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ECULIZUMAB IN ANTIBODY-MEDIATED REJECTION OF PAEDIATRIC RENAL TRANSPLANTATION

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INTRODUCTION

Antibody-mediated rejection (AMR) cause 20-30% of rejection episodes in kidney transplantation, a major impediment to the survival of transplanted kidneys. It requires aggressive treatment involving plasma exchanges (PEs), intravenous immunoglobulins (IVIGs), rituximab and bortezomib to prevent acute graft loss. Since the mechanism of AMR appears to involve complement activation in the setting of high levels of DSA, Eculizumab, an anticomplement protein-C5 monoclonal antibody, has so far proven effective in both the preventive and curative treatment of AMR in patients with severe AMR.

OBJECTIVES

We present four children with active AMR after renal transplantation, resistant to PEs, IVIgs and rituximab treated with eculizumab. We discuss the drug efficacy in active but early and late AMR , the successful in hyperacute C4d negative AMR and possibles causes of eculizumab failure in a patient.

Table 1
Baseline demographic characteristics and alloantibody data in all patients

Category	Case 1	Case 2	Case 3	Case 4
Gender	Male	Female	Male	Female
Kidney transplant number	2nd	3rd	1st	1st
Donor type	cadaveric	cadaveric	live	cadaveric
Age (years) at transplantation	17	8	14	6
Immunosuppression	Thymoglobulin + Methylprednisolone (MP) Tacrolimus + MMF + Prednisolone	Thymoglobulin + MP Tacrolimus + MMF + Prednisolone	Anti-CD25 + MP Everolimus + MMF + Prednisolone	Anti-CD25 + MP Tacrolimus + MMF + Prednisolone
Post-transplantation time at AMR	7 days	18 months	12 months	52 months
CKD origin	Nephronophthisis	Renal dysplasia	Renal dysplasia associated with posterior urethral valves	unknown
Pre-transplant donor-specific alloantibody	positive	negative	negative	negative
DSA Single antigen bead assay MFI	**10000**	**6800**	**9000**	**8000**
Anti-donor antibody specificity	**A26 A68 B38 B40 DR4**	**DQ7 DQ9**	**DR53 DR7 DQ2**	**DR51 DR15 DQ6**
Histology	Cellular IA Banff C4d-negative (delayed renal biopsy)	Cellular IB C4d-positive	Cellular and humoral rejection C4d-positive	NTA C4d-positive
SCr mg/dl at AMR diagnosis	**3,12**	**3,36**	**1.72**	**5.16**

METHODS

The patients were transplanted between 2012 and 2013. The diagnosis AMR was based on graft dysfunction, DSA positivity (Luminex) and renal biopsy (Banff 2013 criteria). Table 1 shows the patients' baseline characteristics. The clinical spectrum include: hyperacute AMR with preexisting DSA and late de novo DSA in three patients. All patients showed acute graft disfunction and clinical AMR. The biopsy of case 1 was performed a month after diagnosis for contraindication because of perirrenal collection. At AMR diagnosis, all patients received the same treatment protocol: thymoglobulin, metilprednisolone bolus, Plasma Exange (PE) (7 sessions), Rituximab (two doses) and IVIGs (100 mg/kg post PE). Eculizumab was used to treat resistant AMR with initial dose 1200 mg/900 (30-50 kg)/600 < 30 kg; then 900 mg/600 < 30 kg weekly for 4 doses; followed by 1200 mg/900 (30-50 kg)/ 600 < 30 kg every other week at weeks 6, 8 and 10 (based on Stegall et al (1)). DSA was analized monthly and IVIG (2 g/kg/month × 4) was combined with Eculizumab for treatment of persistent DSA. The meningoccocal vaccine was contraindicated for acute AMR and antibiotic prophilaxis was administrated up 4 weeks after stopping the treatment.

RESULTS

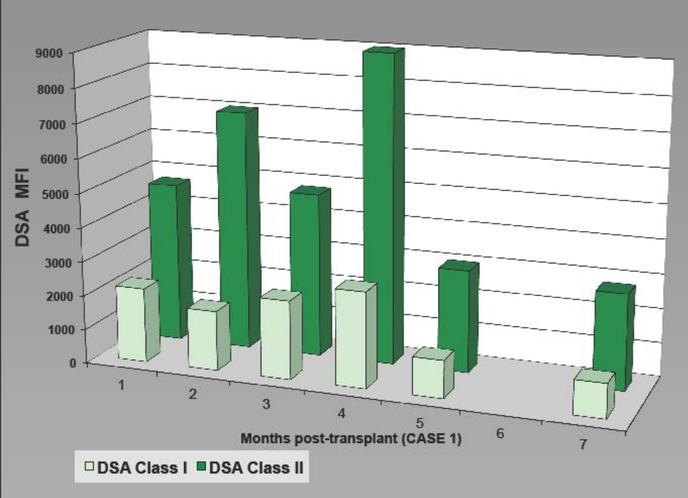
-Three patients have functioning grafts after 36, 24 and 20 months of treatment, with serum creatinine 1.9 , 1.7 and 3 mg/dl respectively (Graph 1). DSA positivity is ongoing in two respondent patient (cases 1 and 3) with MFI 2000 and 3000 respectively (Graph 2).

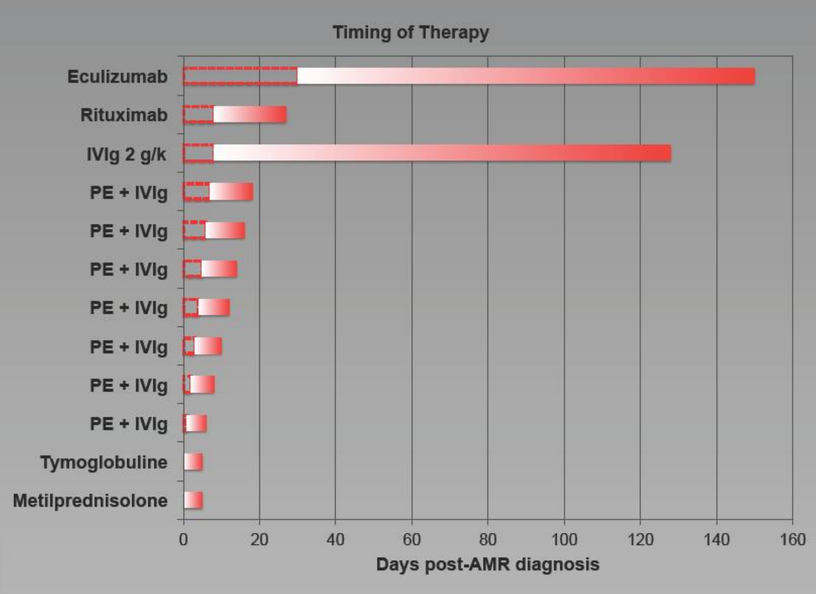
- Hyperacute C4d/C1q-negative AMR with persistent DSA I,II has showed positive response to Eculizumab (Cr 1,9 mg/dl 3 years after treatment). This case suggests that C4d and C1q negativity is possible in eculizumab sensitive AMR with early administration to treat AMR (against other authors in the literature (2)) (Graph 3, Figure 1). However, C4d can be modified by treatment because of delayed biopsy.

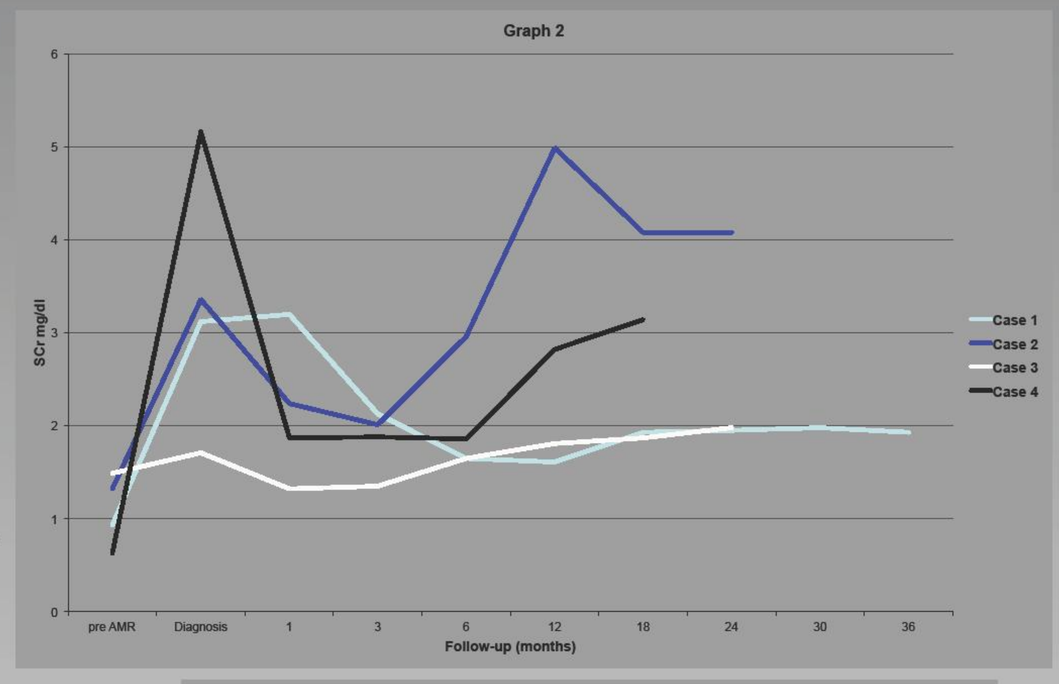
- Case 2 experienced graft loss at 14 months (late C4d-positive AMR, DSA DQ+, histopathology of cellular rejection) despite treatment. Resistance to treatment in AMR C4d-positive patient might be explained by complement-independent or alternative pathway-mediated rejection mechanisms, direct DSA endothelial injury or antibody-dependent cell mediated cytotoxicity.

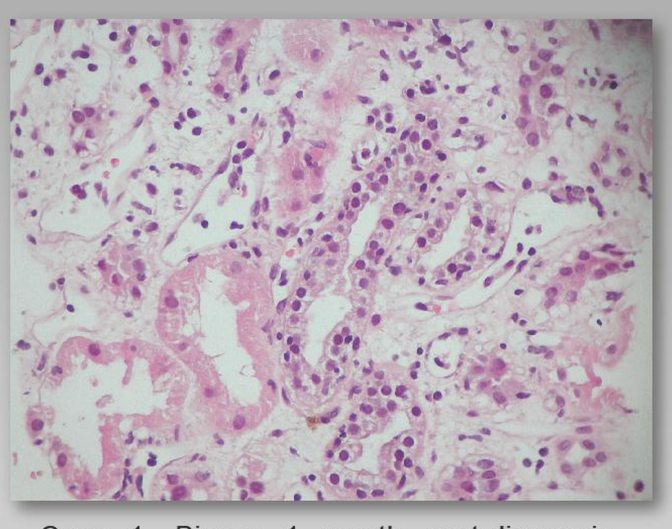
- No opportunistic infections and no adverse effects were observed.

Graph 3. Hyperacute rejection case 1

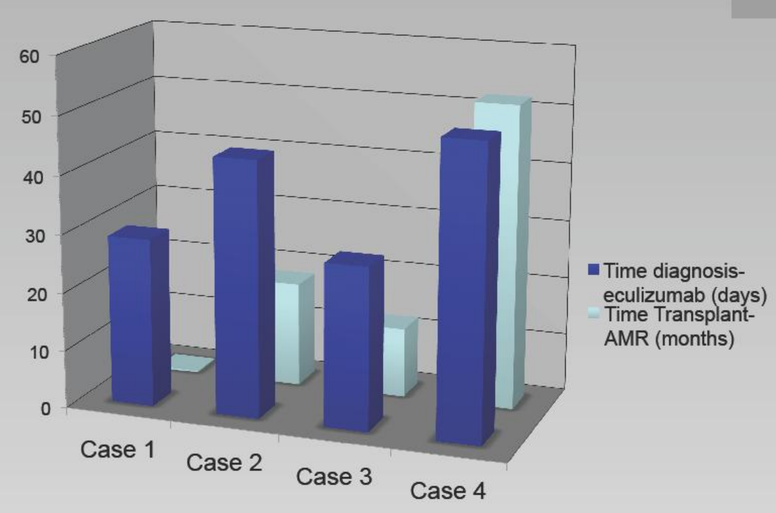


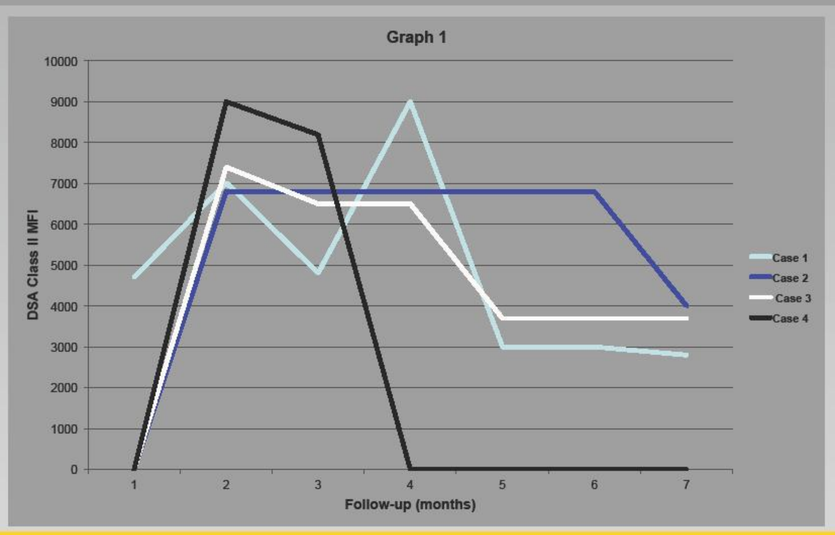






Case 1. Biopsy 1 month post-diagnosis showed mild capilaritis, edema and mononuclear infiltrate i2, tubulitis t2. C4d and SV40 negative wiht DSA MFI >9000





CONCLUSIONS

- In our knowledge, this is the first paediatric cases series describing Eculizumab use to treat acute refractory C4d-positive and C4d-negative AMR in paediatric renal transplantation.
- Discontinue PE prevents removal of Eculizumab. Because of antiC5 treatment not decreases DSA level, combined high-dose IVIg (2g/k) and Rituximb is treatment recomended.
- DSA levels over time are important point to consideres the duration of eculizumab.
- Eculizumab-resistant AMR probably underlies complement-independent endothelial injury, direct DSA endothelial injury or antibody-dependent cell mediated cytotoxicity.
- More experience is necessary for to know the impact of early complement inhibition in order to avoid chronic-antibody-mediated damage.

REFERENCES:

1-Stegall MD et al. Terminal complement inhibition decreases antibody-mediated rejection in sensitized renal transplant recipients. AJT 2011;11:2405-24-13.
2-Burbach M et al. Report of the inefficacy of Eculizumab in two cases of severe antibody-mediated rejectionof renal grafts. Transplantation 2014;00;00-00.
3- Locke JE et al. The use of antibody to complement protein C5 for salvage treatment of severe antibody-mediated rejection. AJT 2009;9:231-23
4- Ghirardo G et al. Plasmapheresis resistant acute humoral rejection successfully treated whit antiC5 antibody. Pediatr Transplant 2014;18:E1-E5
5- Noone D et al: Antibody-mediated rejection associated with complement factor-H related protein 3/1 deficiency successfully treated with Eculizumab. AJT 2012;12 (9) 25-46-2553
6- Chehade H et al. Eculizumab to treat Antibody mediated rejection in a 7-year-old kidney transplant recipient. Pediatrics 2015;135;e551.

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