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Proactive treatment of angiotensin receptor antibodies in kidney transplantation with plasma exchange and/or candesartan is safe and associated with excellent graft survival at 4 years: A single centre Australian experience

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ABSTRACT

High levels of angiotensin receptor antibodies (ATRab) are associated with acute cellular and humoral rejection, vascular occlusion, de novo human leucocyte antigen donor specific antibody (HLA DSA) and poor graft survival in kidney transplant recipients (KTR).

Since 2015 we proactively managed patients "at risk" (AR) with ATRab >17 U/ml with perioperative plasma exchange (PLEX) and/or angiotensin receptor blockade (ARB). 44 patients were treated with this protocol. 265 KTR with ATRab ≤17 U/ml deemed "low risk" (LR) were transplanted under standard conditions.

PLEX and ARB were not associated with increased risk of: delayed graft function requiring haemodialysis (HDx), hyperkalaemia >5.5 mmol/l requiring HDx, and the combined clinical end-point of severe hypotension, blood transfusion and re-operation for bleeding.

Rejection rates were similar at 90 days: 8/44 (18%) in the AR group and 36/265 (14%) in the LR group (p = 0.350).

Death censored graft survival was the same between the AR and LR groups with a 94% 48-month graft survival – hazard ratio (log-rank) 1.16 [95% CI 0.2–5.8] p = 0.844.

Proactive treatment of ATRab >17 U/ml with PLEX and/or ARB is not associated with increased rates of perioperative complications and comparable rates of rejection and death censored graft survival at 4 years compared to KTR <17 U/ml ATRab.

1. Introduction

Atypical antibodies are increasingly being recognised in a variety of diseases. The antibodies include antibodies to MIC-A, K-a-1 tubulin, Vimentin, myosin and the angiotensin type-1 receptor (AT1R). There are now multiple non-HLA antibodies that have been described in organ transplantation that are relevant in terms of graft outcomes. In solid organ transplantation one of the best studied and demonstrated in multiple populations of transplants around the world are the antibodies to the angiotensin type-1 receptor or ATRab [1–3].

Subjects with >17 U/ml ATRab have been deemed "at risk" (AR) of any rejection particularly HLA DSA negative rejection [4,5]. Historically it has been shown that in the absence of angiotensin receptor blockade (ARB) and perioperative plasma exchange (PLEX), subjects

Abbreviations: AR, at risk; ARB, angiotensin receptor blockade; AT1R, angiotensin type-1 receptor; ATG, anti-thymocyte globulin; ATRab, angiotensin receptor antibodies; AUC, area under the curve; CDC, complement dependent cytotoxicity; CIT, cold ischaemic time; CWD, common and well documented; DCD, donation after circulatory death; DSA, donor specific antibody; ELISA, enzyme linked immunosorbent assay; FFP, fresh frozen plasma; HDx, haemodialysis; HLA, human leucocyte antigen; HLA DSA, human leucocyte antigen donor specific antibody; IQR, interquartile range; KTR, kidney transplant recipients; LR, low risk; MFI, mean fluorescence index; MVI, microvascular injury; NKT, natural killer T cells; PLEX, plasma exchange; TCMR, T-cell mediated rejection; TCMR + V, T-cell mediated and vascular rejection; Tx, transplantation

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with >17 or 25 U/ml can experience high levels of microvascular injury [6].

The proportion of the general transplant population that is AR is a significant minority (around 15%) [6]. The prevalence of KTR with antibodies >17 U/ml is increased when different KTR populations are assessed e.g.; biopsy proven transplant glomerulopathy, the prevalence rises to 27–51% [7]. There are also data that KTR with ATRab >17 U/ml have a tendency for levels to increase over time [8].

AR populations have increased rates of HLA DSA formation 28% versus 10% compared to LR groups [9]. ATRab >30 U/ml are associated with vascular occlusion and development of de novo DSA and chronic inflammatory finding on protocol biopsy at 12 months [10].

Even in small cohorts, ATRab >10 U/ml alone or in the presence of HLA DSA (>1000 MFI) are associated with poor graft survival [11]. In AR populations graft survival can be as poor as 59% at 5 years [11]. These findings have been replicated in paediatric and adult populations where the use of ARB is very low i.e.; 2.6%-11% [3,8]. Given the poor outcomes for AR subjects it has been suggested this is a key area for transplant medicine to decide how to pre-emptively manage AR patients [12].

In this regard, we have managed AR groups with perioperative candesartan 4–16 mg per day. In KTR with ATRab >25 U/ml, we additionally use perioperative PLEX.

This protocol has raised concerns regarding the potential risk of using perioperative PLEX and ARB. In a small cohort with a short duration of follow-up, we have shown this protocol is without significant perioperative complications and associated with reduced levels of rejection at 150 days [6]. We now present the 2015–2018 cohort including 44 subjects treated with this protocol with median follow up of 30 months.

2. Materials and methods

2.1. Immunological risk stratification and immunosuppression regimens

309 patients underwent kidney transplant at Royal Adelaide Hospital from 2015 to 2018 (demographic variable listed in Table 1). For deceased donation, patients were allowed to have multiple HLA DSA antibodies with mean fluorescence intensity (MFI) 1000–4000 for HLA Class I and II as long as the T cell CDC crossmatch was negative. For live donors, both T and B CDC and flow crossmatches were negative.

The type of induction regime was based on patient's immunological risk profile. Patients ≤17 U/ml ATRab without HLA DSA were treated with interleukin-2 receptor blocker (Basiliximab 20 mg on day-0 and day-4). Patients with >17 U/ml were treated with prophylactic dose of anti-thymocyte globulin (ATG) 3 mg/kg. For KTR with ATRab >25 U/ml, we additionally use *peri*-operative PLEX with 1–1.5 plasma volumes (⅔ human albumin followed by ⅓ volume blood-group appropriate fresh frozen plasma) pre-operative and two exchanges on post-operative day 1 and 3. For ATRab >17 U/ml, candesartan was titrated to 4–16 mg as tolerated based on blood pressure and serum potassium aiming for <5.5 mmol/l. Conventional immunosuppressions are: 5 mg steroid; tacrolimus C0 7–10 ng/ml; and mycophenolate AUC 20–40 ug.hr/ml.

2.2. Perioperative complications (Table 2)

Delayed graft function was defined as the need of dialysis during the first week of transplantation. Hyperkalaemia was defined as serum potassium >5.5 mmol/L requiring dialysis support. Bleeding events were defined as: need for blood transfusion within the first week, return to theatre for exploration. Severe hypotension was defined as intensive care admission for stabilization of blood pressure irrespective of a concomitant bleeding event.

2.3. Rejection (Fig. 1)

Rejection episodes were biopsy proven and included protocol biopsy at 3 months. Banff 2017 Classifications were used including microvascular injury (MVI), combination of T-cell mediated and vascular rejection (TCMR + V), T-cell mediated rejection (TCMR) and borderline rejection.

2.4. HLA typing

KTR and donor HLA typing was performed using Linkage Biosciences™ LinkSeq™HLA-ABCDRDQA1DQB1 384 kits. HLA A, B, DRB1 were confirmed to CWD alleles by Olerup SBT™ (formerly known as Conexio Genomics SBT Resolver™) and ABI Prism™ BigDye™ Terminator Sanger Sequencing.

2.5. HLA Ab testing and pre and post-transplant HLA DSA (Table 3)

Sera were tested for potential HLA DSA pre and post-transplant. For all KTR on the active waiting list sera were screened Pre-transplantations Class I and Class II HLA antibodies were performed 6 monthly, CDC screen were performed yearly and epitope analysis was performed in selected patients with high cPRA or re-transplantation. While, in post-transplantations HLA DSA were performed at 14 and 28-days post-transplant. In 2017, the post-transplant sera testing was changed to 3 and 12 months. In addition, KTR experiencing rejection or acute graft dysfunction also had sera tested for *de novo* HLA DSA. HLA DSA were detected using LABScreen™ Single Antigen Kits (One Lambda. Inc.) following the manufacturers protocols. HLA DSA positivity was determined by a MFI ≥500 as measured by Luminex MAP^{TM} technology. Only HLA DSA >1000 MFI were defined as significant for the purpose of statistical analysis. Pre-and post HLA DSA are listed in Table 3

2.6. Eplet load (shown in Fig. 2)

HLA Eplet analysis was performed using Duquesnoy's HLA Matchmaker v2.1 using CWD four-digit allele level HLA typing to determine patient / donor Eplet mismatch score for loci HLA-A, B, C, DRB1, DRB3,4,5, and DQB1.

2.7. ATRab testing

ATRab were measured pre-transplant using an ELISA Immunoassay Kit (One Lambda, Canoga Park, CA, USA), following published protocol (Reinsmoen NL, 2010) [2] and performed by the Australian Red Cross Blood Service (ARCBS) in Adelaide. During 2015–2018 C of E Lot numbers (09, 027, 030, 032) were used following extensive in house Pre-Release Acceptance Testing (PRT) using eight known reference sera. A negative value in the ELISA used to measure ATRab is defined as <2.5 U/ml.

2.8. Statistical analysis

Dichotomous variables were expressed as frequencies and percentages, and the differences were evaluated using the Chi-square test. Continuous variables were expressed as mean ± SD and their differences were analysed using independent samples *t*-test. Non-parametric test such as Mann-Whitney-*U* test and Kruskal-Wallis test were used where necessary. A Kaplan-Meier (log-rank) death censored graft survival was used for graft survival. All tests were two sided and a p-value of <0.05 was considered to be statistically significant.

Table 1
Demographic characteristics of all transplant patients (ATRab ≤17 U/mL versus ATRab >17 U/mL). DBD donation after brain death DCD donation after cardiac death.

			ATRab ≤17 U/mL (n = 265)	ATRab >17 U/mL (n = 44)	p value
Recipient age			52.3 ± 13.5	48.3 ± 14.4	0.076[a]
Recipient gender					
	Male		164 (62%)	25 (57%)	0.523[b]
	Female		101 (38%)	19 (43%)	
Primary renal disease					
	Glomerulonephritis		87 (33%)	25 (57%)	
	Polycystic kidney disease		36 (14%)	7 (16%)	
	Diabetic nephropathy		49 (18%)	3 (6.8%)	
	Renovascular disease		30 (11%)	1 (2.3%)	
	Congenital kidney disease Reflux nephropathy		4 (1.5%)26 (9.8%)	1 (2.3%)1 (2.3%)	
	Renal calculi		1 (0.4%)	0 (0.0%)	
	Others		11 (4.2%)	4 (9.1%)	
	Unknown aetiology		21 (7.9%)	2 (4.5%)	
Donor age			47.4 ± 15.9	49.1 ± 13.5	0.496[a]
Type of Transplant					
	Deceased				
		DBD	165 (62%)	25 (57%)	0.291[c]
		DCD	52 (20%)	6 (14%)	
	Living donor		48 (18%)	13 (30%)	
HLA mismatches					
	0		8 (3.0%)	1 (2.3%)	0.074[c]
	1		21 (7.9%)	4 (9.1%)	
	2		38 (14%)	11 (25%)	
	3		29 (11%)	7 (16%)	
	4		60 (23%)	8 (18%)	
	5		76 (29%)	10 (23%)	
	6		33 (13%)	3 (6.8%)	
Total Eplet mismatch at the following loci (HLA-A, B, C, DRB1, DRB3,4,5, and DQB1)			43 ± 23	37 ± 23	0.089[a]
Desensitization					
Plasma exchange (PLEX)			12 (4.5%)	26 (59.1%)	<0.001[c]
Column for blood group incompatiblity			4 (1.5%)	0 (0%)	
PLEX + Column			5 (1.9%)	1 (2.3%)	
Induction					
Anti-thymocyte globulin (ATG)			66 (25%)	38 (86%)	<0.001[c]
IL2 Receptor blocker			198 (75%)	6 (14%)	

[a] Independent samples *t*-test.
[b] Chi-square.
[c] Kruskal Wallis.

3. Results

3.1. Perioperative complications (see Table 2)

Delayed graft function (DGF) and requirement of haemodialysis (HDx) was dependent on cold ischaemic time (CIT) and DCD status (data not shown). CIT was not different between the ATRab groups (Table 2). When excluding DCD kidneys, there was no statistically significant difference in the requirement for HDx post- transplant whether this was due to DGF or high serum potassium. Rates of major bleed and or hypotension were the same between groups.

3.2. Desensitization and induction therapy (see Table 1)

Apart from the standard immunological risk, ATRab level also play an important role in risk stratification of patients. Patients were grouped into 3 cohorts based on their ATRab levels; ≤17 U/mL, 17.1–25 U/mL and >25–40 U/mL. PLEX were performed in 21/22 (96%) in ATRab level >25–40 U/mL, 6/22 (27%) in 17.1–25 U/mL and 21/265 (7.9%) ≤17 U/mL. The desensitization treatments for ATRab level ≤17 U/mL were mainly for immunodominant HLA DSA of ≥4000 MFI or ABO incompatible transplant.

Based on our protocol, patients with ATRab >17 U/ml should be

Table 2
Perioperative complications rate among patients with ATRab ≤17 U/mL and ATRab >17 U/mL. CIT (cold ischaemic time) IQR (interquartile range) DCD – (donation after cardiac death).

	ATRab ≤17 U/mL (n = 265)	ATRab >17 U/mL (n = 44)	p value
CIT median (IQR) hours	10 (5,14)	8 (4,11)	0.104[d]
DCD proportions	52/265 (20%)	6/44 (14%)	0.283[c]
Haemodialysis for delayed graft function in non-DCD	80/213 (38%)	11/38 (29%)	0.310[c]
Hyperkalaemia requiring dialysis in non-DCD	39/213(18%)	4/38(11%)	0.618[b]
Hyperkalaemia requiring dialysis all graft types	62/265 (23%)	5/44 (11%)	0.086[b]
Hypotension/Bleed + Transfusion	24/265 (9%)	2/44 (9%)	0.926[b]

[b] Chi-square.
[c] Kruskal Wallis.
[d] Mann-Whitney *U* test.

Table 3
De Novo DSA > 1000 MFI within 12 months of transplant. Allowed Pre-transplant DSA singular HLA antibodies 1000–4000 MFI in the setting of negative T and B cell CDC crossmatch. DSA – donor specific antibody.

	ATRab ≤17 U/mL	ATRab 17.1–25 U/mL	ATRab >25–40 U/mL	p value
Pre-transplant DSA (MFI 1000–4000)	93/262 (35.5%)	11/22 (50.0%)	8/22 (36.4%)	0.405[c]
Post-transplant DSA (De novo alone)	30/214 (14.0%)	0/16 (0.0%)	3/16 (18.8%)	0.916[c]
Post-transplant DSA (De novo in addition to preexisting DSA)	11/214 (5.1%)	4/16 (25.0%)	1/16 (6.3%)	0.916[c]

[c] Kruskal Wallis.

treated with ATG, however 6 of our patients had received Basiliximab. Two of them had concurrent PLEX while another 4 did not. The level of ATRab in these 4 patients were 17.2, 17.5, 19.8 and 20.9 U/mL respectively. Unfortunately, the later 2 patients with higher level of ATRab developed both TCMR and vascular rejections which were successfully treated with ATG.

3.3. Rejection incidence, type and treatment required to terminate rejection

In the >25–40 U/ml group there were 5/22 (23%) rejection episodes. Three were cellular in nature and all resolved histologically with 3 doses, 500 mg methylprednisolone. Two of these subjects had concurrent multiple Class I HLA DSA (combined MFI 17000 and 5100 respectively). The other two rejections were isolated V1 lesions treated with additional PLEX (3–4.5 plasma volumes) and 3–4 mg/kg ATG). One of these patients had HLA DSA (>1000 MFI) to B35, B55 Cw4. Both had clear repeat biopsies 7–10 days later.

In the 17.1–25 U/ml group there were 3/22 (14%) rejection episodes. One isolated V lesion, treated with 3 mg/kg ATG. One severe tubulitis and vasculitis, requiring 3 doses of 500 mg methylprednisolone to terminate the rejection. The other rejection was an i2t1v2g2 lesion that required ATG and PLEX to terminate the rejection episode.

There were 36/265(14%) rejection episodes in the ≤17 U/ml group. 8/36 required ATG and PLEX to terminate the rejection (median ATG dose 4.5 mg/kg and 3–4.5 plasma volumes). 15/36 had cellular rejection only requiring methylprednisolone to terminate the rejection. 13/36 required ATG to terminate the rejection and all had a vascular lesion with positive i and t scores without microvascular damage.

There was no statistically significant difference in rejection prevalence or type between the ATRab groups (see Fig. 1).

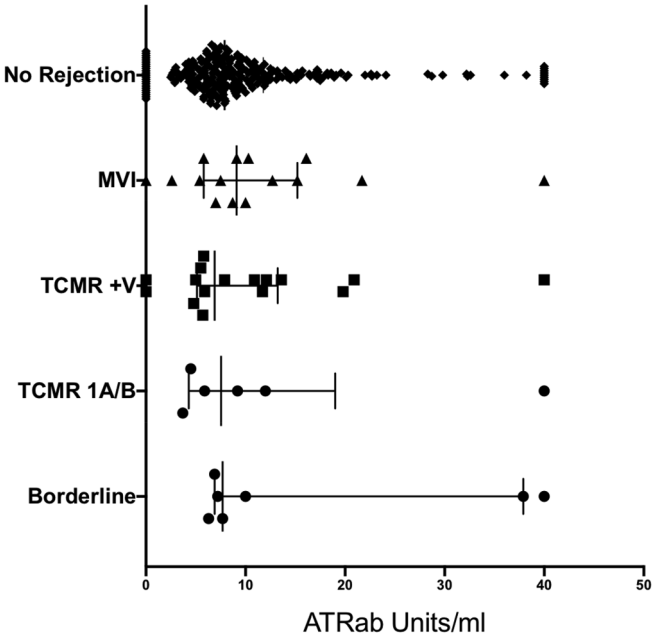

Fig. 1. Rejection type within 3 months of transplant for a given ATRab level at the time of transplant. Dot plot of median and interquartile range. MVI (Banff defined micro vascular injury) TCMR + V (Banff defined vascular lesions with any evidence of a cellular rejection) TCMR 1A/B (Banff defined cellular rejection without a vascular lesion) Borderline (Banff cellular rejection no meeting TCMR 1A/B criteria – treated with methylprednisolone).

3.4. Graft survival

Subjects with ATRab >17 U/ml were followed for longer median, interquartile range (IQR) 30 (20–42) months compared to ≤17 U/ml – 26 (13–37) but this was not statistically significant Mann-Whitney-U (p = 0.108). Death censored graft survival in both groups was 94% at 4 years. Hazard ratio (log-rank) of graft failure ATRab >17 U/ml compared to those with ≤17 U/ml: 1.16 [95% CI 0.2–5.8] p = 0.844. (see Fig. 3)

In the AR group, there were two graft losses: one at 19 months due to BK nephropathy (>40 U/ml); and one at 21 months due to non-adherence to medication and pregnancy (22 U/ml). For the LR population there were multiple causes of graft failure: death with function (n = 7); non-adherence to medication (n = 2); anastomotic bleeds (n = 2); primary non-function (n = 2), chronic fibrosis process that did not respond to therapies.

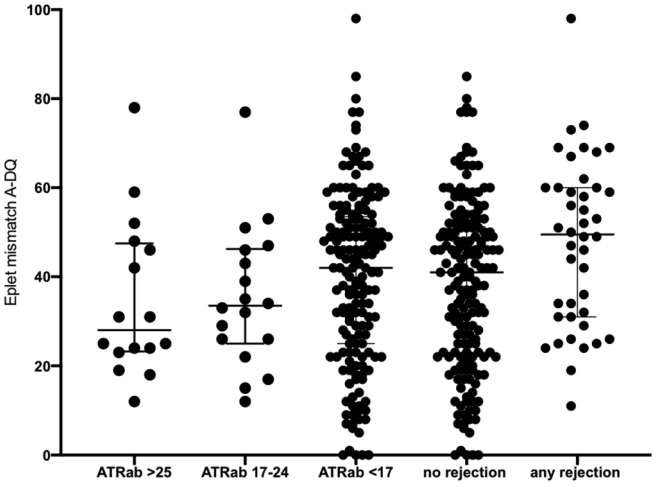

Fig. 2. Dot plot median and interquartile range of HLA A-DQ eplet mismatch for given groups. The A-DQ Eplet calculated load was not different between the ATRab groups. However subjects who experienced no rejection compared to any rejection had lower eplet load 41 vs 50 (p = 0.004).

4. Discussion

In this paper, we present our experience of a prospective protocol for the management of AT1R antibodies (ATRab) using a combination of PLEX and ARB, based on pre-transplant antibody determination on the wait list in an Australian population. This protocol resulted in excellent long term graft survival in the ATRab >17 U/ml group (Fig. 3).

The protocol was well tolerated with only two transfusion reactions (one citrate toxicity and one reaction to FFP) both subsided to allow transplantation and repeat PLEX was performed post operation. There

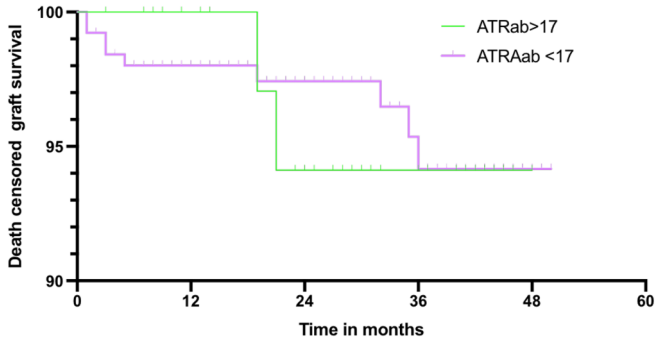

Fig. 3. Kaplan Meier death graft survival ATRab >17 U/nl (n = 44) and ATRab ≤17U/ml (n = 265). Hazard Ratio (logrank) of graft failure ATRab >17 U/ml (green line) compared to those with ≤17 U/ml (purple line) 1.16 [95% CI 0.2–5.8] p = 0.844.

was only 1 patient who had ARB ceased after the first week due to delayed graft function but this was recommenced long-term.

Historically in the absence of ARB, the outcome of subjects with ATRab >17 U/ml have been shown to be inferior to subjects with ≤17 U/ml [3]. Among patients with ATRab >17 U/ml and, microvascular injury on biopsy there was increased risk of graft failure HR 3.94 [95% CI 2.20–7.05] p-value <0.0001 [3]. However, we have shown over a 4-year period in 44 subjects that intervention is associated with similar rates of rejection, de novo DSA formation and graft survival to those with levels ≤17 U/ml. Indeed 4-year survival death censored is excellent at 94%. We did not find increased rate of delayed graft function, hyperkalaemia, perioperative bleed or hypotension in those treated with candesartan or PLEX (Table 2) and in this regards our protocol has acceptable safety profiles. Importantly in the 14 patients with ATRab >40 U/ml there were no episodes of acute graft thrombosis.

The protocol was designed to physically remove ATRab from the circulation at the most critical time for allografts – during the first 24 h by the use of PLEX, which has the added advantage of synchronous removal of HLA DSA. Kohei et al. showed antibody deposition in allografts is maximal during the first 2–4 h post revascularisation [13], thus the strategy of depletion immediately pre-operatively with PLEX is logical first step in treatment. In vitro studies by Lee et al. [14] showed a critical role of complement in antibody mediated graft damage and therefore there is a potential unrecognised benefit of plasma exchange, which can reduce complement levels. The simultaneous use of polyclonal antibody therapy also removes the cellular component of the AMR response. In classical acute AMR, natural killer cells (and NKT cells) are capable of mediating both cytotoxic response as well as responding to pre-formed antibody [15,16]. Finally, we employed AT1R blocking therapy (typically candesartan) pre-operatively in blocking the AT1 receptor.

We also report our experience of the relationship between eplet load and ATRab (see Fig. 2). ATRab did not correlate with eplet load, - but high eplet load did increase risk of any rejection. In patients experiencing rejection who had a low eplet load there was invariably a pre-transplant HLA DSA (data not shown).

Unlike HLA antibodies, which arise by exposure of the immune system to intact (or components of intact) HLA molecules, atypical antibodies are presumed to arise after exposure of the immune system to subcellular components induced by cell death or stress. Antibodies to the angiotensin type-1 receptor (ATRab) are known to target the G-protein coupled receptor (CPCR) of the second extracellular domain of the AT1 receptor. The highest levels of these antibodies occur in patients who have been treated with left ventricular assist devices [17]. One paradox of the atypical antibody field is the presence of potentially high levels of antibody without disease (see Fig. 1). This paradox is still unresolved, but recently evidence has emerged in the systemic sclerosis literature to suggest that autoantibodies to GPCR may form an active part of the normal physiology of the immune system [18]. Whether this is the case for the ATRab is yet to be determined.

We recognise that this is a single centre experience and that these results are not the result of a randomised controlled study. We accept that this cohort although representative of Australian cohorts – has high immunological risk and relatively high levels of pre-transplant HLA DSA (Table 3) and de novo HLA DSA formation – but that population has high levels of eplet mismatch (Fig. 2) and this is a known risk factor for de novo DSA formation. The formation of de novo HLA DSA in our cohorts were still potentially due to the anamnestic responses immediately post transplantation as in 2015–16 sera were tested at 14 and 28-days post-transplantation. However, epitope analysis revealed that these new HLA antibodies were not explained by previous antibody profiles and could be considered de novo DSA. From 2017, onward sera were tested at 3,12 months and therefore new HLA DSA could be considered de novo.

Conflict of interest

There is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humimm.2019.04.005.

References

[1] D. Dragun, R. Catar, A. Philippe, Non-HLA antibodies against endothelial targets bridging allo- and autoimmunity, Kidney Int. 90 (2) (2016) 280–288.
[2] N.L. Reinsmoen, et al., Anti-angiotensin type 1 receptor antibodies associated with antibody mediated rejection in donor HLA antibody negative patients, Transplantation 90 (12) (2010) 1473–1477.
[3] M. Taniguchi, et al., Higher risk of kidney graft failure in the presence of anti-angiotensin II type-1 receptor antibodies, Am. J. Transplant. 13 (10) (2013) 2577–2589.
[4] A. Fuss, et al., C4d Negative antibody mediated rejection with high anti-angiotensin II type I receptor antibodies in absence of donor specific antibodies, Nephrology (Carlton) (2015).
[5] X. Zhang, N.L. Reinsmoen, Impact of Non-human leukocyte antigen-specific antibodies in kidney and heart transplantation, Front. Immunol. 8 (2017) 434.
[6] R.P. Carroll, et al., Angiotensin II type-1 receptor antibody (AT1Rab) associated humoral rejection and the effect of peri operative plasma exchange and candesartan, Hum. Immunol. 77 (12) (2016) 1154–1158.
[7] S. Bussolino, et al., Detection of Angiotensin II type I-receptor antibodies in transplant glomerulopathy, Clin. Transplant. 32 (11) (2018).
[8] M.H. Pearl, et al., Angiotensin II Type 1 receptor antibodies are associated with inflammatory cytokines and poor clinical outcomes in pediatric kidney transplantation, Kidney Int. 93 (1) (2018) 260–269.
[9] A.J. Gareau, et al., Pre-transplant AT1R antibodies correlate with early allograft rejection, Transplant. Immunol. 46 (2018) 29–35.
[10] A. Gonzalez-Almada, et al., Pretransplant angiotensin ii type 1-receptor antibodies point to an increase in renal graft sub-intimal fibrosis in living- donor kidney transplant recipients, Transplant. Immunol. (2018).
[11] A. Fichtner, et al., Association of angiotensin II type 1 receptor antibodies with graft histology, function and survival in paediatric renal transplant recipients, Nephrol. Dial. Transplant. 33 (6) (2018) 1065–1072.
[12] M.C. Philogene, et al., Pre-transplant screening for non-HLA antibodies: who should be tested? Hum. Immunol. 79 (4) (2018) 195–202.

[13] N. Kohei, et al., Sequential analysis of donor-specific antibodies and pathological findings in acute antibody-mediated rejection in a rat renal transplantation model, Kidney Int. 84 (4) (2013) 722–732.
[14] C.Y. Lee, et al., The involvement of FcR mechanisms in antibody-mediated rejection, Transplantation 84 (10) (2007) 1324–1334.
[15] P.F. Halloran, et al., Antibody-mediated rejection, T cell-mediated rejection, and the injury-repair response: new insights from the Genome Canada studies of kidney transplant biopsies, Kidney Int. 85 (2) (2014) 258–264.
[16] N. Kohei, et al., Natural killer cells play a critical role in mediating inflammation and graft failure during antibody-mediated rejection of kidney allografts, Kidney Int. 89 (6) (2016) 1293–1306.
[17] M.J. Barten, et al., 112 Identification of non-HLA antibodies in ventricular assist device recipients, J. Heart Lung Transplant. 31 (2012) S46.
[18] O. Cabral-Marques, et al., GPCR-specific autoantibody signatures are associated with physiological and pathological immune homeostasis, Nat. Commun. 9 (1) (2018) 5224.