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Candidates for liver transplantation with alcoholic liver disease: Psychosocial aspects

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Abstract

In Europe, 30% to 50% of liver transplantations are currently due to alcoholic liver disease (ALD). In the United States, this percentage is 17.2%. Post-transplant

survival and other predictors of clinical course do not differ significantly from those in other types of transplanted patients, as long as there is no relapse of drinking. However, 20%-25% of these patients lapse or relapse to heavy drinking post-operatively, which has been associated with an increased risk of liver damage and mortality. It is therefore crucial to design specific selection and follow-up strategies aimed at this particular type of patient. Several good and poor prognosis factors that could help to predict a relapse have been suggested, among them the duration of abstinence, social support, a family history of alcoholism, abuse diagnosis versus alcohol dependence, non-acceptance of diagnosis related to alcohol use, presence of severe mental illness, non-adherence in a broad sense, number of years of alcoholism, and daily quantity of alcohol consumption. In this article, we discuss these and other, more controversial factors in selecting ALD patients for liver transplantation. Abstinence should be the main goal after transplantation in an ALD patient. In this article, we review the several definitions of post-transplant relapse, its monitoring and the psychopharmacological and psychotherapeutic treatment.

Key words: Liver transplantation; Alcoholic liver disease; Psychosocial assessment; Psychosocial selection

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Core tip: Currently, alcoholic liver disease (ALD) is one of the most common indications for liver transplant, and post-transplantation survival and other predictors of clinical course in ALD patients do not differ significantly from other types of transplanted patients, as long as there is no relapse of drinking. It is crucial to design specific selection and follow-up strategies aimed at this particular type of patient. In this article, we discuss several factors that are important to consider

in the selection and follow-up of liver transplanted ALD patients.

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INTRODUCTION

One of the main indications for liver transplantation is alcoholic liver disease (ALD). In Europe, 30% to 50% of liver transplantations (LTX) are currently due to ALD^[1], and this percentage is lower only than that due to liver disease caused by viruses^[2]. In the United States, between 1988 and 2006, 17.2% of LTX were performed in ALD patients^[2].

In the 1980s, based on studies of ALD patients who underwent LTX, the idea that this particular group of patients had a poor prognosis and clinical course became widespread^[3-5]. Therefore, it was established that very strict criteria were needed to include ALD patients on liver transplantation lists (with the support of the United States National Institutes of Health)^[6].

However, subsequent experience in transplantation has contradicted this evidence. It was concluded that the results of the earliest studies could be linked to the group of ALD patients in question presenting with important comorbidities that concurred with a poor prognosis^[7]. Currently, post-transplantation survival and other predictors of clinical course (such as the length of post-transplantation hospitalization and number of rehospitalizations) do not differ significantly from those in other types of transplanted patients, as long as there is no relapse of drinking^[8-10].

However, it is known that 20%-25% of these patients lapse or relapse post-operatively to heavy drinking^[11], which has been associated with increased risks of liver damage and mortality, especially after several years of alcohol use^[12,13].

Although LTX has become the treatment of choice for several types of liver disease, the need for organs largely exceeds their availability.

Therefore, in the social context of organ unavailability and the extremely high costs associated with the process of transplantation, it is paramount to select candidate patients according to certain criteria^[14].

Due to social and moral factors, ALD patients are not always in the condition of to compete for transplantation under equal conditions with other patients^[7].

This article aims at reviewing, based on the existing literature, the psychosocial aspects related to the selection, monitoring and follow-up of ALD patients subject to liver transplantation.

LITERATURE REVIEW

A literature review was conducted, for articles published between 1990 and 2015, in MEDLINE and PubMed using the following key words: "Alcohol Liver Disease", "Liver Transplantation", "Alcohol Liver Disease Treatment", and "Alcohol Liver Disease in Liver Transplantation". Three textbooks and 2 Web sites were also consulted. The 50 articles reviewed included clinical cases, reviews and original articles (observational studies, cross-sectional studies and observational, longitudinal studies).

RESULTS

Pre-liver transplant selection and relapse predictors

Given the complexity of the disease and transplantation processes, psychosocial evaluation must be incorporated into a more comprehensive consideration of the appropriateness of liver transplant for particular patients^[11]. Several factors have been suggested to be predictors of relapse, with several scales being used for this purpose.

Factors that might determine relapse of drinking

Duration of abstinence: Pretransplant abstinence sometimes occurs in the context of the deterioration of the general condition of the patient, and it is sometimes precipitated by hospitalization; therefore, it should not be regarded as an absolute predictor of post-transplant abstinence^[14].

In December 1996, the United Network for Organ Sharing recommended a minimum period of 6-mo pretransplant abstinence^[7]. Several authors have criticized the use of such a short period of time to predict sustained and maintained abstinence^[15]. Dew observed that a period of pre-transplant abstinence shorter than 6 mo could predict the rate of relapse of drinking^[16]. Dom *et al*^[17] calculated that, for every month increase in pre-LTX abstinence, there was a 5% decrease in the adjusted relapse rate.

Clinically, it has been believed that the imposition of a 6-mo period is not realistic, because some patients presenting for evaluation might not be able to survive 6 mo before being transplanted^[18], as is the case with patients with acute alcoholic hepatitis, in whom the time frame is much shorter^[17]. In contrast, 6 mo of abstinence might not be sufficient to allow some patients to recover their liver function, which might call into question the real need for a liver transplant^[19].

Social support: Since the beginnings of pretransplant selection, psychiatrists such as Beresford and Vaillant have drawn attention to the importance of social support and social stability for good clinical and psychiatric post-transplant outcomes^[20,21]. Dew and Kotylar considered social support to be one of the

most important factors in determining post-transplant alcohol use^[16,22]. Having a stable partner and reliance on family or friends could also be positive factors, reducing the risk of relapse^[17]. In contrast, a lack of social support and continued engagement in alcohol-related social activities could be negatively associated with relapse^[17].

Other factors: Dew also drew attention to predictors of poor prognosis, such as a family history of alcoholism^[16], and Kotylar emphasized a diagnosis related to alcohol use (better prognosis for alcohol abuse than for alcohol dependence)^[22], which has been corroborated by recent studies conducted by authors such as DiMartini^[23]. Also, a history of a severe mental disorder (a psychotic disorder -namely schizophrenia - or a personality disorder - namely antisocial personality disorder) and non-adherence in a broad sense (attendance of visits, compliance with treatment)^[22] can be predictors of a poor prognosis. Yates emphasized the importance of the daily quantity of alcohol and the number of years of alcoholism. According to his model, the risk was greater for a number of drinks greater than 17 and a number of years of alcoholism greater than 25^[24]. Additionally, non-acceptance of a diagnosis of alcohol dependence was found to be correlated negatively with post-LTX alcohol relapse^[25].

Selection scales: Several psychosocial assessment instruments are used during the pretransplant period. Among these instruments, the Psychosocial Assessment of Candidates for Transplantation scale, with which aspects related to social support, mental health, lifestyle and understanding of transplant processes are rated^[26], and the Transplant Evaluation Rating Scale, which assesses the degree of adaptation of the patient in distinct psychosocial and psychiatric areas: previous psychiatric history; current DSM-III psychiatric diagnosis (axes I and II); substance use; compliance; healthy behaviors; social support; previous history of coping; current coping with the disease and treatment; affect; and mental state^[27].

However, there are scales that specifically assess the eligibility of candidates with alcoholic liver disease. Among these scales, the High-Risk Alcoholism Relapse^[24] scale and the Alcoholism Prognosis Scale^[28] should be emphasized.

Moreover, some scales have also been shown to be useful in assessing other factors that might determine relapse of drinking. Among these scales is the Multi-dimensional Adherence Questionnaire, designed by Telles-Correia *et al.*^[29].

Controversial aspects in the selection of ALD candidates

Written contracts: In some transplant centers, the patient is required to sign a contract to formalize his or her acceptance of the diagnosis and the need

for post-transplantation abstinence, as well as his or her commitment not to relapse to drinking^[20,30]. According to Beresford, this contract can help the doctor in cases of a post-transplantation relapse, and it might be a useful instrument to motivate the patient in seeking help^[31]. However, the same author drew attention to the patients accepting diagnoses related to alcohol use in the pre-transplantation period not necessarily predicting their acceptance of the same diagnoses in the post-transplantation period. Therefore, the utility of this instrument might be uncertain.

Pre-transplantation assessment in patients with encephalopathy: The prevalence of hepatic encephalopathy in transplant candidates is high^[32,33].

Therefore, it is only natural that many ALD candidates are encephalopathic at the time of pre-transplant assessment. According to Beresford, there are two problems in these cases: the quality of the assessment itself, which, given the cognitive limitations of the patient, has limited validity, and the utility of referring these patients (after assessment) to alcohol treatment programs if the degree of encephalopathy is maintained. In this way, whenever possible, the author advised that patients should improve their state before being submitted to transplantation^[20]. If improvement is not possible, it might be useful to collect from the family, or a significant other, data from the anamnesis that are relevant to the transplant procedure.

Relapse occurring after listing: A relapse of drinking in the pre-transplantation period, after listing, is a very serious situation. Most centers have opted to exclude from transplant lists patients who, after having stopped drinking and having been accepted for transplant, relapse to drinking. Some centers, while not excluding the patients from the list, prefer to reassess them with particular strictness and to refer them for rehabilitation^[20].

Definition of relapse and post-transplant psychological and psychiatric monitoring and follow-up of the ALD patient

Definition of relapse: The diagnosis of relapse depends on the definition used, and it is necessary to distinguish "relapse of alcoholism" (generally associated with the psychiatric diagnoses of alcohol dependence and abuse) and "relapse of drinking". In the context of liver transplant, "relapse of drinking" is mostly used, which assesses the presence of abstinence and quantified alcohol consumption.

The presence of abstinence must be the main objective after transplantation in an ALD patient^[34], because alcohol use is associated with histological liver lesions, which develop rapidly and lead to fibrosis, so no consumption whatsoever should be allowed at this stage^[32,35].

Along with the presence or absence of abstinence, frequency and intensity of consumption, translated into the number of drinks ingested, should also be assessed^[24].

During the post-transplantation period, Kotylar distinguished "heavy relapse" from "slip". The former corresponds to the consumption of more than 5 drinks over a period of more than 5 consecutive days^[22]. Some studies have reported that a "slip" indicates a much better clinical prognosis (particularly regarding survival rates) than a "heavy relapse"^[36,37].

Relapse monitoring: Relapse monitoring can be undertaken using three strategies: self-reports; reports from family members; and laboratory tests.

The probability of the patient's self-reports being truthful is approximately 65% (compared to the reports from family members and the results of laboratory tests)^[38].

As stated in other sections of the present article, family members can prove to be major allies, and their reports can be very useful in determining the patient's alcohol consumption. For this process to occur, it is paramount that the transplantation team create a solid and transparent relationship with the patient's family^[39].

Many centers resort to laboratory exams. Liver lesion tests can be useful for identifying patients who drink after a rehabilitation program, with sensitivity of 100% and a specificity of 82% when GGT \geq 20%, ALT \geq 40% and AST \geq 20%^[40]. However, these results are not valid in patients with significant liver disease^[41].

Another test frequently used is the carbohydrate-deficient transferrin test. However, as mentioned, recent studies have shown the value of this test in the detection of prolonged alcohol consumption to be uncertain, especially in patients with very severe liver disease^[42].

Alcohol quantification can be performed using urine, breath, blood and hair. While blood, breath and urine tests detect alcohol use in the previous 12-24 h (on average), hair tests can detect it up to 90 d before the exam^[43].

Relapse treatment: Attitudes and behaviors toward treatment are relevant in the context of outcomes, but there have been few studies showing the efficacy of the psychosocial treatment of ALD patients after transplant. Several reasons have been noted for this situation, among them that the patients believe that they no longer have an alcohol-related problem and therefore no longer need treatment, as well as that certain drugs used to prevent relapse of drinking are feared by patients (and often also by their hepatologists) due to possible adverse reactions in patients without fully recovered liver function^[22,44]. This finding explains why the only controlled, randomized study in this area was not completed^[44].

Two types of treatment have been suggested: psychopharmacological and psychotherapeutic^[2,45].

Regarding the former, 5 drugs should be emphasized.

Disulfiram inhibits the aldehyde dehydrogenase enzyme, leading to an accumulation of acetaldehyde (a compound that results from alcohol metabolism and is degraded by aldehyde dehydrogenase), which is very toxic to the organism, causing extreme vasodilation and the consequent drop in blood pressure, tachycardia and cephalaeas. These effects are called "Antabuse" or "disulfiram-like". The use of this drug in transplanted patients is not recommended due to its potentially hepatotoxic and hypotension-inducing effects^[44].

Naltrexone, an opioid receptor antagonist (especially of the μ receptor) is also widely used in alcoholism, having already been shown to reduce cravings and the rate of relapse of drinking^[46]. Although its action is not yet clear, it seems to be mediated by the inhibition of the rewarding effects of alcohol, by blocking the reward circuits in the brain^[47]. The administration of this drug in transplanted patients has been avoided because, according to some manuals, it can cause an increase in aminotransferases (which is generally reversible).

Nalmefene (the mechanism of which is similar to naltrexone but apparently with better liver tolerance) could be an alternative to naltrexone in alcoholism^[48,49], but no studies in transplanted patients have been conducted so far.

Acamprosate, a NMDA-receptor antagonist used in alcoholism, has a very safe profile from a metabolic point of view, and it might be a good candidate for use in transplanted patients^[32,33]. However, the existing studies have not been very optimistic in regarding the maintenance of abstinence^[44].

Badlofen, a γ -aminobutyric acid receptor antagonist, was evaluated in a randomized, controlled study in patients with end-stage alcoholic liver disease, showing both safety and positive effects^[50].

The human difficulty in addressing, accepting and sustaining change is widely known, above all in such a complex life situations as the transplantation process, and for this reason, psychotherapeutic treatment must be implemented during all stages of the transplantation process.

Understanding the patient means being attentive to greater difficulties or to factors that can trigger stress, which, in the case of an ALD patient, can lead to a lapse or a relapse, contributing to worse adherence, which can in turn translate into increases in morbidity and mortality. In this manner, it is important to develop coping strategies to face the factors that trigger stress and that could lead to a relapse. There are several structured models of psychotherapeutic intervention, the most common being MATCH (Matching Alcoholism Treatments to Client Heterogeneity), which has shown similar efficacy to 12-step treatment, cognitive

Table 1 Possible predictors of post-transplant relapse

Good prognosis
Pre-transplantation abstinence > 6 mo (controversial)
Social support
Abuse <i>vs</i> alcohol dependence
Good adherence in a broad sense
Poor prognosis
Family history of alcoholism
Non-acceptance of diagnosis related to alcohol use
Comorbidity with other substance abuse (controversial)
Psychiatric history (psychosis, personality disorder)
Quantity of alcohol/d
Number of years of use

behavioral therapy and motivational enhancement therapy^[51].

CONCLUSION

Currently, ALD is one of the most common indications for liver transplantation, and post-transplantation survival and other predictors of the clinical course in ALD patients do not differ significantly from those of other types of transplanted patients, as long as there is no relapse of drinking.

However, relapse of drinking can have catastrophic consequences. Therefore, it is paramount to perform a psychosocial assessment of the candidate for transplantation and to identify relapse risk factors.

Table 1 lists the possible factors in relapse of drinking (poor and good prognostic factors), according to the literature.

This assessment allows not only for improvement of the selection of the patients who are to be transplanted but also for the design of psychopharmacological/psychotherapeutic interventions whenever necessary (in both the pretransplantation and post-transplantation periods), thus preventing and monitoring relapse.

This treatment should be integrated within the transplantation team and family (or significant others) and should be continued for at least one year post-transplantation^[17].

Therefore, the authors suggest that ALD patients should now be considered a challenge rather than a threat - a challenge requiring special efforts by transplantation teams. Other types of transplanted patients, such as those with FAP (familial amyloid polyneuropathy), a rare genetic disease, for which the most accepted treatment is liver transplantation, can also represent an additional concern in terms of psychosocial adaptation to liver transplantation, and they should also receive special attention^[52].

The authors also suggest that other factors from the immediate post-transplantation period that could also be important relapse risk factors or relapse-preventing factors could be investigated in this context. Factors such as post-transplantation coping strategies and mental status (*e.g.*, depression and anxiety levels)

can predict several markers of good and poor medical and psychosocial outcomes, such as adherence to medication, quality of life, *etc.*^[53], and could also be important factors in predicting alcohol relapse.

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