Review

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A Comprehensive Overview of the Clinical Relevance and Treatment Options for Antibody-mediated Rejection Associated With Non-HLA Antibodies

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Abstract. Although solid organ transplant results have improved significantly in recent decades, a pivotal cause of impaired long-term outcome is the development of antibody-mediated rejection (AMR), a condition characterized by the presence of donor-specific antibodies to HLA or non-HLA antigens. Highly HLA-sensitized recipients are treated with desensitization protocols to rescue the transplantation. These and other therapies are also applied for the treatment of AMR. Therapeutic protocols include removal of antibodies, depletion of plasma and B cells, inhibition of the complement cascade, and suppression of the T-cell–dependent antibody response. As mounting evidence illustrates the importance of non-HLA antibodies in transplant outcome, there is a need to evaluate the efficacy of treatment protocols on non-HLA antibody levels and graft function. Many reviews have been recently published that provide an overview of the literature describing the association of non-HLA antibodies with rejection in transplantation, whereas an overview of the treatment options for non-HLA AMR is still lacking. In this review, we will therefore provide such an overview. Most reports showed positive effects of non-HLA antibody clearance on graft function. However, monitoring non-HLA antibody levels after treatment along with standardization of therapies is needed to optimally treat solid organ transplant recipients.

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INTRODUCTION

Organ transplantation is the best therapeutic option for patients with various end-stage organ diseases. Although short-term graft survival has improved tremendously, 10-y survival rates have remained unchanged in recent decades despite intensive immunosuppressive therapy and—in the case of kidney transplantation—despite extensive screening for donor-specific anti-HLA antibodies (DSAs) before transplantation. The development of antibody-mediated rejection (AMR) resulting in chronic rejection and, in the end, graft loss is a major contributor to poor long-term transplant outcomes.[1,2]

According to the revised Banff 2017 criteria, AMR is defined as a condition in which tissue injury, as well as antibody interactions with the vascular endothelium, is accompanied by serologic evidence of DSAs to HLA or non-HLA antigens.[3]

To decrease the risk of AMR due to pretransplant and/or de novo antibodies, various treatments to remove HLA antibodies have been successfully implemented in daily practice. These therapies include removal of antibodies, depletion of plasma and B cells, inhibition of the complement cascade, and suppression of the T cell-dependent antibody response.[4,5] Although the literature about the relative importance of non-HLA antibodies in graft survival has expanded, no comprehensive overview is available about treatment efficacy across solid organ transplant recipients with either preexisting or de novo non-HLA antibodies. This review focuses on the most commonly used therapies for non-HLA AMR and their effects on non-HLA antibody titers and transplant outcome.

NON-HLA ANTIBODIES

A risk factor for humoral rejection is the presence of both anti-HLA and non-HLA antibodies, the latter developed either to donor epitopes of polymorphic antigens not present in the recipient or to epitopes of self-antigens that become exposed on the cell surface because of

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apoptosis.[6] Research on HLA-identical siblings showing that transplant recipients could still encounter rejection despite HLA matching has underscored the importance of antibodies against antigens other than HLA.[7,8] Terasaki[9] deduced that non-HLA immunological factors contribute more to graft failure than HLA antibodies do (40% and 20%, respectively). Indeed, in different types of solid organ transplantation, non-HLA antibodies against numerous targets were found to be associated with AMR and long-term graft outcome.

Although there is emerging evidence of the association of non-HLA antibodies and graft failure, little is known about their pathogenic involvement in the graft damaging process. Several mechanisms are hypothesized, but these are mainly based on knowledge on the pathogenic effect of anti-HLA antibodies. On antibody binding, cell lysis could be induced via activation of the complement cascade, or of natural-killer cells. Another mechanism by which antibodies directed to intracellular non-HLA antigens contribute to rejection could be exposure of these antigens upon ischemia reperfusion injury, a process by which antibodies could bind their targets and induce cell damage.[10,11]

It is still debated whether these antibodies can act alone or whether they result in worse allograft outcome together with DSAs. For example, the graft survival of recipients without detectable DSAs but with angiotensin II type-1 receptor (AT1R) antibodies at the time of transplant is inferior to the survival in recipients with DSAs but without AT1R antibodies or recipients without antibodies at all.[12] However, in another study, lower freedom from AMR and/or cellular-mediated rejection are seen in heart transplant recipients with both de novo DSAs and AT1R antibodies, whereas AT1R antibodies alone were not significantly associated with AMR.[13] This synergistic detrimental effect has also been suggested for other non-HLA antibodies,[6,14] but more research is needed to better understand the underlying mechanism.

RELEVANCE OF NON-HLA ANTIBODIES IN TRANSPLANT OUTCOME

Major Histocompatibility Complex Class I-related Chain A Antibodies

Major histocompatibility complex class I-related chain A (MICA) is one of the first reported non-HLA antigens found to be important in transplant outcome. It is a highly polymorphic protein, of which several hundred single nucleotide polymorphisms are described.[15] In the context of transplantation, MICA alleles present in donors could differ from those present in recipients, thereby triggering the development of donor-specific antibodies.

MICA donor-specific antibodies have been found in both kidney[16] and heart transplant recipients[17] and have been associated with an increased risk for graft rejection,[18] although others[19] found no association between MICA antibodies and transplant outcome. However, not all studies have analyzed donor specificity of MICA antibodies as donor MICA typing was not performed, which could confound interpretation of some older data.

Antiendothelial Cell Antibodies

As donor endothelial cells (ECs) are the first cell types to be recognized by the recipient's immune system, these cells have received attention in the field of solid organ transplantation. As ECs express a number of antigens to which antibodies could bind that are different from those expressed by lymphocytes, an endothelial-specific crossmatch assay (XM-ONE) was devised to screen for pretransplant donor specific undefined antiendothelial cell antibodies (AECAs). One of the first reported and best-studied group of AECAs is antibodies against G-coupled receptors present on the endothelium: AT1R and endothelin A receptor (ETAR).

Quite recently, low-risk living donor kidney transplant recipients with pretransplant AECAs were found to have an increased risk of impaired renal function.[20] Patients who were positive for the presence of AECAs in serum before and after transplantation have a higher risk of acute rejection (AR) episodes.[20,21] Furthermore, eluates from rejected kidneys showed positivity to EC, and sera taken before rejection also contain AECAs.[22] Both pretransplant and de novo anti-AT1R and ETAR antibodies have been associated with non-HLA AMR and adverse late graft outcome in kidney transplantation,[23-26] and the frequencies of AR, vasculopathy, microvascular inflammation, and arteritis development were higher than in antibody negative recipients.[19,27,28] In a nationwide study, serum reactivity to human ECs was assessed from patients without donor specific HLA antibodies who experienced early acute microvascular rejection (AMVR). AT1R and ETAR antibodies were not found in patients with AMVR, using 17 U/ml as a cutoff value for positivity. However, when using a lower threshold of 10 U/ml, which is also used in the literature, 26% of AMVR patients had positive AT1R levels, suggesting the potential role of AT1R antibodies in AMVR.[29] Recently, pretransplant AT1R antibodies were reported to be an independent risk factor for subintimal fibrosis and a greater percentage of vessel occlusion, along with inflammation and de novo DSA. In this living-donor kidney transplant cohort, no differences in AR occurrence within the first year posttransplant were found between AT1R antibody positive and negative patients using a positive cutoff value of 17 U/ml.[30] Others also failed to find an independent association of pretransplant anti-AT1R antibodies with (long-term) kidney transplant outcome.[31-33]

Hiemann et al[34] studied the presence of AT1R and ETAR antibodies in patients during the first year after heart transplantation. They observed higher antibody levels in patients with acute cellular rejection and AMR. Furthermore, autoantibody titers against AT1R and ETAR were correlated with an increased risk of vasculopathy at 1 y. De novo DSAs were not produced by these patients nor were they correlated with transplant outcome. Antibody levels were the highest in samples collected directly after the transplantation, implicating pretransplant sensitization. In addition, patients on assist devices were more likely to produce high AT1R and ETAR levels. Of note, the assay used to determine AT1R antibody levels in these patients (ELISA) probably lacks the appropriate specificity; therefore, the prevalence of these antibodies may be overestimated.[35]

Pediatric liver recipients can be positive for various non-HLA antibodies, such as antinuclear antibody (12%), antismooth muscle antibody (9.5%), and AT1R antibody (76%), but no significant association with fibrosis has been found.[36] These results are comparable to data obtained from a large adult liver cohort.[37] However,

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preformed AT1R or ETAR antibodies do increase the risk for death when accompanied by preformed DSAs. Liver transplant recipients with de novo antibodies—although rarely produced—had a significantly higher risk of rejection and fibrosis. In addition, antibodies produced after transplantation could activate the complement system.

In 2017, the first reports were published about the negative impact of AT1R and ETAR antibodies on the freedom from AMR after lung transplantation.[38,39]

Overall, both AT1R and ETAR antibodies are associated with worse graft outcome although a strong co-occurrence of ETAR antibodies exists with antibodies directed to AT1R, raising the question whether ETAR antibodies are an independent risk factor for AMR.

Antibodies Against Glomerular Basement Membrane

The basement membrane of glomeruli contains 5 components: collagen IV, laminin, nidogen, proteoglycans (eg, perlecan, agrin), and fibronectin. The third laminin-like globular (LG3) fragment of endorepellin—the C-terminal domain of perlecan—is produced via proteolysis of apoptotic EC.[40] Perlecan is widely expressed in various tissues, including lung, heart, and liver. Expression of kidney-associated self-antigens is seen on exosomes isolated from serum of patients with transplant glomerulopathy (TG).[41]

De novo developed antibodies against collagen IV and fibronectin have been found to be risk factors for TG in both adult[42] and pediatric kidney transplant recipients.[43] Another antiglomerular basement membrane (GBM) autoantibody that has frequently been associated with acute and chronic rejection in solid organ transplantation is against the LG3 fragment of endorepellin/perlecan. Dieudé et al[44] demonstrated that apoptotic exosome-like vesicles contain this LG3 fragment, and injection of these vesicles in mice does consecutively trigger the production of anti-LG3 antibodies. They also showed that the proteasome is active in these exosome-like vesicles, indicating a potential role for proteasome inhibitors in reducing the production of autoantibodies. In kidney transplant recipients, anti-LG3 antibodies were found to be an independent risk factor for early-onset acute vascular rejection.[45] Preformed and persistent antibodies against LG3 were associated with chronic lung allograft dysfunction (CLAD) in lung transplant recipients.[46]

Antibodies against agrin were significantly more present in TG patients than in patients with chronic allograft nephropathy (CAN), and their presence was also associated with more rejection episodes.[47]

Antibodies to Peroxisomal Trans-2-enoyl-CoA Reductase

Another autoantibody that has been associated with TG is reactive to peroxisomal trans-2-enoyl-CoA reductase (PECR), a protein involved in fatty acid biosynthesis. It is highly expressed in the kidney because of the high density of peroxisomes there. Although the reactivity to non-HLA antigens in TG is quite heterogeneous, it was found that the presence of anti-PECR antibodies strongly correlates with TG, but not with its pathologic grade.[48] Furthermore, antibodies against PECR were associated with acute and chronic AMR, independent of DSAs.[49] In lung transplantation, anti-PECR antibodies were strongly correlated with CLAD occurrence.[46]

Antibodies to Phospholipase A2 Receptor

An organ-specific target antigen is phospholipase A2 receptor (Pla2R), a mannose receptor mainly expressed on podocytes and the kidney cortex.[50] The majority of patients with membranous nephropathy (MN), an autoimmune disease, have antibodies against Pla2R. If MN gradually results in renal failure, a kidney transplant will be needed.

As MN may occur in the native kidney, as well as de novo in the transplanted kidney, Pla2R antibodies are quite often found in renal transplant recipients. It has been shown that pretransplant anti-Pla2R antibody levels predict the development of posttransplant recurrence of MN[51] and response to rituximab (RTx) therapy.[52]

The recurrence of MN raises the question whether autoantibodies do play an active role in chronic rejection development, and whether allograft dysfunction caused by autoantibodies could be called rejection. Recent data suggest an active role of autoimmunity in graft rejection independent of alloimmunity.[53,54] However, further research is needed to better understand how autoimmunity contributes to transplant rejection in the absence of alloimmunity.

Autoantibodies to Vimentin and Myosin

Vimentin is a type III intermediate filamental protein, expressed by lymphocytes and macrophages. As a result of tissue injury, vimentin is upregulated, so it can serve as an autoantigen.[55] The contractile protein myosin is a heart tissue-specific protein. It has been shown that exosomes released into the circulation of patients at the time of rejection, express such tissue-specific self-antigens.[41]

In cardiac transplant recipients, de novo autoantibodies to vimentin (AVAs) were an independent risk factor for the development of coronary artery disease.[56] Levels of AVAs were elevated in patients with acute AMR and chronic cardiac allograft vasculopathy (CAV) compared with stable cardiac transplant patients.[57] Interestingly, this increase was preceded by the detection of DSAs. Furthermore, AVAs have been associated with CAN,[58] and pretransplant IgG AVAs were a risk factor for interstitial fibrosis/tubular atrophy, but not for graft loss.[59,60] The incidence of AVAs in heart transplant recipients before transplantation was quite high (34%) compared with healthy controls, but AVA positivity did not predict rejection in a small cohort consisting of 50 heart transplant recipients.[61] Additionally, in kidney transplant recipients, preformed AVAs were not found to be associated with AMVR.[29] In a rat study by Yang et al,[62] it was shown that IgG AVA titers positively correlated with the development of CAN and C4d deposition, indicating that AVAs are complement-fixing antibodies.

Heart transplant recipients with acute AMR and/or chronic CAV have higher levels of antimyosin antibodies than stable patients.[57] Furthermore, in a murine heart transplantation model, the increase in antibody levels coincided with an increased frequency of antigen-specific CD4+ T cells secreting interferon gamma, tumor necrosis factor α, and interleukin (IL)-17, whereas IL-10 producing T cells was significantly reduced. Hence, antibodies against myosin are able to activate the immune system and create a proinflammatory milieu, leading to graft failure.[63]

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Antibodies to Collagen I, Collagen V, and k-alpha Tubulin

Another group of autoantibodies are antibodies against collagen I, collagen V, and k-alpha tubulin. Collagens are extracellular matrix proteins, and tubulin is the major constituent of microtubules. It is thought that upon tissue damage epitopes of these self-antigens become exposed on epithelial cells. Circulating exosomes derived from lung transplant recipients diagnosed with bronchiolitis obliterans syndrome (BOS) contain the lung self-antigens collagen V and k-alpha tubulin[41] and are able to induce an immune response as was shown in a mouse study in which mice immunized with these exosomes demonstrated autoantibody production.[64]

Almost 30% of lung transplant recipients had preformed antibodies to 1 or more of these autoantibodies, and the presence of pretransplant antibodies against collagen I, collagen V, and/or k-alpha tubulin increased the risk of primary graft dysfunction (PGD), which in turn increased the risk of chronic rejection.[65] In contrast with these data, Rao et al[66] found no significant association between these antibodies and PGD development in a relatively small cohort. However, patients with pretransplant autoantibodies did have a significantly decreased BOS-free survival. Interestingly, patients with antibodies against collagen I, collagen V, and/or k-alpha tubulin, either developed pretransplant or de novo, were more likely to have DSAs (79% versus 55% in the autoantibody negative group). Like that of AVAs, the production of autoantibodies followed the detection of DSAs.[67] The association of autoantibody and DSA formation was also reported by Hachem et al.[68] Almost 100% of patients with DSAs also developed antibodies to self-antigens, suggesting an interaction between alloimmunity and autoimmunity. Furthermore, a majority (67%) of lung transplant recipients developed antibodies against either k-alpha tubulin or collagen V after transplantation, which were significantly associated with BOS and death. Another study showed the detection of de novo anti-k-alpha tubulin antibodies several months before the onset of BOS.[69] Antigen-specific T cells from BOS+ patients secreted less IL-10 and more IL-17 and interferon gamma, underscoring the pathological role of an immunological response to self-antigens.[67]

Autoantibodies against collagen V and k-alpha tubulin have also been found in heart transplant recipients, in which antibody positivity is associated with increased secretion of IL-17 and reduced secretion of IL-10 in patients with AMR and CAV.[70]

AMR TREATMENT PROTOCOLS

Since non-HLA AMR is correlated with worse graft survival, much effort has been made to prevent tissue injury and to treat patients adequately. No consistent drug regime is used for the treatment of AMR; instead, treatment protocols differ per transplant center, although some therapies are widely used for the clearance of both DSAs and non-HLA antibodies. One method to remove antibodies is plasmapheresis (PP), a process in which plasma is separated from the blood and replaced. A similar, but more specific, technique is immunoadsorption (IA), by which antibodies are specifically removed from the plasma without the need for replacement of other plasma components. Another commonly accepted therapy to desensitize transplant recipients is treatment with IVIG, an immunomodulatory agent. Although the exact mode of action is still not well known, one of the proposed mechanisms is inhibition of complement activation.[71] IVIG has been proven to reduce antibody levels and improve survival rates.[72]

A second treatment category is the use of monoclonal antibodies that deplete B cells and circulating IgG-producing plasma cells by binding to B-cell receptors. The antibodies currently used in transplantation are RTx and ofatumumab, targeting the CD20 receptor.[73] Drugs with a broader mechanism of action are sirolimus and everolimus, drugs that inhibit cell proliferation in general and so affect antibody production by inducing B cell apoptosis.[74] Because IL-6 plays an important role in the differentiation of B cells into plasma cells, the anti-IL-6 monoclonal antibody tocilizumab has been successfully used for AMR treatment and clearance of anti-HLA antibodies.[75] Other promising reagents are the proteasome inhibitors carfilzomib and bortezomib, which deplete plasma cells, thereby decreasing antibody production by these cells.[76] Bortezomib is also able to decrease the number of graft-infiltrating plasma cells in renal transplant patients with plasma cell-rich AR.[77] In rats, it has been proven that both sirolimus and bortezomib significantly reduce the numbers of B cells, plasma cells, and IgG secreting cells (and T cells) compared with a placebo.[78] Furthermore, a synergistic effect has been observed on the reduction of both antibody titers and peritubular C4d deposition.

A final group of therapeutics target costimulatory molecules that play a role in T-cell–mediated B-cell activation. To this category belongs belatacept, an immunomodulatory agent that inhibits antigen-presenting stimulation of T cells as well as the production of antibodies by effector B cells through CD80/CD86 blockade.[79] Other examples of T cell-acting drugs are a humanized anti-CD52 monoclonal antibody (alemtuzumab), a CD25-binding antibody that inhibits T cell proliferation (basiliximab), and a polyclonal T-cell–depleting antibody [antithymocyte globulin (ATG)].

Transplant recipients with non-HLA AMR are treated with these techniques to lower antibody levels and thereby reverse AMR. The efficacy of these protocols on several non-HLA antibody titers and graft failure will be discussed in the section "Therapeutic Approaches."

THERAPEUTIC APPROACHES

PP, IVIG, and IA

In transplant recipients with antibodies against donor HLA as well as AT1R, PP is used as a single treatment or in combination with other techniques (Table 1). In a study by Eng et al,[80] 16 renal transplant recipients with DSAs and AT1R antibodies were treated with PP and low-dose IVIG. Extended desensitization consisting of 1–5 PP sessions pretransplant and >8 sessions posttransplant effectively depleted AT1R antibodies. However, fewer PP sessions (1–5) resulted in a temporary reduction, as antibody rebound was observed within 6 mo after transplantation,[81] showing the importance of following AT1R antibody titers after stopping treatment. Antibody levels decreased and an endothelial crossmatch became negative after 9 PP sessions and treatment with low-dose IVIG (100 mg/kg), 5–8 mg/ml

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TABLE 1.

Overview of literature describing in vivo effects of PP, IVIG, and IA treatment on non-HLA antibodies in transplant recipients

Treatment	Non-HLA ab	Rejection	Treatment effect	No. Pts	Organ	Reference
IVIG	De novo AECA	Humoral rejection	Blocking binding AECA	12	Kidney	22
(Extensive) PP, antiCMVIg	AT1R	AMR	↓ AT1R ab levels; Pts with fewer PP sessions rebound <6 mo *adverse event: 2 Pts AMR; 1 Pt graft loss*	16	Kidney	80
PP, IVIG, ARB (1 Pt)	AT1R	AMR	↓ AT1R ab levels (50-60%), stable renal function *adverse event: rebound anti-AT1R ab levels*	2	Kidney	81
PP, IVIG	Preformed AT1R, AECAs	[b]	↓ AT1R ab levels; negative EC crossmatch; AMR-negative biopsy	1	Kidney	82
PP, IVIG, ATG, tacrolimus + second round PP, IVIG, RTx	AT1R	AMR	No improvement Stable graft function >8 wk *adverse event: refractory AMR*	1	Kidney	83
PP, IVIG	AT1R	AMR	Resolution AMR; AT1R ab levels still high	1	Kidney	84
Protein A and Glyco-Sorb-ABO IA	De novo AECAs	AMR	Retained renal function	1	Kidney	85
PP, steroids, immunosuppression	Collagen IV	Anti-GBM disease[a]	Good renal outcome and patient survival	>40	Kidney	86

[a]Not transplant recipients.
[b]Treatment started before AMR development.
ab, antibody; AECA, antiendothelial cell antibody; AMR, antibody-mediated rejection; ARB, angiotensin II receptor blocker; ATG, antithymocyte globulin; AT1R, angiotensin II type-1 receptor; CMV, cytomegalovirus; EC, endothelial cell; GBM, glomerular basement membrane; IA, immunoadsorption; PP, plasmapheresis; Pt(s), patients; RTx, rituximab.

tacrolimus, and mycophenolate mofetil (MMF) (2000 mg daily). Other case reports[82-84] also showed that PP was successful in treating AMR in renal transplant patients with anti-AT1R antibodies but without DSAs. Although AT1R antibody titers sometimes returned to the maximal detection level after treatment, refractory AMR was not observed. The authors hypothesized that probably due to the absence of inflammation, ECs may have lower AT1R expression, to which fewer circulating antibodies could bind and cause tissue damage. Larger studies are needed to confirm this hypothesis. To evaluate the blocking efficacy of a single dose of IVIG in vitro, kidney eluates were incubated with 50 g/ml IVIG before adding them to EA.hy 926 cells. In all 5 samples tested, AECA binding was strongly inhibited upon IVIG addition, implying that IVIG could be used in treating AECA-mediated rejection.[22] A kidney transplant recipient receiving a second transplant was successfully treated for acute AMR caused by AECAs with standard rejection therapy and repeated IA.[85]

Patients with polymyositis and dermatomyositis have elevated levels of circulatory anti-myosin autoantibodies. A mouse experimental autoimmune myositis model was used to evaluate the inhibitory effect of IVIG on muscle lesions and autoantibody levels. Administration of 400 mg/kg/d of IVIG for 5 d resulted in a decline in antimyosin antibody titers and a blockade of complement activation.[87] As far as we know, no human data are available about the efficacy of treatment on antibodies against myosin.

Monoclonal Antibody Therapies

A kidney transplant recipient with MICA antibodies who received a second renal transplant underwent desensitization consisting of high-dose IVIG (2 g/kg once a mo for 4 mo) and RTx (750 mg/m^2 in 2 doses) (Table 2). At day 10 after transplantation, the patient was treated with 2 g/kg IVIG over 2 d, 750 mg/m^2 RTx, and PP because of AMR.[88] Donor-specific anti-MICA antibodies were elevated both pretransplant and at the time of rejection but decreased after the start of AMR treatment together with a resolution of AMR, indicating that PP in addition to IVIG and RTx treatment is needed to clear anti-MICA antibodies. Indeed, another study also failed to show effective clearance of antibodies against MICA or DSAs upon monoclonal antibody therapy consisting of RTx and daclizumab (an IL-2-receptor antagonist) given before kidney transplantion.[89]

Patients with anti-GBM disease were successfully treated with corticosteroids and PP.[86] However, some patients did not respond well to this standard treatment or experienced relapsing disease. In a case report of such a patient, administration of 2 doses of 1000 mg RTx 2 wk apart after standard therapy resulted in a clearance of anti-GBM antibodies up to 2 y after treatment.[90] Another study described 5 patients with anti-GBM disease treated with 4 weekly doses of RTx (375 mg/m^2) as a first-line therapy in combination with daily PP. Antibodies became undetectable by a median of 20 d after the first RTx administration, and remained undetectable up to 15 mo after treatment initiation.[91]

In a trial[92] investigating the use of RTx versus cyclosporine A (CsA) in the treatment of MN, 130 patients were included and were randomly assigned to 1 of both groups. The RTx-treated group received 1000 mg twice on days 1 and 15, followed by a second round if partial proteinuria remission was observed after 6 mo. Patients in the other group received 3.5 mg/kg daily CsA for half a year, which was tapered and discontinued over a 2-mo period in the case of complete remission or continued for another 6 mo in the case of partial remission. The higher Pla2R was at 6 mo, the more likely the patient was to have treatment failure. Furthermore, patients with complete remission were

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TABLE 2.

Overview of literature describing in vivo effects of monoclonal antibody and bortezomib treatment on non-HLA antibodies in transplant recipients

Treatment	Non-HLA ab	Rejection	Treatment effect	No. Pts	Organ	Reference
RTx, PP, IVIG	MICA	AMR	↓ MICA ab levels; resolution AMR	1	Kidney	88
RTx, Daclizumab	MICA	AMR	Adverse event: no clearance anti-MICA ab	11	Kidney	89
RTx, PP	GBM	Anti-GBM disease[a]	Negative anti-GBM ab; symptoms free >2 y Adverse event: remained on dialysis	1	Kidney	90
First-line RTx, PP	GBM	Anti-GBM disease[a]	Negative anti-GBM ab >15 mo Adverse event: no significant improvement of renal function	5	Kidney	91
RTx, CsA	Pla2R	MN[a]	Faster, greater, and longer ↓ in Pla2R ab levels in RTx treated group	130	Kidney	92
RTx, CsA	Pla2R	MN[a]	Negative Pla2R ab; complete remission >2 y	1	Kidney	93
RTx	Pla2R	MN	↓ Pla2R ab levels; MN remission	6	Kidney	94
RTx, IVIG	De novo Collagen V, Tubulin	BOS	Clearance non-HLA ab in 30% of Pts	122	Lung	95
Bortezomib, PP, IVIG, steroids	AT1R	AMR	Negative AT1R ab; stable renal function >1 y	1	Kidney	96
Bortezomib, PP, IVIG, steroids	De novo AT1R	AMR	Retained renal function >1 y	1	Kidney	97
Bortezomib	Preformed AT1R	[b]	5 Pts AT1R ab <10 U/ml <1 mo Adverse event: ↑ AT1R ab levels in some Pts	14	Heart	98
Bortezomib, PP, IVIG, Rituxan, Daclizumab, ATG, Eculizumab	AECAs	C4d neg AMR	Clearance AECAs levels Adverse event: vascular rejection; nephronectomy	1	Kidney	99
Tocilizumab	AT1R	AMR	↓ AT1R ab levels; stable renal function	11	Kidney	100

[a]Not transplant recipients.
[b]Treatment started before AMR development.
ab, antibody; AECA, antiendothelial cell antibody; AMR, antibody-mediated rejection; ATG, antithymocyte globulin; AT1R, angiotensin II type-1 receptor; BOS, bronchiolitis obliterans syndrome; CsA, cyclosporine A; GBM, glomerular basement membrane; MICA, major histocompatibility complex class I-related chain A; MN, membranous nephropathy; Pla2R, phospholipase A2 receptor; PP, plasmapheresis; Pt(s), patients; RTx, rituximab.

antibody negative at 24 mo, and those patients treated with RTx showed a faster and longer decrease in anti-Pla2R antibody levels than those treated with CsA. More literature are available indicating the favorable effect of RTx, with or without CsA, on the removal of Pla2R antibodies in MN.[93] Additionally, in 5 kidney transplant recipients, 1–2 doses of RTx at 375 mg/m^2 are effective in reducing anti-Pla2R antibody levels and improving renal function. Interestingly, in 1 patient, antibody levels rose after withdrawal of ATG induction immunosuppression, which was reversed upon RTx administration.[94] It would be worthwhile to consider administration of RTx before transplantation to recipients with detectable anti-Pla2R antibodies.

Only 1 article has been published evaluating the effect of tocilizumab on non-HLA antibody titers in chronic AMR kidney transplant patients with severe TG. At the time of diagnosis, 11 of 13 patients showed elevated anti-AT1R antibody levels, which were significantly reduced after 6 mo of treatment with 8 mg/kg tocilizumab.[100] To the best of our knowledge, no literature is available describing the effects of other monoclonal antibodies on non-HLA antibodies.

The treatment effect on the clearance of antibodies against lung self-antigens has rarely been evaluated. Standard immunosuppression consisting of tacrolimus, azathioprine, and prednisone did not clear antibodies after transplantion.[66] The effects of IVIG, RTx, and extracorporeal photopheresis, on anticollagen and/or antitubulin antibodies in lung transplantation have been reviewed previously by Hachem et al.[95] Since then, no new studies have been published, although the need to test the efficacy of several treatment strategies in larger trials still exists.

Combination Therapy With the Proteasome Inhibitor Bortezomib

Kidney transplant patients with AMR were treated with a multimodal approach including steroids, PP, IVIG, and bortezomib (1.3 mg/m^2 of body surface area twice weekly) (Table 2).[96,97] Graft function was stabilized, and levels of AT1R antibodies and DSAs became undetectable 1 y after therapy. Although bortezomib therapy is effective in reducing AT1R antibody levels in kidney transplant recipients, it has only been effective in a minority (5 of 14) of heart transplant candidates.[98] Moreover, combination therapies did not always result in regaining graft function, as was shown in a renal patient receiving his third transplant. Despite aggressive multimodal treatment (PP, IVIG, RTx, eculizumab, and bortezomib) and clearance of AECAs, the graft was lost because of AMR and vascular rejection.[99] An explanation could be that the antibodies had already caused severe cellular damage before their removal.

An in vitro study by Li et al[101] found higher IgM anti-MICA antibody production by stimulated B cells from kidney transplant recipients than from healthy controls. Furthermore, administration of 100 ng/ml bortezomib or 100 ng/ml mycophenolic acid resulted in a significant inhibition of B-cell proliferation and decreased IgM antibody production.

Although transplanted mice injected with apoptotic exosome-like vesicles generated from ECs treated with 100

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TABLE 3.

Overview of literature describing in vivo effects of T-cell acting drugs, immunosuppressive drugs, and specific therapies on non-HLA antibodies in transplant recipients

Treatment	non-HLA ab	Rejection	Treatment effect	No. Pts	Organ	Reference
CNI + MMF and corticosteroids	LG3	[a]	↓ ab levels >1 mo	31	Kidney	102
Tacrolimus, azathioprine, prednisone	Preformed Collagen I, Collagen V, and Tubulin	BOS	Adverse events: auto-ab persist despite DSA clearance	44	Lung	66
ECP	Collagen I, Collagen V, and Tubulin	BOS	↓ ab levels and proinflammatory cytokines; ↑ anti-inflammatory cytokines	88	Lung	95
ATG, PP, IVIG, methylprednisolone	Vimentin	PGD/AMR	Retained renal function >1 y; ↓ Vimentin expression in biopsy	1	Kidney	103
CsA, corticosteroids + MMF or azathioprine	De novo Vimentin	CAD	↓ ab levels, less risk CAD (1 y) in patients treated with MMF	86	Heart	104
Steroids, azathioprine + CsA or tacrolimus	AECAs/de novo Vimentin	[a]	More Pts IgM Vimentin ab positive in CsA group	170	Heart	105
Candesartan, ATG; AT1R ab >25 U/ml: + PP	AT1R	AMR	↓ Rejection rate	225	Kidney	106
losartan, PP, IVIG	AT1R	Acute rejection	Negative AT1R ab; improved graft survival	7	Kidney	107
ATG, methylprednisolone, PP, candesartan	AT1R	Vascular rejection	Retained renal function >6 wk	1	Kidney	108
Losartan or steroids and ACEi, PP, IVIG	AT1R	AMR Fibrosis Mild rejection	Good graft function (3 Pts losartant; 2 Pts PP + IVIG) Good graft function (1 Pt pulse steroids) Good graft function (1 Pt ACEi, although AT1R ab levels still high)	12	Heart	109
ATG, PP, IVIG, RTx, tacrolimus + MMF After 2 d: losartan, PP Methylprednisolone, PP, ATG, eculizumab	AT1R	ACR Renal thrombosis	Adverse event: graft loss POD21	1	Kidney	110
IdeS, PP, IA	GBM	Anti-GBM disease[b]	Breakdown anti-GBM ab Adverse event: rebound anti-GBM ab levels	3	Kidney	111
ATG, PP, IVIG	Preformed AT1R	PGD/AMR	Adverse event: death	1	Heart	112

[a]Treatment started before AMR development.
[b]Not transplant recipients.
ab, antibody; ACEi, angiotensin convertin enzyme inhibitor; ACR, acute cellular rejection; AECA, antiendothelial cell antibody; AMR, antibody-mediated rejection; ATG, antithymocyte globulin; AT1R, angiotensin II type-1 receptor; BOS, bronchiolitis obliterans syndrome; CAD, cardiac artery disease; CNI, calcineurin inhibitor; CsA, cyclosporine A; DSA, donor-specific anti-HLA antibody; ECP, extracorporeal photopheresis; GBM, glomerular basement membrane; IA, immunoadsorption; IdeS, immunoglobulin G degrading enzyme of *Streptococcus pyogenes*; LG3, third laminin-like globular; MMF, methylphenolate motefil; PGD, primary graft dysfunction; POD, postoperative d; PP, plasmapheresis; Pt(s), patients; RTx, rituximab.

µg/ml bortezomib had decreased anti-LG3 antibody levels and C4d deposition,[44] more human studies are needed to confirm the ability of bortezomib to prevent antibody formation and rejection in transplant recipients with LG3 autoantibodies.

T-cell Acting Drugs

A low-risk kidney patient transplanted with a graft from a living donor presented early-onset acute AMR associated with AVAs (Table 3). The patient was treated with 4–6 mg/kg ATG, methylprednisolone, and PP plus 100 mg/kg/dose IVIG. Detectable levels of AVAs were found in serum, along with widespread expression of vimentin in the kidney. After 5 mo, resolution of rejection was shown in a biopsy, together with only patched vimentin expression. No data were available about the AVA titers.[103]

Immunosuppressive Drugs

In a small renal transplant cohort of patients receiving calcineurin inhibitors, a decrease in anti-LG3 titers was observed 1 mo after transplantation (Table 3). Although these patients also received other immunosuppressive agents, such as MMF, this observation points to the possibility of using CD4-targeted therapies to reduce anti-LG3 antibody levels.[102] The effect of MMF on reducing AVA titers was observed in a cardiac transplant trial.[104] De novo production of AVAs was significantly reduced in heart transplant recipients treated with 3000 mg/d MMF compared with 1.5–3 mg/kg/d azathioprine, and this was also associated with a lower incidence of cardiac artery disease. In an outdated study, the effect on the production of AVAs was compared in heart transplant recipients taking standard immunosuppressive drugs plus CsA

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or tacrolimus. More patients were AVA positive in the CsA group than in the tacrolimus group within 1 y after transplantation.[105]

Other Therapies

Receptor Blockers

Another method to interfere with the interaction between AT1R and antibodies is the use of receptor blockers (Table 3). A few clinical studies—mostly performed in renal transplant recipients—show the utility of blocking AT1R with losartan or candesartan in addition to plasma exchange and ATG treatment. A single-center study evaluating the effect of ATG/candesartan in combination with PP by comparing 2 kidney transplant recipient cohorts showed that this perioperative treatment resulted in a decreased risk of AMR.[106] A total of 14 of 80 patients with AT1R antibody levels >17.5 U/ml were treated with 3–4.5 mg/kg ATG and 4–16 mg/d candesartan. Patients with AT1R antibodies >25 U/ml were also treated with PP. Additionally, kidney transplant patients with vascular rejection remained rejection free and had fewer AT1R antibodies after treatment involving PP, 100 mg of losartan daily plus IVIG,[107] or 4 mg of candesartan daily plus 6 sessions PP, 3 d of 1 g/d methylprednisolone, and 6 doses of 1.5 mg/kg/d ATG.[108] Furthermore, in a case series,[109] it was reported that 9 of the 12 (75%) heart transplant recipients had AT1R antibodies, and 6 out of these 9 developed AMR or mild rejection. Seven patients were treated with 25–100 mg losartan and/or PP and IVIG, and 71% (5 of 7) recovered good graft function. One patient with mild rejection receiving an angiotensin-converting enzyme inhibitor had good graft function, although AT1R antibody levels remained high. Another case report[110] presented a pediatric kidney transplant patient with accelerated vascular rejection and thrombosis despite PP and AT1R blockers. Antibodies against AT1R have procoagulant properties and could be a risk factor for thrombosis. To reduce the risk of vessel coagulation, anticoagulation could be added to the current treatment protocols, as well as immunomodulatory therapies, such as bortezomib to reduce AT1R antibody production. Continued AT1R blockade via administration of losartan in male rats led to increased AT1R expression in the left ventricle of the heart.[113] Although human data are missing, these data indicate that monitoring is very important to avoid worse outcomes after the use of losartan in transplant patients.

Immunoglobulin G Degrading Enzyme of *Streptococcus pyogenes*

A promising drug to clear anti-GBM antibodies is immunoglobulin G degrading enzyme of *Streptococcus pyogenes* (IdeS) (imlifidase). IdeS is an endopeptidase that cleaves all subclasses of human IgG and appears to be effective in DSA clearance in HLA-sensitized kidney transplant recipients.[114,115] Recently, 3 patients with anti-GBM disease were successfully treated with IdeS. Although anti-GBM antibodies were not affected by PP, titers decreased rapidly after 0.25 mg/kg IdeS infusion.[111] However, before this drug can be implemented in solid organ transplant recipients, its efficacy needs to be confirmed in clinical trials.

DISCUSSION

In this review, we have discussed well-studied non-HLA antibodies in relation to rejection after solid organ transplantation. Most articles showed that both pretransplant and de novo AECAs are independent risk factors for AMR, as well as de novo antibodies against vimentin and myosin. The development of anti-GBM antibodies is associated with vascular rejection, and patients with antibodies against lung self-antigens have a higher risk to develop BOS. Anti-LG3 antibodies and anti-PECR antibodies were both strongly correlated with occurrence of CLAD in lung transplant recipients. We were aware of the fact that in single cases, antibodies to other non-HLA antigens have been described. For example, antibodies to Jk^a were found to be associated with hyperacute AMR in a male renal transplant recipient,[116] and a few more studies summarized by Hamilton[117] also described a correlation between anti-Kidd blood group antibodies and rejection. Autoantibodies against Rho GDP-dissociation inhibitor 2 have recently been described to be associated with long-term kidney graft loss.[118] Other antibodies (eg, against platelet factor 4, cardiolipin, or glycoprotein) were associated with rejection in heart and lung transplantation. Treatment with several PP sessions was effective in antibody elimination and graft function improvement.[119] The presence of IgA anti-β2-glycoprotein I antibodies before transplantation was correlated with early kidney and heart allograft failure.[120,121] In recent years, proteomics has been used to explore relevant non-HLA antibody targets on ECs. Examples of such new target antigens in kidney transplant recipients experiencing AMR are endoglin and Fms-like tyrosine kinase-3 ligand, proteins implicated in EC activation.[122] In a study by Butler et al,[123] 3 other novel antigens expressed on EC, namely endomucin, latrophilin 1, and Sjögren syndrome antigen B, were found to be independent biomarkers of AMR and cellular rejection in cardiac transplantation. Although these data need to be confirmed in larger studies, they clearly show the presence of antibodies against a variety of non-HLA and self-antigens in transplant recipients. However, it is important to note that not much is known about the pathogenic effect of these non-HLA antibodies on graft damage. In addition to the broad spectrum of non-HLA antibodies present in transplant recipients, their nonpathogenic presence in patients with stable graft function is a main challenge for clinicians and calls for personalized medicine.

Most published research regarding non-HLA antibodies in solid organ transplantation did not include testing for donor specific non-HLA antibodies before transplantation, although they are important in transplant outcome. In a large cohort of almost 500 first kidney transplant recipients the degree of genetic mismatches in transmembrane and secreted proteins was proven to be an important predictor of graft loss, independent of HLA genetic mismatch.[124] Hence, it would be valuable to develop assays and routinely test for a variety of donor-specific non-HLA antibodies.

Removal of antibodies by standard PP, IVIG, and/or IA is effective at clearing antibodies against AT1R and to resolve AMR. Additionally, patients with MICA antibodies needed PP treatment in addition to RTx because the latter fails as a monotherapy to reduce antibody titers. Administration of RTx to patients with anti-Pla2R antibodies or anticollagen

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and antitubulin antibodies is also successful in eliminating antibodies and resolving rejection. Good results were achieved when using RTx for antibody removal in patients with anti-GBM disease. Studies evaluating the effect of the proteasome inhibitor bortezomib showed a reduction in AT1R antibodies and MICA antibodies in kidney transplant recipients. However, not all heart transplant candidates respond well to bortezomib treatment. The reason is still unknown and needs to be further investigated. Although bortezomib seems to reduce antibody levels in individual patients, in a randomized trial,[125] the ineffectiveness of bortezomib treatment at reducing DSAs or improve graft function in late-onset AMR was demonstrated. More (and more severe) adverse effects were shown in bortezomib-treated patients than in placebo-treated patients. Therefore, it is very important to conduct randomized clinical trials and compare results from patients with early- and late-onset AMR. Patients with AVAs were successfully treated with ATG and/or immunosuppressive drugs. Although most research describes AMR reversal after treatment including ATG in patients with AT1R antibodies, 1 case study of a cardiac transplant patient with antibodies against AT1R and undefined AECAs, reported negative results. Despite a decrease in antibody levels after treatment with PP, IVIG, and ATG, AMR could not be controlled, and the patient developed thrombosis, eventually leading to death.[112] To the best of our knowledge, no clinical studies have evaluated the efficacy of treatment protocols on anti-PECR or anti-myosin clearance. Specific therapies such as AT1R blockers or IdeS seem promising, but their long-term effects need to be investigated before these therapies can be safely implemented. One study has been conducted reporting a positive effect of anti-IL-6 treatment for non-HLA AMR. It might be useful to evaluate this type of therapy in a larger cohort of transplant recipients with AMR associated with non-HLA antibodies, as well as the effects of complement inhibitors in the case of complement-fixing non-HLA antibodies.

AT1R antibodies have been detected with either commercial or homemade enzyme-linked immunosorbent assays, and different cutoff values have been used.[20,29,30,126] To evaluate the relevance of AT1R antibodies and other non-HLA antibodies to transplant outcome, it is very important to use standardized assays and clinically relevant cutoff values, as differences may result in different interpretations.

In conclusion, a variety of non-HLA antibodies play a detrimental role in graft survival after solid organ transplant. Current therapeutic protocols are effective in clearing non-HLA antibodies and improving graft function in the majority of transplant recipients. However, careful monitoring of non-HLA antibody levels after treatment, along with standardization of therapies, is needed for optimal treatment of patients.

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