Donors with Immune Thrombocytopenia: Do they pose a risk to transplant recipients?

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Running Title:

Organ Donors with ITP

Abbreviations

ATG, anti-thymocyte globulin

DBD, Donation after brain death

DCD, Donation after Circulatory death

EMH, extra-medullary haematopoesis

GVHD, graft versus host disease;

HLA, human leukocyte antigen;

HTLV, human T-lymphotropic Virus

ICH, intracranial haemorrhage;

ITP, Immune Thrombocytopaenic Purpura;

IQR, interquartile range;

IVIg, intravenous;

NHSBT, National Health Service Blood and Transplant;

PLS, Passenger Lymphocyte Syndrome;

SPK, Simultaneous Kidney and Pancreas Transplant;

SOT, solid organ transplantation;

TMAT, transplant mediated alloimmune thrombocytopaenia;

UK, United Kingdom;

UKELD, UK model for end stage liver disease;

UKTR, United Kingdom Transplant Registry;

US, United States;

Abstract

Transplant-mediated alloimmune thrombocytopenia (TMAT) from donors with immune thrombocyotopenia (ITP) can result in significant bleeding complications in the recipient. The risk to a recipient of TMAT if they receive an organ from a donor with ITP is unknown. The outcomes of recipients of organs from deceased donors with ITP recorded in the UK Transplant Registry (UKTR) between 2000 and 2015 were reviewed.

21 deceased organ donors had a pre-donation diagnosis of ITP. These donors were significantly more likely to have died from intracranial haemorrhage (ICH) than all other deceased organ donors (18 (85%) vs. 7864 (57%), p<0.001). Organs from these donors resulted in 49 organ transplants (31 kidney, 14 liver, 4 heart), with only one case of TMAT, which occurred in a liver transplant recipient and resulted in death from bleeding complications 18 days post-transplantation. The recipient of a kidney from the same organ donor was not affected.

Unadjusted 5-year patient and graft survival was significantly worse for liver transplant recipients from donors with ITP compared to liver transplant recipients from donors without ITP (9 (64%) vs. 8909 (85%), p=0.012). Organs from donors with ITP may be considered for transplantation, but livers should be used with caution.

Introduction

The transfer of immunocompetent donor lymphocytes originating from transplanted organs, notably the liver, may result in the development of graft versus host disease (GVHD)(1). GVHD following liver transplantation has been reported in between 0.1-2% of liver transplant recipients and may progress to a fatal multi-system disease(1-3). Donor plasma cells or B-lymphocytes transmitted with an allograft have also been reported to cause transient haemolysis when donor specific antibodies react against recipient red cells (the passenger lymphocyte syndrome (PLS)) (4,5). In addition to GVHD and PLS, there have been very occasional case reports documenting the transmission of immune thrombocytopaenia (ITP) from organ donors to liver transplant recipients with serious consequences (6-10). In Transplant Mediated Alloimmune Thrombocytopaenia (TMAT), donor leucocytes from an organ donor with ITP produce anti-platelet antibodies that bind platelet membrane epitopes such as glycoprotein (GP) IIb/IIIa common to both donor and recipient. Only 5 cases of TMAT have been previously reported, all following liver transplantation. In all cases TMAT was distinguished by severe and sudden onset thrombocytopaenia with platelets $<10 \times 10^9$/l within three days of liver transplantation (6-10). While TMAT is a rare complication of liver transplantation, there has been no attempt to estimate the risk of disease transmission from organ donors with recent or past history of ITP. Consequently there is no current guidance in the United Kingdom (UK) or the United States (US) with regards to the safety of using organs from donors with ITP. To help inform policy on the use of organs from donors with a history of ITP we undertook a retrospective registry analysis to establish the number of donors with ITP from which organs were used for transplantation and their associated recipient outcomes.

Methods

Identification of Donors who died of ITP

The UK Transplant Registry (UKTR), a national transplant database overseen by National Health Service Blood and Transplant (NHSBT), was used to identify all organ donors with a diagnosis of ITP. The UKTR was interrogated using the search terms *'ITP' 'Idiopathic Thrombocytopaenic Purpura''Immune Thrombocytopaenia'* (and common misspellings and alternative combinations of these words) for all UK deceased and living organ donors between 1st January 2000 and 31st December 2015. In donors identified as having a pre-donation diagnosis of ITP, a search was made of their records to establish: the duration of ITP, what treatments (if any) had been received and their platelet counts at time of death. A diagnosis or a past medical history of ITP recorded in the UKTR meant that the donor was included in the analysis.

Identification of Recipients from Donors with ITP

The recipients of organs from donors who had ITP were identified from the UKTR. Information regarding patient and graft survival was collected from the registry. The platelet count on the third post-operative day and any subsequent history of TMAT or ITP in the transplant recipient was obtained from the recipients respective transplant center.

Statistical Analysis

Univariate analysis was carried out using t-test for continuous data (to compare donor age and recipient age distribution) and non-normal data (UK End Stage Liver Disease score and Platelet count). Fishers exact test was used to compare categorical data

(donor type, donor cause of death, primary renal disease, primary liver disease, recipient cause of death and recipient cause of graft failure).

Kaplan-Meier estimates (of the survival function) were used to show death censored graft survival and recipient survival. The univariate log-rank test was used to calculate p-values. All analyses were performed using Statistical Analysis System (SAS) (version 9.3) and p-values less than 0.05 were deemed to be statistically significant (11).

HLA and UK End Stage Liver Disease definitions

Human Leukocyte Antigen (HLA) mismatch level was defined according to UK allocation policy for kidneys from brain-death donors and was based on the mismatch between donor and recipient at the HLA-A, -B, and -DR loci: level 1 was a 000 HLA-A, -B, and -DR mismatch; level 2 was a 0 HLA-DR plus 0/1 HLA-B mismatch; level 3 was a 0 HLA-DR plus 2 HLA-B mismatch or a 1 HLA-DR plus 0/1 HLA-B mismatch; and level 4 was a 2 HLA-DR or a 1 HLA-DR plus 2 HLA-B mismatch.

The United Kingdom End-Stage Liver Disease (UKELD) and Model of End Stage Liver Disease (MELD) scores was used when assessing differences in liver recipient characteristics. UKELD score is calculated based on the patient's international normalized ratio (INR), serum creatinine, serum bilirubin, and serum sodium (11). MELD score is calculated based on recipient serum bilirubin and creatinine levels, INR and underlying cause their of liver disease(12,13).

Results

Organ Donors with ITP

Over the 16-year study period there were 20,440 potential deceased donors of which 24 had diagnosis of ITP at the time of organ donation. None of 11,843 living donors over this time period were known to have ITP. Of the 24 deceased donors with history of ITP, information on whether specific treatment was given for ITP was available for 14 of them. Of these, two of the patients with ITP died of ICH before any specific treatment was administered. Of the remaining 12 patients, treatment comprised intravenous immunoglobulin (IVIg) and/or steroids (n=9), splenectomy alone or splenectomy plus rituximab, eltrombopag and romplistim (n=2), and IVIg plus rituximab (n=1). Twenty-one of the 24 potential deceased donors with ITP proceeded to organ donation. Three donors with ITP did not proceed to organ donation, because of withdrawal of family consent (n=1), positive Human T-Lymphotropic Virus (HTLV) n=1***),*** and prolonged time to asystole after withdrawal of life supporting treatment (n=1).

Clinical Characteristics of Donors with ITP

Compared with deceased organ donors who did not have ITP, organ donors with ITP were of similar age (median 49.0 Interquartile range (IQR) (23-63) vs.49.0 (36-59), p=0.520), and gender (10(48%) male vs. 7400(54%) male, p=0.666). Donors with ITP were significantly more likely to have died from ICH (18 (85%) vs. 7864 (57%), p<0.001) and have a lower platelet count at donation (median 56.0 $x10^9$/l IQR (32.5-90.0) vs. median 203 x 10^9/l IQR (147- 267), p<0.001) compared to donors without ITP. Four donors were diagnosed with ITP on presentation to hospital immediately prior to donation, and one further donor had been diagnosed one week prior to

donation. 4 others had been diagnosed within the year preceding organ donation and the other 7 donors had been diagnosed greater than one year prior to donation, with the longest time from diagnosis to donation being 61 years. In 9 cases it was not stated in the registry or in the paper notes that were how long before donation ITP had been diagnosed.

Donors with ITP donated organs, which led to 49 organ transplants [31 kidney transplants (including 3 simultaneous kidney-pancreas (SPK) transplants), 14 liver transplants and 4 heart transplants].

Clinical Characteristics of Kidney transplant recipients

The 31 kidney transplant recipients from organ donors with ITP and recipients of kidneys from those without ITP were of similar age (median 43.0 IQR (35-58) vs. median 48.0 IQR (37-58), p=0.272), gender (17(55%) male vs.14165 (62%), p=0.875), ethnicity (22 (71%) white vs. 18260 (80%) white, p=0.214), and HLA mismatch level (39% mismatch level 1 and 2 vs. 49% mismatch level 1 and 2, p=0.545). None of the 31 recipients developed ITP or TMAT in the early post transplant period, although one recipient developed what was assumed to be sporadic ITP 8 years post-transplantation. The median platelets count on day-three after transplantation with a kidney from donors with ITP was median 179 $x10^{9/}$l (IQR 124-210).

Survival analysis comparing renal transplant recipients from donors with ITP and from all other deceased donors demonstrated no evidence difference in 10 year death censored graft survival (p=0.672) and recipient survival (p=0.695) (supplementary figure 1).

Clinical Characteristics of Liver transplant recipients

The 14 liver transplant recipients from organ donors with ITP and recipients of livers from those without ITP were of similar age, gender, ethnicity, UKELD score, MELD score, primary liver disease, and had the same proportion of recipients that were listed urgently for a liver transplant (table 1).

Platelet counts were recorded for all liver transplant recipients on day zero and day three post transplantation, with a median platelet count on day three of 49 x 10^9/l (IQR 24-76) and a median platelet count drop of 38 x 10^9/l (IQR 17-70) from day zero to day 3 (figure 1). The platelet count of liver transplant recipients fell in 12 of the 14 cases (86%) (figure 1). These platelet counts were compared to the last 3 years of liver transplant recipient's day 0 and day 3 platelet counts at Addenbrookes hospital in Cambridge (n=259). The median day 3 platelet count in this cohort was 44x 10^9/l (IQR 30-58) and when the platelet counts dropped post liver transplantation, the median platelet count drop was 18x10^9/l (IQR 10-31), which was not significantly different to the drop observed in liver recipients from organ donors with ITP (p=0.456). None of the liver transplant recipients from Cambridge had a platelet count <10x 10^9/L on day 3-post transplantation.

In all cases the recipient centers were contacted regarding any possible diagnosis of TMAT. One of the liver recipients, a 61-year-old male, developed TMAT post transplantation. His platelet count dropped on day three to 2 x 10^9/l, and he subsequently died 18 days post liver transplantation, secondary to pulmonary haemorrhage and multi-organ failure. Platelet antibodies specific to GPIb\XI identified in the donor were also found in the recipient following transplantation, but were absent from the recipient's serum sample taken 14 days prior to transplantation. The donor liver time zero biopsy showed marked extramedullary haematopoiesis.

There was no evidence of TMAT in the recipient of a single kidney from the same donor. One liver transplant recipient developed hepatic artery thrombosis and needed urgent re-transplantation and one died secondary to haemorrhage from a ruptured vascular aneurysm (table 1).

Time zero liver biopsies were taken in 2 other donors with ITP. These either found no lymphocytic infiltrate or small lympocytic and neutrophil infiltrate-neither showed marked extramedullary haematopoeisis.

Graft and patient survival were inferior in recipients of livers from donors with ITP compared to those who received livers from all other deceased donors (figure 2).

None of the other early causes of death or graft failure in the liver recipients from donors with ITP were thought to be secondary to TMAT.

Heart Recipients

The four recipients of hearts from organ donors with ITP were of similar age (median 43.0,p=0.736) ethnicity (75% white vs. 90% white, p=0.307), and gender (75% male vs. 62% male, p= 0.604) to all other deceased donor heart transplant recipients. The day three-platelet counts were 143, 96, 53, and 96 x 10^9/l respectively. There were no reported cases of TMAT in any of the four heart transplant recipients.

Discussion

This study has described, for the first time, a national experience of using donors with ITP and has established that clinically significant TMAT is not a common occurrence in organ transplant recipients. Although donors with ITP make up a very small proportion of the total donor pool (0.15%), they made a significant contribution to organ transplantation with a total of 49 organ transplants, and because of the

discrepancy between organ supply and demand it is imperative that organs from donors are not rejected unnecessarily (14,15).

The absence of TMAT in 31 kidney and 4 heart transplant recipients from the series is consistent with three previous TMAT cases following liver transplantation, in which recipients of other organs (5 kidneys and a heart) from the same donors with ITP, did not develop TMAT (7,8,10). Passenger lymphocyte induced haemolysis is most frequent following haematopoietic stem cell transplantation and progressively less likely following heart and lung transplantation, then liver/small bowel/pancreas then kidney transplantation in proportion to the number of transplanted lymphocytes(16). A larger number of lymphocytes transmitted to the recipient in the donor graft may therefore explain why TMAT has occurred following liver but not kidney or heart transplantation. However, TMAT following liver transplantation remains a rare occurrence and is a risk that is not always present when using livers from donors with ITP.

With only one TMAT case in this series it is not possible to identify characteristics of donors with ITP that could distinguish those whose organs carry the greatest risk of TMAT. In this case series, and in all five previous TMAT cases, the donors all died of ICH and had platelets $<20 \times 10^9$/l prior to death (Table 2). Of the five ITP donors with a reported clinical history three had been refractory to multiple therapies including splenectomy, but two died as result of ICH as part of their acute ITP presentation. In the current analysis there were 4 organ donors who were diagnosed with ITP as part of their acute presentation with ICH, none of which resulted in TMAT in the recipient. Failure of the donor with ITP to respond to splenectomy suggests that their

liver is a major site of platelet destruction by the reticuloendothelial system(17,18) (19). In our series, one recipient of a liver from a donor with ITP who had required splenectomy developed TMAT and one did not. Extramedullary haematopoiesis in the donor liver represents a greater burden of transplanted haematopoetic tissue. There were a limited number of time 0 liver biopsies available. One other liver transplant biopsy showed focal lymphocytic and neutrophilic infiltrate but no marked extramedullary haematopoeisis, but the degree of extramedullary haemoatopoiesis and its significance in predicting TMAT could be explored in future studies.

The progressive thrombocytopenia at day zero and three in liver recipients was expected. The platelet count is usually reduced post orthoptic liver transplantation, typically falling to a nadir around post-operative day four, followed by a gradual recovery (20,21). This thrombocytopenia is thought to be caused by factors such as reduced thrombopoietin production, haemodilution and platelet sequestration in the reperfused liver graft. There may also be patient specific variables such as sepsis, bleeding or disseminated intravascular coagulation (increased platelet consumption), medication, viral infection or heparin induced thrombocytopenia (21). Hence other causes of thrombocytopenia must therefore be considered in cases of suspected TMAT. Furthermore like ITP, TMAT remains a clinical diagnosis. Serological testing may be supportive if the same anti-platelet antibodies are found in recipient and donor. However, the significance of these antibodies is unclear since it is unknown whether the can be detected in liver recipients of donors with ITP unaffected by TMAT. Secondly, platelet-associated IgG can be elevated in non-immune-thrombocytopenia and antibodies to specific platelet glycoproteins cannot always be

detected in patients with ITP (22). Hence negative serological testing of donor and recipient does not exclude the presence TMAT.

The natural history and optimal treatment of TMAT is unclear. In three cases the platelet counts had improved within 1-3 weeks with only IVIg ± steroids (7,8,10). In two cases refractory to multiple therapies including splenectomy, the platelets recovered following liver retransplantation day 11 for rejection in one case or following retransplantation day 43 for refractory TMAT in the other (6,9).

The kidney transplant recipient that developed ITP after 8 years post transplantation is not likely to be a donor derived TMAT since lymphocytes do not persists following solid organ transplantation (4). The incidence of ITP is approximately 4 per 100,000 person years but occurs more frequently on the background of immune dysregulation (23). In a series of 256 liver transplant recipients, 8 (0.7%) cases of new ITP occurred at a median of time from transplant of 53.5months (range 1.9-173) (24) .

The risk of TMAT in recipients of livers from donors with ITP is small. It is likely a multifactorial process regarding both recipient and donor characteristics, with a pathogenesis that is poorly understood. Hence, although the risk is present organs from these donors should not be discarded unnecessarily.

There are some limitations to this study. The retrospective nature of the registry analysis may limit the accuracy and completeness of the donor and recipient data. A diagnosis of ITP would have to have been known by the patient's medical team for the SNOD to be able to record the diagnosis in the past medical history of the donor.

So in cases where the treating medical team did not recognize possible ITP these donors would not appear in the analysis; Hence the numbers presented in this study are likely an underestimate of the actual number of donors who had ITP as well as the impact of TMAT, as other than the single TMAT case there were no recipients with severe day three thrombocytopenia. However, we cannot exclude the possibility of milder episodes of TMAT that were not recognized as such by the treating teams. A further limitation with this study is the small number of donors identified with ITP. Hence interpretation of there overall effect on recipient outcome can be difficult. This analysis is also limited by the small number of pre-implantation liver biopsies taken, and hence the importance of the presence of extramedullary haematopoeisis remains unclear.

Conclusions:

Although the exact mechanism of TMAT is not fully understood, there is no evidence from UK experience of using kidneys, pancreases and hearts from donors with ITP to suggest it is unsafe. However, there is a small risk of TMAT following liver transplantation and we have demonstrated inferior recipient survival following liver transplantation from donors with ITP. Transplant teams will have to consider the severity of liver disease and health of a potential recipient when balancing the risk of accepting the liver of a donor with ITP against the risk of further delay in transplantation.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation

Legend

Table 1. Clinical Characteristics of liver transplant recipients from organ donors with ITP and from organ donors without ITP.

Table 2. Cases of recipients of livers from donors with Immune thrombocytopenia (ITP) who have developed transplant mediated allogenic thrombocytopenia (TMAT)

Figure 1. Platelet counts on Day 0 and Day 3 post liver transplantation of liver transplant recipients from donors with ITP

Figure 2. Patient and graft survival of liver transplant recipients from organ donors with ITP versus liver transplant recipients from organ donors with ITP

Supplementary figure 1. Patient and graft survival of kidney transplant recipients from organ donors with ITP versus kidney transplant recipients from organ donors with ITP

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