



What is the role of transplantation in the management of alcoholic liver disease?

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Abstract: Alcoholic liver disease is a major cause of morbidity and mortality with effective pharmacotherapy being limited at present. As such, abstinence remains the cornerstone of therapy, and requires a multidisciplinary approach to address the medical and psychosocial determinants of addiction to effectively prevent relapse. Liver transplantation has a well-established role in the treatment of chronic alcoholic cirrhosis, with outcomes comparable to other aetiologies of chronic liver disease. Transplantation has been shown to be successful in highly selected candidates with acute alcoholic hepatitis (AAH), with favorable outcomes. However, AAH has not gained universal acceptance as an indication for liver transplantation, and remains controversial at present. Designing and applying objective and reliable selection rules while ensuring fair allocation in an era of organ shortage remains a challenge.

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Scope of alcohol-related disorders

Over 3.3 million deaths, or 3.8% of global mortalities, were attributed to excessive alcohol consumption in 2012, as were 4.6% of disability-associated life years—making alcohol misuse a leading cause of morbidity and mortality on a global scale (1). The liver, being the primary site of ethanol metabolism, is particularly susceptible to the toxic effects of alcohol, with great variability in its presentation, ranging from acute alcoholic hepatitis (AAH) to progressive fibrosis and cirrhosis. Indeed, alcohol use disorder is the leading cause of advanced liver disease in Western countries: nearly half of all liver-cirrhosis deaths and disability-adjusted life years lost due to cirrhosis are alcohol-attributable (2). Traditionally, the treatment of alcoholic liver disease hinges on abstinence, as medical therapy is limited. In cases of AAH, corticosteroids have been shown to modestly improve short-term mortality (3). However, nearly 40% of patients

fail to respond to steroid therapy, a situation which portends a very poor prognosis with 6-month survival under 25% (4). It is in this context that the question of possible rescue liver transplantation—and more broadly the appropriate place of transplantation in the management of patients with alcoholic liver disease in general—is raised.

Transplant consideration

Central to the transplant discussion is the dilemma of judicious and ethical organ allocation in the context of chronic organ shortage. Indeed, nearly 115,000 patients are on the organ transplant waiting list in the US alone, and 20 patients die every day waiting for a life-saving transplant (5). This dynamic is a reflection of the relatively static rate of organ donation versus the rising number of patients in need of transplantation. Livers account for 20% of organs transplanted yearly, second after kidneys. This translates to

a mortality rate on the liver transplant waitlist, or delisting, of 10–20% depending on the region.

For this reason, eligibility criteria for transplantation have been set, largely by consensus, to aid in identifying those patients most likely to benefit from the scarce resource that is a transplant. For alcohol use in particular, a 6-month rule of abstinence has been adopted by most programs, though it has not been formally recommended by transplant groups internationally such as UNOS, AASLD, EASL and the French Conference Consensus on Liver Transplantation. The rationale behind a mandated period of abstinence prior to listing is threefold: first, there is evidence in support of liver recovery after a period of abstinence, hence the 6 months allows a time for liver function to improve and possibly avoid the need for transplant altogether. Second, it serves as a trial period to observe if the patient will be compliant and abstain from alcohol, and thus identify those most likely to maintain abstinence post-transplant. Thirdly, it provides time to install a support network to encourage and maintain abstinence, as well to address any pathology driving abuse behaviour (6).

There are some limitations to these arguments, however. First, there is a lack of evidence on the specific time frame of abstinence associated with the lowest relapse rate. Under the current rules, recidivism post transplantation ranges between 15–25%, thus highlighting that transplantation is not a cure for alcoholism. Critics to the 6-month rule point out that recidivism rates were similar in small trials of transplantation for AAH, who did not fulfill 6 months of abstinence, compared to those for alcoholic cirrhosis, where the 6-month rule was enforced, thus suggesting that factors other than time are at play in determining relapse. Indeed, a meta-analysis found that factors associated with recidivism post-transplant included less than 6 months of abstinence, but also a lack of social support or a family history of alcoholism (7). Better recognition of these high-risk features and a multidisciplinary approach to the patient may be needed to reduce relapse rates rather than a strict timeframe alone. Another objection raised against the 6-month rule is that a subset of patients, particularly those with AAH, present after a point of no return, when natural recovery of the liver would be impossible. At 6 months, mortality rates are situated around 80% in severe cases, thus a rigid rule quantifying abstinence effectively excludes these patients from life saving therapy which may seem difficult to justify ethically.

These limitations notwithstanding, most programs in the United States and all programs in Canada currently apply a

6-month rule, and some additionally require participation in a formal rehabilitation or counselling program prior to being listed. There has been a call for a national consensus policy on patients with alcoholic liver disease to formally standardize these practices.

Within the parameters listed above, alcohol-related cirrhosis remains an established indication for liver transplantation. In fact, it represents the third most common reason for liver transplantation after hepatitis C and hepatocellular carcinoma (8). Post-transplant outcomes for patients with alcoholic liver disease are similar if not slightly better than those transplanted for other indications, including autoimmune and chronic viral hepatitis, with 1- and 5-year survival rates of around 85% and 75% respectively (9). The rate of graft loss due to resumption of alcohol post-transplant is low, around 2% at 10 years, which compares similarly to the rate of graft loss due to recurrence of primary biliary cholangitis (10). However, deaths from all social causes as well as suicide rates are double in this population compared to other etiologies of chronic liver disease, highlighting the ongoing vulnerability of this group (9). Compliance with medications post-transplant is also similar between those with alcoholic liver disease compared to other groups.

Transplant for acute alcoholic hepatitis

Considering liver transplantation for AAH is much more contentious than for chronic alcohol-related cirrhosis, largely owing to the fact these patients cannot fulfill the 6-month abstinence requirement. Currently no Canadian transplant program performs transplantation in the AAH setting, while only some centers in the US have cautiously adopted it in very select circumstances. In 2011, a multi-centre pilot trial examined the possibility of early liver transplantation for AAH (11). Patients from seven transplant centres in France and Belgium with severe AAH and a Lille score of ≥ 0.45 or worsening liver function at day 7, indicating non-response to steroids and poor prognosis were carefully selected. Inclusion criteria included: no prior episodes of alcoholic hepatitis, no severe coexisting medical or psychiatric conditions, supportive family members, social integration and a lifelong commitment to alcohol abstinence. Of note, an absolute consensus among 4 team circles of medical and paramedical staff was required prior to listing. Given these stringent criteria, only 26 patients were approved and listed for transplant, with a median of 13 days of non-response to medical therapy. Compared

to a matched group who did not undergo transplantation, the transplanted group had better short- and long-term outcomes: 6-month survival of 78% *vs.* 24% in the non-transplanted group, and a 2-year survival of 72% *vs.* 24% in the non-transplanted group. Three patients (12%) resumed drinking. This study demonstrated that early liver transplantation can improve survival in a highly selected group of patients with a first episode of alcoholic hepatitis.

Two American studies have since reproduced these findings, in similar small numbers of carefully selected patients, with comparable if not more pronounced survival benefit (12,13). Most recently, the American Consortium of Early Liver Transplantation for Alcoholic Hepatitis published the combined experience of 12 centres across the US, totalling 147 patients over 9 years. They report even more impressive 1- and 3-year survival rates following transplantation of 94% and 84%, respectively. Recidivism rates in this cohort were similar to previous reports, situated at 25% for any alcohol use, and 10% for sustained use 1-year post transplant. Return to hazardous drinking post transplant was a strong predictor of death (14).

There have been an increasing number of legal challenges to the denial of transplantation for patients with AAH and enforcement of the 6-month rule in light of these results (15). Most recently, a case in Ontario, Canada prompted the province to pilot a trial protocol of transplantation for AAH, the first in Canada (16). Though promising, the study findings are difficult to generalize given the rigorous and labour-intensive screening and selection process required—thus explaining the lack of widespread uptake of this practice. For the moment, liver transplantation for alcoholic hepatitis remains under study.

Ethical considerations

One of the principal points of contention in the discussion of transplantation for alcoholic liver disease is ethical. Given that the donor pool is already inadequate to meet current needs, the debate over fair organ allocation will be heightened if more patients are denied access to life saving transplantation with controversial indications such as AAH. The second controversy is centered on public perception of alcoholism. Some consider that the self-inflicted nature of alcoholic liver disease should have repercussions on eligibility or priority for transplantation. Most ethicists reject this view, and advocate that personal responsibility for illness should have no bearing on access to life-saving treatment, in this case the decision to transplant. Hepatic

failure for voluntary acetaminophen poisoning, or active drug users with acute hepatitis B for instance are scenarios in which emergency liver transplantation is uncontested (17). Public concerns are not trivial; any change in allocation rules concerning alcoholic patients in particular may affect public willingness to donate organs. Yet, in a recent American survey, 82% of respondents were at least neutral about transplanting patients with AAH, though many had concerns about recidivism resulting in graft damage. Age of the recipient was the most important factor in deciding willingness to donate (18). An open discussion is needed to ensure policies and perceptions surrounding transplantation are based on sound scientific knowledge and principles of equity.

Conclusions

Alcoholic liver disease is among the most common causes of advanced liver disease and the third commonest indication for transplantation. Transplantation offers a survival benefit in both the settings of chronic alcohol-related cirrhosis and in selected patients with AAH. Alcohol relapse post-transplantation affects up to 1/4 of patients. The need for organ transplantation outpaces donation, leading to high mortality on the transplant waitlist and emphasizing the need for extremely cautious patient selection for this scarce resource. The traditional 6-month rule of abstinence fails to adequately predict post-transplant relapse, and is increasingly contested as unethical. A more comprehensive psychosocial assessment will be key in determining eligibility more equitably and ensuring best outcomes.

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