OPTN Kidney & Pancreas Transplantation Committee
Continuous Distribution Workgroup
Meeting Summary
March 26, 2021
Conference Call

Silke Niederhaus, MD, Chair
Rachel Forbes, MD, Vice Chair
Vince Casingal, MD, Chair
Martha Pavlakis, MD, Vice Chair

Introduction

The Kidney & Pancreas Transplantation Committee Continuous Distribution Workgroup (the Workgroup) met via Citrix GoToMeeting teleconference on 3/26/2021 to discuss the following agenda items:

1. Welcome & Review of Project Goals
2. Recap of March 12th Meeting
3. Discussion: Human Leukocyte Antigen (HLA) Data Request

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

1. Welcome & Review of Project Goals

The Workgroup reviewed the goals of the Continuous Distribution project as well as the Workgroup's next steps, including the second phase of the project (assigning values to attributes) and the development of a concept paper summarizing the identification and categorization of attributes.

Summary of discussion:

The Workgroup had no comments or questions.

2. Recap of March 12th Meeting

The Workgroup reviewed highlights from their March 12th meeting, including continued discussions on the HLA matching rating scale related to 0-ABDR mismatches, DQ matching, graft life and pediatric priority, and race and equity in access. A survey was sent to all group members after this meeting to prioritize enhancements for the data request.

Summary of discussion:

The Workgroup had no comments or questions.

3. Discussion: HLA Data Request

The Workgroup reviewed the results of an HLA matching data survey sent to Workgroup members and finalized the data request on HLA matching and post-transplant outcomes.

Data summary:

A large majority of survey participants found graft survival more relevant than patient survival in terms of HLA matching's effect on post-transplant outcomes.

Survey participants had consensus that 5 years was the minimum amount of follow-up time needed to understand the impact of HLA matching on post-transplant outcomes.

Survey participants were considerably split on which HLA matching models were most appropriate for use in understanding HLA matching on post-kidney transplant outcomes. A majority chose 0-ABDRDQ mismatches as their highest preference, with examining independent loci and 0-ABDR mismatches tied for the second highest preference.

A large majority of survey recipients wanted to examine DR and DQ loci independently over A and B loci.

The survey participants had greater representation from the OPTN Kidney Committee than the OPTN Pancreas Committee, and one participant was a representative of the OPTN Histocompatibility Committee.

Summary of discussion:

A Workgroup Chair remarked that while graft survival will address longevity survival related to HLA matching, most transplant data tends to examine both graft and patient survival together. If both patient and graft survival outcomes can be utilized that is preferable. Another Workgroup Chair agreed, adding that graft survival will likely show differences in outcomes later on, but that the benefits of close HLA matching relate more to patient survival. Staff explained that choosing either patient or graft survival will allow the Workgroup to build a more transparent rating scale, particularly as the effects of HLA matching on both outcomes are likely similar in direction and relative impact. A Workgroup Chair noted that graft survival would likely be more strongly impacted by HLA matching than patient survival.

A Workgroup member noted that all patient losses are included in graft losses, and that differences in graft survival may be influenced by patient survival. The member recommended including both patient and graft survival in order to understand the impact of patient survival on graft survival and better capture true immunological graft loss. A representative of the Scientific Registry of Transplant Recipients (SRTR) explained that the Workgroup may request death-censored graft survival data as well, and confirmed that both overall and death-censored graft survival can be included in the data request. A Workgroup Chair noted that patient survival could indicate limited to no relation to graft survival, as well as more direct data, such as increased patient longevity with improved HLA matching, though this effect would require many years of follow to be detectable in the data. Because of this, graft survival and death-censored graft survival are likely the most direct measures of HLA-related post-transplant outcomes.

One Workgroup member recommended looking at patient perspective data from Standardized Outcomes in Nephrology - Transplantation to decide whether graft or patient survival should be utilized, and a Workgroup Chair agreed that patient perspective is critical to the development of continuous distribution allocation. Staff explained that the rating scale and parameterization of attributes are clinical elements of the composite allocation score, separate from values-based decisions of relative importance of donor and candidate attributes. These values decisions will be utilized to determine the relative weight of each attribute in building the composite allocation score, and these discussions will be critical to the development of continuous distribution later on.

One Workgroup member agreed that graft survival was preferable to measure the effect of HLA matching, particularly as HLA has a more direct effect on graft survival, while patient survival is subject to a variety of other variables. A Workgroup Chair added that graft survival is also subject to a number of variables, though fewer than patient survival. One member noted that early technical graft losses in the first 30 or 60 days post-transplant should be considered when examining immunologic graft loss data. Another member agreed that the graft loss data should be adjusted for technical losses, as well as

limited to blood type compatible transplants, such that the data included only standard transplants and grafts that survive at least 30 days. An SRTR representative confirmed that sensitization would be flexibly adjusted for in order to best capture the relationship between calculated panel reactive antibodies (cPRA) and graft failure.

A Workgroup Chair remarked that ideally, the Workgroup could examine graft survival with the amount of immunosuppression taken by recipients, a time varying covariate that is difficult to measure.

One Workgroup Chair asked what the disadvantage of requesting both patient survival and graft survival, and an SRTR representative explained that the Workgroup would review twice as much data and would later need to decide whether to lean more heavily on patient survival or graft survival metrics in building the rating scale. Another Workgroup Chair expressed that the Workgroup had the bandwidth to review data for both patient and graft survival outcomes, particularly as most post-transplant data presents both outcomes. The Chair continued that having both patient and graft survival outcome data will help with the weighting of HLA-matching in the composite allocation score, not confuse it. The Workgroup agreed that both graft survival and patient survival outcomes should be utilized to study HLA matching's impact on post-transplant outcomes.

An SRTR representative confirmed that data related to both graft and patient survival would relate only to the HLA matching for kidney transplant. Workgroup Chairs agreed that the pancreas data request should be developed separately, as pancreas has significantly less data available. Another SRTR representative recommended examining rejection outcomes with the first year post-transplant related to HLA-matching with pancreas, noting that the impact of matching would be better captured within that data than graft survival. Pancreas graft survival data in particular is not robust, though data on rejection cannot be corroborated. Workgroup Chairs agreed that pancreas patient survival data may also lack adequate robustness, and that robust rejection outcome data would be more ideal for pancreas, if it is available. The Workgroup agreed to restrict this discussion to the Kidney data request, and revisit the HLA matching data request for pancreas and kidney-pancreas (KP).

A Workgroup member suggested utilizing a time-to-event analysis for graft loss, particularly with Kaplan Meier curves. SRTR representatives explained the model would likely be a variation of a Cox model adjusted for a number of characteristics, and would include time to event as adjusted.

An SRTR representative noted that 5 years may not be enough follow up time to show significant impact or benefit from HLA matching. Another member agreed that may be a concern, but noted that 5 years follow up makes the most sense clinically. A Workgroup Chair remarked that 5 years is a reasonable time frame, as it balances relevancy to current patient experiences and mid-term graft survival outcomes. The Workgroup agreed.

A Workgroup Chair remarked that it would be ideal to run all of the models, but that the 0ABDR and 0ABDRDQ mismatch models may show the largest differences. It was confirmed that less than 10 percent of DQ mismatching data is missing as far back as 2010, and is more complete for donors. A Workgroup member agreed that running all of the models would be more efficient and expedient, allowing for complete review of relevant data. Several Workgroup members agreed.

One member expressed concern that running all of the models would inundate the Workgroup with data, and recommended examining level of mismatch for ABDRDQ on a 0-8 scale, with an outcome associated for each level. An SRTR representative explained that the post-transplant effects of mismatching differ between loci, and an ABDRDQ mismatch scale would fail to capture that nuance. A Workgroup member remarked that the most recent literature found that Class I loci don't play a strong role in post-transplant outcomes outside of zero mismatch scenarios, so the models should utilize Class II loci matching, 0-ABDR mismatch, and 0-ABDRDQ mismatch. The literature has found Class II loci

matching more critical to long term graft survival. The Workgroup agreed to request binary 0-ABDR mismatch and 0-ABDRDQ mismatch variables, as well as level of matching for DR and DQ loci.

Upcoming Meetings

- April 23, 2021 (Teleconference)

Attendance

- **Committee Members**
  - Silke V. Niederhaus
  - Vincent Casingal
  - Todd Pesavento
  - Jodi Smith
  - Alejandro Diez
  - Cathi Murphey
  - Dierdre Sawinski
  - Elliot Grodstein
  - John Barca
  - Martha Pavlakis
  - Parul Patel
  - Raja Kandaswamy
  - Abigail Martin
- **HRSA Representatives**
  - Jim Bowman
- **SRTR Staff**
  - Ajay Israni
  - Bryn Thompson
  - Jon Miller
  - Nick Salkowski
  - Peter Stock
  - Sommer Gentry
- **UNOS Staff**
  - Lindsay Larkin
  - Joann White
  - Rebecca Brookman
  - Kayla Temple
  - Ross Walton
  - Tina Rhoades
  - Abigail Martin
  - Alison Wilhelm
  - Amanda Robinson
  - Nang Thu Thu Kyaw
  - Ben Wolford
  - Jen Wainwright
  - Kaitlin Swanner
  - Kerrie Masten