

Alcohol Use After Liver Transplantation in Alcoholics: A Clinical Cohort Follow-up Study

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The purposes of this study were to determine among a cohort of long-term alcoholic survivors after liver transplantation (1) the incidence of alcohol use, (2) its effect on allograft integrity and extrahepatic health, and (3) the validity of the pretransplant alcohol prognosis screening process. Retrospective clinical cohort study of all alcoholic patients undergoing orthotopic liver transplantation at a single center from February 1987 until January 1991 with follow-up through December 1994, giving a median duration of follow-up of 63 months (range, 6-89 months). Multidisciplinary liver transplantation program at a tertiary-care academic medical center. Fifty alcoholic, long-term liver transplant recipients. The frequency of alcohol relapse, defined as any alcohol use in the period after transplantation, was determined by two questionnaire studies and by clinical follow-up. Allograft integrity was assessed by coded review of serial percutaneous allograft biopsies. Potential systemic effects of alcohol relapse were assessed by chart review. The alcohol prognosis screening process was evaluated by retrospectively comparing pretransplant estimates of putative indicators of alcoholism prognosis in posttransplant alcohol users and abstainers. Thirty-three recipients (66%) consistently denied any alcohol use throughout the duration of posttransplant follow-up, whereas 17 (34%) were identified as having consumed alcohol at least once since the transplant. There were no significant differences at the time of evaluation between abstainers and alcohol users in age, sex distribution, severity of liver dysfunction, median duration of abstinence, or University of Michigan alcoholism prognosis score. The median interval from transplantation to alcohol relapse was 17 months, with a range of 3 to 45 months. Recurrent alcohol use was associated with significant medical complications sufficient to require admission to the hospital in 6 patients. One patient died of graft dysfunction, noncompliance with immunosuppressant medications, and presumed graft rejection while drinking. Mild or progressive hepatitis, which was the most common abnormality in posttransplant liver biopsy findings, was equally distributed between both alcohol users and abstainers and sometimes occurred in the absence of antibody to hepatitis C virus antibodies. There was a similar frequency of biopsy-proven acute cellular rejection in alcohol users and abstainers. Typical histological features of alcoholic liver injury were

present in posttransplant biopsies from 1 alcohol user only. Alcohol use by alcoholics is uncommon in the first 5 years after liver transplantation, and alcohol-associated liver injury is unusual. Mild nonspecific hepatitis is common in both alcohol users and nonusers alike. Among a small subset of alcoholic transplant recipients, drinking behavior after liver transplantation is associated with considerable morbidity, requiring hospital admissions and occasionally leading to graft loss and death. (HEPATOLOGY 1997;25:1223-1227.)

Orthotopic liver transplantation is an efficacious therapy for severe liver failure associated with alcoholism. Survival rates after liver transplantation are similar among alcoholics and nonalcoholics.^{1,2} There is a significant survival advantage among alcoholics with transplants compared with alcoholic patients refused transplants on psychiatric grounds or compared with alcoholic controls with severe liver disease in a simulated mathematical model.^{2,3} We have shown that more than 50% of alcoholics referred to our program are refused transplants on either medical, surgical, or psychiatric grounds, a rate of refusal that exceeds that for most other chronic liver diseases (unpublished observations).

Alcoholics with end-stage liver disease undergo careful assessment of the risk of recidivism in the future.⁴ There is a relatively low incidence of recidivism in short-term periods of observation after transplantation.^{2,5-8} More recent studies have suggested that the incidence of recidivism, although still low compared with incidence with other forms of therapy for alcoholism, increases with longer follow-up.⁹

It remains uncertain whether alcohol use after liver transplantation has untoward consequences for allograft function. Indeed, Bonet et al. have proposed that a relapse of alcohol abuse by alcoholics after liver transplantation may have paradoxical benefits, including reducing the incidence of acute cellular rejection.¹⁰ The purposes of this study were (1) to document the incidence of alcohol use among a cohort of long-term alcoholic survivors after liver transplantation; (2) to determine the effect of alcohol use on allograft integrity and extrahepatic health in these patients; and (3) in light of these data, to review the pretransplant alcohol prognosis screening process.

PATIENTS AND METHODS

A retrospective review was undertaken of all patients with alcohol abuse or dependence, defined according to the *Diagnostic and Statistical Manual of Mental Disorders* of the American Psychiatric Association (3rd ed., revised) (DSM-III-R), who received a liver transplant between February 1987 and January 1991.¹¹ Forty-five of the present cohort were included in an earlier report of selection for and outcome of liver transplantation in alcoholic liver disease.² All had undergone pretransplantation psychosocial evaluation to estimate the risk for future alcohol use, including determination of the Michigan Alcohol Prognosis Score, an empirical instrument applied during the selection process to stratify candidates into high- and low-risk strata for a return to drinking.¹² It records insight into alcoholism, the presence

Abbreviations: anti-HCV, antibody to hepatitis C virus; HCV, hepatitis C virus.

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TABLE 1. Demography and Clinical Characteristics of 50 Alcoholic Liver Transplant Recipients

	Abstainers	Users	P
n	33	17	NS
Sex (M/F)	24/9	12/5	NS
Age (yr)	46 (31-65)	45 (28-61)	NS
Child's class			
A	0	0	
B	11	3	
C	18	11	
Incomplete	4	3	
Abstinence (mo)	11 (0-180)	4 (0-36)	NS
Waiting time (d)	21 (1-152)	15 (0-67)	NS
University of Michigan Alcoholism Prognosis Scale	17 (8, 18)	16 (9, 18)	NS

NOTE. All data are shown as median and range. Abstinence refers to duration of abstinence at time of evaluation.

of factors suggesting a favorable prognosis for sobriety described by Vaillant, and social stability according to Strauss and Bacon.^{13,14} Severity of liver disease was assessed using Child-Turcotte-Pugh scores.¹⁵ Alcohol use after transplantation was assessed by two formal interview studies, in 1988-1989 published in 1992,¹⁶ and in 1992,¹⁷ and by clinical surveillance at our outpatient clinics and by contacting primary care physicians until December 1994. A formal prospective longitudinal protocol of alcohol use interviews or measurement of blood or urine alcohol levels was not used throughout the duration of the study. Alcohol relapse was defined as any alcohol use revealed in either interview survey or in the course of clinical follow-up. Liver biopsies were performed whenever clinically indicated on the basis of abnormal results of biochemical tests. For the purposes of the study, biopsies were reviewed in blinded fashion under code by two pathologists (K.C. and H.D.A.). Acute cellular rejection was always a histological diagnosis according to the criteria of Snover.¹⁸

Statistics. Qualitative data were compared between users and abstainers using χ^2 tests, and those with continuous variables using Wilcoxon's rank sum test, *P* values of <.05 being considered significant. Survival was estimated by the Life-Table Analysis method of Peto et al.¹⁹

RESULTS

Clinical Features. Fifty-nine alcoholic patients received transplants during the period described. There were 9 early deaths due to perioperative death (*n* = 2), poor graft function, with or without sepsis (*n* = 5), graft-vs.-host disease (*n* = 1), and hepatoma (*n* = 1). Three underwent a second transplantation. The median interval from transplantation to death in this subset was 33 days (range 1-150 days). On review of patients' case records, it was considered that they did not reestablish their health and were consequently unable to exercise a choice regarding a return to drinking. They will not be considered further. Among the remaining cohort of 50 long-term survivors that forms the basis of the present report, the median duration of follow-up was 63 months and was ≥ 4 years in 46 (92%). In this cohort, 33 recipients (66%) reported no alcohol use throughout the duration of posttransplant follow-up and are termed alcoholic abstainers, whereas 17 recipients (34%) were identified as having consumed alcohol at least once since the transplant and are termed alcohol users. Table 1 shows comparative clinical characteristics in these two subgroups. Abstainers and alcohol users were of similar age, sex distribution, and severity of liver dysfunction as shown by Child-Turcotte-Pugh classification at the time of the evaluation.¹⁵ There were 4 alcohol abusers (classification 305) in each group, which was not statistically different. The median length of abstinence before evaluation was greater among abstainers than alcohol users, although this difference did not reach significance. Nine of 17 recipients who returned to alcohol use had pre-evaluation abstinence of less than 6

months, compared with 10 of 33 nonusers who had less than 6 months' abstinence. The duration of time on the liver transplant waiting list was similar in both groups. The University of Michigan alcoholism prognosis score did not distinguish between abstainers and users.

There were 3 late deaths among the abstaining group as a result of unexplained hypoglycemia, recurrent hepatitis B infection, and hepatoma, each in 1 case. There was 1 late death among the alcohol-user group, and this patient will be described below.

Retrospective determination of the date of relapse, according to the patients' own reports, was available in 12 subjects in the user group. The median interval from transplantation to relapse was 17 months, with a range of 3 to 45 months. In 6 patients, recurrent alcohol use was associated with significant medical complications sufficient to require admission(s) to hospital. These events included bouts of uncontrolled drinking followed on separate occasions by delirium tremens and an episode of pneumonia, recurrent cellulitis when drinking and "skin popping" cocaine, repeated episodes of pancreatitis coincident with alcohol use, cholestatic hepatitis associated with a blood alcohol level of 160 mg/dL on admission to the hospital, and an upper gastrointestinal hemorrhage due to gastritis and admitted alcohol use. Finally, 1 patient had graft dysfunction, noncompliance with immunosuppressant medications, and presumed graft rejection while drinking 3 months after transplantation. We decided not to offer this patient retransplantation, and the patient died. Four of the 6 patients with putative medical complications of alcohol relapse reported initial abstinence from alcohol for 12 months or greater from the date of transplantation.

Management of alcohol relapse after transplantation was on a case-by-case basis. For example, 1 patient sought medical assistance for a single episode in which she drank 1 quart of table wine after a family argument. She underwent inpatient rehabilitation and has maintained follow-up attendance at a support group. She has subsequently remained abstinent for more than 4 years. Another patient had repeated hospital admissions for intoxication, pneumonia, delirium tremens, and a myocardial infarction in the first 4 years after transplantation, during which time he refused psychiatric assistance. He then stopped drinking alcohol of his own volition, and he has remained abstinent for 26 months. In contrast, other patients within this cohort continue to consume alcohol on an intermittent or regular basis.

Histology. Forty-five explanted livers were reviewed. All showed cirrhosis. None were accompanied by histological features of acute alcoholic hepatitis, combining a neutrophilic infiltrate, steatosis, Mallory bodies, necrosis of individual hepatocytes, and debris-filled phagocytes. In 14 explants, the cirrhosis had the appearance of end-stage alcoholic injury including small nodules, loss of central zones, and steatosis. The frequencies of histological alcoholic liver disease in the explanted livers were similar in the patients who subsequently went on to alcoholic relapse and those who maintained sobriety after transplant (Table 2). Thirty-one explants lacked etiologic markers, including patterns typical of alcoholic cirrhosis, and would be classified on histological grounds as cryptogenic. Evidence of other causes of liver injury such as α_1 -antitrypsin deficiency, primary biliary cirrhosis, or hepatitis B viral infection was found in 9 explants, always in the patients who subsequently remained abstinent.

All posttransplant biopsies have been reviewed in 33 subjects. Data in Table 2 represent the most abnormal biopsy in the biopsy series from each patient. Mild or progressive hepatitis was the most common abnormality and was equally distributed between both alcohol users and abstainers. In all subjects, hepatitis C antibody testing after transplantation was available for review. Antibody to hepatitis C virus (anti-

TABLE 2. Histological Features in Explanted Liver and Posttransplant Liver Biopsies

	Abstainers	Users
Explants		
n	29	16
Small nodules	5	5
Mallory's hyaline	5	4
Steatosis	2	1
Central zone loss	6	5
Cryptogenic cirrhosis	22	9
Alcoholic cirrhosis	7	7
Acute alcoholic hepatitis	0	0
Posttransplant biopsy		
Subjects studied	20	13
Normal	4	4
Steatosis	1	0
Steatosis + inflammation	3	2
Mild hepatitis	7	6
Progressive hepatitis	6	2
Acute alcoholic hepatitis	0	1
Acute cellular rejection	8	4

NOTE. Data on posttransplant biopsy represent the most abnormal biopsy in each biopsy series from each patient.

HCV) antibodies were present in approximately half of the patients with histological hepatitis among both alcohol users and abstainers (Table 3). Anti-HCV antibodies were common also in the absence of histological hepatitis in both groups. There was a similar frequency of biopsy-proven acute cellular rejection in both users and abstainers. One patient, a post-transplant alcohol user, showed typical features of alcoholic injury on biopsy, including intense central zone steatosis and stellate perisinusoidal fibrosis.

DISCUSSION

Alcoholic cirrhosis was the preoperative diagnosis in 2,499 liver transplants, or 15.6% of all transplantations performed in the United States between 1988 and 1993.²⁰ The growth in the absolute number of liver transplants in alcoholic persons has occurred against a background of an ongoing debate on both the practical and ethical implications of offering liver transplantation to persons with alcoholism.

Previously when we and others have reported our experience of liver transplantation in patients with end-stage alcoholic liver disease, we have concentrated on selection, early mortality, utilization of resources, or short-term recidivism. Table 4 summarizes these studies. They show clearly that mortality for alcoholics does not differ from that reported in nonalcoholic recipients. Table 4 also shows that alcoholic relapse, however defined, is infrequent in the first 24 months after liver transplantation. The frequency of relapse increases as the duration of follow-up is extended. Berlakovich et al. reported on 44 long-term alcoholic survivors after liver transplantation and found that the frequency of relapse increased from 15% at 1 year to 31% at 3 years.⁹ In the present study, we have found a similar incidence of reported alcohol use (34%), usually beginning more than 12 months after transplantation, among 50 alcoholics who were long-term liver transplant survivors. However, the present study also shows alcohol relapse by alcoholics after liver transplantation is a heterogeneous clinical phenomenon.

Alcohol use after transplantation, often labeled as recidivism, is defined inconsistently in various liver transplant studies. Many studies, including our present and previous reports, have combined all or any alcohol use under the rubric "recidivism" because, lacking serial prospective measures, we feared that significant alcohol use would be missed if some degree of moderate or occasional drinking was excluded from

the definition of a relapse. This approach usually relies on the patient's own report of alcohol drinking, because alcoholic cirrhotics show a consistent pattern of underestimation when self-reported alcohol use has been corroborated by serial urine tests.²¹ It is possible, therefore, that self-reported accounts of consumption have underestimated the true frequency of alcohol use after transplantation. In contrast, Bird et al. presumed alcohol use on the basis of liver chemistry and biopsy results even when the patient denied it.²² This approach carries the contrary risk of overestimating or misidentifying recidivists. More recently, Howard et al. have reported on psychiatric interviews in 20 long-term alcoholic liver transplant survivors and found that 19 of 20 had returned to drinking.²³ They attribute their much higher alcohol use to better interview methods, which result when the interviewer is independent of the transplant group. However, this is unlikely to be the only explanation, because the physicians were aware of the drinking relapse in 13 of 19 cases. Lack of a standardized selection process, and inclusion of only 50% of the cohort who received transplants, also compromise Howard's data. In the present study, we have tried to overcome the problems inherent in estimating alcohol use by combining serial interview data with documentation at frequent clinic visits. We realize, however, that only prospective data gathering and aggressive case follow-up of the nonattenders would provide more definitive data.

It is clear from our observations that there is no characteristic pattern of posttransplant alcohol use. Indeed, although we describe 17 alcoholic transplant recipients who returned to alcohol use, this group is made up of 17 individuals who each behaved differently. We saw repeated pathological drinking that continued throughout the observation period, profound pathological drinking followed by sustained abstinence, a single episode of alcohol use leading to rehabilitation and abstinence, and admitted minor alcohol use. The present report includes data from our previously published study comparing drinking behavior in alcoholic and nonalcoholic liver transplant recipients.¹⁶ This showed a similar prevalence of alcohol use after transplantation in both groups, but excessive use only occurred in the alcoholic recipients. Similarly, Berlakovich et al. distinguished between "harmful" and other forms of drinking.⁹ In the more general literature on alcoholism, irrespective of liver transplantation, restoration of a controlled pattern of social alcohol use remains rare.²⁴ As yet, there are no data to support the contention that alcoholic liver transplant recipients can achieve a pattern of moderate controlled alcohol use.

The data presented here show that whereas chronic hepatitis is common, typical alcoholic injury to the grafted liver is not. In our series, no patient who was actively drinking developed acute alcoholic hepatitis. Only 1 patient who was actively drinking developed alcoholic-type steatosis with extensive perisinusoidal fibrosis. The etiology of posttransplant hepatitis in our cohort is unclear. Many patients in both the user and abstinent groups are anti-HCV antibody positive. These results are congruent with the frequent observation of anti-HCV and hepatitis C virus (HCV) RNA in the serum of alcoholic cirrhotics.^{25,26} However as shown in Table 3, the occurrence of hepatitis was poorly associated with anti-HCV.

TABLE 3. Results of HCV Serological Tests, and Histological Study in Posttransplant Biopsies

	Abstainers	Users
n	23	13
anti-HCV positive, hepatitis	7	3
anti-HCV positive, no hepatitis	3	2
Hepatitis, anti-HCV negative	7	3
anti-HCV negative, no hepatitis	6	5

TABLE 4. Summary of Published Data on Alcohol Use by Alcoholic Patients After Liver Transplantation

Author	Study Years	Alcoholism Prognosis	No. of Alcoholics Receiving Transplants (Study Cohort)	No. of Alcoholics Receiving Transplants (Not Study Cohort)	No. of Alcoholics Not Selected	1-yr Survival Rate (%)	5-yr Survival Rate	Duration of Follow-up	Relapse Defined	Relapse Frequency (%)
Kumar ⁵	1982-1988	Abstinent period not required	52	21	Not stated	74	Not stated	Not stated	Any use (phone survey)	12
Bird ²²	1980-1989	Abstinent period not required	18	6	Not stated	66	Not stated	4 mo-7 yr	Any use (laboratory values, biopsy)	17
Knechtle ⁶	1984-1990	Abstinent period not required	32	9	5	83	71%	Not stated	Any use (psychiatric interview)	13
Gish ⁷	1988-1991	Abstinent period not required	29	0	Not stated	93	Not stated	24 mo	Any use (prospective follow-up)	21
Osorio ⁸	1988-1991	6 Months Abstinence	43	0	65	100	Not stated	21 mo	Any use (mail survey)	19
Berlakovich ⁹	1982-1993	Abstinent period not required	44	36	Not stated	71	63%	78 mo	Any use (clinic follow-up)	32
Lucey*	1987-1991	Abstinent period not required	50	9	75	80	77%	63 mo	Any use (see text)	34
Howard ²³	1987-1992	Abstinent period not required	20	20	Not stated	79	Not stated	34 mo	Any use (psychiatric interview)	95

* Present report.

We recognize that anti-HCV antibody measurements may be inaccurate in patients receiving immunosuppressant medication. Consequently, the observation that posttransplant hepatitis may be due to factors other than HCV would be strengthened by measures of HCV RNA in serum using polymerase chain reaction, which were not available in the present study. Even so, whereas HCV may account for some posttransplant hepatitis in alcoholic transplant recipients, it is unlikely to account for all. Previously, Hubscher has shown that nonprogressive low-grade hepatitis of uncertain etiology is common in long-term follow-up biopsies after liver transplantation.²⁷ Evidence is accumulating that HCV and alcohol act synergistically in producing liver damage.^{25,26} It is of interest, therefore, that in the small sample of anti-HCV-positive patients in the alcohol-user group that liver injury was not disproportionately severe.

In our study, alcohol use did not confer any immunosuppressant benefit. Because 80% of acute cellular rejection occurs within the first 8 postoperative weeks, it is unlikely that alcoholic relapse, which usually arises 12 months after transplantation, would play a significant immunity-modulating role.²⁸ Only once did we observe coincident alcohol relapse and a presumptive, i.e., not biopsy-proven, diagnosis of acute cellular rejection, as a result of failure to maintain the prescribed immunosuppressive regimen. It appears uncommon that alcoholic patients are derelict with their medications, even when they are drinking. Indeed, we have previously shown that the frequency of admitted failure to take prescribed immunosuppressive medications is similar for alcoholic and nonalcoholic liver transplant recipients.¹⁶

The present study is the first to demonstrate an impact of alcohol use by alcoholic recipients on extrahepatic health. This arose from our clinical experience in which particular patients developed clinical syndromes that seemed directly associated to pathological drinking. In some cases the association was incontrovertible, such as intoxication and delirium tremens. Other episodes, such as recurrent pancreatitis, were probably alcohol associated given the patients acknowledged use of alcohol and the recurrence of pancreatitis after azathio-

prine had been withdrawn. We have inferred that episodes of cellulitis and of pneumonia were alcohol related because they occurred during heavy drinking bouts, even though we recognize that cellulitis or pneumonia, or for that matter pancreatitis, can arise in liver transplant recipients without alcohol exposure. Despite the caveat that it is impossible to be certain that alcohol use contributed to each of the extrahepatic phenomena described here, it is our impression that persistent alcohol abusers experience more medical problems than their abstinent counterparts and constitute a disproportionate burden on the posttransplant management team.

Therefore, it is our contention that the increased burden of extrahepatic illness in relapsing alcoholic liver transplant recipients justifies pretransplant selection procedures that aim to identify those at greatest risk of posttransplant alcohol relapse. This viewpoint begs the question of whether we are able to identify future drinkers. The determination of alcohol abuse or dependence did not distinguish future users from abstainers. In the present study, the prognosis for future abstinence was assessed in all recipients using the method we have described.²⁴ This method includes a point system, which we have advocated as a tracking system rather than an absolute threshold. As shown in Table 1, there were no differences in the prognosis scores calculated during pretransplant assessment among the subsequently abstinent and alcohol-using transplant recipients. We suspect that the prognosis scoring system is more valuable than it appears to be in these data, in part because the major screening process for alcoholics to gain access to our liver transplant program occurs when the patient is referred by the primary care physician. In a review of 233 patients with alcohol abuse or dependence referred to our center for consideration for liver transplantation, the Michigan Prognosis Score was 12 points or greater in 78.5%, suggesting that stable, insightful alcoholics were most likely to be referred.²⁹

We therefore advocate maintaining a selection process that screens prospective alcoholic liver transplant candidates using a broad-based instrument such as the University of Michigan Alcoholism Prognosis Score rather than a time-based

abstinence rule. Furthermore, we believe that our data indicate the need for carefully constructed multicenter longitudinal studies that prospectively evaluate the evaluation process.

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