Clinically Recurrent Primary Sclerosing Cholangitis Following Liver Transplantation: A Time Course

Jeffrey Campsen, Michael A. Zimmerman, James F. Trotter, Michael Wachs, Thomas Bak, Tracy Steinberg, and Igal Kam

Division of Transplant Surgery and Division of Gastroenterology/Hepatology, University of Colorado Health Sciences Center, Denver, CO

Orthotopic liver transplantation (OLT) is the treatment of choice for patients with end-stage primary sclerosing cholangitis (PSC). This study sought to chronicle the natural history of PSC recurrence following OLT and identify clinical variables that may contribute to disease reemergence. From 1988 to 2006, 1102 OLTs were performed in 1032 adults at the University of Colorado Health Sciences Center. Of these, 130 patients (12.6%) with PSC received 146 allografts. Recurrence was defined by a clinically worsening examination and radiographic evidence. A total of 9 potential predictors were considered, using both bivariate log rank and multivariate Cox analysis, including: age > 55, gender, surgical technique (piggyback technique), presence of inflammatory bowel disease, intact colon before transplant, or cholangiocarcinoma (CCA), cold ischemia time, sirolimus-based immunosuppression, and graft type. The 1, 5, and 10-year recurrence-free survival was 91%, 76%, and 61%, respectively. The crude incidence of disease recurrence was 22 of 130 patients or 16.9%. Patients' risk of recurrent PSC at 1, 5, and 10 years was 2%, 12%, and 20%, respectively (mortality censored). Of the 22 patients that developed recurrent disease, 7 received a second transplant. Of the 9 factors considered, the presence of CCA prior to OLT is significantly predictive of disease recurrence [risk ratio (RR) = 3.77; P = 0.0038]. Once a patient was diagnosed with recurrent disease, the median survival without receiving a second transplant was 39.1 months (95% confidence interval: 27.6-50.6 months). In conclusion, recurrent PSC following OLT is a formidable but protracted problem following OLT. Patients may require a second transplant following reemergent disease with reasonable survival benefit. Liver Transpl 14:181-185, 2008.

© 2008 AASLD.

Received April 6, 2007; accepted July 30, 2007.

See Editorial on Page 130

Orthotopic liver transplantation (OLT) is the treatment of choice for patients with end-stage liver disease due to primary sclerosing cholangitis (PSC). PSC is a chronic cholestatic liver disease of unknown etiology that may progress to fibrosis and biliary stricture. Ultimately, patients may succumb to cholangitis, liver failure, and/or cholangiocarcinoma (CCA). Currently, the diagnosis is made by radiographic imaging revealing strictures of the intrahepatic or extrahepatic biliary tree. Increasing evidence links this disease to immunologic factors including human leukocyte antigen subtypes and the presence of antinuclear antibodies. The close association between PSC and ulcerative colitis suggests that intestinal bacteria or toxins may have a direct pathologic influence. Recurrence of PSC following OLT is a problem for some patients. A recent review estimated that 17% of liver transplant recipients with PSC develop recurrent disease. The natural history of PSC after liver transplantation continues to evolve as the number of patients and follow-up interval continues to increase in

Abbreviations: CCA, cholangiocarcinoma; OLT, orthotopic liver transplantation; PSC, primary sclerosing cholangitis; RR, risk ratio.


Address reprint requests to Michael Zimmerman, M.D., Divisions of Transplant Surgery and Gastroenterology/Hepatology, University of Colorado Health Sciences Center, 1635 North Ursula Street, P.O. Box 6510-C-318, Aurora, CO 80045. Telephone: 720-848-0852; FAX: 720-848-0833; E-mail: michael.zimmerman@uchsc.edu

DOI 10.1002/lt.21313
Published online in Wiley InterScience (www.interscience.wiley.com).
these patients.\textsuperscript{7} At present, it is unclear which clinical and/or pathologic variables, if any, may be predictive of disease recurrence after transplantation. In this study, we examine several potential predictors of PSC recurrence following transplantation, and chronicle the pathologic progression of disease reemergence in the liver allograft. Finally, we sought to define the impact of disease recurrence on long-term outcome.

**PATIENTS AND METHODS**

From 1988 to 2006, 1102 OLTs were performed in 1032 adults at the University of Colorado Health Science Center. Specifically, 130 patients transplanted for PSC with complete records were included in this study. A retrospective review was conducted to identify clinical and pathologic variables associated with long-term survival. Sources of data for the patients in this study included the University of Colorado Transplant Database and patient medical records. This work was approved by the University of Colorado Health Science Center Institutional Review Board.

**Diagnosis and Evaluation**

PSC recurrence was suspected in patients with abnormal liver function tests along with clinical evidence of cholangitis occurring greater than 90 days after transplantation. Protocol biopsies are not performed at our institution. The diagnosis of recurrent PSC in all cases was defined by cholangiographic appearance of biliary strictures by either percutaneous transhepatic cholangiography or endoscopic retrograde cholangiography showing changes consistent with PSC.\textsuperscript{8} PSC recurrence was not diagnosed in patients whose biliary strictures were caused by other diagnosed problems (hepatic artery thrombosis, chronic rejection, cytomegalovirus infection, or isolated anastomotic strictures). Recipients of living donor organs were included in this study.

**Statistical Methods**

Survival and recurrence curves and median time to event estimates were computed using Kaplan-Meier methods, and \( P \) values for their comparison were computed using the log rank test for each potential predictor separately (bivariate analysis). The risk (hazard) ratio (RR) was also reported. The 9 potential predictors were evaluated simultaneously using a Cox proportional hazards model. The 9 potential predictors for PSC recurrence were: age (>55 years), gender, piggyback technique, inflammatory bowel disease, intact colon prior to transplant, CCA, cold ischemia time, cadaveric versus live donation, and sirolimus as primary immunosuppressant.

**RESULTS**

**Recipient Characteristics**

A total of 130 patients received 146 allografts for PSC-mediated end-stage liver disease at the University of Colorado Health Sciences Center between 1988 and 2006. Median age was 46 years and 77% were male (Table 1). Median follow-up time was 66 months. The median cold ischemia time was 6.4 hours and ranged from 0.27 hours to 15.3 hours. A total of 14.6% were live donor right hepatic lobe transplants. A total of 92 patients, or 70.7%, were diagnosed with inflammatory bowel disease. A total of 10 patients had evidence of CCA in the explanted liver. The presence of CCA was known in 8 of the 10 patients with CCA in the explant before transplantation. Sirolimus and a calcineurin inhibitor were used in combination as a primary immunosuppressant in 26 patients. The piggyback technique was used in 69 patients. A total of 115, or 88.5%, had an intact colon prior to transplant.

**Predictors of Overall and Recurrence-Free Survival**

Of the 130, 22 recurred, of which 3 subsequently died (1 before retransplantation, 2 after retransplantation). An additional 21 died without detected recurrence, for a total of 24 deaths. Overall patient survival at 5 years was 84%, PSC recurrence-free survival at 1, 5, and 10 years was 91%, 76%, and 61%, respectively (Fig. 1A). Of the 9 potential factors examined, only the presence of pathologically confirmed CCA (both bivariately and multivariately)
A total of 22 (16.9%) patients had PSC recurrence diagnosed in our cohort. Of the 22 patients with disease recurrence, 15 have not received a second transplant. One is dead from hemorrhage of a ruptured splenic vein varix secondary to worsening recurrent PSC. Of the 14 patients alive, 11 are managed medically without percutaneous biliary drains. The 3 other patients have percutaneous biliary drains and 2 of these have been relisted for transplantation (Fig. 2). Our center will relist patients with recurrent PSC that have ongoing bouts of cholangitis, refractory jaundice, and a Model for End-Stage Liver Disease score greater than 14. No patient with recurrent PSC has died from recurrent CCA.

Of the 7 patients that received a second liver transplant, 5 are alive at the writing of this manuscript. One suffered a recurrence in the second graft and received a third transplant. The remaining 4 have no evidence of disease recurrence. The causes of death of the other 2 patients were myocardial infarction and disease recurrence. This patient did not receive a third transplant due to extreme age.

For the 22 patients with PSC recurrence, once the patient was diagnosed with recurrent disease their risk of being alive without receiving a second transplant at 12 months was 85% (Fig. 3). This decreases to 63% at 36 months, and 45% at 60 months. The median survival time without receiving a second transplant in this group was 39.1 months.

**DISCUSSION**

Transplantation for PSC was first reported in 1980.9 Since that time, accumulating clinical experience has attempted to characterize the disease both before and after OLT. Wiesner et al.10 documented the natural history of this disease before transplantation by prospectively following 174 patients. In patients with symptomatic PSC, the median transplant-free survival was 112 months. A 41% combined rate of liver failure, CCA, and the need for transplantation was observed over a 6-year follow-up. Furthermore, a recent meta-analysis including 14 studies and over 900 patients who underwent transplantation for PSC, documented a recurrence rate at 17%.6 Unfortunately, recurrence after transplantation is difficult to define. Jeyarajah et al.11 reported that recurrence could only be defined by cholangiography and should be suspected in the setting of nonanastomotic strictures appearing at greater than 90 days post-OLT.12

At our center we do not perform protocol biopsies. Thus, patients with suspected recurrence based on clinical examination will receive a percutaneous transhepatic cholangiography and are diagnosed with recurrence based on those radiographic findings. In summary, since our PSC patients are biopsied only “for cause” and not on a protocol basis, all of the PSC patients who underwent liver biopsy had abnormal liver tests. Every patient who had histologic findings consistent for PSC had a cholangiogram shortly after the biopsy to confirm the diagnosis or to evaluate for percu-

---

**Figure 1.** (A) PSC recurrence-free survival. (B) Recurrence-free survival in patients with cholangiocarcinoma discovered in the explanted liver (+CCA) or without cholangiocarcinoma (−CCA). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

---

significantly impacted overall and PSC recurrence-free survival (Table 2) at \( P < 0.05 \). CCA was a significant predictor of PSC recurrence (RR = 3.77; \( P = 0.0038 \)) (Fig. 1B). The presence of an intact colon (RR = 0.46; \( P = 0.079 \)) had a borderline significant relationship ignoring all other covariates; however, under multivariate analysis (RR = 0.50; \( P = 0.163 \)) the directionality was similar but the \( P \) value was no longer significant. The bivariate effects of male gender (RR = 1.31; \( P = 0.49 \)), age greater than 55 (RR = 1.08; \( P = 0.85 \)), the presence of inflammatory bowel disease (RR = 0.86; \( P = 0.64 \)), use of sirolimus as primary immunosuppression (RR = 0.67; \( P = 0.40 \)), a piggyback caval anastomosis (RR = 1.31; \( P = 0.38 \)), and the use of a live donor right hepatic lobe (RR = 0.81; \( P = 0.68 \)) were not statistically significant at \( P < 0.20 \), although some RR's are suggestive. Cold ischemia time, divided into time groups of <4 hours, 4-8 hours, and >8 hours had \( P < 0.20 \) (RR = 2.01, \( P = 0.17 \) for 4-8 hours and RR = 2.29, \( P = 0.13 \) for >8 hours, relative to <4 hours) but was not statistically significant at \( P < 0.10 \). The lack of statistical significance could be in part due to an inadequate sample size or follow-up time; therefore, multivariate RR estimates are not reported.

**Recurrent PSC Following Liver Transplantation**

The risk of disease reemergence at 1, 5, 10 years was 2%, 12%, and 20%, respectively, in surviving patients.
Since we used radiologic criteria for recurrent PSC diagnosis, there may be a “lead time bias” from the studies that used histologic criteria. The disease recurs at the same time posttransplantation but is detected earlier in the patients undergoing protocol biopsies.

At present, several clinical variables have been implicated as possible predictors of disease recurrence, including human leukocyte antigen class I antigen match,13 steroid-resistant rejection,14 and the presence of an intact colon in patients with inflammatory bowel disease.15 Interestingly, inflammatory bowel disease alone was not predictive of long-term outcome.6 In this study, 22 patients (16.9%) were diagnosed with recurrence. Of the 9 factors considered, only the presence of CCA significantly impacted outcome, although some of the other factors are suggestive but not proven.

**TABLE 2. Predictive Variables of PSC Recurrence**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Risk (Hazard) Ratio</th>
<th>Bivariate</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>1.31</td>
<td>0.4975</td>
<td></td>
</tr>
<tr>
<td>Age &gt; 55 (years)</td>
<td>1.08</td>
<td>0.8577</td>
<td></td>
</tr>
<tr>
<td>IBD</td>
<td>0.86</td>
<td>0.6497</td>
<td></td>
</tr>
<tr>
<td>CCA</td>
<td>3.77</td>
<td>0.0038</td>
<td></td>
</tr>
<tr>
<td>Presence of an intact colon before OLT</td>
<td>0.46</td>
<td>0.0792</td>
<td></td>
</tr>
<tr>
<td>Sirolimus as primary immunosuppressant</td>
<td>0.67</td>
<td>0.4051</td>
<td></td>
</tr>
<tr>
<td>Piggyback technique</td>
<td>1.31</td>
<td>0.3859</td>
<td></td>
</tr>
<tr>
<td>Live donor; right lobe</td>
<td>0.81</td>
<td>0.6856</td>
<td></td>
</tr>
<tr>
<td>CIT 4-8 hours*</td>
<td>2.01</td>
<td>0.1658</td>
<td></td>
</tr>
<tr>
<td>CIT &gt; 8 hours*</td>
<td>2.29</td>
<td>0.1264</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CIT, cold ischemia time; IBD, inflammatory bowel disease. *Compared to CIT < 4 hours.

This may in part be due to an inadequate sample size or follow-up.

A preliminary review of our center’s immunosuppression patterns in patients receiving transplantation for PSC suggested that recipients receiving OKT3 were more likely to experience reemergence of PSC following transplantation.16 We have since reported our center’s evolving immunoprophylaxis with both corticosteroids and mammalian target of rapamycin inhibitors.17 Since 1997, our center has attempted to minimize corticosteroid use in all of our liver transplantation recipients. In the mid1990s we initiated a prednisone-withdrawal protocol for chronic patients. In 1997, we began a series of trials to minimize corticosteroid use in all of our de novo liver transplant recipients starting from the time of transplantation. In 1997, corticosteroids were administered for only 14 days after transplantation and then in 2000 corticosteroid use was reduced to only 3 days after transplantation. Finally, every patient that received sirolimus as a primary immunosuppressant also received a calcineurin inhibitor, as we have previously described.

In contrast to various hepatic diseases including viral...
hepatitis and/or hepatocellular carcinoma, these data suggest that PSC recurrence after transplantation has a protracted course. While the risk of disease reemergence is 1% in the first 12 months following OLT, this increases to 20% at 10 years in this cohort. However, once recurrence in the allograft is identified, it can be managed successfully with either nonoperative strategies and/or repeat transplantation. As such, the median survival without receiving a second transplant after diagnosis of PSC recurrence was 39 months. Thus, the course of PSC recurrence after transplantation is similar but less protracted than in symptomatic PSC patients before transplantation. Furthermore, patients with PSC recurrence in the graft have a much longer survival time than patients with symptomatic recurrent hepatitis C after transplantation, for which the death rate may be as high as 50% in 1 year.

Our data should be interpreted with caution. In this series, disease recurrence was based exclusively on radiographic evidence of bile stricture. Radiologic confirmation of disease was sought after identification of abnormal liver tests or cholangitis. Therefore, there may be a fraction of patients with unidentified recurrent disease that is not yet clinically apparent. We acknowledge that our cohort is small. Only 10 of the 130 patients (7.7%) had CCA in the explant and the presence of CCA in the explant is quite possibly a byproduct of severe PSC. The long follow-up may have contributed to the increase in recurrence in this group. Also, our center does not preoperatively stage these patients with surgical exploration. We believe that this may have eliminated poor candidates with metastatic disease prior to transplantation. Importantly, experience from the Mayo Clinic combining transplantation with nonoperative management to successfully extend the life of the allograft. Alternatively, a reasonable survival benefit can be realized from retransplantation. Similar to PSC prior to OLT, recurrent disease is poorly understood and difficult to predict. However, disease reemergence appears to follow a protracted course with reasonable long-term survival in the absence of a retransplantation.

ACKNOWLEDGMENT
A special acknowledgment is given to Dr. Jeffrey Gornbein and the David Geffen School of Medicine, University of California, Los Angeles (UCLA), Department of Biomatics, for excellent work on the statistics.

REFERENCES