Virtual Desensitization to Determine the Number and Strength of Antibody Specificities Driving High cPRA in a Highly Sensitized Kidney Transplant Candidate

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INTRODUCTION

Bw4 and Bw6 are mutually exclusive epitopes associated with all HLA-B antigens. Patients homozygous for B46 have the potential to make antibodies against both Bw4 and Bw6 public epitopes which makes finding a suitable donor difficult. We used solid phase single-antigen bead (SAB) dilution and MagSort bead assay to develop a protocol for virtual desensitization of a very highly sensitized patient who otherwise could not receive a safe transplant.

PATIENT CLINICAL HISTORY

In this case, a 52 year old female was evaluated for her first kidney transplant with B46 +/+. She was highly sensitized with a cPRA of 100%. Opened current <8k MFI not positive at 1:10, still at 99.99% and ABO type is A. Current Status on UNet is 1 (Active). Waiting time >15 years.

HLA TYPING

Figure 1. HLA typing for the patient. HLA typing was performed using the reverse Sequence Specific Oligonucleotide (rSSO) method (LabType, One Lambda). For NMDP allele code designations please see https://hml.nmdp.org/MacUI/. The equivalent serology typing is also included for this patient.

	Molecular		NMDP		Equivalent	
A	11	11	CCHFG	CCHFG	11	11
B	46	46	CUFHE	CUFHF	46	46
Bw	6	6			6	6
C	01	01	CEAVT	CEAVU	1	1
DRB1	08	09	CCMHK	CCYFU	8	9
DRB3						
DRB4		01		CCJVU		53
DRB5						
DQA1	01	03	CCBGS	EER		
DQB1	03	06	CCSCT	CCSCU	9	6
DPA1	02	02	CCBNZ	CCJVC	2	2
DPB1	02	05	BSEJP	CDTEJ	2	5

HLA HAPLOTYPE ANALYSIS

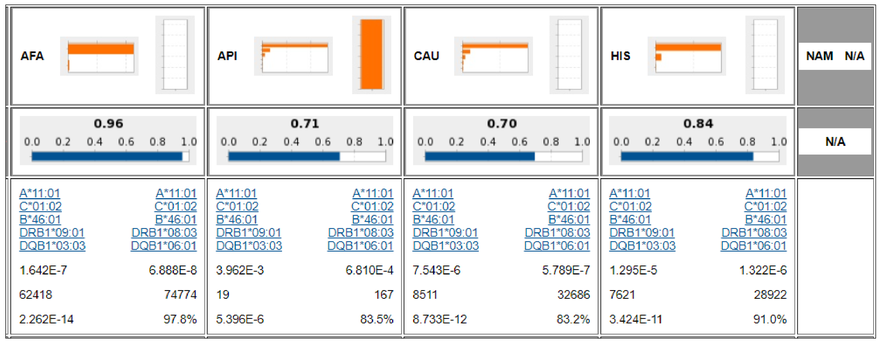

Figure 2. Haplotype analysis for the patient. From the population genotype frequencies, the patient is only common in API (Asian or Pacific Islander).

HLA ANTIBODY TESTING

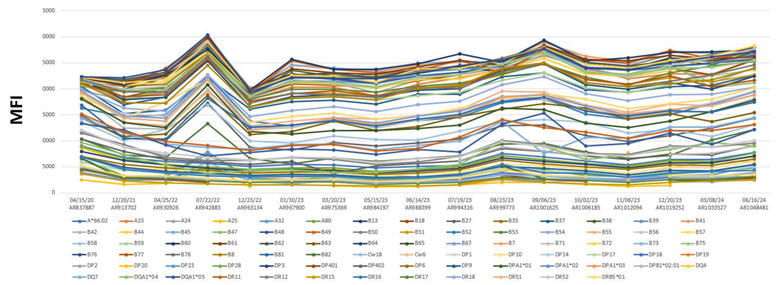

Figure 3. HLA antibody testing at neat was performed on a recent serum sample with the SAB based method (LabScreen, One Lambda). Shown is patient's current and historical antibody testing values at the time of assessment. MFI denotes mean fluorescence intensity.

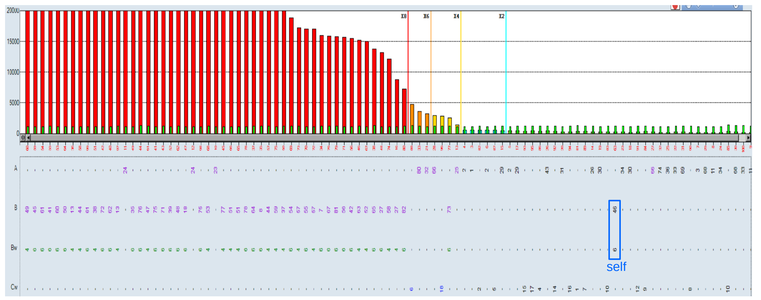

Figure 4. SAB Class I testing of the B46 +/+ patient. From the histogram, the B46+/+ patient has HLA antibodies against both Bw4 and Bw6 public epitopes. This will make getting this patient transplanted very difficult, as they will need a B46+/+ match.

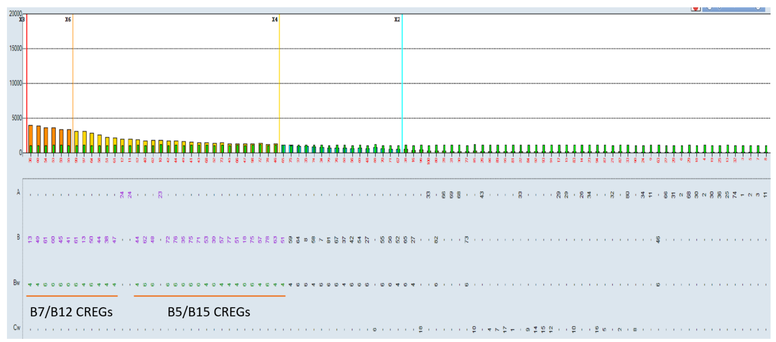

Figure 5. Virtual desensitization using SAB Class I 1:20 dilution for the B46 +/+ patient.

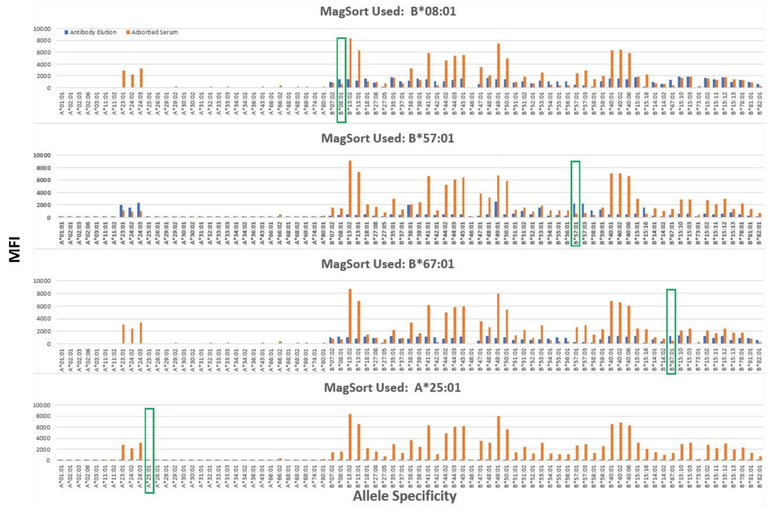

Figure 6. Virtual desensitization using MagSort isolation of specific Abs for the highly sensitized patient. Bw4 (B*57:01 and A*25:01) and Bw6 (B*08:01 and B*67:01) from MagSort were employed to identify unique patterns in sera of sensitized patients for specificity testing. The specific allele is highlighted in the green box. MFI denotes mean fluorescence intensity.

We found the weakest reactivity to antigens of the public epitopes Bw4 and Bw6, antigens of the B8 cross-reactive epitope group (CREG), and private epitopes specific to B27, B42, B37, B54, and B67, indicating these could potentially be crossed following initial rounds of desensitization. Moderate reactivity was found to antigens of the B5/B15 CREGs, indicating further rounds of desensitization would be needed to cross them. Very strong reactivity was found to antigens of the B7/B12 CREGs, indicating the antigens need to remain blocked in donor registries to avoid risk of antibody-mediated rejection associated with transplanting across strong DSA.

DISCUSSION

Our virtual desensitization protocol can be used to determine the number and strength of antibodies driving the 100% cPRA in highly sensitized candidates waiting for a kidney donor, such as those with B46-homozygous typing, providing a roadmap along the desensitization journey for expected antigens able to be crossed following initial versus multiple rounds of antibody-depleting therapies.