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Transplantation for alcoholic liver disease: the wrong arguments

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A 1983 National Institute of Health consensus panel accepted alcoholic liver disease as an indication for liver transplantation "for patients in whom evidence of progressive liver failure develops despite medical treatment and abstinence from alcohol" [1]. In published series, 16–17% of patients transplanted receive a new liver for this indication [2, 3] and in databanks these figures are higher with, in 1998, 24% according to UNOS and 27% according to the *Etablissement Français des Greffes*. In the transplant programme of the Inselspital in Bern, Switzerland, 20% of transplantations were performed for alcohol-induced liver disease. Nevertheless, this indication still polarises opinion. The suitability of such patients for transplantation is viewed either with excessive enthusiasm or with overt disapproval. Four arguments regarding alcohol consumption and liver transplantation are frequently used, most of the time wrongly.

The first misconception states that *persons with alcoholic liver disease should not be transplanted because they are responsible for their damaged liver*. Leaving ethical issues aside, all adults are exposed to alcohol. But only a minority of individuals who drink regularly develop alcohol-induced liver disease and only a fraction of them progress to end-stage liver disease. While it is important to distinguish between the somatic and the psychiatric aspect of alcohol intake, the two overlap as liver disease progresses. Alcohol dependence has been diagnosed in 75% of patients transplanted for alcoholic liver disease [4]. These patients suffer from impaired control and therefore cannot be considered responsible for their alcohol intake. More important is the fact that not only alcoholism but also alcohol-induced liver disease are partly genetic diseases. Twin studies have identified a stronger genetic component for male dependence on alcohol than for arterial hypertension [5]. Sons of alcohol-dependent fathers tend to be more tolerant to alcohol and to have fewer hangovers, a fact which renders alcohol more pleasurable to them [6]. The C2–promoter allele of the gene coding for the cytochrome 450CYP2E1 shows a significantly different distribution in heavy drinkers. This C2–allele, which leads to higher expression, is present in 6% of healthy heavy drinkers, in 19% of heavy drinkers with alcoholic liver disease and in 33% of heavy drinkers with cirrhosis [7]. Similarly, homozygosity for the allele ADH3*2 of alcohol dehydrogenase 3 is differently expressed in healthy heavy drinkers (7%) and in heavy drinkers with alcoholic liver disease (31%, statistically significant) [7]. A polymorphism in the promoter region of human CD14, which leads to a higher expression on monocytes and therefore higher susceptibility to endotoxin, has been linked to the development of fibrosis in alcoholic liver disease [8]. Hence if we agree to transplant patients with α_1-antitrypsin deficiency, with Wilson's disease or with hereditary haemochromatosis, there is no reason to deny liver transplantation to patients with alcohol-induced liver disease.

The second misconception is that transplantation is the ultimate sobering experience, being such a harsh experience for patients that they never touch alcohol again. Posttransplantation abstinence lasts longer (14.5 months) in patients transplanted for alcohol-induced liver disease than in patients transplanted for another disease (6 months) [2]. But, as time goes by, the frequency of reported alcohol use after liver transplantation in patients transplanted for alcohol-induced liver disease increases linearly [9]. Thus most patients resume some degree of drinking after transplantation, but recidivism leading to new liver disease in the graft is fortunately rare [10].

The third misconception concerns the period of six months' abstinence as predictive of posttransplantation abstinence. This is a rule laid down by most transplant centres (85%) [11] and supported by six studies [3, 12–16]. In a retrospective study of 24 alcoholic patients Bird reported that 3 patients were transplanted despite the fact that they were drinking at the time of transplantation. All of these 3 patients denied post-transplantation drinking but the investigators thought otherwise in the light of indirect evidence [14]. In a study of 37 alcoholic liver transplant patients, 7 were not abstinent after surgery and 2 drank during the 6 months' period [3]. Finally, Kumar assessed abstinence in 52 alcohol-dependent patients followed for an average of 25 months. Seven of these patients admitted drinking during the 6 months' period and 3 conceded drinking after transplantation. This compares to 3 patients resuming drinking after transplantation out of 45 patients sober during the 6 months' period [16].

If in these studies 1 or 2 patients were miscategorised, significance will be lost. Hence it is not surprising to find more studies suggesting that pretransplantation abstinence for 6 months does not predict recidivism [2, 17, 18, 19–22]. The 6 months' period has the advantages of defining a goal for both the transplant team and the patient and of allowing hepatic function to recover. Some patients recover so well that at the end of the 6 months' period it becomes clear that they no longer need a liver transplant. On the other hand, this rule should be applied with flexibility, since some patients cannot wait for 6 months before receiving a new liver. Pretransplantation abstinence has shown poor sensitivity (61–84%) and poor specificity (64–68%) in predicting posttransplantation abstinence [13]. In their study Platz et al. found that severity of drinking prior to OLT, education, age and pre- and posttransplantation patient compliance failed to correlate with recurrence of alcoholic disease. Social environment and personal stability assessed by psychologists correlated significantly with recurrence [23]. Most transplant centres insist on a psychological evaluation before the transplantation. They require successful treatment of alcoholism with proven abstinence and good prospects of sustained patient compliance and continued abstinence from alcohol. Since family tensions and professional or social circumstances can create psychological difficulties and lead to drinking problems, these issues should be considered before and after liver transplantation listing.

The fourth misconception states that *course including survival after transplantation for alcoholic liver disease is similar to other indications*. Acute rejection of the liver transplant after alcohol-induced liver disease is significantly less frequent than for other indications. About 50% of patients transplanted for primary sclerosing cholangitis or autoimmune hepatitis will have an acute rejection episode in the first 2 months following transplantation. This is significantly more than the 30% of patients transplanted for alcoholic liver disease [24]. Only patients transplanted for hepatitis B have less acute rejections, but the immunomodulatory effect of the intravenous immunoglobulins given to prevent graft infection may explain this low rate. Data obtained from the Birmingham centre confirm that patients transplanted for alcoholic liver disease have less acute rejection compared with patients transplanted for primary biliary cirrhosis or primary sclerosing cholangitis (20, 43 and 50% respectively) [25]. Alcohol probably has an immunological effect by diminishing the recipient's capacity to build an immune response resulting in acute rejection. The flip side is that in the month following transplantation more than 50% of them will show evidence of bacterial infection, a significantly higher incidence than in patients transplanted for other indications [24]. Consequently, patients transplanted for alcoholic liver disease would probably benefit from less immunosuppression.

Several studies with a short follow-up have shown that survival after transplantation for alcohol-related liver disease or alcohol-unrelated liver cirrhosis is comparable. However, this seems to be the case only during the initial 5 years posttransplantation; beyond 5 years, patients transplanted for alcohol-induced liver cirrhosis are doing less well [26]. They die from cardiorespiratory problems and from tumours. The relative rate of

cancers 5 years after liver transplantation for alcohol-induced liver disease is 25% for oesophageal cancers and 4% for lung cancers [20]. The frequency of oropharyngeal cancers after liver transplantation in patients with alcohol-induced liver disease was 17% compared with 0% in patients transplanted for other indications [27]. These patients thus need specific and careful evaluation if the development of such tumours is to be identified early. 16–27% of liver transplantations are performed for alcohol-induced liver disease. Long-term posttransplantation abstinence is rare, but significant recidivism is also rare. The rule of 6 months' abstinence before listing is not predictive of posttransplantation abstinence. Patients transplanted for alcoholic liver disease have less acute rejections. In the long term they develop more cancers. Transplantation for alcoholic liver disease will remain a complex issue. It should not be seen as a panacea or as an inappropriate use of scarce resources. Many patients transplanted for alcohol-induced liver disease enjoy a normal, productive life.

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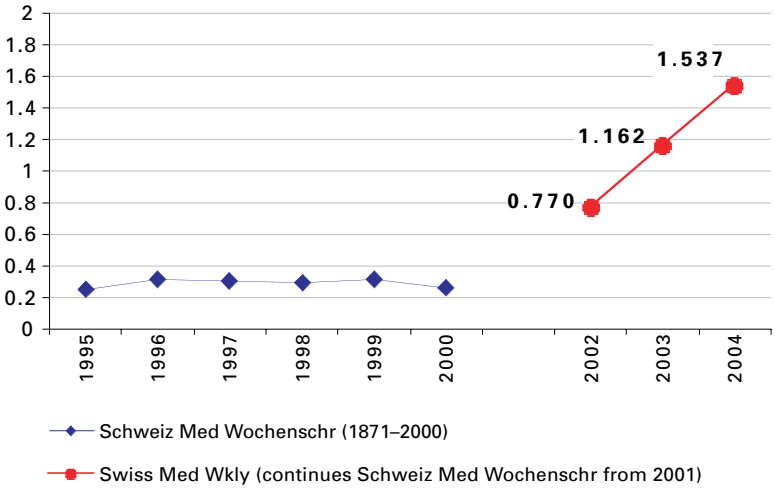

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