Alcohol Use Following Liver Transplantation

A Comparison of Follow-up Methods

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Alcoholic cirrhosis is one of the most common indications for liver transplantation. Previous researchers have studied rates of return to drinking following transplantation, however, few have employed prospective measures of alcohol use. The authors prospectively studied the alcohol use of patients transplanted for alcoholic liver disease. The authors improved the accuracy of monitoring alcohol use by using various methods for tracking patient's alcohol consumption, and we report on the time to first alcohol use after transplantation comparing these different methods. The authors found that alcohol use can occur very early after transplantation, even within the first 3 months posttransplant. Thirty-eight percent of the patients consumed any alcohol after transplantation. The clinical interviews by the psychiatrist were the most successful method for identifying posttransplant alcohol use. Posttransplant alcohol use was significantly associated with prior nonalcohol substance use ($P<0.025$*), family history of alcoholism in a first-degree relative (*$P<0.025$*), and prior alcohol rehabilitation experience (*$P<0.05$*) but not with a prior psychiatric history or less than 6 months of pretransplant sobriety. The authors indicate that prospective monitoring, using a combination of methods, is the most accurate approach to identify alcohol consumption. With this type of accuracy, risk factors can be identified and alcohol use can be compared with alcohol-related morbidity posttransplant.*

(Psychosomatics 2001; 42:55–62)

Alcohol-induced liver disease (ALD) is the most common cause of liver disease in the United States. When end-stage liver disease occurs and abstinence fails to stop the progression of hepatic failure, liver transplantation is the only available treatment option. In the United States, alcoholic cirrhosis is the largest single diagnostic group receiving liver transplantation (27% of recipients in 1995),[1] and the number of patients receiving liver transplants for ALD is increasing in Europe.[2] Despite the success of transplantation for ALD, for which survival rates can exceed those of patients transplanted for other types of liver disease,[1] issues surrounding this patient population remain controversial. Both physicians[3] and philosophers[4] argue that patients with alcohol-induced cirrhosis should have lower priority for receiving a liver transplant than patients who develop other types of end-stage liver disease "through no fault of their own." Others perceive patients with alcohol-induced cirrhosis to be a patient group that

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would be noncompliant[5,6] or believe that alcoholism will prevent long-term survival because of redevelopment of liver disease.[7] However, before patients with alcohol-induced cirrhosis are categorically regarded as poor candidates, more research on outcomes and risk factors is needed.

Physicians, clinicians, and researchers have been studying patients with ALD both pre- and posttransplant for over a decade. Most often reported to date are descriptive data on this patient population, including the incidence of return to drinking over 1–2 years posttransplant, morbidity, and survival. Few reports have used a combination of measures to identify alcohol use. Patient interviews are the most commonly cited method, and the accuracy of reporting can be increased if administered by someone who is not a member of the transplant team.[8] Some studies have used biochemical markers to monitor alcohol use in the peritransplant period. However, Heinemann et al.[9] found an unacceptable specificity rate (as low as 20%–40%), resulting in a high rate of false positives when using carbohydrate deficient transferrin (CDT) levels to monitor pretransplant alcohol use. We contend that without a careful follow-up protocol with longitudinal, repeated measurements of alcohol use, alcohol outcomes, and biochemical markers, linkages of alcohol use to specific alcohol-related morbidity and mortality are difficult, if not impossible, to determine.

Therefore, the accuracy of determining alcohol use is the critical component when studying posttransplant outcome in this population. We present prospective data on the return to alcohol use following liver transplantation for alcohol-related liver disease. Using a variety of self-report, clinical, and biochemical measures, we tracked the amount and frequency of alcohol use for patients in our study. We are reporting on the time to first alcohol use posttransplant and the psychosocial history factors associated with return to alcohol use. We will compare different methods for tracking alcohol use and will discuss their utility in monitoring transplant recipients.

METHODS

Enrollment

All patients transplanted for ALD at the Thomas E. Starzl Transplant Institute (TESTI) from May 1998 to April 1999 were eligible for our study. At the time of enrollment, patients needed to be at least 3 months posttransplant and discharged from the medical facility. After agreeing to participate and signing informed consent, the patients were voluntarily enrolled in our study. The diagnosis of an alcohol-related liver disease was determined by a consensus diagnosis from interviews and examinations by our transplant surgeons, hepatologists, and psychiatry team (psychiatric nurse clinical specialists-MGF/JM and psychiatrist-AD). Patients with ALD had a history of excessive alcohol use defined as greater than 20 g ethanol/day for women or greater than 60 g ethanol/day for men.[10] The majority of patients had consumed this amount for 10 years or longer.

Most studies of transplant cohorts report the medical diagnosis (ALD) rather than the behavioral diagnosis. We also chose ALD as the diagnosis of inclusion, but unlike many other studies, we also interviewed our patients using Structured Clinical Interview for DSM-III-R (SCID)[11] and identified the DSM-IV[12] behavioral diagnoses of alcohol dependence or alcohol abuse.

During the period of study recruitment 44 patients had either a primary or secondary diagnosis of ALD. Of these 44, 36 were eligible for the present study, 5 additional patients died before initial enrollment at 3 months posttransplant, and 3 patients are beyond the 3-month enrollment criterion but were still hospitalized. Two of the 36 patients refused to participate in completing our alcohol measures and questionnaires, but these 2 nonparticipating patients continued to receive our standard follow-up care, including random blood alcohol levels (BALs), and they provided informed consent for us to check biochemical markers (specifically CDT). Our cohort is demographically similar to prior published studies of patients transplanted for ALD[1,13–15] and to a prior study from our center[16] (see Table 1 for cohort characteristics).

Pretransplant Variables

Before transplantation, patients underwent psychiatric evaluation during which pretransplant information on alcohol diagnosis, alcohol consumption patterns, length of sobriety, psychiatric history, other substance use, and alcohol rehabilitation experience were obtained and documented on a structured medical record form. At enrollment, the psychiatric diagnoses of alcohol abuse or dependence were confirmed with the SCID.[11] These data make up the pretransplantation items (see Table 1).

The duration of pretransplant sobriety was defined as the time (in months) from the last drink of alcohol to the date of transplantation. Before abstinence, most patients drank on a daily basis. For the others, the average weekly

alcohol usage was converted into average daily standard drinks for purposes of comparison. Standard drinks were defined as one shot of hard liquor, one 12-ounce beer, or 6–8 ounces of wine. Daily alcohol consumption was calculated as the average number of daily standard drinks, by patient report, converted into average daily grams of ethanol. This was calculated by converting the ounces of alcoholic beverage to ounces of pure ethanol and then converting the ounces into grams of ethanol. Years of drinking were defined as the years a patient drank at the average daily amount. For lifetime ethanol exposure (in kilograms), the average daily amount was multiplied by 365 days and then by years of drinking. (See Table 2 for pretransplant drinking profiles).

Procedures

Interviews and Questionnaires. Three measures of alcohol use since transplant were obtained. First, every 3 months for the first posttransplant year, patients prospectively completed a series of questionnaires containing the Alcohol-Timeline Followback questionnaire (ATLFB).[17] The ATLFB is a daily drinking measure that can profile the quantity, frequency, and pattern of alcohol use for the intervals between follow-up interviews. The ATLFB has good psychometric characteristics and allows the dimensions of drinking to be examined separately. It has high test-retest reliability and validity across multiple populations of drinkers derived from clinical and general population samples.[18]

When possible, the ATLFB was completed by interview with a research assistant. To maximize the honesty of questionnaire answers, especially with respect to alcohol use, a research assistant interviewed the patient separately from the transplant team. If patients were not returning to the transplant clinic at the questionnaire timepoint, the questionnaires were completed by telephone interview or mail. The patients were informed that this information was kept confidential, would not become a part of the medical record, and would not be revealed to any member of the transplant team. The research assistant was not blinded to the patients' diagnosis or history.

Second, a caregiver who knew the patient best (usually a spouse or family member) filled out a quantity-frequency questionnaire specifically asking about the patient's alcohol use since transplant. The caregiver questionnaire was patterned after the National Institute on Alcohol Abuse and Alcoholism Quantity-Frequency measure[19] and asked questions on the number of drinking days and the amount of alcohol consumed.

Third, clinic interviews during routine posttransplant clinic follow-up visits were performed by the transplant psychiatrist (AD) who was blinded to the data obtained by the research assistant. Responses to questions about alcohol use from the psychiatrist's interview were corroborated with information given by the patient to the transplant coordinators and surgeons and were recorded as quantity-frequency information with specific dates and amounts of use on a monthly calendar form. Patients were seen in the transplant clinic as medically indicated. However, when possible, most patients were seen twice weekly for the first month after discharge from their hospital admission, then monthly until 3 months posttransplant, then every 3 months thereafter.

TABLE 1. Background characteristics of 36 liver recipients

	%
Pretransplant Items[a]	
Alcohol Histories	
Alcohol diagnosis, % dependence	71
1st degree family member with alcoholism	60
Rehabilitation	
Any form of rehabilitation	46
Inpatient treatment	23
Outpatient treatment	29
Alcoholics Anonymous meetings	43
Mental Health	
Depressive disorder	36
Anxiety disorder	9
Substance abuse/dependence (nonalcohol)	51
Sociodemographics	
Men	89
Age, ≤50	50
White	92
Married	50
Education, ≤high school	83
Last occupation, nonprofessional[b]	78

Note: [a] These percentages obtained at baseline evaluation represent those patients that ever had the item prior to transplant.

[b] Based on respondents' most recent occupation, classified according to Hollingshead (1975).

Biochemical Markers

As part of our routine clinical care, random BALs were obtained on these patients when in clinic. BALs were performed by gas chromatography and considered positive if any alcohol was identified. Positive BALs are reported in mg/dL with a limit of detection at our lab of 10 mg/dL. Using a positive BAL and the patient's weight, additional information on the quantity of alcohol consumed can be

estimated. From the equation $Q = Vd \times Css$ where Q = loading dose (in grams of ethanol), Vd = volume of distribution (in liters) = 0.54 l/kg × patient weight in kilograms, and Css = concentration at steady state (in grams/liters), we can predict the loading dose of ethanol required to achieve a specific BAL.

As part of the research, every 3 months a CDT level was also obtained on each patient. CDTs are processed according to Axis Biochemicals immunoassay for quantitative measurement of CDT in human serum and are reported as CDT percentage in proportion to the total transferrin.[20] The CDT range for total abstainers is from 0% to 5%. CDT levels above 6% are considered to be positive for alcohol use. A CDT level can become positive after 2 weeks of heavy drinking (defined as 60 g ethanol/day) and even with abstinence the values normalize with a mean half-life of 14–17 days.[21]

At our center, as at other transplant programs, liver enzymes and erythrocyte mean cell volumes (MCV) are routinely collected as part of the posttransplant clinical care. Gamma glutamyl-transferase (GGTP) (normal range IU/L <65), aspartate amino transferase (AST) (normal range <40 IU/L), and alanine amino transferase (ALT) (normal range <40 IU/L) were reviewed for abnormalities. MCV (normal range 80–100 fL) was also examined as a marker of heavy alcohol use. Although alcohol can result in a significantly elevated MCV,[22] it may only be positive in 50%–64% of those who consume at least 80 g ethanol/day.[23] In a recent study,[24] the sensitivity and specificity, respectively, of these methods for very excessive drinkers were 0.37 and 0.92 for CDT, 0.53 and 0.76 for GGTP, and 0.33 and 0.94 for MCV. However, liver enzymes were difficult to interpret because of the frequency of rejection episodes and the recurrence of viral hepatitis in the first postoperative year. In addition, MCV were also difficult to interpret due to the frequency of elevated MCV from nutritional deficiencies pretransplant that persisted into the posttransplant phase. Therefore, this information was used descriptively to supplement the other data but not considered in the final analysis.

Statistical Analysis

Continuous variables are presented as the mean ± standard deviation (SD) and categorical variables as proportions. Alcohol outcome (time to first use) was calculated separately for each of the five measures (ATLFB, clinical interview, caregiver report, BAL, CDT) from the date of liver transplantation until the event of first alcohol use. Data from each patient were included until the end of the observation period or until the data were censored. Event history curves were generated using the Life table actuarial method for specific time intervals (i.e., the biochemical markers) and the Kaplan-Meier method for continuous variables (i.e., the quantity/frequency calendars). For specific psychosocial history variables, prevalence rates of return to drinking during the first year posttransplant were calculated by converting the raw data to person-years of observation.[25] The resulting rates are interpretable similar to lifetime rates. They represent percentages with a base of 100 one-year units of observation (i.e., equivalent of 100 persons followed for 1 year each). Differences in these prevalence rates were then evaluated by computing a test statistic *R* analogous to and distributed as chi square.[26,27] A *P*-value less than 0.05 was considered statistically significant. All analyses were performed using

TABLE 2. Drinking histories of liver recipients

	Median	Minimum	Maximum
Pretransplant sobriety, months			
Men ($n = 31$)	28	0[a]	288
Women ($n = 4$)	19	13	36
Years of heavy drinking			
Men ($n = 31$)	20	5	50
Women ($n = 4$)	11	4	23
Average daily standard[b] drinks			
Men($n = 27$)	10	2	68
Women ($n = 4$)	18	3	45
Lifetime ethanol exposure, kilograms			
Men ($n = 27$)	759	104	6,949
Women ($n = 4$)	339	131	3,813

Note: [a]While patients were expected to have at least 6 months sobriety, the transplant team was unaware that the patient continued to use alcohol.
[b]Standard drinks were defined as one ounce of hard liquor, one 12 ounce beer, or 6-8 ounces of wine.

Statistical Package for Social Sciences (SPSS) for Windows software (v.9.0).

RESULTS

Alcohol Use Posttransplant

Interviews and Questionnaires. Within the first year of the study, 8 patients reported using any alcohol. All 8 patients reported using alcohol to the transplant psychiatrist (AD) during transplant clinic interviews. The ATLFB questionnaire, administered by the research assistant, captured 6 patients who were using alcohol. One of these 6 patients first reported alcohol use on the ATLFB before revealing alcohol use to the team at the next clinic appointment. Two additional patients were known to the transplant psychiatrist and not to the research assistant because 1 patient declined to fill out the questionnaires and the other died before the next questionnaire time point. The caregiver's reports of the patients' alcohol use concurred in 5 of the 8 cases. No caregivers reported drinking in a person who did not first self-identify as drinking. For the remaining 28 patients none of these 3 measures indicated any alcohol use.

Biochemical Markers. A ninth patient who denied using alcohol had an elevated CDT (7%) at 3 months posttransplant. This was the only positive CDT result. Two patients had positive BALs but had already reported alcohol use to the transplant team. One patient who admitted drinking an occasional beer reported consuming 4 beers the night prior to clinic. The next morning in clinic he had a positive BAL of 165 mg/dL. Using the equation $Q = Vd \times Css$, we predicted the loading dose of ethanol required to achieve this BAL. For this patient, assuming minimal time in between ingestion and the sampling of the blood (Css), the loading dose required to reach this peak concentration would be 51 g of ethanol or approximately 5 beers. The other patient who had a BAL of 137 mg/dL could not recall the exact amount consumed but must have at least drank 93 g of ethanol or approximately 9 standard drinks.

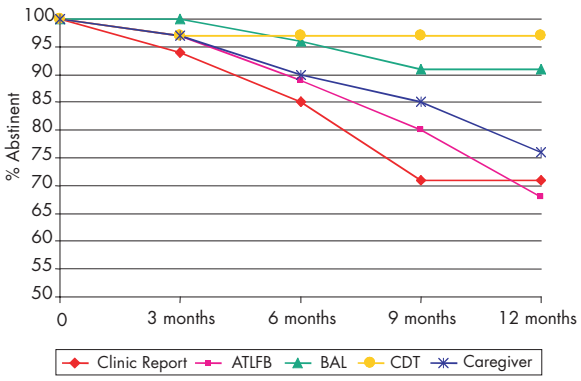
Liver enzymes were elevated in 5 of the 8 patients who admitted drinking any alcohol, though the majority of the time this was clinically interpreted as rejection or recurrent viral hepatitis. In only 3 of the total 9 patients who used alcohol, the liver enzymes were elevated enough to warrant liver biopsy for histologic examination. In 2 patients, the biopsy was suggestive of alcohol use (minor fatty deposits in one and steatosis in another). One of these patients claimed to be drinking sporadically but had steatosis on liver biopsy at 5 and 12 months posttransplant with a concurrent elevation in his MCV, liver enzymes, and an increase in CDT from baseline (though not into the positive range). The biopsy of the third patient showed evidence of recurrent hepatitis C.

All Methods. Considering all methods (interviews, questionnaires, and biochemical markers) and assuming that a CDT value of 7% represents a drinking episode, we have 9 patients who used alcohol (or an adjusted incidence rate of 37.8% for the first 12 months posttransplant). Event history analysis curves, plotted as the time to first drink for each method of alcohol use identification, provided greater detail of the timing of alcohol use events (Figure 1). One patient used alcohol by 2 months posttransplant, another used alcohol by 3 months, 4 others had their first drink by 6 months, and the remaining 3 patients drank between 7 and 12 months posttransplant.

Risk Factors for Alcohol Use

We examined the relationships between pretransplant characteristics (e.g., lifetime psychiatric histories, family history of alcoholism in first-degree relatives, and alcohol-use histories) and posttransplant alcohol use. We used all methods of alcohol use identification (i.e., a total of 9 patients who drank). Posttransplant alcohol use was significantly associated with prior nonalcohol substance use ($Z^2 = 5.35$, $P < 0.025$), family history of alcoholism in a first-degree relative ($Z^2 = 5.18$, $P < 0.025$), and prior alcohol rehabilitation experience ($Z^2 = 4.25$, $P < 0.05$) but not with a prior psychiatric history or less than 6 months of pretransplant sobriety (see Table 3).

FIGURE 1. Time to first drink posttransplant by various methods



DISCUSSION

Our first year data demonstrate a cumulative adjusted incidence rate of alcohol use since the transplant of 37.8%. By using event history analysis, the timing of drinking events became clearer. The first reported drinking episode by 2 months shows that patients may be at risk to resume drinking soon after transplant. Preliminary analysis of patients' background characteristics shows that certain groups may be at higher risk for relapse (e.g., patients with prior substance use, family history, and prior rehabilitation). Although it may seem surprising that prior alcohol rehabilitation would be associated with higher risk for relapse, these patients may have had more severe addiction histories requiring formal rehabilitation. Although widely studied as a factor associated with posttransplant relapse, in our study less than 6 months of sobriety pretransplant was not associated with posttransplant alcohol use.

Although we are currently focusing on any alcohol use and the time to first drink of alcohol, it is important to report on the morbidity of repeated alcohol-use episodes. Of those who drank, only 1 patient developed steatosis. However, during this 12-month period, 2 other patients required inpatient psychiatric hospitalization for alcohol use. Two additional patients drank heavily enough to warrant behavioral diagnoses; recurrent alcohol dependence in one and alcohol abuse in another.

Comparison of Methods

Clinical interviews obtained by the transplant psychiatrist were the most successful method for identifying posttransplant alcohol use. Establishing and maintaining open rapport with patients not only helped in the identification of alcohol use but also allowed an opportunity for continued reeducation on the dangers of alcohol consumption and recommendations for appropriate treatment. The ATLFB was just as effective as the clinical interviews but was limited by the number of patients willing to participate in research interviews. It appeared as if caregivers were reluctant to reveal any alcohol use unless they knew the patient had already reported use.

A positive CDT level may be able to capture episodes of covert drinking, but it will need to be further tested in liver transplant recipients and patients with liver disease. In our study, 1 patient who denied alcohol use had a positive CDT suggesting that alcohol consumption was daily and heavy (>60 g ethanol/day). Although BALs can be a valuable tool to monitor patients, depending on the amount consumed and the rate of metabolism, the BAL will only

TABLE 3. Prevalence of psychosocial history variables among 36 liver recipients

	Positive Alcohol Consumption		
Psychosocial History Variables	**Rate[a] (cases/100 persons)**	**S.E.**	**Test Statistic[b]**
Lifetime Prevalence			
Psychiatric history	43.3	6.58	1.01
No psychiatric history	34.4	5.86	
Substance use[c]	63.3	7.96	5.35[d]
No substance use	15.7	3.96	
Family history for alcoholism	51.4	7.17	5.18[d]
No family history for alcoholism	10.6	3.26	
Any rehabilitation	60.2	7.76	4.25[e]
No rehabilitation	21.7	4.66	
≤6 Months Sobriety	25.0	5.0	2.0
>6 Months Sobriety	41.3	6.43	

Note: [a] For specific psychosocial history variables prevalence rates of return to drinking during the first year posttransplant, were calculated by converting the raw data to person-years of observation. The resulting rates are interpretable similar to lifetime rates. They represent percentages with a base of 100 1 year units of observation (i.e., equivalent of 100 persons followed for 1 year each). Differences in these prevalence rates were then evaluated by computing a test statistic.

R analogous to and distributed as χ^2.

[b] Z^2 is distributed as χ^2 with 1 df.

[c] Substance use included stimulants, cocaine, opioids, psychedelics, and THC.

[d] $P \leq 0.05$.

[e] $P \leq 0.025$.

positively identify recent drinking. In our study, two patients had positive BALs, but they had also admitted drinking to the clinical staff before the lab results were available. Nevertheless, in these cases, a calculation using the blood ethanol concentration allowed us to determine the required ethanol loading dose, which clarified the patients' reported consumption. Thus, these biochemical markers may help in the determination of the quantity of alcohol use.

Comparison to Prior Studies

Using a yearly time interval, previous reports have shown the percentage of patients who use alcohol by the first posttransplant year[28] or the incidence of drinking after liver transplantation.[29] However, these rates are difficult to interpret because they do not correct for censoring because of patient death or patients lost to follow-up. Thus, with frequent monitoring and repeated data collection, we have captured the details of alcohol use within the first posttransplant year and have identified the time to onset of alcohol use. Some previous studies excluded patients who did not survive 6 months posttransplant[30] or were not alive at the time of cross-sectional interview of the cohort.[31] These methods could underestimate alcohol use as we found alcohol use can occur early posttransplant, even within the first several months.

Prior studies have used medical or surgical clinic interviews,[16,30,31] alcohol-use documentation in the medical chart, telephone interviews,[16,31] or laboratory evidence suggestive of return to drinking.[32,33] Some studies report randomly checking BALs to identify alcohol use.[16] Some studies presumed alcohol use on the basis of liver biopsy results[32,33] or liver enzyme profiles,[33] even when patients denied using alcohol. Some centers report using collateral sources (such as reports from transplant coordinators and family members) to help identify posttransplant alcohol use.[8,16] We found that to identify the quantity and frequency of alcohol use, a range of methods of follow-up are required, as not all methods concurred on every case of alcohol use. Comparing methods (such as verbal reports to physical markers of alcohol use, that is, BAL, CDT) provides greater accuracy, as patients may be reporting drinking episodes, but some are underestimating the amount or frequency of alcohol use.

We hypothesize that risk for return to drinking will increase with time posttransplant. At these points other measures, such as the ATLFB or CDT, may become more important in the overall identification of alcohol use. Our continued data collection in this prospective, longitudinal study will provide information on the quantity, frequency, and duration of posttransplant alcohol use. In addition, it will identify connections between the amount of alcohol consumed and specific alcohol-related morbidity and mortality.

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