejection. American Journal of Transplantation. 2009;**9**:2075-2084

[27] Berry GJ, Angelini A, Burke MM, et al. The ISHLT working formulation for pathologic diagnosis of antibody-mediated rejection in heart transplantation: Evolution and current status (2005-2011). The Journal of Heart and Lung Transplantation. 2011;**30**:601-611

[28] Berry GJ, Burke MM, Andersen C, et al. The 2013 International Society for Heart and Lung Transplantation working formulation for the standardization of nomenclature in the pathologic diagnosis of antibody-mediated rejection in heart transplantation. The Journal of Heart and Lung Transplantation. 2013;**32**:1147-1162

[29] Ratliff NB, McMahon JT. Activation of intravascular macrophages within myocardial small vessels is a feature of acute vascular rejection in human heart transplants. The Journal of Heart and Lung Transplantation. 1995;**14**:338-345

[30] Fishbein MC, Kobashigawa J. Biopsy-negative cardiac transplant rejection: Etiology, diagnosis, and therapy. Current Opinion in Cardiology. 2004;**19**:166-169

[31] Takemoto SK, Zeevi A, Feng S. National conference to assess antibody-mediated rejection in solid organ transplantation. American Journal of Transplantation. 2004;**4**:1033-1041

[32] Kfoury AG, Hammond ME, Snow GL, et al. The Journal of Heart and Lung Transplantation. 2007;**26**(12):1264-1269

[33] Crespo-Leiro MG, Veiga-Barreiro A, Doménech N, et al. Humoral heart rejection (severe allograft dysfunction with no signs of cellular rejection or ischemia): Incidence, management, and the value of C4d for diagnosis. American Journal of Transplantation. 2005;**5**: 2560-2564

[34] Almuti K, Haythe J, Dwyer E, et al. The changing pattern of humoral rejection in cardiac transplant recipients. Transplantation. 2007;**84**(4):498-503

[35] Pajaro OE, Jaroszewski DE, Scott RL, Kalya AV, Tazelaar HD, Arabia FA. Antibody-mediated rejection in heart transplantation: Case presentation with a review of current international guidelines. Journal of Transplantation. 2011;**2011**:1-7

[36] Kobashigawa J, Crespo-Leiro MG, Ensminger SM, et al. Report from a consensus conference on antibody-mediated rejection in heart transplantation. The Journal of Heart and Lung Transplantation. 2011;**30**(3):252-269

[37] Bonnefoy-Berard N, Jean-Pierre R. Mechanisms of immunosuppression induced by antithymocyte globulins and OKT3. The Journal of Heart and Lung Transplantation. 1996; **15**:435-442

[38] Zand MS. B-cell activity of polyclonal antithymocyte globulins. Transplantation. 2006;**82**: 1387-1395

[39] Garrett HE Jr, Duvall-Seaman D, Helsley B, Groshart K. Treatment of vascular rejection with rituximab in cardiac transplantation. Journal of Heart and Lung Transplantation. 2005;**24**(9):1337-1342

[40] Kaczmarek I, Deutsch MA, Sadoni S, et al. Successful management of antibody-mediated cardiac allograft rejection with combined immunoadsorption and anti-CD20 monoclonal antibody treatment: Case report and literature review. Journal of Heart and Lung Transplantation. 2007;**26**(5):511-515

[41] Parker CJ, Kar S, Kirkpatrick P. Eculizumab. Nature Reviews Drug Discovery. 2007;**6**(7): 515-516

[42] Parker C. Eculizumab for paroxysmal nocturnal haemoglobinuria. Lancet. 2009;**373** (9665):759-767

[43] Berger M, Baldwin WM, Jordan SC. Potential roles for C1 inhibitor in transplantation. Transplantation. 2016;**100**(7):1415-1424

[44] Muller YD, Ghaleb N, Rotman S, et al. Rituximab as monotherapy for the treatment of chronic active antibody-mediated rejection after kidney transplantation. Transplant International. 2018;**31**(4):451-455

[45] Berinert [Package Insert]. Kankakee, IL: CSL Behring LLC; 2015

[46] Cinryze [Package Insert]. Lexington, MA: Shire ViroPharma, Inc.; 2014

[47] Vo AA, Zeevi A, Choi J, et al. A phase I/II placebo-controlled trial of C1-inhibitor for prevention of antibody-mediated rejection in HLA sensitized patients. Transplantation. 2015;**99**:299-308

[48] Chih S, Chruscinski A, Ross HJ, Tinckam K, Butany J, Rao V. Antibody-mediated rejection: An evolving entity in heart transplantation. Journal of Transplantation. 2012;**2012**:1-10. DOI: 10.1155/2012/210210

[49] Woodle ES, Light J, Franklin W. A multicenter prospective, collaborative evaluation of proteasome inhibition for the treatment of antibody-mediated rejection in solid organ transplantation. American Journal of Transplantation. 2011;**10**(4):159-164

[50] Walsh RC, Alloway RR, Woodle ES. Proteasome inhibition for antibody-mediated rejection. Current Opinion in Organ Transplantation. 2009;**14**(6):662-666

[51] Everly JJ, Walsh RC, Alloway RR, et al. Proteasome inhibition for antibody-mediated rejection. Curr Opin Organ Transplant 2009;**14**:662-666

[52] Everly MJ, Everly JJ, Susskind B, et al. Bortezomib provides effective therapy for antibody- and cell-mediated acute rejection. Transplantation. 2008;**86**:1754-1761

[53] Frampton JE, Wagstaff AJ. Alemtuzumab. Drugs. 2003;**63**:1229-1243

[54] Woodside KJ, Lick SD. Alemtuzumab(Campath 1H) as successful salvage therapy for recurrent steroid-resistant heart transplant rejection. The Journal of Heart and Lung Transplantation. 2007;**26**:750-752

[55] Choi J, Aubert O, Vo A, et al. Assessment of tocilizumab (anti-IL-6 receptor monoclonal) as a potential treatment for chronic antibody mediated rejection and transplant glomerulopathy in HLA sensitized renal allograft recipients. American Journal of Transplantation. 2017;**17**:2381-2389

[56] Montgomery RA, Loupy A, Dl S. Antibody-mediated rejection: New approaches in prevention and management. American Journal of Transplantation. 2018;**18**(Suppl. 3):3-17. DOI: 10.1111/ajt.14584

[57] Hammond EA, Yowell RL, Greenwood J, et al. Prevention of adverse clinical outcome after cardiac transplant patients for murine monoclonal CD3 antibody (OKT3) sensitization. Transplantation. 1993;**55**:1061-1063

[58] Salter SP, Salter MM, Kirklin JK, Bourge RC, Naftel DC. Total lymphoid irradiation in the treatment of early or recurrent heart transplant rejection. International Journal of Radiation Oncology Biology Physics. 1995;**33**(1):83-88

[59] Wu G, Kobashigawa J, Fishbein M, et al. Asymptomatic antibody-mediated rejection after heart transplantation predicts poor outcomes. The Journal of Heart and Lung Transplantation. 2009;**28**:417-422