HLA Tissue Typing Has No Effect on the Outcome of Patients Undergoing a Living-donor Liver Transplant: A Single-center Experience in Egypt

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Abstract

Objectives: To analyze the effect of human leukocyte antigen tissue typing on outcome of live-donor liver transplant.

Materials and Methods: Fifty recipients underwent live-donor liver transplant in the Dar Al-Fouad Hospital in Egypt and were retrospectively evaluated. Patients were classified into 2 groups: those with human leukocyte antigen +ve, and those with human leukocyte antigen -ve and donors. Hepatitis C virus-related end-stage liver disease was the main indication for transplant. Demographic data, preoperative laboratory data, results of human leukocyte antigen tissue typing, Child score, model for end-stage liver disease score, graft/recipient weight-ratio, ischemia times, surgical complications, postoperative laboratory data, liver biopsy, immunosuppression, and pulse steroids were collected. Graft and patient survivals were studied using Kaplan-Meier curves.

Results: The mean model end-stage liver disease score was 18 ± 3.61 in group 1 and 17.73 ± 3.72 in group 2, with no significant difference. Graft/recipient weight ratio, ischemia times, and postoperative complications showed P = NS. Cyclosporine and tacrolimus were used in 5/9, 8/41, and 4/9 in group 1, and 32/41 in group 2 (P = NS). Rejection and pulse steroids were reported in 3/9 and 12/41 of group 1, and 3/12 and 11/41 of group 2 (P = NS). Hepatitis C virus-recurrence was diagnosed in 5/9 of patients (55%) and 8/41 of patients (29.5%) in groups 1 and 2 (P < .05). No statistical difference was found regarding mortality; 5-year patient and graft survival was 35/50 (70% in group 1 [human leukocyte antigen +ve]), 7/9 (77.8%), and 28/41 in group 2 (68.3%) (human leukocyte antigen -ve).

Conclusions: Positive human leukocyte antigen typing before live-donor liver transplant has no effect on the incidence of postoperative complications, rejection episodes, and patient or graft survival. Recipients with positive human leukocyte antigen typing may have increased risk of hepatitis C virus-recurrence after live-donor liver transplant.

Key words: HLA, Liver transplantatio, Outcome

Introduction

Adult live-donor liver transplant (LDLT) offers several advantages over deceased-donor liver transplant: more-expedient transplant, scheduling of procedures on an elective basis, and a positive effect on the deceased donor organ shortage. Also, LDLT may have the advantage of a more-favorable human leukocyte antigen (HLA) match profile among closely related donor and recipient pairs.1

The role of HLA matching between a donor and a recipient in organ transplant rejection and survival has been widely studied and proven to increase graft survival after kidney, heart, and other organ transplants, and to reduce the incidence of acute or chronic rejection.2, 3 In contrast, major histocompatibility complex analysis is not routinely done in a liver transplant because its importance remains controversial, with improved outcomes in some cases, poor outcomes in others, and no effect in the remaining cases.1, 4
It has been reported that some patients gain benefit from high degrees of HLA matching. Possible increased recurrence of primary disease with good HLA compatibility has been studied. Hepatitis C virus-related end-stage liver disease already accounts for more than 40% of adult elective liver transplants performed in Europe and North America, and the number of referrals for transplant is projected to double within the next decade. Hepatitis C virus-related graft hepatitis occurs in about 50% of these patients, and up to 30% develop cirrhosis. This study sought to analyze the effect of human leukocyte antigen (HLA) matching on outcome, recurrence of hepatitis C genotype 4, and survival of the patient and the graft after LDLT.

Materials and Methods

This study is a retrospective one conducted on 50 adult male recipients (no sex selection intention) who underwent LDLT in single private center in Egypt. The patients were classified into 2 groups; 9 patients were HLA +ve and 41 patients were HLA -ve. All protocols were approved by the local ethics committee of the institution before the study began and conformed to the ethical guidelines of the 1975 Helsinki Declaration.

Preoperative data

Preoperative data for the donors and the recipients included age, blood group, preoperative laboratory data; complete blood count (CBC), liver, renal, bleeding and lipid profiles, lactate dehydrogenase (LDH), fetal bovine serum (FBS), postprandial blood sugar (PPBS), amylase, Ca, Fe, and total iron binding capacity (TIBC), tumor markers: CA19.9, CA125, alpha fetoprotein and CEA, viral profile: hepatitis A, B, and C (HAV, HBV, HCV) (including qualitative and quantitative polymerase chain reaction [PCR], Epstein-Barr virus [EBV], Cytomegalovirus [CMV]), and herpes 1 and 2. Child-Pugh and Mayo end-stage liver disease (MELD) scores were done for the recipients.

Serologic typing of HLA class I and class II antigens was done using the complement-mediated microlymphocytotoxicity technique. Human leukocyte antigen antibody screening was done by testing the patient’s serum against a panel of lymphocytes with known HLA types. Peripheral blood lymphocytes (PBLs) express HLA class I antigens and are used for serologic typing of HLA-A, HLA-B, and HLA-C. Human leukocyte antigen class II typing is done with B lymphocytes isolated from PBLs because these cells express class II molecules. Human leukocyte antigen typing is performed in multiwell plastic trays, with each well containing a serum of known HLA specificity. Lymphocytes are plated in the well and incubated, and the complement (rabbit serum as a source) is added to mediate the lysis of antibody-bound lymphocytes.

Operative data

Operative data included actual graft size and actual graft recipient weight ratio (at least 0.8%), and any surgical details that may jeopardize the outcome of the graft or the patient survival.

Postoperative data

Postoperative data included total hospital and intensive care unit (ICU) stay, operative-related complications, immunosuppressant levels (plasma level of tacrolimus was kept between 10 to 15 μg/L and later on level kept between 7 to 10 μg/L). Regarding cyclosporine, c2 levels were kept between 500 and 800 μg/L), episodes of acute rejection were marked by fever, malaise, decrease quality/quantity of bile, increase in serum total bilirubin, direct bilirubin, ALT, AST, AKP, GGT, decreased serum albumin, increased ascites, and graft site tenderness. Courses of pulse steroid used (methylprednisolone 1000 mg on day one, 750 mg on day two, and 500 mg on day three, another more-aggressive regimen may used in severe rejection episode; 1000 mg on day one, two, and 750 mg on day three).

Pathological findings of liver biopsy, if done, and recurrence of HCV diagnosed by liver biopsy, were demonstrative of subsequent progression to cirrhosis. After discharge, patients were assessed on an outpatient basis weekly for first month; then every 2 weeks for the second month; then monthly for first year; and then every 3 months thereafter according to clinical situation.

Statistical Analyses

Statistical analyses were performed with SPSS software (SPSS: An IBM Company, version 15.0, IBM Corporation, Armonk, New York, USA). Qualitative data were compared by chi-square test or the Fisher exact test. Quantitative data were compared using the t test. A Kaplan-Meier curve was constructed for
survival of the patients. In all tests, a $P$ value was significant if it was less than .05.

Results

Basic characteristics of the recipients and donors (n=50) are presented in Table 1. Pretransplant HCV PCR was done to all patients before being subjected to LDLT; mild, moderate, and high viremia was detected in 17 (54.8%), 12 (38.7%), and 2 (6.5%) of HCV +ve patients (47) (Table 1). Hepatitis C virus recurrence rate was 55.6% with HLA +ve compared to 19.5% in HLA -ve group with significant statistical difference ($P = .023$). Mortality in recipients of both groups is shown in Table 2. In group 1, one case died owing to an accident, and 1 died owing to surgical complications. In group two, 2 cases died (15.4%) owing to biliary causes, 3 died (23.1%) owing to graft failure, 1 case died (7.7%) owing to HCC, and 2 cases died (15.4%) owing to surgical complications.

Discussion

In many end-stage liver diseases, hepatic transplant often constitutes the only therapeutic option available. Studies performed in clinical solid organ transplants have sought to gain insight into immunologic parameters that could be important in altering the course of allograft tolerance, thus modifying the prognosis. Two main factors, donor-recipient HLA compatibility and the absence of preformed, donor-specific anti-HLA cytotoxic antibodies (giving rise to a positive crossmatch), are known to contribute to a more-favorable outcome in renal and heart transplants.

In this study, based on studying the effect of a positive crossmatch on the outcome after liver transplant in our own patient population, it was found that both groups showed no statistical difference regarding total hospital and ICU stay, immunosuppressive use, rejection episodes, pulse steroid use, graft failure, mortality, and 5-year patient and graft survival. Similarly, in the largest multicenter cohort of liver transplant patients, Navarro and associates observed that HLA matching had no significant clinical effect on transplant outcome. Similarly, Neumann and associates reported, in a single-center analysis, that HLA compatibility had no effect on graft survival. Many other studies support this finding. In contrast, Nikaein and associates demonstrated increased survival in transplants in which there was a greater degree of HLA donor-recipient compatibility. Markus and associates showed that diminished allograft survival was associated with

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**Table 1. Basic characteristics of the recipients and donors.**

<table>
<thead>
<tr>
<th>Variables</th>
<th>HLA +ve (n=9)</th>
<th>HLA -ve (n=41)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipients’ age (y)</td>
<td>47.89 ± 5</td>
<td>48.22 ± 7</td>
<td>.89 (NS)</td>
</tr>
<tr>
<td>Recipients’ sex % (M/F)</td>
<td>100/0</td>
<td>100/0</td>
<td>(NS)</td>
</tr>
<tr>
<td>Donors’ age (y)</td>
<td>27.78 ± 5</td>
<td>28.17 ± 6</td>
<td>.85 (NS)</td>
</tr>
<tr>
<td>Donors’ sex % (M/F)</td>
<td>67/33</td>
<td>78/22</td>
<td>.67 (NS)</td>
</tr>
<tr>
<td>Relatives (%)</td>
<td>33.3</td>
<td>48.8</td>
<td>.48 (NS)</td>
</tr>
<tr>
<td>Cause of ESLD (%)</td>
<td>(HCV/NON HCV)</td>
<td>100/0</td>
<td>92/8</td>
</tr>
<tr>
<td>Viremia (%)</td>
<td>(mild/moderate/high)</td>
<td>28.6/71.4/0</td>
<td>62.5/29.2/8.3</td>
</tr>
<tr>
<td>MELD</td>
<td>18.56 ± 3.61</td>
<td>17.73 ± 3.72</td>
<td>.55 (NS)</td>
</tr>
<tr>
<td>Child score (%) (B/C)</td>
<td>0/100</td>
<td>9/91</td>
<td>1 (NS)</td>
</tr>
<tr>
<td>GRWR</td>
<td>0.99 ± 0.10</td>
<td>0.91 ± 0.11</td>
<td>.79 (NS)</td>
</tr>
<tr>
<td>Cold ischemia (min)</td>
<td>106.88 ± 18.70</td>
<td>112.20 ± 17.68</td>
<td>.44 (NS)</td>
</tr>
<tr>
<td>Warm ischemia (min)</td>
<td>34.38 ± 8.63</td>
<td>31.59 ± 6.17</td>
<td>.28 (NS)</td>
</tr>
</tbody>
</table>

**Table 2. Patient outcomes in both groups.**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1 (n=9)</th>
<th>Group 2 (n=41)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical cholestasis</td>
<td>1 (11.1%)</td>
<td>6 (14.6%)</td>
<td>.78 (NS)</td>
</tr>
<tr>
<td>Graft failure</td>
<td>0 (0%)</td>
<td>3 (23.1%)</td>
<td>.10 (NS)</td>
</tr>
<tr>
<td>Immunosuppressive drugs</td>
<td></td>
<td></td>
<td>.08 (NS)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>5 (55.6%)</td>
<td>8 (19.5%)</td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>4 (44.4%)</td>
<td>32 (78%)</td>
<td></td>
</tr>
<tr>
<td>Sirolimus</td>
<td>0 (0%)</td>
<td>1 (2.4%)</td>
<td></td>
</tr>
<tr>
<td>HCV recurrence</td>
<td>5 (55.6%)</td>
<td>8 (19.5%)</td>
<td>.023 (S)</td>
</tr>
<tr>
<td>Rejection episodes</td>
<td>3 (33.3%)</td>
<td>12 (29.3%)</td>
<td>.81 (NS)</td>
</tr>
<tr>
<td>Pulse steroid</td>
<td>3 (33.3%)</td>
<td>11 (26.8%)</td>
<td>.7 (NS)</td>
</tr>
<tr>
<td>Hospital stay</td>
<td>38 ± 20.79</td>
<td>32.71 ± 27.05</td>
<td>.6 (NS)</td>
</tr>
<tr>
<td>ICU stay</td>
<td>11 ± 5.45</td>
<td>9.29 ± 5.08</td>
<td>.39 (NS)</td>
</tr>
<tr>
<td>Death</td>
<td>2 (22.2%)</td>
<td>13 (31.7%)</td>
<td>.71 (NS)</td>
</tr>
</tbody>
</table>

**Abbreviations:** ESLD, end-stage liver disease; F, female; GRWR, graft volume/recipient body weight ratio; HCV, hepatitis C virus; M, male; MELD, model for end-stage liver disease.

**Figure 1. Patients’ survival post LDLT.**
HLA compatibility, but in retransplants, a higher incidence of failure owing to rejection correlated with a lower degree of HLA compatibility. The authors explained this apparent contradiction by conferring a dualistic effect to HLA compatibility, by which it could reduce rejection yet simultaneously initiate a cascade of immunologic mechanisms leading to graft loss, by enhancing recurrent underlying diseases like hepatitis B and C. The results of lymphocytotoxic crossmatches have been more reliable; positive crossmatches are associated with decreased graft survival and increased acute rejection.\(^{15,17}\)

In this study, HCV recurrence increased significantly in recipients with positive HLA crossmatch. After LT, the viral load increased up to 10 times pretransplant levels,\(^{18}\) which is thought to reflect suppression of the host effector immune responses usually controlling HCV replication. These observations underscore the hypothesis that long-term immunosuppression after liver transplant may play a major role in the rapid progression of recurrent HCV infection after LT.

In our study, all patients were exposed to similar circumstances, there is no significant difference regarding donor age, cold and warm ischemia time, viremia, MELD, and Child-Pugh score in both groups. All patients received adequate graft size with appropriate GRWR, none of our series had small for size syndrome, so we did not find any effect for graft size and GRWR on outcome of transplant.

In conclusion, positive HLA crossmatching pre-LDLT has no effect on the incidence of postoperative complications, rejection episodes, and patient or graft survival. Recipients with positive HLA crossmatching may have increased risk of HCV recurrence after LDLT. The challenges in maintaining and improving the outcome of HCV-positive patients is rising, since in recent years, progress of HCV recurrence after LT has increased.\(^{28,29}\) In addition to the immunosuppressive treatment, viral factors, donor age, and immunologic factors (like MHC I-restricted T-cell responses) may be involved in the course of recurrent HCV. The lower risk for rejection in patients receiving a better-matched graft may lead to individualized immunosuppressive protocols, and therefore, improved, long-term outcome of HCV-positive patients after LT.\(^{27}\) Further studies are required to clarify the correlation between HLA positive crossmatch and HCV recurrence after live-donor liver transplant.

### References


