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ANTIBODY-MEDIATED REJECTION IN HEART TRANSPLANTATION

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The role of antibody-mediated rejection in predicting survival among heart recipients has been studied in clinical transplantology for over 20 years. This condition is a significant risk factor for heart failure and graft vasculopathy. Antibody-mediated rejection results from activation of the humoral immune system and production of donor-specific antibodies that cause myocardial injury through the complement system. The presence of donor-specific antibodies is associated with lower allograft survival. Treatment of antibody-mediated rejection should take into account the rejection category and the presence or absence of graft dysfunction. The main principle of treatment is to suppress humoral immunity at different levels. World clinical practice has made significant inroads into the study of this issue. However, further research is required to identify and develop optimal treatment regimens for patients with humoral rejection in cardiac transplantation.

Keywords: antibody-mediated (humoral) rejection, graft dysfunction, donor-specific antibodies, heart transplantation.

INTRODUCTION

It took about 25 years to recognize antibody-mediated rejection (AMR), also known as humoral rejection, as an independent disease, develop diagnostic criteria and treatment regimens [1]. The first reports on this new type of heart transplant rejection in the absence of lymphocytic infiltration in biopsy specimens appeared in the late 1980s [2]. Moreover, it was only in 2003 that the first conference dedicated to this issue was held at the National Institute of Health [3]. Over time, the role of complement component deposition in tissues and immune damage to the heart graft has been increasing [4].

In 2010, an international consensus conference was held by the International Society for Heart and Lung Transplantation (ISHLT) to discuss the current status of AMR in heart transplantation. The conference included 67 heart transplant centers defined the criteria for a preliminary pathological diagnosis of AMR and introduced the concept of asymptomatic humoral rejection, which has an impact on patient and allograft survival. Guidelines were made for the timing for specific staining of endomyocardial biopsy specimens. Guidelines for management and future clinical trials were also provided [5]. In 2013, under the leadership of Kobashigawa J.A., director of the severe heart disease department at Cedars-Sinai Medical Center, Los Angeles, the pathological criteria for antibody-mediated heart graft rejection were standardized [1], under which AMR began to be considered as a pathologic diagnosis regardless of the presence or absence of graft dysfunction. The paper also outlined the timing of routine monitoring of donor-specific antibodies (DSA).

Endomyocardial biopsy (EMB) with histological examination of biopsy specimens, immunoperoxidase test and immunofluorescence reaction for complement component C4d performed 2 weeks, 1, 3, 6 and 12 months after transplantation were required for diagnosis of humoral rejection. The presence of complement deposits suggested the presence of AMR. Circulating DSA were monitored by solid-phase analysis also at 2 weeks, 1, 3, 6, and 12 months after transplantation [1].

Circulating antibodies may not always be detected in patients with clinical and pathological signs of AMR, but they can be detected in asymptomatic patients [6]. AMR diagnosis requires clinical manifestations of graft dysfunction, morphological changes in EMB in the form of microvascular damage due mainly to deposition of complement component C4d, and the presence of circulating DSA. Despite the prognostic importance of each of these three criteria [7], once at least two of them are detected, specific treatment should be initiated [8].

Initial AMR therapies included pulse therapy with glucocorticoids, plasmapheresis, and intravenous (IVIg) immunoglobulin infusion. Later these methods were supplemented with rituximab, bortezomib, and complement component antibodies [3]. The use of basic immunosuppressive therapy with tacrolimus and microphenolate mofetil has been shown to be most effective in preventing AMR with the fewest side effects [9].

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AMR classification

According to current diagnostic criteria, routine EMB remains the criterion standard for diagnosing AMR. It is classified into antibody-mediated rejection (pAMR) grades 0–3 depending on the presence of specific histological and immunopathological changes that are either present in isolation pAMR-1 (suspected humoral rejection), or in combination pAMR-2 (confirmed humoral rejection), and pAMR-3 (severe humoral rejection) [8]. The classification is presented in Table 1.

Prevalence

Due to the large number of constantly changing diagnostic criteria for AMR (which included both histopathological changes in EMB and presence/absence of clinical manifestations), as well as the varying frequency of screening studies performed, the prevalence of AMR detected by biopsy varied considerably between 3% and 85% in different sources (starting from 1986) [10].

According to Kfoury et al, prevalence of humoral rejection by 100 days after heart transplantation (HTx) was 85%, using as diagnostic criteria histological changes and immunofluorescence data obtained from routine endomyocardial biopsy in 870 heart recipients [11].

The Michaels et al. study of humoral heart transplant rejection enrolled 600 patients. During the follow-up period from July 1997 to January 2001, AMR was detected in 56 recipients, who underwent a total of 116 biopsies. Of this group of patients, a total of 44 patients (4 to 74 years old, 77 EMBs) showed evidence of isolated AMR, 12 patients had mixed AMR and cellular rejection. AMR was diagnosed by immunofluorescence (presence of immunoglobulin, deposition of complement components C1q and C3 in capillaries, or presence of CD58+ cells in immunoperoxidase assay) as well as by histological criteria (interstitial edema, microthrombosis). It should be noted that although females comprised only 26% of the studied cohort, 23 out of the 44 patients (52%) with humoral rejection were female. Moreover, women had a higher prevalence of heart transplant dysfunction (65%) [12].

Crespo-Leiro et al [13] reported an AMR prevalence of <3%, when using the criteria of graft dysfunction and complement component C4d deposition in capillaries. Using the 2004 and 2006 ISHLT criteria, which included, among others, graft dysfunction, serologic evidence of DSA, and evidence of complement component deposition in capillaries in EMB, AMR incidence was 3% and 5%, respectively [14].

Table 1

ISHLT AMR grading scale (2011)

Grade	Pathological signs
pAMR 0 No AMR	No histologic or immunologic signs of AMR, no DSA detected.
pAMR 1 (H+) Histopathologic AMR	Only histologic changes, no DSA.
pAMR 1 (I+) Immunohistochemical AMR	High titer of DSA in blood plasma as well as products of activation of complement components, fibrin and its degradation products are detected.
pAMR 2 Positive AMR	Both histological and immunopathological signs of AMR.
pAMR 3 Severe AMR	Interstitial hemorrhages, capillary edema and fragmentation, necrotizing vasculitis, myocardial mononuclear infiltration, pycnosis of nuclei and karyorexis. Heart failure increases rapidly and there is a high risk of graft loss.

AMR, antibody-mediated rejection; pAMR, pathological antibody-mediated rejection category; DSA, donor-specific antibody.

Table 2

AMR risk factors [10, 12, 15]

1. Female gender
2. Presence of DSA
3. High panel-reactive antibody index (PRA)
4. Presence of cytomegalovirus infection according to serological study
5. A history of mechanical circulatory support
6. Use of muromonab-CD3 as induction therapy and development of murine monoclonal antibodies
7. Heart retransplantation
8. Number of pregnancies
9. Positive cross-match test

Risk factors for humoral rejection

AMR risk factors are presented in Table 2.

It should be noted that AMR is significantly more common in women than in men, and its prevalence reaches 50% of the total number of heart recipients (despite the fact that women undergo heart transplantation much less frequently than men. Currently, the presence of circulating anti-human leukocyte antigen antibodies (anti-HLA antibodies) and histological signs of AMR has been found to have a strong correlation [16, 17].

AMR pathogenesis

The development of AMR is due to the recipient's immune response consisting in the production of DSA directed against HLA and other non-HLA antibodies that may be expressed on the vascular endothelium of the allograft [18].

The pathological process initiated by the antigen-antibody reaction is localized mainly on the vascular endothelium of the allograft. In some cases, the graft may develop resistance to antibody-mediated reactions, and in others ischemic damage occurs, which is accompanied by diffuse myocardial damage, graft dysfunction with development of heart failure, and cardiac allograft vasculopathy (CAV) [4].

DSA-induced damage can occur without the involvement of the complement system. The most potent complement activators are IgG3, but IgG4 may also be involved and often bind to IgG2 in a "non-complement-fixing complex" [19].

It should be noted that a polyclonal immune reaction usually occurs against HLA epitopes, in which several IgG subclasses are involved, leading to different allograft damage mechanisms. Thus, the relationship between AMR and the complement system, previously considered a must, is now becoming a subject of debate, since AMR may develop even in the absence of deposition of complement components in the capillaries [18].

Prognosis

Humoral rejection can lead to graft dysfunction and increased mortality in cardiac recipients, as well as increased incidence of CAV [20].

Clerkin K.J. et al. at Columbia University Medical Center, USA, conducted a single-center retrospective cohort study that included 689 patients with humoral rejection detected at different times after heart transplantation. More than one-third of patients were diagnosed with AMR late after surgery (mean 1,084 days), with the remaining recipients having a median AMR of 23 days. Graft dysfunction was less common with early rejection (25.6); further survival prognosis in this group of patients did not differ from the non-AMR recipients. In contrast, more than half of patients with late AMR (56%) had graft dysfunction. In addition, late AMR correlated with a higher incidence of CAV (50% at 1 year) and higher mortality. The authors suggest that antibody-mediated endothelial damage and the development of microvascular inflammation lead to the development of CAV [21].

In the Michaels et al. study, hemodynamic abnormalities were detected in 47% of recipients. One year after transplantation, AMR patients had a higher CAV prevalence than the controls (15% vs. 5%, $p = 0.09$). After 5 years, 86% of AMR patients had CAV, compared with 22% of controls) [12, 20].

Detection of antibody-mediated allograft rejection within 1 year after transplantation, late diagnosis of chronic AMR combined with graft dysfunction is associated with 50–60% mortality [22].

DONOR-SPECIFIC ANTIBODIES

A study by Manfredini V. et al. showed that the detection of donor-specific antibodies serves as an accurate prognostic marker of antibody-mediated rejection, but nevertheless may not have clinical significance. To stratify the risk of AMR complications and develop a treatment strategy, it is necessary to determine the DSA subclasses and complement binding activity [18].

Pre-HTx DSA is a known risk factor for poor allograft and recipient survival, especially in the first year after surgery [23].

The presence of HLA antibodies in the blood of heart recipients ("humoral sensitization") has been shown to be accompanied by increased incidence of acute graft rejection and poorer patient survival [24].

CAV is the main cause of graft dysfunction in the long-term period (5–7 years) after surgery. CAV is multifactorial in nature, involving both immune and non-immune mechanisms. HLA antigen mismatches are often noted in heart transplantation, which implies that DSA production after transplantation may contribute to the progression of this disease [23].

In global clinical practice, de novo donor-specific antibodies (dnDSA) are detected using a Luminex-based solid-phase crossmatch assay. A noninvasive biomarker is used to identify patients at increased risk of AMR. The versatility of Luminex-based solid-phase analysis lies not only in the risk stratification and prediction of allograft rejection before transplantation, but also in the possibility of performing screening studies in order to monitor the effectiveness of the therapy in the perioperative period [25].

Detection of HLA antigens A, B and DR and measurement of sensitization to them play an important role in the examination of cardiac recipients. Besides, blood testing of potential cardiac recipients for circulating HLA antibodies to determine the panel-reactive antibody index (PRA) is generally accepted. PRA test result is usually presented as a percentage of panel reactivity (that is, the ratio of the number of wells with positive reactivity to the total number of wells ×100). If there is a significant increase in PRA, a targeted test of the recipient's blood against the lymphocytes of the potential donor – a crossmatch reaction – is required.

Indications for treatment of sensitized patients before heart transplantation vary considerably. Betkowski et al. of St. Louis University Medical Center, Missouri, interviewed the heads of 65 centers involved in organ transplantation in the United States about the use of PRA study protocols and treatment of sensitized patients at these centers. Such treatment was provided at 39 of the

65 centers surveyed. Treatment programs included intravenous immunoglobulin (IVIg) infusion (21 of 39, 53.8%), plasmapheresis (17 of 39, 43.6%), administration of cyclophosphamide (11 of 29, 28.2%), mycophenolate mofetil (9 of 39, 23.1%) and azathioprine (1 of 39, 2.6%).

In some of the protocols, treatment was given before transplantation regardless of PRA index (9 of 39, 23.1%) or immediately before surgery (6 of 39, 15.4%), and 4 centers used an individualized approach to recipient management (4 of 39, 10.2%). In five programs, therapy was given only to sensitized patients on mechanical circulatory support (MSC).

Similarly, another single-center study suggested that heart recipients with pre-existing T and B lymphocyte PRA = 10%, despite a negative crossmatch reaction by the time of transplantation, have earlier and more severe rejection episodes with significantly lower survival rates [26].

A retrospective analysis of data from 19,443 cardiac recipients from the UNOS registry between October 1987 and December 1996 showed that an elevated PRA (20%) correlates with a significantly higher risk of mortality. The risk progressively increases in parallel with the PRA index and higher in MCS patients [24].

The cross-match reaction in cardiac recipients is usually performed in the presence of an elevated pretransplant PRA. Humoral sensitization can occur due to previous hemotransfusions, pregnancies, and the use of MCS as a "bridge" to transplantation.

In a retrospective cohort study conducted by Nwakanma et al, the association between post-transplant PRA index and three primary end points, patient survival, allograft survival, and development of rejection within 1 year of transplantation were analyzed in primary heart recipients (all patients who underwent heart transplantation were excluded) from January 1, 2000 to December 31, 2004.

PRA testing prior to heart transplantation was performed in a total of 8,160 primary heart recipients. All patients were divided into 4 groups: PRA was 0% in 6,481 (79.4%) patients (group 1), 1% to 10% in 930 (11.4%) patients (group 2), 11% to 25% in 309 (3.8%) patients (group 3), and >25% in 440 (5.4%) patients (group 4).

The groups of patients with an elevated PRA were distinguished by their younger age, higher proportion of women, and lower body mass index. These groups also included a greater number of patients with a history of hemotransfusion before transplantation or who had a congenital heart defect or were on the waiting list for a long time.

Patients with a PRA >25% had a statistically significant increase in the risk of rejection within 1 year.

In a study by Loh et al. including 125 heart recipients, it was found that increased PRA (>25%) by the time of transplantation may be a risk factor for poor long-term survival [27].

Lavee et al., conducted a cohort study of 463 heart recipients and found that a PRA >10% serves as a risk factor for rejection and related complications, and a negative lymphocytotoxic cross-match test in patients with elevated PRA does not reduce the risk of death from acute and chronic rejection. In addition, PRA and duration of acute rejection episodes in the first 3 months after transplantation were found to have a positive linear relationship [28].

These findings were supported by Kobashigawa et al, who also found that patients with a PRA >11% at the time of transplantation had more severe rejection episodes with significantly lower post-transplant survival despite a negative cross-match response [26]. In addition, the proportion of sensitized patients increased with increasing frequency of MCS as a "bridge" to transplantation [29].

Sensitized patients with PRA >25% had a statistically significant increase in the risk of rejection compared to patients with PRA of 0%.

Patients with PRA >0% had a poorer post-transplant prognosis compared to patients without PRA; so, their careful evaluation before transplantation is required. Patients with PRA >25% have a particularly high risk of rejection, so they are advised to perform a cross-match reaction [30].

Anti-HLA to donor lymphocytes are detected in 3–11% of patients at the time of heart transplantation, while dnDSA (predominantly anti-HLA class II) develops after transplantation in 10–30% of patients. Although, isolated detection of DSA in heart recipients is not considered a histologic criterion for diagnosis of humoral rejection, circulating DSA is found in almost all AMR cases. The treatment of patients with DSA before and after heart transplantation varies, but most centers treat this case with plasmapheresis or immunoadsorption with intravenous infusion of rituximab and/or immunoglobulin.

In recent years, there has been a significant decrease in the incidence of early allograft rejection after orthotopic heart transplantation (OHT). Currently, only 12% of heart recipients require rejection treatment within the first year after transplantation. The goal of treatment is increasingly becoming to prevent AMR, a major risk factor for mortality, leading to 35–40% mortality within 5 years after heart transplantation [31]. Chronic AMR, often combined with rapidly progressing CAV, plays an important role in the development of graft dysfunction [32]. There is a growing body of evidence indicating that DSA are involved in speeding up CAV development [7].

DSA and survival outcomes after heart transplantation

There is strong evidence of a significant increase in the risk of graft loss and mortality in heart recipients with DSA [33]. In a study involving 213 adult patients (mean follow-up at antibody measurements was 7 years), the overall survival of DSA-positive patients after 5, 10, and 15 years were 89.3%, 80.3%, and 53.6%, respectively, compared with 98.4% after 5 years and 97.3% after 10 and 15 years for a control group of non-DSA patients (only long-term survivors were examined during routine follow-up visits) [34]. This study did not distinguish between pre-transplantation DSA and de novo DSA rates, but there is a clear difference in survival in patients with pre-existing DSA or dnDSA.

Reinsmoen et al. evaluated outcomes in 295 adult heart recipients, 14 of whom had DSA at the time of transplantation and persisted after surgery, and 32 developed dnDSA [33]. At 2 years after transplantation, persisting pre-existing DSA group had 100% graft survival compared with 73% survival in the dnDSA group.

Clerkin et al. had similar results in a cohort study of 221 consecutively enrolled adult patients with a mean follow-up of 3.5 years [6]. Patients who died within the first 30 days were not included in the study. The highest survival rate was seen in patients with pre-existing DSA, and was higher than in patients without DSA. In contrast, 69 patients with dnDSA had a significantly lower survival rate than patients who did not have DSA (p = 0.027) (Fig. 1).

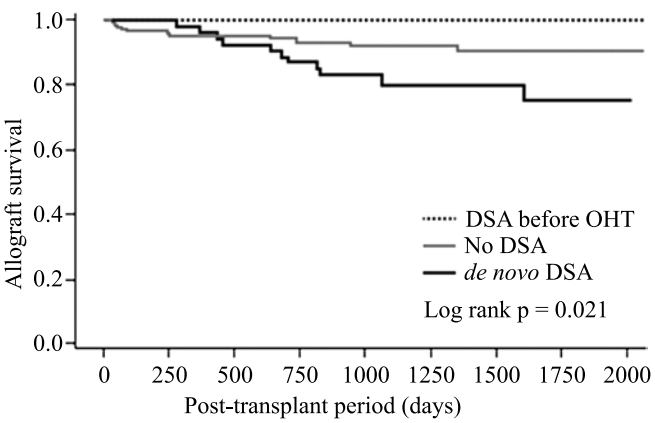

Fig. 1. Allograft survival without adverse events in heart recipients included in the study. DSA, donor-specific antibody; OHT, orthotopic heart transplantation

Table 3

Multivariate analysis of the association between persistent de novo DSA (n = 48) and mortality risk in 243 adult heart recipients in a single-center study. Anti-HLA were measured annually (maximum follow-up was 13 years) [31]

Indicator	Risk ratio	CI 95%	P
Persistent DSA de novo	4.33	1.92, 9.76	**<0.001**
HLA-DR miss-match	2.33	1.08, 5.05	0.032
Donor's age	1.03	1.00, 1.08	0.26
Hemodynamic compromise	0.36	1.00, 5.58	0.050
Treatment of rejection by 1 year after OHT	0.42	1.83, 0.95	0.038

HLA, human leukocyte antigens; DSA, donor-specific antibody; OHT, orthotopic heart transplantation.

De novo DSA

Smith et al. analyzed 243 adult heart recipients with a follow-up period of 13 years. It was found that dnDSA had a significant effect on the risk of adverse events: the hazard ratio (HR) was 3.067 for dnDSA (n = 57) compared with patients who had no HLA antibodies (n = 116). According to multivariate analysis, dnDSA increased the risk of mortality more than any other factor in both adult and pediatric recipients (Table 3) [23]. In a study by Tran et al, 5-year graft survival was 21% in dnDSA patients compared with 72% in patients who had no DSA in a cohort of 105 pediatric heart recipients (p < 0.001%) [7].

There are limited data on the effect of the timing of dnDSA in transplanted heart patients. Ho et al. examined HLA antibodies in 799 heart recipients based on analysis of routine biopsies performed within 15 years of heart transplantation [35]. There was no difference between DSA and non-DSA anti-HLA; however, there was a clear difference in long-term survival between patients who developed DSA before 1 year after transplantation (n = 221) compared with DSA arising at a later date (n = 118). Survival rates were 52% and 40%, respectively, compared with 70% in patients who had no antibodies (p < 0.05 and p < 0.001, respectively).

DSA and cardiac transplant vasculopathy

AMR is common in patients with CAV. Late onset of AMR or asymptomatic AMR is accompanied by a higher risk of developing CAV [36]. There is a possibility that DSA occurring in humoral rejection are involved in CAV development. Moreover, isolated DSA can cause direct damage to endothelial cells by activation and fixation of complement component C4d or acting on natural killer cells (NK-cells) and macrophages, potentially contributing to accelerated progression of atherosclerosis [37].

In a retrospective analysis of 213 patients, Kaczmarek et al. proved that CAV is significantly more common with long-term follow-up in patients with pre-existing or de novo DSA. Significant differences with patients without DSA appeared approximately six years after heart transplantation, reflecting the progressive nature of this disease [34]. The time interval between development of DSA and graft dysfunction due to vasculopathy can be

many months or even years due to slow progression of stenotic arterial disease [38].

Presence of DSA in sensitized patients

Sensitized patients awaiting heart transplantation have a high waitlist mortality because of the difficulty in matching a transplant with a cross-match reaction. Therefore, treatment strategies for patients with anti-HLA should be used. Several studies indicate comparable survival rates in both sensitized adults and children with a positive cross-match reaction compared to patients with negative test results [39, 40]. Various treatment regimens have been studied, including plasmapheresis with or without rituximab, therapy with IVIg [41], CD52 monoclonal antibodies (alemtuzumab), proteosome inhibitors (bortezomib) or complement inhibitors (eculizumab) [42]. Nevertheless, the choice of optimal pre-transplant treatment aimed at improving immunological compliance remains a matter of debate due to low-quality studies involving small cohorts of patients with a short follow-up period [42].

It remains unclear when anti-HLA treatment should be initiated. The timing of transplantation cannot be predicted, so delaying treatment until a donor heart is available would require a very short protocol. On the other hand, preventive intervention while on the waiting list puts patients at increased risk of infection and also creates the possibility of anti-HLA reappearance before transplantation.

As one would expect, sensitizing factors such as re-transplantation, pregnancy, hemotransfusion, or acute rejection (an indicator of a high immunological response) are also associated with the development of high dnDSA levels. Godown et al, directly examined risk factors for dnDSA in a cohort of 121 pediatric heart recipients, 40 of whom developed dnDSA at a mean follow-up of 4.1 years. In a multivariate analysis, only mechanical circulatory support during transplantation, the Negroid race, and donor death from gunshot wounds showed a clear correlation with development of DSA [43].

Rafiei et al. conducted a retrospective study of 196 nonsensitized patients evaluating the effect of immunosuppression on antibody production after heart transplantation. On induction therapy with rabbit antithymocyte globulin (rATG), the proportion of patients who did not develop de novo antibodies one year after surgery was significantly higher (total dose 4.5–7.5 mg/kg) compared to patients without cATG (89% vs 71%, $p = 0.043$) [44]. It is assumed that the mechanism of action of rATG lies in inhibition of pre-existing memory T cells responding to donor antigens and, possibly, apoptosis of DSA-producing plasma cells [45].

Treatment tactics for recipients with DSA in world practice

Barten M.J. et al. collected current information on the diagnosis and management strategies for DSA recipients at 15 centers in Germany, Austria, and Switzerland (including one pediatric specialty center) (Table 4). Between 2006 and 2016, 3,456 heart transplants were performed at these centers. Routine DSA monitoring after HTx was performed in 80% of the centers. The first study of DSA levels was performed between 0 and 90 days after surgery, followed by monitoring at 3, 6, and 12 months. One year after transplantation, anti-HLA levels were screened less frequently (every 3–12 months). All centers examined DSA levels in cases of primary or idiopathic graft dysfunction; in most centers, the presence of DSA was evaluated when acute rejection or allograft vasculopathy developed. Luminex-based solid-phase analysis was universally used; C1q monitoring, complement-dependent cytotoxicity, and flow cytometry were used less frequently. Two-thirds of the centers considered thresholds of mean immunofluorescence intensity (1000–3000) of dnDSA against HLA classes I or II when deciding whether to initiate treatment or not [22].

TREATMENT TACTICS

To date, there is no unified standard for the treatment of humoral heart transplant rejection. Treatment tactics vary considerably from country to country, due to the lack of optimal screening and treatment protocols [22].

The basic immunosuppression protocol includes various combinations of calcineurin inhibitors (cyclosporine or tacrolimus), antimetabolites (mycophenolic acid preparations, azathioprine), proliferative signal inhibitors (sirolimus or everolimus) and corticosteroids (prednisolone, methylprednisolone) [46].

In the United States, Kobashigawa et al. conducted a randomized trial evaluating the efficacy of three different immunosuppressive regimens: (1) cyclosporine, mycophenolate mofetil and corticosteroids; (2) tacrolimus, mycophenolate mofetil and corticosteroids; (3) tacrolimus, sirolimus and corticosteroids. The study included 334 patients over 18 years of age. The end point was either 2R cellular rejection or humoral rejection of the graft with impaired hemodynamics. The follow-up period was one year. The result of the study showed a significant reduction in rejection incidence with both tacrolimus/sirolimus (35.1%) and tacrolimus/mycophenolate mofetil (42.1%) compared with cyclosporine/mycophenolate mofetil (59.6%) [5].

However, a study by Nguyen V.P. et al. showed different results. According to the 2020 publication, adequately chosen induction and immunosuppressive therapy can reduce AMR risk. Stable patients with high risk of

AMR can be transferred to proliferative signal inhibitors (sirolimus, everolimus), which will reduce the incidence of graft rejection [47].

Principles of treatment for humoral rejection include removal of circulating antibodies, reduction of additional alloantibody production, and suppression of T cell and

Table 4

Diagnosis and treatment in DSA detection: key criteria according to a 2017 study from 15 heart transplant centers in Germany, Austria, and Switzerland. Data for each section do not fully converge depending on center

Number of heart transplants	3,456 in all 15 centers from 2006 to 2016. Adults and children Average number of transactions per year: 21
Pre-transplant HLA antibody treatment (a)	Plasmapheresis (pre- and perioperative): 100% Immunoadsorption: 53% Immunoglobulin treatment (pre- and perioperative): 100% Rituximab – 73% Bortezomib – 33% rATG (perioperative): 67% (8/10 thymoglobulin, 2/10 neovil)
Baseline immunosuppression in sensitized patients	Tacrolimus: 87% Cyclosporine: 40% Mycophenolic acid: 100% Everolimus: 13% GCs: 100%
Standard DSA monitoring after transplantation	Conducted in 80% of centers. 6/12 started at month 1, 4/12 at month 3, 1 at day 0, 1 on the day of inclusion in the waiting list. After 3 months, monitoring every 3–6 months until 1 year in all 12 centers where routine monitoring was performed. 7/12 centers continued screening at least once a year after 12 months.
Monitoring of DSA levels after cardiac transplantation in clinical manifestations	The centers conducted a DSA study for the following events: Acute rejection: 93% Graft vasculopathy: 67% Primary graft dysfunction: 100% Idiopathic graft dysfunction: 100%
DSA detection methods	Luminex: 100% C1q: 33% pre-transplant, 20% post-transplant Complement-dependent cytotoxicity: 53% before and 73% after transplantation Flow cytometry: 20%
Mean immunofluorescence intensity threshold at which treatment for DSA was considered	Treatment was conducted in 40% Among the 4 centers, thresholds were: HLA DSA I: 1000–1500 in 3/4 centers, 3000 in 1/4 center HLA DSA II: 1000–1500 in 3/4 centers, 3000 in 1/4 center
Criteria for initiation of treatment for dnDSA	dnDSA alone: 60% dnDSA + echocardiographic signs of graft dysfunction: 100% dnDSA + AMR: 100% dnDSA + allograft dysfunction: 73%
DSA treatment	Immunoglobulins: 79% Rituximab: 79% Immunoadsorption: 50% rATG: 50% (4/7 thymoglobulin, 3/7 Neovia) Plasmapheresis: 43% Extracorporeal photopheresis: 29% Basiliximab: 14% Bortezomib: 7%
Changes in immunosuppressive therapy when dnDSA is detected	Conducted: 64% 7 centers provided information: Tacrolimus dose escalation: 2/7 Replacing cyclosporine with tacrolimus: 1/7 Replacing mycophenolate mofetil with everolimus: 3/7 rATG: 1/7 (thymoglobulin)

HLA, human leukocyte antigens; dnDSA, de novo donor-specific antibodies; GCs, glucocorticoids; DSA, donor-specific antibody; rATG, rabbit anti-thymocyte globulin.

B cell responses. The ISHLT guidelines for AMR treatment are based on the current consensus and have the C evidence level [20].

Methods of treatment of humoral rejection are based on the following principles:

– Suppression of T cell response;
– Elimination of circulating antibodies;
– Inhibition of residual antibodies;
– Suppression or depletion of B cells;
– Suppression or depletion of plasma cells;
– Complement inhibition.

Fig. 2 shows the use of specific treatments for different clinical scenarios, taking into account the degree of humoral rejection, the presence or absence of DSA and graft dysfunction. The algorithm was developed by Chin S. et al. based on an online survey of 184 ISHLT members, with participation mainly from transplant centers in North America and Europe [8].

The ISHLT guidelines for the treatment of antibody-mediated heart transplant rejection recommend high-dose intravenous glucocorticoid infusion and cytolytic drugs. Plasmapheresis or IVIg infusion is used to eliminate or inactivate autoantibodies. In hemodynamic disorders, inotropic and vasopressor drugs may be required to maintain graft function. Systemic anticoagulant therapy can reduce the risk of intravascular thrombosis. Control endomyocardial biopsy should be performed several weeks after treatment had been initiated and should be performed dynamically until complete regression of immunopathological signs. In refractory humoral rejection, monoclonal antibodies have proven effective against common B cell marker (rituximab). If the treatment is ineffective, cardiac retransplantation should be considered [48].

One type of treatment for humoral rejection is the use of therapeutic plasmapheresis. The purpose of this method is mechanical removal of circulating antibodies [49]. Using membrane filtration or centrifugation, extracorporeal separation of plasma from cellular blood components takes place. The removed volume of fluid is replenished with the help of replacement solutions.

There have been no studies investigating therapeutic plasmapheresis (TP) as a monotherapy for AMR.

The use of glucocorticoids is widely used as basic therapy not only for the treatment of cellular rejection, but also in humoral rejection of a heart transplant [49].

Steroids have potent immunosuppressive and anti-inflammatory effects that affect the number, distribution and function of all types of white blood cells and endothelial cells [50]. The use of glucocorticoids is included in the regimen in all clinical trials describing various treatments for humoral rejection.

In addition, anti-lymphocyte globulins, which are antibodies directed against T cell lymphocytes or thymocytes, are widely used. There are two types of antibodies: monoclonal (muromonab-CD3, rituximab) and polyclonal (the best known are rabbit and equine antithymocyte globulins). Antithymocyte globulins are used to treat humoral rejection, but there have been no studies on their role in the treatment of AMR [51].

Rituximab is a genetically engineered, chimeric mouse and human monoclonal antibody directed against the B-cell lineage specific CD20 antigen. For the treatment of humoral rejection or as a desensitizing therapy, rituximab is usually used in combination with other therapies. That is why is it difficult to evaluate its efficacy as a stand-alone drug. There are much evidence of the effectiveness of in the treatment of refractory antibody-mediated rejection (when combined therapy with cytolytic antibodies, corticosteroids, plasmapheresis and cyclophosphamide is not effective) [52]. When using rituximab, there was reduced PRA index in sensitized patients who were refractory to therapy with IVIg, plasmapheresis and mycophenolate mofetil [53].

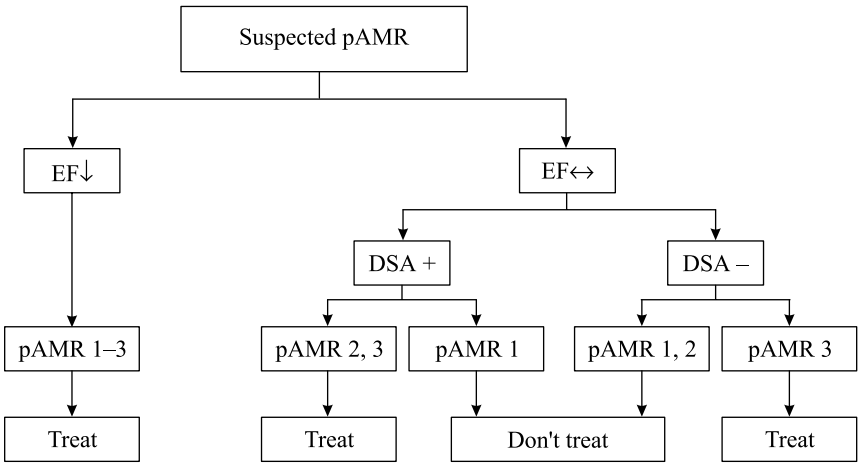

Fig. 2. Treatment modalities for different clinical scenarios, taking into account the humoral rejection category. pAMR, pathological antibody-mediated rejection category; DSA, donor-specific antibody; EF, ejection fraction

Most of the above treatments are usually used in combination, either simultaneously or consecutively [49].

Although plasmapheresis, IVIg, rituximab, and high-dose cyclophosphamide have been successful in reducing circulating antibody levels in sensitized patients prior to heart transplantation, there are large numbers of patients who are immune to these therapies. Patel J. et al. from Los Angeles conducted a pilot study to determine the effectiveness of bortezomib-based desensitization in patients resistant to IVIg, rituximab, and plasmapheresis. Bortezomib is an inhibitor of the 26S proteasome that has a pro-apoptotic effect on plasma cells and reduces antibody production. Seven patients awaiting heart transplantation with a 50% PRA were included in the study. The mean baseline PRA was 62%, which decreased to a mean of 35% after treatment. The study showed that bortezomib reduced PRA in patients who were immune to desensitization with IVIg, rituximab, and plasmapheresis [5].

The need to treat asymptomatic AMR has long been discussed [48].

The feasibility of treating milder forms of humoral rejection, such as pAMR1 (including pAMR1-H and pAMR1-I) and pAMR2 (with or without clinical signs) is in doubt, since the effectiveness of the current therapy for subclinical AMR has not been established.

The decision to treat pAMR 0–2 is based on clinical signs of rejection, such as appearance of heart failure symptoms, presence of graft dysfunction, and immunologic findings (increased existing or de novo DSA).

In asymptomatic humoral rejection, optimization of basic immunosuppressive therapy may be advisable [20].

However, due to increased risks of graft vasculopathy and death in asymptomatic rejection, it may be prudent to treat when all cases of humoral rejection are detected [48].

DSA detection is considered an important prognostic factor for the development of humoral rejection after heart transplantation, but their presence alone is not sufficient to make a diagnosis of AMR and initiate specific therapy. Nevertheless, the appearance of DSA should not be ignored. That's why Manfredini V. et al. developed an algorithm of actions that takes into account the correlation of DSA with symptoms and pathological signs of AMR, the time of their detection and the ability to bind complement (Fig. 3). When DSA is present early after transplantation, there is a clearer association with the development of acute humoral rejection, which responds well to treatment. Occurrence of DSA in the late post-transplant period can lead to chronic allograft damage and development of vasculopathy if not diagnosed on time. Association of DSA with the development of AMR justifies the initiation of specific treatment, especially in the presence of signs of graft dysfunction [18].

Table 5 presents a list of protocols used by several centers of excellence [20].

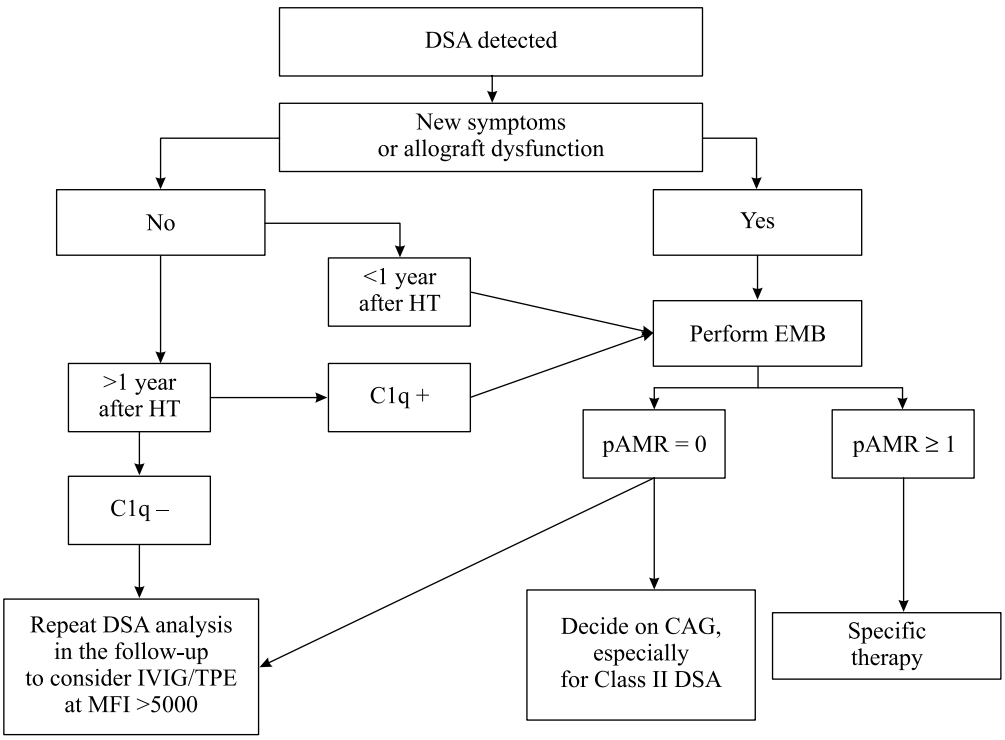

Fig. 3. Algorithm of action when DSA is detected. DSA, donor-specific antibody; HT, heart transplant; EMB, endomyocardial biopsy; C1q, complement binding activity; MFI, mean fluorescence intensity; pAMR, pathological antibody-mediated rejection category

AMR treatment in children

Prevention and treatment of humoral rejection in children is prescribed empirically and encompasses the full range of treatments that are described in adult patients. Diagnostic criteria do not differ from those for adult heart transplantation, and are based on histopathologic and immunopathologic changes. The presence of DSA, pretransplant and post-transplant anti-HLA class I antibodies negatively affects the long-term survival of patients. Therapies aimed at removing circulating antibodies include IVIg or cyclophosphamide before transplantation, intraoperative plasma exchange, and postoperative use of IVIg, therapeutic plasmapheresis, rituximab, or cyclophosphamide [20].

Treatment of sensitized patients awaiting heart transplant

For highly sensitized waitlisted patients, preoperative plasmapheresis is used to reduce circulating antibody levels, which can greatly increase the chances of obtaining a negative cross-match with the donor.

Also, a chimeric high-affinity monoclonal antibody, rituximab, which binds to CD20 lymphocyte receptors that inhibit B cell activation and differentiation, is used as desensitization in highly susceptible patients. The drug dosage is based on the patient's body surface area (375 mg/m^2). An intravenous infusion once a week is recommended, with a treatment duration of up to 4 weeks [5].

Table 5

AMR treatment strategies for adult heart transplant recipients

Center	AMR treatment
University of Utah	Subclinical pAMR-1: No treatment; consider gradual reduction of corticosteroid dose if early after transplantation; pAMR-2 without graft dysfunction or DSA: pulse steroids only; pAMR-2 with graft dysfunction and/or DSA: pulse steroids, IVIg, plasmapheresis, rituximab/bortezomib; pAMR-3: pulse steroids, IVIg, plasmapheresis, rituximab/bortezomib (plus rATG if hemodynamically compromised).
Cedars-Sinai Medical Center	Methylprednisolone 500 mg/d for 3 days; rATG; Plasmapheresis for hemodynamic compromise; IVIg 2 g/kg on days 1 and 30 (day 1 after completion of rATG treatment); Rituximab 1 g (375 mg/m^2 for smaller patients) on days 7 and 21; Refractory patients: add bortezomib 1.3 mg/m^2 on days 1, 4, 7, and 10.
Cleveland Clinic	Methylprednisolone 1 g/d for 3 days; Plasmapheresis 4–5 times over a week, then as needed; Unresolved: consider the following: – IVIg 2 g/kg; – Rituximab 375 mg/m^2 (up to 4 doses); – Bortezomib 1.3 mg/m^2 IV for 4 doses over 2 weeks; – Continue plasmapheresis; Refractory: consider photopheresis or total lymphoid irradiation.
Columbia University	Methylprednisolone; Plasmapheresis 5–6 cycles over 10–14 days; Cyclophosphamide 0.5–1 g/m^2 every 3 weeks for 4–6 months.
Stanford University	Low-risk patients: no treatment or augmentation of baseline immunosuppression with follow-up EMB; High-risk patients (positive DSA, allosensitization): IVIg or rituximab infusion; Hemodynamic compromise: – Any patient presenting with unexplained graft dysfunction is presumptively treated with methylprednisolone sodium succinate IV 500 mg/d to 1000 mg/d for 3 days; – Plasmapheresis daily or every other day (at least 5 sessions); – IVIg immediately after plasmapheresis 2 g/kg divided into 2 doses over 2 consecutive days (not to exceed 140 g) on days 1 and 2 and days 29 and 30. Repeat if there is no effect; – Consider rATG 1.5 mg/kg per day for 3 consecutive days with plasmapheresis in severe hemodynamic compromise; – Rituximab 1 g/d on days 7 and 22; Alternate modalities: – Augmentation of baseline immunosuppression; – Change from cyclosporine to tacrolimus and/or addition of cyclophosphamide 1.5 mg/kg per day; – Bortezomib 1.3 mg/m^2 per day on days 1, 4, 8, and 11

pAMR, pathological antibody-mediated rejection category; IVIg, intravenous immunoglobulin; DSA, donor-specific antibody; rATG, rabbit anti-thymocyte globulin.

IVIg are immunoglobulins, mainly of the IgG class, isolated from donor plasma. This drug reduces antibody levels in sensitized patients prior to heart transplantation. IVIg suppresses anti-HLA in vitro and in vivo. Polyclonal preparations of human immunoglobulin have activity against HLA class I and II molecules, cytokines and their receptors, and T cell receptors. The main immune effects of IVIg can be explained by blockade of Fc-γ receptors, inhibition of complement system, neutralization of autoantibodies and cytokines, and suppression of B-cell receptors [20].

Antibody drugs, especially rATG in combination with IVIg infusion, plasmapheresis and rituximab are used as induction therapy in sensitized patients. Currently, regimens that include polyclonal antibodies are preferable [20].

CONCLUSION

The primary goal of post-heart transplant patient management is to improve long-term survival. Antibody-mediated heart transplant rejection is the leading cause of early morbidity and mortality after surgery. Despite the various treatment options for humoral rejection, to date, there is no single standard of therapy, thereby requiring an individualized approach to each case. Currently, additional randomized clinical trials are required to determine a more precise management tactics for patients with AMR.

The authors declare no conflict of interest.

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