OUTCOME OF LIVER TRANSPLANTATION IN CRITICALLY ILL PATIENTS WITH ALCOHOLIC CIRRHOSIS: Survival According to Medical Variables and Sobriety

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Abstract

Background. At our center from August 1989 to December 1992, 834 adults underwent orthotopic liver transplantation (OLT) using tacrolimus as the primary immunosuppressive agent. A total of 183 adults (22%) had alcohol-related liver disease. Patients with alcoholic cirrhosis had a better though not statistically significant 5-year survival rate compared with all other patients. We were interested in specific predictors of survival, particularly for alcoholic cirrhotics who were gravely ill at the point of transplantation.

Methods. For the 78 patients with alcohol-related liver disease who were United Network for Organ Sharing status IIA (critically ill) at the point of transplantation, variables of length of sobriety, alcohol rehabilitation,
and medical variables (ventilator support, dialysis, vasopressor support, degree of encephalopathy, and infection) were assessed for contribution to survival.

Results. Although there was a trend toward poorer survival in patients with the shortest length of sobriety (≤1 month), pre-OLT length of sobriety or alcohol rehabilitation did not predict survival. However, these patients tended to be in multiorgan failure and encephalopathic. Nevertheless, pre-OLT dialysis requirement was the only variable that predicted poorer survival (P<0.002). This study was not designed to evaluate recidivism. However, we know that 24% of these patients have used alcohol at some point after OLT.

Conclusions. Short pre-OLT length of sobriety may not predict which patients are likely to resume alcohol consumption after OLT, but it may identify patients in whom there will exist a variety of poor outcome variables. In our study, in these patients, post-OLT survival was associated with medical rather than alcohol history variables.

The controversy over transplanting patients with alcohol-induced liver disease began early in the development of hepatic transplantation. Early reports suggested that these patients were high operative risks, and posttransplant survival for alcoholic cirrhotics was poor (20% 3-year survival rate) [1]. It was suggested that patients with alcoholic cirrhosis had other alcohol-related organ system damage that compromised their ability to undergo transplantation [2]. In 1988, Starzl and co-workers [3] reported that alcoholic cirrhotics undergoing liver transplantation while receiving cyclosporine-based immunosuppression had survival outcomes similar to those of other etiologies. This has been verified in other studies showing that the short-term outcome (1- to 2-year actuarial survival rate) of alcoholic cirrhotics is comparable to [4-7] or better than [8,9] that of patients who receive transplants for other types of liver
The controversy of transplanting patients with alcoholic cirrhosis is still debated on moral and ethical grounds [10]. Certainly the patient's demonstrated commitment to sobriety is a significant factor in their selection for transplantation. However, there is no consensus between programs or clinicians as to criteria or eligibility on such grounds. A 1992 survey of 18 liver transplant programs across the United States demonstrated the enormous disparity in selection of patients with alcoholic liver disease, from one center being willing to consider patients who drank up until the transplant to other centers categorically refusing all alcoholics with less than 6 months of sobriety [11]. Nevertheless, alcoholic cirrhosis has become the most common indication for liver transplantation (21% of recipients in 1991) [9].

At our center and others, short pretransplant length of sobriety (i.e., <=6 months) did not reliably predict postransplant relapse [12-15]. However, short length of pretransplant sobriety was associated with longer hospitalizations (total and postoperative) [12]. Because pretransplant length of sobriety is routinely collected and used in candidacy determinations, we questioned whether it could it be useful for predicting medical outcome if not relapse. These previous studies of length of sobriety have investigated the total alcoholic cirrhotic group. We are particularly interested in whether length of pre-orthotopic liver transplantation (OLT*) sobriety was associated with medical outcome in patients who were critically ill at the point of transplantation. Patients with alcoholic cirrhosis who initially enter the transplant process so critically ill that they cannot accrue a significant length of sobriety or cannot participate in alcohol rehabilitation present some of the greatest clinical challenges to our team. Our study focused on this group as a high-risk group to clarify issues of outcome and identify variables of the medical and alcohol history that predict survival in these patients.
Study population. From August 1989 to December 1992, 834 adults underwent OLT at the University of Pittsburgh, using tacrolimus (FK506; Fujisawa Pharmaceutical Co., Deerfield, IL) as the primary immunosuppressive agent. A total of 183 patients (22%) had alcohol-related liver disease (ALD) as their primary liver disease. The diagnosis of alcoholic liver disease was made based on a history of alcohol abuse/dependence in conjunction with laboratory data (liver biopsy, serum alcohol levels, liver enzyme profiles). Patients with other types of liver disease received a similar evaluation, and the contribution of alcohol consumption to their liver failure was ruled out. Of the 183 patients with alcoholic liver disease, 78 (43%) were classified as new United Network for Organ Sharing (UNOS) status IIA (critically ill, requiring intensive care unit monitoring [old UNOS IV status]) at the time of transplantation. Of these 78 patients, 73% were male and the mean age was 49.5±9.7 years. Eleven patients were more than 60 years old. At our center, patients with ALD undergo psychiatric evaluation and attend alcohol rehabilitation when indicated. Depending on the individual’s needs, completion of alcohol rehabilitation and/or at least 6 months of demonstrated sobriety is a requirement for candidacy.

Definitions. Length of sobriety was defined as the time (in months) from a patient’s last drink of alcohol to the point of transplantation. Alcohol rehabilitation included any formal inpatient or outpatient alcohol rehabilitation program as well as regular (at least weekly) attendance at Alcoholics Anonymous meetings. Pre-OLT relapse refers to those patients who relapsed after formal alcohol rehabilitation but before transplant evaluation. These patients either repeated alcohol rehabilitation programs or had to demonstrate sobriety before they were considered for transplantation. The degree of hepatic encephalopathy was determined from the documented daily neurologic examinations by the treating physicians and nurses. It was graded as absent (no signs of confusion or disorientation), mild (minimally disoriented to place or time), moderate (obvious confusion or disorientation), or severe (grossly confused, agitated, hallucinating, or stuporous to comatose). For UNOS status, in our paper UNOS IIA is defined as intensive care unit bound (old
UNOS status IV) with chronic liver disease.

Procedure. A chart review of the 78 patients with ALD who were UNOS IIA was performed to identify additional variables of length of sobriety, attendance at alcohol rehabilitation, and medical variables (i.e., ventilator support, dialysis, vasopressor support, degree of encephalopathy, and infection) that were present at the time of transplantation. Length of sobriety was categorized as <= 1 month sobriety, > 1 to <= 6 months sobriety, and > 6 months sobriety.

Statistical analyses. Continuous variables are presented as the mean ± SD, and categorical variables are shown as proportions. The standard two-sample t test and one-way analysis of variance were used to test differences between means; differences in proportions were tested using either Pearson's chi-square test or Fisher's exact test. The Wilcoxon rank sum test, a nonparametric equivalent to the standard two-sample t test, was used for highly skewed data.

Patient survival was calculated from the date of liver transplantation until death, and primary graft survival was calculated from the date of liver transplantation until first retransplantation or patient death. Survival curves were generated using the Kaplan-Meier (product-limit) method (16) and compared by the log-rank (Mantel-Cox) test (17). Cox's proportional hazards model (18) was used to compute the relative risk of graft failure and relative risk of death and 95% confidence intervals. All tests were two-tailed. A P-value less than 0.05 was considered statistically significant. All analyses were performed using Statistical Package for Social Sciences SPSS for Windows software (SPSS, Inc., Chicago, IL).

RESULTS

Demographics. At the time of OLT, 19 patients were on hemodialysis, 15 were on antibiotics for infections, 17 were on vasopressor support, and
35 were on ventilator support. Hepatic encephalopathy was determined from documented mental status examinations. The degree of hepatic encephalopathy was graded as not present (n=23), mild (n=14), moderate (n=20), or severe or comatose (n=21). Laboratory values (mean ± SD) for the group included total bilirubin: 10.2±12.6 mg/dl, albumin: 2.9±0.6 g/dl, prothrombin time: 15.7±2.5 sec, and ammonia: 81.4±33.4 µmol/L.

Of the 78 patients, 19 (24%) had undergone some form of alcohol rehabilitation before transplantation, most before evaluation for transplantation. Eleven patients had relapsed after their first alcohol rehabilitation. Pre-OLT length of sobriety (known for n=72) was <= 1 month for 10 patients, > 1 to 6 months for 21 patients, and > 6 months for 41 patients. Out of the 31 patients with <= 6 months of sobriety, 20 had not undergone prior alcohol rehabilitation and were not medically stable enough to attend rehabilitation before transplantation. Of these 20 patients, 17 were in multiorgan failure at the time of transplantation. Therefore, medical stabilization to allow completion of pretransplant alcohol rehabilitation was not possible. For six patients, the pre-OLT length of sobriety was unknown. All six of these patients were on ventilator support at the time of transplantation and most were stuporous to comatose.

Medical and alcohol variables predicting survival in critically ill ALD patients. Pretransplant length of sobriety was not statistically associated with patient survival, although there was a trend toward poorer survival in those patients with the shortest length of sobriety (<= 1 month) (Fig. 1). Similarly, primary graft survival appeared to be worse in those patients with <= 1 month sobriety, although this was not statistically significant (Fig. 2). Compared with other alcoholic cirrhotics, patients with the shortest length of sobriety tended to be sicker, having other organ system involvement and greater physiologic decompensation in addition to liver failure (Table 1). Only dialysis (n=19) was independently associated with survival (P=0.002). None of the other medical factors analyzed were associated with survival (Table 2). Multivariate analysis on
all factors showed dialysis was independently associated with mortality. Short length of pre-OLT sobriety was associated with dialysis (Table 1). Therefore, the association between survival and short length of sobriety was attributable to dialysis. There were no differences in survival for those who underwent alcohol rehabilitation and those patients who did not (P=0.74, log-rank test).

Recidivism in critically ill ALD patients after OLT. Although we were not specifically looking at recidivism as an outcome, we follow our patients closely in our postOLT clinic, and the transplant nurse coordinators know the details of each patient’s clinical course. Specific alcohol measures are not used, although blood alcohol levels are checked randomly if alcohol use is suspected. From our interviews in the post-OLT clinic, we have determined that 15 patients (24% of the patients surviving >6 months after OLT) have used some alcohol after OLT. Although this percentage of recidivism is similar to that of a prior study at our center that focused on alcohol relapse after OLT (12), this data represents only those patients who were critically ill at the point of transplantation and therefore is not representative of our total cohort of patients who received transplants for alcoholic cirrhosis. Statistical analysis was not done and we did not separate each group for analysis.

Conclusions. Survival is only one measure of outcome, although it is the primary measure of success. Since length of sobriety is commonly used as the benchmark for transplant candidacy, we investigated whether it had an impact on survival in alcoholic cirrhotics, particularly when the patient was critically ill. In our study, we examined pretransplant medical variables and variables of the alcohol history (length of sobriety and rehabilitation) to determine the contribution to survival. Although the lowest survival rate occurred in critically ill alcoholics with the shortest length of sobriety (<=1 month), this group was more likely to be on dialysis, on vasopressor support, and severely encephalopathic. However, even in
this group, pretransplant length of sobriety or prior alcohol rehabilitation did not predict posttransplant survival. Dialysis was the only variable that was statistically correlated with poor survival (P<0.002). Renal failure requiring hemodialysis far outweighed any contribution of other medical or addiction variables to survival.

**DISCUSSION**

Before patients with alcoholic cirrhosis were routinely receiving transplants, the predictive value of pre-OLT renal function was demonstrated for patients with other types of liver disease. Of 27 pre-OLT clinical and laboratory variables studied, serum creatinine >1.72 mg/dl was the greatest risk factor for post-OLT mortality (19). Although this was in the short-term survival period (i.e., deaths prior to discharge from the transplant hospitalization), in our study, dialysis was associated with mortality in long-term, 5-year survival. An earlier study at our center found elevated preoperative creatinine levels to also be associated with graft failure after OLT (odds ratio of 1.12 for each 1-mg increase) (20).

Alcoholic cirrhosis has become the most common reason for liver transplantation, but it can still cause significant controversy with patient selection. A patient who has a short length of sobriety or is too encephalopathic to participate in an adequate psychiatric and addiction assessment or attend recommended alcohol rehabilitation presents one of the greatest challenges for candidate selection. Fortunately, these situations are not common. In a 3.5-year period at our center, only 20 patients with alcoholic cirrhosis had no alcohol rehabilitation experience, were sober for <=6 months, and were too medically unstable to attend rehabilitation before transplantation. The majority of these patients were earlier in the study period, prior
to 1991. Seventeen of these patients were in multiorgan failure. In addition, an earlier study at our center showed that pretransplant length of sobriety did not predict posttransplant return to alcohol consumption (12).

Patients with end-stage liver disease are not expected to survive long without transplantation. Advanced alcoholic liver disease carries a 5-year survival rate of only 50% (21), a prognosis worsened by ascites, portal hypertension, bleeding varies, hepatic encephalopathy, and hepatorenal syndrome (22). For patients with alcoholic cirrhosis, delaying transplantation may have fatal results. In a study of patients referred for transplantation, alcoholic cirrhotics with end-stage liver disease who did not undergo transplantation had significantly poorer survival than alcoholics who did at 1-year (50% vs. 78%) and 2-year (30% vs. 73%) follow-up; in this study, the nontransplanted group included patients initially deemed “too well” to receive a transplant (6). However, even survival in the alcoholic group considered “too well” for transplantation declined to 59% at 24-month follow-up (6). At one center, chemically dependent patients had a pretransplant death rate of 48% compared with 34% for the non-chemically dependent patients (23). Of the chemically dependent patients whose pretransplant cause of death was known, 48% died while in the process of meeting pretransplant sobriety/rehabilitation requirements (23). In fact, in 1986, a legal precedent was set with the Allen v Mansour case, in which the United States District Court ruled Medicaid’s 2-year abstinence requirement was “arbitrary and unreasonable.” This decision was based on evidence that alcoholic cirrhotics could deteriorate into high operative risks or may not survive this time period (24).

At our center, criteria for candidacy include the explicit admission of alcoholism by the patient and family and a commitment to effect behavioral change. If these criteria are established, our center’s
philosophy has held that the imposition of an arbitrary period of abstinence prior to transplantation could be medically unsound or even inhumane (3). However, we do not support or encourage a short length of pretransplant sobriety. We expect patients with addiction histories to complete recommended rehabilitation and demonstrate sobriety. In addition, aspects of the patient’s social, emotional, and addiction history that may identify their long-term ability to care for themselves, remain sober, and comply with medical treatment are weighed in the decision. For example, multiple failed attempts at abstinence or inadequate social supports would make a short length of sobriety less acceptable. Fortunately, most patients can achieve a significant period of sobriety before transplantation. At our center, the average length of sobriety is 12 months at the point of transplant evaluation (25), and patients are frequently monitored during the pre-OLT period to verify continued abstinence. However, in exceptional cases, rather than allow a patient’s condition to deteriorate while attempting to meet sobriety requirements, our choice has been to proceed with the transplant before the operative risk becomes too great. Nevertheless, over this 3.5-year period at our center, these exceptions were rare and now are almost nonexistent because of the shortage of organs and our attempts to utilize this limited resource in a consistent and equitable manner.

If outcome in patients with alcoholic cirrhosis who are gravely ill at the point of transplantation is compromised because of specific medical factors, such as dialysis, perhaps decisions of candidacy should be determined more by medical criteria. Nevertheless, current data on survival in alcoholic cirrhotics are encouraging. A previous study at our center showed that the 6-month survival rate of all cirrhotics listed as UNOS IV (old classification) at the time of transplantation was 68%, compared with 89% for patients who were listed as UNOS I (26). In our study, the 1-year actuarial survival rate of all alcoholic cirrhotics who were UNOS IIA was 81%, and the survival rate of the most medically compromised patients(<=1 month
sobriety) was 70%. However, long-term medical and psychiatric follow-up is necessary before we can identify pre-OLT variables that predict outcome and can guide clinical decisions.

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Figure 1: Kaplan-Meier patient survival after liver transplantation according to length of sobriety.
Figure 2. Kaplan-Meier primary graft survival after liver transplantation according to length of sobriety.

Table 1. Length of sobriety and medical variables: cross-tabulations and chi-square tests

<table>
<thead>
<tr>
<th>Length of sobriety</th>
<th>≤1 month n (%)</th>
<th>1-6 months n (%)</th>
<th>&gt;6 months n (%)</th>
<th>Total n (%)</th>
<th>Chi-square tests (P)</th>
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</thead>
<tbody>
<tr>
<td>On dialysis</td>
<td>6 (60%)</td>
<td>6 (28.6%)</td>
<td>5 (12.2%)</td>
<td>17 (23.6%)</td>
<td>0.005</td>
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<tr>
<td>On vasopressors</td>
<td>4 (40%)</td>
<td>1 (4.8%)</td>
<td>9 (22%)</td>
<td>14 (19.4%)</td>
<td>0.05</td>
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<tr>
<td>On ventilator</td>
<td>6 (60%)</td>
<td>6 (28.6%)</td>
<td>17 (41.5%)</td>
<td>29 (40.3%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Infection</td>
<td>1 (10%)</td>
<td>1 (4.8%)</td>
<td>9 (22%)</td>
<td>11 (15.3%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>8 (80%)</td>
<td>14 (66.7%)</td>
<td>31 (75.6%)</td>
<td>51 (73.6%)</td>
<td>0.66</td>
</tr>
<tr>
<td>Survival analysis</td>
<td>$P$</td>
<td></td>
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<td>------------------------</td>
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<td>Dialysis</td>
<td>0.002</td>
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<td>Gender (female)</td>
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<td>Infection</td>
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Table 2. Patient survival and medical variables