Journal of Clinical and Experimental Transplantation

El Hennawy, J Clin Exp Transplant 2018, 3:2
DOI: 10.4172/2475-7640.1000125

Review Article Open Access

Non-HLA Antibodies in Renal Transplantation, Where Do We Stand?

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Abstract

Objective: This review discusses current findings in the subject and addresses the clinical relevance of Non-HLA antibodies.

Methods: This traditional narrative review used PubMed and Medline searches for English language reports on Non HLA abs during last 20 years. The search included the key words: non-human leukocyte; antibodies; kidney; transplantation.

Results: 65 related articles and review were found.

Conclusion: Non-HLA immunity is associated with poor graft survival, rejection and chronic graft loss. Moreover, they could be used as biomarkers of ongoing immune response and as predictors of graft failure.

Keywords: Non-human leukocyte; Antibodies; Kidney; Transplantation

Abbreviations: Abs: Antibodies; AEPCA: Anti-Endothelial Precursor Cell Antibodies; AECA: Anti-Endothelial cell Antibodies; AMR: Antibody-Mediated Rejection; Anti-Col: Anti-Collagens; AT1R: Angiotensin II Type 1 Receptor; Anti-Ka1 tubulin: Anti-Tubulin ; AVA: Anti-Vimentin Antibody; C4D: Complement Component 4d; DSA: Donor-Specific Antibodies; EC: Endothelial Cell; ELISA: Enzyme-Linked Immunosorbent Assay; ETAR: Endothelin-1 Type A Receptor; FSGS: Focal Segmental Glomerulosclerosis; HLA: Human Leukocyte Antigen; MHC: Major Histocompatibility Complex; MICA: Major Histocompatibility Complex Class I Chain-Related Gene A; Non-HLA abs: Non-Human Leukocyte antibodies; XM: Crossmatch

Introduction

Non-HLA antigens include antigens expressed on endothelial, epithelial cells, parenchymal cells and circulating immune cells [1-3]. Non HLA abs can be directed against auto- or allo-antigens and be either present pre-transplant or *de novo* formed post transplantation [3]. Furthermore, The most reported Non-HLA abs include those directed against Angiotensin II Type 1 Receptor (AT1R-Ab), Endothelin Type A Receptor (ETAR), MHC Class I Chain-Related Antigen A (MICA-Ab), Vimentin (AVA), Tubulin (anti-Ka1 tubulin), Collagens (anti-Col) Anti Endothelial Cell Antibodies (AECA), anti-heat shock protein, and anti-phospholipid (Table 1) [4,5].

Moreover, the triggers of activation or transition of these Non-HLA abs toward pathogenicity are likely acute rejection, hypoperfusion, ischemia reperfusion, calcineurin toxicity, infection, and recurrent diseases [6].

Non-HLA abs have a stronger role in graft dysfunction and rejection; Antibody-Mediated Rejection (AMR) or C4d deposition in the absence of circulating donor specific Non-HLA abs than previously thought [1,5-7]. The aim of this review is to shed light on Non-HLA abs development, mechanism of action, clinical relevance, and treatment.

Mechanism of NON-HLA antibodies production

Injury of graft endothelium by Non HLA abs can lead to exposure of neo-antigens which consecutively stimulate the production of antibodies against non-HLA antigens [1,4,5,7-9]. Furthermore, Cytokine storm during brain death and inflammation associated with an ischemia–reperfusion injury, vascular injury, and/or rejection may cause increased expression of cryptic autoantigens, and may stimulate Non-HLA abs production. Additionally, immune activation, tapered immunosuppression in transplant recipients may stimulate Non HLA abs production [10].

However, several studies reported other ways of Non-HLA abs development other than sensitization [1,11-13]. For example, an A5.1 mutation in the donor, which is related to the MICA*008 allele, is associated with a strongly increased MICA expression on donor endothelial cells compared to wild type donors and therefore these mutated MICA molecules are important targets for antibody formation [14]. Additionally, mismatching on certain amino acid residues leads to increased MICA antibody formation and it can be that based on the 3D-structure of MICA, these structures are more accessible for antibodies [1,13].

HLA antibodies and NON-HLA antibodies correlation

Conversely, inflammatory response induced by Non-HLA abs could sequentially upregulate HLA expression, increase the risk for a patient to develop HLA-specific antibodies and thus make the allograft more susceptible to an allo-immune response involving both humoral and cellular [1,2,4,5,8,15].

Numerous studies showed that patients with both HLA and non-HLA antibodies had lower graft survival rates compared to patients with either one of them [16]. It is assumed that HLA and non-HLA

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Received November 25, 2018; **Accepted** December 18, 2018; **Published** December 26, 2018

Citation: El Hennawy HM (2018) Non-HLA Antibodies in Renal Transplantation, Where Do We Stand?. J Clin Exp Transplant 3: 125. doi: 10.4172/2475-7640.1000125

antibodies have a synergistic effect [4,15].

Non-HLA antibodies incidence and pathogenicity

Non-HLA abs may function as complement- and non-complement-fixing antibodies and they may induce a large variety of allograft injuries, reflecting the complexity of their acute and chronic actions [17].

Complement-dependent and complement-independent mechanisms are not mutually exclusive [8,18]. For example, Anti-Vimentin Antibodies [AVA] seem to fix complement [19]. Similarly, MICA Abs have been shown to be more efficient at complement activation and have been associated with C4d ▪ AMR [2]. In contrast, 40%-50% of cases with severe vascular changes such as fibrinoid necrosis are C4d-negative, implicating involvement of either non-complement-fixing antibodies or other mediators, as noticed in of cases of AMR in the presence of AT1R-Ab or AECA that occurred without evidence of complement activation [2, 20,21].

Besides, antibodies can induce lysis of target-cells with membrane bound antibodies through activation of natural-killer cells, a process called antibody-dependent cell mediated cytotoxicity [1,22]. Furthermore, Non-HLA abs may also contribute to short and long-term structural changes in the arterial wall or duct epithelia that promote clotting or/and narrowing [8].

Additionally, The capability of Non-HLA abs to mediate allograft injury may depend on their specificity and affinity, density of the target antigen, and synergy with HLA antibodies [2].It is unlikely that Non-HLA abs can directly induce major graft damage since hyperacute rejection induced by these antibodies rarely occurs (Table 2) [23-37].

Non-HLA Antibodies as Biomarkers of Injury

On the other hand, other studies claimed that Non-HLA abs may represent a marker for injury or humoral activation rather than having independent pathogenic potential [2,11]. Therefore, in the near future, Non-HLA abs may be used as biomarkers of ongoing immune response and herald the need for more suitable immunosuppression [8].

Compartment specificity

Non-HLA immune responses, including anti-MICA antibodies, were detected against kidney compartment-specific antigens, with highest post-transplant recognition for renal pelvis and cortex specific antigens (78%). The compartment specificity of selected antibodies was confirmed by IHC [7].

Targets for Non-HLA Antibodies
• Major histocompatibility complex class I chain-related gene: A (MICA), B (MICB) • Antibodies against G Protein-Coupled Receptors (GPCRs): AT1R (Angiotensin II type 1 receptor) and Endothelin-1 type A receptor (ETAR) • Antiendothelial cell antibodies (AECAs) • Anti endothelial precursor cell antibodies (AEPCA) • LG3 (Perlecan) • Intercellular adhesion molecule 4 (ICAM4) • Anti-GBM Glomerular basement membrane (GBM) • Antivimentin*: Intermediate Filaments – Vimentin* (AVA) • Duffy antibody (a chemokine receptor) • Agrin antibody • Fibronectin and • Anti collagen IV antibodies (anti-Col) • Myosin antibody • Anti-Ka1 tubulin antibody • Anti heat shock protein • Anti-phospholipid

Table 1: Targets for Non-HLA Antibodies.

Non HLA Antibodies Incidence and Mechanism of Action		
Antibody	**Incidence**	**Mechanism of Action**
Major histocompatibility complex class I chain-related gene A (MICA)	*13.9% and 5.4% pre and post-transplant, respectively [25].	*Complement-activating antibodies (fix C1q) [2,23]. *Activate NK cell *via* MICA/NKG2D interactions with subsequent cytotoxic proteins and IFN-γ release [26].
Angiotensin II type 1 receptor (AT1R) AT1R	*22% [27], 23% [28], 47%[29] and 59% [30] using a cutoff ≥ 9 units/ml. *Higher rate of AT1R-Ab positivity in patients with previous transplants [31].	*Activate complement independent pathways. In addition, increased tissue factor expression and thrombotic occlusion [18,23]. *Induce Erk1/2 signal transduction cascade that directly affect endothelial and vascular smooth muscle cells [23]. *Increase DNA binding activity of NF-B transcription factor, and increase expression of NF-B proinflammatory target genes such are chemokines 1 and RANTES [23].
Endothelin-1 type A receptor (ETAR)		*Damaging endothelial cells and increasing downstream effectors of GPCR signaling. *Cause obliterative vasculopathy and progressive tissue fibrosis [32].
Antiendothelial cell antibodies (AECAs)	*23 % [1,7] *In 50% of renal patients who had DSA to HLA [1,7]. *Higher rate of AECA positivity was found in patients with failed renal transplants [1,7].	*Activate endothelial cell and produce of inflammatory cytokines [2,3]. * Increase HLA expression on endothelial cells, which may explain the severity of antibody-mediated injury in recipients when both AECAs and HLA-DSA were detected [2]. *Lead to AMR by activating complement [34].
LG3 (Perlecan)		*Cause vascular injury and neointimal formation. *Elicit humoral immune responses that accelerate immune-mediated vascular injury [35].
Intercellular adhesion molecule 4 (ICAM4)		*Activate Erk-mitogen-activated protein kinase pathway. * Activate endothelial cell *via* induction of downstream proinflammatory signaling pathways [36].
Anti-GBM		*Targeting perlecan *via* proteolysis and degradation of perlecan induce profound changes in its biological activity [37].

Table 2: Non HLA antibodies incidence and mechanism of action.

Clinical relevance of Non-HLA antibodies in renal transplantation

Non-HLA immunity has a much stronger role in clinical transplantation than previously thought. 10% of cases with C4d positivity fail to show circulating anti-HLA antibody is suggestive that Non-HLA abs also are to be considered [38]. In contrast to immunity against HLA mediated by antibodies present before transplantation, which leads to early acute graft rejection, non-HLA immunity is associated with chronic graft loss [39]. Moreover, the influence of non-HLA directed immunity was of similar magnitude to that of antibodies against HLA on long term follow up (Table 3) [39].

Clinical Relevance of Non-HLA antibodies	
Antibody	**Clinical Relevance**
Antivimentin (AVA)	*Expression increases during rejection [2]. *Post-transplant development of IgG AVA was a risk factor associated with chronic injury such as interstitial fibrosis and tubular atrophy [27, 40-41].
Major histocompatibility complex class I chain-related gene: A (MICA)	*Correlated with rejection (acute and chronic) and poor allograft survival (only significant in low immunological risk transplantations: well matched for the HLA) [1,7,42,44] * Contrary to expectations, patients with positive pretransplant MICA antibodies had superior death-censored renal allograft survival when compared with MICA-negative patients [1].
Anti-endothelial precursor cell antibodies (AEPCA)	*Strongly associated with acute rejections and increased serum creatinine levels at 3 and 6 months post-Tx [45].
Angiotensin II type 1 receptor (AT1R)	*Associated with a higher incidence of graft loss [1,28,49], severe rejection [chronic and acute rejection (AMR and cellular mediated) and malignant hypertension [7,27,29,46]. *Patients with bothAT1R-Ab and HLA-DSA had greater incidence of allograft damage and graft loss [29,46-47]. *Patients with anti-AT1R Abs level >9 U/ml run a higher risk of graft failure independently of classical immunological risk factors [28]. *Patients with both anti-AT1R and DSA had lower graft survival than those with DSA alone [48].
Endothelin-1 type A receptor (ETAR)	*Associated with a higher incidence of graft loss and rejection during the first post-transplant year [1,5,49]. *Vasculopathy or arteritis were observed in patients with anti-ETAR ≥ 2.5 U/mL (p=0.0275) [5].
Duffy antibody (a chemokine receptor)	*Associated with chronic renal allograft histological injury [7].
Agrin antibody	*Associated with transplant glomerulopathy [7].
fibronectin and collagen IV antibodies	*A significant risk factor for development of transplant glomerulopathy, a chronic lesion characterized by duplication of glomerular basement [27,50].
Antiendothelial cell antibodies (AECA)	*AECAs are a risk marker for acute rejection [51] *associate with both severe rejection (cellular mediated rejection and (AMR)) in kidney transplant recipients [2,52]. *high prevalence of C4d negative microcirculation injury [53].

Table 3: Clinical relevance of non-HLA antibodies.

Non-HLA antibodies monitoring and graft failure prediction

Many of the late graft failures attributable to non-HLA effects might be preventable [39]. The possibility of identifying recipients at increased risk of late graft loss before transplantation could be used to fashion specific immunosuppressive strategies for these patients [39-54]. For instance, the detection of anti-AT1R Abs seems to be a complementary risk factor for the identification of patients with higher immunological risk. Moreover, Banasik et al. proved that the occurrence of pre-transplant anti-AT1R Abs >9 U/ml is an independent risk factor for graft failure [28,29]. Therefore, monitoring for Non HLA abs should mirror that performed for HLA-DSA to identify those high risk patients [2].

Other possible uses of Non-HLA antibodies

Pre-transplant auto-antibody titers could have implications in terms of organ allocation. For instance, avoid use of organs with expected long cold ischemic time or coming from a donor after cardiocirculatory arrest for patients with elevated pre-transplant autoantibody titers [10].

Furthermore, Pre-transplant autoantibody levels could be added to the current clinical and laboratory variables used to assess the risk of rejection or delayed graft function, which in turn, could help transplant physicians select the most appropriate induction therapy [10]. For example, Pre-transplantation screening of recipients for AT1R-Abs may help to improve individual risk assessment and offer patients with AT1R-Abs preemptive specific treatment. Unfortunately, early AMR due to non-HLA antibodies is rare and seems difficult to predict by currently available assays including the AT1R-Ab-ELISA [53].

Who should be tested for Non-HLA antibodies?

Philogene et al. suggested performing pre-transplant Non HLA abs testing and post-transplant monitoring for high risk group of patients [2]. The risk factors include re-transplanted, male gender, young age, and those with FSGS at time of transplantation were positive for AT1R-Abs and AECAs prior to transplantation [2]. Furthermore, testing for non-HLA antibodies is often performed when histological evidence suggests an antibody mediated process in the absence of HLA-DSA [2].

Non-HLA abs and Pediatric age group

Chaudhuri et al. reported that 24% of children with renal transplant have *de novo* antibodies, mostly directed against HLA. 6% of *de novo* antibodies were DSA Ab and 6% anti MHC class 1 related chain A (MICA), and were equally found either on steroid-free or steroid-based regimens. The presence of anti HLA and anti-MICA Ab was significantly associated with acute and chronic rejection with faster graft loss [54].

Interestingly, Matthew et al. reported a case of hyperacute rejection in 17 month old boy due to non-HLA antibodies. Pre-transplant Single antigen testing confirmed the absence of Donor Specific HLA Abs (DSA). Moreover, initial, final flow cross matches and 2 days post-Txp HLA-DSA were negative. Pre-Txp (pre-14 days) and post-Txp (post-24 days) samples were sent out for AT1R Abs screening and donor specific endothelial cell crossmatch (XM-One). The XM-One assay using endothelial precursors isolated from the donor as targets was strongly positive using a pre-Txp serum but negative using post-Txp serum. Approximately two month's post-Txp, the patient developed HLA Abs, on top of the AT1R antibodies [55].

Detection of Non-HLA Antibody

Considering the technical difficulties of current Non-HLA abs assays and the large variation in reported incidences of antibodies even with the same assays, continuous efforts to develop reliable and sensitive diagnostic tests are essential. Besides, measuring a panel of antibodies instead of one antibody at a time will provide valuable information regarding the role of Non-HLA abs in rejection and could eventually help identifying different risk profiles for rejection and impaired graft survival [1].

Currently, Non-HLA abs can be reliably detected by solid-phase assays (antibodies targeting G protein-coupled receptors (angiotensin type 1 receptor), MICA, collagen-V, vimentin), immunofluorescence

Non HLA Detection	
Antibody	**Test**
AT1R	Single plex ELISA [100% specificity and 88% sensitivity] [9]
ETAR	Single plex ELISA [9]
MICA	Single antigen Luminex assays [9]
AECA	* Indirect immunofluorescence HUVECs test. * Flow cytometry endothelial crossmatch test (ECXM) [62]
Anti-endothelial precursor cell antibodies(AEPCA)	Endothelial precursor cell crossmatch [45]
Multiple non-HLA Antibodies	*Luminex based assay [4] *Multiplex solid-phase assays [9]

Table 4: Non HLA detection.

(antibodies against antigens expressed on umbilical vein endothelial cells), ELISA or flow-crossmatch techniques (antibodies against donor endothelial progenitors) (Table 4) [3].

At present, use of both ELISA and cytotoxicity assays in parallel for pre-transplant testing seems judicious to allow a separation of anti-HLA from anti-non-HLA activities [14].

Current Treatment Modalities for Pathogenic Non-HLA Antibodies

The presence of Non-HLA abs are not an absolute contraindication to transplantation, but rather may suggest previous or ongoing tissue injury, and may be useful in identifying patients who should be treated either prior to transplantation or post-transplantation to avoid graft injury [2].

Furthermore, immunologic risk stratification before transplantation, by comprehensive diagnostic assessment strategies focusing on both HLA-DSA and Non HLA abs responses, could help to better define sub-phenotypes of antibody-mediated rejection, or delayed graft function, and lead to timely initiation of targeted therapies [10]. Accordingly, early treatment of patients with increased immunologic risk factors and with circulating Non HLA abs is required [2].

Treatment to reduce levels of Non HLA abs is similar to what is commonly used for HLA antibodies (intravenous immunoglobulin, plasmapheresis, rituximab, and bortezomib) [56]. However, Combination therapies with Plasmapheresis (pre- and/or post-transplant), intravenous immunoglobulin (100mg/kg) and rituximab may lead to more durable antibody elimination [2,9,57].

Angiotensin receptor blockers such as losartan have also been used to block the activity of angiotensin receptor in patients with AT_1R-Ab-mediated rejection [54,57]. However, a more recent study shows that chronic use of losartan can upregulate AT1R expression resulting in worse outcomes [58].

Recently, bortezomib was used to block the production of anti-LG3 auto-antibodies triggered by exosome-like vesicles may prove useful to help define therapeutic options for preventing auto-antibody production before transplantation [10,59].

Conclusions

The role of Non-HLA abs in renal transplantation is progressively being recognized. Non-HLA immunity is associated with poor graft survival, rejection and chronic graft loss. Moreover, they could be used as biomarkers of ongoing immune response and as predictors of graft failure. Therefore, they may herald the need for more suitable immunosuppression. Strong efforts to investigate Non HLA abs and their effect on graft outcome are still ongoing.

Disclosure

The author declared no competing interests.

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