Review

Role of liver transplantation in severe alcoholic hepatitis

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Severe alcoholic hepatitis has very high short term mortality and corticosteroids have been the mainstay of treatment for decades. Patients with Lille score >0.45 are considered non-responders to steroids and have poor outcome. Recently Orthotopic Liver Transplantation (OLT) is being increasingly used as rescue treatment for these patients, without waiting for 6 months of abstinence. Liver transplant is the only rescue treatment which can potentially provide long term benefit for patients who are steroid non-responders. However, with scarcity of organs being a concern, all patients of severe alcoholic hepatitis cannot be chosen for transplantation in an arbitrary way. There is a need for development of predictive tools and objective protocols to select patients who can justify the use of precious liver grafts. With a stringent criteria for selection of patients receiving the graft, liver transplantation in severe alcoholic hepatitis can become a viable rescue therapeutic option conferring significant survival advantage of both short- and long-term basis. The optimal criteria for selection will also prevent misuse of the liver donor pool as well as to prevent mortality in salvageable patients. Further research needs to be done to identify subset of patients which are at low risk of recidivism and also cannot be managed with pharmacotherapy alone. We reviewed the current knowledge on role of OLT in patient with acute severe alcoholic hepatitis in the present review. **(Clin Mol Hepatol 2018;24:43-50)**

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INTRODUCTION

Alcohol-related liver injury has a varied spectrum ranging from simple steatosis to cirrhosis.[1] Alcoholic liver disease has often been grouped into three histological stages: fatty liver disease or simple steatosis; alcoholic hepatitis (AH); and cirrhosis. AH is a clinical syndrome of progressive inflammatory liver injury occurring in persons with active and chronic intake of ethanol. The exact incidence of AH is unknown, but approximate prevalence in a cohort of 1604 patients with alcoholism who underwent liver biopsy was 20%.[2] The cardinal sign of AH is the recent and rapid onset of jaundice.[3] Other common signs and symptoms include easy fatigability, fever, ascites, and proximal muscle loss. Some patients with severe AH may present with encephalopathy. The liver is enlarged and tender on palpation.[3] The ratio of the aspartate aminotransferase (AST) level to the alanine aminotransferase (ALT) level is characteristically greater than 2, although this finding is neither specific nor sensitive.[4] The peripheral-blood white cell count, neutrophil count, total serum bilirubin level, and international normalized ratio (INR) are elevated.[5]

AH is the most florid manifestation of alcohol-related disease with high mortality, but is potentially reversible.[6] Mild AH without encephalopathy, jaundice, or coagulopathy has mortality of less than 5%. Severe AH has a poor prognosis without treat-

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ment, with a 28-day mortality rate of 30-50%.[7] Over the years various prognostic models in patients with AH have been developed, such as the DF score, Model for End-Stage Liver Disease (MELD) score, ABIC (Age, Bilirubin, International Normalized Ratio, Creatinine) score, Glasgow Alcoholic Hepatitis Score (GAHS), Early Change in bilirubin Level (ECBL) and Lille model.[8] In clinical practice mDF >32 or MELD >20 are considered severe AH.[6,9]

TREATMENT MODALITIES

Abstinence

Abstinence is the foremost aspect of management in patients with alcoholic liver disease irrespective of stage and severity.[10] Patients with mild AH show significant response to abstinence and minimal medical support.[11] The STOPAH trial highlighted that abstinence at 90 days after enrollment was the only factor associated with survival at 1 year.[12] Importantly, any alcohol use at all at day 90, including less than 2 drinks/day, was associated with a 2- to 3-fold increase in mortality.[12] Thus, all patients must be explained that slips i.e temporary return to drinking, often at low levels; or relapse which is more sustained resumption of drinking; lead to recurrent liver disease and increase risk of death. Pharmacological deaddiction should be advised to all patients.[6]

Nutrition

Protein energy malnutrition is very common in patients with AH with reported Prevalence of 100% in hospitalized patients.[13] AH is considered a hypercatabolic disease and thus require prompt nutritional intervention with a high-calorie enteral or parenteral formula.[14] Deterioration in nutritional parameters is a significant risk factor for survival in patients with severe AH, and this deterioration is potentially reversible with nutritional rehabilitation.[15] The enteral route for supplementing nutrition is advantageous as it is less expensive, maintains gut mucosal integrity, and subsequently decreases the risk of bacterial translocation and infections.[16] In a study of 71 patients, it was found that enteral feeding was not worse than steroids in the short-term treatment of severe AH.[17] Enteral supplementation when compared with standard dietary intake, showed better nutritional status but without survival benefit.[18]

Pharmacotherapy

Pharmacotherapy for severe AH has chiefly revolved around two drugs, steroids and pentoxifylline, which have been recommended in various treatment guidelines.[6,9,10] Since the first major study demonstrating mortality benefit with corticosteroid therapy by Maddrey, et al, about four decades ago, not much has changed in the medical therapy of AH.[19] Over the years steroids have remained mainstay of medical therapy for severe AH, even though the data supporting the beneficial role is varied. Corticosteroids target the overly aggressive immune system provoked by increased generation of neo-antigens like epitopes of protein–aldehyde adducts and cytokines. EASL and AASLD recommend the use of prednisolone 40 mg/day for 4 weeks and then tapered over 2 to 4 weeks or stopped.[6,9,10] In a meta-analysis by Mathurin, et al, glucocorticoid therapy was found to decrease 28-day mortality by 14% which made the authors conclude that steroids should be administered in severe AH.[20] On the other hand in the largest RCT on AH, the STOPAH trial, corticosteroid therapy was associated with a trend toward reduction in 28-day mortality with a reduction in mortality of 4%. However, this benefit did not persist at 90 days or 1 year.[12] The probable reason for this divergence was patients were in general younger and had less hepatic encephalopathy as compared with those in the most recent trials included in the meta-analysis, this could have mitigated the benefit of glucocorticoid.

Major drawback of steroid therapy is ineligibility of significant proportion of patients (due to GI bleed, acute kidney injury and active infections) along with the side effects which increase with duration of the therapy. Despite being the only drug to have stood the test of time, physicians remain reluctant to consider corticosteroid treatment.[21] To identify the subset of patients who would eventually not respond to the therapy, early change in bilirubin levels at 1 week from the start of treatment and the Lille model were developed.[22] A Lille score (continuous score between 0 and 1 calculated at 1 week from the start of therapy) of ≤0.45 is considered a good response to corticosteroid therapy whereas a score of >0.45 is considered as non-response. In non-responders, steroids should be discontinued to avoid the side-effects.[22] Moreover the six-month mortality is approximately 15% for patients who respond to therapy; it rises to over 75% for non-respondents.[22] Thus, the non-responders to steroids remain at extremely high risk of short-term mortality.

Pentoxifylline, with its better safety profile, was seen as an attractive alternative to steroids especially in subset of patients in

Table 1. Studies on liver transplantation for severe alcoholic hepatitis.

| Author | Number of patients Listed/transplanted | Study characteristics | Survival at 6 months | | Survival at 2 years | | Relapse | Percentage of total transplants |
			With LT (%)	Without LT (%)	With LT (%)	Without LT (%)		
Mathurin P, et al.[32] (2011)	-/26	Strict selection criteria 2006-2010	77+8	23+8	71+9	23+8	3 -relapse	2.9
Hasanin M, et al.[33] (2015)	130/55	UNOS data set based (2004-2010) retrospective			91	84	-	-
Im GY, et al.[34] (2016)	15/9	Prospective Jan 2012-Jan 2015	89	11			1 –relapse 2 –slips	3
Lee BP, et al.[51] (2017)	-/17	Retrospective Oct 2012 to Jun 2015	100				23.5% resumed harmful drinking	

whom steroids could not be given.[23] Pentoxifylline, a methylxanthine, mitigates production of tumor necrosis factor alpha which plays a role in the pathogenesis of AH.[24] Frequent side effects include vomiting, diarrhoea and headache leading to drug discontinuation.[25] The larger studies and a head-to-head randomized trial demonstrated inferiority of pentoxifylline as compared with steroids in terms of mortality benefit.[26] Furthermore, the STOPAH trial with 1,103 patients demonstrated no benefit to pentoxifylline over placebo in preventing short-term mortality in severe AH.[12] The role of pentoxifylline in severe AH needs to be relooked into.

N-acetylcysteine (NAC) has been shown to reconstitute glutathione reserves to reduce oxidative stress. In a multicenter, RCT on 174 patients, use of IV N-acetylcysteine (dose as used in patients with acetaminophen toxicity, but with maintenance dose extended to a total of 5 days) in combination with corticosteroids was compared with steroids alone and better patient survival at 1 month was found in combination group (8% vs 24%; P=0.006), however there was no survival benefit at 3 or 6 months.[27] This trial, although a negative trial as the primary end point was survival at 6 months, is an important study and further trials are needed to investigate its role in this cohort.

LIVER TRANSPLANTATION AS AN OPTION FOR SEVERE AH

Managing steroid non-responders and patients in whom steroids are contraindicated remains a challenge and unsolved medical problem.[23] The therapeutic armamentarium at disposal, leaves no other option other than orthotopic liver transplantation (OLT). With death staring at these patients, whether rescue OLT should be offered has been a matter of debate.

In the past OLT was not considered as a treatment option for severe AH even though almost 23% of transplants are done for alcoholic liver disease.[28] Data from the European Liver Transplant Registry showed that patients who have undergone an OLT for alcohol related liver disease have as higher life expectancy compared to those with viral and cryptogenic etiologies.[29,30] In the primary work published in 1993 by Bonet, et al in 147 ALD patients, similar survival post liver transplant for AH and decompensated alcoholic cirrhosis was reported.[31] The French workers led by Mathurin in 2011, conducted a landmark pilot study, performed OLT for highly selected AH patients (Table 1).[32] In this prospective case control study, 26 OLT recipients for AH were compared with 26 AH patients who had failed steroid therapy, but did not receive OLT. They found that of the patients receiving liver transplants, 77±8% survived for 6 months which was similar to a matched group of steroid responders (Lille score <0.45, 85%±4%) and significantly better than that of a matched group of steroid non-responders who did not receive liver transplants (23±8%). After 2 years, 71±9% of transplant recipients were still alive. Of them three recipients returned to drinking at 3 years. Lesser than 2% of patients with severe AH received a liver transplant, and 3% of liver grafts were used for transplantation into patients with AH. This study had opened the window of opportunity for these patients.

In the years since, several American transplant centers have begun transplanting selected patients with severe AH. In a survey of 45 transplant centres, 11 had transplanted patients for acute AH

over the last 5 years, constituting 45/3290 (1.37%) of total transplants at these centers.[33] Among the 45 patients who were transplanted, 39/42 (93%) were alive at 6 months post-liver transplantation, 37/40 (93%) at 1 year, and 27/31 (87%) at 5 years demonstrating excellent patient survival.[33]

Im, et al studied the feasibility of LT in non-responder subset of patients with SAH in United States.[34] They evaluated 94 patients with severe AH not responding to medical therapy for early OLT. Nine (9.6%) candidates with favourable psychosocial profiles underwent early OLT which were 3% of all adult OLT during the study period. The early OLT group compared with matched controls had better 6-month survival rate (89% vs. 11%, $P<0.001$).[34] Clearly, liver transplantation for severe AH is associated with a dramatic survival benefit in both a study and real-world experience.

WHY THERE IS STILL A DEBATE OVER LT IN AH?

Problems with liver transplantation for patients with AH are manifold. Beginning with, whether a patient with self-inflicted disease deserves the available liver graft which is a scarce resource.[35] Second, recidivism and relapse are major concerns in these patients. Third, the fact that alcoholism is multisystem disease which precludes good result from surgery along with the risk of poor compliance in these patients.[36] Fourth and the most debatable is the proper selection of patients who should be transplanted: the ones who are likely to die without a liver transplant and those who are unlikely to return to drinking.[37] About 25% of the steroid null-responders will eventually recover with medical management and if transplanted at early stage would lead to wastage of precious liver grafts.[22] The public perceptions of use of organs for patients with alcoholism complicate the issue further.[38,39]

The American Society of Transplantation and AASLD recommended the minimal criteria for listing of patients with ALD should include "approval by the center evaluation committee. and favorable assessment by a substance abuse professional and reported abstinence of at least six months at time of listing".[40] This was known as the "6-month rule". The authors recognized that the last criterion excluded patients with severe AH, and thus they left open the possibility of exceptions.[40] Six months of abstinence for alcoholic cirrhosis was recommended to allow liver function to recover from the acute effect of alcoholism.[41] In 1997, following a meeting organised for placement on a liver transplant waiting list, this be-

came a general requirement.[42,43] However, since then this rule has also been used to determine the risk of recidivism after OLT.

Although labeled as a "rule", it is an expert opinion and not based on randomised control trials. Even in carefully chosen patients with alcoholic liver disease who remain abstinent for 6 months, high rates of relapse have been demonstrated.[43] The data on 6 months of abstinence as a predictor of recidivism after OLT has been inconsistent. In a systematic review of 22 studies, only 2 of the 11 studies confirmed 6 months of abstinence to predict recidivism.[44] Longer duration with zero alcohol consumption does decrease the probability relapse, 5% decrease with each additional month in the adjusted relapse rate.[42] However, it is impossible to exactly pinpoint the clinical cut-off that would ensure abstinence after an OLT. Of the three patients who had relapsed, none of them did so in the first six months.[32]

Other obstacles for OLT include listing, evaluating and transplantation in short span of time (weeks) and giving these patients priority as they tend to have higher MELD score over patients waiting in the queue with decompensated CLD. Advantages of the MELD score as the listing criteria for patients with cirrhosis are its statistical validation and the use of objective widely available laboratory tests. The impact of the MELD allocation policy resulted in a reduction in waiting list registration by 12%, a reduction in death on the waiting list by 5%, decreased median waiting times from 676 to 416 days, and patients transplanted within 30 days of listing increased from 23% in the pre-MELD era to 37% in the post-MELD era.[45,46] However, MELD as a listing criteria for patients with AH is still not validated.

RISK OF RELAPSE AND ITS EFFECTS

One of important determinant of long term survival post liver transplant for alcoholic liver disease has been recidivism.[47] Foremost issue in this regard is defining relapse. Some experts believe any drinking as relapse whereas others consider heavy alcohol abuse as it is associated with liver injury.[48] Considering relapse as any alcohol intake after LT contrasts with the definition of relapse in addiction medicine, in which relapse is considered only in the presence of recurrence of heavy drinking. Varied rate of relapse after LT with range from 10% to 50% is explained by lack of consensus on definition of alcohol relapse.[49-51] Another caveat about these estimates relates to the difficulty of getting accurate data on drinking behaviour.[50] There were no differences in the proportion of liver transplant recipients that drank after a transplant due

to ALD compared with those with non-ALD: 4% vs. 5% at 6 months and 17% vs. 16% at 12 months.[52] Recipients who resume heavy drinking have shorter long-term survival than abstinent recipients or patients with minor relapse.[53] A French study, conducted between 1990 and 2007, included 712 patients transplanted for alcoholic cirrhosis who survived beyond 6 months post liver transplantation. They were followed for a median of 9 years. Of the total, 18% experienced severe alcoholic relapse at a median of 25 months following liver transplantation and among them, 41/128 (32%) were diagnosed with recurrent alcoholic cirrhosis at a median of 5.1 years after liver transplantation.[54] A review of American transplant data between 1995 and 2007 had similar findings where 16% of patients transplanted for alcoholic liver disease relapsed to drinking.[55] A meta-analysis of 50 studies identified 3 significant risk factors for relapse: poor social support, sobriety for less than 6 months before liver transplantation, and a family history of alcoholism.[56] Psychological or psychiatric comorbidities are associated with an increased risk of relapse.[57] A meta-analysis of risk for relapse to substance abuse after liver or other solid organ found that the relapse to any alcohol use after liver transplantation was over twice as common as relapse with heavy alcohol use (almost 6 vs. less than 3 cases per 100 persons per year).[56]

A correlation between impaired long-term survival and alcohol recidivism has been observed, but mostly due to increased incidence of cardiovascular events and malignancy rather than to toxic effects of alcohol on the liver graft.[47] In this setting, duration of pre-transplant abstinence does not correlate with post-transplant survival.[58] Smoking has been associated to be an important risk factor for development of malignancy.[59]

Some studies have demonstrated no direct deleterious effects of alcohol drinking on post-transplant outcomes, including therapeutic compliance, graft function, and graft survival[60], while others have reported negative impacts of heavy drinking on outcomes.[46] These conflicting data underline the need for better distinction of the different types of alcohol drinking after transplantation, ranging from occasional to moderate or severe, when alcohol habits could correspond to use, abuse, or dependence.[48]

Consensus regarding risk factors for alcohol recidivism is lacking. Which subset of patients with AH merit liver transplant and will have least risk of recidivism is still unanswered. The previously proposed sobriety rule has been questioned and challenged. Moreover, highly selected patients were transplanted in the published studies which comprised of only 1.4%-2.4% of the liver donor pool.[32,34]

For selection of recipient with minimal risk of recidivism and optimal use of liver grafts various protocols have been suggested. The potential candidates for transplant must be assessed by a multidisciplinary team. One of the recently published protocols, the New York-Presbyterian Hospital Center for Liver Disease and Transplantation Protocol, consisted of set of medical and psychosocial requirements.[61] The need for psychosocial support should not be underestimated. Patient should have no prior formal substance abuse treatment, no current or past psychiatric diagnoses, no comorbid substance abuse, excluding tobacco along with stable housing and family support.

The most important factor is identification of the right patients who are best suited for such an aggressive intervention and, in fact, a small number of patients fall into this group.[62] As in study by Mathurin, et al, patients with first episode of AH and those demonstrating willingness to abstain from alcohol and adherence to medical regimen can be considered for transplantation.[32] This requires coordinated interactions in the team which can include the hepatologist, psychiatrist, surgeon, as well as the broader support team including the nurse coordinator, social worker, and addiction counsellor.[61,62] This criteria although restrictive is based on the concept that patients who had previous episodes of liver failure intentionally chose to ignore the warning and hence have developed the subsequent episode. The other issue here is considerable amount of subjectivity in group decision making as it may be influenced by individual authorities.[37] Post OLT these patients should have intense social and psychological support and monitoring prevention and early detection of relapse.[59]

Another debatable issue is role of living donor liver transplant (LDLT) in these patients as related living donor graft will not overburden the graft pool. The logic of treating a self-inflicted disease with help of family members can be easily understood. But, compared to deceased donor liver transplant (DDLT), complications like biliary leak (32% vs. 10%), re-exploration (26% vs. 17%) and vascular issues (9% vs. 2%) are significantly more frequent after LDLT.[63] The donor related complications (1.1 % being serious) also needs to be considered in such situations.[64]

SHOULD WE OFFER TRANSPLANTATION TO PATIENTS NOT RESPONDING TO STEROIDS?

Given these excellent outcomes as shown the recent studies,[32-34] should we offer transplantation to steroid non-responders with severe AH who have not demonstrated a period of abstinence

from alcohol? To answer this very pertaining question one has to look at a larger picture. The 6-month survival is less than 25% in steroid non-responders who do not receive liver transplants.[32] This dismal prognosis calls for the use of OLT for these sick patients. However, liver graft is very scarce resource which needs to be utilized judiciously. An argument against the use is based on perception of disservice to patients awaiting OLT for already established indications. Additionally, a moral point of view that disease is self-inflicted has been invoked as a reason not to transplant such patients. Moreover, there is no surety that post-transplant the patient would remain sober. Also, there is constant worry of patients relapse and development of liver graft injury. The proponents of the transplant in these patients believe that the 6-month rule is arbitrary and has been challenged.

Although alcoholic recidivism occurs, it may not affect compliance to treatment profoundly or to compromise graft function.[65] Moreover, the patients with severe AH seldom survive till 6 months to prove their abstinence as to fulfill the criteria.[22] This clearly goes against the concept of beneficence, as the patients who need and will benefit the most of transplant are more often excluded. Furthermore, rescue OLT is the only alternative in such patients for survival. With excellent outcomes post-transplant, it is even more unreasonable to withhold transplant in these patients who have high short-term mortality.[32]

The argument of self-inflicted disease is not a valid one. An emergency OLT is approved for patients with suicidal acetaminophen resulting in fulminant hepatic failure.[66] On similar lines OLT for patients with prior I.V drug use resulting in viral hepatitis or obesity leading to nonalcoholic fatty liver disease continue to form major chunk of all OLTs.[67] The denial of treatment on moral or judgemental grounds is akin to robbing the patient of a fundamental right to treatment without discrimination (The Universal Declaration of Human Rights, article 25).[68] This type of contradictory practice could discredit the entire transplant system. Alcoholism is a disease, and should be treated as one.

CONCLUSIONS

Severe AH is florid manifestation of alcohol related to liver disease with high short-term mortality. Corticosteroids have been shown to decrease the short-term mortality. Steroid non-responders are left with continuation of supportive therapy to avoid steroid related side effects. These patients are in particular at very high risk of mortality. Liver transplant is the only rescue treatment which also provides long term benefit. With scarcity of organs being a concern, candidates cannot be chosen in an arbitrary way. There is a need for development of predictive tools and objective protocols to select patients who can justify the use of precious liver grafts. Further research needs to be done to identify subset of patients which are at low risk of recidivism and also cannot be managed with pharmacotherapy alone.

Authors' contribution

Conceptualization: Anil Arora; literature review and drafting of manuscript: Ravi Daswani, Ashish Kumar; critical evaluation of the manuscript: Praveen Sharma, Vikas Singla

Conflicts of Interest

The authors have no conflicts to disclose.

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