GUIDELINE

The Authors' Perspective on 'Summary of the International Society for Heart and Lung Transplantation Consensus Conference on Emerging Understanding of Antibodies and Antibody-mediated Rejection in Heart Transplantation'

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1. BACKGROUND

The understanding of circulating antibodies and their relationship to antibody-mediated rejection (AMR) has yet to be fully elucidated in heart transplantation. Managing detected antibodies before and after heart transplantation and its accompanying clinical findings remains variable and based on limited objective data. The International Society for Heart and Lung Transplantation (ISHLT) Consensus Conference on emerging understanding of antibodies and antibody-mediated rejection in heart transplantation[1] took place on April 18, 2023, in Denver, CO, USA, and included 52 U.S. and 23 international multidisciplinary experts in cardiac transplantation and transplant immunology as part of an update to previously held ISHLT Consensus Conferences on Sensitized Patients Awaiting Heart Transplant (2008),[2] Antibody-Mediated Rejection in Heart Transplantation (2010),[3] Management of

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Antibodies in Heart Transplantation (2016).[4] This conference was designed to apprise the heart transplant community on the current understanding of the role of human leukocyte antigen (HLA), non-HLA, ABO antibodies, and biopsy-proven AMR in heart transplantation, discuss risk factors for the development of antibodies and strategies for risk stratification, identify effective modes of therapy to treat the sensitized and highly sensitized patient before, during, and after transplant, and explore a framework and criteria (sensitization threshold) for potential higher-status listing or priority access to compatible donors for highly sensitized patients awaiting heart transplantation.

2. TOP TAKEAWAYS

The following 10 Items highlight key and relevant changes from the last antibody conference:

1. Stratify antibody risk by Mean Fluorescent Intensity (MFI) in the undiluted assay:

- Low risk < 5,000 MFI
- Moderate risk 5,000-8,000 MFI
- High risk > 8,000 MFI.

2. Consider desensitizing if the calculated panel reactive antibody (cPRA) is >50%, depending on patient/antibody characteristics and center support/infrastructure. The goal of pre-transplant desensitization therapy is to lower the cPRA to broaden the donor pool and minimize the risk of post-transplant AMR.
3. There is a need for precision in defining ABO-related histocompatibility between donor and recipient to enable clinicians to carefully analyze risk and benefit while expanding this platform from infants to older children and select adults.
4. Induction therapy (antithymocyte globulin (ATG) or basiliximab) may be considered peri-transplant for sensitized patients.
5. Crossing donor-specific antibodies (DSA) in experienced centers may be considered for sensitized patients but should take into account patient characteristics, antibody attributes, and their biological significance.
6. If crossing DSA at the time of heart transplant, induction therapy (ATG) or IVIG/plasmapheresis are common therapies.
7. Several variables should be considered to treat patients with post-transplant DSA, including cardiac dysfunction by imaging, abnormal hemodynamics, an increasing MFI trend in DSA, the presence of early DSA, antibody attributes (C1q+ binding, detection of DSA in dilution assay), biopsy-proven pAMR ≥ 2, and abnormal molecular findings (dd-cfDNA and/or the MMDx) as available. However, the clinical utility of treating asymptomatic post-transplant DSA remains unclear.
8. Endomyocardial biopsy is not mandated in patients with asymptomatic post-transplant DSA but should be performed when DSA are associated with signs of clinical or subclinical graft dysfunction or graft injury.
9. Testing and treatment of non-HLA antibodies have not been recommended until a causal role in graft injury and defined thresholds are established.
10. Sensitization should be factored into donor heart allocation policy.

3. CONCLUSION

The conference represented a collaborative multidisciplinary effort by experts in cardiothoracic transplantation worldwide to discuss the optimum approach and treatment of circulating antibodies and AMR in heart transplant candidates and recipients and better understand their impact on clinical outcomes. We hope the results of this consensus conference will provide a more standardized pathway for evaluating patients for heart transplantation and post-transplant monitoring and pave the way for future studies.

This paper is dedicated to the memory of Jignesh Patel MD, PhD

DISCLOSURE STATEMENT

Jon Kobashigawa: received research grants from CareDx Inc., Sanofi-Genzyme, and CSL-Behringer. Andreas Zuckermann: held leadership position at ISHLT (past president, board of directors). Monica Colvin: received grant support from Natera and serves on Natera's scientific advisory board. Anne Dipchand: received support for attending meetings and/or travel from the Hospital for Sick Children and holds leadership positions at the American Society of Transplantation and David Foster Foundation. Marta Farrero: received personal payment from Chiesi and received support for attending meetings from Novonordisk and Abbott, holds a leadership position at ISHLT, and her institution received equipment support from Astra-Zeneca. Marlena Habal: received grant support from Bristol Myer Squibb. Annette M. Jackson: received consulting fees from Hansa Biopharma, received an honorarium from One Lambda ThermoFisher- Speaker Bureau, and received HLA typing reagents from CareDx. Kavitha Muthiah: received speaker honorarium from Abbott and Novartis. Luciano Potena: received consulting fees from Biotest, Roche diagnostics, received honorarium from Takeda, Abbott, Biotest, and holds a leadership position at ESOT. Elaine F. Reed: received several grants (R01AI173050, 1U19AI172713-01, P01AI120944, 2R01AI135201-06, 1U01AI179524-01), received consulting fees from Regeneron, received support for attending meetings from the Federation of Clinical Immunology Societies, and serves on the board of the federation. Palak Shah: received NIH K23 - 1K23HL143179 grant, received consulting fees from Merck, Natera, JVP Labs, Tosoh Biosciences, and Ortho Clinical Diagnostics, and has Stock Options in Procyrion. Simon Urschel: received a grant from the Canadian National Donation and Transplant Research Program and serves on the program's data safety monitoring board. Lori West: received support from the Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, Canadian Glycomics Network, Heart and Stroke Foundation of Canada, Enduring Hearts Foundation, and Women and Children's Health Research Institute, and serves as a member of AVIVO scientific advisory board. Jignesh Patel: received research grants from Alexion Pharmaceuticals, Pfizer, Alnylam Pharmaceuticals, and Astra Zeneca. All other authors have no conflicts of interest to disclose.

APPENDIX

Participants in the consensus conference and pre-meeting calls

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