Soaking it up: Analysis of HLA antibody adsorption via dilutions after heart-after-liver transplantation.

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Abstract

High degree of HLA sensitization is a known barrier to heart transplantation, particularly in patients with cPRA > 90%. Desensitization employing plasmapheresis in conjunction with different immunomodulatory and biologic agents have demonstrated varying degrees of efficacy in lowering antibody burden. In recent years, Heart-After-Liver Transplant (HALT) has emerged as an alternative to traditional desensitization[1-4]. The procedure involves transplanting the liver from an HLA incompatible donor to serve as a reservoir to adsorb donor-specific antibodies (DSA) thereby permitting subsequent transplant of the same donor's heart without rejection. The recipient's native liver can then be dominoed to another recipient.

Herein we describe our institution's experience with its first four cases of HALT, focusing on the HLA antibody response throughout the procedure and the use of serial dilutions to help determine prognostic markers of response.

Heart After Liver Transplant (HALT) Procedure

Reverse Transplant Sequence

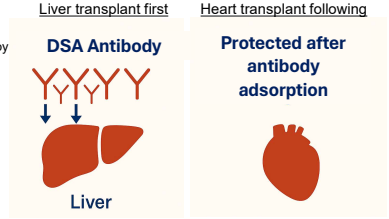
HALT reverses traditional transplant order by transplanting the liver before the heart to improve outcomes.

Liver as Antibody Sink

The liver adsorbs and neutralizes donor-specific antibodies reducing their circulating levels effectively.

Immunologic Conditioning

The liver transplant acts as an active immunologic conditioning step before heart transplantation.



Case Series

Patient	Demographics & MCS	Sensitization	Clinical Outcome
1	52F, NICM HVAD, recurrent VT, RV failure Sensitization: G6P2, VAD, transfusions	cPRA 99.98%	Normal graft function 0R biopsy at 9 months
2	59F, NICM Axillary Impella, CKD3 Sensitization: G3P3, Impella, transfusions	cPRA 99.67%	Normal graft function 0R biopsy at 4 months
3	19M, complex CHD Biventricular HM3 support Sensitization: lifelong transfusions, mechanical support	cPRA 99.97%	Died ~6 weeks (E. coli sepsis) Early PGD requiring VA-ECMO
4	34F, NICM Sensitization: G5P2, transfusions	cPRA 99.99%	Normal graft function 0R biopsy at 6 weeks

Methods and Materials

HLA antibodies were tracked by Class I and Class II single antigen bead testing (LABScreen®, One Lambda, ThermoFisher) pre-transplant, post-plasmapheresis (PLEX), post-liver implantation, post-heart implantation, post-closure, and post-operatively (see **Figure 1**).

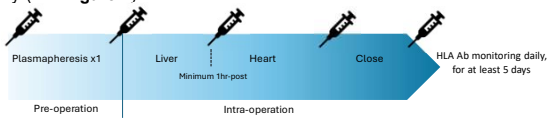


Figure 1. Pre- and intra-operative HLA testing timeline. Samples were isolated Pre-PLEX, Post-PLEX, Post-liver, Post-heart, and Post-closure.

The MFI values for positive HLA antibodies in the Pre-PLEX ("Pre-transplant") sample were compared in subsequent samples. Serial dilutions (undiluted="neat" to 1:4096) of the Pre-PLEX sample were performed and titer was identified by isolating the dilution at which the DSA fell below the program threshold for unacceptable antigens at our center (8000 MFI).

Results

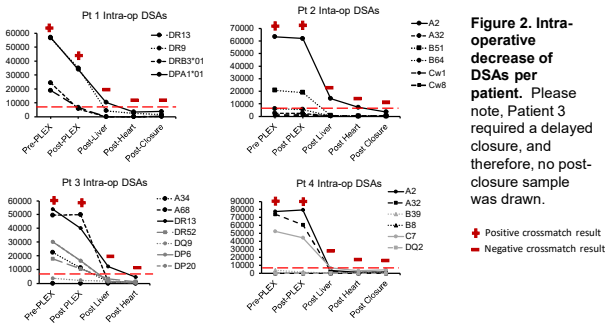


Figure 2. Intra-operative decrease of DSAs per patient. Please note, Patient 3 required a delayed closure, and therefore, no post-closure sample was drawn.

Positive crossmatch result
Negative crossmatch result

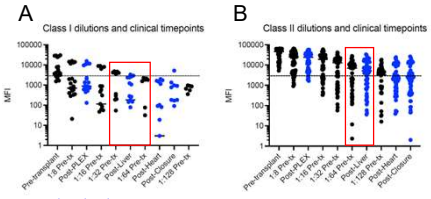


Figure 3. MFI of all HLA antibodies decreased intra-op. To determine if all HLA antibodies decreased, MFI of all beads >3000 MFI on the pre-transplant sample for Patient 1 was assessed. Class I (**A**) and Class II (**B**) beads are shown. Blue samples are clinical samples obtained post-PLEX and intra-operatively. Black samples represent the dilution series performed with the pre-transplant sample from neat to 1:128.

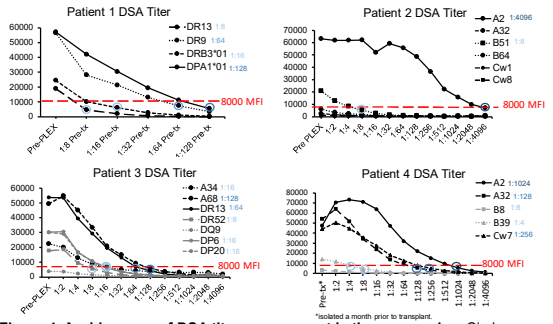


Figure 4. A wide range of DSA titers are present in the case series. Circles represent the titer for each DSA initially above threshold (8000 MFI) and are depicted to the right of the legend. Darker blue indicates higher titer; lighter blue = lower titer.

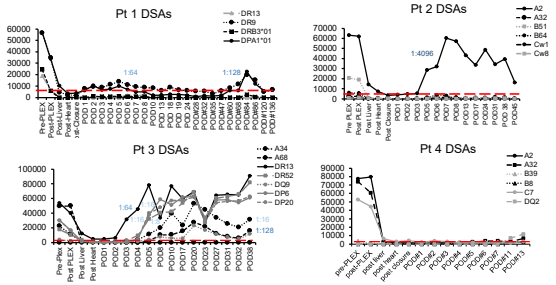


Figure 5. DSA time course for each patient. Titer of rebounded DSAs are shown.

Discussion

All DSAs decreased to a safe level intra-operatively, including those with the highest pre-transplant titer (1:4096). All patients had a negative T/B physical crossmatch following the liver transplant (**Figure 2**).

- *Non-DSAs* also decreased (**Figure 3**) and may be due to a dilutional effect due to blood products and replacement fluid received intra-op.

Rebound occurred as early as Day 3 post-op (**Figure 5**) and rebound prediction was variable.

- Pt 2 exhibited profound rebound of a Class I DSA that had a pre-transplant titer of 1:4096, however patient 4 with a Class I DSA at 1:1024 did not. Patient 1 with 4 Class II DSAs all below 1:128 did not experience profound rebound, but DSAs were still present above threshold. Patient 3 experienced profound rebound of all 6 Class I and II DSAs despite being below 1:128.
- Rebound was not associated with rejection. In those that received biopsies (3/4), these were graded as 0R.

Conclusions

This limited case series suggests that while PLEX minimally affects DSAs, liver adsorption is profound, resulting in negative physical crossmatches despite initial high titer DSAs. Further, rebound detected in patients did not lead to worse graft outcomes as evidence by 0R biopsy gradings, suggesting a tolerogenic affect of the liver on DSAs in addition to reducing the antibody burden intra-op. More cases are needed to assess the interaction of titer with the below factors in determining rebound and maintained graft function:

- HLA locus of DSA (Class I vs II, high expressors vs low expressors)
- Number of DSAs
- DSA IgG subclass
- Presence and number of long-lived plasma cells
- Soluble MHC generation
- Tolerogenic regulatory T cell presence/function

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References

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