Liver Transplantation for Autoimmune Hepatitis: A Single-Center Experience

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ABSTRACT

Objective. To present our experience with deceased donor liver transplantation (DDLT) and living-donor liver transplantation (LDLT) for autoimmune hepatitis (AIH).

Patients and Method. Between April 2001 and November 2006, a total of 116 LT procedures were performed (73 DDLTs and 43 LDLTs) in 112 patients (4 retransplants). Of the 112 recipients, 16 patients (14.3%) were transplanted for AIH (15 DDLTs and 1 LDLT). All recipients received FK506- and steroid-based immunosuppressive regimens.

Results. The male/female ratio was 3/13, median age was 22 years (range, 15 to 35), and the median MELD score was 25 (range, 11 to 40). Arterial reconstruction was needed in four DDLTs due to severe steroid-induced angiopathy. After a median follow-up period of 530 days (range, 11 to 2016), the overall patient and graft survival rates were 93.8%. Only one patient died following LDLT due to primary graft nonfunction. Histopathologic recurrence was seen in three patients (18.7%) and was successfully treated by optimizing immunosuppression. Markedly elevated serum CA19-9 levels (median, 1069; range, 217 to 2855) was seen in four patients (28%), malignancy was ruled out and all patients normalized serum CA19-9 levels within the first 3 months posttransplant. Steroids withdrawal failed in all recipients and was always accompanied with almost immediate elevation of liver enzymes.

Conclusions. In our experience, LT for AIH shows excellent long-term outcomes, patients are usually young women who present with acute deterioration and high MELD scores, and usually require long-term steroids to prevent rejection and disease recurrence. Some patients have markedly high CA19-9 in absence of malignancy. Some patients also have severe steroid-induced hepatic artery angiopathy necessitating arterial reconstruction during the transplant surgery.

Autoimmune Hepatitis (AIH) is a generally progressive, chronic hepatitis of unknown cause that occurs in children and adults of all ages, and although the cause of autoimmune hepatitis is unknown, aberrant auto-reactivity is thought to have a role in its pathogenesis. Since the first descriptions of this disorder >50 years ago, many labels have been applied, but autoimmune hepatitis has been accepted as the most appropriate and least redundant term. Variant, overlapping, or mixed forms of AIH that share features with other putative autoimmune liver diseases, primary biliary cirrhosis, and primary sclerosing cholangitis occur as well; the distinctions among these disorders at present are necessarily descriptive. The diagnosis is based on histologic abnormalities, characteristic clinical and biochemical findings, and abnormal levels of serum globulins, including autoantibodies. Occasionally, it has a fluctuating course, with periods of increased or decreased activity. Despite its clinical heterogeneity, AIH generally responds to anti-inflammatory or immunosup-
pressive treatment, or both.9–12 Liver transplantation (LT) is required in patients who are refractory to or intolerant of immunosuppressive therapy and in whom end-stage liver disease develops.13–16 Herein we report our experience with LT for AIH, including both deceased donor liver transplantation (DDLT) and living-donor liver transplantation (LDLT).

PATIENTS AND METHODS
At King Faisal Specialist Hospital and Research Center from April 2001 to November 2006, a total of 116 LTs were performed (73 DDLTs and 43 LDLTs) in 112 patients (4 retransplants). Of 112 recipients, 16 patients (14.3%) were transplanted for AIH (15 DDLTs and 1 LDLT). Arterial reconstruction was needed during the transplant procedure in four patients who had very fragile intima of the hepatic artery, probably caused by long-term corticosteroid use as a treatment for AIH. Aortic conduit interposition bypass graft between the recipient’s aorta and the allograft’s hepatic artery was used to bridge the diseased vessels; the bypass graft was done by using the iliac artery graft obtained from the cadaver donors. All patients were regularly followed in our outpatient department, aiming to optimize immunosuppression and diagnose AIH recurrence early. We did not perform routine protocol biopsies to detect recurrence; however, liver biopsy was performed whenever biochemically warranted. Steroids withdrawal was attempted in all recipients after completion of the first postoperative year.

RESULTS
Characteristics of 16 patient transplanted for AIH are shown in Table 1; the male/female ratio was 3/13; median age was 22 years (range, 15 to 35); median MELD score was 25 (range, 11 to 40); median blood transfusion was 6 U (range, 0 to 65); median ICU stay was 5 days (range, 2 to 24), and median hospital stay was 11 days (range, 7 to 58). Out of 16 patients transplanted for AIH, 7 patients (44%) were not known to have any liver disease and they presented to our service with the clinical picture similar to acute hepatic failure. Antinuclear antibodies were positive in 9 (56%) out of 16 patients transplanted for AIH.

Of 16 recipients, 4 patients (25%) had markedly elevated serum CA19-9 levels (median, 1200; range, 217 to 2800), thorough pretransplant work ruled out the presence of malignancy; histopathologic examination of the explanted livers also ruled out the presence of malignancy, and showed markedly nodular livers with severe macro-nodular cirrhosis and extensive bile ductular proliferation (Fig 1); immunohistochemical stains for CA19-9 showed very intense membranous and cytoplasmic uptake of CA19-9 antibody in all bile ductules (Fig 2). Proliferative indices using Ki-67 antibody showed low levels of proliferation (<1%), which is strongly against the presence of malig-

Table 1. Summary of Characteristics in 16 Patients Transplanted for Autoimmune Hepatitis

<table>
<thead>
<tr>
<th>No</th>
<th>Age</th>
<th>Gender</th>
<th>Clinical Presentation</th>
<th>Pretransplant Workup</th>
<th>Evidence of AIH in Explanted Liver</th>
<th>Days Posttransplant</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>F</td>
<td>ESLD</td>
<td>MELD: 16, CA19-9: 77, ANA: +</td>
<td>Possible</td>
<td>2016</td>
<td>Alive</td>
</tr>
<tr>
<td>2</td>
<td>23</td>
<td>F</td>
<td>ESLD</td>
<td>MELD: 17, CA19-9: 68, ANA: +</td>
<td>Strong</td>
<td>1814</td>
<td>Alive</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>F</td>
<td>ESLD</td>
<td>MELD: 15, CA19-9: 73, ANA: +</td>
<td>Strong</td>
<td>1791</td>
<td>Alive</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>F</td>
<td>ESLD</td>
<td>MELD: 28, CA19-9: 140, ANA: +</td>
<td>Possible</td>
<td>1027</td>
<td>Alive</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>F</td>
<td>AHF</td>
<td>MELD: 26, CA19-9: 2855, ANA: +</td>
<td>Possible</td>
<td>752</td>
<td>Alive</td>
</tr>
<tr>
<td>6</td>
<td>22</td>
<td>F</td>
<td>ESLD</td>
<td>MELD: 12, CA19-9: 66, ANA: +</td>
<td>Possible</td>
<td>653</td>
<td>Alive</td>
</tr>
<tr>
<td>7</td>
<td>21</td>
<td>F</td>
<td>AHF</td>
<td>MELD: 29, CA19-9: 40, ANA: +</td>
<td>Absent</td>
<td>559</td>
<td>Alive</td>
</tr>
<tr>
<td>8</td>
<td>15</td>
<td>F</td>
<td>ESLD</td>
<td>MELD: 33, CA19-9: 80, ANA: +</td>
<td>Strong</td>
<td>538</td>
<td>Died</td>
</tr>
<tr>
<td>9</td>
<td>20</td>
<td>M</td>
<td>AHF</td>
<td>MELD: 38, CA19-9: 217, ANA: +</td>
<td>Possible</td>
<td>521</td>
<td>Alive</td>
</tr>
<tr>
<td>10</td>
<td>35</td>
<td>F</td>
<td>AHF</td>
<td>MELD: 24, CA19-9: 810, ANA: +</td>
<td>Possible</td>
<td>434</td>
<td>Alive</td>
</tr>
<tr>
<td>11</td>
<td>17</td>
<td>F</td>
<td>ESLD</td>
<td>MELD: 21, CA19-9: 15, ANA: +</td>
<td>Possible</td>
<td>403</td>
<td>Alive</td>
</tr>
<tr>
<td>12</td>
<td>24</td>
<td>F</td>
<td>AHF</td>
<td>MELD: 40, CA19-9: 1328, ANA: +</td>
<td>Possible</td>
<td>329</td>
<td>Alive</td>
</tr>
<tr>
<td>13</td>
<td>34</td>
<td>M</td>
<td>AHF</td>
<td>MELD: 30, CA19-9: 62, ANA: +</td>
<td>Possible</td>
<td>308</td>
<td>Alive</td>
</tr>
<tr>
<td>14</td>
<td>20</td>
<td>F</td>
<td>ESLD</td>
<td>MELD: 18, CA19-9: 95, ANA: +</td>
<td>Possible</td>
<td>279</td>
<td>Alive</td>
</tr>
<tr>
<td>15</td>
<td>23</td>
<td>F</td>
<td>AHF</td>
<td>MELD: 40, CA19-9: 65, ANA: +</td>
<td>Possible</td>
<td>63</td>
<td>Alive</td>
</tr>
<tr>
<td>16</td>
<td>30</td>
<td>M</td>
<td>ESLD</td>
<td>MELD: 11, CA19-9: 14, ANA: +</td>
<td>Possible</td>
<td>11</td>
<td>Alive</td>
</tr>
</tbody>
</table>

Abbreviations: ESLD, end-stage liver disease; AHF, acute hepatic failure; MELD, Model for End-Stage Liver Disease; ANA, antinuclear antibodies.

Fig 1. High-power view of the explanted liver in a patient with high serum CA19-9 level with arrows showing clusters of extensive bile ductular proliferation and bile plugs.
nancy (Fig 3). All patients four patients normalized their serum CA19-9 levels within the first 3 months posttransplant (Fig 4).

Of 16 patients transplanted for AIH, 9 were known to be on long-term steroid therapy, and out of those 9 patient who were on steroid therapy, 4 (44%) were found during surgery to have severely diseased vessels with very fragile intima of the hepatic artery, probably caused by long-term corticosteroid use as a treatment for AIH; in all 4 patients arterial reconstruction using an aortic conduit had to be done to secure sufficient arterial blood supply to the transplanted liver. Histopathologic examination of the explanted livers showed picture typical of AIH in only 3 patients; in the remaining 13 patients, the histopathologic picture was suggestive of but not conclusive for AIH.

After a median follow-up period of 530 days (range, 11 to 2016), the overall patient and graft survival rates were 93.8%. Only one patient died from primary graft nonfunction; she underwent LDLT with a MELD score of 33, and she suffered from severe coagulopathy and bleeding possibly due to small-for-size graft.

Steroid withdrawal was attempted in all patients after completion of the first postoperative year; this was done gradually and with close monitoring of liver function tests. Although dose reduction was possible in almost all patients, complete steroid withdrawal failed in all recipients and was always accompanied with almost immediate elevation of liver enzymes due to either rejection or disease recurrence. In our experience, 3 of 16 patients (18.7%) had biochemical and histopathologic evidence of recurrence; all 3 patients showed good biochemical response to increased immunosuppression. In this study, 3 of 16 patients (18.7%) had biochemical and histopathological evidence of AIH recurrence; they were successfully treated with optimizing immunosuppression. It has been reported that approximately 20% to 30% of patients undergoing liver transplantation for AIH develop features of recurrent disease. Diagnostic criteria for recurrent AIH include, in varying combinations, biochemical, serologic, and histologic abnormalities and steroid dependency. However, these criteria are more difficult to apply in the liver allograft because of potential interactions between recurrent AIH and other complications of liver transplantation, particularly rejection, and the uncertain effects of long-term immunosuppression. It is also reported that histologic evidence of recurrence may precede clinical and biochemical evidence of recurrence; therefore, protocol liver biopsy might be of use in early detection of AIH recurrence. Risk factors that have been

**DISCUSSION**

Liver transplantation is the final therapeutic option for about 10% of patients with AIH who do not respond to medical therapy. The reported grafts and patients survival rate at 5 years after liver transplantation is approximately 80% to 90%, the 10-year survival rate is approximately 75%, and the recurrence rate has been reported to be as high as 42%. In our experience, patients transplanted for AIH showed an exceptional good long-term outcome with the 3-year patient and graft survival approximately at 90%; this survival rate was the highest among all other indications for LT in our program.

Our patients were mostly young women who presented with either acute hepatic failure without previous history of chronic liver disease or as acute deterioration on top of known chronic AIH. In this study, 44% of patients with AIH presented with a clinical picture similar to fulminant hepatic failure, and they were successfully transplanted on priority basis; all of them had a similar postoperative course and survival rates as those presenting with endstage liver disease due to chronic AIH. Similar findings were also reported in many clinical studies.

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associated with the development of recurrent AIH include suboptimal immunosuppression, HLA phenotype, disease type, severity in the native liver, and duration of follow-up. In many cases in which recurrent AIH seems to be related to underimmunosuppression, biochemical and histologic features rapidly resolve once adequate immunosuppression is restored. However, in other cases, recurrent AIH behaves more aggressively, with progression to cirrhosis and graft failure.1,22

Despite our attempt to completely stop steroid therapy in our patients, we were not able to safely discontinue steroids in any of our patients; all our attempts were always accompanied by biochemical changes suggestive of AIH recurrence. However, we were able to reduce prednisolone to around 5 to 10 mg once daily in almost all patients. Although corticosteroid withdrawal after LT represents an attractive therapeutic option for ameliorating its metabolic complications, several reports suggest patients who undergo transplantation for AIH may have a greater incidence of acute and chronic rejection when withdrawn from corticosteroid therapy.17,18,26–32; other reports have proposed that corticosteroid withdrawal should be attempted in patients with transplanted for AIH because most benefit without significantly jeopardizing the liver allograft.33–35

Some of our patients had remarkably high CA19-9 levels despite absence of malignancy; CA19-9 is a tumor marker known to be useful in the diagnosis of malignancies of the pancreas and bile ducts.36,37 Several studies have also reported increased concentrations of CA19-9 in benign conditions such as obstructive jaundice without malignancy; however, in most of those cases, the serum concentrations of CA19-9 have been only mildly elevated.38–40 At concentrations >1000 U/mL, the specificity of the CA19-9 assay is reportedly >99% for malignant gastrointestinal disease. There have been very few reports of marked increase in CA19-9 in patients with autoimmune hepatitis and it was speculated that the raised serum CA19-9 was derived from the proliferated bile duct cells; which are positive for proliferating cell nuclear antigen and might be able to produced high concentrations of CA19-9.41

Finally, 44% of our patients who were transplanted for AIH and on long-term steroid therapy before LT were found to have significantly diseased wall of the hepatic artery mostly in the form of fragile intima and low flow blood. This finding can be explained by steroid-induced angiopathy related to hypercholesteremia and the diabetogenic effect of steroids.42,43 Transplant surgeons should be aware of this fact whenever performing LT on AIH patients who have been on steroids for a long time; cadaveric iliac artery grafts harvested from cadaveric donors should always be harvested and made available whenever operating on such patients.

In conclusion, LT for AIH have been successfully performed at King Faisal Specialist Hospital and Research Center with excellent long-term outcomes. In our experience, we have observed that patients are usually young women who present with acute deterioration and high MELD scores, and they usually require long-term post-transplant steroid therapy to prevent rejection and avoid disease recurrence. Some of the patients have markedly high CA19-9 in absence of malignancy. And finally some patients have significant steroid-induced angiopathy of the hepatic artery necessitating arterial reconstruct during the transplant surgery.

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