

## Liver Transplantation for Alcoholic Hepatitis: Light at the End of Tunnel

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### Editorial

Alcoholic cirrhosis is the currently the 3rd most common cause for liver transplantation after hepatitis C or non-alcoholic fatty liver diseases and accounts for about 25% of all transplants in the US including HCV positive drinkers [1]. Until early 1990s alcoholic liver disease used to be considered as a contraindication for liver transplantation. This changed with report of NIH consensus workshop on cases selection of patient with alcoholic cirrhosis [2]. One of the criteria proposed in this consensus workshop was need for minimum six months of abstinence before considering liver transplantation in a patient with alcoholic cirrhosis. Rationale for six months of abstinence requirement was to allow for the liver function recovery with abstinence from the acute hepatocellular effect of alcohol intake [2]. Several studies since then have reported in select patients with alcoholic cirrhosis with outcomes to be as good as any other indication except for hepatitis C [1,3].

Alcoholic hepatitis is a unique clinical syndrome in patients with chronic and active alcohol abuse and severe episode often presents with acute on chronic liver failure with potential for short term mortality at one month of as high as 30-50% [4,5]. With the recent report on the largest randomized study, the STOPAH study which showed that corticosteroids are the only effective therapy for patients with severe alcoholic hepatitis. In this study, pentoxifylline, which used to be an alternative therapy when corticosteroids could not be used for any contraindications for their use, was not found to be useful for these patients. However, only about 40-50% of patients with severe alcoholic hepatitis respond to corticosteroids therapy [4-6]. Therefore, these sick patients in spite of treatment with the only currently effective available treatment option of corticosteroids remain at risk for about 20-25% risk of dying at 1 month from clinical presentation [6].

Liver transplantation, an established treatment option for patients with end-stage liver disease secondary to alcoholic cirrhosis cannot be routinely applied to these sick patients with alcoholic hepatitis patients with non-response to steroids (NRS). Shortage of donor organ pool and socio-cultural factors with public opinion that alcoholic liver disease is self-inflicted are some of the challenges and barriers to accept this treatment option for patients with alcoholic hepatitis [7]. Most of these challenges revolve around the fact that alcoholic hepatitis patients are at high risk for recidivism (relapse to alcohol use) after liver transplantation as they are actively drinking up to about 3-4 weeks prior to the clinical presentation, and are unable to meet with requirement of minimum six months of alcohol abstinence [4]. However, six months of alcohol abstinence has not been shown to be an accurate predictor of recidivism. For example, in a systematic review, six months of abstinence accurately predicted recidivism in only two of eight studies evaluating this variable. Social support, young

age, and psychiatric comorbidities in this systematic review were more accurate predictors of recidivism [8].

French workers challenged this 'six months rule' and transplanted select 26 patients with first episode of alcoholic hepatitis with documented NRS and with excellent psychosocial support. In this case control prospective study, these 26 transplanted patients were compared with matched 26 alcoholic hepatitis patients with NRS who did not receive liver transplantation. Results showed that liver transplantation improved survival compared to non-transplanted patients at six months and two years (77% vs. 23%,  $P < 0.0001$ ) [9]. It becomes very clear that if these sick alcoholic hepatitis patients with NRS are to be salvaged, they cannot afford to wait for 6 months as about 80% of these patients would die by that time frame if not transplanted. In contrast, transplantation saved about 80% of these patients. In this study, only 3 of 26 patients reported recidivism by two years of follow up, with only one of these reported heavy alcohol use [9]. The recidivism rate reported in this study is similar to what is reported in alcoholic cirrhosis patients transplanted with minimum six months pre-transplant alcohol abstinence, with 5.7% per year for any alcohol use and 2.5% of heavy alcohol use [10].

Although, alcoholic hepatitis remains a relative contraindication for liver transplantation, patients with alcoholic hepatitis are being randomly transplanted in the US. In a recent survey of liver transplant center directors with about 45% response rate, about 45 such transplants were performed at 11 of 45 centers responding to this survey (unpublished data). Similar observation was made when the UNOS database was queried for transplants for alcoholic hepatitis with finding of about 55 such transplants performed from 2005 to 2010. Five years survival of these 55 transplants was similar to 165 matched liver transplant recipients for alcoholic cirrhosis (80 vs. 78%,  $P = 0.91$ ) [11].

One of the issues with accepting transplantation for alcoholic hepatitis is the shortage of donor livers [7]. However, if only select cases are transplanted as reported in the French study, only 2-3% of all alcoholic hepatitis patients would qualify for this treatment option [9]. Similarly, in a recent survey of transplant centers, only about 1.5% of all transplants performed were performed for alcoholic hepatitis (unpublished data). Of about 6,000 annual liver transplants performed in the US, 1 about 10 would be used for alcoholic hepatitis. Given that alcoholic hepatitis is a disease of young and middle age, liver transplantation seems to be cost effective and ethical option for alcoholic hepatitis [4,5,12]. However, before accepting this option in routine clinical practice, more data are needed as a basis of validating the European data as well as developing uniform protocol for case selection and their post-transplant follow up. For example, in the French study 80% survival at six months is much inferior to reported one year survival of over 90% for patients with cirrhosis including

alcoholic cirrhosis [9]. Further, five of the six deaths in French study were due to invasive fungal infection, suggesting intensive pre-transplant surveillance for fungal infections and possible change in immune suppression regimen to prevent this complication [9]. Until more prospective multicenter data are obtained on the use of liver transplantation in alcoholic hepatitis, there remains light at the end of tunnel with liver transplantation as an effective option to salvage select patients with alcoholic hepatitis.

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