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Authors
Pearl, Meghan H
Reed, Elaine F

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Angiotensin II Type I Receptor Antibodies in Pediatric Solid Organ Transplant

Meghan H. Pearl[1], **Elaine F. Reed**[2]

[1]University of California Los Angeles, Department of Pediatrics, Division of Pediatric Nephrology

[2]University of California Los Angeles, Department of Pathology and Laboratory Medicine

Abstract

Minimizing immunologic complications is critical for long-term patient survival in pediatric solid organ transplant recipients. Multiple factors distinguish pediatric from adult organ transplant recipients which may influence the risk and manifestations of immunologic responses. Angiotensin II type 1 receptor antibody (AT1R-Ab) is a non-HLA antibody that has been has been associated with poor clinical outcomes in adult kidney transplant recipients. There is now limited evidence available to suggest that AT1R-Ab may be an important part of the immunologic milieu impacting pediatric organ transplant outcomes and that differences in this phenomenon may exist between pediatric and adult patients. The mechanisms by which autoimmunity is provoked and mediates organ dysfunction in childhood and effective treatment options require further research.

Keywords

angiotensin II type 1 receptor antibody; transplantation; pediatric; non-human leukocyte antigen antibody

Introduction

Maximizing long-term allograft survival is critical in the pediatric population given that they have the highest number of expected life years of any age group [1], yet most will require re-transplantation in their lifetimes. The role of alloantibody responses against Human Leukocyte Antigens (HLA) in mediating antibody-mediated rejection (AMR) has been a primary focus in both adult and pediatric transplantation [2–5]. Non-HLA antibodies have recently been recognized as potential mediators of allograft injury [6, 7], but the pathogenesis of non-HLA antibody mediated AMR is poorly understood and evidence for routine non-HLA antibody testing remains insufficient [8]. AT1R-Ab, in particular, has been

Meghan Pearl, Division of Pediatric Nephrology, Department of Pediatrics, Mattel Children's Hospital at UCLA, David Geffen School of Medicine, 10833 Le Conte Avenue, Box 951752, Los Angeles, CA 90095-1752, Phone: (310) 206-6987, Fax: (310) 825-0442, mpearl@mednet.ucla.edu.

associated with rejection, vascular injury, decline in renal function, and allograft failure in adult kidney transplant recipients [9–16].

There are multiple factors specific to children hypothesized to impact immunologic complications and transplant outcomes including differences in the immature vs mature immune system, rates of primary viral infection, and variations in immunosuppression drug metabolism [17]. This review explores the current literature on the role of AT1R-Ab in pediatric solid organ transplant outcomes. Though available evidence remains limited, we aim to highlight possible differences in the adult and pediatric populations in this regard and emphasize areas in need of further investigation.

Discussion

Prevalence of AT1R-Ab in Pediatric Patients

There are many challenges hindering our understanding of the prevalence and clinical impact of AT1R-Ab in the pediatric transplant population. Firstly, cutoffs for determining AT1R-Ab positivity by ELISA range from 9-17 U/mL. This is typically determined by the laboratory, the kit used to conduct the testing, and, in some cases, a receiver operating curve analysis. Second, the potential variability between kits, lots of reagents, and manufacturers add an additional layer of challenges. Development of a standardized approach to reduce variation across AT1R-Ab ELISA assays is needed to define cutoff values (which may vary based on clinical context), to precisely measure prevalence and clinical utility in the population, and to translate this test into widespread clinical use.

With this limitation in mind, there are some data available to help estimate the prevalence of AT1R-Ab in the pediatric population (Table 1). Bjerre et al. found the median level of AT1R-Ab to be 6.5 and 13.3 U/mL in healthy adults and children respectively, lower than in both kidney transplant populations (11 and 40 U/mL respectively) [18]. The prevalence of pre-transplant AT1R-Ab in adult kidney transplant patients ranges from 8-47.2% [10–12, 14–16, 19–22] with cutoffs for positivity ranging from 9-17 U/mL. One study of 29 pediatric kidney transplant recipients [23] found no patients with pre-transplant AT1R-Ab. However, this finding is difficult to interpret because the cutoff is not reported. Similar to adult studies, another study found pre-transplant AT1R-Ab >17 U/mL in 23% of pediatric patients [24]. Less data exist on the post-transplant development of AT1R-Ab in patients known to be negative pre-transplant. In the adult kidney transplant population, development of AT1R-Ab post-transplant ranges from 3-13% [12, 21] (with mean follow up of approximately 5-9 years post-transplant), while in children the only available study with longitudinal samples suggests a rate of 26% in the first 2 years post-transplant [24]. In cross-sectional analyses of patients tested at the time of indication biopsy, 32% of adult [25] and 52% of pediatric [26] kidney transplant recipients have been reported to be AT1R-Ab positive. In pediatric liver transplant, 46% of patients on an immunosuppression withdrawal protocol were observed to have AT1R-Ab >17 U/mL at the time of indication biopsy [27], however, there are no adult data in liver transplantation available for comparison.

Taken together, there is some suggestion that pediatric patients (both healthy and post-transplant) have higher levels of AT1R-Ab and may be more likely to develop AT1R-Ab

post-transplant. The reason for this finding remains unclear. The trigger for AT1R-Ab production is unknown. However, the development of AT1R-Ab in other diseases has been linked to organ ischemia [28] (Figure 1), and a possible role of ischemia reperfusion injury in kidney transplantation has been suggested [6]. It is therefore possible that the smaller size and therefore higher risk of hemodynamic instability and vascular injury at the time of transplant may put pediatric transplant patients at higher risk of developing AT1R Ab. The potential role of the maturing immune system and viral exposures in this interplay and risk for autoimmunity has also yet to be explored. Furthermore, more data are needed to better understand the possible need for age specific cutoffs for AT1R-Ab positivity.

AT1R-Ab and Allograft Injury in Pediatric Transplantation

The phenotype of AT1R-Ab associated allograft injury was initially reported in adult kidney transplantation as AMR with severe hypertension [9]. Since this first report, AT1R-Ab has been associated with C4d positive and negative AMR, acute cellular rejection, vascular injury, decline in renal function, and allograft failure in adult kidney transplant recipients [9–16, 22]. AT1R-Ab has also been associated with allograft rejection in adult heart [29] and lung [30, 31] transplant recipients.

In pediatric kidney transplantation, the 2 largest cohort studies have shown an association between AT1R-Ab and allograft loss and decline in eGFR [24, 26] (Table 1). Interestingly, this was true in both the longitudinal cohort study[24] and a cross-sectional examination of AT1R-Ab at the time of indication biopsy [26]. Furthermore, both studies showed an association between AT1R-Ab and vascular inflammation, but not necessarily with the diagnosis of rejection. No association with rejection was also noted in one other smaller study [23]. The 2 cohort studies differed in the association between AT1R-Ab positivity and hypertension and HLA DSA; The longitudinal study found no association with hypertension or HLA DSA[24], while the cross-sectional study found associations with HLA Class II DSA and higher systolic blood pressure[26]. These differences may be related to the evaluation time points (both protocol and at time of indication biopsy vs. time of indication biopsy alone) and require further investigation. In pediatric liver transplantation, a cross-sectional cohort study examined AT1R-Ab positivity in living donor liver transplant patients who underwent immunosuppression withdrawal. AT1R-Ab was more frequent in the advanced fibrosis group vs the control group [27] (Table 1). This finding is interesting given the known pro-fibrotic effects of AT1R activation and a recent study in kidney transplantation showing increased sub-intimal fibrosis in adult patients with AT1R-Ab [22]. In addition to the small number of available cohort studies, there are 3 case reports in kidney [32–34] and 1 in liver transplantation reporting on acute AMR associated with AT1R-Ab in pediatric patients (Table 2).

The mechanisms of pathogenicity involved in AT1R-Ab mediated injury, particularly in pediatric patients, remain unclear. Current evidence, similar to adult data, suggests an association with endothelial cell injury and vascular inflammation. The involvement of complement activation appears inconsistent. Importantly, there may be multiple pathways of AT1R-Ab related injury given some patients develop classical cases of acute AMR with hypertension while others may have a more gradual decline of eGFR and allograft loss.

Furthermore, given that even healthy pediatric patients may have higher AT1R-Ab levels than adults [18], understanding how to identify which patients are at risk for pathology is critical to determining appropriate screening and treatment protocols. Patients may be at highest risk at times of concomitant allograft injury, for example, peri-operatively or in the presence of other pathogenic antibodies such as HLA DSA. The role of additional potentially relevant factors, such as the regulation of expression of AT1R on the allograft or synergy with other non-HLA antibodies, remains to be determined.

Therapy for AT1R-Ab Mediated Allograft Injury

There is currently no standardized treatment strategy to address AT1R-Ab mediated injury in the transplant setting. In the original paper describing acute AMR and hypertension in kidney transplantation, a treatment strategy including plasmapheresis, IVIG, and angiotensin receptor blockade was effective in reducing AT1R-Ab activity and improving allograft pathology (Figure 1) [9]. One paper in adult patients, described a preemptive strategy of screening for AT1R-Ab pre-transplant and induction of patients with ATG, angiotensin receptor blocker, and peri-operative plasmapheresis (in patients with AT1R-Ab > 25 U/mL) with improved outcomes compared to historical controls [35]. There are no studies examining the role of angiotensin receptor blockade in patients with AT1R-Ab without acute AMR.

In pediatrics, the available case reports show mixed results with these treatment strategies (Table 2). In 2 cases, kidney transplant patients were treated for AT1R-Ab associated acute AMR successfully using angiotensin receptor blockade and various additional treatments [32, 34]. In one case, though the patient initially was improving with aggressive treatment, the allograft eventually failed from thrombosis [33]. Given AT1R activation is associated with tissue factor expression [9], the role of anticoagulation as an adjunctive treatment strategy in these cases also has yet to be explored (Figure 1). In the liver transplant case report, multiple AMR treatments were unsuccessful, however, this case was also complicated by additional vascular complications making the impact of treatment on the AT1R-Ab mediated component difficult to ascertain [36].

In children, the need for additional access for plasmapheresis in some cases can be technically challenging and is accompanied by higher risk of damaging future dialysis or total parenteral nutrition access options. Therefore, identification of appropriate candidates for preemptive peri-operative plasmapheresis in pediatrics is a critical question. Angiotensin receptor blockers are considered safe in pediatric patients for the treatment of hypertension, and therefore, are generally an attractive treatment option. However, the benefit of treatment in the context of AT1R-Ab positivity has not yet been adequately studied. Also of interest, AT1R-Ab has been associated with elevated cytokine levels in pediatric patients [24]. The role of blockade of these pathways in treatment of AT1R-Ab associated pathology with, for example, agents such as tocilizumab (anti-I L6 receptor antibody), has yet to be formally examined (Figure 1). Tocilizumab has been reported to have been used successfully in 3 adult patients with AT1R-Ab associated AMR in a recent case series [37]. Further studies are needed to understand the effectiveness of this approach.

Conclusions and Future Questions

AT1R-Ab positivity may be a frequent phenomenon in pediatric transplant recipients, however, many questions remain regarding its associated phenotypes, mechanisms of injury, synergy with HLA and other non-HLA antibodies, and determinants of pathogenicity. Studies in pediatric heart, lung, and multi-visceral transplant patients are currently lacking and additional work is needed in all fields of pediatric solid organ transplant. Further studies are necessary to effectively identify which pediatric patients are at highest risk for AT1R-Ab mediated allograft injury to create effective clinical screening and treatment protocols. Studies assessing serial AT1R-Ab levels at both protocol and indication time points using a standardized testing method in a multicenter group of pediatric transplant recipients would be a foundational first step in defining the natural history. Furthermore, an in depth examination of allograft pathology in patients with and without clinical allograft dysfunction, including AT1R expression and signaling, would be of great interest to better understand the role of AT1R-Ab in allograft pathophysiology. Additionally, the role of AT1R-Ab in pediatric pathology outside of organ transplantation, for example, in chronic kidney disease is of interest.

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Abbreviations:

AT1R	angiotensin II type 1 receptor
AT1R-Ab	angiotensin II type 1 receptor antibody
HLA	human leukocyte antigen
AMR	antibody-mediated rejection

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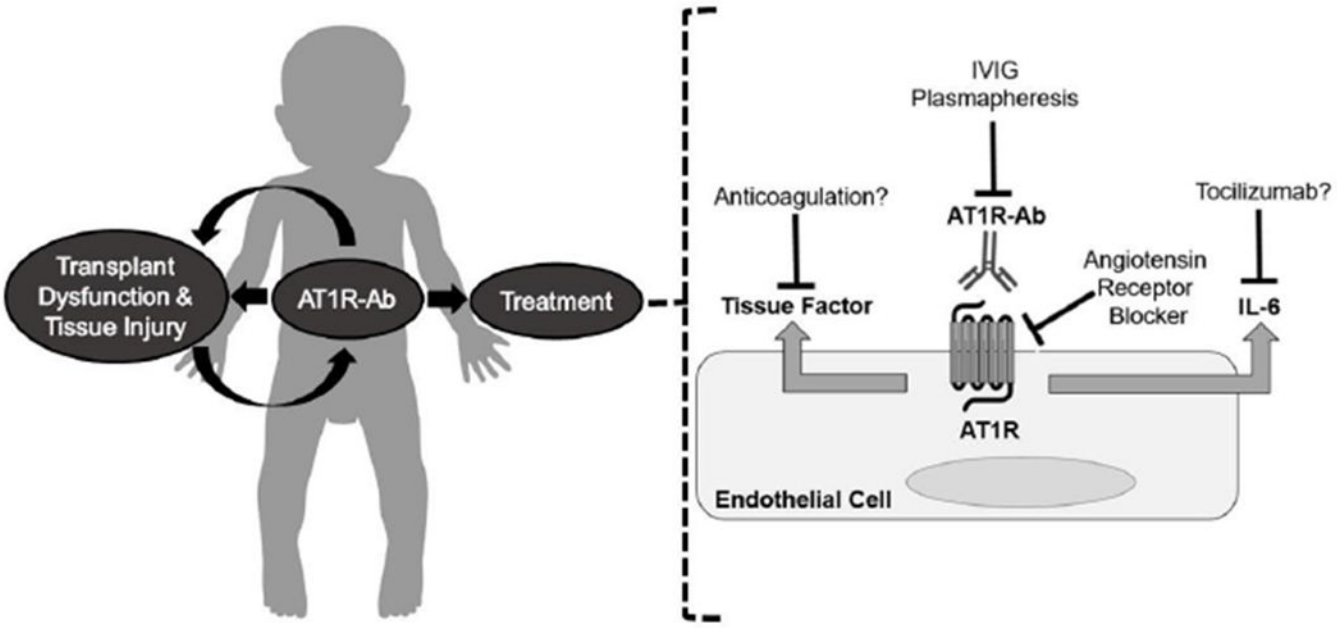

Figure 1: Potential Relationship between AT1R-Ab, Allograft Dyfunction, and Treatment Options in Pediatric Transplantation:

The development of AT1R-Ab in pediatric transplant patients may be related to tissue injury. The presence of AT1R-Ab may provoke further injury, however, treatment options exist which could potentially disrupt this cycle. Removal of AT1R-Ab using plasmapheresis and IVIG in conjunction with the use of angiotensin receptor blockers to inhibit AT1R activation has been described in the succesful treatment of AT1R-Ab mediated antibody-mediated rejection. Activation of the AT1R has been associated with tissue factor release and elevated IL-6, therefore, anticoagulation and/or blockade of the IL-6 pathway may be considered therpeautic options in future investigations. AT1R, angiotensin II type 1 receptor; AT1R-Ab, angiotensin II type 1 receptor antibody; IL-6, interleukin 6

Table 1:
Pediatric Cohort Studies Examining AT1R-Ab in Solid Organ transplant.

U, units; AMR, antibody-mediated rejection; m, months; tx, transplant; KTRs, kidney transplant recipients; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; LDLT, living donor liver transplant; IS, immunosuppression

Cohort	Time of AT1R-Ab Testing	AT1R-Ab Cutoff	AT1R-Ab Prevalence	Key Findings	Synergy with HLA DSA	Ref No.
Kidney						
30 pediatric and 28 adult stable KTRs as well as 51 pediatric and 199 adult healthy controls examined cross-sectionally	Median time of 5 and 18 years post-tx in the pediatric and adult KTRs respectively	N/A	N/A	Median AT1R-Ab levels were higher in pediatric [40 (14.48-40)] vs adult [10.95 (8.2-25.53)] KTRs. Both pediatric and adult KTRs had higher median AT1R-Ab levels than their respective control groups.	N/A	[18]
29 pediatric KTRs followed for 12m	Pre-tx for 28 subjects and unspecified times from 0-12m post-tx for 20 subjects (144 samples)	>2 SD above the mean in control group (healthy adults). Number not provided.	- 0% pre-tx - 40% on at least one post-tx sample	AT1R-Ab was a frequent finding post-tx in pediatric patients and was not associated with infection or rejection.	N/A	[23]
65 pediatric KTRs followed longitudinally for 24m	Pre-tx, 6m, 12m, 24m, and at times of suspected rejection.	17 U/mL	- 58% at any time from pre- to 24m post-tx -23% pre-formed -26% negative pre- and positive post-tx -9% positive post- and unknown pre-tx	AT1R-Ab associated with allograft loss, decline in eGFR, elevated TNF-a, IL-1β, and IL-8, and glomerulitis or arteritis on biopsy.	No	[24]
62 pediatric KTRs followed for 60m	At time of indication biopsy > 12m post-tx, median time post-tx 53.5m (33.8-75).	9.5 U/mL	- 52% at time of indication biopsy	AT1R-Ab was associated with allograft loss, ≥ 50% decline in eGFR, HLA DSA Class II positivity, and elevated SBP. AT1R-Ab levels were higher in patients with AMR and ptc.	Yes	[26]
Liver						
81 pediatric LDLT patients who underwent IS withdrawal examined cross-sectionally	At time of protocol or indication biopsy, median time post-tx of 16.2 (5.1-22.5) years	17 U/mL	- 46% in the entire cohort - 65% in the advanced fibrosis group vs 36% in the control group	AT1R-Ab was significantly more frequent in the advanced fibrosis group vs. control.	Yes	[27]

Table 2:
Pediatric Case Reports describing AT1R-Ab in Solid Organ Transplant.

yo, years old; mo, months old; Cr, creatinine; POD, post op day; U, units; AMR, antibody-mediated rejection, IVIG, intravenous immunoglobulin; ACR, acute cellular rejection; m, months; HTN, hypertension; PP, plasmapheresis; OLT, orthotopic liver transplantation

Case Report	Timing and Level of AT1R-Ab	HLA DSA	Biopsy Findings	HTN	Treatment	Outcome	Ref No.
Kidney							
9yo Female with acute elevation in Cr on POD 5	Pre-tx: >40 U/mL Time of Rejection biopsy >40 U/mL	Yes, HLA DSA Class II	C4d positive AMR	Yes, severe causing encephalopathy	PP × 10, IVIG Rituximab Ramipril Irbesartan	Recovery. AT1R-Ab < 10 U/mL after treatment.	[32]
7 yo male with acute elevation in Cr on POD 15	Pre-Tx: 109.55 U/mL Time of rejection biopsy: 17 U/mL	No	ACR 1B with endarteritis C4d Negative AMR	Yes, mild, normalized with losartan	Pre-TX: PP, IVIG, Rituximab Rejection: PP Eculizumab (×1) Steroid Pulse ATG Losartan started POD 2.	Initially improving with treatment, but on POD 21 developed acute allograft thrombosis requiring allograft nephrectomy.	[33]
13 yo male with elevation in Cr on POD 10 and 3m post-tx	During rejection of 1st Tx: 128 U/mL Time of 3m rejection: 37 U/mL	No	POD 10: Weakly C4d positive AMR 3m post-tx: Weakly C4d positive AMR 8m post-tx: Weakly C4d positive AMR 11 m post-tx: No rejection	Yes, mild, normal with medications including Losartan started at 3m post-tx	POD 10: PP Steroid Pulse 3 mo post-tx Rituximab Losartan 8 mo post-tx: Increased Losartan	Stable at 3 years post-tx.	[34]
Liver							
6 mo with 2nd OLT with continued liver dysfunction	Throughout 2nd transplant course	Yes (weak HLA DSA on only 1 test)	Progressive injury suggestive of vascular compromise. Patient notably with history of severe hepatic artery stenosis	Not Discussed	IVIG Rituximab Bortezomib Plasmapheresis	Patient died on POD 144 from massive ascites and resulting respiratory compromise.	[36]