Review Article

Physicians' All-Inclusive Guide on De Novo Donor-Specific Antibodies after Heart Transplantation

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Abstract: Antibodies against donor-specific human leukocyte antigens (HLAs) can be detected de novo after heart transplantation and are critical for long-term survival. Death, rejection caused by antibodies, and vasculopathy from heart transplants have all been related to de novo donor-specific antibodies (dnDSAs). Global norms and advancements in detection technology have facilitated the adoption of screening protocols in cardiac transplant hospitals. There is considerable debate over what ought to happen after dnDSA discovery. Even while some dnDSAs show symptoms years before graft failure is discovered, therapy is usually started as soon as antibody-mediated rejection is noticeable, and by then the damage may already be irreversible. In particular, class II, anti-HLA-DQ, complement binding, and persistent dnDSAs have been associated with worse outcomes. Growing evidence points to a more proactive strategy to managing dnDSA. Therefore, more advanced diagnostic tools are needed to identify subclinical transplant harm. Strain techniques, coronary physiology assessments, or cardiac magnetic resonance imaging may provide valuable information to identify individuals who are at risk. Although their effectiveness is still up for debate, plasmapheresis, intravenous immunoglobulin, immunoadsorption, and ritxumab are frequently used in the treatment of diffuse diffuse delayed-onset diabetes (dnDSA). Creating effective treatment regimens that will improve the long-term survival of heart transplant recipients should be the aim of future research.

Keywords: antibiotics, heart transplantation, donor specific antibody, immunosuppression

1. INTRODUCTION

Human leukocyte antigen (HLA) molecules are a class of highly polymorphic antigens that are encoded by the major histocompatibility complex. Short peptides from the intracellular and extracellular compartments are supplied to T cells by them. All nucleated cells have HLA class I on their surface, but antigen-presenting cells are the only cells that produce HLA class II [1]. HLA molecules play a major role in the recognition of "non-self" antigens by the human immune system, which in turn activates defense mechanisms [2]. Their polymorphism in the field of transplantation puts graft survival at danger. The development of antibodies that specifically target foreign HLAs is referred to as "HLA sensitization". In the case of transplant recipients, donor-specific antibodies (DSAs) are antibodies that specifically target donor antigens. Not all DSAs are anti-HLA antibodies; there has been evidence of antibodies to other donor antigens in recent years. Results of solid organ transplantation have been continuously associated with anti-HLA DSAs [3, 4]. De novo DSA, also referred to as de novo DSA, can occur before transplantation

(preformed DSA) or after transplantation. Preexisting antibodies limit the pool of potential donors for transplantation since preformed DSA is linked to worse post-HT outcomes [5]. However, recipients of transplants are believed to be at significant risk from dnDSAs [6, 7]. Heart transplant (HT) recipients have been associated with death [12–14], antibody-mediated rejection (AMR) [6, 8], cardiac allograft vasculopathy (CAV) [9, 10], and graft dysfunction [11]. The HT scientific community considers them to be one of their main worries due to their tight link with long-term outcomes, which have not altered much in recent years [15]. Solid-phase assay development has allowed for precise DSA detection and identification, which has led to significant advancements in the field. Their growing usage has improved our knowledge of antibody relevance and enabled us to implement regular monitoring procedures in most HT teams [16]. It has evolved into a powerful, non-invasive method for tracking HT patients. But with the amount of information increasing, there are more questions than ever about dnDSA. A few of the subjects being studied are the best way to manage DSA in the event that there is no visible graft injury, the timing of DSA injury on the graft, and the efficacy of current treatments. This paper's goal is to review the dnDSA data that is now available in order to provide physicians with a helpful foundation for next studies and decision-making.

2. LITERATURE REVIEW

De novo DSAs (dnDSAs) are new DSAs that appear more than three months after transplant and are believed to represent an alloimmune primary reaction, in contrast to preformed DSAs, which originate prior to transplant [17]. DSAs found in the first three months following HT are also considered preformed [17], as they are suggestive of alloimmune memory, which is the recollection of a stimulus by a patient who has already been sensitized to it [18]. Sensitization occurs after exposure to "non-self" HLA during pregnancy, blood transfusions, or transplantation, as well as after an HLA-unrelated immune stimulation, most likely as a result of cross-reactivity between pathogens and HLA [19]. However, not all sensitizing events result in the generation of antibodies. Theoretically, alloimmunization requires a "double hit"—a non-self stimulus, such as foreign HLA, and a risk stimulus, such as surgery, tissue injury, or other inflammatory states [20–22]. Antibodies target highly variable regions on HLA molecules called epitopes. One antibody can react with several antigens because the same epitope can appear on different HLA molecules [2].

DSAs cause disease via the graft endothelium, which acts as a barrier between the circulating blood of the receptor and the donor's tissue. Inflammation brought induced by tissue damage following transplantation stimulates endothelial cells to express HLA class II [23]. The traditional complement cascade is triggered when DSA binds to endothelial HLA. This leads to the formation of the membrane attack complex and lymphocyte cell lysis. As a result, in positive AMR biopsies, C4d, a component of the classical complement system, is frequently seen [20]. However, innate immune cells like as natural killer cells that damage the graft by antibody-dependent cell-mediated cytotoxicity can also result in graft destruction from DSA in the absence of complement activation. Other side effects of DSA, such as microvascular damage and C4d-negative antibody-mediated rejection, could also be explained by this mechanism [24, 25]. DSA binding to endothelial cells ultimately triggers signaling pathways that induce the intimal proliferation and fibrosis seen in chronic AMR [20, 23]. T-helper cells are crucial to the immunological response brought on by DSA binding because they both activate and regulate other immune and non-immune cells. A novel approach to defining T-helper cells is to categorize them based on the cells they assist, as opposed to their cytokine composition. B cells, polymorphonucleated granulocytes (Type 2), mononuclear phagocytes (Type 1), and non-immune tissue cells such endothelium

graft cells (Type 3) can all be supported by T-helper cells [26]. This tripartite classification contributes to a better understanding of the immunological mechanisms observed in tissue engineering, regenerative medicine, and transplantation [27]. The effects of performed DSA and dnDSA on heart allografts can differ, as McCaughan et al. describe. Performed DSAs intervene in the early post-transplant period while patients are under close supervision. Prior to other immune cells engaging in graft harm, which is reliant on complement activation and antibody-dependent cell-mediated cytotoxicity, early intervention can avert persistent damage. On the other hand, the creation of dnDSA points to a deeper immune system activation, in which an inflammatory incident sets off the graft's primary HLA class II production. In this case, producing antibodies requires de novo B cell activation and the production of plasma cells, implying the participation of innate immune cells during a period of reduced surveillance. Because dnDSAs can cause significant harm before they are clinically identified, treatments are less effective in this case [20, 28]. Solid-phase single-antigen bead (SAB) assays utilizing the Luminex platform are currently the gold standard for the detection of dnDSA [16]. Before performing a SAB assay, many labs perform a screening test using pooled antigen arrays. Without providing HLA specificity, these panels detect class I or class II anti-HLA antibodies [29]. In the SAB assay, multiple fluorochrome-infused beads coated with different HLA molecules are exposed to the recipient's serum. Anti-Ig G antibodies labeled with a fluorescent dye bind to anti-HLA antibodies after they have bound to homologous HLA molecules. In order to identify a specific bead and determine if an antibody is bound, a dual laser is employed to analyze beads [20]. The result is the mean fluorescence intensity (MFI) for each anti-HLA antibody. It is recommended to interpret MFI readings as semiquantitative estimates of the antibody quantity [30].

Solid organ transplantation has undergone a revolution thanks to SAB tests, which yield the best sensitivity and resolution. The ability to precisely determine antibody specificity and detect DSA has been made possible by advancements in HLA typing techniques over time [31]. To further stratify the risk of DSA, laboratories also use variants of the SAB technique that evaluate Ig G subclasses or complement binding (C1q, C3d, and C4d). Complement-fixing DSAs have been associated with a worse prognosis and a higher rate of allograft rejection compared to non-complement-fixing DSAs [32–34]. The information about the differing effects of Ig G subclasses is less clear; IgG1 and IgG3, which bind complement, are more detrimental than IgG2 and IgG4 [33, 35]. Non-HLA antibody testing has become more and more common in recent years because it may be the source of AMR without detectable DSA. These days, many labs also look for antibodies that are not HLA-related, such as those that target the endothelium, vimentin, MICA/B (MHC class I polypeptide-related sequence A/B), or the angiotensin-1 receptor [16].

The frequency of dnDSAs following HT varies between 10% and 30%; they are more frequently found targeting HLA class II than HLA class I or both classes [6-14,28,38-40]. Less than a year [13,40] to more than seven years [10], according to the research with the longest follow-up, was the median period to develop dnDSA. The incidence of dnDSA with time has only been recorded in a limited number of investigations. While dnDSA development seems to be more common in the first year [41], cases of dnDSAs have been reported to develop up to 19.5 years after HT [42]. More than one-third of HT organizations stop screening after the first year after HT, despite the fact that the research suggests anti-HLA screening should be done permanently [16]. HLA-directed DSAs appear to be more prevalent than other dnDSAs; they tend to form later and become persistent more frequently [38–40].

The 2018 ISHLT consensus report states that DSA monitoring should be customized to the risk level of each patient; however, people who have already received sensitization should only be categorized as high-risk. Actually, research on kidney transplantation provides much of the knowledge regarding the risk

factors related to HT patients, and nothing else is known. Pre-sensitized individuals with non-donor-specific preformed anti-HLA antibodies or preformed DSA appear to be more likely to develop dnDSA than non-sensitized patients [39, 43, 44]. However, in contrast to late dnDSA, dnDSA development seems to occur faster in non-sensitized individuals. It might also respond to stimulation of memory B cells rather than naïve B cell activation. Therefore, it would seem reasonable to keep a closer eye on those who have become sensitized, if only for the first year following HT. Not much is known about how different immunosuppressive regimens affect the development of dnDSA. It seems safe, as evidenced by the fact that early corticosteroid elimination did not increase the risk of developing dnDSA in a randomized trial of kidney transplant recipients or a retrospective analysis of 229 HT patients [45, 46]. An early switch from calcineurin inhibitor to mechanistic target of rapamycin (mTOR) inhibitor monotherapy may increase the risk of developing diffuse diffuse sensitization syndrome (dnDSA); however, late conversion or the use of mTOR inhibitor in conjunction with reduced-exposure calcineurin inhibitor appears to be safe [47]. Pro-inflammatory events such as immunizations, surgery, and infections can trigger a broader immune response because they increase the production of anti-HLA antibodies [48, 49] but not DSA. Finally, while having a left ventricular assist device has been associated with a higher risk of creating anti-HLA antibodies before to HT, there is no evidence that this increases the likelihood of developing dnDSA [50-53].

There is also strong evidence linking dnDSA to CAV. Most studies indicate that patients with DSA had a higher incidence of CAV [54, 55]. Smith et al. examined the causes of death and found that patients with DSA were more likely to die from CAV or rejection than from other causes, despite their inability to uncover a connection between DSA and CAV [12]. These variations are most likely due to the complex pathophysiology of CAV development, which involves both immune and non-immune systems. The impact of non-immune mechanisms, such as recipient and donor age and cardiovascular risk factors, may obscure the link between CAV and dnDSA. Furthermore, it seems that dnDSA affects the cardiac vasculature gradually, possibly taking months or even years [56]. In the Kaczmarek et al. study, the Kaplan-Meier curves for independence from CAV separated roughly six years after HT [9]. In contrast to early dnDSAs, complement-fixing DSAs and late dnDSAs (discovered more than a year after HT) appear to raise the risk of CAV [57], highlighting the more aggressive nature of complement-fixing antibodies [58]. While Wang et al.'s study did not differentiate between preformed and de novo DSA, it did find a correlation between more severe CAV and chronic, 1:8 dilution, C1q-positive, and class II DSA [59].

3. CONCLUSION

The long-term survival of a patient can be determined by dnDSA, hence its importance should never be underestimated. Mechanistic investigations are necessary to provide a fuller understanding of the variety of long-term effects of dnDSA on cardiac allografts. This data can be used to develop diagnostic tools that, in situations where current methods are not successful, can detect subclinical graft deterioration. Even though pathological results are not totally conclusive, cardiac magnetic resonance imaging certainly provides a useful tool for diagnosing graft deterioration when dnDSAs are detected. More research on non-HLA antibodies is also extremely needed, since it will help to better understand AMR cases when anti-HLA dnDSAs are negative. Since non-HLA antibodies may provide complementary data, luminex tests must be developed to identify non-HLA antibodies in addition to anti-HLA antibodies. Clinicians are likely to manage drug-induced side effects more assertively once randomized research offer strong information regarding therapeutic efficacy. Potential means of delivering tailored therapy specific to dnDSA could be biological agents. Since improvements in dnDSA and AMR are often made in these areas, clinical trials in

renal transplantation can provide insightful information. For example, clazakizumab is being evaluated in a large global placebo-controlled clinical trial for chronic antimicrobial resistance. Recipients of HT grants ought to make similar efforts. The greatest method to enhance long-term results is definitely to prevent the onset of dnDSA, even though improvements in diagnosis and treatment choices are also important. Therefore, having instruments that could predict the evolution of dnDSA would be quite beneficial. Gene expression profiles and elevations in dd-cfDNA have been associated with the subsequent identification of dnDSA. Even if a causal relationship has not been established, dd-cfDNA or gene expression profile monitoring may help customize immunosuppressive regimens. In the near future, post-transplant surveillance will probably rely on a thorough assessment of the patient's immunological condition utilizing a mix of genomic and proteomic data obtained from developing molecular technologies. Further investigation is necessary to completely comprehend the connection between dnDSA and microRNA, dd-cfDNA, and gene and protein expression patterns.

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