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TOPIC HIGHLIGHT

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Liver transplantation in acute alcoholic hepatitis: Current status and future development

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Abstract

Acute alcoholic hepatitis (AH) is a distinct clinical entity amongst patients with chronic alcohol abuse. Patients with severe AH are at risk of dying in about 20%-25% cases despite specific treatment with corticosteroids and/or pentoxifylline. Clearly, a need for an additional more effective treatment option is unmet currently. Liver transplantation (LT), a definitive treatment option for alcoholic cirrhosis requires 6 mo abstinence. However, this rule cannot be applied to patients with AH as these patients are actively drinking prior to their presentation. Shortage of donors, ethical issues, and fear of recidivism after transplantation with less than 6 mo pretransplant abstinence are some of the reasons behind this rule of 6 mo of abstinence and hesitancy of transplanting patients with AH. These issues are debated at length in this manuscript. Further, retrospective studies have shown that patients undergoing transplantation for alcoholic cirrhosis and having histological changes of AH have been shown to fare as well when compared to patients without these histological changes. Recently, French workers have reported a case matched prospective study showing encouraging data on the usefulness of LT for patients who are non-responders to corticosteroid and/or pentoxifylline therapy. Future studies are needed to identify patients with severe AH who are going to benefit most with LT. In the light of emerging data on the efficacy of LT in improving survival of patients with severe acute AH who do not respond to corticosteroids, the time is ripe to re-evaluate our policy of LT in patients with AH.

Key words: Alcoholic hepatitis; Liver transplantation; Recidivism; Alcohol abstinence

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NEED FOR LIVER TRANSPLANTATION IN ALCOHOLIC HEPATITIS

Acute alcoholic hepatitis (AH) is a distinct clinical syndrome that manifests as jaundice, abdominal pain, fever and acute hepatic decompensation of variable degrees depending on the severity of the disease, and may commonly be associated with underlying chronic liver disease[1]. It is caused by excessive alcohol consumption of prolonged duration which is invariably heavy and increased in the last few weeks to months prior to presentation[1]. Patients with mild to moderate AH may respond to conservative management and abstinence. However, patients with severe disease (discriminant function index or Maddrey score of $\geqslant$ 32) have an overall mortality of

about 40% within 6 mo[1]. Current available treatment options are corticosteroids and pentoxifylline but have limited efficacy, with a survival benefit of only around 50%[2,3]. Clearly, there is a need for more effective and definitive treatment options in order to improve prognosis and outcome of patients with severe AH.

CURRENT STATUS OF LIVER TRANSPLANTATION IN AH

Liver transplantation (LT) is a definitive treatment option for patients with end-stage liver disease who have > 10% risk of dying within 1 year. LT is an accepted treatment modality for patients with alcohol related chronic liver disease (ALD). The outcome after LT for ALD is as good as for other causes of liver disease[4]. However, LT as a treatment option for patients with severe AH remains controversial despite the fact that it is an established treatment option for most etiologies of acute liver failure (ALF)[1]. Many issues preclude physicians and transplant hepatologists to uniformly adopt this treatment modality for this group of acutely sick patients. These issues are related to (1) ethical concerns of transplanting patients with active alcohol abuse; (2) lack of applicability of 6 mo abstinence rule to these patients as by definition AH occurs among people who are currently actively drinking until at least a few weeks prior to presentation; and (3) risk of recidivism to alcohol drinking after LT that affects the graft and patient survival.

Ethical concerns and issues

One of the major ethical concerns is a shortage of organs for LT. The public opinion about a patient who is actively abusing alcohol is that this problem is self-inflicted by the patient and should be his or her own responsibility[5]. Why should the liver be given to someone who has reached this disease stage which could have been avoided with timely alcohol abstinence. However, in our opinion this argument is not justified for many reasons. First, alcoholism and ALD should not be clubbed together since significant liver disease develops in only 15% of all people who drink alcohol excessively[6]. So, clearly other etiologies such as genetic predisposition, hepatitis C and other viral infections, such as influenza[7-9], may contribute to the development of the disease. Further, there are other liver diseases such as hepatitis B, hepatitis C, non-alcoholic fatty liver disease and acetaminophen overdose where patient behavior is an important component either in the acquisition of these diseases or in their adequate management. The question therefore, is why should ALD be treated differently from these diseases?

The 6 mo abstinence rule

The criteria for listing patients with ALD on a LT recipient list are similar to any other chronic liver disease qualifying for LT except that in ALD there is an additional requirement for abstinence for ≥ 6 mo ("6 mo rule")[10]. The same "6 mo rule" is being applied currently in transplant centers, including in the United States, for patients with AH[11,12]. Patients with severe AH who do not respond to corticosteroids or pentoxifylline have a mortality of 50%-75% at 6 mo[12]. Hence, this rule of 6 mo abstinence cannot be applied if these patients are to be better managed and salvaged. Clearly, there is an urgent need for changing this policy of abstinence of 6 mo[12]. Before we take this drastic action, let us examine critically what the effect of abstinence of 6 mo on the rate of alcohol relapse after LT (recidivism) has been.

The most authoritative prospective study on this issue is reported by DiMartini *et al*[13] on a follow up of 167 patients with orthotopic liver transplantation (OLT) who underwent OLT after a minimum abstinence period of 6 mo. The authors showed that although pre-OLT abstinence duration was a predictor on the frequency as well as time to relapse to alcohol abuse after OLT, even in patients who were sober for 36 mo, only 40% remained sober after OLT[13]. The lack of correlation of post-OLT recidivism with 6 mo abstinence prior to OLT was also shown by McCallum *et al*[14] in their systematic review of 11 studies. Only 2 of the studies showed an association while 9 studies did not show an association between 6 mo pre-OLT abstinence and post-OLT recidivism[14]. Does this mean that recidivism after OLT is not important? The answer is no. What we can say so far is that there is no evidence for the 6 mo abstinence rule to be considered as a necessary pre condition for OLT. Let us now examine recidivism after OLT, its frequency, its impact on the graft and patient survival and the factors predictive of recidivism.

Recidivism after orthotopic liver transplantation

The rate of alcohol relapse use after LT varies according to different authors. In a review of 22 studies on alcoholic liver disease, relapse ranged from 3% to 49%, with graft dysfunction and death ranging from 0% to 27% and 0% to 6.5%, respectively[6]. One problem is that these rates include any amount of drinking, including social drinking. For the purposes of graft and OLT outcome, the consideration should be a relapse to harmful drinking sufficient to cause liver damage[14]. Heavy drinking after LT in alcoholic liver disease as a whole is reported in less than 10% of patients[15]. Moreover, the definition of harmful drinking varies from study to study[14]. Further, documenting alcohol use by history taking is not always accurate since patients may not always tell the truth[16]. Even after accounting for recidivism for harmful drinking, the 5-year graft survival rates are better in patients with ALD compared to patients with hepatitis C induced liver disease[17]. This is because recurrence of HCV is almost universal after OLT with 20%-25% patients developing cirrhosis within 5 years of OLT[18]. However, in a retrospective study on long-term follow up (median follow up of 7.5 years), patients who relapsed to harmful drinking had poorer survival when compared to abstainers (45% *vs* 86%, $P < 0.05$)[19]. Therefore, the issue of recidivism is essential to accurately identify patients

prior to OLT who are likely to relapse to harmful drinking after the OLT. In a systematic review on 22 studies, McCallum *et al*[14] identified factors consistently associated with recidivism-younger age (2 studies), associated poly substance abuse (3 studies), lack of social support (7 studies), family history of alcohol abuse in a first degree relative (3 studies), poor response to previous rehabilitation programs (2 studies) and non-compliance (2 studies). Concomitant mental and psychiatric disorders were associated in 2 studies while 2 studies did not find this association. A lack of insight was not a predictor in any of the 3 studies[14].

DATA ON LIVER TRANSPLANTATION IN ALCOHOLIC HEPATITIS

Before implementing and rethinking our policy of LT in patients with severe AH, let us first examine the available data on the outcome of patients with AH after OLT. These data are limited and restricted to retrospective analyses. In one such study, among a series of 246 cases of ALD, 110 underwent OLT. About 7.2% (8 cases) had histological evidence of AH on the explants. Comparison of these 8 cases with the remaining 102 cases without histological AH in the explants showed similar patient survival post-OLT recidivism[20]. Similar data have been reported by other investigators[21-23]. Recidivism rates were similar irrespective of presence or absence of AH in the explant[21]. Further, there were no differences on the outcome between patients with mild AH and severe AH[21]. The problems with these studies is their retrospective design and the fact that histological changes of AH can persist for a long duration even after response to treatment[23]. Prospective data on the use of LT in this group of patients with severe AH are scant. In a recently reported study at the American association for the study of liver disease 2009 in Boston from the French group, 18 patients with severe AH non-responsive to steroids (NRS: defined as $\geqslant$ 0.45 Lille score) were studied prospectively to assess the role of LT[24]. Each case was matched to a control patient (who did not undergo LT and continued to receive medical management) for age, sex, DFI and Lille score. Patients received LT within an average of 9 d from the day they were labeled as NRS. At the end of 1 year, patient survival in the transplanted group was higher compared to those not receiving LT (83% *vs* 44%, $P = 0.009$)[24]. Among the non-transplanted patients, 50%-90% deaths occurred within first 2 mo. Only one patient relapsed to drinking about 2.5 years after LT. That patient was classified a social drinker without any impact on the graft function[24].

CURRENT STATUS AND FUTURE PROSPECTS

AH remains, for the moment, a contraindication for transplant in the majority of liver centers in the United States. However, we think that the time is right to re-evaluate our policy[12]. Current data clearly show that LT is a definitive treatment option for the group of patients with severe AH who continue to deteriorate despite intensive medical treatment. Further, 6 mo of abstinence does not affect recidivism after OLT. However, before we routinely use this modality of definitive treatment for severe AH, we need to (1) derive long-term outcome of patients and graft in this setting; (2) determine the best criteria to identify candidates with the least risk of recidivism to harmful drinking; and (3) develop homogeneity in the definition of harmful drinking, drinking patterns and alcohol abuse questionnaires. Then we will be able to implement guidelines that are fair and scientifically sound for the optimal utilization of available organs in the setting of AH in the same way we are doing for other etiologies of ALF. Although the destination is far, there seems to be light at the end of the tunnel which will allow us to make the right decision and a life or death difference in many cases of severe AH.

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