



Previous Intravenous Substance Use and Outcome of Liver Transplantation in Patients With Chronic Hepatitis C Infection

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ABSTRACT

Background. End-stage liver disease due to hepatitis C viral (HCV) infection is the most common reason for liver transplantation. One of the major risk factors for infection with HCV is intravenous drug use (IVDU). The pretransplantation characteristics and outcome of liver transplantation in patients with chronic hepatitis C (CHC) infected after IVDU are poorly known.

Methods. We performed a retrospective cohort study in patients with CHC who underwent liver transplantation between 1998 and 2002 in Belgium. Seven patients with and 60 patients without a history of IVDU were compared.

Results. Patients with CHC infected after IVDU were primarily men, significantly younger, and affected more by genotype 2 or 3. There was no relapse in substance use. No patients required a second transplantation or developed surgical complications. Progression to fibrosis in the posttransplantation period seemed to be slower. Graft and patient survival, and compliance were similar in both groups.

Conclusions. Compared with patients in the non-IVDU group, patients with CHC infected after IVDU in complete remission have the same compliance, and patient and graft survival after liver transplantation. Therefore, patients with IVDU should not be excluded for liver transplantation because of HCV-induced cirrhosis.

ALCOHOL-RELATED end-stage liver disease was, for many years, the most common reason for liver transplantation,¹ but has been superseded by end-stage liver disease due to hepatitis C viral (HCV) infection.² In the past, blood transfusion was considered the major risk factor for HCV infection in Belgium; however, more recently, intravenous drug use (IVDU) is the major risk factor.³ Therefore, more patients with end-stage liver disease due to chronic hepatitis C (CHC) infection after substance use will be treated in liver transplant centers in the near future. The experience with liver transplantation in substance users is limited.^{4,5} Recently, more data about the outcome of liver transplantation in patients treated in a methadone maintenance program⁶ and characteristics of substance relapse after liver transplantation⁷ have become available.

Substance users can be classified according to *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) criteria in different groups: (1) subjects in long-term complete remission, (2) subjects in long-term partial remission who may also be receiving agonist therapy as methadone

maintenance therapy, and (3) subjects with substance dependence or substance abuse.⁸

At present, no data are available about the outcome of liver transplantation in subjects in complete remission. Therefore, we performed a retrospective cohort study to compare the characteristics and outcome of liver transplan-

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tation for end-stage liver disease in patients with CHC infected after substance use who were in remission vs patients with CHC without substance use. We especially proposed to study patient and graft survival, patient characteristics, rejection rate, postoperative complications, compliance and substance addiction, repeat transplantation, reinfection with HCV, evolution of fibrosis, and potential causes for differences in outcome.

MATERIALS AND METHODS

This retrospective cohort study included all HCV-positive patients who underwent liver transplantation between December 1998 and January 2002 in three transplant units in Belgium. Patients with and without a history of IVDU were compared. Follow-up was to the beginning of 2006.

Included in the study were patients who underwent a first liver transplantation because of end-stage liver disease due to CHC viral infection. Patients were considered intravenous substance users when infected after IVDU. Patients who had not recovered completely from substance use were stably treated in a long-term methadone maintenance program. Patients with a history of substance abuse were advised not to return to their previous deleterious lifestyle. Counseling was offered to patients who thought they needed it.

The immunosuppression regimens in the various transplant centers consisted of steroids in combination with azathioprine or mycophenolate mofetil and tacrolimus or cyclosporine immediately after transplantation, after 3 months of bitherapy with tacrolimus or cyclosporine, and after 1 year of monotherapy with tacrolimus or cyclosporine.

Patients with CHC were treated posttransplantation with interferon or pegylated interferon in association with ribavirin when a relapse of CHC virus infection was documented and evolution to fibrosis was diagnosed in liver biopsy tissue.

All rejection episodes and recurrence of HCV infection were histologically proved, and all patients underwent a protocol biopsy after 1 year. Fibrosis was scored according to the Metavir scoring system, which scores fibrosis from F0 to F4.⁹

The characteristics and clinical evolution of the IVDU group, including surgical complications, rejection rate, CMV infection necessitating ganciclovir treatment, biliary stenosis, renal impairment, need for antihypertensive treatment, emergence of new diabetes mellitus, compliance, and repeats transplantation rate, were compared with those in patients with HCV without a history of substance abuse.

Pretransplantation data on hepatitis B viral infection and human immunodeficiency virus coinfection, concomitant liver disease, comorbidities, route of infection, genotype, and previous antiviral treatment were collected for both groups. An overview of drug abuse history was also asked for in the IVDU group.

Compliance was defined as presentation at the outpatient clinic for more than 80% of the scheduled appointments.

Statistical Analysis

All data were analyzed using commercially available software (SPSS version 12.0 for Windows; SPSS, Inc, Chicago, Illinois). To compare groups for categorical variables, χ^2 and Fisher exact tests were used. The two-sample *t* test was used for significance testing between the groups for continuous data. The Wilcoxon rank sum test was used if data were not normally distributed. The log-rank test was used to investigate differences in Kaplan-Meier survival

curves for time-to-event data. *P* = .05 (two-tailed) was considered statistically significant.

RESULTS

Demographic and Pretransplantation Characteristics of the Study Population

Overall, 67 patients underwent a first liver transplantation during the study. Seven patients (10%) had a documented history of substance abuse before transplantation (group 1), and 60 patients had no evidence of substance abuse (group 2). Patients with a history of substance abuse were all infected after needle and paraphernalia sharing during intravenous drug use. In the non-IVDU group, some were infected by transfusion (10%) or tattoo (2%). However, in most of those patients (88%), the source of the infection was unknown.

Patients in the IVDU group were predominantly men (86%) and were significantly (*P* = .001) younger (47 ± 2.2 years) than those in the non-IVDU group (58 ± 1 years) at transplantation (Table 1). There was no difference in race/ethnicity, body mass index, concomitant causes of liver disease (eg, alcohol-induced liver disease), or prevalence of hepatocellular carcinoma between the patient groups (Table 1).

Comorbidities were rare in patients in the IVDU group, whereas a substantial number of patients in the non-IVDU group had comorbidities at transplantation. The differences, however, did not reach statistical significance (co-

Table 1. Patient Characteristics

Variable	Group Infected After IVDU (n = 7)	Non-IVDU Group (n = 60)	<i>P</i> Value
Age at Tx, mean (SEM), y	47 (2.2)	58 (1.0)	.001
Male sex, No. (%)	6 (86)	37 (62)	.41
White race/ethnicity, No. (%)	7 (100)	59 (98)	.99
BMI, mean (SEM)	27 (4)	26 (5)	.59
Genotype, %			
1, 4, 5	2 (40)	32 (84)	.05
2, 3	3 (60)	7 (16)	
Concomitant liver disease, No. (%)			
Alcoholism	2 (28)	1 (17)	.61
Hepatocellular carcinoma	1 (14)	21 (35)	.41
Waiting time, mean (SEM), d	195 (107)	142 (163)	.09
Ischemia time, min			
Cold	598 (134)	574 (161)	.83
Warm	54 (9)	64 (21)	.22
Donor age, mean (SEM), y	43 (2.3)	44 (6.4)	.92
Donor liver CMV-positive, No. (%)	4 (57)	25 (48)	.71

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; CMV, cytomegalovirus; IVDU, intravenous drug use; Tx, transplantation.

morbidity in the non-IVDU group compared with the IVDU group: diabetes mellitus, $n = 12$ [21%] vs $n = 1$ [14%], $P = .72$; cardiac diseases, $n = 3$ [5%] vs $n = 0$, $P = .54$; and renal impairment, $n = 10$ [17%] vs $n = 0$, $P = .24$. No patients were coinfecting with hepatitis B virus and human immunodeficiency virus.

Patients in the IVDU group were more frequently infected with genotype 2 or 3 HCV (60% vs 16% in the non-IVDU group). Fifty-seven percent of patients in the IVDU group and 54% of patients in the non-IVDU group received antiviral treatment against HCV before transplantation. None of the patients achieved sustained virologic response.

In the IVDU group, one patient actively used soft drugs at baseline and one patient was receiving methadone maintenance therapy. Among the remaining five patients, four abstained from substance use for more than 5 years before liver transplantation.

Outcome After Transplantation

All patients in the IVDU group underwent cadaveric orthotopic liver transplantation, and 2 patients in the non-IVDU group underwent living donor liver transplantation (Table 2). There was no difference between groups 1 and 2 in so far as waiting time, and organ cold and warm ischemia periods.

Rejection Rate

The rejection rate was similar in the IVDU and non-IVDU groups during the first year after transplantation (3 [43%] vs 25 [42%]; $P = 1.0$). Rejection occurred predominantly within the first year after transplantation. There was no difference in immunosuppression regimens used in the two patient groups within the first year or subsequent years after

transplantation. Most patients ($n = 35$ [52%]) received combined tacrolimus, mycophenolate mofetil, and steroid therapy. Most patients were steroid free after 1 year ($n = 41$ [79%]).

Patient and Graft Survival

The mean (SEM) follow-up in the IVDU and non-IVDU groups was 80.6 (11.33) and 74.34 (4.57) months, respectively. There was no difference ($P = .70$) in patient survival in the IVDU group compared with the non-IVDU group (Fig 1). Patient survival at 1, 3, and 5 years was 86%, 84%, and 81%, respectively, in the non-IVDU group and 84% at each of the three periods in the IVDU group. There was no difference ($P = .40$) in graft survival between the IVDU and non-IVDU groups (Fig 1). Graft survival at 1, 3, and 5 years was 82%, 77%, and 71% respectively, in the non-IVDU group and 84% at each of the three periods in the IVDU group.

Postoperative Complications

Before transplantation, no concomitant disease and after transplantation no surgical complications were noted in the IVDU group (Table 2). However, in the non-IVDU group, concomitant disease and surgical complications (lymphocele, biliary leak, celiac trunk stenosis, hepatic artery obstruction, bilioma, pneumothorax and hemothorax, and intra-abdominal hemorrhage) after transplantation were more prevalent. An equal number of medical complications after liver transplantation such as arterial hypertension, diabetes mellitus, biliary stenosis, and clinically significant cytomegalovirus infections were noted in the IVDU and non-IVDU groups (Table 2).

During follow-up, no tumors were noted in the IVDU group. In the non-IVDU group, one patient each developed a colon tumor, a glioblastoma, and a stomach adenocarcinoma, respectively, 5, 6, and 6 1/2 years after liver transplantation.

Repeat Transplantation

In the IVDU group, no patient underwent a second transplantation, whereas six patients (10%) in the non-IVDU group required a second liver transplantation during follow-up (Table 2). The causes were hepatic artery thrombosis ($n = 2$), primary nonfunctioning liver, necrosis of the biliary tree, chronic rejection, and cirrhosis due to HCV reinfection. The difference is statistically not significant. One patient (1.7%) underwent three transplantations (living donor, because of biliary complications after 5 years).

Reinfection with HCV and Evolution to Fibrosis

The clinical HCV graft reinfection rate was not different between the two patient groups (Table 3). One year after transplantation, two of seven (29%) patients in the IVDU group developed minor fibrosis (F1) (Table 3). In contrast,

Table 2. Evolution After Liver Transplantation*

Variable	Group Infected After IVDU (n = 7)	Non-IVDU Group (n = 60)	P Value
Surgical complications	0	20 (33)	.09
Rejection rate, biopsy-based			
<1 y after Tx	3 (43)	25 (42)	.99
>1 y after Tx	0	1 (2)	.99
CMV infection requiring ganciclovir therapy	3 (43)	7 (12)	.06
Biliary stenosis	2 (29)	12 (20)	.63
Serum creatinine concentration >1.2 mg/dL	5 (71)	6 (43)	.23
Antihypertensive therapy	4 (57)	28 (47)	.70
Development of diabetes mellitus	1 (14)	17 (28)	.90
Compliance with >80% of outpatient visits	7 (100)	57 (95)	.99
Repeat transplantation	0	6 (10)	.56

Abbreviations: CMV, cytomegalovirus; IVDU, intravenous drug use; Tx, transplantation.

*Values are given as No. of patients (%).

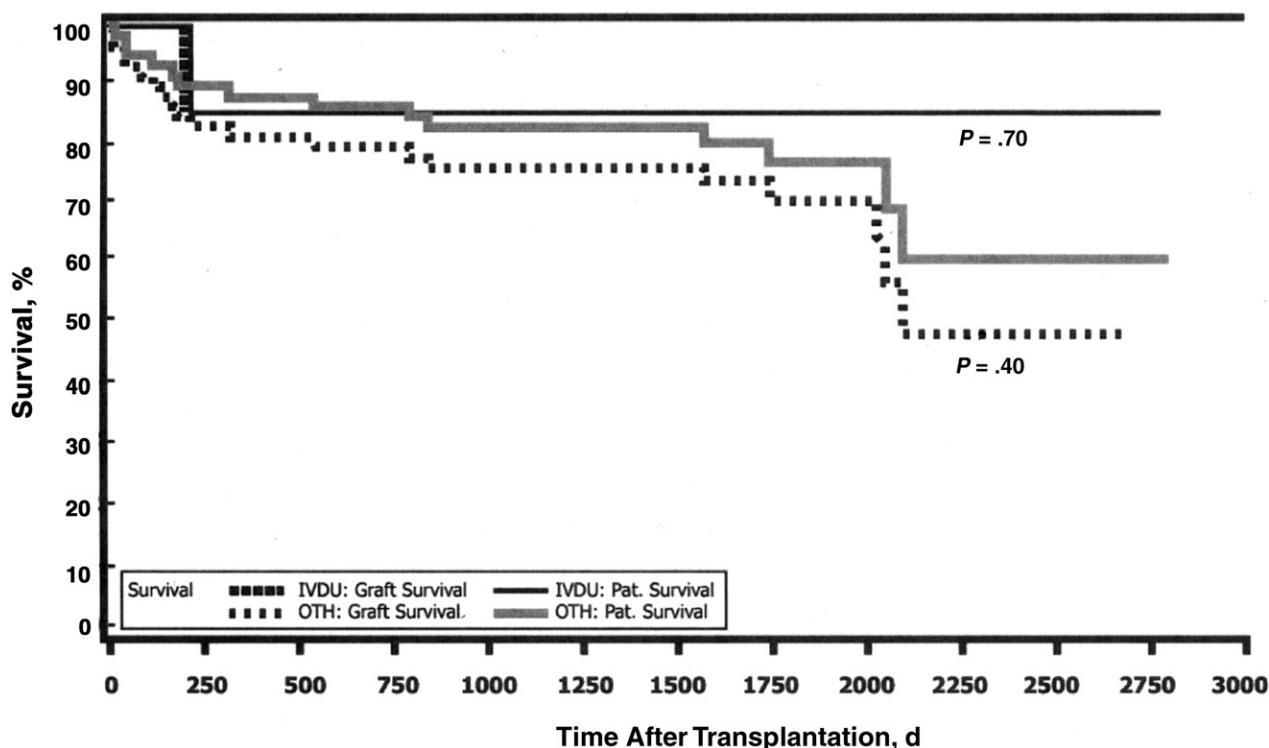


Fig 1. Kaplan Meyer analysis of patient and graft survival in chronic hepatitis C patients infected after IVDU in comparison with non-IVDU patients.

32 of 48 patients (67% in the non-IVDU group) developed fibrosis 1 year after transplantation; fibrosis score was F1 in 21 patients (44%), F2 in nine patients (19%), and F3-4 in two patients (4%). Overall, the frequency of fibrosis grade (lower than F2) 1 year after transplantation was lower in patients aged 50 years or younger at transplantation and receiving a liver from a donor aged 50 years or younger (4/13 [31%]) compared with patients older than 50 years at

transplantation receiving a liver from a donor aged 50 years or younger (12/20 [60%]) and patients older than 50 years at transplantation receiving a liver from a donor older than 50 years (13/17 [76%]; $P = .01$). Five of seven patients (71%) in the IVDU group with CHC infection vs nine of (15%) in the non-IVDU group who underwent a liver transplantation were younger than 50 years. Five of seven patients (71%) in the IVDU group with CHC infection received a liver from a donor younger than 50 years compared with 34 of 60 patients (56%) in the non-IVDU group.

In patients infected after IVDU only one patient was treated with antiviral therapy without achieving a sustained virologic response. That patient was intolerant to interferon therapy and was receiving methadone maintenance therapy. In the non-IVDU group, 28 patients required antiviral therapy. In 14 patients (50%), a sustained virologic response was obtained. Five patients were intolerant to antiviral therapy. Five patients (29%) received prolonged treatment (>1 year) with interferon in an attempt to stop evolution to fibrosis.

Table 3. Evolution of HCV After Liver Transplantation*

Variable	Group Infected After IVDU (n = 7)	Non-IVDU Group (n = 60)	P Value
HCV reinfection after Tx			
<1 year	3 (43)	32 (64)	.41
>1 year	4 (67)	32 (74)	.65
Antiviral therapy after Tx			
<1 year	0	18 (35) [†]	.09
>1 year	1 (14)	24 (49) [†]	.12
Fibrosis score after Tx [‡]			
<1 year	2 (29)	32 (67)	.09
F1	2 (29)	21 (44)	
F2		9 (19)	
F3-F4		2 (4)	
>1 year	2 (67)	24 (83)	.48

Abbreviations: HCV, hepatitis C virus; IVDU, intravenous drug use; Tx, transplantation.

*Values are given as No. of patients (%).

[†]Sustained virologic response rate, 50%.

[‡]Scale of 1 to 4.

Compliance and Substance Addiction

Compliance as measured by attendance at appointments in the outpatient clinic was not different between the two

patient groups (Table 2). During follow-up, there was no relapse in drug use. Six years after transplantation, one patient originally infected after IVDU was still receiving methadone therapy, 35 mg/d, with no relapse in drug use. The patient is alive; however, depression developed that required treatment with a selective serotonin reuptake inhibitor. There was no problematic alcohol abuse in the IVDU group; however, alcohol abuse was noted in three of 53 patients (5.6%) in the non-IVDU group.

DISCUSSION

In recent years, substance use has become the major risk factor for infection with HCV. More patients with a history of substance use are being treated at liver transplant centers. Although for patients in a methadone maintenance program a 6-month abstinence period is required,⁶ no comparative data about the long-term outcome of liver transplantation in substance users in prolonged complete remission are available.

To our knowledge, this is the first comparative study of posttransplantation survival outcomes in patients with CHC infected after substance use. Those patients were in complete remission. We found no difference in patient and graft survival between patients infected after substance use and patients with CHC infected by other sources. Moreover, after transplantation, no surgical complications were noted and no second transplantation procedures were required during follow-up. No patients required antiviral therapy in the first year after transplantation. In comparison with the non-IVDU group, there were nearly no concomitant pathologic findings, possibly because these patients were younger.

In this patient group, there was no recidivism in substance or alcohol use during follow-up of 6.6 years after transplantation. Despite the retrospective design of the study and that no systematic urine samples were taken, no clinically important recidivism was noted. Although this is in agreement with recidivism rates between 0% and 11% in noncontrolled studies,^{4,5} our results must be interpreted with caution given the relatively small number of patients in the IVDU group. Patients in the IVDU group were in stable condition. Before transplantation, they no longer used IV drugs for periods varying from 5 to more than 20 years. One patient used soft drugs and continued using them after liver transplantation. One patient was included in a methadone maintenance treatment program and he progressed well without any major complications, shorter patient or graft survival, or faster histologic evolution to fibrosis. This is in accord with previous reports of patients receiving methadone therapy in whom a 6-month abstinence period was required. He had similar long-term outcomes after liver transplantation compared with patients not receiving methadone who underwent orthotopic liver transplantation during the same period.⁶ The relapse rate is clearly lower than in a recent study

reporting a recidivism rate of substance abuse of 29%.⁷ Although several possible factors predictive for relapse were taken into consideration in this study, duration of abstinence was not examined.

In the present study, patients with CHC infected after substance use developed no or only minor fibrosis during the first year after transplantation. This may be due to the predominant infection by genotypes 2 and 3. It is, however, more likely that the younger age of the patients and the donor livers in the IVDU group had a significant role in the more favorable evolution after liver transplantation. Younger donor age influences posttransplantation outcome.¹⁰ In addition, after transplantation, only one patient in the IVDU group received antiviral treatment although those patients had the same rate of reinfection as patients with CHC in the non-IVDU group,¹¹ which might suggest that the evolution of the HCV infection might be less aggressive.

Several limitations of the present study must be acknowledged. Some data, for example, the route of infection, might have been missed because of the retrospective design of the study. Moreover, the number of the patients studied was small. However, to reach statistical significance, the sample size would have to be 231 in each group, which is almost impossible to achieve, especially at present in the IVDU group.

In conclusion, in this retrospective study, patients in the IVDU group who underwent transplantation because of chronic HCV infection in complete remission had a similar patient and graft survival compared with patients with CHC with other sources of infection. The evolution of HCV-induced disease was rather benign in the IVDU group, and compliance in these patients was as good as in the other patients with CHC. In addition, no relapse in substance use was documented after follow-up of 6.6 years. These findings suggest that carefully selected former IV drug users with HCV infection might be reasonably good candidates for liver transplantation. However, larger studies with a longer follow-up in IV drug users with CHC are needed to confirm or refute these findings.

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