Risk for relapse of alcohol use after liver transplantation for alcoholic liver disease : A review and proposal of a set of risk assessment criteria

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Abstract

Background : Liver transplantation for end stage alcoholic liver disease is becoming an increasingly frequent procedure. Within this context assessing the risk on relapse in alcohol use is a major issue. However, up to now, there is a clear lack in validated criteria that can be used to assess future relapse risk.

Method : Literature review based upon Medline search identifying all new studies that have been published after the latest meta-analysis on this subject (2007-2009).

Results : Five new original studies were identified. They provide new evidence for the prospective validity of different criteria ; pretransplant abstinence duration, diagnosis of alcohol dependence versus abuse, level of social support, additional psychiatric co morbidity.

Conclusions : These criteria seem promising as to the prediction of relapse in alcohol after livertransplantation. Based upon these results a new comprehensive assessment scale is proposed. (Acta gastroenterol. belg., **2010**, 73, **247-251**).

Key words : alcoholic liver cirrhosis, liver transplantation, relapse risk.

Introduction

Transplantation of vital organs such as kidneys, lungs, and livers has changed from a last-hope effort to become an increasingly accepted strategy of tertiary care. Closely related to these developments, there has been a gradual increase in interest in how outcome after solid organ transplantation is assessed. Although organ survival and patient survival remain the crucial endpoints, an increasing emphasis is being placed on morbidity after transplantation as long-term survival is steadily increasing (1). The recurrence of the original disease and the development of new diseases are of vital importance since they may affect both organ and recipient prognosis and survival.

Within the framework of end stage liver disease, relapse of alcohol use and abuse is of extreme importance. Alcohol abuse and dependence are chronic medical disorders that are, given a lifetime prevalence of 13.5%, extremely common in our Western society. Although multiple factors mediate the risk to develop alcohol-related liver diseases, rates of cirrhosis are influenced directly by alcohol consumption in a population (2). Furthermore, continuing use of alcohol after the diagnosis of alcoholic liver cirrhosis correlates negatively with survival. In a recent study Verrill *et al.* (2) demonstrated that abstinence from alcohol at one month after the diagnosis of cirrhosis was the most important factor determining survival, with a 7-year survival of 72% for the abstinent patients versus 44% for the patients continuing to drink. Abstinence at 30 days after diagnosis appeared to be an excellent predictor of abstinence at follow-up 3.4 years later. However, with respect to liver transplantation (LT), very few studies up to date have explored neither the effect of alcohol use post transplantation nor the factors that are predictive of relapse of alcohol use/abuse after transplantation, the latter item representing a major caveat in our knowledge. Given the fact that both in Europe as in the US alcoholic liver disease is among the most common indications for liver transplantation (3), there is a real need for valid criteria allowing to assess the relapse risk of alcohol use after transplantation. Indeed, although in most transplantation centres a psychiatric evaluation currently constitutes an integral element of the pretransplant screening/indication procedure, no validated guidelines or set of criteria have been developed. In a recent meta-analysis including all publications up to March 2007, Dew *et al.* (3) found that poor social support, family alcohol history, and pretransplantation abstinence of less than 6 months showed a small but significant association with relapse (r = 0.17-0.21). They concluded that future research should focus on improving the prediction of risk for substance use relapse, and on testing interventions to promote continued abstinence post transplantation.

In this review we build upon the work of Dew *et al.* (3) and review the current literature on risk assessment and post transplantation interventions that has been published from March 2007 until May 2009. Secondly and based upon these findings, we present a set of criteria that might be useful in assessing relapse risk within transplant candidates for end-stage alcoholic liver disease, and therefore might provide a framework that can be of use both clinically and in future longitudinal studies.

Methods

We searched Medline database with following terms ; liver transplantation And alcohol And relapse And cirrhosis. Only original research articles published from March 2007 until May 2009 were included. References within these articles were explored to look for additional studies.

Results

Five original research studies were identified that have been published after the meta-analysis of Dew *et al.* (4). Results are presented in Table 1.

Nickels *et al.* (5) and Gedaly *et al.* (6) have used retrospective data analysis, based upon review of earlier medical charts. De Gottardi *et al.* (7), DiMartini *et al.* (8), and Aguilera *et al.* (9) used a longitudinal approach. It is of notice that the three latter studies have a sizeable sample that is much larger than the mean sample size (71 ± 48) in the meta-analysis by Dew *et al.* (4).

The study of Nickels *et al.* (5) is a retrospective study with a small sample size. Although polysubstance has been put forward, the actual sample consisted mostly of alcohol use disorder patients. They could not identify any significant relation between patient variables and relapse in alcohol or substance use. It remains, however, an open question whether these findings relate to the very small sample size or do effectively exclude these variables as significant predictors. In a larger, but also retrospective study, Gedaly *et al.* (6) found a significant relation between pretransplant abstinence time, prior rehabilitation treatment episode and relapse. On multivariate analysis of these two former factors, duration of pretransplant abstinence of less than 12 months was the only independent predictor of relapse. However, it needs to be noted that in this study only 29 patients out of 147 were abstinent less than 12 months before LT, indicating that the sample in this study consisted mainly of exceptionally long abstinent pre LT patients.

The longitudinal study by De Gottardi *et al.* (7) is both conceptually as according to sample size very interesting. It is up to now the first study using, in addition to clinical diagnosis and heteroanamnestic information, a standardized scale, the High-Risk Alcoholism Relapse score (HRAR) (10). The HRAR provides a total score based upon different variables and cut-off values (Table 2). Findings are interesting and provide a significant

Table 1. — **Overview different studies published from 2007-2009**

Study	N	Study method	Screening method	Outcome variable	Sec outcome	Predictors relapse
Nickels *et al.*, 2007 (5)	27 transplant patients with SUD[1] (24 AUD[2]) Inclusion nr months pre-transplant abstinence : no data	Retrospective 1999-2004	Reviewing charts (e.g. transplant psychiatrist)	Patient survival : 10 died 1 y. survival curves relapsers (100%) versus non-relapsers (83,9%)	Relapse substance use 29,6%	Age, sex, race, FH abuse, legal, psychiatric diagnosis, SU variables = no significant differences between relapse and no relapse
De Gottardi *et al.*, 2007 (7)	N = 387 LT[3] pat for alcoholic cirrhosis Inclusion > 3 m. abstinence	Longitudinal 1989-2005 Mean follow-up time 61.2 months	Psychiatric diagnosis (DSM[4] IV) HRAR[5] scale	–	Relapse of harmful alcohol use in 11.9%	Age > 50 Abstinence < 6 m. Psychiatric comorbidity Presence of life partner High score HRAR scale
Gedaly *et al.*, 2008 (6)	N = 387 LT ALD[6] = 147 (38%) Inclusion > 6 m. abstinence	Retrospective 1995-2007	Reviewing charts	5 y survival 84,6% significant association depression scores & recurrence alcohol intake	19% of the AUD patients returned to (any amount) alcohol after LT	Significant : Pretransplant abstinence < 12 m. Participation in rehabilitation
Di Martini *et al.*, 2008 (8)	N = 113 ALD LT patients	Longitudinal 1998-2002	Semi-structured diagnostic interview pretransplant ATLFB[7] every 3 m. Posttrans.	-	Relapse (first any use & first binge use) : no overall data presented	Risk posttransplant relapse (first any use & first binge use) : Alcohol dependence > alcohol abuse
Aguilera *et al.*, 2009 (9)	LT patients : HCV[8] (n = 170) HCV + Alc (n = 60) Alc (n = 107) Inclusion > 6 m. abstinence	Longitudinal 1997-2001	Psychiatric assessment alcohol	Patient and graft survival (HCV < HCV + Alc < Alc) Histological analysis Metabolic complications	Post LT alcohol consumption Relapse = > 1 drink/week for 6 months Relapse rate alcohol : HVC group : 3% HVC + Alc : 8% Alc group : 18%	No predictors evaluated

(1) SUD : Substance Use Disorders ; (2) AUD : Alcohol Use Disorders ; (3) LT : Liver Transplantation ; (4) DSM : Diagnostic and Statistical Manual of Psychiatric Disorders ; (5) HRAR : High-Risk Alcoholism Relapse Scale ; (6) ALD : Alcoholic Liver Disease ; (7) ATLFB : Alcohol Time Line Follow Back ; (8) HCV : Hepatitis C Virus.

Table 2. — **High-Risk Alcoholism Relapse Scale (HRAR scale). After De Gottardi *et al.* (7)**

Item	Score
Duration of heavy drinking, years	
≤ 11 11-25 ≥ 25	0 1 2
Daily drinks, No. (one drink = 12 g. alcohol)	
≤ 9 9-17 ≥ 17	0 1 2
Prior alcoholism inpatient treatments, No.	
0 1 ≥ 1	0 1 2

correlation between relapse and duration of abstinence of less than 6 months, presence of a life partner [both these factors were also identified by Dew *et al.*, (4)], the presence of psychiatric co-morbidity, and a high score on the HRAR. Both latter factors represent newly identified predictive risk factors. A high (4-6) score on the HRAH (Table 2) specifically correlated positively with the risk of relapse. The longitudinal study by DiMartini *et al.* (8) elucidates the importance of the diagnostic difference between alcohol abuse and dependence. In a well-designed study, using a standardized semi-structured interview (SCID-I) they showed that patients with, pre LT, alcohol abuse had a better outcome (time to first drink and time to first binge episode) than patients fulfilling DSM-IV alcohol dependence criteria.

Finally, the study by Aguilera *et al.* (9) included three sizeable groups of LT patients (HCV, HCV + alcohol, and alcohol) and compared, in a longitudinal design, different outcome measures including relapse in alcohol use. Unfortunately they did not evaluate potential predictors for relapse. Remarkably they did find a better survival outcome for the alcoholic cirrhosis patients over the mixed groups and the HCV group.

Proposal of a screening protocol

The large and well performed meta-analysis done by Dew *et al.* (4), reviewing all studies that have been done up to March 2007, provided some variables that significantly correlated with post transplantation relapse in alcohol use/abuse. These measures are : poorer social support, family alcohol history, and pretransplantation abstinence of ≤ 6 months. The studies, published after this major review suggest some additional measures that show to be predictive of postransplantation alcohol relapse : presence of psychiatric co morbidity, a high score on the HRAR (7), and a diagnosis of DSM-IV alcohol dependence (8).

Although the number of studies exploring relapse risk after LT is still very limited, warranting replication in additional large and longitudinal studies, the results sup-

port the procedure as presented in Table 3, assessing the criteria that have been proven to be predictive of subsequent relapse.

Discussion

Since the publication of the exhaustive meta-analysis by Dew *et al.* (4), a limited number of important longitudinal studies with large sample size have been published that yield new information on risk assessment of relapse of alcohol use.

The current review allowed to identify three new clinical variables that were significantly associated with post LT relapse : psychiatric co morbidity, a DSM-IV diagnosis of alcohol dependence and a high HRAR score.

The finding that psychiatric co morbidities such as mood or anxiety disorders are associated with the risk of relapse of harmful drinking is important. These findings are reflective of other outcome studies in non-transplant alcohol dependent patient samples. Indeed, co-morbid mood and anxiety disorders are known to correlate with poorer alcohol related outcome (11). These findings underscore the need for a thorough psychiatric screening. Of importance, mood and anxiety disorders can be treated effectively in alcohol abusing or dependent patients. However, few studies in patients with alcohol related liver disease have been done exploring the safety and effectiveness of antidepressant pharmacotherapy. Given the fact that most antidepressant drugs are metabolized hepatically, concerns about both safety and overdosing are eminent in this population. It is therefore important to refer to studies showing that the effectiveness of cognitive behavioural therapy on depressive symptoms in the case of mild to moderate mood and/or anxiety disorders is comparable to the results of pharmacotherapy (11). Thus, when diagnosed in alcoholic liver patients there is a rationale to start treatment of mood disorders first by cognitive behavioural psychotherapy.

DiMartini *et al.* (8) showed that the DSM-IV diagnosis category was associated with differences in relapse risk. Patients who fulfilled the criteria of alcohol dependence were more likely to relapse than patients who were diagnosed with abuse. Overall, longitudinal studies on the natural course of alcoholism within population samples show that the outcome for dependency is poorer compared to abusing individuals. DiMartini *et al.* (8) thus confirm the higher relapse rate in individuals with a more severe phenotype of the disorder in a population of patients with terminal alcoholic liver disease. This is, however, a first report needing confirmation.

Overall, the risk factors identified in the current review combined with those identified by Dew *et al.* (4), might allow construct a model of six criteria that may increase the accuracy of risk assessment. Although the model as presented in Table 3 is supported by the current literature and seems to be easily implementable in clinical practice, many things remain to be further explored. First, it needs to be established whether these 6 factors

Table 3. — **Evaluation risk factors predictive of relapse alcohol abuse after liver transplantation**

Method	Risk factors (6)
Psychiatric interview with Axis I DSM-IV diagnosis	1. alcohol dependence versus abuse, heavy drinking, or social use 2. Axis I psychiatric comorbidity 3. First degree family history of alcoholism
Heteroanamnestic interview and exploration social system	4. Social support (including spouse, close family, friends). High/poor support
Labo, heteroanamnestic interview, patient interview	5. Monitoring pre LT abstinence </> 6 months
HRAR scale	6. High/low score

indeed constitute independent, not overlapping, factors of relapse. Second, although all factors are significantly associated with relapse risk, the strength of their associations is widely variable and often weak. Dew *et al.* (4) noted already that poor social support, family history and pretransplantation abstinence each showed small associations (r = 0.17 - 0.21). Of the other factors, only high HRAR scores seem to be strongly associated with relapse. However, the validity and relative strength of these factors to predict relapse need to be explored prospectively in new cohorts of patients. Finally, it needs to be explored whether a combined score will ultimately provide a more valid relapse assessment. The results of study by De Gottardi *et al.* (7) provide a first indication of this. In their study they found that while one factor alone was associated with a risk of recidivism below 20%, the combination of the 2 or 3 factors resulted in a risk of recidivism exceeding 60%. Taken together, although the model as proposed in Table 3 proves to be promising, and seems to be clinically useful, future studies should explore the validity of the model and its 6 factors.

Risk assessment regarding relapse in alcohol use within the framework of alcoholic liver disease and liver transplantation should be considered within the broader context of the current knowledge on relapse to drinking within alcohol abusing or dependent individuals. Two broad lines of research can be identified. First there are a number of studies that explore the course of alcohol use disorders in individuals, within the general population, that are not seeking treatment. Remission rates within non-treatment seeking alcoholic individuals in the general population vary broadly between studies ; from 33 to 75% for alcohol dependence and between 46% to 85% for alcohol abuse (12,13). These data indicate that alcohol abuse has a better course and prognosis compared to dependence, which has more characteristics of a chronic medical disorder. Within these prospective studies several factors where identified that significantly proved to be associated with a more negative outcome. The most important are : male gender, co morbid illicit drug use/abuse, duration and severity of alcohol dependence, unemployment, and a positive family history of alcoholism (12,13,14).

In addition to non-treatment seeking populations a number of studies have explored outcome and remission within treatment-seeking populations. In their review, Schippers and Broekman (15) concluded that overall, within clinical populations, abstinence was achieved by 53% of the alcohol dependent patients, during the first two years after treatment, a number that dropped to 31% after four years. Generally, treatment-seeking alcohol dependent populations differ with non-treatment seeking as to the severity and duration of their disorder, number and severity of psychiatric and somatic co-morbidity and social support systems. All of these factors are associated with a worse outcome. In addition, the number of previous alcohol treatments, neuropsychological impairments, and personality disorders, all have been, significantly, associated with a negative outcome (16,17). Finally, one of the factors that has been studied extensively within the framework of relapse is the stage of motivation to change drinking behaviour. Motivation can be described in multiple ways as simply the accumulation of consequences that push change, a shift in intentions, or engagement in various tasks that are part of a larger process of change. Initial motivation and readiness to change (RC), are complex constructs and have been important but inconsistent predictors of treatment attendance and drinking outcomes in studies of alcoholism treatment (18). Taken together, up till now the evidence is not strong enough to use the stage of motivation, as measured with questionnaires such as the RC-Questionnaire, as a strong predictor of relapse in alcohol use.

To summarize, although alcohol use disorders have traditionally been considered to be chronic disorders, both their "natural history" and the course after treatment indicate a broad variety in outcome. Multiple factors have been identified to be associated with relapse. Several of these factors, as indicated by the results of our review, seem to play an equally negative role within the specific population of liver transplant candidates.

Three concluding remarks need to be put forward.

First, the importance as a risk factor for relapse of a 6-month pretransplantation abstinence was confirmed in the results of studies included in the current review. However, it remains to be noted that this finding most possibly reflects an inclusion bias. Indeed, most if not all studies include only patients that have achieved six months of abstinence. Thus, it is impossible based on the current data to evaluate the relevance of this period.

Indeed, and as suggested recently by Verrill *et al.* (2) abstinence during the first 30 days after the diagnosis of alcoholic liver cirrhosis might prove very indicative for long term abstinence.

Second, we note that this review focused on the most recent literature on risk assessment of alcohol use relapse after liver transplantation. In the literature alcohol relapse has received the greatest attention to date. However, and although alcohol use disorders still are by far the most prevalent substance use disorders within our Western societies, illicit substance use and most prominently polysubstances use are becoming increasingly frequent. Specifically for patients infected by HCV, illicit drug use might prove to be an important substance use pattern. Whether the criteria as suggested for assessment for alcohol relapse might prove also valid patients abusing other substances remains an open question. Very few studies have focused on these patients. In this respect, it needs to be noted that the only study included in this review that focused on polysubstance abuse did in fact use both a very small sample which additionally was composed of a majority of alcohol-dependent patients. Thus, new and larger studies including polysubstance abusers are needed to evaluate whether the same relapse assessment criteria could be used in these populations.

Third and finally, due to the vital importance of the decision regarding transplantation, it should be questioned, whether on an ethical point of view, factors associated with relapse rates should influence the decision, compared for instance to other criteria such as the age, the presence of young children, or the ability to follow strictly the rejection prevention treatment. Indeed, given the significant, but relatively weak, association between the identified risk factors and relapse in drinking and the still unanswered question whether, if patients relapse after transplant, this really would consist the main factor in a negative post-transplant outcome, one should be reluctant to use relapse risk as the main deciding criterion. All factors should be carefully taken in consideration, within a broader multidisciplinary team decision process, ideally supported by a well-developed and ethically advised protocol.

Conclusion

Patients with end-stage alcoholic liver cirrhosis make up a large part of the possible candidates for liver transplantation. It is remarkable that these patients fare well as to graft and survival outcome. However, both given the negative impact of continuous alcohol use and the scarecity of donor organs, it is of major importance that those patients can be selected who have a low risk on alcohol relapse. This review explored the current state of research exploring factors associated with relapse risk.

The latest studies allow to identify new factors, which, together with earlier identified risk factors, may combine into a new model with a higher predictive potential.

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