OPTN/UNOS Histocompatibility (Histo) Committee
Meeting Minutes
January 8, 2019
Conference Call

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Introduction

The Histocompatibility (Histo) Committee met via Citrix GoTo teleconference on 01/08/2019 to discuss the following agenda items:

1. Update from OPTN/UNOS Board of Directors Meeting
2. Correction to CPRA Calculator Table in OPTN/UNOS Policy
3. Questions regarding OPTN Policy 4.10, Table 4-14 HLA DPB1 Unacceptable Antigen Equivalences
4. Project Discussion-Change CPRA Calculator

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

1. Update from OPTN/UNOS Board of Directors (BOD) Meeting

The committee received a debrief from the OPTN/UNOS Board of Directors Meeting held in Dallas, TX from 12/3/18- 12/4/18.

Data summary:

UNOS staff highlighted some key points that the Histocompatibility committee should be aware of following the December 2018 Board of Directors meeting:

- Proposals on the consent agenda was passed in a block vote with 37 votes for yes, 0 votes for no, and 1 for abstain (37-0-1).
- The discussion agenda included *Changes to Islet Cell Program Requirements* (37-1-1 inclusive of one amendment), *Frameworks for Organ Distribution concept document* (36-1-0 supporting the continuous distribution model) and *Eliminate the Use of DSAs or Regions in Liver Distribution* (30-7-2 supporting the Acuity Circle (AC) model). The latter proposal garnered lengthy discussion, including amendments.

The BOD addressed other important business, including electing another at-large member, approved nominees for board vacancies, approved minutes from June 2018 Board meeting, approved a revised OPTN operating budget for the 2019 fiscal year, and a reduction in the candidate registration fee.

The Chair thanked UNOS staff for the update. With no questions from members, he segued to the next item on the Committee's agenda.

2. Correction to the CPRA Calculator Table in OPTN/UNOS Policy

UNOS Staff profiled a correction to OPTN/UNOS Policy 4.10 *Reference Tables of HLA Antigen Values and Split Equivalences* pertaining to the CPRA Calculator table.

Data summary:

The Chair updated the Committee on the progress of the policy correction to *OPTN/UNOS Policy 4.10, specifically in Table 4-15: Additional Unacceptable Antigen Equivalences to be used in the Calculated Panel Reactive Antibody (CPRA) Only*.

- Table 4-15 was amended to include additional alleles for CPRA calculation and these change were implemented by UNOS in December 2018. Following implementation, an error in Table 4-15 was discovered that artificially inflated CPRA for transplant candidates with these alleles. This was inaccurate because these alleles have zero frequencies in the population and therefore should not be used in CPRA calculation.
- The correction is to edit the tables and take out selected alleles and leave in DR 51, 52, 53 until there is data to support the frequencies for these alleles.

Summary of discussion:

Members asked when the correction will be made and the Chair reminded the Committee that this policy clarification will be going to the OPTN/UNOS Executive Committee mid-January 2019. In addition, UNOS IT staff have been working on this correction to help decrease the time for implementation. There were additional questions on the notification process for this change, and how many people were impacted by this issue. UNOS staff described the communication plan to the transplant community and summarized the candidate impact.

Next steps:

The policy clarification will considered by the Executive Committee on January 16, 2019. If approved, the changes will be implemented on January 17, 2019 along with a notice to the transplant community.

3. Questions regarding OPTN/UNOS Policy 4.10, Table 4-14 *HLA DPB1 Unacceptable Antigen Equivalences*

The committee will discuss the differences between Table 4-14 in OPTN/UNOS Policy and programming in Waitlist and Kidney Paired Donation systems.

Summary of discussion:

The Chair summarized recent questions and concerns that UNOS received about the DP antigens in the last few months. Specifically, the appearance of discrepancies between alleles listed in Table 4-14 and options to select in UNet. The Chair reminded the Committee of a discussion during the last in person meeting, “At that time they [Committee] were not ready to address DP antibodies as epitopes yet, because they did not have an idea of what epitopes and what groups they wanted to add to the equivalency tables in policy 4.10.” The final decision made by the committee was to screen all DP antibodies manually.

Following this the Chair asked, should the committee revisit the idea of entering all DP antibodies as avoids and not just the one’s the vendor kits defines. Members discussed the advantages and disadvantages of histocompatibility laboratories entering all DP antibodies as avoids. Concerns included:

- Not including the antibodies in UNet due to the risk of data entry errors and the overwhelming presentation it would create.
- How to report infrequently occurring DP antibodies, e.g: any in the 600’s. Members expressed this was challenging to perform due to limited availability of high resolution testing services e.g.: services not available or not performed during overnight hours.

There was a consensus among the members to create a list of all the common and well documented (CWD) antibodies and program that list in UNet and KPD.

Members then discussed with invited subject matter experts (SMEs) on the call if the content of data was available in the National Marrow Donor Program (NMDP) databases; was there frequency data associated with DP antibodies?

They responded that the NMDP did have this frequency data and offered to share it with the OPTN. Members were pleased to hear this information and commented the additional data set would create a very through list of CWD antibodies in the population.

Another membered offered a solution to the circumstance of encountering new alleles using the SSO (sequence-specific oligonucleotides) method and real time polymerase chain reaction (PCR) simultaneously to type deceased donors. Discrepancies discovered between these two methods in regards to DP antibodies could be rectified by utilizing SSP (Sequence-Specific Primer Typing). Uncertainty on how to enter these results may result in programming in UNet to generate a match run based on one DP allele and allocate the organ based on physical cross-matching due to uncertainty over the second DP allele.

At the conclusion of the discussion, the Committee agreed that the Equivalency Subcommittee responsible for the annual update of the HLA equivalency tables needs to consider the CDW DP antigens using both UNOS data and the NMDP frequency data to screen off CWD antibodies not just the one defined in the vendor kits. It should be presented in the next equivalency tables update.

UNOS staff then proposed more Committee member involvement in user testing of Histocompatibility-related programming in the future. Several members agreed this was important and volunteered to serve in this capacity. The Chair pointed out the difference between being shown how programs work and robust user testing them. UNOS staff asked members interested to respond by email.

Next Steps:

UNOS staff will:

- Email the relevant members on the Equivalency Subcommittee for the equivalency table update and provide them prudent information.
- Work on developing a HLA Equivalency Table Update project in 2019 in conjunction with subcommittee members.
- UNOS Research staff will provide a response to a data request about all the DP antibodies reported to the OPTN in the past two years.

4. Project Discussion-Change CPRA Calculator

The Committee will discuss the progress to date and next steps to develop this project

Data summary:

The Chair gave a brief history of the issues/questions thus far:

- Is the OPTN versus NMDP data comparable? Does it give the same source of information?
- Does it include DQA and DP? Because these patients are being disadvantaged. Those that have those antibodies are not being counted toward their CPRA currently.
- Discussion on whether the committee should consider haplotype data or count method and what the data may look like.

Following this summary, the invited SMEs presented an update on the project.

- A brief review of CPRA and how it mathematically calculated was discussed.
- Hypothesis: Is the currently UNOS panel undersized?

- Findings:
  - The researches then presented a plot of the 10 most frequent HLA haplotypes for Caucasians in 3 panels. A: Standard OPTN reference panel B. NMDP reference panel C: recomputed UNOS reference panel. More haplotypes similarities in the NMDP than to the standard OPTN panel. The standard OPTN panel frequencies are not what is expected based on current literature. Overall, the Caucasian haplotype frequencies are incorrect.
  - Showed the validation in the shortcomings of the current OPTN CPRA values (OPTN CPRA) in terms of linkage disequilibrium (LE) values. In the data there is a decrease in linkage disequilibrium in HLA C and HLA DQ loci compared to the other loci.
    - The next figure was a scatterplot of NMDP CPRA and OPTN CPRA values for each candidate. Overall it showed a systematic over estimation of CPRA while using OPTN frequencies.
      - Note: The NMDP CPRA values for this scatterplot were taken from NMDP haplotypes. A calculator was created based on that reference panel and was compared to OPTN CPRA values.
    - The next figure looked at a candidates OPTNCPRA and the point groups they would be in compared to the CPRA NMDP point groups. Looking at a candidate with a 100% CPRA OPTN, 12% in that category would reclassified into a lower point group based on NMDP CPRA. Several other point groups increase and/or decreased based on the NMDP CPRA.
    - The same data was used to compare kidney offers per year and it showed that the NMDP CPRA effects the highly sensitized candidates. In the current framework NMDP CPRA is more reflective of the frequency of haplotypes in the population.

Summary of discussion:

Members of the committee found this data very informative. The Chair asked the Committee, should DP and DQA loci be added later, or incorporate all at one time? The consensus in the Committee was to incorporate all the new loci at once to decease disadvantaging transplant candidates and prevent any problems with new allocation frameworks that are being presented by several committees.

Following this discussion, the Chair suggested two timelines

1. Public comment in August 2019 and BOD in December of 2019, or
2. Public comment in January 2020 and BOD in June 2020

There was a brief discussion but no timeline was solidified and the Committee is waiting for the invited SMEs to provide the final data to the Committee during a future conference call or meeting.

Next Steps:

Project Researches will send the data to the committee and UNOS staff will keep in touch with project researchers in the next coming months for any updates.

Upcoming Meetings

- February 15th, 2019 Full Committee teleconference call
- March 26, 2019 In-Person Committee meeting Chicago, IL