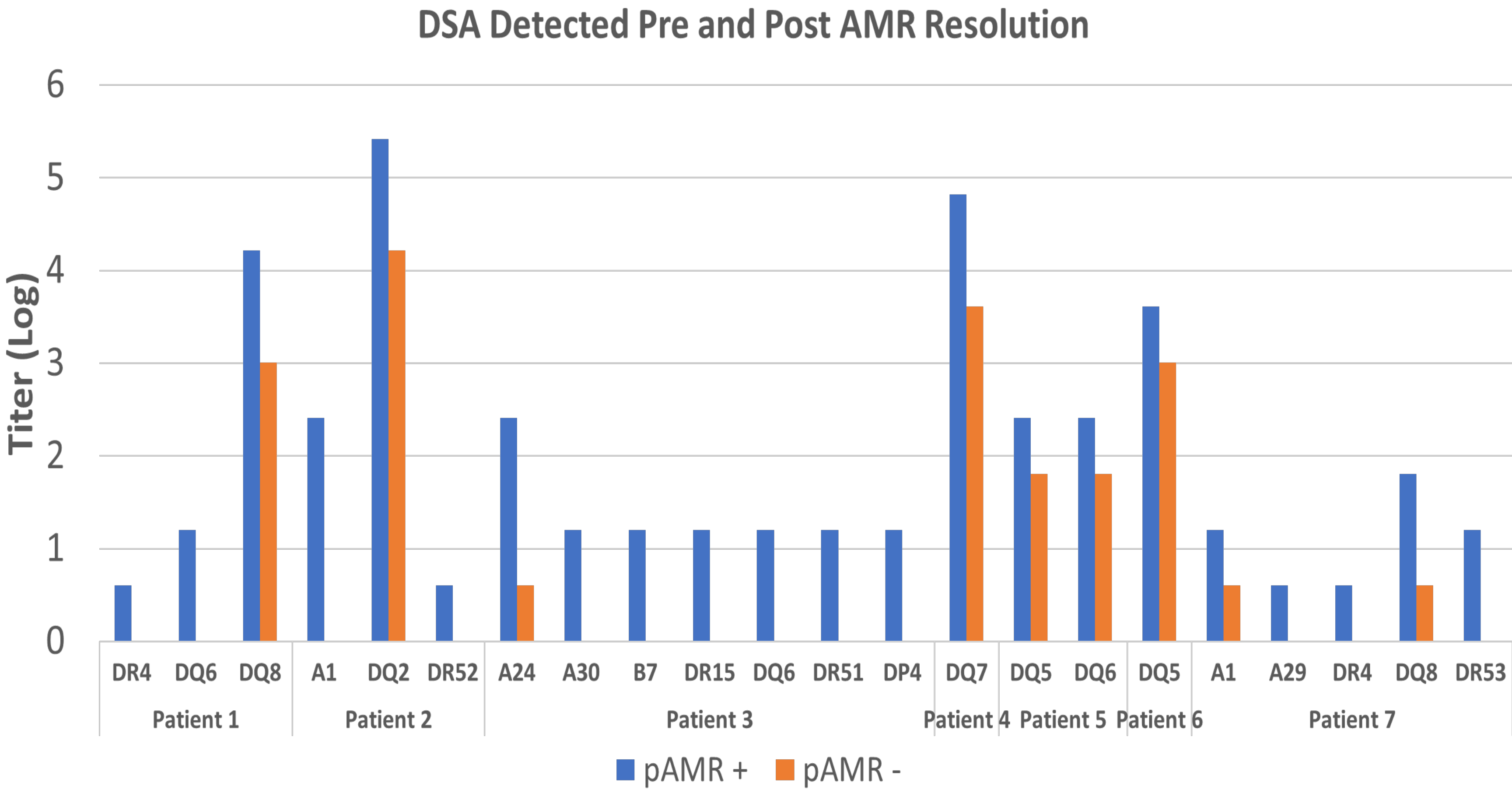


Introduction

- Antibody-mediated rejection (AMR) due to donor specific anti-HLA antibodies (DSA) poses a significant threat to allograft survival in solid organ transplantation [1].
- This is primarily due to the limited effectiveness of current therapies, such as Rituximab, that fail to target long-lived B- and plasma- cells residing in the bone marrow and responsible for DSA production against human leukocyte antigens (HLA) [2].
- Recent studies in kidney and heart transplantation have introduced Daratumumab (Dara) as a potential therapeutic agent to combat AMR [3].
- Dara is an IgG1κ anti-human CD38 mAb primarily used in treatment of multiple myeloma to deplete CD38+ B- and plasma-cells [3].
- In this case series, we present outcomes of Dara treatment on anti-HLA DSA serum levels in pediatric heart transplant recipients who did not respond to our center’s standard AMR protocol.

Case Report

- Five pediatric heart patients (10.6-22.1 years old) were diagnosed with AMR (C4d+ biopsy, pAMR ≥ 1)
- Each received ≥ 2 cycles of Dara with intravenous immunoglobulin and 6/7 tolerated the treatment.
- Anti-HLA DSA levels were measured using Luminex solid phase assays.
- DSA titers decreased by a median of 16-fold in all patients when AMR- (C4d-, pAMR = 0).
- Previous DSA reactive with HLA-B, -DRB1, -DRB345, and –DPB1 were negative when all patients achieved pAMR = 0 .
- DSA reactive with HLA-DQ was persistent in 6/7 patients after AMR resolution, however, it is important to note that that there was a marked reduction in HLA-DQ titer.
- All patients resolved AMR in a median of 57 days post-treatment initiation.
- Number of DSA detected in each patient was variable (1 to 7 per patient).



Discussion

This case series highlights the potential of Daratumumab as a therapeutic agent in AMR treatment. Interestingly, Dara appeared to be less effective in diminishing antibody reactive with HLA-DQ compared to other loci. However, this observation is likely due to an important factor of antibody concentration (titer). AMR+ patients with HLA-DSA present at a titer > 1:256 were not DSA negative once achieving AMR- status. Daratumumab was a useful in help treating these AMR+ patients. Although a multi-center study is required to confirm the efficacy of Daratumumab in reducing anti-HLA antibodies, the results of this case series are promising.

References

1. Colvin, R.B. and R.N. Smith, *Antibody-mediated organ-allograft rejection*. Nat Rev Immunol, 2005. 5(10): p. 807-17.
2. de Sousa, M.V., et al., *Treatment of Antibody-Mediated Rejection After Kidney Transplantation: Immunological Effects, Clinical Response, and Histological Findings*. Ann Transplant, 2020. 25: p. e925488.
3. Spica, D., et al., *Daratumumab for Treatment of Antibody-Mediated Rejection after ABO-Incompatible Kidney Transplantation*. Case Rep Nephrol Dial, 2019. 9(3): p. 149-157.

*Titer extrapolated from MFI value at 1:1024

	Age (y)	Initial Biopsy pAMR Grade	pAMR = 0 (Days)	Treatment Cycles	AMR (Number of DSAs)	AMR+ (Peak DSA Titer)	AMR- (Peak DSA Titer)	HLA CI DSA (AMR-)	HLA CII DSA (AMR-)	Titer Reduction (Fold)
Patient 1	10.6	1	57	6	3	1:16,384	1:1,024	None	DQ8	16
Patient 2	22.1	2	63	2	3	1:262,144	1:16,384	None	DQ2	16
Patient 3	16.7	2	27	2	7	1:256	1:4	A24	None	64
Patient 4	15.5	2	77	2	1	*1:65,556	1:4,096	None	DQ7	16
Patient 5	16.1	2	71	3	2	1:256	1:64	None	DQ5 DQ6	4
Patient 6	4.3	2	33	3	1	1:4096	1:1,024	None	DQ5	4
Patient 7	15.9	2	48	2	5	1:64	1:4	A1	DQ8	16