OPTN Histocompatibility Committee
Meeting Summary
August 10, 2021
Conference Call

Peter Lalli, Ph.D., D(ABHI), Chair
John Lunz, Ph.D., D(ABHI), Vice Chair

Introduction

The Histocompatibility Committee met via Citrix GoToMeeting teleconference on 08/10/2021 to discuss the following agenda items:

1. Impact of HLA Matching on Graft Survival in Kidney Transplant Recipients
2. NMDP and OPTN HLA Data Collection Comparison

The following is a summary of the Committee's discussions.

1. Impact of HLA Matching on Graft Survival in Kidney Transplant Recipients

SRTR staff presented results from a data request from the Kidney and Pancreas Continuous Distribution Workgroup on the effects of matching at HLA-A, B, DR, and DQ loci on graft survival in kidney recipients whose transplants occurred between January 1, 2016 and December 1, 2020.

Summary of discussion:

A committee member asked if the study was looking at antigen-level mismatches or allele or epitope-level mismatches. SRTR staff confirmed that the study was looking at antigen-level mismatches. The committee chair said that the data was surprising, since the committee had expected a strong correlation with DQ matching and graft survival, but that the data is clear that DR antigen-level matching drives outcomes. SRTR staff clarified that in the data report appendix, they found that DQ and DR were heavily correlated as well, and that the effect of DQ matching may be slightly obscured by its heavy correlation with DR matching. A committee member asked if the protective effect of DR matching might be due to its use in allocation priority, and the SRTR staff member replied that its use in policy could help explain why it's such a strong predictor for graft outcome, but that he would have to look at the data in more detail to make a determination.

Committee members discussed whether or not high resolution typing and epitope-level matching could change these results. The main concern was that it's not currently relevant to organ transplant, as donors are only being typed at the antigen level at the time of match run, so epitope-level matching wouldn't be able to be implemented in the near future.

Committee members also discussed that the maximum follow-up data is currently 5 years, but that 10-year follow-up for graft survival may be more predictive. A UNOS staff member pointed out that HLA-DQ data fields were only implemented in 2016, so currently there isn't longer than 5 year outcomes based on donor and recipient DQ matching in the OPTN data set.

Committee members asked whether or not HLA matching looked at equity, as they were concerned for the potential to disadvantage minority groups by incorporating HLA matching in allocation. The committee agreed that the survival benefit of HLA matching is important, but that if it disadvantages minority groups it might not be worth prioritizing. One member posed that epitope matching may be

able to be implemented more equitably, but another pointed out that high resolution typing still won't be available for deceased donors so it won't be practical to implement within the allocation system.

Committee members ultimately agreed that for antigen-level donor and recipient HLA, only DR-matching should be incorporated into kidney and pancreas allocation moving forward. In addition, they agreed that there should be an equity analysis prior to implementation.

Next steps:

Committee leadership will take the recommendation to only include DR matching in kidney/pancreas allocation to the kidney/pancreas continuous distribution workgroup. Committee leadership will also recommend that the analysis for future allocation models evaluate equity before including any form of HLA matching.

2. NMDP and OPTN HLA Data Collection Comparison

Committee chair presented on the differences in OPTN and NMDP HLA data collection and its impact on the CPRA calculator project.

OPTN HLA Data Collection:

- Labs report HLA data as they define, without standardized typing methods
    - Since March 2019, labs have also been required to upload HLA typing source documentation for deceased donors
    - No standardization in documentation required
- About 15% of typings on the Donor Histocompatibility Form (DHF) are at two-field resolution
- The nine most commonly reported DPB1 alleles are the lowest in the p-group
    - The committee previously had guidance to report the lowest allele in the group if the typing was ambiguous
    - These made up >86% of the DPB1 typing for deceased donors from January 21, 2016-October 31, 2018
- OPTN HLA data collection 3/15/15-12/21/20
    - DQA1: Implemented 2015 (56667 deceased donor typings)
        - 12128 total alleles reported
    - DPA1: Implemented 2015 (44282 deceased donor typings)
        - 14020 total alleles reported
    - DPB1 (56596 deceased donor typings)
        - 110680 total alleles reported
    - There are two alleles reported per donor, and each allele can be reported at different resolutions
    - For allele-level typing at all three loci, there is a similar ethnic distribution in reporting to overall deceased donors

NMDP HLA Data Collection:

- Standardized recruitment typing for A, B, C, DR, DQB, DPB at NMDP-operated donor centers
- Transplant centers can perform additional typing at DQA/DPA and report back to NMDP, but this is not required or standardized
- Labs report the sequences obtained from typing, NMDP defines the alleles
- Class II alleles that only differ outside of Exons 2 and 3 will not be distinguishable in the NMDP data set of recruitment typings
    - Will be more granular than previous data set that was rolled into ARD groups

- Cohort for DQA and DPA much smaller than other loci
    - Using all typing methods, 590,000 DQA typings and 550,000 DPA typings

HLA Data Translation: New NMDP Data Set

- Previous NMDP data set included all recruitment typings, including SSO/SSP typings at intermediate resolution, rolled into antigen recognition domains for the frequency data set

NMDP HLA Data Collection by Era:

- Pre-2005: SSO
    - Class I: 6 million with A/B/C
    - DR/DQB1: 4 million
    - DPB1: 3 million
    - DPA/DQA: <200,000
- 2005-2010: SBT- Exons 2/3 Class I, Exon 2 Class II
    - Class I: 5.6 Million with A/B/C
    - DR/DQB1: 2.8 Million
    - DPB1: 3 million
    - DPA/DQA: <200,000
- 2010-2015: NGS- ARD-only, Exons 2/3 Class I, Exon 2 Class II
    - Class I: 4.8 million with A/B/C
    - DR/DQB1: 2 million
    - DPB1: 3 million
    - DPA/DQA: <200,000
- 2015-Present: NGS- Exons 1-8 Class I, Exons 2/3 Class II
    - Class I: 2.5 million with A/B/C
    - DR/DQB1: 1.4 million
    - DPB1: 2.4 million
    - DPA/DQA: <50,000

Takeaway question for the committee:

- For SOT, are Class II exons beyond 2 and 3 currently typed, or clinically necessary to be typed?
    - Could differences in amino acid residues in the leader peptide be clinically relevant or necessary to distinguish within our tables at this time?

Summary of Discussion:

Two committee members pointed out that regardless of the data limitations from the NMDP data set, it would still be far better than the current CPRA calculation in use. Another committee member agreed, and pointed out that a fair number of the discrepancies between the two data sets aren't even in most single antigen beads, so this data set would be perfectly adequate.

Another member asked if the data set would be adequate for future upgrades to the system. A UNOS staff member replied that a part of the requirements for the contract were a frequency set that would be more easily updatable to include common alleles in CPRA, and that it wouldn't require the same level of effort to update as the current haplotype-based frequency set does.

One member recommended that the OPTN modify the data collection for follow-up forms to start collecting higher resolution data, since a large number of centers are now performing confirmatory typings by NGS for deceased donors. Another member said that might be a good idea to consider, and that the data collection isn't up to date with current practices. The first member recommended allowing

programs to perform automated XML uploads for typings as well. UNOS staff said that if the committee would like to evaluate the current HLA data collection in follow-up forms, it would be most efficient to do so for the entire form at once, since it would require OMB approval prior to implementation and would be most efficient to package together.

Upcoming Meetings

- August 30, 2021, 2 PM EDT, Teleconference
- September 14, 2021, 12 PM EDT, Teleconference
- October 12, 2021, 12 PM EDT, Teleconference

Attendance

- **Committee Members**
  - Bill Goggins
  - Caroline Alquist
  - Eric Weimer
  - Evan Kransdorf
  - Gerald Morris
  - Jennifer Schiller
  - John Lunz
  - Manu Varma
  - Marcelo Pando
  - Omar Moussa
  - Pete Lalli
  - Phyllis Weech
  - Reut Hod Dvorai
  - Valia Bravo-Egana
  - Vikram Pattanayak
- **HRSA Representatives**
  - Jim Bowman
- **SRTR Staff**
  - Bryn Thompson
  - Jon Miller
  - Katie Audette
- **UNOS Staff**
  - Abby Fox
  - Amanda Robinson
  - Courtney Jett
  - Emily Kniepp
  - Joann White
  - Kelsi Lindblad
  - Leah Slife
  - Lindsay Larkin
  - Nicole Benjamin
  - Susan Tlusty
- **Other Attendees**
  - Annette Jackson
  - Cathi Murphey
  - Jim Kim
  - Martha Pavlakis
  - Medhat Askar
  - William Hildebrand