LEADING ARTICLE

Liver transplantation alcohol related liver disease: (deliberately) stirring a hornet's nest!

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Outcomes after liver transplantation for alcohol related liver disease compare very favourably with those documented for other causes of cirrhosis. Despite this, 5% or less of patients with advanced alcohol related liver disease are considered for transplantation. The reasons for this are complex but include professional reluctance to refer these patients for formal assessment as well as a limited and dwindling number of organs available for transplantation. Demonstrating abstinence from alcohol consumption remains central to the assessment of candidates for transplantation. Return to alcohol consumption after transplantation can follow a pattern of abuse with consequences for health and survival but may also be controlled and of little clinical significance. A better understanding of the issues influencing these outcomes should decrease the tension that currently exists between patient expectations, professional opinion, and the attitude of the general public who gift organs for donation.

The basic facts about liver transplantation for alcoholic liver disease are straightforward. Alcohol induced liver disease is either the first or second commonest specific indication for liver transplant throughout Europe and the USA. Survival rates after liver transplantation are comparable to other aetiologies of cirrhosis.[1] Rejection of the graft is no longer a particularly challenging problem in liver transplantation but is even less so in patients transplanted for alcohol related disease. The disease recurs in a minority of patients but histologically proven disease recurrence is less frequent than with hepatitis C, primary biliary cirrhosis, autoimmune hepatitis, or primary sclerosing cholangitis. Disease recurrence has little impact on graft survival rates within 7–10 years of transplantation, in marked contrast with hepatitis C. An increased incidence of upper gastrointestinal tract malignancies is a peculiarity of this population but the incidence is not sufficiently high to contraindicate transplantation in this group.[2 3] Patients receiving transplants for alcohol related liver disease have the same level of societal reintegration as for other aetiological cohorts.[4]

The synopsis outlined above belies the considerable controversy that entangles this subject. From the patient's perspective, liver transplantation is made available to a highly select minority of patients with advanced alcohol related liver disease. An Austrian study found that only 5% of patients dying from alcohol related liver disease received transplants.[5] The UK data relating to the number of deaths from cirrhosis and transplant activity support this finding, indicating that 95% of patients with life threatening alcohol related liver disease are never formally assessed for liver transplantation. Access to the transplant waiting list depends on the ability to convince a series of professionals who appear somewhat cynical about their motives and set apparently arbitrary tests to determine access to a life saving intervention. Some patients labelled as having alcoholic liver disease are surprised given that their perception of their alcohol usage is moderate and in line with their peers. Some are mystified, if not annoyed, that honesty about alcohol consumption is penalised while more wily counterparts know how to ''tick the boxes'' and progress through the system.

> ''95% of patients with life threatening alcohol related liver disease are never formally assessed for liver transplantation''

There is a perception that the media and general public are antagonistic towards liver transplantation for patients with alcohol related liver disease. Articulation of attitudes about the allocation of organs to patients with alcohol related liver disease tends to be unidimensional and based heavily on the assertion that the disease is self inflicted. The general public is seen as being entitled to hold a view given that it gifts the pool of cadaveric organs to the medical profession and ultimately to the recipient population. Tests of public opinion in the USA and the UK have demonstrated little enthusiasm for offering liver transplants to patients with alcohol related liver disease.[6 7]

The polarised views outlined above reflect a lack of insight in the understanding of the manifestations of excessive alcohol consumption. A fundamental problem is failure to emphasise that alcoholism (alcohol dependency syndrome) and alcohol related liver disease are common problems that may, but do not necessarily, coexist. The majority of alcoholics escape significant liver injury and many patients with alcohol related liver disease have no associated dependency syndromes. Untreatable alcoholism is, and should be, a contraindication to transplantation but 34–48% of patients with alcoholism are successfully treated and 60–75% of alcohol abusers recover spontaneously.[8] It is not

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widely appreciated that many patients who present with ''alcoholic'' liver disease are not alcoholics but simply drink on par with their peers and develop alcohol related liver disease because of genetic factors, sex, or coexistent hepatitis C.

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The requirement to be abstinent from alcohol for at least six months prior to transplantation is widely applied but much criticised. Its value as a screen to identify patients with a better prognosis with respect to future alcohol consumption has been questioned on the basis of conflicting findings.[8 9] However, recent studies again point to the length of abstinence before transplantation as being one of the most important determinants of long term sobriety.[10 11] The undisputed role of a period of enforced abstinence is to screen for the ability for clinical stabilisation and subsequent improvement to occur with the potential for the factors indicating transplantation to resolve. Six months has been considered to be a reasonable period over which to test the potential reversibility of the clinical liver disease but recent experience with the increasing waiting times suggests that the potential extends beyond this interval in some patients. Critics of the need to demonstrate ability to abstain from alcohol point to the lack of opportunity to fulfil this in patients with the most advanced disease. This is particularly true of patients with acute alcoholic hepatitis that has in the main been considered a contraindication to transplantation. The justification for this is a combination of the absence of abstinence and the perception that patients with severe acute alcoholic hepatitis are high risk candidates for liver transplantation, despite the fact the limited available data do not support this point of view.[8 12] However, patients who received transplants for acute alcoholic hepatitis in these studies were young or were able to abstain from alcohol for at least three months before transplantation and are not representative of the overall patient population. At present, application of liver transplantation in patients with severe acute alcoholic hepatitis should be considered clinically unproven and politically challenging.

The third dimension to the requirement of a defined period of abstinence before transplantation is equity and transparency. Equity and uniformity of practice is important, even if the scientific basis for the requirement for abstinence is open to challenge. In this regard, national guidelines for assessment of patients with alcoholic liver disease in the UK have been agreed and these endorse the six month rule.[13] The rigid requirement for abstinence is also likely to be welcomed by the general population and the rule should be retained as long as their good will remains pivotal to the conduct of a liver transplant service. A history of cycles of withdrawal from alcohol followed by relapse prior to transplantation has been linked to a return to alcohol usage after liver transplantation,[10] and this is reflected in the national guidelines in that patients relapsing despite clear medical advice will not be assessed favourably.[13]

''Resumption of alcohol consumption after liver transplantation is often deemed a failure of the intervention''

Resumption of alcohol consumption after liver transplantation is often deemed a failure of the intervention. However, alcohol consumption follows a number of patterns with different consequences. The easiest pattern of alcohol consumption to detect is alcohol abuse that was diagnosed in 13–22% of cases in recent experience.[10 11 14 15] One study documented a 45% survival rate at 10 years in patients who returned to alcohol consumption compared with 86% in their counterparts who continued to abstain.[16] However, most other studies report serious consequences from alcohol consumption on an anecdotal basis, albeit sometimes dramatically with progression to death or cirrhosis within a few years of transplantation or loss of the graft through rejection contributed to by poor compliance with the post transplant regimen. Assessments of the proportions consuming any alcohol in these recent studies have ranged from 10% to 52%.[10–12 14–17] One interpretation of this fairly broad range is that it reflects the skill of the investigators in detecting alcohol usage rather than a fundamental difference in behavioural patterns in the different centres. An alternative explanation is that it is a function of different selection criteria and thresholds for accepting patients for liver transplantation. Provision of a structured management programme after liver transplantation, something that is not uniformly provided by UK transplant programmes, was shown to more than halve the rate of return to alcohol consumption in one Scandinavian study.[14] Most, if not all, estimates are likely to be underestimates. An early but telling study found that when patients, who were more than five years out from transplantation, were interviewed by a professional unattached to the transplant programme, a history of alcohol consumption was elicited in 95%.[18] However, the average amount of alcohol consumed was only about 10% of that imbibed prior to the transplant. Should this be interpreted as near total failure or a dual success of treating the liver disease while achieving controlled drinking patterns?

''The current state of provision of liver transplant services for patients with alcohol related liver disease in the UK is suboptimal''

The current state of provision of liver transplant services for patients with alcohol related liver disease in the UK is suboptimal when evaluated by the parameters that are normally applied to assessment of a service, including equity of access and state of the art comprehensive treatment. This situation is semi-legitimised by the limitation imposed by the availability of donor organs, and there is little evidence that this will be resolved by provision of living related liver transplantation.[19] Organ donation from deceased donors is steadily declining to the extent that the UK has slipped, in football parlance, from a position of leadership through mid-table mediocrity to flirting with the relegation zone. Adjustment of organ donation rates to the levels seen in Spain and Italy, considered by many in the transplant community to be achievable with investment coupled with political and professional deftness, would go a considerable away to enabling access for treatable patients with alcohol related liver disease to the full range of appropriate therapy. However, an obvious criticism of this viewpoint is that the negative portrayal of practice regarding liver transplantation has contributed to the decline in organ donation. At present, it is very difficult to determine whether this is a real or perceived phenomenon.

''The perception of the futility of intervention generated by the stereotypical recalcitrant alcoholic must be challenged and replaced by a positive message about the availability of effective treatment for many patients with alcohol related disease''

A finger could be pointed at the medical profession for failing to engage the general population with an appropriate level of sophistication regarding alcohol consumption and its sequelae. The only advice on consumption widely recognised is the weekly limit on the number of units that eliminates the risk of developing cirrhosis. This information is important for a section of society but it lacks credibility in the population of regular alcohol consumers who recognise that in the real world most people can exceed that level of consumption throughout their lifetime and come to no harm. Behavioural patterns are more likely to be changed within this group by information with which they can empathise that graduates the risk from zero to medium and high. Regular alcohol consumers are also more likely to be receptive to advice that reduces risk (for example, regular short periods of abstinence, good nutrition). Linkage between alcoholism and alcohol related liver disease needs to be broken and the individual components of disease dealt with separately. The perception of the futility of intervention generated by the stereotypical recalcitrant alcoholic must be challenged and replaced by a positive message about the availability of effective treatment for many patients with alcohol related disease. This level of engagement could be a major step in closing the loop between the public, the patient, and the profession, and allow liver transplantation for alcohol related liver disease to both progress and be assessed in a more appropriate light. From the ivory tower of a transplant centre, it would appear that we could, and should, do better.

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REFERENCES

1 **Roberts MS**, Angus DC, Bryce CL, *et al*. Survival after liver transplantation in the United States: a disease-specific analysis of the UNOS database. *Liver Transpl* 2004;**10**:886–97.
2 **Saigal S**, Norris S, Muiesan, et al. Evidence of differential risk of posttransplantion malignancy based on pretransplant cause in patients undergoing liver transplantation. *Liver Transpl* 2002;**8**:482–7.
3 **Kenngott S**, Gerbes AL, Schauer R, *et al*. Rapid development of esophageal squamous cell carcinoma after liver transplantation for alcohol-induced cirrhosis. *Transpl Int* 2003;**16**:639–41.
4 **Cowling T**, Jennings LW, Goldstein RM, *et al*. Societal reintegration after liver transplantation: findings in alcohol-related and non-alcohol-related transplant recipients. *Ann Surg* 2004;**239**:93–8.
5 **Berlakovich**. Wasting your organ with your lifestyle and receiving a new one? *Ann Transplant* 2005;**10**:38–43.
6 **Neuberger J**, Adams D, McMaster P, *et al*. Assessing priority for allocation of donor grafts: survey of public and clinicians. *BMJ* 1998;**317**:172–5.
7 **Dixon J**, Welch HG. Priority setting: lesson from Oregon. *Lancet* 1991;**1**:891–4.
8 **Neuberger J**, Schultz K-H, Day C, *et al*. Transplantation for alcoholic liver disease. *J Hepatol* 2002;**36**:130–7.
9 **Lim JK**, Keefe EB. Liver transplantation for alcoholic liver disease: current concepts and lengths of sobriety. *Liver Transplant* 2004;**10**:S31–8.
10 **Perney P**, Bismuth M, Siguard H, *et al*. Are preoperative patterns of alcohol consumption predictive of relapse after liver transplantation for alcoholic liver disease? *Transpl Int* 2005;**18**:1292–7.
11 **Miguet M**, Monnet E, Vanlemmens C, *et al*. Predictive factors of alcohol relapse after orthotopic live transplantation for alcoholic liver disease. *Castroenterol Clinic Biolog* 2004;**28**:845–51.
12 **Tome S**, Martinez-Rey C, Gonzales-Quintela A, *et al*. Influence of superimposed alcoholic hepatitis on the outcome of liver transplantation for end-stage alcoholic liver disease. *J Hepatol* 2002;**36**:793–8.
13 **Bathgate A**. UK liver transplant group recommendations for alcohol-related liver disease. *Lancet* 2006;**367**:2045–6.
14 **Bjornsson E**, Olsson J, Rydell A, *et al*. Long-term follow-up of patients with alcoholic liver disease after liver transplantation in Sweden: impact of structured management on recidivism. *Scand J Gastroenterol* 2005;**40**:206–16.
15 **Pageaux GP**, Bismuth M, Perbey P, *et al*. Alcohol relapse after liver transplantation for alcoholic liver disease: does it matter? *J Hepatol* 2003;**38**:629–34.
16 **Caudrado A**, Fabrega E, Casafont F, *et al*. Alcohol recidivism impairs long-term patient survival after orthotopic liver transplantation for alcoholic liver disease. *Liver Transpl* 2005;**11**:420–6.
17 **Jauhar S**, Talwalkar JA, Schneekloth T, *et al*. Analysis of factors that predict alcohol relapse following liver transplantation. *Liver Transpl* 2004;**10**:408–11.
18 **Howard L**, Fahy T, Wong P, *et al*. Psychiatric outcome in alcoholic liver transplant patients. *Q J Med* 1994;**87**:731–6.
19 **Rudow DL**, Russo MW, Hafliger S, *et al*. Clinical and ethnic differences in candidates listed for liver transplantation with and without potential living donors. *Liver Transpl* 2003;**9**:254–9.