Different Immunosuppressive Regimens and Recurrence of Primary Sclerosing Cholangitis After Liver Transplantation

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Primary sclerosing cholangitis (PSC) is the fourth leading diagnosis in liver transplant recipients in the United States. The disease is known to recur in 15% to 30% of liver transplant recipients. We set out to investigate how different immunosuppression regimens affected natural history of PSC after liver transplantation at our center. We reviewed records of all patients who underwent a liver transplantation at our institution in between 1988 and 2000 and had a diagnosis of PSC at the time of liver transplantation. Primary sclerosing cholangitis recurred in 15 of 71 patients (21.1%) who had complete records and survived more than 30 days after liver transplantation. Although recurrence of primary sclerosing cholangitis was most often seen (but not statistically significantly so) in patients who received maintenance corticosteroids, the time to recurrence was not significantly different between those who were treated with maintenance, those who were not successfully weaned, and those who successfully weaned off corticosteroids within 3 months after liver transplantation. Orthoclone (OKT3) therapy (Ortho-Biotech, Inc., Raritan, NJ) was associated with a higher risk of primary sclerosing cholangitis recurrence (29% versus 10%, $P < .05$). Recurrence was not influenced by immunosuppression with either cyclosporine or tacrolimus. Coexistent inflammatory bowel disease was a cause of failure to wean off corticosteroids, was associated with a shorter time to recurrence of sclerosing cholangitis, and was responsible for significant comorbidity (colon cancer in 7.3%). Primary sclerosing cholangitis recurrence is commonly seen after liver transplantation. More immunosuppression seems to be detrimental to the outcome of our patients with sclerosing cholangitis: use of OKT3 was associated with a greater incidence of recurrence. Length of corticosteroid use did not affect timing or risk of recurrence, and because it has been proven that early corticosteroid withdrawal after liver transplantation is beneficial, we continue to recommend this practice. (*Liver Transpl 2003;9:727-732.*)

Primary sclerosing cholangitis (PSC) is a chronic inflammatory disease of the biliary tree that classically progresses to fibrosis, stricture of bile ducts, and death from cholangitis, liver failure, or cholangiocarcinoma.[1,2] Liver transplantation (LT) is the treatment of choice for patients with end-stage PSC.[3,4] Currently, PSC represents the fourth leading indication for liver transplantation in the United States.

The cause and pathogenesis of PSC are unknown, and medical therapy is empiric and unsatisfactory. For these reasons many patients with PSC will experience progressive liver disease and require LT. However, PSC recurs in some patients after LT, and the factors or clinical features that predict recurrence are largely unknown.

Certain clinical associations suggest that PSC is an autoimmune disease. These include hereditary susceptibility as indicated by linkage to certain human leukocyte antigen (HLA) antigens,[5] a strong association with inflammatory bowel disease (IBD),[6,7] presence of antineutrophil cytoplasmic antibody,[8] and autoimmune hepatitis.[9] Despite the autoimmune nature of PSC, immunosuppressive therapy is ineffective in controlling the course of this disease.[10-12]

Corticosteroids (CS) are commonly used in transplant patients to prevent and treat allograft rejection. In addition, use of CS posttransplantation in patients with PSC may also be necessary to manage coexistent IBD. Despite their use, CS have not been effective in the management of PSC, either pretransplantation or posttransplantation. Furthermore, CS may cause or worsen certain metabolic complications that occur after liver transplantation. For these reasons, it has been our practice to withdraw CS very early (within 14 days) after liver transplantation. Our experience indicates that early steroid withdrawal reduces the incidence and allows better control of hypertension, hyperlipidemia, diabetes mellitus, and obesity.[13]

In this article we review our center's experience with liver transplantation in PSC and very early steroid with-

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drawal to gain insight into the nature of its posttransplantation recurrence. Our goals were to identify risk factors for recurrence and to determine whether different immunosuppressive regimens used at our center affected the timing and severity of PSC recurrence.

Patients and Methods

This is a retrospective analysis of our center's experience with PSC after liver transplantation. We performed 595 adult liver transplants between December 1988 and June 2000 at the University of Colorado Health Sciences Center. Of these, 77 patients (13%) were diagnosed with PSC pretransplantation; the diagnosis was confirmed by examination of the liver explant. We excluded patients who underwent transplantation at other institutions for whom we did not have confirmation of the PSC diagnosis. We also excluded patients who underwent transplantation at our institution who had a diagnosis other than PSC before liver transplantation even if they eventually developed typical changes in the allograft. Five patients who died in the perioperative period (1 to 30 days) and 1 patient with insufficient data were excluded from analysis; the latter patient died 9 months after transplantation. Results presented in this article are based on the remaining 71 patients.

We diagnosed recurrent PSC (rPSC) by abnormal liver tests followed by a percutaneous transhepatic cholangiogram (PTC) or liver biopsy (LBx) showing changes consistent with PSC.[14,15] Diagnostic features of rPSC on PTC were multiple focal segmental strictures of intrahepatic bile ducts, extrahepatic bile ducts, or both in the absence of vascular thromboses or a dominant biliary anastomotic stricture. Histologic criteria for rPSC on liver biopsy included lymphocytic portal inflammatory changes with periductal fibrosis and obliterative fibrous cholangitis in the absence of chronic allograft rejection. Patients were excluded from the study if they had had an ABO-incompatible allograft, showed a dominant anastomotic stricture, had prolonged cold ischemia time, or had hepatic artery thrombosis.

From 1988 to 1994, our immunosuppressive regimen was cyclosporine A (CyA)–based, combined with CS and azathioprine. From 1994 to 2000, patients were sequentially assigned to receive either tacrolimus (TAC) or CyA as primary immunosuppression and underwent rapid steroid taper (off CS by day 15). From 1995 to 1997, patients were still sequentially assigned to receive CyA or TAC with rapid steroid taper, and also received 6 months of mycophenolate mofetil. Since January 2000, we have used CyA or TACas the primary immunosuppressant in combination with low-dose sirolimus (one-time loading dose of 6 mg, followed by 2 mg daily). With this latter immunosuppressive regimen, we have truncated our CS treatment to three doses: 1 g perioperatively and 500 mg on days 1 and 2 posttransplantation (off CS by day 3).

Statistical Analyses

For the analysis of the impact of immunosuppression on the recurrence of PSC after liver transplantation, we decided to divide our cohort into three groups: Group 1 (n = 32) included all patients who received corticosteroids as maintenance immunosuppression (from 1998 until December 1995). In groups 2 and 3,early tapering off of corticosteroids (since 1995) was tried; those in group 2 (n = 18) were able to stay off of CS, whereas in group 3 (n = 21), CS withdrawal failed (n = 3) or patients had to receive maintenance CS for other reasons (n = 18), most commonly IBD.

Continuous variables are expressed as mean ± standard error. Categorical variables are expressed as frequencies along with corresponding percentages. The association of IBD, OKT3, CS treatment group, and other categorical variables with rPSC were examined initially using Chi-squared or Fisher's exact tests, as appropriate; the resulting *P* values are reported, along with odds ratios (OR) and their 95% confidence intervals (CI).

A Kaplan-Meier approach was used to examine the rPSC experience of patients posttransplantation, and to calculate product-limit estimates of the time to recurrence for the three corticosteroid treatments; a log-rank Chi squared statistic (LRCS) was used to test the homogeneity of recurrence times between treatments. The influences of alkaline phosphatase, IBD, and OKT3 on the time to recurrence were examined by their inclusion—individually and simultaneously, in the above analysis as covariates. Times to recurrence for comparison subgroups are given in median number of months with 95% confidence intervals. All analyses were implemented with SAS statistical software (SAS STAT, Version 8.1, SAS Institute, Inc, Cary, North Carolina, 2000).

Results

Demographics of the 71 patients are listed in Table 1. These 71 patients received 79 grafts; 4 were right liver lobes from live donors. Ten patients died during follow-up (range, 14 to 91 months). The causes of death are listed in Table 2. Malignancy was the most common cause of death in long-term survivors (60%, 6 of 10). Two patients with recurrent PSC have died, in both cases (sepsis and splenic vein rupture) PSC was thought to be associated with the cause of death. One-year survival for the 77 patients was 92%. PSC recurrence did not affect 5-year survival; it was 86% for those not having a recurrence and 92% for those with rPSC. Eight recipients of cadaveric livers and no recipients of live donor livers underwent retransplantation. Seven retransplantations were for early complications: four for hepatic artery complications (none receiving sirolimus) and three for primary nonfunction. The 1- and 6-year graft survival was 90% and 79%, respectively. None of the hepatic artery complications occurred in patients

Table 1. Patient Demographics

	R-PSC (%)	No Recurrence (%)	Total
Patients	15 (21.1)	56 (78.9)	71
Age at Transplantation (yr)	45.6	43.6	44
Gender (M/F)	12/3 (20.1/23.1)	46/10 (79.9/76.9)	58/13
Primary immunosuppression (C/T/both)*	10/2/3 (31.5/11.1/14.3)	22/16/18 (68.5/88.9/85.7)	32/18/21
OKT3	12 (29.3)	29 (70.7)	41
IBD	10 (18.2)	45 (81.8)	55

*C, cyclosporine A; T, tacrolimus; both, patients were switched from one to the other for various reasons.

receiving sirolimus. The overall retransplantation rate of 10% for patients with PSC is similar to that of our program as a whole (9%), both for cadaveric and for live donor liver transplants.

PSC Recurrence

PSC recurred in 15 of 71 patients (21.1%). Twelve of 58 male and 3 of 13 female patients experienced PSC recurrence (20.7% versus 23.1%), gender was not associated with recurrence (OR, 1.03; CI, 0.75-1.43; $P = .99$). The diagnosis of rPSC was made initially by cholangiographic findings (PTC) in 12 cases and by histology (liver biopsy) in 3; in 1 of these cases a diagnostic PTC and liver biopsy were simultaneously obtained. Mean time to recurrence was 53.2 months (range, 12 to 110 months).The characteristics of patients who experienced recurrence of PSC are depicted in Table 3.

Impact of CS on PSC Recurrence

We examined the role of CS in the posttransplantation course of PSC by comparing rPSC in three cohorts of transplant recipients. Group 1 (n = 32) included all patients who received corticosteroids as maintenance immunosuppression (from 1998 until December 1995). In groups 2 and 3, early tapering off of corticosteroids (since 1995) was tried. Patients in group 2 (n = 18) were those who received CS for less than 90 days after liver transplantation and were able to stay off of CS thereafter. In patients in group 3 (n = 21), CS withdrawal failed (n = 3) or the patients had to receive maintenance CS for other reasons (n = 18). The reasons for failure to wean off of CS in patients in group 3 included allograft rejection (n = 12), autoimmune hepatitis (n = 1), or activity of IBD (n = 8). Patients in group 1 (those on maintenance CS) received and average of 10.7 mg/day of prednisone for an average of 52.1 months after transplantation. Patients in group 3 (failed CS withdrawal) received an average of 13 mg/day of prednisone for an average of 13.3 months.

Ten of 32 (31.3%) of the patients who received maintenance CS, 2 of the 18 (11.1%) who received short-term CS, and 3 of the 21 (14.3%) in whom steroid weaning failed experienced rPSC ($P = .21$).

Although rPSC was most often seen in patients who received long treatment with corticosteroids, the time to recurrence was not significantly different between the three CS treatment groups (LRCS, 0.44; df, 2; $P = .80$; Fig. 1). The effect of CS treatment on time to recurrence remained not significant after adjustment for OKT3 (LRCS, 0.48; df, 1; $P = .49$) or IBD (LRCS, 0.17; df , 1; $P = .68$). An increasing alkaline phosphatase level (data not shown) was significantly associated with time to recurrence (LRCS, 17.3; df, 1; $P < .0001$).

Table 2. Causes of Late Death After Liver Transplantation for Primary Sclerosing Cholangitis

	Cause	Time After Transplantation (mo)	Recurrent PSC
1	Cholangiocacinoma	14	
2	Cholangiocacinoma	25	
3	Sepsis	34	Yes
4	Colon cancer	36	
5	Gun shot wound	37	
6	Lymphoma	56	
7	Colon cancer	66	
8	Cholangiocarcinoma	77	
9	Intestinal perforation	86	
10	Splenic vein rupture	90	Yes

Impact of Immunosuppression on PSC Recurrence

OKT3 therapy was associated with a higher risk of PSC recurrence; 12 of 41 patients who received OKT3 therapy and 3 of 30 who did not experienced rPSC (29% versus 10%; OR, 3.7; CI, 1.0, 14.6; $P < .05$), but the

Table 3. Characteristics of Patients With Recurrent Primary Sclerosing Cholangitis after Liver Transplantation

	Gender	Age at Liver Transplantation	Time to r-PSC (mo)	Diagnosis	CS before r-PSC*	OKT3	IBD	Cause of Death
1	F	45	127	PTC	MA	Y	Y	
2	M	42	74	PTC	MA	Y	Y	
3	M	51	110	LBx	MA	Y	Y	
4	M	46	31	LBx	MA	N	N	PHT
5	M	48	28	PTC	MA	Y	Y	Sepsis
6	M	28	91	LBx	MA	Y	Y	
7	F	42	47	PTC	MA	N	Y	
8	F	43	75	PTC	MA	Y	N	
9	M	49	51	PTC	MA	Y	Y	
10	M	49	64	PTC	MA	Y	Y	
11	M	35	51	PTC	S	Y	Y	
12	M	57	43	PTC	FW, S	Y	N	
13	M	43	29	PTC	S	N	N	
14	M	44	12	PTC	FW	Y	N	
15	M	54	13	PTC	FW	Y	Y	

Abbreviations: r-PSC, recurrent primary sclerosing cholangitis; CS, corticosteroid treatment; MA, maintenance; S, short-term; FW, failure to wean; LBx, liver biopsy; PTC, percutaneous transhepatic cholangiogram; PHT, portal hypertension.

time to recurrence in months was not significantly different (LRCS, 2.8; df, 1; $P = .09$). Patients in group 2 received less OKT3 than those in groups 1 or 3 (39%, 66%, and 67%, respectively), a fact that may explain why patients in group 2 showed a trend toward less PSC recurrence. PSC recurrence was not influenced by primary immunosuppression with either CyA or TAC. In the era of sequential assignment of patients to CyA or TAC since 1994, 7 patients experienced rPSC, 4 on CyA and 3 on TAC. Overall more patients receiving CyA than TAC experienced disease recurrence, but that is because a cohort underwent transplantation before

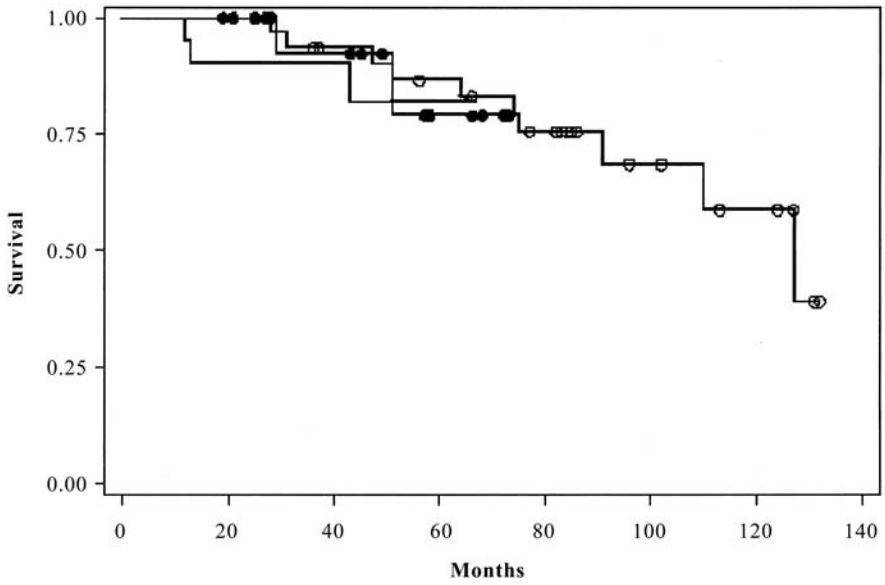

Figure 1. Kaplan-Meier analysis of Primary Sclerosing Cholangitis recurrence according to length of corticosteroid administration after liver transplantation. Straight line — Failed Early Corticosteroid Withdrawal. Line with filled circles — Early Corticosteroid Withdrawal. Line with open circles — Long-Term Use of Corticosteroids.

1994 and all of those received CyA as primary immunosuppression.

Impact of IBD on PSC Recurrence

Fifty-five patients (77.5%) had IBD. Steroid withdrawal failed because of IBD flare-ups in 21 of 39 patients (53.8%) who underwent transplantation after December 1995. Ten of 55 patients with IBD (18.2%) and 5 of 16 patients without IBD (31.3%) experienced rPSC, but the risk of recurrent PSC was not associated with IBD (OR, 0.49; CI, 0.14, 1.72; $P = .30$). Although the frequency of occurrence of rPSC was not significantly different between patients with and without IBD, the length of time before rPSC was significantly shorter between those with IBD and without (LRCS, 7.1; df, 1; $P < .01$). Four patients in the IBD group experienced de novo colon carcinoma (7.3%), and in 3 of them it was the cause of death.

Biliary Complications

Biliary complications unrelated to rPSC occurred in 8 patients (11.3%) and included two bile leaks and six biliary stenoses that responded to endoscopic, radiologic, or surgical therapy. Late biliary stenoses occurred in 17 patients (23.9%) and were invariably associated with rPSC or cholangiocarcinoma. Three patients who had cholangiocarcinoma at the time of liver transplantation had recurrence that eventually was the cause of death at 14, 25, and 77 months after the liver transplantation.

Discussion

PSC is a chronic inflammatory disease of the biliary tree with presumed, but not defined, autoimmune pathophysiology. The clinical course is highly variable, but a significant number of patients progress to end-stage biliary complications, cirrhosis, or cholangiocarcinoma.[1,2,16] Patients with PSC are often treated with endoscopic, radiologic, surgical, or medical therapies. The latter may include antibiotics, ursodeoxycholic acid, immunosuppressants, anti-inflammatory agents, and vitamins. However, none of these treatments or approaches have been shown to positively impact patient survival or eliminate the need for liver transplantation.

Liver transplantation is the treatment of choice for patients with end-stage PSC. Several large series have been published showing excellent patient and graft survival. Long-term follow-up of patients who underwent transplantation for PSC indicates that the disease does recur after liver transplantation. The incidence of PSC recurrence in our series was 21.1%, and the mean time to recurrence was 53 months; both of these are consistent with previously published results.[3,17,18]

Protocol biopsies and cholangiograms are not routinely performed for patients who underwent transplantation for primary sclerosing cholangitis at our institution. We think that more patients would actually be diagnosed with recurrent PSC, but no intervention would be warranted until jaundice, significantly abnormal elevation of liver test results, or cholangitis developed. The diagnosis of recurrent disease was made in our series when one of these situations triggered a workup. As such this under represents the true incidence of recurrent disease, but not that of biochemically or clinically evident recurrent disease.

Biliary complications in our series, as in others, occurred in a significant amount of patients (35.2%). Early biliary complications, unrelated to rPSC, included bile leaks and anastomotic strictures that were successfully managed with endoscopic, radiologic, or surgical intervention. Late biliary strictures were invariably associated with either rPSC or recurrent cholangiocarcinoma. The latter cases were typically managed with PTC and external biliary drainage, because most patients undergoing liver transplantation for PSC receive Roux-en-Y choledochojejunostomy at our center.

As in other series, 77% of our PSC patients have chronic ulcerative colitis (CUC, n = 50), or colonic Crohn disease (n = 3), or nonspecific colitis (n = 2). Coexistent IBD was not associated with more PSC recurrence, but it did accelerate its onset. IBD was associated with failure to withdraw steroids in 8 of 39 patients (20.5%), but no grafts were lost because of protracted rejection. In contrast, CUC was associated with morbidity and mortality because of development of colorectal adenocarcinoma in 4 patients (7.3%). The higher risk of colorectal neoplasia in immunosuppressed patients with coexistent PSC and CUC has been previously described.[19,20]

The goal of our study was to assess the effect of immunosuppression practices at our center in the natural history of PSC after transplantation. We found no evidence that primary immunosuppression with either CyA or TAC affected the risk of PSC recurrence. We found a significant difference in PSC recurrence in between patients who required OKT3 therapy for refractory acute cellular rejection and those who did not. The reasons for this observation remain unclear; whether it is greater immunosuppression or opportunistic (yet undetected) infections of the biliary tree that lead to greater rPSC in those receiving OKT3 remains unclear at this time. We also found that patients in whom we were able to discontinue corticosteroids

within 3 months of liver transplantation had a trend toward lesser rPSC (11.1% versus those on long-term CS 31.3%, but NS). These patients also received less OKT3 than those in groups 1 or 3, and that may also be the reason why we saw less rPSC (39% in group 2 versus 66% and 67% in groups 1 and 3 respectively). These data suggest that we should not use OKT3 unless absolutely necessary. Our recommendation regarding corticosteroid use has to be based on its adverse metabolic consequences, but strengthened by the trend shown toward a higher likelihood of recurrence in those patients exposed to corticosteroids chronically. This recommendation is tempered somewhat by the fact that our patients with short-term CS courses have had lesser follow-up than those who received long-term courses of CS and underwent transplantation earlier at our program (shorter CS course may delay rPSC rather than decrease the recurrence). Nonetheless, we did not find any untoward consequences from early steroid withdrawal in our cohort, and our group has already proven the beneficial effects of early steroid withdrawal in liver transplant recipients.[13]

Conclusion

Liver transplantation is effective in the management of PSC with excellent short- and medium-term patient and graft survival. However, PSC does recur after liver transplantation; in our series 21.1% of patients had recurrence after a mean of 53 months. Longer periods of follow-up may show an even greater cumulative risk for recurrence. IBD affected the course of liver disease in our cohort by preventing CS withdrawal, shortening the time to rPSC, and increasing the risk of dying from colonic neoplasia. Patients who received OKT3 were more likely to experience recurrence of PSC, thus its use should be re-evaluated in these patients. We favor steroid withdrawal in this group of patients because it poses no increased risk of allograft failure and it offers better control of several metabolic complications, including hyperlipidemia, diabetes mellitus, and hypertension.

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