The Complexity for Transplanting HLA-B46 Homozygous Renal Candidates

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Abstract

HLA-B46 homozygous (B46$^{+/+}$) candidates for kidney transplantation are capable of making antibodies against both Bw4 and Bw6 public epitopes, therefore making finding a suitable donor difficult with a cPRA of 100%. Here, we examined potential strategies for four highly sensitized B46-homozygous candidates for renal transplantation.

In summary, the risk for graft rejection in the presence of Bw4 and Bw6 specificities, and a unique situation for HLA-B46$^{+/+}$ patients because of a recombination event between HLA-B*15:01 and HLA-C*01:02 loci in the Asian and Pacific Islander (API) population, is detrimental.

Impact: Some of these patients could become transplantable using a personalized strategy for desensitization, whereas others would only benefit from a change in donor allocation such as a steep continuous point scale for cPRA.

Introduction

The unacceptable waiting time for **HLA-B46** homozygous candidates in this study ranges from 9 to 16 years, with no current end insight. These renal transplant candidates carry atypical Bw6 and Bw4 epitopes resulting from **a recombination event between HLA-B*15:01 and HLA-C*01:02**. And, because HLA-B46 is mostly found in Eastern Asian countries, as indicated by the B*4601 allele frequency map pated below, this phenomenon translates into a limited donor pool towards performing HLA identical renal transplants in the US [1]. Secondly, high-titer specificities against Bw4 and Bw6 epitopes mostly found in HLA-B46$^{+/+}$ female patients commonly block 100% of available donors. In summary, distinction among public and private Bw4/Bw6 specificities among highly sensitized HLA-B46$^{+/+}$ candidates can be useful for expanding the donor pool for these patients, and increase the odds for organ allocation, with acceptable risk of rejection [2,3].

B*4601

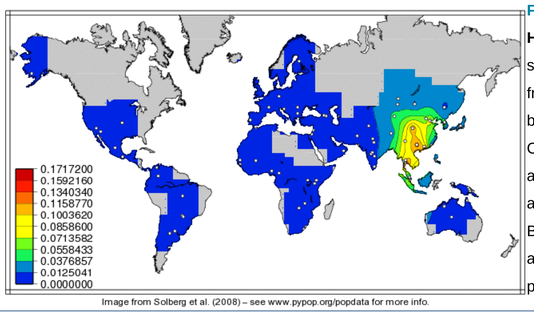


Image from Solberg et al. (2008) – see www.pypop.org/popdata for more info.

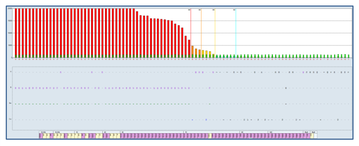
Figure 1. HLA-B46.

HLA-B*46:01 (B46) is commonly seen in East Asia and resulted from a recombination event between HLA-B*15:01 and HLA-C*01:02. HLA-B46$^{+/+}$ patients awaiting renal transplantation are known to have Bw4 and/or Bw6 antibodies, making renal allocation a very challenging process for these patients.

Results

Two of the four patients had suggested reactivity to private epitopes on single antigens or cross-reactive groups based on titration studies. This reactivity was confirmed by negative FCXMs (*T-cell < 50 MCS*) with either HLA-Bw4+/+ or Bw6+/+ cells. This indicates the possibility for successful desensitization whereby weaker specificities are removed as unacceptable antigens (UAgs) as they are reduced through antibody-depleting therapies. The other two patients had patterns suggestive of strong reactivity to only the Bw4 and Bw6 public epitopes, which was confirmed by positive reactivity of FCXM with either HLA-Bw4+/+ or Bw6+/+ cells despite expressing specific B locus antigens that were negative in the diluted serum's SAB. These results indicate the patient would not likely benefit from desensitization and would need a B46 homozygous matched donor in order to be transplanted.

Figure 2A. 52 y.o. female (HLA-B46$^{+/+}$) with 15 years of UNet waiting time. All cPRA%: 100%

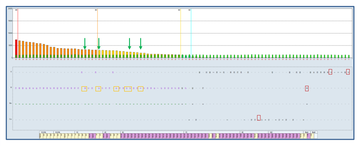


SAB-I neat serum at 14 years post Unet listing. Patient listed as status 1 and active with no history of previous transplants. ABO: A. UNet cPRA%, *99.99%*.

Figure 2B. 52 y.o. female (HLA-B46$^{+/+}$) with >1 year of waiting time. All cPRA%: 100%

SAB-I neat serum at <1 years post monitoring. Patient not listed in Unet and has no history of previous transplants.

Figure 2C. 10X serum from 52 y.o. female (HLA-B46$^{+/+}$) candidate (2A).



SAB-I 10X-titer serum showed significant decrease in antibody strengths, suggesting a possibility for desensitization therapy. ***HLA-B51 (2939 MFI), B57 (2348 MFI); (Bw4)*** | ***HLA-B8 (1958 MFI), B39 (3248 MFI); (Bw6)*** lymphocytes were used to assessed a predictive negative FCXM based MFI-value corresponding to a private epitope. SAB-II (10X) was positive with no DSA.

Figure 2D. 100X serum from 52 y.o. female (HLA-B46$^{+/+}$) candidate (2B).

SAB-I 100X-titer serum showed significant decrease in antibody strengths. ***HLA-B51 (2167 MFI), B57 (1120 MFI); (Bw4)*** | ***HLA-B8 (1903 MFI), B39 (2642 MFI); (Bw6)*** lymphocytes were used to assessed a predictive negative FCXM based MFI-value corresponding to a private epitope. SAB-II (100X) was negative.

Figure 3A. Public epitope (Bw4 / Bw6) analyte verification strategy using a pronase FCXM

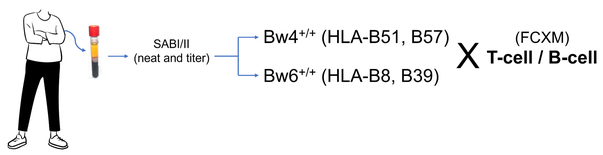
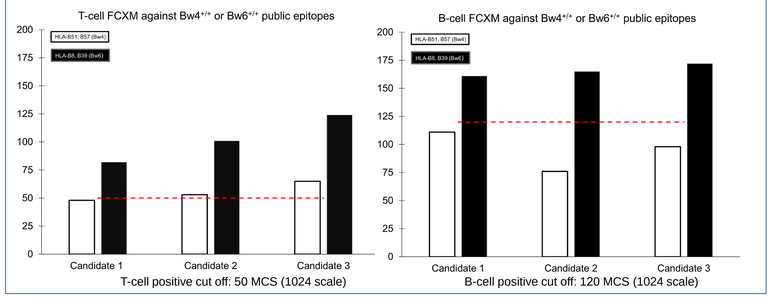


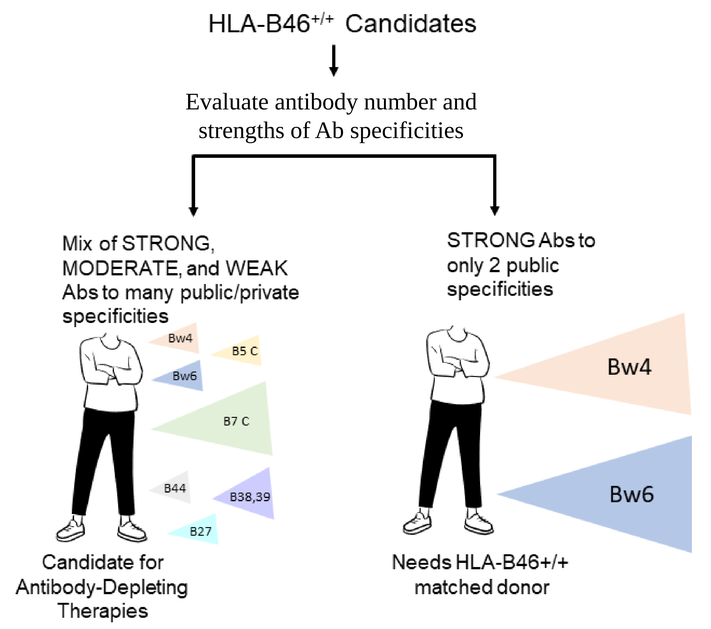
Figure 3B. Bw6 specificities have less potential for desensitization therapy *vs.* Bw4-related epitopes



Methods and Materials

Methods: SAB I/II (One Lambda) with titration and surrogate flow cytometry crossmatches (FCXM) were performed to determine the number and strength of specificities driving the high cPRA. Sample Size, n=4. One patient was amputated for B-cell FCXM analysis due to DSA against class II antigens.

Discussion



Assessment of patient antibody reactivity to public vs private epitopes can inform likely success of antibody depleting therapies. Patients who have a mix of antibody strengths and specificities may potentially be able to cross antibodies that become weaker through desensitization. Patients who make only strong antibodies to the two Bw4/6 public epitopes require an HLAB-46$^{+/+}$ matched donor.

- Highly sensitized HLA-B46 patients' donor pool can be expanded by differentiating private from public epitopes.
- Routine serum titers for HLA class I antibody monitoring can be informative for predicting effective desensitization therapy for HLA-B46$^{+/+}$ carrying Bw4 and Bw6 specificities.
- Surrogate physical crossmatches (FCXM) should be performed to support a private epitope specificity prior to unblocking or crossing DSAs.
- This pilot study suggest that weak Bw4 specificities are more likely to produce a negative physical crossmatch (FCXM).
- The schematic shown above suggest two different strategies for organ allocation among highly sensitized HLA-B46$^{+/+}$ patients.

Conclusions

- Personalized assessment of HLA-B46$^{+/+}$ renal candidates with cPRA% > 99.99% may uncover private vs public specificities.
- Identification of patients with a mix of strong, moderate, and weak antibodies to many public/private specificities may guide personalized desensitization strategies.
- Changes in donor allocation such as a steep continuous point scale for cPRA may improve the transplant rates for these patients.

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