Research Article

JOURNAL OF HEPATOLOGY

Risk factors for recurrent primary sclerosing cholangitis after liver transplantation

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Abstract

Background & Aims: The association between primary sclerosing cholangitis (PSC) and inflammatory bowel disease (IBD) is well recognised. However, the relationship between IBD and recurrent PSC (rPSC) is less well understood. We assessed the prevalence of rPSC and analysed the factors associated with rPSC post-liver transplantation and its influence on graft and patient survival.

Methods: This is a UK multicentre observational cohort study across six of the seven national liver transplant units. All patients undergoing a first liver transplant for PSC between January 1 1990 and December 31 2010 were included. Prospectively collected liver transplant data was obtained from NHSBT and colitis data was retrospectively collected from individual units.

Results: There were 679 (8.8%) first transplants for PSC. 347 patients (61.4%) had IBD, of which 306 (88.2%) had ulcerative colitis (UC). 81 (14.3%) patients developed rPSC and 37 (48.7%) of them developed graft failure from rPSC. Presence of UC post-liver transplant (HR = 2.40, 95% CI 1.44–4.02) and younger age (HR = 0.78, 95% CI 0.66–0.93) were the only factors significantly associated with rPSC. rPSC was associated with over a 4-fold increase in the risk of death (HR = 4.71, 95% CI 3.39, 6.56) with 1, 5, and 10-year graft survival rates of 98%, 84%, and 56% respectively compared to 95%, 88%, and 72% in patients who did not develop rPSC.

Conclusion: The presence of UC post-liver transplant is associated with a significantly increased risk of rPSC. Furthermore, the presence of rPSC increases the rate of graft failure and death, with higher re-transplantation rates.

Keywords: Recurrent PSC; Ulcerative colitis; Colectomy; Liver transplantation; Patients and graft survival.

Received 13 June 2014; received in revised form 13 June 2015; accepted 2 July 2015; available online 14 July 2015

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Introduction

Primary sclerosing cholangitis (PSC) is an autoimmune disease of the intrahepatic and/or extrahepatic biliary tree with variable clinical course and no curative treatment [1]. It is a progressive disorder that can lead to cirrhosis and hepatic decompensation. PSC co-exists with inflammatory bowel disease (IBD), mainly ulcerative colitis (UC), in 60–70% of the patients [1].

At present, the only effective therapeutic option for patients with PSC and end-stage liver disease is liver transplantation. Nevertheless, PSC can recur after liver transplantation, with an incidence of 8.6 to 47% depending on the criteria used to define recurrence [2]. The factors associated with post-transplant recurrence are unclear but have been assessed in small cohort studies. These have suggested that gender [3], presence of IBD or an intact colon after liver transplantation [3–7] and recurrent acute cellular rejection or steroid resistant rejection [8,9] are potential risk factors for recurrent PSC (rPSC), although findings were inconsistent.

The association between the status of colitis and rPSC is of particular interest. This implies an interaction between the bowel and the liver which is reinforced by additional associations; UC in patients with PSC pre-transplant is often clinically quiescent, but involves the whole of the colon with more right-sided colitis and carries a higher risk of bowel cancer compared to UC alone [10,11]. When patients with UC/PSC are transplanted for PSC, the number and severity of UC flares increase post-transplant [12]. On the other hand, colectomy in patients with PSC/UC has no effect on liver biochemistry or patient survival in the pre-transplant setting [13].

This UK multicentre study assessed the rate and analysed the factors associated with rPSC post-liver transplantation. In particular, it aimed to explore the influence of colitis and the associations of the presence, timing and type of colectomy with recurrence in patients with PSC/UC. It also assessed the influence of rPSC on graft and patient survival.

Materials and methods

Patients

This is a UK multicentre observational cohort study that involved six of the seven national liver transplant units. All patients undergoing a first liver transplant for PSC between January 1 1990 and December 31 2010 were included. National ethical approval, National Health Service Blood and Transplant (NHSBT) approval and National Information Governance Board approval were obtained to perform this multicentre study. Prospectively collected liver transplant data was obtained from NHSBT and colitis data was retrospectively collected from individual units. Retrospective data was obtained from electronic patient records, patient notes and hospital databases. Individual patient records at each centre were examined to further establish the presence of rPSC and to determine the modality of diagnosis of rPSC. The following liver transplant data was collected: indication for transplantation, cause and date of death, demographic data, presence of associated cholangiocarcinoma (CCA), initial use and type of immunosuppression, annual follow-up data for the entire follow-up period, presence of rPSC, patients and graft survival. The following colitis data was collected: presence and type of colitis, date of diagnosis, timing and type of colectomy.

Diagnosis of rPSC

Cases of rPSC were identified in the dataset through the centre reporting an rPSC diagnosis or graft failure due to recurrence reported by NHSBT. After liver transplantation, patients are investigated by Doppler ultrasonography, CT or MRI, magnetic resonance cholangiography (MRCP) or liver biopsy if indicated by abnormal liver function tests. Routine/protocol angiographic imaging or liver biopsies for the diagnosis of rPSC were not performed in patients with normal liver function tests in the absence of clinical indications. The diagnosis of rPSC was guided by the Mayo Clinic criteria [14,15]. Patients with autoimmune hepatitis overlap were excluded. The diagnosis of rPSC at centres was based on histological and radiological features of PSC in the absence of defined causes of secondary sclerosing cholangitis and non-anastamotic biliary strictures [15]. Histological evidence of rPSC was based on the findings of periductular fibrosis, obliterative ductular lesions and bile duct loss in the absence of chronic allograft rejection [15–17]. Radiological features of rPSC were defined as intra and/or extrahepatic non-anastomotic biliary strictures in the presence of normal vascular supply [15]. Dedicated liver radiologists and histopathologists performed all radiological and histological evaluations.

Statistical analysis

Risk factors for rPSC were assessed using Kaplan-Meier and Cox Proportional Hazards (CPH) models with baseline and time updated covariates. For these analyses, follow-up was calculated from date of first liver transplant to recurrence of PSC, as defined above, and censored at graft failure for other reasons, death or 31st December 2013. Time updated CPH models also investigated the effect of rPSC and presence of UC on patient survival (calculated at a patient level) and both graft survival and a combined endpoint of graft survival or death (calculated at a graft-level), with follow-up calculated from liver transplant until graft failure or death.

Results

Recipient characteristics

A total of 9068 liver transplants were performed in 8186 patients, of which 679 (8.3%) were first liver transplants for PSC. A total of 114 patients were excluded from the final analysis (48 patients with hepatic artery thrombosis, 11 with primary graft non-function and 55 who died within 6 months of transplant), in keeping with other published series. This left a final cohort of 565 patients in the final analysis.

The leading cause of death within the first 6 months of transplantation was sepsis (13 patients) and multi-organ failure (12 patients). The median age at transplantation was 49 years (interquartile range (IQR) 40–57), with a greater preponderance of men to women (71.8% and 28.2% respectively) (Table 1). Median follow-up was 9 years (IQR 5–14 years). 347 patients (61.4%) had IBD, of which 306 (88.2%) had UC, 29 (8.4%) had Crohn's colitis and 12 (3.5%) had indeterminate colitis. 235 patients had a diagnosis of UC prior to transplantation, of whom 35 (14.9%) had a colectomy prior to transplant, 4 (1.7%) had a colectomy during their transplant and 37 (15.8%) had colectomy post-transplant. The timing of colitis diagnosis relative to liver transplant was unknown for 43 (12.4%) patients, of which 27 patients had a diagnosis of UC. 36 (11.8%) patients were diagnosed with UC after their liver transplant. 7 (19.4%) of these patients had a colectomy.

Recurrent PSC population

One hundred and fifteen cases of rPSC were identified within the NHSBT dataset, 81 (14.3%) of which were subsequently conclusively confirmed as such by the individual centres (11 cases had biliary complications).

Thirty-seven (48.7%) patients with rPSC developed graft failure secondary to recurrent disease, of which 17 (45.9%) patients died and 17 (45.9%) patients were re-grafted at a median (IQR) of 7.4 (5.3–10.5) years after the first transplant (Fig. 1). One patient transplanted for PSC who required a second transplant for non-thrombotic infarction, underwent a third transplant for graft failure secondary to rPSC. In the 81 patients diagnosed with rPSC on their first liver transplant, 17 were diagnosed with MRCP, 43 with histology from a liver biopsy and 18 with both MRCP and a liver biopsy. Histology from liver biopsies revealed features typical of rPSC in 33 patients and compatible with rPSC in 28 patients. No details were available for 3 patients.

Of 484 individuals who did not have rPSC, only 76 (15.7%) experienced graft failure. 16 of these patients were re-transplanted for hepatitis C cirrhosis (n = 2), biliary complications (n = 2), and non-thrombotic infarction (n = 1). No cause was identified for 6 patients. 13 patients with rPSC patients developed

Table 1. Characteristics of patients who underwent a liver transplant for PSC.

Recipient characteristic	Cohort n = 565
Age, median (IQR)	49 (40-57)
Gender, n(%)	
Male	405 (71.8)
Female	159 (28.26)
Follow-up (years), median (IQR)	9 (5-14)
Calendar year:	
1990-2000	232
2001-2010	333
Patients with IBD, n(%)	347 (61.4)
UC, n(%)	306 (54.2)
Crohn's, n(%)	29 (5.1)
Other, n(%)	12 (2.1)
UC diagnosed pre-LTx, n(%)	235 (76.8)
Colectomy pre/during LTx, n(%)	39 (16.6)
Colectomy after LTx, n(%)	37 (15.7)
UC diagnosed post-LTx, n(%)	36 (11.8)
Colectomy, n(%)	8 (22.2)

IQR, interquartile range; n, number; IBD, inflammatory bowel disease; UC, ulcerative colitis; LTx, liver transplantation.