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The impact of non-HLA antibodies directed against endothelin-1 type A receptors (ETAR) on early renal transplant outcomes ☆☆

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ABSTRACT

Background: Non-HLA antibodies (Abs) targeting vascular receptors are considered to have an influence on renal transplant injury. Anti-endothelin-1 type A receptor (anti-ETAR) antibodies were associated with cellular and antibody-mediated rejection and early onset of vasculopathy in heart transplant patients but their role in renal transplantation remains unclear. The aim of our study was to assess the incidence and importance of anti-ETAR antibodies and their impact on renal transplant during the first year observation.
Methods: We evaluated the presence of anti-ETAR antibodies in 116 consecutive renal transplant recipients in pre- and post-transplant screening (before and in 1st, 3rd, 6th, 12th month after transplantation). Additionally, we assessed the presence of anti-HLA antibodies. Anti-ETAR antibodies were assayed by ELISA. The diagnosis of acute rejection was based on the Banff criteria.
Results: Anti-ETAR antibodies were observed in 55 (47.4%) of the analyzed recipients before transplantation. The function of renal transplant was significantly worse in the anti-ETAR(+) group compared to the anti-ETAR(−) group during the first post-transplant year. One month after transplantation the serum creatinine in anti-ETAR (+) patients (pts) was 1.86 ± 0.8 mg/dl and 1.51 ± 0.5 in anti-ETAR(−) pts ($p = 0.009$). Twelve months after transplantation the difference between the groups was still observed 1.70 ± 0.7 vs. 1.40 ± 0.4 ($p = 0.04$). Biopsy proven acute rejection was recognized in 8/55 (14.5%) in ETAR(+) and 9/61 (14.8%) in ETAR(−) patients but cases with mild to severe intimal arteritis (v1–v3) were more often observed in patients with the presence of anti-ETAR Abs 4/55 (7.2%) comparing with 1/61 (1.6%) in anti-ETAR(−) patients. The anti-ETAR antibody levels varied at different measurement intervals during the one-year follow-up.
Conclusions: The presence of anti-ETAR antibodies is associated with a worse renal transplant function during the first 12 months after transplantation. Including anti-ETAR antibodies in the diagnostics of renal transplant recipient immune status should be considered to provide comprehensive assessment of humoral alloimmunity.

1. Introduction

There is accepted evidence for an important role of anti-HLA antibodies (Abs) in acute and chronic rejection of renal transplant [1–7]. Humoral response to non-HLA antigens is primarily directed to antigens expressed on endothelial cells. The understanding of frequency and clinical importance of non-HLA antibodies production is incomplete [8]. The lack of knowledge is connected with the identity of non-HLA targets and validated diagnostic screening assays for non-HLA antibodies detection [1]. Endothelial cells of vessels may be the primary target for antibodies [9]. It has been mentioned that antigenic targets — two G-protein coupled receptors: angiotensin II type 1 receptor and endothelin type A receptor may have an important clinical significance in transplantation [10]. Dragun et al. described the role of anti-angiotensin II type 1 receptor antibodies (anti-AT1R Abs) in renal transplant damage [11,12]. We have noticed the importance of non-HLA antibodies long time after transplantation [13]. Elevated levels of anti-AT1R Abs and anti-endothelin-1 type A receptor antibodies (anti-ETAR Abs) were observed as associated with cellular and humoral rejection and early onset of microvasculopathy after heart transplantation [14]. We decided to verify the activity and incidence of anti-ETAR Abs in renal transplant recipients early after transplantation.

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Endothelin (endothelin-1, ET-1) is a vasoconstrictor peptide originated from endothelium. It was isolated from culture media of vascular endothelial cells (EC) [15]. There are three distinct ET isopeptides assayed — ET-1, ET-2 and ET-3 [16]. Because of a polymorphic nature of some of non-HLA antigens the way of sensitization may be analogous to that those of anti-HLA antibodies. Another other possibility is connected with injury. Under physiologic conditions antigenic determinants from targets for non-HLA antibodies are protected but become accessible after injury [17]. Liberation and presentation of non-HLA antigens at that time may induce an autoimmune response. Non-HLA antibodies may also occur secondary to immune activation or in connection with acute rejection [18]. Anti-ETAR Abs may also alone induce endothelial activation stimulating proinflammatory, proproliferative, and profibrotic response [19].

The aim of our study was to assess the incidence and importance of anti-ETAR antibodies and their impact on renal transplant during the first year observation.

2. Methods

We prospectively evaluated the presence of anti-ETAR antibodies in 116 consecutive renal transplant recipients in pre- and post-transplant screening (before and in 1st, 3rd, 6th, 12th month after transplantation). Additionally, we assessed the presence of anti-HLA antibodies. Anti-ETAR antibodies were assayed by ELISA (CellTrend). The presence of Anti-HLA antibodies was tested by the flow-PRA method (One Lambda). The diagnosis of acute rejection was based on the Banff criteria. Patients' characteristics were presented in Table 1. The immunosuppression consisted of: tacrolimus or cyclosporine, mycophenolate mofetil, steroids and occasionally basiliximab (Table 2). In case of acute rejection, the recipients received steroids. Patients' sera for the determination of antibody concentrations were obtained along the routine examinations. Venous blood was drawn into sterile 10 mL serum separator tubes. Samples were centrifuged at 1000 ×g for 15 min, serum was collected and stored at (−80 °C) until the day of measurement. The concentration of anti-ETAR IgG antibody in serum was measured by enzyme-linked immunosorbent assay using commercially available kits according to the manufacturer's instruction (CellTrend, Luckenwalde, Germany). The samples were assayed on endothelin-receptor A pre-coated microtiter plate. Standards and diluted 1:100 samples were added into the wells, and incubated for 2 h at the temperature of 2–8 °C. After washing steps, anti-ETAR antibody was detected with POD labeled anti-human IgG antibody (1:100) followed by color development with TMB substrate solution measured at 450 nm, with the correction wavelength set at 630 nm. Optical densities were then converted into concentration through standard curve. The positive detection range of the test was ≥2.5 U/mL and the negative one amounted to <2.5 U/mL.

There was no statistically significant difference considering recipients' and donors' age or gender, cold ischemia time, the number of HLA mismatches, the number of presensitized patients, immunosuppressive regiment or patients with the presence of anti-HLA antibodies between the groups. The ethical commission of the Wroclaw Medical University approved all study protocols and the informed consent was obtained from all the patients.

Table 1
Patient population characteristics (n = 116).

	Anti-ETAR(+) n = 55	Anti-ETAR(−) n = 61	p-Value
Recipients age (years)	44.6 ± 15	49.1 ± 14	NS
Male gender, n (%)	39 (70.1%)	34 (55.7%)	NS
Time on dialysis before transplantation (days)	1076 ± 1184	1217 ± 972	NS
First transplant	48	56	NS
Second/third transplant	6/1	5/0	NS
No of HLA mismatches	3.4 ± 1.4	3.5 ± 1.1	NS
No of presensitized patients	22/55	23/61	NS
PRA <10%	12	10	NS
PRA 10–50%	8	12	NS
PRA >50%	2	1	NS
Cold ischemia time (hours)	21.0 ± 8.2	21.4 ± 10.5	NS
Donor gender (%)			
Female	39	39.1	NS
Male	61	60.9	NS
Donor age (years)	47.0 ± 15.0	45.2 ± 16.4	NS
Delayed graft function (days)	7.1 ± 5.4	6.4 ± 7.6	NS
Cause of chronic renal failure:			
Chronic glomerulonephritis	17	16	NS
Diabetic nephropathy	4	5	NS
Hypertonic nephropathy	5	7	NS
Polycystic kidney disease	11	9	NS
Pyelonephritis	8	6	NS
Others	10	18	NS

HLA—human leukocyte antigen, PRA—panel reactive antibodies.

Table 2
Initial immunosuppression.

	Anti-ETAR(+) n = 55	Anti-ETAR(−) n = 61	p-Value
TAC-MMF/MPA + P	38	40	NS
CsA-MMF/MPA + P	17	21	NS
Simulect + TAC-MMF/MPA + P	3	5	NS
Simulect + CsA-MMF/MPA + P	1	0	NS

TAC—tacrolimus, MMF—mycophenolate mofetil, MPA—mycophenolic acid, P—prednizon, CsA—cyclosporin.

2.1. Statistics

Statistica version 10 was used for statistical analysis. Continuous data were presented as the mean ± SEM. The comparison between the groups was performed using a Student t-test and the Mann–Whitney *U* test for metric variables, while the chi-square test was used to identify a connection between acute rejection and the presence of antibodies. Univariate and multivariate logistic regression analyses were performed to evaluate the association of chronic rejection risk factors with anti-ETAR antibodies. The Fisher test was performed to assess the influence of anti-ETAR antibodies level on arteritis and chronic vasculopathy in the performed renal biopsies. The Spearman correlation was also performed to choose the anti-ETAR level.

p value below 0.05 was considered significant.

3. Results

Anti-ETAR antibodies were observed in 55 (47.4%) of the analyzed recipients before transplantation. The patients were divided into two groups: anti-ETAR positive (n = 55) and anti-ETAR negative (n = 61).

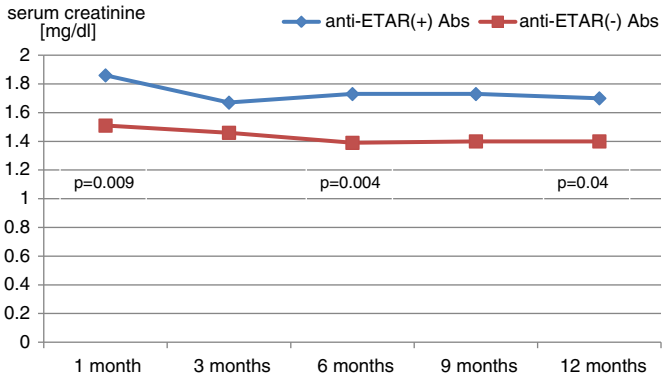

Fig. 1. Renal transplant function (serum creatinine) during one year after transplantation.

Table 3
Biopsy proven acute rejection, stages according to the Banff criteria.

	Anti-ETAR (+)	Anti-ETAR(−)
Acute rejection	8/55 (14.5%)	9/61 (14.8%)
IA, IB	3/55 (5.4%)	7/61 (11.5%)
IIA, IIB	4/55 (7.2%)	1/61 (1.6%)
AHR	1/55 (1.8%)	1/61 (1.6%)

IA, IB—cases with interstitial infiltration and tubulitis.
IIA, IIB—cases with arteritis.
AHR—acute humoral rejection.

The function of renal transplant was significantly worse in the anti-ETAR(+) group compared to the anti-ETAR(−) group during the first post-transplant year (Fig. 1). One month after transplantation serum creatinine in the anti-ETAR (+) patients (pts) was 1.86 ± 0.8 mg/dl and 1.51 ± 0.5 in the anti-ETAR(−) pts ($p = 0.009$). Twelve months after transplantation the difference between the groups was still observed 1.70 ± 0.7 vs. 1.40 ± 0.4 ($p = 0.04$).

Biopsy proven acute rejection was recognized in 8/55 (14.5%) in the ETAR(+) and 9/61 (14.8%) in the ETAR(−) patients (Table 3). Cases with mild to severe intimal arteritis (v1–v3) were more often observed in patients with the presence of anti-ETAR Abs 4/55 (7.2%), comparing with 1/61 (1.6%) in the anti-ETAR(−) patients but did not achieve statistical significance. Acute humoral rejection was diagnosed in 1 case in each of the observed groups. Four renal transplant recipients with Banff IIA or IIB acute rejection did not develop anti-HLA antibodies verified by flow cytometry during a one-year observation.

Arteritis and chronic vasculopathy were assessed according to anti-ETAR level (Table 6). The incidence of vasculopathy or arteritis among patients with anti-ETAR ≥ 2.5 U/mL was higher ($p = 0.0275$).

The mean level of anti-ETAR Abs in patients with acute rejection described as IIA and IIB according to Banff classification was 9.0 U/mL.

The association of chronic rejection risk factors with the presence of anti-ETAR was checked by univariate and multivariate logistic regression analyses (Table 4). We checked influence of a recipient's age or gender, the duration of dialysis treatment, the number of grafts, last or max PRA, the number of HLA mismatches or anti-HLA antibodies on the presence of anti-ETAR. The association of creatinine (6th and 12th month) with the presence of anti-ETAR was checked by univariate logistic regression with significant influence (Table 5).

4. Discussion

We have demonstrated that renal transplant patients have preformed non-HLA anti-ETAR antibodies and their presence has an influence on renal transplant function during the first year after transplantation.

Antibody mediated activity directed against a variety of non-HLA antigens is established in renal transplant recipients. Identified non-HLA targets include MICA [20,21], vimentin [22], angiotensin II type 1 receptor [12,23], tubulin [24], myosin [25], and collagen [26].

Vascular endothelium is thought to be a primary target of non-HLA antibodies [9]. The endothelium has a crucial location between the intravascular and interstitial compartment. It is responsible for the hemodynamics regulation, angiogenic vascular remodeling but also metabolic, synthetic and anti-inflammatory or antithrombogenic mechanisms [17]. Vascular abnormalities can be observed during acute but also chronic renal allograft rejection [27,28]. They are associated with glomerulopathy, fibrointimal hyperplasia of arteries and arteriolar hyalinosis. Such an injury is considered to be mainly an antibody-mediated injury response to mismatched immunogenic epitopes after renal transplantation. The role of donor specific anti-HLA antibodies in renal transplant damage is known, while the significance of non-HLA antibodies remains an unresolved concern [29–31]. Non-HLA antibodies both allo- or autoantibodies may also participate in the arterial wall structural injury, which supports clothing and/or narrowing. For instance, anti-angiotensin type 1 receptor (AT1R) antibodies may act as an allosteric activator similar to natural ligand for the AT1R [23]. Antigenic targets for non-HLA antibodies can be produced in activated or injured cells. Moreover, the cytokine mediated endothelial cell activation may also induce non-HLA response. Cytokine storm during brain death and inflammation associated with an ischemia–reperfusion injury can cause an increased expression of antigens and can stimulate the non-HLA antibody creation [17,32].

Anti-ETAR antibodies may alone induce endothelial activation [19]. The basic function of endothelin receptor is to promote vasoconstriction, growth and inflammation. Endothelins also support the growth and proliferation of vascular smooth muscle cells. The effect appears to be ETA receptor-mediated and involves not only the activation of mitogen-activated protein kinases but also the transactivation of epidermal growth factor receptor [33]. Endothelin receptors are pleiotropic and possibly activate proinflammatory, proproliferative and profibrotic responses as well [19].

Dragun et al. reported the presence of similar non-HLA, agonistic angiotensin type 1 receptor (AT1R) antibodies in 16 recipients of renal allograft who had severe vascular rejection [23].

They described the AT1-receptor activity in steroid-refractory, C4d negative renal allograft rejection in patients with hypertension. AT1-R antibodies can induce phosphorylation of ERK 1/2 in the cells of endothelium. The researchers indicate that binding AT1R Abs to the AT1 receptor is a critical step for the activation of the signaling cascade and the induction of a renal graft damage.

Hiemann et al. prospectively tested the influence of anti-ETAR and anti-AT1R antibodies in heart transplant recipients at the time of transplantation and in the first year after transplantation. They noticed that elevated levels of anti-AT1R Abs and anti-ETAR Abs are connected with cellular and humoral rejection and additionally with early onset of microvasculopathy [14]. Hiemann et al. noticed a strong correlation between anti-ETAR and anti-AT1R Abs levels at all time points monitored after heart transplantation ($r = 0.953$; $p < 0.001$). Dragun et al. discovered anti-AT1R antibodies which revealed arteritis and/or vascular necrosis in 16/33 renal recipients with vascular rejection in renal transplantation [11,23,34]. Recently it has also been discussed that antigenic targets — two G-protein coupled receptors: AT1 and ETA receptors may have an important clinical significance in transplantation [10]. To our knowledge we are the first who decided to check the influence of anti-ETAR antibodies on renal function in consecutive recipients and analyze the renal biopsy changes, especially in vessels. Knowing numerous studies of Dragun et al. and bearing in mind a high correlation of anti-ETAR and anti-AT1R antibodies in Hiemann et al. study we decided to examine the significance of anti-ETAR antibodies without anti-AT1R Abs. We supposed that endothelium antigens expressed on endothelial cells play an important role in vessel injury leading to vasculopathy and renal insufficiency.

Table 4
Risk factors for anti-ETAR.

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p	Coefficient	Std. error	p
Male Recipient	1.9357	0.8957–4.1832	0.0930	1.6409	0.6667	0.0138
Recipient's age	0.9819	0.9576–1.0068	0.1522	−0.0026077	0.023291	0.9109
Duration of dialysis	0.9999	0.9995–1.0002	0.5065	−0.00026903	0.00025924	0.2994
No. of grafts	0.9602	0.351–2.9258	0.9431	0.32830	1.07488	0.7600
Max PRA	1.0038	0.947–1.0338	0.8003	0.012329	0.025229	0.6251
No. of MM HLA ABDR	0.9121	0.6778–12273	0.5433	−0.13636	0.27062	0.6144
anti-HLA Abs	0.8164	0.3294–.0234	0.6614	0.36312	0.72378	0.6159

OR—odds ratio, PRA—panel reactive antibodies, MM—mismatch, No.—number, HLA ABDR—human leukocyte antigen A, B, DR, Abs—antibodies.

Table 5
The association of creatinine (6th and 12th month) with the presence of anti-ETAR (univariate logistic regression).

Parameter	Coefficient	Std. error	p-Value
Anti-ETAR (creatinine 6th month)	0.3307	0.1055	0.0024
Anti-ETAR (creatinine 12th month)	0.2988	0.1296	0.0239

We decided to check the impact of anti-ETAR Abs in 116 consecutive renal transplant recipients in pre- and post-transplant screening. The function of renal transplant function was significantly worse in patients with anti-ETAR activity comparing to anti-ETAR negative patients. We have also noticed a more often delayed graft function in patients with anti-ETAR Abs (25.4% vs.11.5%).

The presented data support the concept of non-HLA pathways being an important trigger of transplant injury. Patients with anti-ETAR activity may present vascular injury more frequently than patients without anti-ETAR activity after heart transplantation [14]. Renal transplantologists should also consider endothelial activation and dysfunction in the pathogenesis of renal allograft injury. Abs directed against endothelin-1 type A receptor (ETAR) may alone induce endothelial activation and damage of renal transplant. In our patients with anti-ETAR Abs four of them developed changes characteristic of vascular damage with mild to severe arteritis (Banff IIA, IIB) previously described as vascular rejection. It should be emphasized that more cases of vasculopathy or arteritis were observed in patients with anti-ETAR $\geq$ 2.5 U/mL ($p = 0.0275$).

Recently two interesting studies describing the non-HLA role after renal transplantation have been published. Giral et al. noticed the important role of pretransplant anti-AT1R Abs as an independent risk factor for long-term graft loss in association with a higher risk of early AR episodes [35]. The study included 599 kidney recipients whose pretransplant sera were examined for the presence of anti-AT1R Abs using a quantitative solid-phase assay. Taniguchi et al. tested anti-AT1R Abs and DSA (anti-HLA) in pre- and posttransplant sera from 351 consecutive kidney recipients. Patients with both anti-AT1R and DSA had lower graft survival than those with DSA alone [36]. The confirmation that non-HLA antibodies are associated with graft injury is increasing but the exact triggers for this response and the impact on graft injury remain unclear [37]. Non-HLA Abs induced by transplant have been described for all solid organ allografts with incidence ranges from 10% to 100% of recipients [37]. An important issue of transplant associated humoral immunity is how non-HLA antibodies participate in the development of allograft vasculopathy. A stronger effect, acute vascular rejection and malignant hypertension in renal transplant recipients have been described with the presence of anti-AT1R antibodies [23] but also in our observations. Vascular injury, mild to severe intimal arteritis (v1–v3) were more often observed in the patients with the presence of anti-ETAR Abs 4/55 (7.2%) comparing with 1/61 (1.6%) in the anti-ETAR(−) patients (Table 2). However, the incidence of non-HLA antibody mediated acute vascular rejection may be critical but not a major clinical problem after renal transplantation. Antibody mediated non-HLA immunity due to its chronicity can have an important impact on gradual progression of allograft vasculopathy and chronic allograft injury [31,38,39].

Table 6
The presence of arteritis or vasculopathy in renal biopsy in patients with anti-ETAR antibodies.

	Anti-ETAR antibodies level	
	<2.5 U/mL	≥2.5 U/mL
a) Arteritis		
Cases with arteritis	1	4
Cases without arteritis	8	4
	Significance level $p = 0.13$	
b) Chronic vasculopathy		
Cases with chronic vasculopathy	1	6
Cases without chronic vasculopathy	8	2
	Significance level $p = 0.015$	
c) Arteritis or chronic vasculopathy		
Cases with arteritis or chronic vasculopathy	7	1
Cases without arteritis or chronic vasculopathy	2	7
	Significance level $p = 0.0275$	

Non-HLA antibodies which target vascular receptors (anti-AT1R Abs and anti-ETAR Abs) increase alloimmune activity and microvasculopathy after transplantation of a heart (HTx) [14]. Patients after HTx with elevated anti-AT1R (53%) or ETAR Abs (50%) developed microvasculopathy more often (67% vs. 23%) comparing to patients without it [14]. These observations allow putting forward a conclusion that elevated levels of anti-AT1R and anti-ETAR Abs are associated with cellular and humoral rejection and microvasculopathy and thus should be regularly monitored after heart transplantation [14].

We realized that we were not able to indicate how high the level of Abs which may surely trigger graft injury should be, but we showed that the 2.5 U/mL cut-off determined a worse graft function and more cases of vasculopathy or arteritis. We analyzed the results repeatedly at different times: before transplantation and then in 1st, 3rd, 6th, 12th month after transplantation. If the result before was <2.5 U/mL, it was very rarely observed higher in 1st, 3rd, 6th, 12th month after transplantation, but if the result was ≥2.5 U/mL before transplantation it was susceptible to changes after transplantation and very often reached even more than 10 U/mL. Such findings led to performing the analysis for different levels and finally resulted in noticing the biggest significant difference in transplant function (Fig. 1) but also more cases with vasculopathy or arteritis ($p = 0.0275$) when the level of anti-ETAR was ≥2.5 U/mL. The Spearman correlation test additionally confirmed the significant difference in renal function.

The relationship between non-HLA antibodies and graft failure does not automatically mean that antibody is responsible for graft injury. It may specify nonpathogenic “spectator” activation that is triggered by aggressive immune response. There are two elementary deliberations which determine whether humoral immunity stimulates allograft rejection or not: expression of target antigens on graft and the possibility of triggering injury during Abs ligation.

The mechanism of triggering vasculopathy can be considered as cell lysis or endothelial cells activation [37]. Cultures with antiendothelial antibodies may induce endothelial cell (EC) apoptosis [40]. It can be stimulated in the absence of complement, which is suggested by direct signal transduction but binding of antibody to EC may also interact with complement (C1q component) to activate the classical pathway. The membrane attack complex (MAC) kills target EC through necrosis or apoptosis [37,41]. Another other mechanism for triggering vasculopathy is through intracellular signaling cascades activating EC which can involve tyrosine phosphorylation of focal adhesion kinase, upregulation of Rho proteins and activation of Mammalian target of rapamycin pathways [42–44]. Focal adhesion kinase and the Rho family proteins participate in fiber formation and cytoskeletal organization, which might be the explanation why binding of alloantibodies induces EC proliferation [44,45]. Rho kinase inhibitor therapy blocked vasculopathy development in a mouse after HTx model [46].

Hiemann et al. observed that a significant proportion of patients with elevated anti-AT1R Abs and anti-ETAR Abs developed microvasculopathy in biopsy already in the first year after HTx. Microvasculopathy is characterized by a proliferation of vascular smooth muscle cells and vascular remodeling of capillaries [47,48]. ETAR antibodies are expressed not only on vascular cells but also in cardiomyocytes, fibroblasts, and immune cells [49]. Hiemann et al. even cautiously suggest that not only AT1R, but also ETAR Abs can function not only as EC Abs but also part of high-risk immunologic profile capable of triggering an alloimmune response [14].

Endothelial dysfunction together with alloimmune reaction might cause earlier onset of microvascular remodeling [14]. The significance of ETAR Abs may be supported by research which shows that ETAR antagonist LU 302146 (LU) not only abrogated chronic transplant vasculopathy model in rats but also attenuated chronic transplant nephropathy in the Fisher-to-Lewis rat model [50,51].

The collapse of B-cell self-tolerance seems to be crucial in understanding chronic rejection injury [10]. Presentation of antigens in various cell stress conditions may induce an autoimmune response. Inflammatory events connected, among others, with ischemia or anti-HLA activity may direct to de-novo expression of autoantigens and a loss of tolerance [52]. Further research is required to confirm our findings and establish diagnostic or maybe even targeted therapies in the future. Pharmacologic antagonists at the ETAR are applied in pulmonary arterial hypertension treatment but also tested in other diseases. Plasmapheresis or immunoadsorption are known and approved in the reduction of antibodies titers [10].

Our analysis showed that the presence of anti-ETAR antibodies is linked with a worse renal transplant function during the first 12 months after transplantation and also revealed more cases with mild to severe intimal arteritis in pts with anti-ETAR antibodies. Including anti-ETAR antibodies in diagnostics of renal transplant recipient immune status should be considered for comprehensive assessment of humoral alloimmunity.

The study suggests monitoring of ETAR antibodies before and after renal transplantation for the purpose of further assessment of immunologic risk profiles and the identification of patients highly susceptible to immunologic events, glomerulopathy and graft loss.

In conclusion, anti-ETAR antibodies targeting vascular receptors may be useful as novel biomarkers for the detection of renal transplant recipients at risk of alloimmune activity. The detection and monitoring of anti-ETAR antibodies might help in the overall immunological assessment.

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