OPTN Histocompatibility Committee
Meeting Summary
November 14, 2023
Conference Call

John Lunz, Ph.D., F(ACHI), Chair
Gerald Morris, MD, Ph.D., Vice Chair

Introduction

The Histocompatibility Committee, the Committee, met via WebEx teleconference on 11/14/2023 to discuss the following agenda items:

1. P-Groups and Unacceptable Antigens in the OPTN Waiting List
2. P-Groups and Eplet Reactivity Patterns
3. FDA Proposed Rule: Laboratory-Developed Tests

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

1. P-Groups and Unacceptable Antigens in the OPTN Waiting List

The Committee continued previous discussions regarding p-groups and unacceptable antigens.

Presentation summary:

Background:

- Goal: Determine if screening off the P-groups from the higher allele-specific unacceptable antigens would be an expected behavior based on current unacceptable antigen listing patterns
    - Would adding P-groups as equivalent to higher number alleles be an anticipated change, based on current practices?
- Cohort: All candidates currently waiting as of 10/7/2023
    - 46,059 candidates waiting with at least one unacceptable antigen listed, with 598,161 total unacceptable antigens listed

Key Takeaways:

- In total, these higher-number alleles appear separated from their parent serologic antigens and P-groups 36% of the time these alleles were listed as unacceptable, in 2,266 unique cases
    - This accounts for 0.4% of all unacceptable antigens listed in the OPTN Computer System
- This would also change the CPRA scores for all candidates who have the allele-specific unacceptable antigens listed without the parent serologic antigens
- While less common than listing alongside the antigen and first allele in the P-group, people are listing higher alleles separately
    - Adding all the alleles within the P-group to the higher allele unacceptable antigen would not be expected behavior—it would no longer allow for the practice of listing higher allele unacceptable antigens separately, and may screen candidates off of more match runs than intended

Summary of discussion:

The Committee did not make any decisions; however, they did discuss whether to include p-groups as equivalents to specific unacceptable antigens.

A member expressed that certain centers prefer to separately list specific alleles for their patients, even if these alleles belong to a higher category within the same p-group. The member highlighted that existing listing practices prioritize antigens to alleles compared to p-group alleles to individual alleles, aiming to avoid the automatic broad screening of antigens or alleles. Additionally, the member pointed out that treating p-groups as equivalent to specific unacceptable antigens may inadvertently exclude a wide range of patients, which might not align with the intended goals of transplant centers that are specifying antibodies in their listings.

A participant emphasized the importance of recognizing that the Committee may be assuming laboratories listing unacceptable antigens have comprehensive knowledge of all members in the p-group. She noted that, based on her experience, there is generally a limited understanding of the intricate details of p-groups within the transplant centers where she operates. The participant stressed that if all members of a p-group are immunologically identical, their inclusion as equivalents should be advanced. The member also highlighted that failing to do so could lead to delays in organ allocation. Specifically, if these alleles are not automatically screened out, laboratories would need to invest additional time in conducting a virtual crossmatch.

2. P-Groups and Eplet Reactivity Patterns

The Committee reviewed cases in which an epitope may have a unique antigenic immunogenicity that would potentially allow it to be recognized differently from other members within that p-group.

Presentation summary:

Background:

- Goal: Determine if P-groups listed in the HLA equivalency tables should be listed under the same allele-specific unacceptable antigens, based on identified eplet reactivity
    - Will all alleles within a P-group react the same way, serologically?
- Example: C*02:02P-02:02/02:10
    - 24 “shared eplets, 1 “split” eplet
    - 211T contains *02:02 but NOT *02:10

Key Takeaway:

- Not all alleles within a p-group will share serologic reactivity with all other alleles within a p-group

Summary of discussion:

Decision #1: By way of a vote, the Committee decided to exclude p-group alleles as equivalents and will move the proposal forward for implementation.

Vote: Yes (4), No (6), Abstain (1)

Decision #2: By way of a vote, the Committee decided to approve the *Update HLA Equivalency Tables, 2023* proposal for implementation.

Vote: Yes (11), No (0), Abstain (0)

Decision #1: By way of a vote, the Committee decided to exclude p-group alleles as equivalents and will move the proposal forward for implementation.

In deliberating whether to designate p-groups as equivalents, a Committee member shared the belief that individuals may not be intentionally listing specific alleles but rather lack awareness of p-group members. The Chair acknowledged the heterogeneity in how antibodies are reported, recognizing that some antigens might be listed due to a genuine understanding. However, he stressed that the Committee should operate on the premise that laboratory directors, who oversee operations, have input into how antibodies, particularly unacceptable ones, are reported. The Chair cautioned against assuming that reporting specific alleles as unacceptable solely stems from inexperience or lack of knowledge within p-group members. He highlighted the importance of considering that some laboratories may intentionally list specific alleles separately. The Chair emphasized that the decision on how to list should be determined by laboratory practices and driven by the director's discretion.

A member emphasized the significance of the HLA community comprehending the scientific rationale behind listing practices. Specifically, there is a need for understanding how allele-specific antibodies function in cell binding and contribute to positive cross matches. The member expressed concern that if the proposed change is enacted, leading to automatic screening, individuals might not progress to the stage of conducting a crossmatch to delve deeper into p-group information.

An individual noted that thus far, there haven't been any adverse effects from the current system configuration. Consequently, they recommended that the Committee shift its focus towards education and promoting the use of p-groups. This approach aims to enhance people's understanding of how incorporating p-groups can facilitate organ allocation and streamline compatibility assessments. The Chair concurred, deeming it a valuable suggestion, and suggested considering it for inclusion in a forthcoming guidance document.

OPTN contractor staff prompted a vote on whether to include p-groups as equivalents for unacceptable antigens in the *Update HLA Equivalency Tables, 2023* proposal. They explained that if included, a second round of public comments would be required, while exclusion would lead to the finalization of the proposal. A member expressed concern that omitting p-groups might burden laboratories, requiring virtual cross-matching for confirmation. The Chair argued that this wouldn't be an additional burden, aligning with the current practice.

Vote: Should p-groups be included as an equivalent to specific unacceptable antigens?

Yes (4), No (6), Abstain (1)

Decision #2: By way of a vote, the Committee decided to approve the *Update HLA Equivalency Tables, 2023* proposal for implementation.

Following the Committee's decision to exclude p-group equivalents in their proposal they were prompted to participate in a final vote. This vote intended to determine whether the proposal in total should be finalized for implementation.

Vote: Approve for implementation?

Yes: (11), No: (0), Abstain: (0)

Next steps:

OPTN contractor staff will move forward with finalizing the proposal for implementation.

3. FDA Proposed Rule: Laboratory-Developed Tests

The Committee discussed potential public comments from the Histocompatibility Committee for the proposed rule that the FDA released related to laboratory-developed tests (LDTs).

Presentation summary:

- FDA released a proposed rule on Laboratory Developed Tests (LDTs) on 10/3/2023, Public Comment open through 12/4/2023
- The Histocompatibility Committee can provide a public comment to the OPTN Executive Committee to review/approve posting to the FDA on behalf of the OPTN
- The FDA rule would require premarket review of LDTs by the FDA, for those manufactured by a lab and offered
- FDA intends to continue to exercise enforcement discretion for LDTs designed, manufactured, and used in a single laboratory that is CLIA-certified and meets requirements to perform high-complexity histocompatibility testing when used in context of organ, stem cell, and tissue transplantation to perform HLA allele typing, for HLA antibody screening and monitoring, or for conducting real and "virtual" HLA crossmatch tests
- FDA preliminary determination that this testing is unique in that they are generally developed, and the testing is generally performed, in urgent, life-saving situations for the patient

Summary of discussion:

The Committee did not make any decisions; however, a member commented on the proposed rule.

A member stated that the Committee should be in approval of the histocompatibility test consideration proposed by the FDA. Considering that histocompatibility testing is a rather unique set of LDTs, this consideration is critical. He urged that the group support its consideration.

Next steps:

Committee members will send in their comments by email so OPTN contractor staff may summarize the sentiment into one document. This document will then be sent to the Executive Committee who will review it prior to posting it as a public comment.

Upcoming Meeting(s)

- December 12, 2023
- January 9, 2023

Attendance

- **Committee Members**
  - John Lunz
  - Gerald Morris
  - Caroline Alquist
  - Laurine Bow
  - Amber Carriker
  - Julie Houp
  - Andres Jaramillo
  - Helene McMurray
  - Darryl Nethercot
  - Hemant Parekh
  - Crystal Usenko
  - Qingyong Xu
- **HRSA Representatives**
  - Jim Bowman
- **SRTR Staff**
  - Katie Audette
  - Jon Miller
  - Rajalingam Raja
- **UNOS Staff**
  - Courtney Jett
  - Alex Carmack
  - Amelia Devereaux
  - Thomas Dolan
  - Laura Schmitt
  - Kaitlin Swanner