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ORIGINAL ARTICLE

The impact of disease recurrence on graft survival following liver transplantation: a single centre experience

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Summary

Many diseases that cause liver failure may recur after transplantation. A retrospective analysis of the rate and cause of graft loss of 1840 consecutive adults receiving a primary liver transplant between 1982 and 2004 was performed to evaluate the rate of graft loss from disease recurrence. The risk of graft loss from recurrent disease was greatest, when compared to primary biliary cirrhosis (PBC), in those transplanted for hepatitis C virus (HCV) [hazard ratio (HR) 11.6; 95% confidence interval (CI) 5.1–26.6], primary sclerosing cholangitis (PSC) (HR 6.0; 95% CI 2.5–14.2) and autoimmune hepatitis (AIH) (HR 4.1; 95% CI 1.3–12.6). The overall risk of graft loss was also significantly greater in HCV (HR 2.1 vs. PBC; 95% CI 1.5–3.0), PSC (HR 1.6 vs. PBC; 95% CI 1.2–2.3) and AIH (HR 1.6; 95% CI 1.0–2.4) than in PBC. There was no statistically significant difference in the risk of graft loss because of recurrent disease, when compared with PBC, for patients transplanted for alcohol related liver disease, nonalcoholic steatohepatitis and fulminant hepatic failure. Disease recurrence is a significant cause of graft loss particularly in HCV, PSC and AIH. Recurrent disease, in part, explains the increased overall risk of graft loss in these groups.

Introduction

Early graft loss has been reduced, in part, through improvements in surgical and anaesthetic techniques and advances in organ preservation. As the rate of early graft loss improves, long term survival becomes increasingly important. The factors affecting long term survival include those related to immunosuppression, which may be related to immunosuppression *per se* (such as increased risk of cardiovascular disease infections and some cancers) or drug-specific (such as renal failure or diabetes) [1]. Factors related to the aetiology of liver disease are also associated with long term survival and many diseases, both metabolic and immunologic, may recur after transplantation. The overall rates of disease recurrence in all diseases vary widely between reports [2–13] and those for autoimmune liver disease have been recently reviewed [14]. Particular interest has focused on recurrence of alcohol related liver disease (ALD). Alcohol related liver disease is one of the most common indications for liver transplantation in both the United States and Europe [15,16]. Despite this, it remains controversial and only a small proportion of patients with ALD are ever considered for transplantation at least in part because of concerns regarding recidivism [17]. Those who are referred undergo extensive evaluation for both alcohol related physical disease as well as full evaluation for alcohol dependence [18].

To investigate further the role of nonmalignant disease recurrence on long term survival, we evaluated the rate and impact of graft loss caused by disease recurrence in a large cohort of patients undergoing liver transplantation in a single centre.

Patients and methods

All adult patients (aged 17 years or more) undergoing transplantation in our centre between 1982 and 2004 were included. Data on patient demographics, aetiology of liver disease, cause of graft loss and graft survival time were collected prospectively. The study endpoint was graft loss from any cause, either through patient death or retransplantation. Only data relating to the first transplant in those patients who were re-grafted were studied. Immunosuppression was commenced in all patients in accordance with the unit protocols (as published in detail elsewhere [19]): standard maintenance treatment was initially with azathioprine (1–2 mg/kg/day) and ciclosporin (target trough whole blood levels 100–150 ng/ml), and since the year 2000 with azathioprine and tacrolimus (target trough whole blood levels 5–10 ng/ml) although tacrolimus was used in selected patients in patients enrolled in clinical trials and in those with resistant rejection before this period. Patients transplanted during the study period underwent regular protocol graft biopsies, the frequency of which was determined by the aetiology of the primary disease.

The aetiology of liver disease was categorized by the primary aetiology into: ALD, primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), autoimmune hepatitis (AIH), hepatitis B virus infection (HBV), hepatitis C virus infection (HCV), cryptogenic, nonalcoholic fatty liver disease (NAFLD), cancer, metabolic and other. In patients transplanted for hepatocellular carcinoma (HCC), the underlying liver disease was categorized, for example, patients transplanted for HCV and HCC were classified as HCV. Fulminant hepatic failure (FHF) was divided in to acetaminophen and nonacetaminophen related. Although controversial, given the likelihood that those patients with cryptogenic cirrhosis had NAFLD [20], these groups are analysed together. Since the year 2000, those patients transplanted for HBV related liver disease have been treated with lamivudine and hepatitis B immunoglobulin. Given that there is an effective prophylactic treatment in lamivudine and hepatitis B immunoglobulin [21,22], which prevents disease recurrence in patients transplanted for hepatitis B, these patients were excluded from the risk analysis. Since the year 2004, selected patients transplanted for HCV related liver disease who have developed significant fibrosis from recurrent disease in the transplanted liver have received treatment with interferon and ribavirin. In those transplanted for other disease indications, recurrent disease was treated in line with recommendations for the primary disease. In the last 5 years, patients transplanted for AIH have been maintained on long term low dose corticosteroids (Prednisolone 5–10 mg/day) and those transplanted for PBC have been treated with ursodeoxycholic acid (10–15 mg/kg/day).

The cause of graft loss was categorized as recurrent disease related or nonrecurrent disease related. Those categorized as recurrent disease related were grafts lost because of disease recurrence or, in the case of those transplanted for ALD or acetaminophen related FHF, documented noncompliance leading to graft loss through chronic rejection. Grafts lost as a consequence of the underlying mental health issues of patients presenting with acetaminophen related FHF (e.g. to deliberate self-poisoning) were also categorized as disease recurrence. All diagnoses of disease recurrence were based on biopsy findings, typical findings on appropriate imaging, or studies of the explanted liver. Recurrent disease in PBC was defined on the basis of compatible histology and exclusion of other causes of bile duct damage, such as features of acute or chronic rejection, biliary outflow obstruction and vascular abnormalities. A diagnosis of recurrent PSC was made on histological and radiological grounds in the absence of defined causes of secondary sclerosing cholangitis (including blood supply abnormalities, and preservation, or reperfusion injury). Radiological recurrence was defined as the presence of multiple intra- or extrahepatic biliary nonanastomotic strictures in the presence of a normal blood supply. Histological recurrence was defined by the presence of periductal fibrosis, sclerosing ductular lesions and bile duct loss in association with features of chronic biliary obstruction (such as periportal fibrosis, ductular proliferation and accumulation of copper associated protein). Recurrence of AIH was diagnosed on the basis of the following criteria: presence of antinuclear or anti-smooth muscle or anti-liver-kidney microsome at a titre of 1:40 or higher with a raised immunoglobulin G; elevation of aspartate transaminase (AST) to at least three times the upper limit of normal; histological features of autoimmune hepatitis including: portal inflammatory infiltration by mononuclear cells associated with interface hepatitis and/or lobular inflammation associated with confluent or bridging necrosis; and lack of serum markers of hepatitis A, B and C. Recurrence of ALD was diagnosed on clinical grounds; all patients were asked about alcohol consumption, and where indicated, blood was tested for alcohol. The presence of steatosis on liver biopsy led us to consider disease recurrence when the patients were evaluated clinically. A diagnosis of recurrent HCV was made in the presence of continued HCV RNA positivity and chronic hepatitis on biopsy. Recurrence of disease in NAFLD was defined by the clinical assessment, the exclusion of alcohol excess and biopsy evidence of steatohepatitis. In patients transplanted following acetaminophen related FHF, recurrence was defined on clinical grounds and included deliberate noncompliance leading

to chronic rejection and graft loss. To eliminate those grafts lost for reasons where recurrence was very unlikely, late graft loss was defined as those grafts lost after 90 days.

Data on patients not reaching the study end point were censored on 1st January 2006. Hazard ratios for graft loss were calculated with the use of a Cox regression model including aetiology of liver disease alone. Fisher's exact test and chi-square test were used to compare categorical data. All statistical analyses were performed with SPSS v. 15.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 1840 patients underwent orthotopic liver transplantation from deceased donors and received a total of 2027 grafts. Of these, 1678 patients received a single graft only, 142 patients received two grafts and 20 patients were transplanted more than twice. Data were available for more than 95% of recipients. The median age at first liver transplant was 50.3 years (interquartile range 41.1–57.8 years). Of those transplanted, 48.0% were male. The median follow up period was 2053 days (interquartile range 703–3791 days). When only first transplants were considered, 341 grafts (18.5%) were lost in the first 90 postoperative days. Of the remaining 1499 grafts, 417 (27.8%) were lost in the follow-up period. The estimated median first graft survival was 4913 days (95% confidence interval 4170–5655 days) and the estimated overall median patient survival was 5727 days (95% confidence interval 4877–6576 days).

The most common disease aetiology in the study period was PBC accounting for 29.4% of first transplants with a median follow up time of 2868 days (interquartile range 986–4502 days). The next most common disease aetiologies in order were PSC, HCV and ALD (Table 1). 161 patients were transplanted for HCC, and of those 15 were transplanted for HCC alone. The high numbers of patents transplanted for PBC reflects the practice in our centre in the first decade of transplantation when most patients were transplanted for PBC. Currently, the most

Table 1. Number of first transplants performed and median follow up time by aetiology of liver disease.

Aetiology of liver disease	Number of transplants (% of total)	Median follow up in days (interquartile range)
PBC	541 (29.4)	2868 (986–4502)
ALD	179 (9.7)	1758 (766–3426)
PSC	200 (10.9)	1957 (719–3913)
HCV	181 (9.8)	1732 (842–2581)
Acetaminophen related FHF	53 (2.9)	1351 (26–3699)
Nonacetaminophen related FHF	151 (8.2)	1956 (630–3769)
Cryptogenic/NAFLD	114 (6.2)	1793 (683–3817)
AIH	103 (5.6)	1834 (147–3563)

PBC, primary biliary cirrhosis; HCV, hepatitis C virus; PSC, primary sclerosing cholangitis; AIH, autoimmune hepatitis; FHF, Fulminant hepatic failure; PSC, primary sclerosing cholangitis; NAFLD, nonalcoholic fatty liver disease; ALD, alcohol related liver disease.

Table 2. Risk of overall graft loss and graft loss due to recurrent disease by aetiology of liver disease in comparison to published estimated risk of disease recurrence in the transplanted liver.

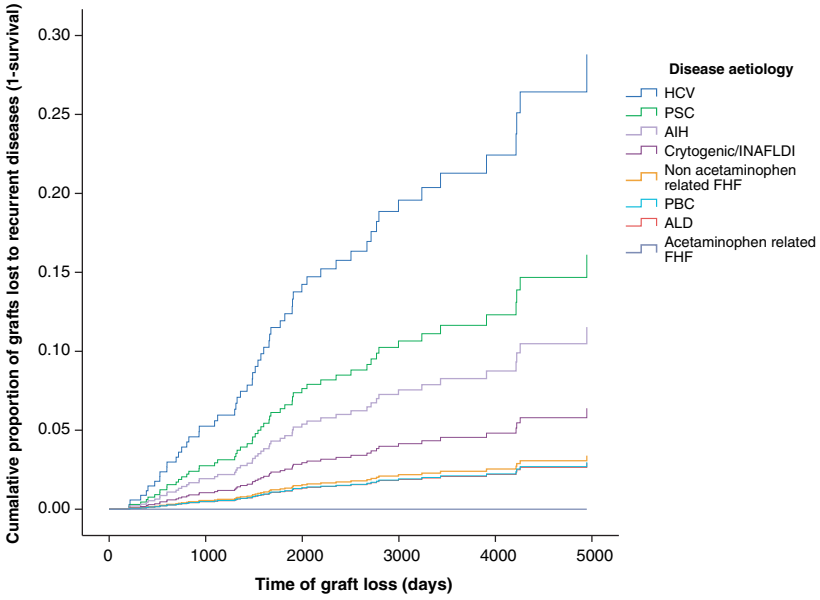
	Percentage of grafts lost after 90 postoperative days		Published risk of developing recurrent disease in graft		
Aetiology of liver disease	Total %	To recurrent disease %	Overall % [references]	Our centre % [references]	Risk of graft loss to recurrent disease Hazard ratio versus PBC (95% confidence interval)
PBC	24.6	1.3	18 [14]	24 [10]	N/A
ALD	25.8	3.2	5–20 [2,3]	24 [3]	1.0 (0.2–4.9)
PSC	33.1†	8.4†	11 [14]	37 [11]	6.0 (2.5–14.2)
HCV	32.3†	14.3†	62–80 [5,6]	77 [7]	11.6 (5.1–26.6)
Acetaminophen related FHF	20.6	0	12 [9]		N/A§
Nonacetaminophen related FHF	23.4	2.7			1.7 (0.4–6.6)
Cryptogenic/NAFLD	24.7	3.2	25–33‡ [4]		2.2 (0.6–8.4)
AIH	33.3*	6.2*	22 [14]	28 [13]	4.1 (1.3–12.6)

PBC, primary biliary cirrhosis; HCV, hepatitis C virus; HR, hazard ratio; PSC, primary sclerosing cholangitis; AIH, autoimmune hepatitis; FHF, Fulminant hepatic failure; PSC, primary sclerosing cholangitis; NAFLD, nonalcoholic fatty liver disease; ALD, alcohol related liver disease.
*$P < 0.05$, †$P < 0.005$ vs. PBC, Cox proportional hazard method.
‡Rate of steatohepatitis.
§No grafts lost to disease recurrence in the study period.

common disease indications for liver transplant in our centre, as with other European centres are ALD and HCV related liver disease.

Disease related graft loss was most common in those transplanted for HCV with 44.2% of all grafts being lost to recurrent disease. The proportion of grafts lost to recurrent disease was 5.4% of all grafts lost in those grafted for PBC and this compares with 12.5% for those grafted for ALD. Although no grafts were lost after 90 days in those patients transplanted for acetaminophen related FHF to factors related to underlying mental illness, one patient committed suicide before this time. In patients transplanted for HCC, the proportion of grafts lost to recurrent disease was 47.9% of all grafts lost. The highest risk of nonmalignant disease related graft loss when compared to the PBC group is the HCV related liver disease group (hazard ratio, 11.6; 95% CI 5.1–26.6). The other groups at increased risk of recurrent disease related graft loss were the PSC group (hazard ratio, 6.0; 95% CI 2.5–14.2) and the AIH group (hazard ratio 4.1; 95% CI 1.3–12.6). Patients transplanted for HCC were at high risk of disease recurrence when compared to those transplanted for PBC (hazard ratio 22.4; 95% CI 9.1–55.4). As compared with the PBC group there was no difference in the risk of graft loss from recurrent disease in the other indications for liver transplantation where disease recurs (Table 2, Fig. 1).

The highest risk of graft loss from all causes after 90 postoperative days, when compared to PBC, was seen in those transplanted for HCV (hazard ratio 2.1; 95% CI 1.5–3.0), PSC (hazard ratio 1.6; 95% CI 1.2–2.3) and AIH (hazard ratio 1.6; 95% CI 1.0–2.4) (Table 2). No difference was seen when comparing the rate of graft loss from all causes after 90 postoperative days between ALD and PBC (hazard ratio 1.4; 95% CI 0.9–2.0). Patients transplanted for HCC in the study period were also at high risk of graft loss from all causes (hazard ratio 2.5; 95% CI 1.8–3.6) when compared to those patients transplanted for PBC. When disease recurrence is excluded as a cause of graft loss no significant differences are seen between PBC and the other groups where nonmalignant disease recurs (including HCV: hazard ratio 1.4; 95% CI 0.9–2.1, PSC: hazard ratio 1.4; 95% CI 0.9–2.0 and AIH: hazard ratio 1.4; 95% CI 0.9–2.2) (Table 2).



Aetiology of liver disease (*n*)	Grafts at risk (post operative days)					
	90	1000	2000	3000	4000	5000
HCV (181)	161	117	69	30	12	3
PSC (200)	166	132	84	68	40	19
AIH (103)	81	66	48	32	21	11
Cryptogenic/NAFLD (114)	93	70	50	38	24	10
Non acetaminophen related FHF (151)	111	94	66	41	28	15
PBC (541)	450	383	311	243	162	82
ALD (179)	155	116	82	51	24	5
Acetaminophen related FHF (53)	34	28	21	18	9	6

Figure 1 Proportion of all grafts lost after 90 postoperative days to disease recurrence by aetiology of liver disease. Diseases listed in descending order of proportion of grafts lost to disease recurrence (Cox regression model, 1-survival curve).

The median time to graft loss from disease recurrence varies between indications. The shortest time to graft loss from disease recurrence is in patients transplanted for AIH (525 days). In patients transplanted for PBC, the median time to graft loss from recurrent disease is 2838 days. The numbers of grafts lost by aetiology of liver disease and year of transplant is shown in Table 3. In patients transplanted for HBV, the proportion of grafts lost because of recurrent disease has fallen since prophylactic antiviral treatment was introduced (Fisher's exact test $P = 0.008$, patients transplanted before the year 2000 versus those transplanted since). In those patients transplanted for AIH, there has been a nonsignificant fall in the proportion of grafts lost to disease recurrence since the introduction of maintenance steroids after transplant (Fisher's exact test $P = 0.23$, patients transplanted before the year 2000 versus those transplanted since). The proportion of grafts lost to recurrent disease in those transplanted for HCC has also fallen since the year 2000 (chi-square $P = 0.002$) when data published on predictors of recurrence [23] were fully incorporated into the selection criteria for liver transplantation in our centre.

Clear differences are seen when the rates of graft loss from disease recurrence are compared with the rate of disease recurrence for each group. Graft loss from disease recurrence as proportion of grafts affected by disease recurrence was greater in HCV (14.3% of grafts lost to recurrent disease versus 77% of grafts affected by recurrence in our centre [7]), PSC (8.4% vs. 37% [11]) and AIH (6.2% vs. 28% [13]) than in PBC (1.3% vs. 24% [10]).

Table 3. Grafts lost to recurrent disease by year of first liver transplant.

Indication	Median time to graft loss from recurrent disease	Year of liver transplant	Graft lost to recurrent disease	
			Yes (*n*)	No (*n*)
PBC	2833	1982–1989	2	75
		1990–1994	3	149
		1995–1999	1	116
		2000–2004	0	104
ALD	2543	1982–1989	0	0
		1990–1994	3	26
		1995–1999	2	64
		2000–2004	0	61
PSC	1342	1982–1989	1	11
		1990–1994	4	48
		1995–1999	9	42
		2000–2004	0	51
HCV	1429	1982–1989	0	1
		1990–1994	1	19
		1995–1999	13	55
		2000–2004	7	65
Acetaminophen related FHF	N/A	1982–1989	0	0
		1990–1994	0	12
		1995–1999	0	14
		2000–2004	0	8
Nonacetaminophen related FHF	1662	1982–1989	2	11
		1990–1994	1	29
		1995–1999	0	35
		2000–2004	0	33
Cryptogenic/NAFLD	1123	1982–1989	1	8
		1990–1994	0	25
		1995–1999	1	26
		2000–2004	1	31
AIH	525	1982–1989	0	6
		1990–1994	2	26
		1995–1999	3	24
		2000–2004	0	20
HBV	717	1982–1989	2	3
		1990–1994	3	8
		1995–1999	3	24
		2000–2004	0	33
HCC	581	1982–1989	4	6
		1990–1994	5	10
		1995–1999	8	30
		2000–2004	6	71

PBC, primary biliary cirrhosis; HCV, hepatitis C virus; PSC, primary sclerosing cholangitis; AIH, autoimmune hepatitis; FHF, Fulminant hepatic failure; PSC, primary sclerosing cholangitis; NAFLD, nonalcoholic fatty liver disease; ALD, alcohol related liver disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

Discussion

The overall rates of disease recurrence vary widely between reports and it is important to distinguish between disease recurrence and its consequences. We have confirmed the high rate of disease recurrence and subsequent graft loss in those patients transplanted with HCV. The aim of sustained virological response (SVR) prior to transplantation is difficult to achieve in a large proportion of patients with decompensated cirrhosis and unfortunately treatment after transplant is equally difficult although response rates are better [24]. We have so far only treated a small number of patients with HCV and recurrent disease in our centre and there has been insufficient time to see the effect of this on the rate of graft loss. It is likely for the foreseeable future at least that there will be little change in outcome after transplantation in these patients.

For autoimmune diseases, such as PBC, PSC and AIH, the reported recurrence rates vary in part because of the variation in testing for disease recurrence. In particular, it should be noted that reported rates of recurrence will depend on whether routine, protocol biopsies are performed since recurrence particularly of PBC or PSC may be present in the face of normal liver tests. However, although disease may recur the effect on graft survival is

variable and in our centre the rate of disease related graft loss in patients transplanted for PSC is high. Our group has previously published data on disease recurrence in 152 patients with PSC showing evidence for disease recurrence (in accordance with published criteria [12]) in 37% at a median of 36 months [11]. These data and others were recently included in a systematic review from the Mayo Clinic [14]. This review estimated disease recurrence in PSC at 11% but noted significant publication bias with an excess of studies reporting low rates of disease recurrence. We have shown that a significant proportion of those patients with recurrent disease will go on to develop graft failure and graft loss. Importantly disease recurrence does impact on overall graft survival. In HCV, PSC and AIH overall graft survival is reduced when compared to PBC and this difference is lost when those grafts lost to disease recurrence are excluded. The lower numbers of grafts lost to recurrent disease in recent years in patients transplanted for AIH may relate to the maintenance of corticosteroid treatment in these patients. In future, the rates of recurrence may fall further, but continued follow up will be needed to confirm the effect of continued corticosteroid therapy in this setting.

Interestingly, in the same review, the recurrence rate of PBC was estimated at 18% [14]. The rate of graft loss in PBC is much lower than this, and lower than that seen in PSC. This likely represents the slower progression of PBC compared with PSC in the graft and also shows that the more significant outcome is graft loss rather than simply disease recurrence. Even in a study with extended follow-up, there was no difference in graft survival between those patients with recurrent PBC and those without, and treatment in those patients with recurrent disease with ursodeoxycholic acid had no effect on graft outcome [25].

Alcohol related liver disease is an established indication for liver transplantation although it remains controversial. In this study of highly selected patients with ALD, the rate of recurrent disease related late graft loss was low and compared favourably with other indications for liver transplantation. The rate of alcohol relapse has been studied in our centre and others and has been found to be low. This reflects both the process of patient selection and the development of interventions designed to prevent alcohol relapse [26]. Although a significant proportion (up to 50%) of patients return to drinking alcohol, return to harmful drinking is much less common: in our centre, less than 10% of patients return to drinking more than 21 units per week [26,27]. In those patients who return to harmful drinking after transplant, it is not clear what duration of drinking is required to cause irreversible liver dysfunction and graft loss though those grafts lost to recurrent disease in this cohort were all lost within 12 years of transplant. Thus, at least in the medium term, any return to alcohol consumption has only a modest effect on graft survival [28].

This study of graft loss from nonmalignant disease recurrence shows that patients transplanted for HCV, PSC and AIH are at increased risk of graft loss from all causes and this is at least in part because of an increased risk of graft loss from disease recurrence. The impact of graft loss on median patient survival is statistically less meaningful, in part, not only because of the small numbers of patients experiencing graft loss through disease recurrence but also because of changes in practice during the study period. These changes include variation in the proportions of patients transplanted for each indication, changes in immunosuppression treatment regimens, and also changes in the donor pool including increasing age. There is also a significant variation in decisions regarding re-grafting, which are likely to have an impact on these data and for these reasons data on patient survival are not included. Strategies to reduce disease recurrence (as has been successfully developed for patients transplanted for HBV), particularly in patients transplanted for HCV and PSC, are required to reduce morbidity and ultimately graft loss from disease recurrence.

Authorship

IAR: analysed the data and co-wrote the paper. KW: collected the data. BKG: collected the data. NM: collected the data. SH: analysed the data. JN: designed the study and co-wrote the paper.

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