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Angiotensin II type-1 receptor antibody (AT1Rab) associated humoral rejection and the effect of peri operative plasma exchange and candesartan

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ABSTRACT

Angiotensin II type 1 antibodies (AT1Rab) can mediate antibody mediated rejection (AMR). Pre transplant AT1Rab levels, and risk of rejection were assessed in Kidney Transplant Recipients (KTR) transplanted in our centre from 2013 to 2014 (n = 145). 14/145 (9.7%) KTR experienced antibody mediated rejection (AMR). The Hazard Ratio for AMR = 3.7 [95% CI 2–26] (p = 0.009) for KTR with AT1Rab levels >17.5 U/ml. 6/11 of KTR with levels >25 U/ml experienced AMR.

In 2015 (n = 80) KTR were transplanted and 6/80 KTR experienced rejection (2 AMR and 4 TCMR with vascular lesions). 7/80 of KTR had AT1Rab 17.5–25 U/ml and none experienced rejection and were induced with ATG and candesartan. 7/80 had AT1Rab 25–40 U/ml and received pre and post-operative plasma exchange, ATG and candesartan and 1/7 experienced TCMR with a vascular lesion.

This perioperative regimen may alter the risk of rejection in patients with high levels of AT1Ab and further studies are needed.

1. Introduction

Transplantation across a negative complement dependent cytotoxicity (CDC) cross-match, in the presence of anti-Human Leucocyte Antigen (HLA) Donor Specific Antibodies (DSA) is associated with inferior graft survival and antibody mediated rejection (AMR) compared to transplantation where DSA are not present [1–3]. However, acute humoral rejection or AMR may occur in HLA identical transplantation [4] and it has been proposed that non-HLA antibodies, such as anti-angiotensin II type-1 receptor antibodies (AT1Rab) may mediate AMR. The observation of AT1Rab causing acute humoral rejection with a vascular component was first described by Dragun et al. in 2005 [5] and they have now been associated with any rejection type and graft failure independent of HLA mismatch or DSA [5–8].

The angiotensin II type-1 receptor (AT1R) is a G-protein coupled receptor that can be activated by angiotensin II and can be stimulated by agonistic AT1Rab [5]. AT1Rab activate the AT1R and the downstream effects are to activate nuclear factor-κβ, inducing an inflammatory response [5]. It has been hypothesised that ischaemia-reperfusion injury increases the expression of donor AT1R on vascular smooth-muscle and endothelial cells, predisposing the graft to injury by pre-existing AT1Rab [9]. Binding of an AT1R antagonist such as a sartan to AT1R changes its conformation and prevents the binding of AT1Rab. This is the rationale for using sartans together with plasma exchange and Antithymocyte globulin (ATG) to treat AMR mediated by AT1Rab.

Abbreviations: AMR, antibody mediated rejection; ATG, anti-thymocyte globulin; AT1R, angiotensin II type 1 receptor; AT1Rab, angiotensin II type 1 receptor antibody; AUC, area under the curve; CDC, complement dependent cytotoxicity; DSA, donor specific antibody; HLA, human leukocyte antigen; KTR, kidney transplant recipient; MFI, mean fluorescence index; ROC, receiver operator characteristics; TCMR, cell mediated rejection.

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We retrospectively analysed Kidney Transplant Recipients (KTR) from our centre to determine whether the presence of pre-transplant AT1Rab was associated with AMR and TCMR as define by Banff Classifications [10].

2. Materials and methods

From 2013 to 2014 there were 163 KTR transplanted at our centre. Eighteen KTR were excluded because they received pre-emptive plasma exchange and IVIG to achieve a negative cross-match after DSA (MFI >4000) were detected (Fig. 1). The remainder (n = 145) were transplanted across a negative T and B cells cross match and in 16/145 (11%) patients there was at least one DSA (MFI 1500-4000) that did not require the KTR to undergo pre-emptive plasma exchange and therefore were included in the study. 9 of these 16 sensitized KTR received ATG induction and the remainder together with DSA negative patients received anti-IL-2R alpha antibodies. During the period between 2013 and 2014 there were 44 biopsy proven rejection episodes, including 30 TCMR and 14 AMR (Fig. 1). There were 5 KTR with AMR that concurrently had sufficient interstitial infiltrate and tubulitis scores to fulfil TCMR criteria (Banff 13), these KTR were classified as AMR when analysing AT1R effects on AMR and TCMR.

Although a negative value in the ELISA used to measure AT1Rab is defined as <2.5 U/ml literature suggests KTR with, AT1Rab levels >10 U/ml can be considered at increased risk of any rejection and KTR with levels >17.5 U/ml are consider at higher risk of AMR. Based on the high levels of AMR and TCMR with vascular lesions (Banff 2A/2B) in patients with high levels of AT1Rab in the 2013–2014 cohort, we instituted a change in practice for those patients transplanted in 2015. All patients with AT1Rab >17.5 U/ml were treated with three doses of ATG (total dose 3–4.5 mg/kg) instead of our standard unit policy of anti-IL-2R alpha antibodies and were given pre and post operative candesartan (between 4 and 16 mg per day as tolerated). For KTR with AT1Rab >25 U/ml the above procedure was followed with the addition of 1 plasma volume, plasma exchange pre-op and two plasma exchanges post op.

In 2015 (85 patients were transplanted), three patients with AT1Rab 17.5, 20 and 21 U/ml were not treated per protocol: two developed AMR; and one vascular rejection. 2 patients received Eculizumab (AT1Rab 19 and 6 U/ml) and neither experienced rejection. These 5 KTR were excluded from the subsequent analysis.

DSA were assessed in all KTR in routine pre-transplant sera and at 14 and 28 days post transplant. In addition KTR experiencing rejection or acute graft dysfunction also had sera tested for *de novo* DSA. DSA were detected by first using a Lifecodes LifeScreen, Class I and Class II Identification Kit (Immucor Transplant Diagnostics, GA, USA) to identify any anti-HLA antibodies, if positive a secondary test using a Lifecodes single antigen (Class I and Class II) beads (Immucor Transplant Diagnostics) was performed to identify antibody specificity. Both these kits were performed following the manufacturers protocols. DSA positivity was determined by a Mean Fluorescence Index (MFI) $\geqslant$1500 as measured by a Luminex platform. Anti-AT1R antibodies were measured pre transplant and at time of rejection using an ELISA Immunoassay kit (One Lambda, Canoga Park, CA, USA) following published protocol (Reinsmoen NL, 2010) and performed by the Australian Red cross Blood service (ARCBS) in Adelaide.

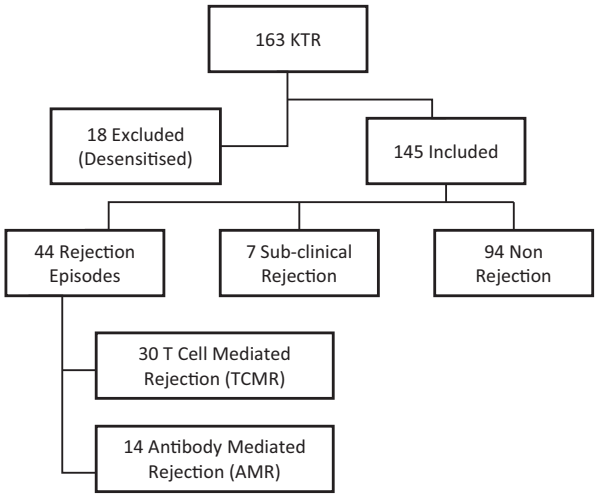

Fig. 1. Flow diagram of Kidney Transplant Recipient (KTR) Included and Excluded from study: There were 163 KTR entries between 2013 and 2014, 18 of these KTR were excluded as they underwent desensitisation, which included plasma exchange and IVIG treatments. There were 44 who rejected, 7 who had subclinical rejection and 94 who did not have a rejection episode. Of those who rejected there were 30 Cell Mediated Rejections (TCMR) as classified with Banff09 criteria and 14 Antibody Mediated Rejection (AMR) episodes classified with Banff13criteria.

3. Results

3.1. 2013–2014 historical observational cohort

All patients underwent a protocol biopsy at creatinine nadir or for cause and were graded using Banff criteria 2009 for TCMR and 2013 for AMR. 44/145 (30%) KTR experienced a rejection episode, consisting of 14 AMR and 30 TCMR (Fig. 1).

The KTR with AMR (n = 14) were more likely to; receive a live donor (p = 0.06), have had shorter cold ischemia time (p = 0.08), have had multiple previous transplants (p = 0.06) and have had

Table 1
Patient Demographics cohort 2013–2014.

Demographics	Non-AMR	AMR (BANFF13)
Number, n	131	14
Male Gender, n (%)	87 (66)	9 (64)
Median Age (IQR)	51 (41–61)	54 (42–60)
Multiple Transplants, n (%)	14 (11)	4 (29)
BDD, n (%)	97 (74)	9 (64)
Live Donor, n (%)	19 (15)	5 (36)
DCD, n (%)	14 (11)	0 (0)
AT1Rab, U/ml	8(0–40)	15(6–40)
Any DSA (MFI >300), n (%)	26 (20)	2 (14)
DSA (MFI 1500–4000), n (%)	14 (11)	2 (14)
de Novo DSA (MFI 1500)	7 (5)	0 (0)
HLA MM <2, n (%)	25 (19)	2 (14)
HLA MM 3–4, n (%)	40 (31)	5 (36)
HLA MM 5–6, n (%)	66 (50)	7 (50)
Ischaemic Time, Median (IQR)	12 (3–34)	6 (4–15)
ATG induction, n (%)	8 (6)	1 (7)
DGF (>7 days), n (%)	41 (31)	6 (43)
CMR, n (%)	30 (23)	5 (36)
Sub-clinical rejection, n (%)	7 (5)	0 (0)
C4d Positive, n (%)	3 (2)	2 (14)
ESRF		
ADPKD, n (%)	20 (15)	5 (36)
Alports, n (%)	6 (5)	0 (0)
Diabetes, n (%)	25 (19)	2 (14)
Hypertension, n (%)	10 (8)	3 (21)
IgA Nephropathy, n (%)	21 (16)	2 (14)
Reflux, n (%)	8 (6)	0 (0)
Other, n (%)	41 (31)	2 (14)

IQR = interquartile range, BDD = brain dead donor, DCD = donations after cardiac death, ATRab = Angiotensin II type 1 receptor antibody, DSA = donor specific antibody, MFI = mean fluorescence index, HLA = human leukocyte antigen, MM = miss-matches, ATG = anti-thymocyte globulin, DGF = delayed graft function, CMR = cell mediated rejection, ADPKD = autosomal dominant polycystic kidney disease.