

THE MULTIDISCIPLINARY SUPPORT IN PREVENTING ALCOHOL RELAPSE AFTER LIVER TRANSPLANTATION: A SINGLE CENTRE EXPERIENCE

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Running title: ALCOHOL RELAPSE AFTER LIVER TRANSPLANT

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Background and aim: Alcoholic liver disease (ALD) represents a frequent indication for liver transplantation(LT). Since 2004, we have adopted a program of multidisciplinary support(MS) to assist patients undergoing LT for ALD. We aimed at analysing the relapse rate and the risk factors for relapse. The relapse rate was also compared with that of a historical group of patients who underwent transplantation. Their survival rate was also analysed.

Patients and methods: Consecutive patients with ALD transplanted from 2004 were included. The most important demographic, psychosocial and clinical characteristics known to be associated with alcohol relapse were recorded.

Results: Sixty-nine patients underwent MS. 8.7% presented alcohol relapse. At multivariate analysis female gender (sHR 9.02, 95%CI 1.71-47.56,p=0.009), alcohol withdrawal syndrome (sHR 5.89, 95%CI 1.42-24.46,p=0.015) and a shorter time of MS program before LT (sHR 0.928 per month, 95% CI 0.870-0.988,p=0.021) were identified as independent risk factors for relapse.

The rate of alcohol relapse was significantly lower than that of the historical group who did not undergo MS (sHR 0.21, 95%CI: 0.06-0.68;p= 0.009).

Conclusion: This study shows that a MS program may contribute to alcohol relapse prevention after LT in ALD patients. However, the relevance of this support needs to be confirmed by Clinical Trials.

Key words: Alcohol abuse, Alcohol dependence, Alcohol relapse after liver transplantation

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Introduction

Alcoholic liver disease (ALD) is one of the main indications of liver transplantation (LT) reaching about 30% in Europe and the United States. During the 1990s, patients undergoing LT for ALD were thought to present a poorer outcome in terms of morbidity and mortality than other patients. Moreover, alcohol use disorder was considered a 'self-inflicted disease', and concerns were present, mostly at the beginning, about the justifiability of letting patients with ALD undergo transplantation¹. However, it has now been confirmed that the outcome of patients undergoing transplantation for ALD is similar to that of patients with end-stage liver disease of different origin²⁻⁴, and ALD is nowadays more accepted as a disease like the others.

The main problem in these patients to be submitted for LT is the likelihood of alcohol relapse. In literature, alcohol relapse within 5 years from LT ranges from 20–50%⁴⁻⁷. Considering that the amount of alcohol is frequently established on the basis of self-reporting, this high relapse rate may even be greatly underestimated. Furthermore, many studies have used a retrospective design that may limit the accuracy of the information obtained from the patients. It is difficult to get accurate data on alcohol relapse, but it is well recognised that alcohol abuse after LT can lead to acute allograft injury and be an important cause of graft loss or death⁵⁻⁷. For this reason, attention has been focused on alcohol abuse and dependence as chronic recurrent conditions and on the need to implement a series of supportive measures to achieve alcohol abstinence before and after LT and to prevent alcohol relapse⁸⁻¹¹.

Multiple studies focused on predictive factors in the pre-LT period have aimed at screening patients at high risk of alcohol relapse¹¹⁻¹⁶. Some of the results of these investigations led to the '6-month abstinence rule', which suggested that patients who did not abstain from alcohol intake for at least 6 months should not be listed for LT due to their high relapse rate¹⁷. However, this rule has recently been reconsidered in many centres and some authors have demonstrated that the opinion of an addiction specialist may be crucial for the inclusion of these patients on the waiting list regardless of the period of abstinence¹⁸.

Few data are available on the procedure and the practice of offering support to the patients before and after LT in order to prevent alcohol relapse¹⁹⁻²¹. It is widely agreed that patients with alcohol use

disorders being considered for LT should undergo evaluation by a professional staff involved in rehabilitation for alcohol abuse and dependence, but there are no definite rules for planning an effective support involving family and caregivers. There are no guidelines indicating the best way to deal with the whole spectrum of the patient's problems (alcohol dependence, abuse of other substances, depression and psychiatric disorders) and how to obtain the best and most fruitful interaction among the various specialists involved in the patient's care²².

With this in mind, a program of multidisciplinary support (MS) was initiated at the Transplant Unit of University of Rome 'Sapienza' in 2004. It was designed to help patients undergoing LT for ALD to cope with their alcohol use disorder.

The aim of this study is to analyse the alcohol relapse rate and risk factors of alcohol relapse in a group of patients prospectively enrolled in a program of MS. The results have also been compared to a historical group of patients receiving no specific support in this regard. Survival of patients, based on the alcohol relapse, has also been analysed.

Patients and Methods

In this study two groups of patients were evaluated: the MS group and the historical group.

Patients undergoing LT for ALD between 2004 and 2013 at the University Hospital Policlinico Umberto I of Rome were included in the study as the MS group.

Indication for LT was based on a) the presence of end-stage liver disease in which LT was the only option for survival; b) the absence of medical or surgical contraindications; c) when clinically possible, a 6-month period of alcohol abstinence to assess possible improvement in liver function associated with alcohol abstinence and to ascertain the patient's willingness and ability to maintain alcohol abstinence. Less than 6 months' follow-up after LT was cause of exclusion from this study as this period of time was considered too short for correct evaluation of a possible alcohol relapse.

Alcohol Addiction Team

The Liver Transplant Unit in our University Hospital includes competent healthcare professionals such as hepatologists, surgeons and radiologists. From 2004 the alcohol addiction team has been a part of the Liver Transplant Unit in order to provide expert clinical support for the evaluation, management and treatment of patients with alcohol use disorder affected by end-stage ALD.

Medical doctors, clinical psychologists and a psychiatrist with expertise in alcoholism and hepatology compose the alcohol addiction team. Members of the addiction team participate in weekly meetings with all the other members of the Liver Transplant Unit playing an important role in the final decision of issues related to patients' alcohol use, such as, including or removing patients from the LT 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.

Pre-Transplant Period

During the evaluation for the listing for LT, the hepatologists refer all the patients to the addiction team to evaluate the possible presence of alcohol use disorders. At this point, clinical and medical counselling sessions are performed in order to evaluate the history of alcohol intake, using specific tools such as Lifetime Drinking History²³. In case of abuse and/or alcohol dependence, the diagnosis is made according to the Diagnostic and Statistical Manual of Mental Disorders²⁴. Assumption of illicit drugs is also detected. If a diagnosis of abuse and/or alcohol dependence is made, the patient is included in a treatment program with repeated evaluation visits to achieve the abstinence from alcohol. Treatment starts at the moment of the diagnosis and continues through all phases leading to and following the transplantation. Patients are usually evaluated as outpatients, but hospitalisation is available if necessary. The program provides a monthly follow-up in the first 6 months after the diagnosis and thereafter the period between the visits is extended; the frequency of the visit increases when clinically indicated.

For the entire duration of the treatment, a caregiver is encouraged to attend clinic visits together with the patient.

At each session, the evaluation of blood alcohol concentration, carbohydrate deficient transferrin, the cumulative treatment days and cumulative abstinence days reported by the patient and the caregiver²³⁻²⁶ are utilised for the assessment of alcohol abstinence. Possible craving symptoms are also evaluated using a visual analog scale²⁷ and/or by the Italian version of the obsessive compulsive drinking scale²⁸ and risk factors for possible relapse are also identified.

Post-Transplant Period

In the first 6 months after transplant the addiction team sessions are scheduled every month, thereafter the period between the visits is extended, if clinically indicated.

Alcohol relapse is defined as a daily alcohol intake ≥ 5 alcoholic units for more than two consecutive days or an overall consumption of 14 drinks or more per week for at least 4 weeks. An alcohol lapse (or slip) has been defined as any episode of alcohol consumption not classified as relapse. Alcohol recidivism (lapse and/or relapse) was evaluated at each follow-up visit ^{1, 14,29,30}.

If a patient lapses or relapses after LT, an intensive individual program is initiated. The patient is followed in a Day Hospital for about two weeks in order to cope with his craving symptoms. After this period a weekly psychological program aimed at supporting motivation and enhancing skills for managing the alcohol use disorder is provided.

For clinical purpose demographic, psychosocial and clinical characteristics are always recorded at enrolment and during subsequent visits: demographic and psychosocial variables (gender, race, marital status, education, family history of alcoholism, employment status, length of abstinence before LT, abuse of other drugs, treatment of alcohol dependency before LT and alcohol use after LT) and clinical characteristics (origin of liver disease, Model For End-Stage Liver Disease (MELD) score at LT, diagnosis of hepatocellular carcinoma before LT, development of allograft rejection). In case of graft loss or patient's death the information is always registered in clinical records.

The historical group was derived from consecutive patients who underwent transplantation in our Centre before 2004. Patients' evaluation before LT, surgical procedures, immunosuppressive therapy, clinical follow-up after LT, were similar to those adopted in the present study. Moreover, the same investigators supported both the populations.

In the historical group, an extensive and accurate alcohol history was not available. The only accessible information was: diagnosis of alcohol abuse before LT (self-reported by patient and family), alcohol abstinence in the period before LT evaluation (self-reported), alcohol abstinence while on the waiting list (supported by biochemical analysis) and evidence of alcohol relapse after LT (reported by medical staff and family). No information was available regarding the type of abuse or dependence, the amount of alcohol units, family support and history of alcohol intake.

The analysis of risk factors associated with alcohol relapse was performed exclusively in patients of MS group due to the lack of appropriate alcohol history in the historical group.

The study was approved by the ethical committee of the Policlinico Umberto I, 'Sapienza' University Hospital of Rome.

Statistical Analysis

Results are expressed as mean \pm SD. To compute the incidence of alcohol relapse we used the Gray method for competing risks (as death is a competing risk for relapse). Similarly, to investigate the relapse risk factors we used univariate and multivariate Fine and Gray competing risk regression models, finally reporting the sub distributional hazards (sHR), which can be interpreted similar to hazard ratios. In order to select the best multivariate model, we used a forward selection strategy aiming at minimisation of the Akaike Information Criterion (AIC). All predictors were considered as candidates for the final multivariable model. Forward selection proceeds in a stepwise fashion. At the first step, all possible univariate models are computed and the one minimising the AIC is selected (is AIC is smaller than the null model with only the intercept). At the second step, all possible bivariate models are computed where the first variable (selected at the previous step) is held fixed. In case no bivariate model yields a lower AIC than the previous optimum, the best univariate model is chosen as the final model. Otherwise the procedure continues until no AIC improvement is obtained. Patient survival rates were analysed using the Kaplan–Meier method and compared with the log-rank test, univariate Cox regression models, and finally multivariate Cox regression models. Statistical analyses and plots were performed using SPSS statistical software (SPSS, Chicago, IL, USA) and R version 3.3.3 (R development core team, Vienna, Austria).

A comparison to historical data was made based on methodology and recommendations from regulatory guidance and published literature^{31–33}, and indicator of being part of the historical or new cohort was treated as a predictor after merging the two data sets.

Results

Demographic characteristics

Between 2004 and 2013, a total of 251 patients underwent LT; 87 of these patients underwent LT for ALD alone or associated with co-morbidities. Nine patients could not undergo MS because they

were monitored in other regions of Italy. Nine patients were excluded due to a follow-up shorter than 6 months after LT, thus, a total of 69 patients were included in the analysis. Demographic characteristics of the 69 patients who underwent MS are shown in Table 1.

Patients transplanted from 2000 to 2003 were investigated as a control group. In this period 136 LTs were carried out; 18 of these patients underwent transplantation for ALD alone or in association with viral hepatitis (61% ALD alone, 39% ALD associated with virus). There was no statistically significant difference between the most important demographic characteristics of the historical group and the MS group apart from the longer follow-up after LT in the historical group (Table 2).

Relapse rates

Of the 69 patients who were enrolled in the MS program, 6 patients relapsed (8.7%). The most of patients relapsed within the first year 3 after LT (4 patients, 57%). Fourteen patients (20.3%) had one slip: 12 of these patients regained abstinence after the intense treatment provided by the alcohol addiction team, whereas 2 were among those who subsequently relapsed. The incidence of relapse in each group is reported in Figure 1. Five-year cumulative incidence was estimated as 33.3% for historical comparisons and 8.3% for patients enrolled in the MS program. The rate of relapse was significantly lower than that of the historical group of patients transplanted from 2000 to 2003 who did not undergo MS (sHR 0.21, 95% CI: 0.06–0.68; $p = 0.009$).

Risk factors associated with alcohol relapse in MS group

Univariate competing risk regression analysis suggested that the female sex is an alcohol relapse risk factor after LT (sHR 8.59, 95% CI: 1.60–46.03; $p = 0.012$). Another risk factor associated with relapse was the presence of alcohol withdrawal syndrome (AWS) before LT (sHR 6.37, 95% CI: 1.33–30.62; $p = 0.021$) (Table 3). At multivariate analysis, in addition to these two risk factors (sHR 9.02, 95% CI 1.71–47.56, $p = 0.009$ for females; sHR 5.89, 95% CI 1.42–24.46, $p = 0.015$ for AWS), a protective effect of duration of the MS program before LT was identified (sHR 0.928 per month, 95% CI 0.870–0.988, $p = 0.021$).

Survival

Of the 69 patients undergoing MS, 13 died. Of these, 4 patients experienced alcohol relapse: 2 died for reason related to recurrent alcoholic cirrhosis, one died for a violent cause of death and one due to cardiovascular disease.

The analysis of mortality of all patients, regardless of the group transplanted before or after 2004, showed no difference in patients who experienced or did not experience alcohol relapse after liver transplantation ($p = 0.38$).

Discussion

The present study shows the importance of the alcohol addiction team in MS program in the prevention of alcohol relapse after LT. Alcohol relapse rate after LT in our patient population enrolled for multidisciplinary support was 8.7%. This rate is substantially lower than those reported in the literature (20–50%)^{8, 34–36}. The impact of MS is also evident when the relapse rate obtained in the MS group is compared to that of the historical group that was significantly higher (8.5% vs. 27.7% respectively; $p = 0.002$). Furthermore, in the historical group the diagnosis of relapse was retrospective and thus the relapse rate was likely underestimated.

Among the patients involved in MS, only a small percentage experienced relapse. However, the timing of relapse was similar to that reported in the literature, with a higher risk during the first 2 years: in fact, in the present study 66.6% of relapses occurred within 2 years after LT.

Another interesting result of the MS program was the surveillance and detection of slip episodes. In fact, being considered a group at higher risk of relapse, the 'slip group' was submitted to more intensive therapy, and as a result, only 2 patients (14.3%) progressed to relapse after slip. Without support, it was likely that all the 14 patients could have easily relapsed to alcohol drinking: considering the MS patients with slip and relapse together as one group, their percentage is in fact similar to that of the patients who relapsed in the historical group (26% vs 28% respectively; $p = ns$) and close to the relapse rate reported in the literature.

Summing up, the data obtained suggest that the MS program with alcohol addiction team effectively helps preventing slip from progressing to relapse by early identification of the high-risk

patients and submitting them to a closer follow-up and intensive support involving caregivers and family.

Another factor supporting the importance of the addiction team in the MS program is that the patients who relapsed were those with a shorter time and fewer sessions of MS before LT.

Only a few studies so far have analysed the efficacy of MS in preventing alcohol relapse after LT^{19,29} and nowadays the behaviour of the different Transplant Centres in preventing alcohol relapse after LT is not standardised. In this scenario, we believe that the availability of a dedicated alcohol addiction team in a liver transplant centre is very important.

Other risk factors of alcohol relapse after LT included the female sex ($p = 0.004$) and AWS before LT ($p = 0.01$). As for gender, Karim et al. reported similar results of their study concluding that female sex as a risk factor may be confounded by a higher incidence of depression and anxiety disorders among women¹³. Unfortunately, the present study did not analyse the presence of psychiatric co-morbidity as a possible risk factor for relapse.

To the best of our knowledge, no study has identified AWS as a relapse risk factor. AWS confirms the severity of alcohol use disorders suggesting that more attention should be paid in the future to the diagnostic criteria of the DSM-5 and to alcohol drinking history in order to obtain a clearer clinical picture of the relapse risk factors.

Concerning the analysis of mortality, we did not find any difference in patients who relapsed and the patients who didn't, considering the entire population (patients transplanted before and after 2004), probably this was due to the lesser number of patients analysed and due to the presence of other confounding factors not considered in the analysis.

Our study has some limitations; it is a monocentre study and the sample size is rather limited. Moreover, as we considered it unethical to randomise patients in a control group without MS, we could only compare our results with those obtained from a database about a historical group of patients who underwent transplantation for ALD from 2000 to 2004 at our centre. Unfortunately, these patients were few and patients who underwent transplantation before 2000 were not included in the database. Among possible reasons for the low prevalence of ALD patients between 2000 and 2004 is the fact that the more frequent aetiologies for end-stage liver disease have changed in the last few years and the number of post viral cirrhosis cases was highly prevalent in that period.

Furthermore, ALD was considered as a 'self-inflicted disease' and this could have facilitated the transplantation for patients with other etiologies¹. The control group, however, had similar demographic characteristics, severity of liver disease and transplant indication and was followed in the same Transplant Unit by surgeons and hepatologists. Surgical techniques and immunosuppressive regimens were not different in the two groups, however, due to lack of a specific approach in alcohol problems, an appropriate alcohol history was lacking, and it was not possible to compare the characteristics of alcohol drinking and time of abstinence between the two groups. Moreover, alcohol use was evaluated through different methods in the two cohorts: in the historical group through a clinical interview by an hepatologist and in presence of pertinent biochemical alterations (elevated GGT, macrocitosis ...); in the MS group the diagnosis of alcohol use was performed by the alcohol addiction team through dedicated interviewing of the patient and the caregiver, also by considering blood alcohol concentration and carbohydrate deficient transferrin levels.

However, if an underestimation of alcohol relapse was present in the historical group, it could further strengthened our results by increasing the difference between the two cohorts. Of notice, MS group tended to have a combined origin of liver disease more often (alcohol + virus) than the historical one. This aspect could have contributed to a different rate of relapse in the two groups.

In conclusion, this study shows the importance of alcohol relapse prevention programs before and after LT and reinforces the recommendation that Liver Transplant Centres should provide MS involving a professional staff involved in rehabilitation for alcohol disorders to improve treatment and ameliorate the outcome of patients with ALD after LT. However, due to the small simple size, and non randomized study design, further studies need to confirm these data.

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