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Rejection in the setting of combined Heart and Liver Transplantation

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ABSTRACT

Introduction: Each year the number of combined heart-liver transplants (HLT) increases, with two distinct patient populations proceeding down this pathway. The first are patients with congenital heart disease (CHD), most commonly single ventricle patients palliated with Fontan. The second group are those with long standing congestive hepatopathy, amyloidosis, hemochromatosis, or alcohol induced myopathies and liver disease.
One argument for HLT has been the low rate of rejection even among sensitized patients, with reported rejection rates ranging from 0% to 31%. Historically, those with CHD have been highly sensitized which in some cases may prevent or at least delay transplantation. As such, a recent consensus statement by Emamaulee et al. suggest that "there may be an immunological benefit to proceed with HLT with significantly fewer acute cellular and humoral rejection episodes". The aim of this study is to demonstrate that HLT patients remain at risk for rejection and have required treatment for it.
Results: There were 15 patients who underwent HLT from January 2017 to February 2022. Of the four patients who did not have CHD, none were considered sensitized, and all underwent induction with basiliximab per our institutional protocol. One of these had rejection. Rejection episodes were identified in four of the 11 CHD patients (36%) patients.
Conclusions: In our study of 15 HLT, including 11 CHD patients (73% denied transplant at $\geq$ 1 center) demonstrated a higher rate of rejection than previously reported. While theoretically, HLT may mitigate the likelihood of rejection, the risk still exists, and patients benefit from close monitoring commensurate with single organ transplant.

1. Background

Each year the number of combined heart-liver transplants (HLT) [1] increases, with two distinct patient populations proceeding down this pathway. The first are patients with congenital heart disease (CHD), most commonly single ventricle patients palliated with Fontan. The second group are those with long standing congestive hepatopathy, amyloidosis, hemochromatosis, or alcohol induced myopathies and liver disease [2].

The path to and timing of transplant for adults with CHD who develop Fontan Associated Liver Disease (FALD), remains complicated and controversial due to the heterogeneity in progression. This ambiguity in identification and management has led some centers to argue that all Fontan patients with advanced liver disease should undergo HLT [3]. Conversely, some centers have promoted heart transplant (HT) alone for their Fontan patients even in the setting of cirrhosis [4]. For

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those patients with end stage liver disease due to causes other than CHD-related hepatopathy, the progression and manifestations of liver disease are similar to that for patients with isolated liver cirrhosis. These include worsening liver synthetic function and consequences of severe portal hypertension including variceal bleeding, ascites and encephalopathy. This occurs as a result of a chronically congested liver and is not related to alterations in cardiac output. Over the course of years, persistent compromise of oxygen supply leads to fibrosis which eventually causes cirrhosis.

One argument for HLT has been the low rate of rejection even among sensitized patients, with reported rejection rates ranging from 0% to 31% [5–7]. Historically, those with CHD have been highly sensitized which in some cases may prevent or at least delay transplantation. As such, a recent consensus statement by Emamaulee et al. suggest that "there may be an immunological benefit to proceed with HLT with significantly fewer acute cellular and humoral rejection episodes" [8,9]. In addition, Daly et al. argue that a liver-before-heart transplantation "enables successful transplantation via near-elimination of donor specific antibodies (DSA) and is effective in preventing adverse immunological outcomes in highly sensitized patients listed for combined HLT"(9). However, the majority of these studies focus on acute cellular rejection (ACR) in the heart allograft alone. The aim of this study is to demonstrate that HLT patients remain at risk for rejection and have required treatment for it.

Here, we present our population of 15 heart-liver transplant patients (11 of them with CHD) and their rates of both ACR and antibody mediated rejection (AMR) in the heart and liver allografts.

2. Methods

All patients who underwent HLT between January 2017 and January 2022 at our institution were included. Data collected included basic demographic data, panel reactive antibodies (PRA), induction immunosuppression, maintenance immunosuppression, rejection episodes, and rejection treatment. Rejection was graded by our institutional pathologists using standardized definitions and collected by chart review [10].

For multi-organ system transplants, our institutional protocol dictates that patients receive basiliximab 20 mg IV (two doses on post operative day 0 and post operative day 4) in addition to steroids: methylprednisolone 500 mg IV for 2 doses in the operating room, followed by 125 mg IV every 8 h for 3 doses with subsequent taper. For patients with other risk factors, most commonly those who are highly sensitized, thymoglobulin may be administered in place of basiliximab (dosing 1–1.5 mg/kg IV to maintain CD3 counts of <50 for 5–7 days). CD3 counts are measured daily. For chronic immunosuppression, patients are started on a calcineurin inhibitor (most commonly tacrolimus with goal of 8–10 if not highly sensitized and goal of 10–12 if highly sensitized), an anti-proliferative agent (most commonly mycophenolate mofetil) and prednisone tapered according to a standard protocol. In most cases, prednisone is discontinued by week 16. If we detect the presence of any anti-HLA antibodies, we consider the patient to be sensitized. We consider patients who have a calculated panel reactive antibodies (cPRA) > 80% to be "highly sensitized".

For heart allograft rejection surveillance, our institutional protocol is to obtain biopsies at weeks 2, 4, 8, 12, 16, and 20, except in highly sensitized patients where a week 1 biopsy is also performed. Echocardiography is implemented for rejection surveillance at weeks 1, 3, 6 and 24. Additional biopsies may occur at any additional time point if there is suspicion of rejection. Heart allograft biopsies were obtained based on standard protocol for our institution with four biopsy specimens sent for histology to evaluate for ACR and two specimens sent for immunofluorescence to evaluate for AMR. Per the International Society for Heart and Lung Transplantation (ISHLT) guidelines [11,12], acute cellular rejection was defined as grade 2R or greater, and AMR was described as pAMR2 with greater than 50% C4D staining. In specific cases, liver biopsy may be performed. Liver biopsies were obtained for patients if there was concern for liver allograft rejection as judged by abnormal liver function tests. Only two of the patients underwent liver biopsy. Acute cellular liver rejection was defined as moderate rejection or greater by Banff criteria, and antibody mediated rejection was defined by the Banff working group 2016(13).

This study was approved by the Vanderbilt University Institutional Review Board.

3. Results

There were 15 patients who underwent HLT from January 2017 to February 2022. The median age at transplant was 36 years (interquartile range (IQR) 32,48), and the cohort was 27% female. Overall anatomy, diagnoses and PRA levels are found in Table 1, and post HLT outcomes are found in Table 2.

Of the four patients who did not have CHD, none were considered

Tables 1
Baseline characteristics.

Patient	Anatomy	Age	Sex	PRA Class 1 (%)	PRA Class 2 (%)	Desensitization
Congenital Heart Disease						
Pt 1	Tricuspid atresia with intracardiac Fontan	25	M	0	0	None
Pt 2	HLHS with intracardiac Fontan	28	M	8	0	None
Pt 3	Tricuspid atresia with extracardiac Fontan	33	F	0	0	None
Pt 4	Unbalanced left dominant AV canal with lateral tunnel Fontan	36	M	0	0	None
Pt 5	Dextrocardia, DORV, pulmonary atresia with lateral tunnel Fontan	26	M	0	0	None
Pt 6	DORV, L-TGA with extracardiac Fontan	49	M	0	0	None
Pt 7	DILV with lateral tunnel Fontan	56	F	0	0	None
Pt 8	Heterotaxy, unbalanced left dominant AV canal, interrupted IVC with classic Fontan	39	F	67	93	PLEX, IVIG, Rituximab
Pt 9	Shone complex	35	M	0	2	None
Pt 10	Tricuspid atresia with classic Fontan	32	F	1	13	None
Pt 11	DORV, malposed great arteries with extracardiac Fontan	35	M	77	73	PLEX, IVIG, Rituximab
Non-Congenital Heart Disease						
Pt 12	NICM due to polysubstance abuse	55	M	0	0	None
Pt 13	ICM congestive hepatopathy	47	M	2	0	None
Pt 14	Hemochromatosis	40	M	5	0	None
Pt 15	NICM due to chemotherapy	60	M	0	0	None

Abbreviations: AV: atrioventricular, AVSD: atrioventricular septal defect, DILV: double inlet left ventricle, DORV: double outlet right ventricle, HLHS: hypoplastic left heart syndrome, ICM: ischemic cardiomyopathy, IVIG: Intravenous gamma globulin, L-TGA: levo-transposition of great arteries, NICM: nonischemic cardiomyopathy, PLEX: plasmapheresis, PRA: panel-reactive antibodies.

Table 2
Post heart and liver transplant outcomes.

Patient	Induction	Crossmatch	Maintenance immunosuppression	Time to therapeutic CNI (days)	Outcome (Death, Rejection, No Rejection)	Time to first rejection (days)	Rejection treatment	DSA post	Ventricular function at the time of biopsy
Pt 1	Basiliximab	NA	Tacrolimus, Prednisone, MMF	NA	Deceased <30 days	NA	NA	NA	NA
Pt 2	Basiliximab	Negative	Tacrolimus, Prednisone, MMF	13	Rejection x 3 (ACR - liver)	396	Methylprednisolone	DR13	Normal
Pt 3	Basiliximab	T cell positive	Cyclosporine, MMF	8	No Rejection	NA	NA	NA	NA
Pt 4	Basiliximab	Negative	Tacrolimus, MMF, Prednisone	34	Rejection (AMR – heart)	15	Methylprednisolone, IVIG, PLEX	NA	Normal
Pt 5	Basiliximab	NA	Tacrolimus, MMF, Prednisone	NA	Deceased <30 days	NA	NA	NA	NA
Pt 6	Basiliximab	Negative	Tacrolimus, MMF	8	No Rejection	NA	NA	NA	NA
Pt 7	Basiliximab	NA	Tacrolimus, MMF, Prednisone	NA	Deceased <30 days	NA	NA	NA	NA
Pt 8	Thymoglobulin	B cell positive	Tacrolimus, MMF, Prednisone	4	No Rejection	NA	NA	NA	NA
Pt 9	Basiliximab	Negative	Tacrolimus, MMF, Prednisone	7	No Rejection	NA	NA	NA	NA
Pt 10	Basiliximab	Negative	Tacrolimus, MMF, Prednisone	16	Rejection (AMR heart and liver)	8	Methylprednisolone (for liver), IVIG, PLEX, Rituximab (for heart)	DQ2	Normal
Pt 11	Thymoglobulin	T and B cell positive	Tacrolimus, MMF, Prednisone	21	Rejection (AMR heart)	7	Solumedrol, IVIG, PLEX	Class II DSA against DRB1	Normal
Pt 12	Basiliximab	Negative	Tacrolimus, MMF, Prednisone	4	No Rejection	NA	NA	NA	NA
Pt 13	Basiliximab	Negative	Tacrolimus, MMF, Prednisone	12	Deceased (ACR liver)	505	Prednisone	NA	NA
Pt 14	Basiliximab	Negative	Tacrolimus, Azathioprine, Prednisone	14	No Rejection	NA	NA	NA	NA
Pt 15	Basiliximab	Negative	Cyclosporine, Prednisone	11	No Rejection	NA	NA	NA	NA

Abbreviations: ACR: acute cell rejection, AMR: antibody-mediated rejection, IVIG: intravenous immunoglobulin, MMF: mycophenolate mofetil, NA: not applicable, PLEX: plasmapheresis.

sensitized, and all underwent induction with basiliximab per our institutional protocol. Median time to therapeutic calcineurin inhibitor (CNI) was 8 days (IQR: 7, 12). One of these patients experienced ACR of the liver approximately 1.4 years after transplant, and subsequently died 1.5 years after HLT due to septic shock and multi-organ system failure from COVID-19.

Eleven patients had CHD including 10 with Fontan physiology. The median age at time of transplant of CHD patients was 35 years (IQR 28, 39), and the cohort was 36% female. Of those adults with CHD, 8 of 11 (73%) had been evaluated and denied HLT at ≥ 1 other transplant centers. Of those with CHD, four patients (36%) were considered sensitized. Two (18%) required desensitization and received plasmapheresis (PLEX), intravenous immunoglobulin (IVIG) and rituximab for desensitization prior to listing. Induction therapy included basiliximab for nine (82%) patients (by protocol for dual organ transplants at our center), and two (18%) patients (those who had undergone desensitization treatments) received thymoglobulin [13]. Three died from multisystem organ failure in the perioperative period.

In our patient cohort, 9 of 11 CHD patients were negative for Donor Specific Antibodies (DSA) prior to transplant, with negative flow and cytotoxic crossmatch results. Two patients had pre-transplant C1q negative DSA with mean fluorescence intensity (MFI) > 4000. As predicted, these patients had positive flow crossmatches and negative cytotoxic crossmatches. We utilize both cytotoxic and flow cytometric crossmatches. The cytotoxic crossmatch is a lymphocytoxicity assay that detects complement binding donor specific antibodies and distinguishes IgM antibodies from IgG antibodies. Flow cytometry crossmatches are performed using donor cells and recipient serum using an optimized three-color flow cytometry Halifaster procedure.

Rejection episodes were identified in four of the 11 CHD patients (36%) patients. One patient was unsensitized prior to transplant but demonstrated liver rejection and de novo DSA (against DR13) one year after transplant. Two patients demonstrated AMR of the heart, one was unsensitized and remained DSA negative, while the other patient had been transplanted across C1q negative DSA and positive flow crossmatch. The fourth patient had early onset AMR of both the heart and the liver. This patient had no pre-transplant DSA and negative crossmatches yet developed high levels of de novo Class II DSA against DQ2. Only one patient transplanted intentionally across positive DSA and crossmatches was negative for rejection.

None of the patients who were treated for rejection had recurrent episodes of rejection after receiving treatments. All patients treated for rejection were alive at one year after treatment. The only death that occurred in a patient who was treated for rejection was due to COVID-19.

The treatment for rejection is described in Table 2.

4. Discussion

There has been increasing interest in the CHD and HT communities regarding HLT for highly sensitized patients, citing the low rejection rates seen in small, single-center studies [7,14,15]. In some institutions, this has led to the development of liver-before-heart protocols [16]. However, our experience with HLT has been incongruous to that published to date highlighting the need for close immunologic monitoring in these patients.

Our single-center retrospective review of 15 HLT included biopsies to evaluate both ACR and AMR in the heart and liver grafts. In doing so, we found that one third of patients who survived their index hospitalization demonstrated rejection in either one or both of their transplanted organs, regardless of sensitization prior to transplantation. This is a higher rate of rejection than the other recently reported data, which was surprising given the purported immunologic protection from the transplanted liver as noted in recent HLT cohorts and previously described in kidney-liver transplantation [5,6].

The differences noted are likely due to three main aspects of care: immunosuppression strategies, definition of level of sensitization, and ability to evaluate for AMR in addition to ACR. Induction strategies and chronic immunosuppression vary greatly across centers. Recent studies have demonstrated use of more potent induction methods and continued higher levels of CNI than used in our cohort of HLT. The study by Sganga et al. largely used thymoglobulin for induction rather than basiliximab seen in our cohort. However, they describe a less highly sensitized cohort of HLT patients who were transplanted without positive crossmatches [14]. Levels of chronic immunosuppression in this study were not provided.

Wong et al. used T cell depleting therapy for all transplants, either monoclonal OKT3 antibody or thymoglobulin in all their HLT(7). Additionally, target levels of CNI were at higher levels in the first few months, cyclosporine at 300–400 ng/mL and tacrolimus 8–14 ng/mL as compared to our institutional protocol. Four of the patients were treated for AMR, though only 1 had biopsy proven AMR the others had high DSAs alone. None had significant ACR requiring treatment. The choice of induction therapy and higher levels of maintenance immunosuppression likely contributed to the decreased rate of rejection observed.

Zhao et al. describe methylprednisolone alone as induction for their HLT and reported that 9.7% had significant rejection (including heart and liver grafts) [15]. They also report that patients with rejection did not develop DSAs. Notably, their population had relatively low level of cPRAs, and the C1q component of any pre-transplant PRAs or post-transplant DSAs was not disclosed. Our study used basiliximab (or occasionally thymoglobulin) in addition to methylprednisolone, and also demonstrates that those who rejected did develop significant DSAs including C1q positivity.

Daly et al. described decreased rejection rates in a small cohort of highly sensitized heart-liver patients who underwent liver before heart transplantation [16]. Their hypothesis was that the transplanted liver protects against immune-mediated rejection, especially when the liver is implanted first. Their study included 7 patients with PRA between 24% and 100%, and a mean fluorescence intensity MFI threshold of 4000 for the threshold of unacceptable antibodies, which is lower than what our center has used for an antibody at risk for causing rejection. Notably their institution does not perform C1q testing, so this data is unavailable. Our institution does perform C1q testing to determine if DSAs are complement fixing. They used an aggressive induction protocol including thymoglobulin induction and eculizumab for selected patients, in addition to PLEX. All patients had positive prospective flow cross match; two had positive prospective cytotoxic crossmatches. No episodes of rejection were observed although pAMR1 (1+) was noted in two patients. Notably, there were four hospitalizations associated with infections and four associated with malignancy which may be linked to high level of immunosuppression.

5. Limitations

Our study has a number of limitations. First, although a relatively large cohort for a single-center study, it is an overall small number of patients. Given the wide variety of practices of induction, maintenance immunosuppression, measurement and reporting of PRAs and DSAs, and rejection surveillance strategies, it is difficult to compare outcomes directly with those of other centers. We are not able to determine causality or association of rejection other than to provide case-based explanations due to the small number of patients.

6. Conclusion

In our study of 15 HLT, including 11 CHD patients (73% denied transplant at $\geq$ 1 center) demonstrated a higher rate of rejection than previously reported. This is in contrast with recent reports contending immunologic protection from the transplanted liver and instead suggests patients remain at risk for both ACR and AMR. Data regarding reduced risk of rejection in those patients with combined HLT may be confounded by a number of characteristics including level of sensitization, type of induction, level of immunosuppression, and method for defining rejection. While theoretically, HLT may mitigate the likelihood of rejection, the risk still exists and patients benefit from close monitoring commensurate with single organ transplant.

CRediT authorship contribution statement

Shuktika Nandkeolyar: Conceptualization, Writing – original draft. **Tripti Gupta:** Conceptualization, Writing – original draft. **D. Marshall Brinkley:** Conceptualization, Writing – review & editing. **Sophoclis Alexopoulos:** Writing – review & editing. **Emily Firsich:** Data curation, Writing – review & editing. **Sally Anne Fossey:** Conceptualization, Data curation, Writing – original draft. **Rachel Fowler:** Conceptualization, Writing – review & editing. **Benjamin Frischhertz:** Writing – review & editing. **Kimberly Harrison:** Conceptualization, Writing – review & editing. **JoAnn Lindenfeld:** Conceptualization, Writing – review & editing. **Martin Montenovo:** Conceptualization, Writing – review & editing. **Dawn Pedrotty:** Conceptualization, Writing – review & editing. **Lynn Punnoose:** Conceptualization, Writing – review & editing. **Aniket Rali:** Conceptualization, Writing – review & editing. **Alexandra Shingina:** Conceptualization, Writing – original draft. **Kelly Schlendorf:** Conceptualization, Writing – review & editing. **Hasan Siddiqi:** Conceptualization, Writing – review & editing. **Ashish Shah:** Conceptualization, Writing – review & editing. **Sandip Zalawadiya:** Conceptualization, Writing – review & editing. **Mark Wigger:** Conceptualization, Writing – review & editing. **Jonathan N. Menachem:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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