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Post-hepatitis primary disease does not influence 6-year survival after liver transplantation beyond 1 year

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Abstract Orthotopic liver transplantation (OLT) is used as a definitive treatment for end-stage liver disease and prolonged posttransplant survival has already been reported. The incidence of late mortality and graft morbidity is, however, not well defined and the role of primary viral disease in the long-term follow-up results is not clear. Data of posttransplant follow-up in 213 patients, 156 adults and 57 children, who survived at least 1 year were reviewed in order to define causes of graft dysfunction, graft loss and death. In 98 patients, 103 persistent graft dysfunctions were found. Thirty-four grafts were later lost [28 deaths and 6 successful retransplantations (re-OLT)]. The results were reviewed grouping patients according to their age and viral hepatitis status at the time of the transplantation. HBV-positive patients (51) showed 4 re-OLT (1 HBV), 3 liver-related deaths (2 HBV), 24 graft dysfunctions (8 HBV, 5 HCV), and 85.2% 6-year survival (based on 100% survival at 1 year). HCV-positive adults (28) showed 1 re-OLT, 3 HCV-related deaths, 24 graft dysfunctions (19 HCV), and 68.8% 6-year survival. HBV–HCV-positive patients (14) showed no graft loss and death, 10 graft dysfunctions (7 HCV, 1 HBV, 2 HBV–HCV), and 81.8% 6-year survival. HBV–HCV-negative adults (63) showed 3 non-hepatitis-related re-OLT, 5 liver-related deaths (2 HCV), 24 graft dysfunctions (6 HCV, 2 HBV), and 83.1% 6-year survival. HBV–HCV-negative children (49) showed no re-OLT, 1 HCV-related death, 14 graft dysfunctions (3 HCV), and 92.6% 6-year survival. HCV-positive children (8) showed 1 HCV-related re-OLT, 2 HCV-related deaths, 4 graft dysfunctions (3 HCV), and 81.3% 6-year survival. The main cause of graft dysfunction was hepatitis (45 HCV and 13 HBV), followed by technical complications (21), rejection (16), recurrent alcoholism (3), HIV infection (1), and unknown causes (4). In this long-term posttransplant follow-up series, viral hepatitis led to graft dysfunction in 58/103 (56.3%) cases, late graft failure was viral hepatitis-related in 11/20 (55%) cases, and, as a total, HCV infection was present in 45/58 (77.5%) cases of viral hepatitis-related graft damage. Looking at the timing of hepatitis-related graft failure, in 70% of cases death occurred after the 5th post-transplant year. In our experience, the occurrence of hepatitis, particularly HCV induced, was common and led to abnormal graft function, but the 6-year posttransplant survival (based on 100% survival at 1 year) in patients surviving for at least 1 year did not differ on the basis of the pretransplant viral hepatitis status. This finding may be consistent with the slow

progression of the viral damage and longer follow-up results remain to be established. Nevertheless, data from the present study suggest that in long-term liver transplant survivors, the risk of deteriorating liver damage and eventual failure after 5 years remains only in those patients experiencing a viral hepatitis infection.

Key words Orthotopic liver transplantation · Hepatitis B virus · Hepatitis C virus · Long-term liver transplant survival · Risk factors

Introduction

Orthotopic liver transplantation is used as a definitive treatment for end-stage liver disease and prolonged posttransplant survival has already been reported [1, 2]. The major causes of early mortality have been discussed in the literature [3] and information has been used to guide selection of candidates for liver replacement and to improve their posttransplant management [4, 5]. Much less information is available on the clinical status and natural history of long-term liver transplant survivors. Factors affecting long-term survival and the frequency of graft disease beyond the first early posttransplant phase are not fully recognized. As long-term survival becomes the rule, the question of recurrent disease becomes more important and viral hepatitis recurrence is of major concern to the debate of long-term liver transplantation results. On this basis, we elected to study the eventual role of pretransplant viral hepatitis infection in the survival of liver transplant recipients with a minimum follow-up of 1 year. We defined this period as late since, in our experience, the main surgical complications and episodes of acute rejection are completed within this time.

Patients and methods

Between 1984 and June 1997, 325 consecutive patients received 365 orthotopic liver transplantations at the Liver Transplant Unit of Ospedale Maggiore of Milan, Italy. At the end of the 1st posttransplant year, 213 recipients were alive and are the subject of the present analysis. There were 88 females and 125 males; 57 were children between 6 months and 15 years (mean 6.3 ± 5 years). The mean age of the 156 adults was 41 ± 10 years (range 16–63 years).

In order to identify the eventual impact of the primary disease on long-term survival, patients were grouped according to their pretransplant viral hepatitis status at the time of liver transplantation. Patients were also stratified according to their age. The indications for liver transplantation are shown in Table 1.

AB0 matching has been adhered to in all patients. The type of induction immunosuppression changed during the history of the program but generally a triple drug therapy based on cyclosporine (Novartis, Basel, Switzerland) was the rule. Steroids were progressively tapered and finally withdrawn over time and, since 1993, it was the rule to stop steroids before the end of the 1st posttransplant year in adults, whereas this was applied to children after 1994. After the 1st posttransplant year, cyclosporine dosage was adjusted to keep whole blood trough levels at 150 ± 50 ng/ml by monitoring using a fluorescence polarized immunoassay with a monoclonal antibody. No consistent attempts were made to withdraw azathioprine (Wellcome, Research Triangle Park, N.C., USA). In 1993, a prospective study protocol started using FK506 (Fujisawa Pharmaceuticals, Osaka, Japan) as primary immunosuppressive agent, and 19 adult patients received this drug. Trough

Table 1 Indications for orthotopic liver transplantation in 213 patients (156 adults and 57 children) who survived beyond the 1st postoperative year and their grouping according to the eventual presence of primary viral hepatitis infection

	Primary disease	HBV positive	HCV positive	HBV-HCV positive	HBV-HCV negative	Total
Adults	Post-hepatitis cirrhosis	34	17	12		63
	Alcoholic cirrhosis		2		18	20
	Primary biliary cirrhosis		2		17	19
	Hepatocellular carcinoma	6	6	1	5	18
	Fulminant hepatitis	10		1	2	13
	Metabolic disorders				11	11
	Sclerosing cholangitis	1	1		4	6
	Cryptogenic cirrhosis				6	6
Total		51	28	14	63	156
Children	Biliary atresia		2		25	27
	Metabolic disorders		3		8	11
	Byler's disease		1		6	7
	Alagylle's syndrome				3	3
	Sclerosing cholangitis				2	2
	Cryptogenic cirrhosis				2	2
	Fulminant hepatitis				2	2
	Post-hepatitis cirrhosis		2			2
	Hepatocellular carcinoma				1	1
Total		0	8	0	49	57

FK506 drug levels were maintained between 5 and 15 ng/ml, as measured by enzyme immunoassay. Two patients received neither cyclosporine nor FK506 because of chronic renal impairment. They were maintained on combined azathioprine and steroid treatment.

Rejection episodes were treated by steroid boluses and/or recycle and, between 1986 and 1993, the occurrence of resistant rejection in the early posttransplant phase led to OKT3 (Ortho Pharmaceuticals, Raritan, N.J., USA) administration in 43 patients. After 1993, FK506 was given to 32 recipients (20 adults and 12 children) who exhibited steroid-resistant rejection episodes, and OKT3 was administered to 5 patients. Five more patients were switched to FK506 administration because of cyclosporine-related side effects (severe gingival hyperplasia and/or severe hirsutism). Late conversions (beyond the 1st posttransplant year) to FK506 treatment have been applied after a median time of 42.7 months in ten patients (seven adults and three children), because of rejection in six and cyclosporine-related side effects in the others. At the time of the present analysis, 7 patients were under triple drug therapy, 61 were off steroids but receiving double drug therapy, and the others were under cyclosporine (96) or FK506 (47) monotherapy.

Since 1988, all patients harboring hepatitis B virus (HBV) infection at the time of transplantation entered a program of continuous anti-HBV prophylaxis using specific polyclonal immunoglobulin administration and monitoring the anti-HBV titer during follow-up, as reported elsewhere [6].

The regular patient follow-up in this study was 100%. The follow-up ranged from 12 months to a maximum of 142 months (mean 57.5 ± 32.7 months). Data were reviewed in order to define causes of graft dysfunction, graft loss, and death. All post-mortem records were reviewed and correlated with the clinical findings. The persistent elevation of the hepatic blood biochemical test results was indicated as graft dysfunction. In order to identify the causes of graft dysfunction all patients underwent diagnostic evaluations at our center at the time of its occurrence: when the findings of the hepatic ultrasonography and Doppler analysis were normal, a percutaneous liver biopsy was performed. If a biliary obstruction was suspected, an endoscopic or percutaneous cholangiogram was carried out. An hepatic angiogram was performed if an impaired hepatic arterial perfusion was suspected and whenever patients were listed for retransplantation.

Biliary anastomotic strictures were the most common finding, leading to the diagnosis of biliary obstruction. Biliary obstructions were treated by percutaneous dilatation in five patients, stent placement in one, reconstructive surgery in eight patients, and retransplantation in two patients. In the case of viral hepatitis infection, no antiviral therapy was started and immunosuppression was carefully reduced. After 1993, particular attempts were carried out to stop steroid administration before the 6th post-operative month in pretransplant viral hepatitis-infected recipients. The occurrence of repeated rejection episodes suggested modification of the primary immunosuppressive agent from cyclosporine to FK506 (26 patients before 12 months and 6 other patients thereafter). Both the presence of intractable rejection and hepatic artery thrombosis led to a conservative treatment and patients were eventually listed for retransplantation at the first signs of liver failure.

The pathological matherials for the study consisted of needle hepatic biopsies obtained percutaneously or intraoperatively, explanted livers from patients receiving a second transplantation, and livers from autopsies.

Actuarial survival rates were calculated using the Kaplan-Meier method with log-rank comparison. The chi-square test has been applied where indicated. A P value of 0.01 or less was considered statistically significant.

Results

The most common indication for liver transplantation was post-hepatitis cirrhosis in adults and biliary atresia in children. Ninety-eight patients (46%) (81 adults and 17 children) showed 100 persistent hepatic dysfunctions during the last follow-up period, 2 patients showing deteriorating liver function after regrafting, and 53 recipients were already experiencing graft damage 12 months after transplantation. Among the latter, six patients improved within the last follow-up (four rejections recovered after treatment and two biliary obstructions were successfully treated by surgical reconstruction). In three patients a double concomitant factor leading to graft damage was present [two patients showed HBV and hepatitis C virus (HCV) recurrent coinfection and one patient exhibited biliary obstruction and rejection]. Causes of dysfunction are shown in Table 2. Twenty-eight patients (13%) (25 adults and 3 children) died at varying times after the 1st posttransplant year, and 14 of them died because of graft failure (Table 3). Eighteen (64%) of the 28 deaths were clustered in the time period 13–52 months after liver transplantation. Ten recipients died after 5 posttransplant years. Viral hepatitis-related deaths occurred more commonly beyond the 5th posttransplant year when compared to other causes of death. Viral hepatitis and immunological complications together accounted for the deaths of 58% of the patients after 1 year. Cardiovascular complications accounted for another 18%, followed by cancer recurrence (14%). Viral hepatitis infection was the most common (55%) cause of graft loss (Table 4), followed by technical complications (20%), and rejection (15%). Six patients have been rescued by retransplantation and causes of graft failure were intractable rejection in two patients, biliary obstruction in two, HBV recurrence in one, and hepatic arterial thrombosis in the latter. Thirteen (65%) of the 20 graft failures as the cause of death or retransplantation were clustered at 12–52 months. No retransplantation was performed after 5 years, while seven patients exhibited liver-related deaths after that time, in all cases because of viral hepatitis. The global actuarial 3- and 6-year survival rates, based on 100% at the 1st posttransplant year, were 92.7% and 85%, respectively.

For the purpose of the present analysis, our 213 patients were sorted in the following six groups according to their viral hepatitis infection status and age at the time of transplantation (Table 5): HBV-infected adults (51), HCV-infected adults (28), HBV and HCV-coinfected adults (14), HBV and HCV-negative adults (63), HBV and HCV-negative children (49), and HCV-infected children (8).

Table 2 Causes of 103 graft dysfunctions in 100 liver transplantations that showed 20 graft failures (in parenthesis). Patients are sorted on the basis of their age and viral hepatitis status at the time of transplantation. No significant statistical differences have been found in the rate of graft dysfunction comparing HBV-HCV-negative adults with HBV-HCV-negative children ($P = 0.393$), HBV-HCV-positive with HBV-positive adults ($P = 0.188$), HBV-HCV-negative with HBV-positive adults ($P = 0.439$), HBV-HCV-negative with HBV-HCV-positive adults ($P = 0.048$), and HBV-HCV-positive with HCV-positive adults ($P = 0.487$). Significance has been reached comparing HCV-positive with HBV-positive adults ($P = 0.002$) and HCV-positive with HBV-HCV-negative adults ($P < 0.0001$). (*BO* Biliary obstruction, *HAT* hepatic artery thrombosis, *UC* unrecognized cause, *Alcohol* alcohol recidivsim)

Group	HBV	HCV	BO	HAT	Rejection	Alcohol	HIV	UC	Total
HBV-positive adults	8[a] (3)	5	2[a] (1)	1 (1)	6 (1)		1	1	24 (6)
HCV-positive adults		19 (3)	3[c]	2 (1)	1[c]				24 (4)
HBB-HCV-positive adults	3[d]	9[d]							10
HBV-HCV-negative adults	2	6 (2)	8[b] (1)		4[b] (2)	3 (1)		1 (1)	24 (7)
HBV-HCV-negative children		3 (1)	5		4			2	14 (1)
HCV-positive children		3 (2)			1				4 (2)
Total	13 (3)	45 (8)	18 (2)	3 (2)	16 (3)	3 (1)	1	4 (1)	

[a] One patient with HBV recurrence was successfully retransplanted and developed biliary obstruction
[b] One patient with biliary obstruction was successfully retransplanted and developed rejection
[c] One patient showed both rejection and biliary obstruction
[d] Two patients showed both HBV and HCV recurrences

Table 3 Causes of late death in 28 (13%) long-term surviving patients

Cause	HBV-positive adults	HCV-positive adults	HBV-HCV-positive adults	HBV-HCV-negative adults	HBV-HCV-negative children	HCV-positive children	Time after transplantation (months)
Related to viral hepatitis infection (10, 36.5%)							
HCV recurrence		3				2	25, 52, 60, 79, 110
De novo HCV				2	1		60, 80, 116
HBV recurrence	2						16, 70
							(median 65)
Related to immunosuppression (6, 21.5%)							
De novo cancer			1	2			19, 64, 72
Sepsis	2						32, 52
Rejection				1			45
							(median 48.5)
Related to cardiovascular complications (5, 18%)							
Sudden death	1	1		1			36, 49, 99
Cerebral hemorrhage				1			32
Myocardial infarction				1			20
							(median 36)
Related to cancer recurrence (4, 14%)							
	1	2		1			13, 31, 32, 49
							(median 31.5)
Other causes (3, 10%)							
Alcohol recidivism				1			14
Biliary obstruction	1						23
Unknown liver failure				1			18

HBV-infected adults (51)

In 34 patients of this group, HBV infection was associated with Delta virus infection. Among the 51 patients of this group, 44 are currently alive and 7 died for the following reasons: sepsis in two patients at 32 and 52 months (the latter patient was also suffering from HBV recurrence); recurrent HBV in two patients at 16 and 70 months; recurrent tumor in one recipient at 32 months; hemorrhage after retransplantation because of biliary obstruction in another at 23 months; and sudden cardiac death in one patient at 36 months. In this group of patients there were six graft losses, which caused two deaths from HBV recurrence and led to four retransplantations (one for biliary obstruction followed by death, and three followed by success and performed because of rejection at 12 months, hepatic artery thrombosis at 19 months, and HBV recurrence at

Table 4 Causes of graft loss including those that were treated by retransplantation *(Re-OLT)*. The *underlined* cases are those successfully rescued by retransplantation

Cause of graft loss	*n* (%)	Time after transplantation (months)	Re-OLT
Viral hepatitis	11 (55%)	16, 25, 41, 52, 60, 60, 70, 79, 80, 110, 116	2
Technical complications	4 (20%)	19, 23, 44, 45	4
Rejection	3 (15%)	12, 45, 54	3
Alcohol recidivism	1 (5%)	14	
Unknown	1 (5%)	18	
Total	20		9

Table 5 A total of 213 long-term (beyond 12 months) survivors were grouped according to their age and viral hepatitis status at the time of liver transplantation. Data were analyzed focusing on graft loss and persistent graft dysfunction, especially when hepatitis induced. Patients groups' actuarial survival (based on 100% at 1 year) was evaluated. Statistical evaluation: Age, HCV-positive vs HBV-positive adults $P < 0.0001$, HCV-positive vs HBV-HCV-positive adults $P < 0.0001$, HCV-positive vs HBV-HCV-negative adults $P = 0.045$; Follow-up, HBV-HCV-positive vs HCV-positive adults $P = 0.019$, HBV-HCV-positive vs HBV-positive adults $P = 0.041$, HBV-HCV-positive vs HBV-HCV-negative adults $P = 0.003$; 6-year survival, HCV-positive vs HBV-positive adults $P = 0.138$, HCV-positive vs HBV-HCV-negative adults $P = 0.184$, HBV-HCV-negative vs HCV-positive children $P = 0.739$

Group (*n*)	Age (years: mean ± SD)	Follow-up (months: mean ± SD)	Late retransplantation	Late-liver-related deaths	Graft dysfunction	Actuarial 3- and 6-year survival
Adults HBV positive (51)	37.6 ± 9	65.2 ± 34	4 (1 HBV)	3 (2 HBV)	24 (48%) (8 HBV; 5 HCV)	88.5% 85.2%
HCV positive (28)	46.8 ± 8.8	58.5 ± 36	1	3 (3 HCV)	24 (90%) (19 HCV)	91.6% 68.8%
HBV-HCV-positive (14)	34.8 ± 10	86.4 ± 32.7	0	0	10 (77%) (7 HCV, 1 HBV, 2 HBV-HCV)	100% 81.8%
HBV-HDV-negative (63)	42.3 ± 10.1	57.5 ± 31	3	5 (2 HCV)	24 (39%) 6 HCV, 2 HBV)	89.3% 83.1%
Children HGV-HCV-negative (49)	6.4 ± 5	41.5 ± 24	0	1 (1 HCV)	14 (28.5%) (3 HCV)	100% 92.6%
HCV-positive (8)	6.2 ± 4.8	61.8 ± 34.8	1 (1 HCV)	2 (2 HCV)	4 (50%) (3 HCV)	100% 83.3%

41 months). Twenty-four patients showed graft dysfunction, which was commonly related to hepatitis (eight HBV, five HCV), and other causes were rejection (seven), technical complications (three, one after retransplantation for HBV recurrence), HIV infection (one), and unknown hepatitis (one). Among the eight HBV-reinfected recipients, one patient died because of fibrosing cholestatic hepatitis 16 months after the transplantation and another, who experienced post-transplant HBV reinfection because of a viral mutation [7] which caused resistance to anti-HBV immunoglobulins, died because of failure due to recurrent cirrhosis 70 months after transplantation; moreover, one patient died because of sepsis at 52 months posttransplantation, and another underwent retransplantation 41 months after the first grafting because of recurrent cirrhosis (he is currently alive with biliary obstruction 89 months after retransplantation). One further patient showed HBV reinfection 96 months after transplantation but spontaneously cleared HBV both in the serum and in the liver 3 months later (she is currently stable and free from HBV 15 months after the reinfection episode). Finally, three other HBV-reinfected patients showed stable hepatic function 76, 81, and 126 months after transplantation, but long-term biopsies were not available. Long-term histology was available in eight posttransplant HBV-free patients showing resistant rejection in three of them (one underwent retransplantation at 12 months follow-up because of rapidly progressive liver failure which was non-responsive to FK506, two were successfully switched to FK506 at 20 and 48 months), rejection that responded to steroids in three others (at 12, 52, and 71 months), and mild hepatitis in two (one HCV and one steato-hepatitis of unknown origin at 31 and 32 months). Twenty-seven patients who were HBV infected at the time of transplantation remained HBV free, showing normal hepatic enzyme levels during a mean follow-up of 55 months; and 24 are currently alive and well. In five a liver biopsy was performed for a prospective therapeutical study protocol at 12, 17, 30, 58, and 81 months, and histology was normal in all. Three- and 6-year actuarial survival

rates in pretransplant HBV-infected patients were 88.5% and 85.2%, respectively.

HCV-infected adults (28)

Among these 28 patients, 22 are currently alive and 6 have died. Causes of deaths were: HCV recurrence in three patients, at 25, 60, and 110 months; tumor recurrence associated with HCV hepatitis in two patients at 13 and 49 months; and sudden cardiac death in one at 49 months. In this group of patients, there were four graft losses (three patients died from HCV recurrence and another was successfully retransplantated 44 months after the first grafting because of hepatic artery thrombosis). Chronic HCV hepatitis was found in 14 living recipients and histologically proven recurrent cirrhosis was found in four (at the present, two are in a stable condition at 47 and 79 months, respectively, and two others demonstrate hepatic decompensation at 57 and 102 months). Other causes of graft dysfunction were hepatic arterial thromboses (one retransplanted patient and another at the present listed for retransplantation) and biliary obstructions (three). In a diabetic patient, a biliary obstruction was associated with rejection and steato-hepatitis in the presence of persistent negativity of serum HCV RNA detection 60 months after the transplant. Finally, four living patients showed persistent normal graft function at 18, 60, and 119 months but serum HCV RNA tested positive in all of them (long-term biopsies not available). Three- and 6-year actuarial survival rates in HCV-infected patients were 91.6% and 68.8%, respectively.

HBV–HCV-coinfected adults (14)

In 11 patients of this group HBV infection was associated with Delta virus infection. Among the 14 patients of this group, 13 are currently alive and one died because of lymphoma at 72 months. At autopsy, the liver showed minor histological changes in this recipient, who was HBV free and tested HCV RNA positive in the serum. In this group of patients there was no graft loss, but hepatitis recurrence caused graft dysfunction in ten patients, as follows: seven HCV, one HBV and two HBV–HCV coinfection. Chronic hepatitis was histologically found in four HCV-infected patients in biopsies obtained at 54, 64, 70, and 112 months. In another recipient, a recurrent cirrhosis was found at 121 months when an impairment in liver function occurred. The history of another patient revealed an early onset of HCV-related graft damage (1 month after surgery) with persistent elevation in hepatic enzyme levels during follow-up; 55 months after the transplantation HBV recurred despite immunoprophylaxis and persistent elevation of the serum HBV DNA levels was associated with a dramatic fall in the serum HCV viremia. During this period of time transaminase levels were normal. Histology revealed a damage morphologically typical of HCV hepatitis and histochemistry for HBV tested positive. Up to now, 11 months since the HBV recurrence, the liver enzyme levels remain in the normal range and the patient is still well. Long-term biopsies were not available in four other stable patients (two HCV infected, one HBV infected, and one HBV–HCV infected) after 36, 46, 59, and 114 months. Finally, in the remaining three HBV-free living patients, liver function tests remained within normal limits during a follow-up at 81, 86, and 95 months, but liver biopsies were not available. Serum HCV RNA detection was found positive in 12 patients, and negative in 2 others. Three- and 6-year actuarial survival rates in HBV–HCV-infected patients were 100% and 83.3%, respectively.

HBV and HCV-negative adults (63)

Among these 63 patients, 51 are currently alive and 11 have died. Causes of death were: HCV infection in two patients, at 80 and 116 months; cardiovascular disease in three patients, at 20, 32, and 99 months; de novo malignancies in two patients (one colonic cancer at 19 months and one cancer of the hypopharynx 64 months after transplantation); rejection in one, who shortly died after retransplantation performed 45 months after the first grafting; cancer recurrence in another at 31 months; recurrent alcoholism and renal failure associated with non-compliance in one patient, 14 months after the transplant; and graft failure because of unknown origin in one patient at 18 months. In this group of patients there were seven graft losses (five deaths and two successful retransplantations performed 45 and 54 months after the first grafting because of biliary obstruction and rejection, respectively). Hepatic dysfunction was present in 24 patients and among the 19 living recipients it was due to biliary obstruction in eight patients (one retransplantation), HCV infection in four patients, rejection in three patients (two required retransplantations and the other showed rejection after retransplantation for biliary obstruction and responded to steroids), HBV infection in two, and recurrent alcoholism in the last two recipients. Among patients with viral hepatitis, a long-term biopsy was available only in one HCV-infected recipient showing cirrhosis at 80 months and the patient was listed for retransplantation. The other five hepatitis-infected patients showed good clinical condition at 28, 85, 88, 94, and 114 months. The patient who recovered from rejection after FK506 conversion is currently well at 67 months. Three- and 6-year actuarial survival rates in HBV–HCV-negative adults were 89.3% and 83.1%, respectively.

HBV and HCV-negative children (49)

Among these 49 patients, 48 are currently alive and 1 died because of HCV-related graft failure at 60 months this was the only case of graft failure in this group of patients. Among the survivors, 13 showed hepatic dysfunction and their causes were: de novo HCV infection in two patients, at 51 and 24 months; rejection in four patients, rejection in one patient was induced by his voluntary withdrawal of the immunosuppression treatment and the restart of administration of cyclosporine recovered the dysfunction episode; biliary obstruction in five patients, this was successfully treated by reconstructive surgery in three cases, percutaneous dilatation in one patient and the last was listed for retransplantation; and unknown causes in two recipients. In the 35 long-term survivors showing normal graft function, long-term biopsies were not available. Three- and 6-year actuarial survival rates in HBV–HCV negative children were 100% and 92.6%, respectively.

HCV-infected children (8)

Among these eight patients, six are currently alive and two died from HCV-related graft failure, at 52 and 79 months, and only these latter patients, both transplanted because of post-hepatitis cirrhosis, exhibited liver failure in this group of recipients. One of the dead patients underwent retransplantation in another center abroad but he died shortly after because of technical complications. Among the survivors, one patient showed chronic hepatitis and currently is stable 73 months after transplantation. Another patient showed severe rejection 80 months after transplantation and improved after FK506 conversion. Three patients showing normal graft function (follow-up 13, 22, and 79 months) apparently cleared HCV infection, as suggested by the repeated negativity in serum HCV RNA during follow-up, but long-term graft biopsies were not available. Finally, in one patient, HCV RNA was found positive during follow-up without abnormalities in the hepatic enzyme levels 92 months after transplantation. Three- and 6-year actuarial survival rates in HCV-infected children were 100% and 83.3%, respectively.

Discussion

After liver transplantation, most deaths still occur within the first few posttransplant months. Whereas the spectrum of early morbidity has been well documented [3], the clinicopathological features of patients with late graft dysfunction have been less clearly defined. Currently, most recipients overcome the early posttransplant phase and survive beyond the 1st year so that greater attention [8–10] is being focused on long-term survival in order to define whether the long-term survivors can expect an almost normal life span or if there is a constant gradual risk of graft loss year by year. The rates of both late deteriorating liver function after transplantation and liver-related mortality are still not well defined. In this setting, particular attention needs to be paid to those recipients with a primary liver disease notorious for recurrence [8, 11, 12]. However, the eventual role that the occurrence of a posttransplant viral hepatitis infection may play is poorly understood [13, 14]. On this basis, we analyzed the impact of the primary viral disease on long-term outcome in recipients surviving for at least 1 year.

In the report by Slapak et al. [10], an unexpectedly high number of liver abnormalities were detected pathologically in long-term liver transplantation survivors, a figure similar to that found in the present clinicopathological study. After a mean follow-up of 5 years, almost half of our patients showed the presence of graft dysfunction, which in 20% of cases, progressed to liver failure. The causes of late death and graft loss represent a wide spectrum of diagnoses. Viral hepatitis was the major progressive disease leading to graft failure. Retransplantation was performed in only two (18%) viral hepatitis-related graft failures and in one it was followed by prolonged success. HCV was the predominant agent causing posttransplant hepatitis and it accounted for the main single cause of graft dysfunction. Other common causes of liver functional impairment were technical complications and rejection. In these non-virally-infected patients, progression to hepatic failure led to retransplantation in 77% of patients, and was followed by success in 71% of cases. In this report, technical complications accounted for 20% of graft losses and among these biliary obstruction was the major event. The presentation of biliary obstructions was usually atypical with an asymptomatic increase in liver enzyme levels. Occasionally, patients developed cholangitis and, less commonly, intrahepatic duct dilatation was found by ultrasonography. Some patients simply showed histological evidence of bile duct obstruction. A high index of suspicion and the subsequent performance of a cholangiogram allowed a definitive diagnosis. When biliary complications escaped recognition or were mismanaged, graft damage progressed and retransplantation was needed. These findings were similar to those reported by others [10, 15, 16]. Most noteworthy is the low rate of graft loss and death from irreversible rejection that we found in the present series. The prevalence of late rejection was 11%. Late rejection responded to high-dose steroids in 25% of cases and, furthermore, it was successfully recovered by FK506 conversion in 63% of patients. Finally, need for retransplantation occurred in 12% of cases. These findings seem to differ from those previously reported [9, 15], which outlined rejection as

a major cause of late deaths after liver replacement. Both Asfar et al. [9] and Backman et al. [15], however, reported experience with patients who underwent liver transplantation mainly because of cholestatic rather than post-hepatitis disease, and it has been suggested that particularly in primary sclerosing cholangitis, rejection may be a relevant event [17]. Moreover, in the report by Backman et al. [15] there was no mention of the use of FK506, while Asfar et al. [9] reported that FK506 was still not available at the time of their analysis. The unavailability of FK506 might be a factor in the comparison of the experience with irreversible rejection reported in those studies with that found in the present survey. A decline in the rate of intractable rejection has recently been reported by others [17]. We believe that efforts to reduce rejection must be maintained in long-term follow-up and late FK506 conversion may be a powerful tool in achieving this result.

In our experience, the rate of hepatitis recurrence was high, especially in the case of pretransplant HCV infection. Pretransplant HCV-positive adults showed a higher graft dysfunction rate than both pretransplant HBV-positive recipients and pretransplant HBV–HCV-negative adults. Actually, at the time of transplantation, the age of HCV-infected adults was found to be significantly higher than that of HBV-infected patients; whether this difference might play a role in the allograft dysfunction rate may be point of discussion. In fact, in four of our HCV-infected adults showing viral hepatitis-induced graft failure, a contraindication to retransplantation was their advanced age.

Philosophe et al. [14] reported a lower survival in HBV-positive recipients, but this was not the case in thia series, as already shown in another report of ours [18]. In fact, the majority of our HBV-infected patients had been transplanted using continuous anti-HBV immunoprophylaxis and Delta virus infection was present in most of them. In a large retrospective series from Europe [5], both these factors proved protective in both HBV recurrence and posttransplant survival rate.

Another relevant finding from our data was that patients exhibiting HBV–HCV coinfection at the time of transplantation did not experience graft failure after a mean follow-up of 7 years and showed a high survival rate. This result may be the expression of a competition between the two viruses, with a final decrease in the replication of both, as proposed for chronic HBV–HCV hepatitis outside the transplant setting [19]. This hypothesis seems to be confirmed by the course shown by one of our coinfected patients who experienced a late HBV reactivation that occurred on a graft already harboring chronic HCV hepatitis. After the HBV recurrence, the patient showed a stable normalization in his hepatic enzyme levels which had previously been found to be elevated. Our HBV–HCV-positive recipients' age at the time of transplantation differed from that of our HCV-positive adults, the former being significantly younger than the latter. Whether this difference might play a role in the occurrence of graft dysfunction probably needs to be assessed. No statistically significant differences were found in comparing the survival rate of this group of patients with that of the others.

In this study, the rate of graft dysfunction in children who were negative for hepatitis at the time of transplant was apparently lower than that recorded in adults negative for pretransplant hepatitis, but long-term biopsies were only occasionally available in children. The occurrence of graft damage during long-term follow-up in our patients may be underestimated because of the use of biochemical parameters in order to identify this condition. It was our policy not to perform protocol biopsies during follow-up and it has been reported that asymptomatic graft damage may be relevant in late follow-up after liver transplantation [10]. Nevertheless, it is particularly striking that a high number of patients, already rescued from end-stage liver disease by liver transplantation, reproduce a disease affecting their hepatic grafts and eventually die because of liver failure. In the present analysis, 28 survivors beyond the 1st posttransplant year subsequently died and in 14 of them death was liver-related over a wide period of time, ranging from 14 to 116 months. All late non-hepatitis-related graft failures occurred within 54 months (median 23 months), and hepatitis-related graft failures occurred during a period of time ranging from 16 to 116 months (median 60 months). In our experience, patients who did not show a viral hepatitis infection after transplantation neither suffered progressive graft dysfunction nor exhibited hepatic failure beyond the 4th posttransplant year. These results suggest that in long-term liver transplant survivors, the risk of deteriorating liver damage and eventual failure beyond 5 years remains only in those patients experiencing a viral hepatitis infection. However, once the causes of graft loss have been sorted on the basis of the pretransplant evidence of viral hepatitis infection, results showed that graft failure rate did not differ in the various groups of patients and long-term actuarial survival rates were not statistically different. Santoni et al. [20] did not find any influence of initial liver pathology on liver function 1 year after transplantation. We argue that the presence in our experience of some cases of graft failure secondary to de novo viral hepatitis could, however, have increased the rate of graft failure in patients who were not at high risk for primary disease recurrence. Moreover, looking at the timing of hepatitis-related graft failure, in the majority of cases death occurred after the 5th posttransplant year (median 65 months). This finding is consistent with the slow progression of viral damage, especially HCV induced, and longer follow-up may be necessary in order to clarify the eventual role of the pretransplant viral hepatitis infection on the ultra-long-term survival [12, 21–23].

In summary, almost half of our long-term survivors exhibited graft dysfunction and this progressed toward failure with graft loss in 20% of cases. Moreover, 13% of those liver transplanted patients who survived beyond 1 year died in the ensuing years. In half of the patients who died, the cause of death was found to be liver related. The main cause of late graft dysfunction, graft loss, and death was always viral hepatitis, particularly HCV dependent. This study failed, however, to demonstrate an influence of primary viral hepatitis on 6-year survival rate in liver transplant recipients who survived beyond the 1st posttransplant year. These results emphasize the previously reported high rate of late HCV-related morbidity after liver transplantation. Longer follow-up may be necessary before the full impact of HCV on graft survival becomes known due to the slow progression of this disease. Emphasis must still be on the decrease of viral hepatitis recurrence, and there still is a need for a safe, potent, and efficient adjuvant regimen. The results of HCV infection therapy using interferon, ribavirin or a combination of both still need to be evaluated in long-term studies.

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