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EDITORIAL

When a liver transplant recipient goes back to alcohol abuse: Should we be more selective?

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Abstract

Alcoholic liver disease (ALD) is one of the most common indications for liver transplantation (LT). However, it has always remained as a complicated topic from both medical and ethical grounds, as it is seen for many a "self-inflicted disease". Over the years, the survival rate of transplanted patients has significantly improved. The allocation system and the inclusion criteria for LT has also undergone some modifications. Early LT for acute alcoholic hepatitis has been subject to recent clinical studies with encouraging results in highly selected patients. We have learned from studies the importance of a multidisciplinary evaluation of candidates for LT. Complete abstinence should be attempted to overcome addiction issues and to allow spontaneous liver recovery. Risk factors for relapse include the presence of anxiety or depressive disorder, short duration of sobriety pre-LT and lack of social support. The identification of risk factors and the strengthen of social support system may decrease relapse among these patients. Family counseling of candidates is highly encouraged to prevent relapse to alcohol. Relapse has been associated with different histopathological changes, graft damage, graft loss and even decrease in survival among some studies. Therefore, each patient should be carefully selected and priority is to continue to lean on patients with high probability of success. The ethical issue remains as to the patient returning to drinking after the LT, hindering the way for other patients who could have received the same organ.

Key words: Liver transplantation; Alcoholic liver disease; Alcoholic cirrhosis; Selection criteria; Relapses

Core tip: Alcoholic liver disease is one of the most common indications for liver transplantation (LT). The selection criteria of the majority of transplant programs require 6-mo of complete abstinence, with the aim to allow spontaneous liver recovery and to overcome addiction issues. The evaluation of LT candidates should be multidisciplinary with a strong emphasis in family and social support and a strong patient commitment of abstinence to prevent relapses.

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Liver transplantation (LT) has become an accepted therapy for some patients with end-stage liver disease. The use of LT for alcoholic liver disease (ALD) continues to be controversial from both medical and ethical point of view[1,2]. However, it remains a common indication for LT worldwide[1,3,4].

One of the strongest ethical arguments against LT for ALD is the probability of relapse. For a patient to be listed as candidate for LT, 6 mo of abstinence must be achieved in most liver transplantation centers. Studies differ in the validation of this "6-mo rule" as well as in the real impact that relapse to drinking could have on the transplanted liver[5-8]. Recent studies have shown similar survival rates among LT for ALD and other chronic causes of end-stage liver disease recipients[1]. Early transplantation for acute alcoholic hepatitis (AAH), for example, has promising results[9,10]. However, a special multidisciplinary approach for alcoholic patients pre- and post-LT should be pursue with a goal of complete abstinence when possible.

Ever since Starzl *et al*[11], reported in 1963 the first three successful cases of liver transplantations in humans, an interest in increasing the use of life-saving intervention has evolved. By 1968, these investigators, reported the results of seven patients, one of them with 1-year post-transplant survival[12]. The next decade was characterized by important advances in tissue preservation, surgical techniques, control of infections and advances in immunosuppressive therapy with decrease in tissue rejection[13]. By 1979 there were about 318 human LT reported worldwide. The majority of them, performed at the University of Colorado (United States) and at the University Hospital at Cambridge and King's College Hospital (United Kingdom)[14]. In 1979, 15 years after the first LT, the 1-year survival rate had improved from to 28% to 50%[13]. Years later, the Organ Procurement and Transplantation Network was established by the United States government in 1987, operating under the United Network for Organ Sharing (UNOS)[15].

After the experimental years and over the last decades, there have been several changes in liver transplant indications and allocation system (UNOS). Initially, priority allocation was established based on "sickest first", meaning ICU's patients with acute complications - acute esophageal varices, hepatorenal syndrome or portosystemic encephalopathy[15]. The original allocation system was based on the Child-Turcotte-Pugh score. This was later proven to be sub-optimal in predicting the mortality and prioritization of patients[15]. In 2002, the national UNOS adopted the model for end stage liver disease (MELD) allocation system[16]. The MELD was developed to screen for short-term prognosis, and prioritize candidates according to disease severity, based on serum creatinine, serum bilirubin, international normalized ratio of prothrombin time (INR) and serum sodium[17].

Given the geographical disparity in organ allocation as seen by the disparities in waiting list and differences between units of organ, in 2013, the "Share 35" policy was implemented. Such policy instructs to give priority to candidate recipients for LT with MELD > 35[18]. Following this implementation, the waiting list for patients with MELD > 35 decreased from 18 d to 9 d in the last 2 years[19].

Currently, the accepted indications for LT are: acute liver failure, cirrhosis (with complications), liver metabolic diseases with systemic manifestations and systemic complications of chronic liver disease[20]. The latest guidelines for LT emphasize the importance of a multidisciplinary evaluation process; hepatology evaluation, surgical evaluation, laboratory testing, cardiac evaluation, hepatic imaging, psychiatry, psychology or mental health professional consultation, social work evaluation, financial and insurance counseling and nutritional evaluation[20].

As noted, ALD accounts for the second most common indication for LT[3,21]. ALD comprises subclinical biochemical damage, fatty liver, steatohepatitis, fibrosis and cirrhosis that can end up in end stage liver disease[21,22]. Other alcohol-induced entities include AAH and hepatocellular carcinoma[3,21,22]. On alcohol-induced injuries, the current guidelines continue to enforce the minimum of 6-mo of abstinence, this time is required to allow addiction issues to be addressed and helps in allowing spontaneous liver recovery. For patients with cirrhosis, LT is recommended once complications (ascites, hepatic encephalopathy, variceal hemorrhage or hepatocellular dysfunction) results in a MELD score > 15[20]. An entity that requires special consideration is AAH, a syndrome presenting with abdominal pain, fever, jaundice and acute hepatic decompensation[3]. Without transplantation, the probability of death in this group of patients is high and 70%-80% die within 6 mo[9,23,24].

Significant controversy on LT for alcoholic hepatitis exist[9]. Mathurin and coworkers examined patients that were not responding to medical treatment and that underwent an early liver transplant. Those pati-

ents that received an early LT had a significant higher survival than the patients in the medical therapy group[9]. Despite the favorable results, it should be noted that all the patients in this study were carefully selected and that 90% of non-responders to medical treatment were excluded due to a predisposition to addiction or unfavorable social or familial profiles. One of the key inclusion criteria for the enrollment in this pilot study, was the patient agreement to adhere to total alcohol abstinence. After LT, 3 out of 26 had alcohol consumption (11.5%). The authors concluded that the low rate of alcohol relapse was probably related to the carefully selection of recipients. More recently, Im and associates conducted a similar study in the United States, where early LT, in highly selected patients with severe alcoholic hepatitis, resulted in improved outcomes[10].

The main concerns remain the high chance of alcohol intake relapse after LT, which has been reported from 7%-95%[25]. The significant differences among data can be explained by differences in the use of terms "recidivism" and "relapse", which some studies utilize to define any alcohol intake, and in others to define heavy drinking[1,3,26-28]. Relapse to "harmful drinking" has been reported in 8%-21% of LT recipients[7,8,29-31]. Occasional drinks "slips", may not cause a significant graft damage, but with a history of alcoholism, it would be difficult to predict if these so called "slips", could end up in complete relapse and harmful alcohol abuse[1,32,33].

In an attempt to predict this risk, several analyses have been done[29,34-36]. Yates and coworkers used the high-risk alcoholism relapse (HRAR) scale, which consisted of evaluating the duration of heavy drinking, usual number of daily drinks, and inpatient treatment due to alcohol consumption[37]. In another study, 387 LT recipients were retrospectively analyzed by De Gottardi *et al*[29], finding an 11.9% relapse (harmful alcohol consumption). The presence of anxiety or depressive disorder, duration of sobriety of less than 6 mo, elevated HRAR score and age, were among the factors associated with increased risk of alcohol relapse[29].

Alcohol-induced injuries to allografts have been well documented[8,28,38]. In a retrospective study, Rice and coworkers evaluated the association between relapse and graft damage[28]. In this study, any alcoholic relapse was associated with increased risk of damage to the transplanted liver and particularly heavy drinking was associated with allograft loss (P = 0.008)[28]. Although most studies have found evidence of liver damage among relapse patients, they differ in reference to alcohol relapse and mortality rates[27,38].

Despite the established criteria regarding the 6-mo rule of abstinence, the sobriety time before LT is a strong predictor of relapse among recipients[6]. While on the waiting list, mandatory blood alcohol levels, urinary ethyl glucuronide and assistance to alcohol addiction units (AAU) could be used as strategies to prevent relapses[26,39,40]. In addition, the support of an AAU within the LT center has showed to decrease the prevalence of alcohol relapse. Carbonneau *et al*[40] studied the incidence of drinking while on the LT waiting list. They randomly checked blood alcohol levels, and 17% of them were found to relapse on drinking alcohol while on the LT waiting list. The time of relapse ranged from 2-23 mo. Interestingly, the increase of random blood alcohol level measurements was related to a decrease in alcohol use. Patients may have had lower alcohol ingestion by the fear of being caught and withdrawn from the list[40].

Addolorato *et al*[26] implemented the presence of an AUU in the LT center. Patients who were follow-up at the AUU had a lower relapse than the patients who were not seen by this unit (16.4% *vs* 35.1% respectively).

LT as a therapeutic option for alcoholic liver disease continues to be controversial. Different ethical and medical opinions preclude it to be fully accepted. Organ allocation for patients in whom the liver damage is considered to be self-inflicted may not be well accepted[2,29,41]. Yet, this practice continues. This may be causing conflict with the public opinion and may result in an unfavorable change in willingness to donate[2,5].

In an effort to assess the opinion on allocation priorities for LT, Neuberger *et al*[42] conducted a survey based study among general public, family doctors and gastroenterologists. Among groups a hypothetical alcoholic man and a prisoner were found to have lower priority for liver transplant allocation[42].

It is clear that given the current organ shortage, priority should be given to patients with high probability of success. For ALD, complete abstinence should be sought to allow possible liver repair and avoid unnecessary LT. Abstinence pre and post LT may be reinforced by the implementation of strict clinical and laboratory screening for alcohol relapses and strong support groups. AAU and strong social support system along with closer follow-up post transplant may help in preventing relapse on alcohol. The selection criteria should play a strong emphasis of the family environment and social structure and family counseling and alcohol abstinence should be also sought from family members prior to transplanting the patient with alcoholic liver disease to prevent future relapse. In cases of AAH, more multi-center studies with larger samples are needed to make solid conclusions.

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