Journal of Gastrointestinal & Digestive System

Rasheed, et al., J Gastrointest Dig Syst 2015, 5:5
DOI: 10.4172/2161-069X.1000334

Review Article Open Access

Place of Liver Transplant in Alcoholic Hepatitis

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Rec date: July 21, 2015; **Acc date:** August 29, 2015; **Pub date:** September 5, 2015

Abstract

In the United States and Europe, after viral hepatitis, alcoholic liver disease (ALD) is the second most commonly recognized indication for liver transplantation. Issues of conflicting data on six-month abstinence, eligibility criteria for selection of patients, and clarity of definition of post-transplant relapse are still under debate. Despite high early mortality, acute alcoholic hepatitis continues to be a contraindication to transplant despite data demonstrating the successful outcome of liver transplantation in these individuals. Disagreements arise due to the trepidation that these patients may relapse resulting in damage to the graft or non-compliance causing graft rejection. However, 1-year, 3-year, and 5-year patient and graft survival after transplant are comparable to transplantation for other etiologies. Studies have revealed that pre-OLT abstinence is a poor forecaster of post-OLT relapse. Life-threatening liver failure can potentially develop in this time frame, resulting in augmentation in waitlist mortality. Due to the paucity of available livers for donation, it is considered by many authorities to be obligatory to choose candidates with a lesser risk for relapse with the utilization of existing prophetic factors and mandatory clinical and psychological pre-transplant evaluations by substance abuse specialists and psychiatrists/psychologists. There is concern that if amendments in guidelines for liver transplantation are made for these patients, it may lead to a significant decline in willingness to donate. However, patients with fulminant hepatic failure due to intentional acetaminophen poisoning or due to intravenous-drug use-related acute hepatitis-B virus infection, did not come across this issue. Therefore, a further exploration into this field and these issues is needed.

Keywords: Alcoholic hepatitis; Liver transplant; Recidivism

Introduction

Severe alcoholic hepatitis (AH) can result in death within two months of the acute illness and, despite early successful liver transplantation for these individuals, the treatment approach remains controversial [1,2]. Although data regarding the six-month abstinence rule as a predictor of long-term sobriety is controversial, such abstinence is usually requisite before patients with severe alcoholic hepatitis are considered for liver transplantation [3]. However, the United Network for Organ Sharing (UNOS) and the French Consensus Conference does not regard this to be a formal guideline [4]. Patients whose hepatitis is not responding to medical therapy have a six-month survival rate of approximately 30%. The Lille model enables early identification of patients unlikely to respond to medical treatment [5,6]. Strict application of the six-month abstinence rule may be detrimental to such patients, as 70 to 80% of them die within that period [7,8]. Taken together, all available treatment options, including early transplantation in this high-risk group of patients, may be considered as recommended by the latest French consensus [4].

Epidemiology and Mortality

Although AH is an acute condition, nearly 50% of patients have established cirrhosis at the time of clinical presentation [9]. AH is a distinct clinical entity caused by chronic alcohol abuse carrying poor prognosis with a 28-day mortality ranging from 30% to 50% [10]. The amount of alcohol consumption that places an individual at risk of developing AH is unknown. However, most patients with AH drink more than 100 gm/d (which corresponds to six to seven alcoholic drinks per day where one drink contains 13-15 gm of alcohol, with 150-200 gm/d being common) [11,12]. The typical age at presentation of AH is between 40 and 50 years, with the majority occurring before the age of 60 years [13,14]. The precise incidence of AH is unknown, although a prevalence of approximately 20% was noted in a cohort of 1604 patients with alcoholism who underwent liver biopsy [11]. The true prevalence of AH is difficult to assess because AH may be completely asymptomatic and often remains undiagnosed. About 10 to 35% of all alcoholics have changes consistent with AH and the estimated number of AH patients in the United States may be nearly 5 million [15].

Overall mortality is 15% at day 30 and 39% at 1 year. However, it varies with disease severity with about 20% in mild cases, and between 30% to 60% in severe AH [16]. In a study on a cohort of patients with AH followed for over 4 years, survival was about 58% in uncomplicated AH, and 35% in AH with cirrhosis. The probability of developing cirrhosis in patients with AH is approximately 10% to 20% per year, and approximately 70% of patients with AH will ultimately develop cirrhosis [17,18]. Recent analysis confirmed patients without treatment and with a Hepatitis Discriminant Factor score of 32 or higher and/or the presence of encephalopathy have a 28-day survival of about 68% [19]. At least 3 studies have suggested that the Model for End Stage Liver Disease (MELD) score may also predict mortality in patients hospitalized for AH [20-22]. A MELD score of 21 had a sensitivity of 75% and specificity of 75% for predicting 90-day mortality. As suggested, the rates of deaths related to AH did not increase over the 24-year period [23]. However, this may signify an incomplete picture as AH is often misdiagnosed and the true burden of

AH related deaths may be undervalued [15]. Additional studies are required to assess the actual incidence and prevalence of AH along with strategies to decrease the mortality rates in severe cases.

Six Months Abstinence Rule

Patients with alcoholic liver disease (ALD) classically have taken a back seat when it comes to allocation for liver transplantation. This stemmed from the belief that ALD transplant recipients would relapse and that these patients are less deserving of scarce donor organs because of their connivance in causing liver damage [24-27].

Currently, Pre-OLT (Orthotropic liver transplant) abstinence is obliging, but setting a fixed period of abstinence remains divisive [28-32]. The advocated standard is a 'six-month abstinence' rule but its validity to lessen the risk of relapse remains questionable as its selection is completely random being driven by custom and practice rather than evidence-based [33,34]. Karim et al. confirmed that duration of abstinence for at least six months was the strongest predictor of recidivism after OLT. Based on this, a minimum of six months of abstinence before OLT would appear to be reliable [35,36]. Further, few authors even argued that patients with alcohol abstinence shorter than six months should be excluded from OLT programs since recurrence and death rates were increased in this subgroup of patients [35].

However, the six-month pre-transplant abstinence rule did not emerge as a predictor of recidivism as suggested by a pooled analysis of 32 studies. Such pre-OLT abstinence inaccurately predicts post-OLT relapse [36-39] and life-threatening liver failure can potentially develop in this period, resulting in heightened waitlist mortality [34,40,41]. Rather, factors such as patient's insight, social support, and comorbid psychiatric disorders were stronger predictors. Therefore, the six-month abstinence rule should be treated as a recovery period and not as a predictor of recidivism risk. It may allow some patients enough time to recuperate their liver to an extent that they may no longer require OLT. It may also serve to buy professionals time for assessing patients for potential of compliance with post-transplant requirements.

In patients with severe AH with or without advance ALD, the pre-OLT abstinence period should be decreased, especially if the liver function is rapidly deteriorating, at least in those who are being strictly followed by an alcohol addiction unit, to help reduce organ wastage [30,42]. Evidence from the UNOS database, single-center studies and the prospective data presented by Mathurin et al., reflected that early liver transplantation clearly improves the probability of six-month survival in patients who continue to deteriorate after three months of abstinence or those who fail medical therapy [40,41]. Thus abstinence alone should not be the sole deciding factor for OLT since many patients present beyond the chance for natural liver recovery and transplant is their only option.

Despite this, patients with AH, particularly in the United States and United Kingdom, remain excluded from the indications for liver transplantation. Therefore, the six-month abstinence rule remains an insurmountable barrier [29,31], except in isolated cases. This will probably be followed until a new consensus emerges.

McCallum and Masterton identified multiple factors consistently associated with recidivism such as younger age, associated polysubstance abuse, lack of social support, family history of alcohol abuse in a first-degree relative, poor response to previous rehabilitation programs, and noncompliance. These factors can guide in carefully selecting a subset of the patients with acute severe AH who might benefit from LT [43]. Equally important is to deal with pre-existing psychiatric conditions before and after OLT and provide unrelenting support to prevent relapse to achieve sustained abstinence. Thus, efforts are needed in the form of multicenter randomized trials to develop the best criteria for abstinence prior to OLT. This will help identify and recognize candidates who would benefit the most and are the least at risk of recidivism to harmful drinking. It will also help ensure optimal utilization of available organs for AH as that for acute liver failure secondary to other causes [43].

Role and effectiveness of available medical therapy

The American Association of Study of Liver Diseases (AASLD) guidelines suggest a MELD score cutoff of 18 to predict severe AH and as the measure for initiating medical treatment [9]. Many agents have been tried for the treatment of severe AH. No long term survival benefit has been proven with corticosteroids [43]. Side effects including fatal gastrointestinal bleeding and sepsis in patients with severe AH preclude their use [44,45]. Unfortunately, many of the early trials on corticosteroids were small with limited statistical power but they suggested an encouraging role in patients with acute AH and hepatic encephalopathy without active gastrointestinal bleeding, by reducing short-term mortality [46].

Follow up studies failed to confirm these beneficial results [47]. Further, the efficacy of corticosteroids has not been evaluated in patients with concomitant pancreatitis, gastrointestinal bleeding, renal failure, or active infection. In one report, patients with a Maddrey score of greater than 54 who received corticosteroids had higher mortality than those who had not received them [45]. According to the AASLD and the European Association for the Study of the Liver (EASL), pentoxifylline is recommended for severe AH, when there are contraindications to corticosteroids like sepsis and GI bleed [48,49]. Although there has been reduced incidence of fatal hepatorenal syndrome with pentoxifylline compared with placebo, no survival benefit at one-month was demonstrated [50]. In addition, no difference was found between trials of pentoxifylline versus corticosteroids versus combination therapy [51,52]. More studies are required to reach a consensus on the efficacy and role of medical therapy and consideration should be given to early liver transplant in targeted groups of severe AH patients with high mortality.

Early Liver Transplant

Patients with severe AH pose a particular challenge for transplant as they have invariably consumed alcohol in the preceding weeks. Reluctance to perform transplantation in such patients is often based on the view that they are responsible for their illness and are likely to recommence alcohol use after transplantation [52]. Strict application of the rule requiring six months of sobriety may be disadvantageous to such patients, as 70 to 80% of them die within that period due to non-response to medical therapy [53]. The Lille model facilitates early identification of such patients who are unlikely to respond to medical treatment [5,6]. Although alcoholic hepatitis was an absolute contraindication for placement on the transplant waiting list according to the AASLD and the UK Liver Advisory Group [54,55], the UNOS and the French Consensus Conference do not consider it to be a formal guideline. They rather recommend a balanced analysis of the individual patient [9]. Using the UNOS database, evidence supporting the benefit of LT for severe AH has been reported in a study of 55 patients who were transplanted for AH compared with 165 matched

patients transplanted for alcoholic cirrhosis. The AH patients had similar five-year liver graft survival rates at 85% compared to 87 % in those transplanted for alcoholic cirrhosis with P=0.21. Patient survival in the AH versus alcoholic cirrhosis group was 91% versus 89%, *P*=0.35. This suggests that LT may be effective in a highly selected cohort of patients with AH [56].

Findings from a European multicenter study suggested that selected group of patients suffering from their first episode of severe AH who failed medical treatment but received a favorable psychosocial assessment, had excellent survival and low frequency of harmful drinking after LT [4]. Likewise, Mathurin et al., compared patients with severe AH nonresponsive to steroids (defined as ≥0.45 Lille score) who underwent early OLT (within nine days of listing from first episode of severe AH) to patients who did not undergo OLT in a case-controlled French study. At six months, the patient survival rate amongst the early-transplanted group was higher compared to the control group (83.3% vs. 44%). Among the non-transplanted, 50% to 90% deaths occurred within first two months. This benefit of early transplantation was maintained through two years of follow-up [56]. Thus, early OLT should be considered as one of the treatment options in select groups of patients with AH who are unresponsive to medical therapy and unlikely to survive to complete the six-month abstinence period, but are otherwise suitable candidates for transplantation. [43,56-61]. However, the above studies had few inherent limitations including post-transplant infection, significant perioperative transplant mortality and a finite risk of relapse to drinking, making the overall benefit of early transplantation questionable and non-generalizable to all patients with AH.

Conclusion

In light of the available literature, we may need to reconsider the concept of an approved abstinence period as the only condition for transplant eligibility as well as the fact that alcoholic hepatitis is a contraindication for transplantation [62]. This condition of an abstinence period may also delay listing of a considerable number of candidates for transplantation with a low probability of relapse [63-70]. Further, the duration of abstinence before transplantation is a poor predictor of relapse to drinking and stringent selection of candidates can result in a low rate of relapse. Early liver transplantation may be an appropriate rescue option for selected patients whose first episode of severe alcoholic hepatitis is not responsive to medical therapy, after careful assessment of their addiction profile. Existing data clearly show that LT is a potential treatment option for the group of patients with severe AH who continue to deteriorate despite intensive medical treatment. Further, six months of abstinence does not affect recidivism after OLT. In order to pick the patients who would gain the most benefit, we need to evolve the best criteria to categorize candidates with the least risk of recidivism to harmful drinking, for the optimal utilization of available organs in the setting of AH, in the same way as is being done for acute liver failure secondary to other etiologies.

Take home message

1. Large prospective studies are required to provide guidelines for abstinence prior to OLT in alcoholic hepatitis patients who have failed medical therapy or are at high risk of death. In addition, it is equally important to deal with pre-existing psychiatric conditions before and after OLT to provide unrelenting support to prevent relapse and achieve sustained abstinence.

2. As six months of abstinence does not completely affect recidivism after OLT, pursuing the best available criteria to categorize and stratify candidates with the least risk of recidivism to harmful drinking is desired for the optimal utilization of available organs for patients with severe alcoholic hepatitis.

3. Abstinence should not be the only deciding factor for OLT since many patients present beyond the chance for natural liver recovery and transplant is their only option.

4. Existing data shows that liver transplant is a potential treatment option for the specific group of patients with severe AH who continue to deteriorate despite intensive medical treatment.

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