

Using Candesartan to Treat Angiotensin II Type 1 Receptor Antibody and Renal Allograft Vascular Rejection.

Joseph Lau¹

¹Pharmacy Department St Vincent's Hospital Melbourne



ST VINCENT'S HOSPITAL
MELBOURNE

A FACILITY OF ST VINCENT'S HEALTH AUSTRALIA

Objective

To report the successful treatment of using candesartan in a patient who had refractory renal allograft vascular rejection and elevated post-transplant level of angiotensin II type 1 receptor antibodies (AT1R-Ab).

Clinical features

A 53 year old Caucasian female with end stage kidney disease secondary to polycystic kidney disease who received a renal allograft cadaveric transplant showed early signs of delayed graft function Day 4 into transplant with oliguria and plateauing serum creatinine between 400 to 500 µmol/L.

Day 21 biopsy was performed and under the Banff classification, the results showed the patient was having ongoing Grade IIA acute rejection which was C4d negative. Extra information from the biopsy entails: mild to moderate glomerulitis (g2), focal mild intimal arteritis (v1), moderate to marked loose fibrous intimal thickening of an arcuate artery (cv3), mild focal peritubular capillaritis (ptc1) and moderate arteriolar hyalinosis (ah2).

This biopsy report is consistent with acute vascular rejection.

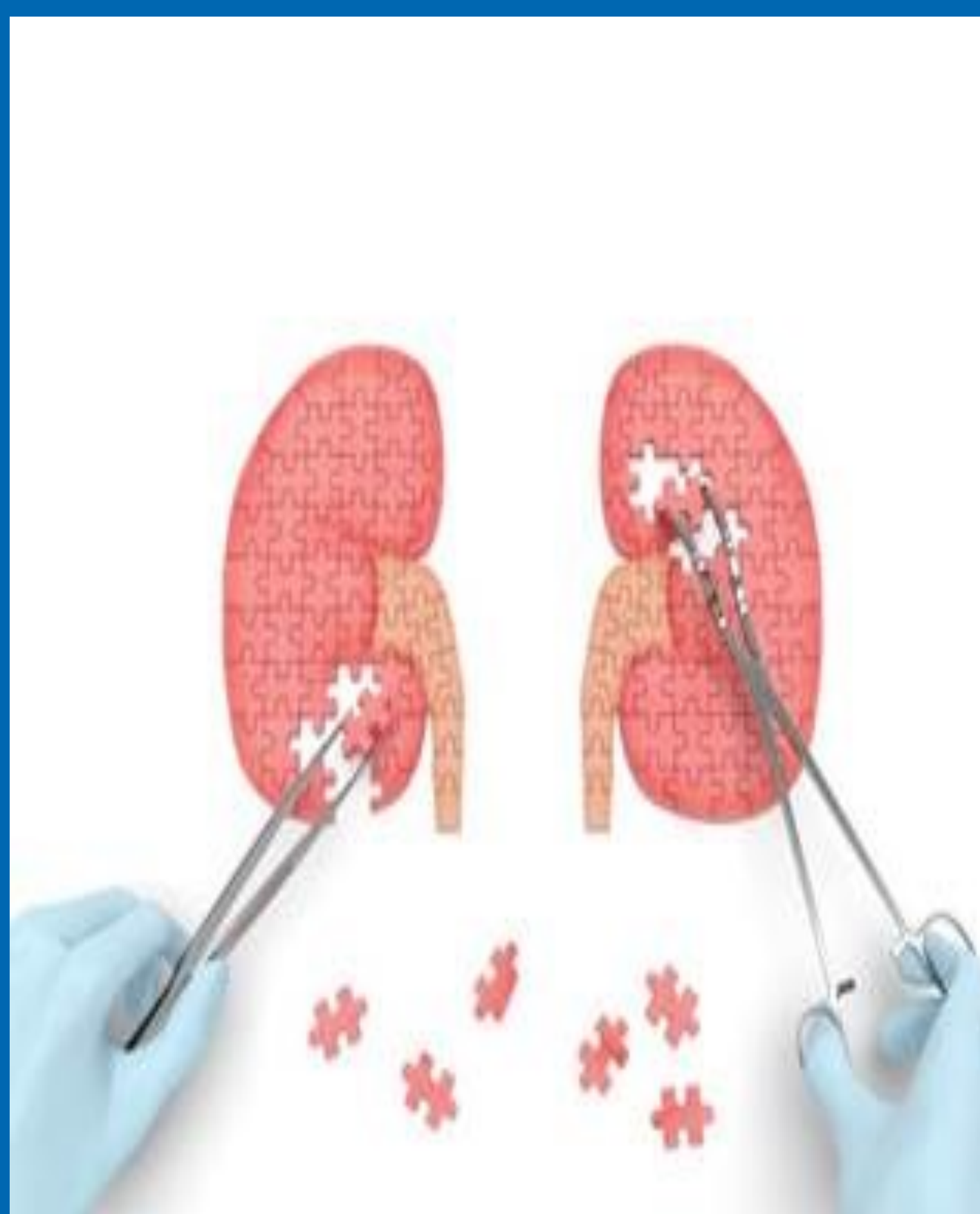
Case Progress and Outcome

Severe vascular changes coupled with CD4 negative staining suggest possible involvement of non-HLA antibodies. To combat this antibody mediated grade 3 rejection, pulse steroids, plasmapheresis, rabbit anti-thymocyte globulin (ATG fresenius®) and intravenous immunoglobulin were started with slight improvement to renal function.

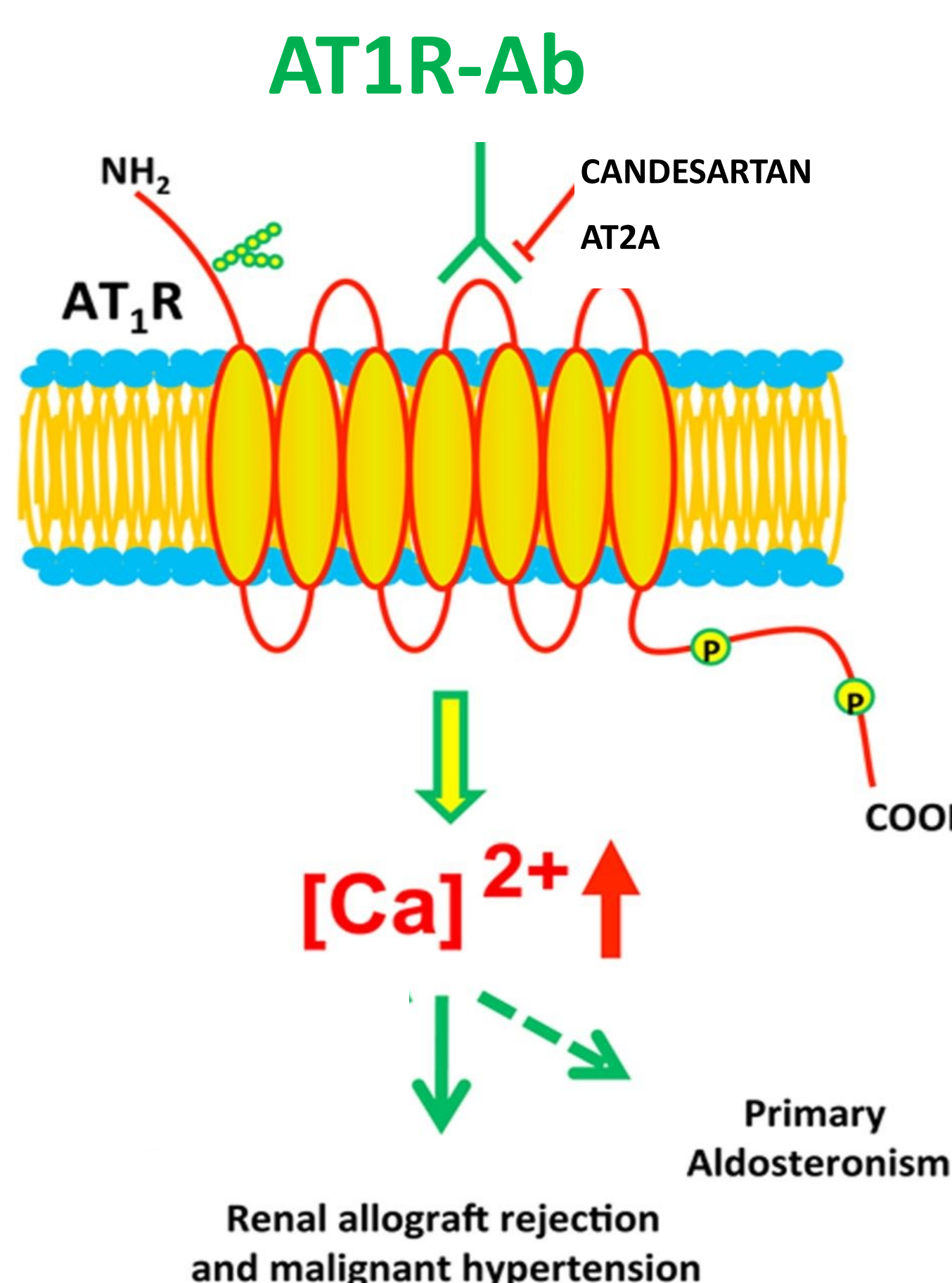
Day 30, the patient was readmitted with refractory acute rejection and a creatinine of 388 µmol/L. She was immediately started on the previous round of anti-rejection therapy and also preemptively this time with an angiotensin II receptor antagonist in the form of candesartan 4mg per day for suspicion of AT1R-ab mediated rejection.

The patient's renal function improved significantly to a serum creatinine of around 180 µmol/L, which was better than the previous baseline levels.

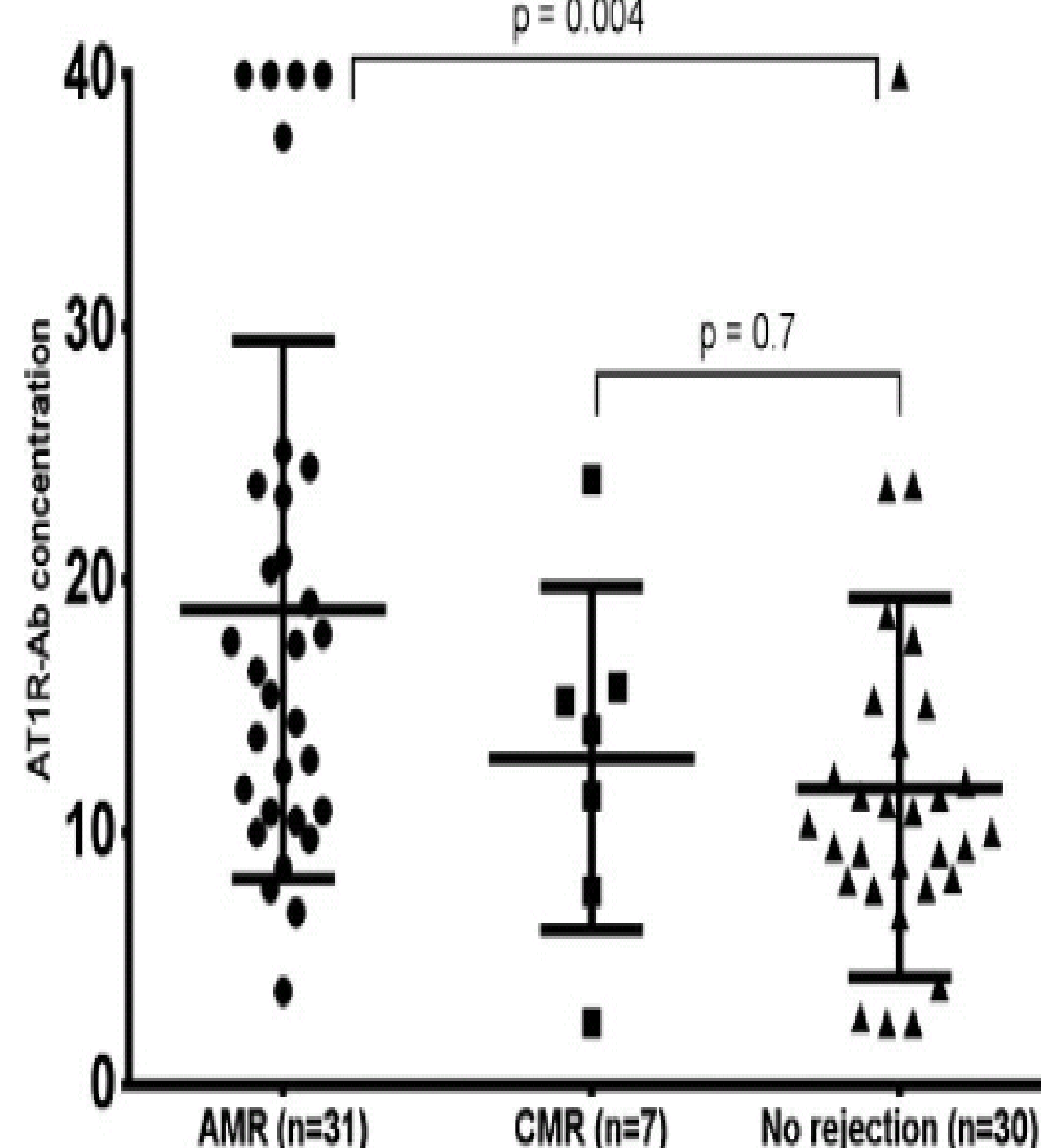
Currently in our treatment center, the AT1R-Ab assay isn't part of the screening test in pre-transplants. For our patient, the AT1R-antibody assay results revealed a level of 10.5 U/mL.



AT1R-Ab Pathophysiology



AT1R-Ab concentration and rejection



AT1R-Ab concentration in patients with antibody mediated rejection (AMR), cell mediated rejection (CMR) and no rejection. There were significantly higher AT1R-Ab concentrations in patients with AMR compared to those with no rejection. There was no significant difference with CMR.

[5]

Discussion

HLA (human leukocyte antigen) matching of all kidney donors and recipients reduces the probability of acute rejection episodes. But for a patient with matching HLA status between donor and recipient, approximately 50% of antibody mediated rejection with vascular damage and negative C4d results can be attributed to non-HLA antibodies [1,3]. The AT1R-Ab has been recognised as one of the non-HLA antibodies.

Angiotensin II type 1 receptor (AT1R) is a receptor that is found in both immune and endothelial cells, which when activated, promotes vasoconstriction, inflammatory response and aldosterone release. The activation of inflammatory cytokines in a solid organ transplant, especially for a renal transplant in this case study, can cause atherosclerosis and renal tissue damage [2,4].

AT1R-Ab levels were higher in patients diagnosed with antibody mediated rejection compared to those with no rejection [5]. Ultimately, the testing of AT1R-antibodies may predict patients at higher risk for antibody mediated rejection [5]. There is yet to be a definitive range for AT1R-antibody levels; however several studies have suggested a range of: <2.5 U/mL = negative, >10 U/mL = moderate risk, >17 U/mL = high risk [1,5].

To combat AT1R antibody rejection, the use of angiotensin II receptor antagonist which acts as a selective AT1R antagonist could mitigate the harmful effects of antibodies. Studies have demonstrated starting treatment of candesartan or losartan can have an improvement in renal allograft survival and reduction of AT1R-antibodies, leading to longer rejection free periods [4,6].

Conclusion

The importance of AT1R antibody studies is gaining prominence and should be a supplemental test especially in the non-HLA antibody mediated rejection and atypical graft dysfunction. The use of angiotensin II receptor antagonist (candesartan) to treat refractory C4d-negative antibody mediated renal allograft vascular rejection was shown to be effective in this case.

Contact

Joseph Lau— Clinical Pharmacist
Joseph.Lau@svha.org.au

References

1. Shamseddin M et al, Can't Always Blame Anti-HLA Antibody: Angiotensin II Type 1 Receptor (AT1R) Antibody and Renal Allograft Vascular Rejection. Imedpub, 2017
2. Jobert A et al, Angiotensin II type 1 receptor antibody precipitating acute. Nephrol, 2015 vascular rejection in kidney transplantation
3. Nickleleit V et al, Kidney transplants, antibodies and rejection: Is C4d a magic marker? Nephrol Dial Transplant, 2003
4. Dragun D et al, Angiotensin II type 1-receptor activating antibodies in renal allograft rejection. N Engl J Med, 2005
5. Philogene M et al, Anti-Angiotensin II Type 1 Receptor and Anti-Endothelial Cell Antibodies: A Cross-Sectional Analysis of Pathological Findings in Allograft Biopsies. Transplant, 2017
6. Fuss A et al, C4d-negative antibody-mediated rejection with high anti-angiotensin II type I receptor antibodies in absence of donor-specific antibodies. Nephrol, 2015