Human Immunology 80 (2019) 583–587

Contents lists available at ScienceDirect

Human Immunology

journal homepage: www.elsevier.com/locate/humimm

The impact of non-HLA antibodies on outcomes after lung transplantation and implications for therapeutic approaches

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ARTICLE INFO

Keywords:
Non-HLA antibodies
Lung transplantation
Chronic Lung Allograft Dysfunction
Antibody-mediated rejection

ABSTRACT

The role of donor-specific antibodies (DSA) to mismatched human leukocyte antigens (HLA) in lung allograft rejection has been recognized over the past 20 years. During this time, there has been growing experience and recognition of an important role for non-HLA antibodies in lung allograft rejection. Multiple self-antigens have been identified that elicit autoimmune responses including collagen V, K-α 1 tubulin, angiotensin type 1 receptor, and endothelin type A receptor, but it is likely that other antigens elicit similar responses. The paradigm for the pathogenesis of these autoimmune responses consists of exposure of sequestered self-antigens followed by loss of peripheral tolerance, which then promotes allograft rejection. Studies have focused mainly on the impact of autoimmune responses on the development of Bronchiolitis Obliterans Syndrome or its mouse model surrogate. However, there are emerging data that illustrate that non-HLA antibodies can induce acute antibody-mediated rejection (AMR) after lung transplantation. Treatment has focused on antibody-depletion protocols, but experience is limited to cohort studies and appropriate controlled trials have not been conducted. It is noteworthy that depletion of non-HLA antibodies has been associated with favorable clinical outcomes. Clearly, additional studies are needed to identify the optimal therapeutic approaches to non-HLA antibodies in clinical practice.

1. Introduction

Lung transplantation is the ultimate treatment option for patients with end-stage lung disease. According to the International Society for Heart and Lung Transplantation (ISHLT) Registry, over 4000 lung transplants are performed annually for adults worldwide in recent years (1). The most common indication for lung transplantation today is pulmonary fibrosis due to Interstitial Lung Disease (ILD), which accounts for over 30% of all transplants worldwide and over 40% of all transplants in North America [1]. Transplantation is associated with an improvement in survival and quality of life for patients with end-stage lung disease [2–6]. Furthermore, there has been consistent improvement in survival after transplantation since the late 1980s, and the median survival in the most recent era, between 2009 and 2016, is 6.5 years [1]. However, the 5-year survival after lung transplantation remains significantly worse than after other solid organ transplants including kidney, heart, and liver [1,7–9]. Infections and allograft failure due to Primary Graft Dysfunction (PGD) are the leading causes of death in the first year after lung transplantation [1]. However, Chronic Lung Allograft Dysfunction (CLAD) is the leading cause of death beyond the first year after transplantation accounting for approximately 40–50% of deaths [1].

CLAD is generally categorized into 2 phenotypes, but there is often overlap between these. Bronchiolitis Obliterans Syndrome (BOS) is the prototypic form of CLAD and was recognized early in the history of lung transplantation as the most significant barrier to better long-term outcomes [10,11]. The underlying pathology is Obliterative Bronchiolitis (OB), a fibroproliferative scarring of respiratory and membranous bronchioles that manifests clinically with declining allograft function and an obstructive ventilatory defect [10–13]. Restrictive Allograft Syndrome (RAS) has been recently recognized as a more aggressive phenotype of CLAD presenting with parenchymal fibrosis and a restrictive ventilatory defect [14–17]. However, it is notable that early reports that identified OB as the characteristic histology of chronic

Abbreviations: ACR, acute cellular rejection; AMR, antibody-mediated rejection; AT1R, angiotensin type 1 receptor; BAL, bronchoalveolar lavage; BOS, Bronchiolitis Obliterans Syndrome; CARV, community-acquired respiratory viral; CLAD, Chronic Lung Allograft Dysfunction; DSA, donor-specific antibodies; ECP, extracorporeal photopheresis; ETAR, endothelin type A receptor; GERD, gastro-esophageal reflux disease; HLA, human leukocyte antigens; ILD, Interstitial Lung Disease; ISHLT, International Society for Heart and Lung Transplantation; IVIG, intravenous immune globulin; MHC, Major Histocompatibility Complex; MICA, MHC class I related chain A; MMP, matrix metalloproteinases; OB, Obliterative Bronchiolitis; PGD, Primary Graft Dysfunction; RAS, Restrictive Allograft Syndrome

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https://doi.org/10.1016/j.humimm.2019.04.008
Received 1 February 2019; Received in revised form 9 April 2019; Accepted 13 April 2019
Available online 17 April 2019

rejection after heart-lung transplantation in the 1980s described concomitant extensive parenchymal fibrosis underscoring the mixed features of CLAD [18,19].

The pathogenesis of CLAD is not well understood, but because it is recognized as chronic rejection, alloimmunity is thought to be the underlying primary cause. Indeed, multiple studies have consistently identified the same clinical risk factors for CLAD including episodes of acute cellular rejection (ACR), lymphocytic bronchiolitis, antibody-mediated rejection (AMR), and the development of donor-specific antibodies (DSA) to mismatched human leukocyte antigens (HLA) [20–23]. Additionally, risk factors for CLAD that appear to be non-alloimmune in nature such as PGD, community-acquired respiratory viral (CARV) infections, and gastro-esophageal reflux disease (GERD) may exact their risk by activating alloimmune responses [24–26].

Emerging evidence over the past 15 years has identified an important role for autoimmune responses in allograft rejection after kidney, heart, and lung transplantation [27–30]. According to this paradigm, sequestered self-antigens are exposed as a result of transplant-associated injury and tissue repair (e.g., PGD, ACR, or DSA). This is followed by loss of peripheral tolerance and expansion of autoimmune responses that promote allograft rejection. Both cellular and humoral autoimmune responses have been implicated in allograft rejection, but this review will focus on the role of humoral responses and potential therapeutic strategies.

1.1. Sequestered self-antigens

The development of antibodies to myosin, vimentin, and G protein coupled receptors (angiotensin type 1 receptor (AT1R) and endothelin type A receptor (ETAR)) after heart transplantation has been associated with the development of AMR and cardiac allograft vasculopathy [27,31,32]. Similarly, antibodies to AT1R have been linked to kidney allograft rejection [27–29]. In lung transplantation, collagen V, K-α 1 tubulin, AT1R, and ETAR have received the most attention as self-antigens that elicit an autoimmune response that promotes allograft rejection [33–35]. However, it is likely that these are prototypic sequestered self-antigens, and others exist that elicit similar responses [36]. Collagen V is a minor collagen in the lung that co-assembles with collagen I into heterotypic fibrils and remains sequestered under normal conditions [37]. Allograft injury and repair processes expose collagen V through the increased activity of matrix metalloproteinases (MMP) [38]. Indeed, increased collagen V levels are noted during inflammation and in bronchoalveolar lavage (BAL) fluid in human and rat lung allograft rejection [39,40]. Similarly, K-α 1 tubulin is an epithelial surface gap junction cytoskeletal protein that is sequestered under normal conditions but is exposed with inflammation and tissue repair [33]. Importantly, the binding of K-α 1 tubulin by its specific antibody results in the increased expression of fibrogenic growth factors, the activation of cell cycle signaling, and fibroproliferation suggesting that antibodies to K-α 1 tubulin exert a direct pathogenic effect in the development of OB [33]. AT1R and ETAR are expressed on endothelial cells, epithelial cells, fibroblasts, and immune cells [41]. Antibody binding to AT1R and ETAR results in endothelial and immune cell activation and the release of inflammatory and fibroproliferative cytokines [42,43]. Antibodies to AT1R and ETAR have been associated with systemic sclerosis and cystic fibrosis [44,45]. Immune responses to Major Histocompatibility Complex (MHC) class I related chain A (MICA) have also been linked to the development of BOS after lung transplantation [46].

1.2. Interactions between alloimmune and autoimmune responses

In an early study examining interactions between alloimmune and autoimmune responses, collagen V-reactive IL-10-producing T-cells could be detected in stable lung transplant recipients' serum, but when patients developed BOS, there was a decline in IL-10-producing T-cells and an expansion of collagen V-specific IFN-γ-producing T-cells [47]. The change from IL to 10-producing to IFN-γ-producing T-cells was mediated by the depletion of CD4 + 25 + regulatory T-cells [47]. The authors suggested that the decline of CD4 + 25 + regulatory T-cells may be due to therapeutic immunosuppression since regulatory T-cells function is dependent on IL-2, which is inhibited by calcineurin inhibitors [47]. In addition, an association between the development of DSA to mismatched HLA and antibodies to self-antigens has been recognized. In a prospective study of 103 lung transplant recipients, 42% developed HLA DSA and 30% developed both DSA and antibodies to K-α 1 tubulin and collagen V [34]. On the other hand, 12% of patients with HLA DSA did not have antibodies to self-antigens, and 12% of those with antibodies to self-antigens did not have HLA DSA. Those who developed BOS had significantly higher concentrations of antibodies to K-α 1 tubulin and collagen V in serum and BAL fluid [34]. Importantly, the development of HLA DSA preceded the development of antibodies to self-antigens and although the detection of DSA was transient in some cases, antibodies to self-antigens persisted. This study also illustrates that among patients who developed BOS, 16% had antibodies to self-antigens but never had DSA, suggesting that other forms of allograft injury may induce the development of antibodies to self-antigens [34]. Potential insults include PGD, ACR, AMR, GERD, and respiratory viral infections, however the impact of these on the development of antibodies to self-antigens has not been thoroughly investigated.

The development of autoimmune responses requires an initial insult to expose sequestered self-antigens through inflammation and tissue repair. In a syngeneic orthotopic mouse lung transplant model, the administration of antibodies to K-α 1 tubulin or collagen V resulted in cellular infiltration and bronchiolar fibrosis similar to human OB [48]. Of note, antibodies to K-α 1 tubulin elicited cellular and humoral responses to collagen V before the onset of fibrosis and vice versa, suggesting that epitope spreading that promotes bronchiolar fibrosis similar to human OB may occur in an alloantigen independent manner [48]. A multi-center study evaluated the correlation between antibodies to ETAR and AT1R and DSA and the impact of these antibodies on allograft rejection [35]. Here, pre-transplant antibodies to ETAR and AT1R increased the risk of developing HLA DSA post-transplant. In addition, the development of HLA DSA and strong binding antibodies to ETAR and AT1R were associated with a significantly higher risk of AMR although the association with ACR was not statistically significant [35].

Emerging data have described an important role for exosomes in the development of antibodies to self-antigens and allograft rejection [49,50]. Exosomes are small membrane vesicles produced by endocytic pathways and secreted by fusion with the cell membrane. Different cell types release exosomes including epithelial cells and immune cells, and their composition depends on the cell of origin. Epithelial cell-derived exosomes can activate macrophages and trigger airway inflammation [51]. In a recent study, self-antigens collagen V and K-α 1 tubulin and donor HLA were identified on the surface of exosomes isolated from serum and BAL fluid of lung transplant recipients who developed ACR and BOS but not clinically stable recipients [52]. In addition, exosomes with self-antigens were detectable before the onset of ACR and BOS. Lastly, exosomes from patients who developed ACR and BOS contained immunomodulatory miRNA. Taken together, these findings suggest that exosomes released during episodes of rejection may elicit immune responses to self-antigens and promote rejection pathology.

1.3. Therapeutic options – non-HLA antibodies and CLAD

Although an important role for non-HLA antibodies in the development of CLAD has been recognized for over 10 years, there is a dearth of evidence to guide clinical management. In fact, there have been no randomized controlled trials and no head-to-head comparisons of different treatments. Until recently, the lack of a widely available commercial assay to detect non-HLA antibodies has been one barrier to conducting such clinical trials. However, it should be noted that there

have been no randomized controlled trials or head-to-head comparisons of different regimens for the treatment of HLA DSA in lung transplantation in spite of solid phase assays being available at every center's histocompatibility laboratory. Indeed, this is illustrative of the challenges of conducting clinical trials in lung transplantation. The sample size at any one center is generally too small for sufficiently powered studies, and multi-center studies are often hampered by different clinical protocols that need to be aligned in a clinical trial. Furthermore, interest in lung transplantation by the pharmaceutical industry has been limited as kidney and liver transplantation dominate the transplant arena and autoimmune diseases (e.g., rheumatoid arthritis, inflammatory bowel disease) dominate the non-transplant market share. However, appropriate clinical trials focusing on the management of non-HLA antibodies have not been conducted in kidney transplantation, and there have been few well designed randomized controlled trials of the management of HLA DSA and AMR [53]. Clearly, designing and conducting these studies is challenging and expensive, but these are necessary to advance the field and improve clinical outcomes. Below is a review of the available limited data on the management of non-HLA antibodies in lung transplantation.

One study described the effect of an antibody-depletion protocol clinically prescribed for HLA DSA on non-HLA antibodies and clinical outcomes [54]. This was a single-center, retrospective study that included 122 consecutive lung transplant recipients over a 2-year period. Patients were screened for the development of HLA DSA prospectively and treated with Rituximab and monthly doses of intravenous immune globulin (IVIG) or IVIG alone if they developed DSA. In this cohort, 108 patients had serum available for retrospective analysis for antibodies to K-α 1 Tubulin and collagen V. Among these, 57 (53%) developed DSA, 72 (67%) developed antibodies to either K-α 1 Tubulin or collagen V, and 64 (59%) developed antibodies to both non-HLA antigens. Of note, 55 of the 57 (96%) who developed HLA DSA had antibodies to K-α 1 Tubulin or collagen V, and 54 were treated with Rituximab and IVIG (n = 38) or IVIG alone (n = 16). Interestingly, there were no demographic differences or differences in acute rejection profiles between those who developed non-HLA antibodies and those who did not. Importantly, the development of non-HLA antibodies was associated with a significantly higher risk of BOS and death, and there was a direct association between the serum concentration of non-HLA antibodies and the risk of BOS. On follow-up testing after treatment, only 16 (30%) cleared non-HLA antibodies compared to 31 (57%) who cleared the HLA DSA. In addition, a greater proportion of those treated with Rituximab and IVIG (14 of 38, 37%) cleared non-HLA antibodies than those treated with IVIG alone (2 of 16, 13%), but this was not statistically significant (p = 0.07). Those who cleared the non-HLA antibodies were significantly less likely to develop BOS than those who had persistent antibodies, and this was independent of HLA DSA clearance. In addition, clearance of non-HLA antibodies was associated with significant decreases of serum concentrations of pro-inflammatory cytokines including IL-1β, IL-17, and interferon-γ, and significant increases of anti-inflammatory IL-10. This study underscores the role of non-HLA antibodies in the development of BOS and illustrates that clearance of non-HLA antibodies is less likely than HLA DSA. However, there are multiple limitations to this study inherent to its design. There was no control group, and patients were not randomized to an antibody-depletion protocol. Thus, it is difficult to make any conclusions about the relative efficacy of Rituximab in addition to IVIG. More importantly, only 30% of patients cleared non-HLA antibodies in spite of an aggressive treatment protocol. It is possible that other antibody-depleting regimens, including the use of plasma exchange, may be more effective, but evidence supporting the use of other regimens in lung transplantation is lacking. This clearly emphasizes the need for additional studies with a randomized controlled design to better identify effective therapies.

Another single-center retrospective study examined the impact of extracorporeal photopheresis (ECP) on HLA DSA, non-HLA antibodies (to K-α 1 Tubulin, collagen I, and collagen V), and lung function [55]. ECP is an immunomodulatory treatment that has been used for cutaneous T-cell lymphoma, the prevention of cardiac allograft rejection, and the management of graft versus host disease after stem cell transplantation [56,57]. In addition, there is growing experience using ECP for progressive BOS and early studies suggest that approximately 25% of patients experience improvement in lung function [58]. In the study examining the effect of ECP on non-HLA antibodies, 88 patients who were treated with ECP for progressive BOS were included and mean serum concentrations of antibodies to K-α 1 Tubulin, collagen I, and collagen V decreased significantly [55]. All patients had a decline in at least 1 antibody, 74 (84%) had a decline in 2 antibodies, and 43 (49%) had a decline in all 3 antibodies. In addition, there was a concomitant decrease in pro-inflammatory cytokines and an increase in anti-inflammatory cytokines with ECP treatment. However, there was no significant association between the reduction in serum concentrations of non-HLA antibodies and the effect of ECP on lung function [55]. Although the effect of ECP on non-HLA antibodies reported in this study is provocative, the clinical significance of this finding remains unclear and additional studies are necessary to determine the role of ECP in the management of non-HLA antibody-associated allograft dysfunction.

The role of autoimmune responses and non-HLA antibodies in particular in the development of RAS has not been examined yet. Studies have focused exclusively on the development of BOS, but this is likely because RAS was only recently characterized and a definition has not yet been widely accepted although an ISHLT working group is currently developing a definition. In general, RAS follows a more rapidly progressive clinical course and is less likely to respond to treatment than BOS. Consequently, survival after the diagnosis of RAS is significantly worse than after the diagnosis of BOS [15,16]. Additionally, the immunopathogenesis of RAS is poorly understood. Thus, if autoimmune responses and non-HLA antibodies play an important role in the development of RAS, this would present a significant advancement in our understanding of the mechanisms of RAS and an identification of a potential therapeutic target. Clearly, studies examining a possible role for non-HLA antibodies and autoimmune responses in the development of RAS are necessary.

1.4. Non-HLA antibodies and AMR

There have been multiple reports of AMR due to non-HLA antibodies after kidney transplantation, and antibodies to AT1R, glutathione S-transferase theta-1, and C-terminal fragment of perlecan have been implicated [29,59–61]. Treatment, when detailed, has consisted of antibody-depleting protocols as in HLA DSA-induced AMR. However, the literature describing AMR due to non-HLA antibodies after lung transplantation is less robust. The diagnosis of AMR after lung transplantation remains difficult although the recently proposed ISHLT definition increased awareness of AMR as a cause of acute allograft dysfunction or failure [62]. The diagnosis is based on the following criteria: allograft dysfunction, circulating DSA, abnormal lung pathology, exclusion of other causes of allograft dysfunction, and C4d deposition in the capillary endothelium [62]. Importantly, the working group recognized that C4d deposition has been problematic in lung transplantation and that AMR can be diagnosed confidently in the absence of C4d deposition if all other criteria are present [62]. It is noteworthy that there is no specific histology for the diagnosis of AMR and that many cases are C4d-negative [63,64]. In the absence of HLA DSA, establishing the diagnosis of AMR becomes difficult because the histology is non-specific. It is likely that cases of AMR due to non-HLA antibodies have been unrecognized, and this has hampered the field's experience with this form of rejection.

A recent small study reported AMR due to antibodies to collagen V, collagen I, and K-α 1 Tubulin that occurred early in 2 single lung recipients transplanted from the same donor [65]. AMR occurred immediately after transplant in one patient who had pre-existing

antibodies to collagen V, collagen I, and K-α 1 Tubulin. The other recipient did not have pre-existing non-HLA antibodies and did well until day 24 when he presented with AMR and antibodies to collagen V, collagen I, and K-α 1 Tubulin. Neither patient had HLA DSA, but the pathology was characteristic of AMR with neutrophilic capillaritis, diffuse alveolar damage, and C4d deposition. Both patients responded well to antibody-depletion therapy consisting of IVIG, Rituximab, and Bortezomib in one patient and plasmapheresis, IVIG, and Rituximab in the other [65]. The fact that 2 recipients of lungs from the same donor developed early AMR due to non-HLA antibodies raises the suspicion that donor factors may influence the development on non-HLA antibodies and resultant AMR. However, it is noteworthy that collagen V, collagen I, and K-α 1 Tubulin are highly conserved tissue restricted self-antigens. Clearly, additional studies are needed to define the role of donor factors in the development of non-HLA antibodies. Furthermore, identifying non-HLA antibodies before transplantation raises questions about the optimal approach to immunosuppression after transplantation. There is a dearth of evidence to guide the management of such patients, but close clinical observation is indicated given the identified risk. Another recent case report of AMR after lung transplantation due to non-HLA antibodies highlighted the role of anti-red blood cell antibodies [66]. Here, a patient developed suspected AMR approximately 6 weeks after single lung transplantation, but testing for HLA DSA and commonly recognized non-HLA antibodies including those directed at perlecan, MICA, AT1R, K-α 1 Tubulin, and collagen V were negative. The patient developed anemia and thrombocytopenia and was noted to have a new anti-A1 antibody with a titer of 2. In spite of treatment with high-dose steroids and plasmapheresis, the patient had no clinical response and died [66]. Although limited, these reports illustrate that non-HLA antibodies can cause AMR after lung transplantation and suggest that this is an under-recognized form of rejection that can cause allograft failure.

2. Conclusions

The role of autoimmune responses in allograft rejection has been increasingly recognized over the past 10 years. These comprise both cellular and humoral responses. There is clear evidence that non-HLA antibodies are associated with an in creased risk of BOS and death after lung transplantation. Furthermore, clearance of these antibodies is associated with a lower risk of BOS. However, it is not clear which treatment regimen is most effective. In addition, a role for non-HLA antibodies in AMR after lung transplantation has only recently been reported in isolated cases suggesting that this may be an under-recognized form of rejection. Although basic and translational studies have advanced the field, clinical studies, and randomized controlled trials in particular, have lagged behind. This has made capitalizing on these experimental advances to improve clinical care and patient outcomes difficult. Until recently, the lack of widely available commercial assays to detect and grade the intensity of autoimmune responses has been a considerable barrier to improving the clinical approach to autoimmunity in lung transplantation. However, commercially available kits for detecting antibodies to AT1R and ETAR are now available, and these may improve the recognition of autoimmune responses in allograft rejection. Importantly, future studies that evaluate different treatment regimens for non-HLA antibodies will be necessary to improve patient care. In addition, future studies will need to examine the possible role for non-HLA antibodies in the development of RAS.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humimm.2019.04.008.

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