LIVER TRANSPLANTATION FOR ALCOHOLIC LIVER DISEASE – TIME FOR A PARADIGM SHIFT?

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ABSTRACT

Liver transplantation for alcoholic liver disease (ALD) is controversially discussed. Although overall survival after liver transplantation is similar to other indications, long-term survival is significantly reduced in patients with recurrence of excessive alcohol consumption. Criteria of transplant eligibility and prediction of risk of alcohol relapse after transplantation are the core concerns in this setting. Most transplant centres therefore require an abstention period of 6 months prior to listing. However, data on the '6-month rule' as a surrogate parameter for prediction of relapse are conflicting, and first reports on liver transplantation in highly selected patients with acute alcoholic hepatitis without response to medical treatment are promising. Therefore, a thorough pre-transplant evaluation by an experienced addiction specialist in addition to regular counselling and a highly supportive social surrounding after transplantation seem to be the key factors for long-term survival in ALD patients.

Keywords: Liver transplantation, alcoholic liver disease, alcohol markers, abstention period, relapse.

INTRODUCTION

Excessive alcohol consumption is responsible for 4% of mortality and presents the third leading risk factor for disease and disability worldwide.[1] Alcoholic liver disease (ALD) is the most prevalent liver disease in Europe and is the second most common indication for liver transplantation (LT) in Europe and the United States.[2,3] It comprises of a wide range of hepatic manifestations including alcoholic fatty liver disease, alcoholic steatohepatitis (ASH), and liver cirrhosis complicated by portal hypertension. LT has been well established as a life-saving treatment for end-stage ALD. However, as determined by the shortage of donor livers, alcoholic cirrhosis as an indication for LT is discussed controversially. Since alcoholism is a life-long disease and is not cured by LT, optimal selection of patients with a low risk of alcohol relapse, as well as continuous monitoring and support after LT, are essential.

DIAGNOSIS OF ALCOHOL ADDICTION AND ALD

Alcohol dependence has to be differentiated from alcohol abuse (DSM-IV), or hazardous and harmful drinking (WHO),[1] as well as from sporadic drinking episodes.[4,5] This classification is of particular importance within the transplant setting, since patients may be denied LT in the case of suspected alcohol abuse. Moreover, alcohol relapse in transplant recipients has to be detected at an early stage to provide psychomedical support and preserve long-term graft function. Clear diagnosis of alcohol consumption and ALD is complicated by the lack of definite cut-off values of ethanol, identified as harmful in certain populations.

Hepatic steatosis was found in 60% of patients with regular alcohol intake >60 g/day.[6,7] Liver cirrhosis was confirmed by liver biopsy in 29% of a large series of patients with alcoholism.[8] In a meta-analysis the daily consumption of >25 g ethanol has been associated with an increased risk of liver cirrhosis and its complications.[9]

Recently, increased risk of mortality due to liver cirrhosis was even found with consumption <25 g of ethanol per day (12-24 g/day).[10] Thus, patients might be put at risk even if ethanol levels are below the current public recommendations for alcohol consumption. Differential diagnosis to non-alcoholic fatty liver (NAFL) and steatohepatitis (ethanol cut-off: 20 g/day for women, 30 g/day for men), and the assessment of alcohol as an additional hit to the liver in other liver diseases are difficult.

RISK FOR ALCOHOL RELAPSE AND IMPACT ON OUTCOME

Outcome of LT for ALD in Europe is similar to other indications with a 5 and 10-year survival of 73%, and 59%, respectively.[11] Relapse of alcohol consumption occurs in 10-50% of patients undergoing LT for end-stage ALD.[4,12-14] Of these, 10-36% of patients resume drinking heavily.[5,14,15] Graft dysfunction can be found in up to 17% of patients.[16]

Cuadrado et al.[17] reported significantly reduced 10-year survival rates of 45% versus 86% in transplant recipients returning to alcohol use. Similarly, a recently published study - investigating alcohol relapse rates in living donor LT (LDLT) in Japan - described 10-year survival rates of 22% (versus 74%) in patients with alcohol relapse.[18] Of note, in contrast to patients with recurrence of heavy drinking, who suffer from subsequent organ dysfunction due to recurrent ALD and have mainly liver-related mortality, the majority of patients with low-to-moderate alcohol consumption (in the absence of other liver diseases), or those who are long-term abstainers, die from *de novo* malignancies, cardiovascular disease, or infections.[13]

Reports studying non-adherence to immunosuppression in patients with alcohol relapse show a wide range of 3-47%.[19-21] However, non-adherence is not directly associated with alcohol relapse, but rather with each patient's personality.[22] Unexpectedly, patients with LT due to ALD have, in general, a lower rejection risk than patients transplanted due to other indications, suggesting an immune-inhibitory effect of alcohol.[3,23,24]

Lower social support, psychobehavioural comorbidities, family history of alcoholism, diagnosis of alcohol dependence, repeated attempts at rehabilitation, non-compliance with clinic visits after LT, and smoking were all identified as risk factors for alcohol relapse after LT, along with pre-transplant abstinence period;[4,25,26] protective factors include patient insight and perception of the negative consequences of alcohol.[24,26] Therefore, thorough evaluation of psychosocial influencing factors and psychobehavioural disorders should be considered the core of the risk assessment prior to transplantation.

ELIGIBILITY FOR LT

The '6-Month Rule'

Originating from the fact that alcohol abstention can lead to dramatic improvement in liver function to a point where LT is no longer necessary, most transplant centres require a 6-month abstention period before patients become listed for LT. Above all, plausible abstention ≥6 months has been used as a surrogate parameter for long-term sobriety after LT to identify patients who will most benefit from LT. However, data on the '6-month rule' are controversial and a clear rationale is lacking.[27] Although shorter sobriety periods prior to LT are predictive of future relapses,[4,13,28] sobriety becomes robust only after 5 years of alcohol abstention.[29,30] On the one hand, this may be a result of inconsistent definition of alcohol use and alcohol dependence used in these studies, on the other hand, this may be due to the difficulty in evaluation and detection of alcohol abuse and relapse. Therefore, the UK Liver Transplant Group, rather than using a specified period of abstinence, agreed on certain contraindications for listing, including: alcoholic hepatitis, repetitive episodes of non-compliance with medical care, returning to drinking following full professional assessment, and concurrent illicit drug use.[31-33]

LT for Alcoholic Hepatitis

The discussion concerning selection criteria of patients with ALD becomes even more controversial in the context of alcoholic hepatitis. Historically, patients suffering from acute ASH have been denied LT due to active alcohol consumption.[34] However, mortality in patients failing to respond to corticosteroids in comparison to responders is veritably high (28-day survival 53% versus 91%, 6-months survival 30%).[35] Particularly, recent reports on favourable outcomes after LT for severe ASH have led to a change in therapeutic algorithms, and according to the

European Association for the Study of the Liver (EASL) guidelines, LT could be a treatment option for highly selected patients.[36] Singal et al.[37] demonstrated similar 5-year patient survival rates in patients transplanted for ASH compared to patients transplanted for alcoholic liver cirrhosis (73% versus 78%). Furthermore, a case-control study by Mathurin et al.[38] showed a dramatically improved survival at 6-month follow-up for patients who had received LT in comparison to patients who had received medical treatment, but who only partially responded or were non-responders (77% versus 23%). Only patients without prior episodes of ASH, as well as patients with good family support, lack of relevant comorbidities, and commitment to alcohol abstention, were included in the study. Of note, only 3 of 26 patients relapsed to alcohol consumption after 2 years.

On the other hand, in the context of organ shortage, major ethical concerns may be raised. Frequently, alcoholism is seen as a self-inflicted disease not only by the public, but also among medical personnel, and LT for ALD has led to sustained controversies. Unselected organ distribution can thus result in decreasing donor numbers. Therefore, transparent selection criteria for LT patients with ALD, and particularly ASH, are mandatory.[39]

MONITORING CONSUMPTION AND MANAGING RELAPSE

Identification of patients at risk of alcohol relapse displays a challenge for multidisciplinary transplant teams. Alcohol relapse, in contrast to temporary slips (which are recognised by the patient as potentially harmful and may foster a new abstinence), is defined by abusive consumption (at least four drinks per day or one drink in ≥4 consecutive days).[40,41] In a patient population where optimal selection is difficult, the treating physicians in particular must be aware of signs of recidivism. Whereas alcohol relapse prior to LT may preclude patients from the waiting list,[42,43] good psychosocial and medical support of patients may be decisive to prevent or to detect the signs of alcohol relapse earlier after LT in order to support long-term graft survival.[44] As such, most centres have implemented regular follow-up visits by addiction specialists after LT,[42,45] thereby achieving a significant reduction of recidivism;[20,46] intervention trials were only of limited success.[47,48]

To guarantee optimal patient selection for LT and best psychological and medical support, in addition to assessment by experienced addiction professionals, objective tools for alcohol detection are mandatory. In fear of negative socioeconomic consequences or of being denied LT, patients frequently do not admit alcohol consumption, adapt their drinking patterns to scheduled hospital visits (in order to be able to provide negative alcohol tests), or do not indicate actual amounts of alcohol intake.[43,49] To face these challenges some centres have implemented random alcohol testing without prior notice for patients on the waiting list.[50,51]

The National Institute on Alcohol Abuse and Alcoholism of the National Institutes of Health (Bethesda, MD) recommend a combination of carbohydrate deficient transferrin (CDT), mean corpuscular volume (MCV), and gamma glutamyl transferase (GGT) for alcohol screening,[52] reaching a sensitivity and specificity of 88% and 95%, respectively.[53-55] However, MCV and GGT, as well as the commonly used liver enzymes such as alanine-amino transferase (ALT) and aspartate-amino transferase (AST), have only low specificity in patients with end-stage liver disease or LT recipients.[43,56] Besides self-reporting questionnaires, such as Alcohol Use Disorders Identification Test (AUDIT-C),[57,58] and interviews by addiction specialists, a combination of alcohol markers in the blood (CDT), urine (urinary ethylglucuronide [uEtG]), and hair (hEtG) have been reported to be of high value in this patient cohort.[43,50] In particular, EtG in hair - a metabolite of ethanol - has the advantage of differentiating between excessive drinking (<60 g ethanol/day), moderate alcohol consumption (10-40 g ethanol/day), and teetotallers or very moderate drinkers (<10 g ethanol/day) for up to 6 months before, independent of the severity of liver disease.

Importantly, since a recent study proved the negative effect of excessive alcohol consumption on long-term patient survival regardless of the indication for LT, screening for alcohol consumption also in non-ALD transplant recipients should be included.[59] Due to the potentiated negative effect of alcohol in hepatitis C, we should be especially aware of alcohol consumption in this patient population.[2]

CONCLUSION

LT for alcoholic cirrhosis is a matter of continuous controversy since Starzl et al.[60] first drew attention to successful outcomes of LT for ALD. The most relevant concerns within the context of ALD and LT are the reliable pre and post-transplant perceptions of alcohol dependence and relapse. Universally applicable criteria for the evaluation of patient eligibility for LT border their limits when it comes to the individual patient, and the frequently applied '6-month rule' should be reconsidered. Moreover, in highly selected patients where spontaneous recovery of liver function cannot be expected, such as acute alcoholic hepatitis not responding to medical treatment, the '6-month rule' is not applicable. To develop an individual risk profile based on psychosocial factors in combination with the analysis of drinking patterns seems to be more decisive. In addition to routine visits by a multidisciplinary transplant team, including an addiction specialist prior to and after LT, screening for alcohol consumption and relapse by the use of biomarkers in blood, urine, and/or hair should be performed on a regular basis. Early detection of recurrence of harmful drinking and alcohol dependence is mandatory to preserve long-term graft function.

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