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Liver Transplantation for Alcoholic Liver Disease

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Abstract

Alcohol is one of the main causes of liver disease in the Western world. Total alcohol abstinence represents the cornerstone of the management of alcoholic liver disease. When total alcohol abstinence does not result in a significant improvement of liver function, liver transplantation represents the gold standard treatment for alcoholic hepatitis and end-stage alcohol-related cirrhosis. Liver transplantation for patients with alcoholic liver disease still represents matter of debate, principally due to concerns about the risk of post-transplantation recidivism and its effect on the outcome. These issues, coupled with a perception that these patients are likely to have contraindications to transplantation (e.g. extra hepatic alcohol-related disease or lack of self-care) have contributed to a reluctance of many centers to offer liver transplantation to patients affected by alcoholic liver disease. The aim of the present review is to discuss the controversies of liver transplantation for alcoholic liver disease.

Keywords: Alcoholism; Alcohol-dependence; Alcoholic hepatitis; Cirrhosis; OLT

Introduction

Alcohol consumption, in particular harmful alcohol use related to Alcohol Use Disorders (AUD) accounts for 3.8% of global mortality and 4.6% of Disability-Adjusted Life Years (DALYs) worldwide [1]. A total of 9.5% of alcohol-related DALYs is due to Alcoholic Liver Disease (ALD) [2]. At present alcohol still represents the most common cause of liver cirrhosis in the Western countries [3]. The development of ALD is influenced by environmental and host factors other than AUD. In particular, the duration of alcohol abuse, the drinking pattern and the alcohol amount have been reported as the most important factors for ALD. However the disease profile induced by comparable levels of consumed alcohol shows a high individual variability in terms of severity and rapidity of progression. It has been reported that nutritional status, gender, ethnicity, iron overload, co-existing metabolic syndrome, chronic viral co-infections (particularly hepatitis B and C viruses), polymorphisms of genes involved in alcohol metabolism and in the regulation of endotoxin-mediated cytokines release are important additional elements [4]. All these factors can contribute to the progression from the early stage of ALD (fatty liver disease/steatosis) to steato-hepatitis, fibrosis, cirrhosis and its complications (e.g. hepatocellular carcinoma).

Independently from the stage of disease, total alcohol abstinence represents the cornerstone of the management of ALD [5]. When liver function fails to improve with abstinence, Liver Transplantation (OLT) is the treatment of choice. However the indication to list AUD patients for OLT remains controversial. In particular, the risk of alcohol recidivism after OLT, the organ shortage and the persistent perception of ALD as a "self-inflicted disease", have contributed to create reluctance to list AUD patients for OLT. The aim of the present review is to discuss the controversies of OLT in ALD.

Alcoholic Hepatitis

Alcoholic hepatitis is a clinical syndrome characterized by rapid onset of jaundice and liver failure that occurs in patients with chronic alcohol abuse. The histologic picture consists of ballooned hepatocytes, Mallory bodies and lobular neutrophils. Common signs and symptoms include encephalopathy, fever, ascites, and proximal muscle loss; typically, the liver is enlarged and tender [6]. Alcohol abstinence is mandatory in alcoholic hepatitis, and in its milder forms is sufficient for clinical recovery. In the more severe clinical presentation, in which serum bilirubin levels are markedly elevated, death is common despite stopping drinking [7]. Patients with severe alcohol hepatitis (Maddrey Discriminant Function>32) should be considered as candidates for corticosteroids therapy or, in case of ongoing sepsis or bleeding, for pentoxiphylline treatment [7]. Response to therapy should be evaluated after 7 days of therapy using the Lille model. In non-responders (Lille score>0.45), the interruption of corticosteroids is recommended, particularly in those classified as null responders (Lille score>0.56). These patients, in particular those with favourable addiction profile, should be considered for early OLT [8]. To date, few studies analysed the survival rates of patient transplanted for alcoholic hepatitis; Tome et al. [9] showed that in patients with alcoholic cirrhosis plus alcoholic hepatitis detected in the explanted liver survival after OLT is similar to that of patients transplanted for other reasons, and the presence of severe alcoholic hepatitis does not worsen the outcome of OLT for end-stage alcoholic liver disease. Moreover, in the study by Wells and co-workers the presence of histological acute alcoholic hepatitis in the explanted recipient liver did not predict a poorer outcome in terms of allograft survival or patient survival among liver transplant recipients [10]. These studies show that OLT can be done successfully in alcoholic hepatitis, until 2011 alcoholic hepatitis has been considered as an absolute contraindication to OLT. In fact most transplant centres require 6 months of abstinence prior to OLT, while the great percentage of patients whose hepatitis is not responding to medical therapy have a survival rate less than 6-month. Since most of deaths due to alcoholic hepatitis occur within 2 months, early OLT is attractive but controversial. Recently a French and Belgian group selected and listed for OLT 26 patients with severe alcoholic hepatitis within a median of

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13 days after non response to medical therapy. These patients had no prior episodes of alcoholic hepatitis or severe coexisting conditions, also had supportive family members, and a commitment to alcohol abstinence. The survival rate was compared between patients who underwent to early OLT and patients who did not. The cumulative 6-month survival rate was significantly higher among patients who received early OLT, with a benefit maintained through 2 years of follow-up. In total 3 patients resumed drinking alcohol, in particular, one at 720 days, one at 740 days, and one at 1140 days after OLT [11]. This trial suggests the need to rethink the 6-month rule at least in patients with severe disease and favourable addiction profile patients [12]. In summary, early OLT may only be considered in highly selected patients with severe alcoholic hepatitis and favourable addiction profile, that not responding to medical therapy [8].

Alcohol-related Cirrhosis

The treatment of patients with alcohol-related cirrhosis is mainly symptomatic and no other therapies are currently available [3]. Recently, several drugs have been tested to improve survival in patients with alcohol-related cirrhosis, including propylthiouracil, colchicine, antioxidants and phosphatidylcholine. However, although some have shown to be promising, no drugs have shown a survival improvement in these clusters of patients [13-16]. Total alcohol abstinence is the main outcome to achieve in these patients [3]. Alcohol abstinence may reduce the disease progression; several studies showed that a stable liver function and a recover from advanced liver failure can be achieved with alcohol abstinence in AUD patients with advanced ALD [6,17]. To achieve total alcohol abstinence, these patients need to be managed by clinicians with expertise in AUD in order to provide a comprehensive evaluation of the patient and to plan specific therapeutic approaches. At present psychosocial approach combined with pharmacotherapy seems to be effective to help these patients to achieve and maintain alcohol abstinence [5]. When even total alcohol abstinence does not result in a significant improvement of liver function, OLT represents the gold standard treatment for end-stage alcohol-related cirrhosis [18]. At date, alcohol-related cirrhosis is the main indication for OLT in males; after viral hepatitis, is the second commonest indication overall in the United States and Europe [19]. In patients with advanced ALD the 5-year survival without OLT is less than 25% [20], while it is higher than 70% if liver transplantation is performed [21]. Moreover, survival rates after liver transplantation for ALD are similar or higher than survival rates of patients transplanted for other aetiologies [22]. This observation has been recently confirmed in a recent study based on ELTR (European Liver Transplant Registry) database, which showed a better survival rates in patients transplanted for ALD with respect to the survival rates of patients transplanted for other aetiologies [23]. However advanced ALD is still considered a controversial indication for OLT. The reluctance to transplant AUD patients stems in part from the view that AUD patients bear responsibility for their illness [24] and there is also the perception that the AUD patient is likely to relapse into alcohol use after transplantation and thereby damage the allograft. Therefore there is the need to identify those at risk of relapsing to alcohol use post-transplant as well as defining exactly what constitutes a relapse [25]. Moreover, AUD patients with advanced ALD usually have several co-morbidities, such as heart disease and impaired nutritional status that might limit the potential success of OLT. In particular alcohol-related cardiomyopathy and coronary heart disease are associated to a significant mortality and morbidity during OLT [18]; poor pre-operative nutritional status is associated with longer intensive care unit stay and increased likelihood of post-transplant infections [26]. AUD patients show high prevalence of psychiatric co-morbidity such as anxiety disorders, affective disorders, schizophrenia and other drugs addiction [27]. In addition, AUD patients, after OLT, appear to have a higher incidence of malignancies, especially of the upper airways and upper gastrointestinal tract such as, cancers of mouth, larynx, pharynx, and oesophagus [28]. The incidence of these malignancies as cause of death is at least two fold higher in patients transplanted for ALD with respect to other indications [23], and it seems related in particular to relapse in heavy drinking [18].

On the other hand AUD patients, after transplantation, have fewer episodes of acute cellular rejection than patients transplanted for other indications [29,30]. The incidence of retransplantation and histological recurrence of disease after OLT in these patients is less frequent than other liver diseases [31]. To make a comparison with Hepatitis C Virus (HCV), it is well known that virtually all transplanted patients have an HCV allograft infection, with a 10- to 20-fold increase in levels of viremia after liver transplantation; in these patients the progression to HCV-related cirrhosis is estimated to reach 20-30% at 5-year follow-up [32]. On the contrary, in AUD patients an adequate therapeutic approach for maintaining abstinence could completely eliminate the pathogenic agent [33] with no recurrence of the disease. However OLT for HCV-related cirrhosis and in HCV-infected patient does not represent a debated indication, notwithstanding the "risk" of the HCV re-infection after surgery [12].

Finally AUD should not be considered a self-inflicted illness. It is a chronic relapsing disease according to the DSM-V criteria [34], with genetic and environmental influences and it should not be used to exclude patients from transplantation. Obviously an accurate stratification of potential candidates to identify those most likely to remain abstinent after OLT is needed. A multidisciplinary collaboration of transplant hepatologists, surgeons and clinicians with expertise in AUD is mandatory to identified psychosocial predictors of long term sobriety and compliance after OLT in AUD patients [35,36]. Relapse rates after OLT is lower if the patient successfully completed an alcohol rehabilitation program prior to OLT [19].

Because of the shortage of cadaveric donors, some countries have developed Living Donor Liver Transplant (LDLT) as an alternative procedure for patients awaiting OLT. However, many ethical and technical problems, such as organ trade, physical and psychological harms for donor are related to LDLT; therefore, at present there are worldwide strategies in order to remedy to organ shortage, increase donor awareness and promote organ donor registration [37].

All these evidences strongly suggest considering some important points when OLT is considered in an AUD patients with ALD: the appropriate management by a team of specialists, including physician with expertise in AUD management, the optimal timing for transplantation, the pretransplant abstinence (6 month-rule) and risk of recidivism after OLT.

Management of Alcohol use Disorder before and After Liver Transplantation

Several approaches have been evaluated to manage AUD patients with ALD before and after OLT, but there is no standardized approach, and available data are few and often controversial. In some liver transplant centres, AUD patients are encouraged to attend support groups, even if data on the efficacy of such treatment in this cluster of patients are at present lacking. In a pilot study, Georgiou et al. [38] reported that psychosocial interventions could be a valid approach to

support motivation in these patients. However, this study was conducted on a limited number of patients, and the efficacy of this intervention on alcohol recidivism after OLT was not evaluated. Bjornsson et al. [39] evaluated the impact of the management of AUD patients by addiction psychiatrists, social workers, and tutors in the period before OLT and reported a 22% prevalence of alcohol recidivism in the treated group versus 48% in the untreated group. Erim et al. [40] evaluated the impact of psycho educational therapy in this cluster of patients, showing low rates of alcohol recidivism. However, alcohol abstinence was only evaluated using Blood Alcohol Concentration (BAC) determinations. In a recent trial, Weinrieb et al. [41] evaluated the impact of motivational therapy versus standard treatment (counselling or support groups) in AUD patients waiting for OLT. A modest effect of the motivational treatment was shown.

Recently, Addolorato et al. [35] retrospectively compared 55 alcoholic-related cirrhosis patients who underwent OLT followed by Alcohol Addiction Unit (AAU) within Liver Transplant Centre with 37 alcoholic-related cirrhosis patients who underwent OLT followed by a team of psychiatrists with expertise in addiction medicine not affiliated to Liver Transplanted Centre. The analysis showed that patients followed by AAU presented lower prevalence of alcohol recidivism and a significantly lower mortality. In conclusion, this study, with the limitations of the retrospective design and of the small sample size, indicates that the presence of an AAU within the Liver Transplantation Centre could reduce alcohol recidivism after OLT. A large sample prospective study is needed to evaluate this approach in the management of AUD patients before and after OLT.

Regarding pharmacological treatment, a randomized clinical trial with naltrexone administration after OLT failed to recruit patients, because patients refuse treatments with anticraving medications [42]. In the study by Addolorato et al, a very small subgroup of patients received a treatment with baclofen as part of the multimodal treatment before OLT. No patients in this subgroup showed alcohol recidivism after OLT [35]. This preliminary observation is consistent with the ability of baclofen to promote abstinence, reduce alcohol craving and drinking in patients with severe liver disease [43]. Larger prospective studies are needed to evaluate the potential use of baclofen before and after OLT to prevent alcohol recidivism.

Timing for Liver Transplantation

In an era of organ shortage, although OLT is recognised to improve survival in patients with advanced alcohol-related cirrhosis, it is important to recognise which group of patients could be offered standard treatment and which group of patients should be immediately listed for transplantation.

Poynard et al. [44] evaluated the survival rate of transplanted patients for alcoholic-related cirrhosis with respect to a conservatively treated control group. The Authors found that the probability of 5 years survival was significantly higher in transplanted patients than in control groups. However the better survival outcome was restricted only to patients with Child-Pugh C score. A further study demonstrated that immediate listing for OLT of AUD patients with Child-Pugh stage B cirrhosis did not show a survival benefit compared with conservative standard care and increased the risk of extra hepatic cancer [45]. Previous studies have failed to demonstrate that other clinical manifestations of liver decompensation, such as variceal haemorrhage, hepatic encephalopathy, new onset ascites or spontaneous bacterial peritonitis, were independent predictors of survival over and above the MELD score [46]. Nonetheless, the onset of any of these features in an abstinent alcoholic should prompt the managing physician to consider referral to a transplant centre [8]. In conclusion, OLT confers a survival benefit in patients with ALD classified as Child-Pugh C and/or MELD ≥ 15 [8].

The 6-month Rule

In 1997, a consensus conference of the American Association for the Study of Liver Diseases and the American Society of Transplantation concluded that there is a strong consensus for requiring that AUD patients should be abstinent from alcohol for at least 6 months before they can be listed for OLT [47]. This is often called the 6-month rule and the first purpose was to allow recovery of liver function. However, since then, the 6-month rule has mostly been discussed as a prognostic tool for predicting subsequent alcoholic recidivism. However, this approach has been questioned, since it seems arbitrary and not evidence based [48] and there is growing evidence that the "6-month rule" is unable to predict alcohol recidivism risk [49,50]. Alcohol abstinence time usually produces an improvement of liver function, and a period of total alcohol abstinence is a mandatory criterion for the eligibility to OLT [8]. However, in some patients, the overall clinical status does not allow for a 6 months waiting time. The above mentioned study by Addolorato et al. [35] showed no difference in the rate of alcohol recidivism in AUD patients followed by Alcoholic Addiction Unit within liver transplantation centre with either >6 or <6 months of alcohol abstinence before OLT. Therefore this study suggests that a pre-transplant abstinence period could be shortened, at least in selected patients managed by specialized Alcohol Addiction Unit. In this regard, some reports already support this hypothesis [51,52] and some investigators suggest that the cut-off could be reduced to >3 months in selected patients [53]. Future prospective studies are needed, however, to shed light on this point.

Recidivism

Most of the concerns about OLT are related to the risk of alcohol recidivism often reported as the major argument against OLT eligibility [48,52,54]. There is still no consensus about the meaning of recidivism, relapse and slips after OLT among clinicians with expertise in AUD and hepatologists. Some experts define a return to alcohol consumption at a lower rate as a slip, and relapse as consuming over a set amount (such as 21 units/week for males and 14 units/week for females) [55]. However, since alcohol use after OLT leads to a higher incidence of graft loss due to poor compliance to the immunosuppressive therapy [56], lower survival of these patients [57] due to extra hepatic alcohol-related damage [56,58] and increased number of complications that require hospitalization and may even determine the loss of the transplanted organ [58] many hepatologists define any post-liver transplantation alcohol consumption as recidivism [59]. The lack of a commonly accepted definition of recidivism, the different post-OLT follow-up periods, and the different tools used to investigate the amounts of alcohol consumed by this patients could explain the highly variable rate of recidivism after OLT reported in the literature, with a percentage ranging from 10 to 95% [39,60]. A psycho-social assessment of such patients plays a fundamental role in the evaluation of the risk of recidivism [22]. Several social factors, including living alone, lack of a stable partner or adequate family or friend support, lack or refusal of alcohol rehabilitation program before OLT, a family history of alcoholism in a first-degree relative and psychiatric co-morbidities predicted early post- OLT alcoholic recidivism [61-64]. However, as recently reported by Neuberger and Webb [65], existing psychometric tools and assessments are not able to accurately predict post-OLT relapse; further prospective studies on the topic are necessary [48].

Conclusion

In conclusion, advanced ALD is a widely accepted indication for OLT. The experience of transplantation in patients with acute alcoholic hepatitis is very positive, although at moment it is limited to a restricted number of patients with specific selection criteria. The survival rate after OLT is better than other indications. It is possible to put patients with ALD in the OLT waiting list. In this case the management of AUD should be started as soon as possible by alcohol specialists able to help patients achieving and maintaining alcohol abstinence, monitoring abstinence in those patients on the OLT waiting list, and offering therapeutic support to prevent recidivism before and after OLT. Alcohol specialists should participate to the meetings with all the other members of the OLT group and should play a key role in the final decision of those issues related to patients' alcohol use, such as, for example, including or removing patients from the OLT waiting list, as well as approving in some specific cases the inclusion in the waiting list of patients with <6 months of total alcohol abstinence [35].

The main future goals are to formulate a well-defined pre-transplant approach, a single definition of alcohol recidivism and to establish the useful strategies to manage alcoholic patient and prevent recidivism.

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