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ORIGINAL ARTICLE

Liver transplantation for alcoholic cirrhosis with anti-HCV antibodies

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Abstract The results of orthotopic liver transplantation (OLT) in patients with alcoholic liver cirrhosis (ALC) are currently similar to those obtained in patients with other indications. However, the frequent association of ALC with hepatitis C virus (HCV) infection may impair these results. We retrospectively studied the consequences of HCV infection on survival and graft function in 59 patients with ALC undergoing OLT. Patients were classified into two groups depending on their HCV serology before transplantation: group 1 comprised 24 anti-HCV-positive patients, and group 2, 35 anti-HCV-negative patients. Patient and graft survival were similar in both groups. Liver function tests 1 and 4 years after OLT showed AST and ALT values that were significantly higher in group 1 patients and post-transplant histologically proven chronic hepatitis was found in 45 % and 61 % of these patients at 1 and 4 years, respectively. We conclude that pretransplant HCV infection in patients with ALC does not affect survival after OLT. However, one must bear in mind the high incidence of post-transplant chronic hepatitis secondary to recurrence of HCV infection and be cautious when drawing this conclusion.

Key words Liver transplantation, cirrhosis, anti-HCV antibodies · Cirrhosis, liver transplantation, anti-HCV antibodies · Anti-HCV antibodies, liver transplantation, cirrhosis · Alcoholic chirrosis, liver transplantation

Introduction

The results of orthotopic liver transplantation (OLT) in patients with alcoholic liver cirrhosis (ALC) are similar to those obtained in patients with other indications [5, 12]. To achieve these results, it is very important that patients be selected who have no history of alcohol dependence, no serious disease in other organs, and good social support [6]. However, ALC is frequently associated with hepatitis C virus (HCV) infection [13], and this fact may impair the overall results in this type of patient because of the high recurrence rate of viral infection after OLT [14]. The aim of this study was to investigate the possible consequences of HCV infection on survival and graft function in patients with ALC undergoing OLT.

Materials and methods

Study population

Data on 348 consecutive patients who underwent OLT at the Hospital Clinic of Barcelona between August 1989 and February 1994 were reviewed. Sixty-eight patients with ALC underwent OLT during the study period. The diagnosis of ALC was established on the basis of two main features: (1) a history of alcohol intake greater than 80 g/day in males or 60 g/day in females lasting 10 years or more and (2) the presence of cirrhosis, histologically proven by liver biopsy taken prior to transplantation (22 patients) or by examination of the explanted liver (37 patients). Since, in our liver transplant program, a 6-month period of abstinence from alcohol is required for alcoholic patients prior to transplantation, no histological signs of the alcoholic etiology of cirrhosis could be demonstrated in the explanted livers. Nine pa-

Table 1 Characteristics of patients undergoing OLT for alcoholic cirrhosis classified according to the presence (group 1) or absence (group 2) of pretransplant hepatitis C virus infection

	Group 1 ($n = 24$)	Group 2 ($n = 35$)	P
Age (years)[a]	48 ± 7	45 ± 7	NS
Male (%)	19 (79 %)	31 (88 %)	NS
Child-Pugh group:			
A	1 (4 %)	0 (0 %)	NS
B	9 (38 %)	17 (49 %)	NS
C	14 (58 %)	18 (51 %)	NS
Associated hepatocellular carcinoma	5 (21 %)	1 (3 %)	< 0.05
Perioperative blood product transfusion[a]:			
Packed RBC (units)	11 ± 7	13 ± 8	NS
FFP (liters)	6 ± 4	5 ± 4	NS
Platelets (units)	14 ± 10	11 ± 8	NS
30-day mortality	1 (4 %)	2 (6 %)	NS

[a] Mean ± SE

tients whose pre-transplant anti-HCV status was unknown were excluded from the analysis. The remaining 59 patients were classified into two groups, according to their HCV serology before OLT. Group 1 comprised 24 anti-HCV-positive patients and group 2, 35 anti-HCV-negative patients. Anti-HCV antibodies were determined by an enzyme-linked assay of second or third generation (Ortho Diagnostics, Raritan, N.J., USA). In patients undergoing OLT before 1992, the test was performed using stored sera. In 14 patients, HCV RNA was determined by PCR in stored sera.

Baseline immunosuppression included cyclosporin, steroids (usually discontinued by the 12th–18th month post-OLT), and azathioprine (administered only during the 1st postoperative month). This schedule was not significantly modified in patients developing hepatic graft damage. Treatment of rejection consisted of methylprednisolone, 1 g/day for 3 days, and OKT3 in cases of steroid-resistant rejection.

Methods

Both groups were compared with respect to age, gender, pretransplant Child-Pugh classification, associated hepatocellular carcinoma, blood product transfusion during operation, liver function and histology at different periods after OLT, and patient and graft survival. Liver function was assessed according to biochemical studies including serum levels of total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), GGTB γ-glutamiltranspeptidase gammaglutamiltranspeptidase, and alkaline phosphatase (AP). During the follow-up, liver biopsies were performed when liver dysfunction appeared. All liver biopsies were read by a single pathologist.

Statistics

Data were analyzed using the chi-square test to compare frequencies and the ANOVA to compare mean values between groups. Survival curves were made according to the method of Kaplan and Meier and compared by the log rank test. A P value below 0.05 was considered significant.

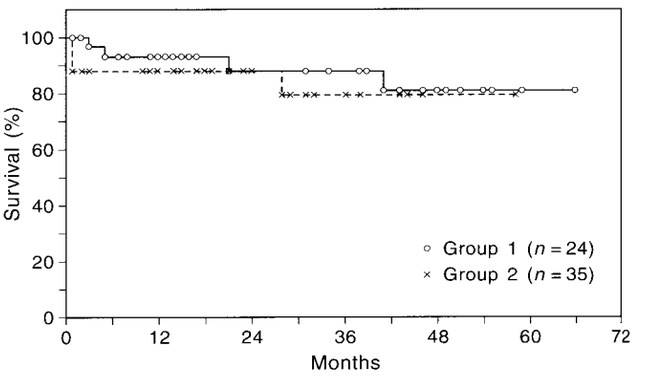

Fig. 1 Actuarial survival in liver transplant patients with alcoholic cirrhosis who presented (group 1) or did not present (group 2) pretransplant anti-HCV antibodies. Survival probability curves were not significantly different

Results

Groups 1 and 2 were similar in age, sex, and pretransplant Child-Pugh classification. As expected, hepatocellular carcinoma was more frequent in patients in group 1 than in those in group 2. No difference between the two groups was found with regard to blood product requirements during the operation. Furthermore, there was no difference with respect to 30-day mortality (Table 1). Thirteen patients in group 1 and 12 patients in group 2 presented one episode of acute rejection, which was treated with short courses of high-dose steroids. Two patients in group 1 and three in group 2 required OKT3 for treatment of rejection.

Twelve patients died during the entire study period. Five patients in group 1 died, the causes of death being rejection ($n = 2$), pneumonia ($n = 1$), CMV infection ($n = 1$), and renal failure ($n = 1$). Seven patients in group 2 died; the causes were rejection ($n = 2$), cerebral toxoplasmosis ($n = 2$), encephalopathy of unknown etiology ($n = 1$), acute liver failure caused by de novo HBV infection ($n = 1$), and suicide ($n = 1$). The actuarial survival rate did not significantly differ in the two groups of patients: 93 % vs 87 % at 1 year, and 82 % vs 78 % at 4 years (Fig. 1).

Nor were there differences between the two groups with respect to graft survival, which was 88 % vs 83 % at 1 year and 80 % vs 76 % at 4 years. Five patients received a second transplant during the study period, three in group 1 and two in group 2. The causes of retransplantation were rejection ($n = 4$) and cirrhosis due to recurrence of HCV infection ($n = 1$ in group 1). No case of recurrence of hepatocellular carcinoma was found during the follow-up period.

Table 2 shows liver function tests determined at 1 and 4 years after OLT in group 1 and 2 patients. Values of serum AST and ALT were significantly higher in patients in

Table 2 Liver function tests 1 year and 4 years post-transplant in patients undergoing OLT classified according to the presence (group 1) or absence (group 2) of pretransplant hepatitis C virus infection

	1 year[a]		*P*	4 years[a]		*P*
	Group 1 ($n = 22$)	Group 2 ($n = 31$)		Group 1 ($n = 13$)	Group 2 ($n = 20$)	
Bilirubin (mg/dl)	2.5 ± 0.9	1.5 ± 0.5	NS	1.7 ± 0.7	0.9 ± 0.1	NS
AST (U/l)	100 ± 21	33 ± 14	< 0.05	120 ± 14	37 ± 10	< 0.05
ALT (U/l)	154 ± 35	54 ± 12	< 0.05	115 ± 21	38 ± 6	< 0.05
AP (U/l)	331 ± 52	259 ± 41	NS	316 ± 52	197 ± 30	NS
GGTP (U/l)	352 ± 86	193 ± 81	NS	423 ± 56	91 ± 21	< 0.05

[a] 53 and 33 patients reached 1 year and 4 years of follow-up, respectively

Table 3 Liver biopsies performed 1 year and 4 years post-transplant in patients undergoing OLT classified according to the presence (group 1) or absence (group 2) of pretransplant hepatitis C virus infection

	1 year[a]		*P*	4 years[a]		*P*
	Group 1 ($n = 22$)	Group 2 ($n = 31$)		Group 1 ($n = 13$)	Group 2 ($n = 20$)	
Acute hepatitis	2 (9 %)	2 (6 %)	NS	0 (0 %)	1 (5 %)	NS
Chronic hepatitis	10 (45 %)	2 (6 %)	< 0.05	8 (61 %)	3 (15 %)	< 0.05
Rejection	1 (5 %)	3 (10 %)	NS	1 (8 %)	1 (5 %)	NS
Fatty liver	1 (5 %)	1 (3 %)	NS	0 (0 %)	1 (5 %)	NS
Other	2 (9 %)	5 (16 %)	NS	1 (8 %)	1 (5 %)	NS
Not performed	5 (22 %)	18 (59 %)	< 0.05	2 (15 %)	13 (65 %)	< 0.05
Cirrhosis	0 (0 %)	0 (0 %)	NS	1 (8 %)	0 (0 %)	NS

[a] 53 and 33 patients reached 1 year and 4 years of follow-up, respectively

group 1. Serum GGTP levels were also higher in group 1 patients only 4 years after OLT. Twenty-one patients in group 1 (95 %) had persistence of anti-HCV antibodies after OLT. Of the 31 patients in group 2, 3 (10 %) became positive for anti-HCV after OLT. In seven patients who were anti-HCV-positive, HCV-RNA was determined and found to be positive in all seven. In seven anti-HCV-negative patients, HCV-RNA was also negative.

Results obtained in liver biopsies performed at 1 and 4 years post-transplant are depicted in Table 3. Biopsies performed on patients in group 1, 1 year post-transplant showed a significantly higher incidence of chronic hepatitis (45 %) than in group 2 patients (6 %). This difference between the two groups was also present at 4 years. One patient in this group with chronic hepatitis developed cirrhosis during the follow-up and required re-transplantation.

Discussion

Although ALC is one of the most common causes of end-stage liver failure in Europe, alcoholic patients have, until recently, been excluded from transplantation programs. The risk of their falling back into alcohol dependence, of their not appearing for follow-up, and of low immunosuppressive drug compliance, as well as the deleterious effect of alcohol on other organs were the main reasons for the resistance to transplantation for alcoholic patients [7].

Nevertheless, during the last years, indications for liver transplantation have included patients with ALC who have no serious disease in other organs, no history of alcohol dependence, and a good social support system [3, 11]. Currently, the results of OLT in patients with ALC are similar to those obtained for other indications [5, 12]. In our institution, apart from the standard work-up for evaluating liver transplant candidates, patients with ALC undergo a psychopathological evaluation before transplantation. A 6-month period of abstinence from alcohol is required prior to transplantation. In cases where it is necessary to perform the OLT before these 6 months have elapsed, patients are required to have a good psychopathological prognosis, i.e., a good social and familiar support system, no serious psychiatric problems, and an awareness of alcohol dependence and toxicity. In our study, only two patients resumed alcohol intake after transplantation.

HCV infection, assessed by the positivity of anti-HCV, has been reported to be frequently associated with ALC [2, 4, 8, 13]. In our series, 24 (41 %) of 59 patients with ALC concomitantly had anti-HCV antibodies before OLT. In almost all of these 24 patients, anti-HCV antibodies persisted after transplantation. Nevertheless, detection of viral RNA by the polymerase chain reaction (PCR) is considered to be necessary be-

cause anti-HCV antibodies provide only indirect evidence of infection, particularly in the setting of liver transplantation [1, 9, 10]. In our study, PCR techniques to detect serum HCV-RNA were performed in only a few patients; however, in each of the seven patients with long-lasting persistence of anti-HCV antibodies in whom HCV-RNA was tested by PCR, a positive HCV-RNA was also found, whereas HCV-RNA was negative in all seven anti-HCV-negative patients in whom PCR was done.

This high concordance strongly suggests that all patients with persistent anti-HCV antibodies really had recurrent infection. However, in spite of this high rate of recurrence of viral infection in patients with pretransplant ALC and HCV infection, the long-term patient and graft survival in group 1 was similar to that in group 2. It would, therefore, appear that pretransplant HCV infection has no influence on the postoperative course in patients undergoing OLT for ALC. Nevertheless, the noticeably high incidence of liver graft damage secondary to recurrence of HCV infection suggests cautious with regard to this conclusion since this HCV-related liver damage consists of potentially progressive disease, mainly chronic hepatitis. For this reason, studies on ALC patients followed for more prolonged periods of time are necessary to ascertain whether pretransplant HCV infection may represent a harmful event in these patients.

References

1. Feray C, Gigou M, Samuel D (1994) The course of hepatitis C virus infection after liver transplantation. Hepatology 20: 1137–1143
2. Fong TL, Kanel GG, Conrad A, Valinluck B, Charboneau F, Adkins RH (1994) Clinical significance of concomitant hepatitis C infection in patients with alcoholic liver disease. Hepatology 19: 554–557
3. Gish RG, Lee AH, Keeffe EB, Rome H, Concepcion W, Esquivel CO (1993) Liver transplantation for patients with alcoholism and end-stage liver disease. (Am J Gastroenterol) 88: 1337–1342
4. Halimi C, Deny P, Gotheil C, Trinchet JC, Mal F, Scavizzi M, Beaugrand M (1991) Pathogenesis of liver cirrhosis in alcoholic patients: histological evidence for hepatitis C virus responsibility. Liver 11: 329–333
5. Kilpe VE, Krakauer H, Wren RE (1993) An analysis of liver transplant experience from 37 transplant centers as reported to Medicare. Transplantation 56: 554–561
6. Lucey MR, Merion RM, Henley KS, Campbell DA, Turcotte JG, Nostrant TT, Blow FC, Beresford TP (1992) Selection for and outcome of liver transplantation in alcoholic liver disease. Gastroenterology 102: 1736–1741
7. Neuberger JM (1989) Transplantation for alcoholic liver disease. Contraindicated by alcohol dependence or extrahepatic disease. BMJ 299: 693–694
8. Parés A, Barrera JM, Caballeria J, Ercilla G, Bruguera M, Caballeria Ll, Castillo R, Rodés J (1990) Hepatitis C virus antibodies in chronic alcoholic patients: association with severity of liver injury. Hepatology 12: 1295–1299
9. Poterucha JJ, Gross JB Jr (1995) Hepatitis C after liver transplantation. Gastroenterology 108: 1314–1317
10. Shah G, Demetris AJ, Gavaler JS, Lewis JH, Todo S, Starzl TE, Van Thiel DH (1992) Incidence, prevalence, and clinical course of hepatitis C following liver transplantation. Gastroenterology 103: 323–329
11. Sorrell MF, Donovan JP, Shaw BW (1992) Transplantation in the alcoholic: a stalking horse for a larger problem. Gastroenterology 102: 1806–1808
12. Starzl TE, Van Thiel D, Tzakis AG, Iwatsuki S, Todo S, Marsh JW, Konern B, Staschak B, Stieber A, Gordon RD (1988) Orthotopic liver transplantation for alcoholic cirrhosis. JAMA 260: 2542–2544
13. Wands JR, Blum HE (1991) Hepatitis B and C virus and alcohol induced liver injury. Hepatology 14: 730–733
14. Wright TL, Donegan E, Hsu HH, Ferrell L, Lake JR, Kim M, Combs C, Fennessy S, Roberts JP, Ascher NL, Greenberg HB (1992) Recurrent and acquired hepatitis C viral infection in liver transplant recipients. Gastroenterology 103: 317–322