

Model of Chronic Allograft Injury in Alloantibody Positive Renal Transplant Patients

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Abstract

Despite significant efforts, long-term outcomes in transplantation have not substantially improved over the past few decades. Nonetheless, innovations in immunosuppression have led to the control or a better understanding of T-cell mediated responses. By improving control of the T-cell immune response with immunosuppression, acute cellular rejections have substantially decreased while long-term outcomes remain the same. Transplant researchers have now shifted their focus to the humoral arm of the immune system. It is thought that a significant proportion of transplants experience failure as a result of human leukocyte antigen antibody-mediated injury. Recent studies of the natural history, mechanisms, and pathologic signatures for antibody-mediated injury have led to advancements. This review outlines these advancements and the current understanding of the model of chronic alloantibody-mediated injury and describes a path to improve outcomes as they relate to alloantibodies in transplantation.

Keywords: Alloantibodies; Human leukocyte Antigen; Organ Transplantation

Introduction

Improving long-term outcomes has always been a primary focus among researchers and clinicians in solid organ transplant. In the early days of transplant, long-term outcomes were measured in weeks and months. By using immunosuppressive regimens and through innovation in histocompatibility, long-term survival in the late 1960s and 1970s improved many years [1-8]. The half-life of deceased donor kidney transplants performed between 1966 and 1975 was 7.5 years [9]. By the 1980s, primary renal allograft survival was promising, but early acute cellular rejection occurring in >50% of the cases seemed to be a barrier for achieving better long-term outcomes [10]. This led to a focus on reduction in early acute cellular rejection rates. However, despite significant advancements in immunosuppression between 1980 and 2000, leading to 1-year acute cellular rejection rates of 10-15%, long-term survival did not improve [11-13].

Today, the understanding of barriers to improve long-term outcomes has shifted away from preventing acute cellular rejection and has moved toward the humoral theory of transplantation. Since 2003, there has been a steadily increasing focus on anti-HLA antibodies that are directed toward donor

Human Leukocyte Antigens (HLA) (donor-specific anti-HLA antibodies, DSA). Circulating DSA detected after implantation of the donor transplanted organ [de novo immunoglobulin G (IgG) DSA (dnDSA)] are now thought to be the major cause of allograft loss [14,15]. In the last 15 years, the body of knowledge on DSA has grown dramatically [14-34]. In the beginning, the research focused on the association between DSA and allograft loss [33-36]. With more recent longitudinal studies, there is an increase understanding of the temporal relationship between DSA, DSA changes, and allograft loss [20,37-40]. In addition to the research on DSA, pathology research over the last decade, through clinical and protocol biopsies, has improved the understanding of antibody-mediated injury and chronic rejection pathology [22,38,41-46]. This review discusses about the developments in these areas and how together they provide the framework for developing a model of chronic allograft injury in alloantibody positive renal transplant patients.

Incidence and Etiology of DSA

There are two groups of patients with DSA: those who have HLA antibodies before transplant that are the same serologic specificity as the donor allograft's HLA antigens ("preformed DSA") and those who develop HLA antibodies after transplant directly as a result of an immunologic reaction to the implanted donor HLA antigens on the allograft (dnDSA). In both groups, there is a clear risk of chronic rejection. Approximately 30% of wait-listed kidney transplant candidates are sensitized to HLA and thus have potential "preformed DSA". The most common means by which a pre-transplant patient may develop non-self HLA antibodies are through blood transfusion and pregnancy. Despite the efforts to find donors against whom these patients have no HLA antibodies, many within this cohort of patients will never be transplanted. Transplanting across HLA antibodies may be the only realistic option for these patients as it is still preferable to stay on dialysis [47].

Post-transplant, it has been shown that 50% of HLA-mismatched primary renal transplant recipients who do not have HLA antibodies to the donor at transplant will later develop IgM HLA DSA [48-50]. Of these patients, half will eventually develop dnDSA (IgG to the same serologic specificity) [17,18,20,38]. The majority of dnDSA has been shown to occur in the first post-

transplant year with a rate of around 10% [51,52]. The number of new patients who develop dnDSA drops off after the first post-transplant year to about 1-5% per year, reaching 20% by 5-years post-transplantation. Risk factors for dnDSA development include young age (18-35 years of age at transplant), African-American ethnicity, DQ mismatch, DR β 1 mismatch, high total HLA mismatch, deceased donor transplant recipient, and delayed allograft function [18,20,37,38]. In addition, dnDSA has been correlated with post-transplant low immunosuppression states such as immunosuppression non-adherence [38,43], post-transplant infection (leading to immunosuppression reduction) [53,54], or physician-directed immunosuppression minimization [55-59].

Allograft Failure with Circulating DSA

Detection of DSA in a patient's serum is one of the only known predictors for allograft loss. Current studies have investigated the rate of failure following DSA, specifically IgG DSA. In the case of "preformed DSA", the antibody and antigen interact immediately after implantation of the allograft. Conversely, with de novo DSA, there is a response that occurs to the allograft over the first few post-transplant months. The rate at which the humoral response occurs varies among patients depending on the patient's immune system, expression of the alloantigen, and degree of immunosuppression. However, whether the DSA is "preformed" or "de novo", the rate of failure following DSA is similar with respect to the post-transplant time the IgG is first detected in the sera. In the first year following DSA appearance, the risk of allograft failure is 7-9% [20,60]. By 3-years of post-DSA, 21-24% of patients will progress to chronic alloantibody-mediated rejection and failure.

After looking at the post-DSA survival reports, it is clear that many DSA positive patients will have good graft function for three or more years after DSA [60,61]. This stable group accounts for approximately three-fourths of DSA positive patients. This may be primarily due to the each patient's immune system and the degree of immunosuppression. In addition, this could be correlated with the ability and way the allograft heals in the setting of alloantibody-mediated injury. One theory is that with adequate immunosuppression, DSA injury will not outpace endothelial repair. This could make the kidney more resistant to damage over time as donor endothelium could be replaced by recipient endothelium [62-65]. Further studies in this area are needed to fully understand the interaction of the allograft and the immune response.

Models of Chronic Allograft Injury after DSA Appearance

Recent studies have looked at serial pathology and seral antibody characteristics that correlate with chronic injury and allograft loss [20,38,46,48,60,66-70]. The proposed stages from DSA to allograft failure were first described based on the primate study by Smith, et al. [31]. In this study, un-immunosuppressed primates showed rapid deterioration from circulating DSA appearance (stage I), then went on to C4d deposition in

the allograft (stage II), which was followed by transplant glomerulopathy (stage III) and ended with a rapid deterioration of allograft function (stage IV). This model however, may differ from the post-transplant human model primarily in the use of immunosuppression. Data from Wiebe, et al. [38] looking at post-transplant (not post-DSA) protocol biopsies in patients with dnDSA has further stratified the model to include peritubular capillaritis within stage II, glomerulonephritis following stage II and prior to stage III, and proteinuria in stage IV.

It is clearly plausible that the stages suggested by Smith, et al; Wiebe, et al. constitute the primary model of chronic alloimmune injury. However, research on complete antibody characterization, chronic rejection pathology, serum and urinary biomarkers, and microRNA indicate that further stratification of this general model is highly likely [71-77]. Recent evidence suggests further characterization of DSA into subclasses can stratify DSA risk groups. IgG3 subclass, in particular, may be an indicator of the poorest allograft prognosis [48]. Aside from DSA, the pathologic finding of inflammation in the area of interstitial fibrosis and tubular atrophy may indicate a different type of DSA positive patient or may just be another stage of alloimmune injury [42,68,78]. Regarding serum and urinary biomarkers, ACY-1, B2M, CXCL9, and CCL-2 have all been shown to correlate with future graft loss. Finally, detection of Tribbles-1 protein in the blood has been shown to be up regulated during inflammatory events such as chronic antibody-mediated rejection [77]. Future studies combining these tests, with respect to time post-DSA, would yield new information and further lead to the differentiation of the model of chronicity in alloantibody positive transplant patients.

In addition to the accounting for new testing and pathology, the condition that leads to DSA may also play into the fate and course of the model. Patients with non-adherence to medication will likely progress to allograft failure rapidly and may have a vastly different signature than those who have immunosuppression reduction due to BK-virus. In addition, patients who are on near adequate levels of immunosuppression and have stable DSA may progress differently. These differences need to be accounted for the future of model refinement.

Conclusion

Over the last decade, our understanding of DSA has greatly improved. Moving forward, the next step in improving outcomes in alloantibody positive transplant patients is to obtain a better view of the pathway of chronicity. This can be done through multifaceted, collaborative, longitudinal research that collects and tests all potential markers (pathologic or serologic) together. This research will allow us to identify and differentiate allograft dysfunction risk among the DSA positive patients. Additionally, treatment trials of DSA, based on the current model of chronic allograft injury, have already begun. From these trials, unique information on how a change in pathologic or serologic markers may emerge, thereby adding to our understanding of the model. In all, there is optimism that in the next decade, DSA will be better managed and long-term outcomes will be substantially better in transplantation.

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