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The Role of Liver Transplantation in the Treatment of Alcoholic Liver Disease

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1. Introduction

In 1988 Starzl challenged the consensus view from 1983 that only a small percentage of patients with alcoholic liver disease (ALD) would be expected to meet the criteria for transplantation (National Institute of Health [NIH], 1984). Starzl and his team reported the successful liver transplantation (LT) of patients with ALD, and suggested that few patients returned to alcohol after liver transplantation (Starzl et al., 1988). Since then ALD has become one of the most common indications for LT in adults. However, despite this success, there remains significant debate and controversy regarding the indication, as several studies over time have shown that the public may not be supportive of the idea of allocating a limited resource, such as the liver graft, to patients with ALD. This chapter will discuss the pre-transplant evaluation of patients with ALD, the debate over the treatment of acute alcoholic hepatitis, and the outcome of LT for ALD, including the issue of relapse. Finally, certain ethical concerns such as the use of living donors and future challenges will be analyzed.

2. Pre-transplant evaluation of patients with ALD

Patients with ALD, as part of their pre-transplant evaluation, are assessed by a multi-disciplinary team consisting of hepatologists, surgeons, social workers and psychiatrists. The decision to list the patient depends on the status of the liver disease, which is expressed in most centers by the Model for End-stage Liver Disease (MELD) score. This is a relatively objective measurement of the patients' degree of liver disease by using the patient's bilirubin, creatinine and INR serum values to calculate the MELD score. The latter is empirically capped at 40 and represents a continuous variable ranging from 6 to 40 and it has proven to be highly accurate in assessing 3 month mortality once a cirrhotic patient is on the waiting list (Kamath et al., 2001). There is however the assertion that ALD patients may be under-referred for LT in the United States (Kotlyar et al. 2008). This may be because ALD may represent a negative determinant for many physicians to refer patients for LT, or there may be a lack of recognition of the contribution of excessive alcohol consumption to liver failure in the community. One study identified patients with liver failure in whom alcohol consumption was not recognized or acknowledged by the referring physicians (Day et al., 2008). It is not clear whether this was a purposeful omission or a genuine lack of recognition, but it does underscore the need for careful attention to the presence of alcoholic disorders in patients with liver failure.

2.1 Abstinence prior to LT for ALD

Patients with ALD undergo the standard pre-transplant evaluation, whose goal is to determine the suitability of the potential candidate to undergo the LT, as well as the urgency with which this has to be performed, based on the severity of the liver disease. Specifically for patients with ALD the issue of abstinence is critical in making these determinations. The apprehension that candidates for LT with ALD are likely to relapse and cause damage to the graft, makes it important to select those patients with the lower risk of relapse. To ensure this formal pretransplant substance misuse evaluations are required, including a broad psychosocial and substance abuse assessment. Factors analyzed include the pattern of previous alcohol use, diagnosis of alcohol use disorder, length of abstinence and features that would indicate a higher risk of future return to alcohol consumption (Dobbels et al., 2009; Gedaly et al., 2008). People judged suitable for LT are patients with severe end-stage liver disease, a clear understanding of the risks and benefits involved in the procedure, and a favorable psychiatric profile including acceptance of their alcoholism and factors in their family and social network that would ensure post-transplant sobriety.

Pretransplant abstinence offers the advantages of allowing the liver disease an opportunity to stabilize, as well as testing the patient's commitment and resolve to proceed with this treatment. The transplant team with the support of the psychiatrists and the abuse specialists has the ability during that period to evaluate the patient and the presence of a support network, as well as monitor their resolve through frequent visits, as well as unannounced testing. There remains significant debate regarding the extent of the required abstinence period. Specifically, the vast majority of transplant centers (85%) in the United States require 6 months of abstinence prior to transplantation, with a significant number expecting the patients to sign a formal contract (Everhart & Beresford, 1997). This view was changed in 2005, following the UNOS and French Consensus Conference on LT, as there was not an agreement in the literature regarding the 6 month sobriety period (Mathurin, 2005).

People in favor of the 6 month abstinence period cite 3 main advantages. First, the period of pretransplantation abstinence may allow liver recovery, even to the extent of a LT becoming unnecessary, with one study showing significant improvement within 3 months (Veldt et al., 2002). Second, it can help identify those patients unable to abstain, and thus more likely to relapse after the LT. This cannot happen reliably when a patient presents with decompensated liver disease, as "death-bed repentance", no matter how genuine, may not accurately reflect future intentions. Finally, the time of abstinence can and should be used for intensive rehabilitation and treatment for the alcohol dependence, as relapse is more frequent within the first year after quitting alcohol. Others have questioned the need for an arbitrary period of abstinence pre-LT. All agree that the 6 month period is not based on prospectively gathered data, but rather on custom and practice (Neuberger et al., 2002). The main argument against the enforced time period of abstinence has been that it may be more of a selection method favored by insurance companies, rather than an effective predictor for post-transplant abstinence. Some of the key studies in the field have advocated that full psychosocial assessment as part of the pretransplant evaluation of the ALD patient may be more important than a universal application of a 6 month abstinence rule (Pfitzmann et al., 2007). Additionally, these studies have shown that the frequency of both minor and harmful drinking is frequent in the first 5 years after LT, despite careful pre-transplant assessment, although it is equally useful to distinguish between harmful drinking and "slips" (DiMartini et al., 2006; Pfitzmann

et al., 2007). Setting a fixed time period for pre-LT abstinence as a rigid rule, fails to take into account the multiple clinical and psychosocial variables of ALD patients. Patients with ALD are not immune from hepatocellular carcinoma (HCC), and as such cannot have an arbitrary waiting time period placed on them, as in that case there is the real danger of the HCC getting outside Milan criteria, and thereby precluding any chance of a LT. This is not to say that there should not be a proper evaluation of the severity of the alcohol dependence in these patients, or measures taken to achieve sustained abstinence and prevent relapse; however, in order to reach a consensus on a period of abstinence prior to the LT, large, multicentric, randomized longitudinal prospective studies are needed to analyze the decision making methods carefully and completely (Beresford & Everson, 2000).

The question of the 6 month abstinence period prior to a LT is only part of the effort to identify predictors of post-LT relapse. In addition to the studies supporting that the length of sobriety is a strong predictor of recidivism, there are others reporting that patients with a DSM-IV diagnosis of abuse had a lower relapse probability than those with alcohol dependence (DiMartini et al., 2006; Karim et al., 2010). DiMartini et al. showed that variables such as alcohol dependence, short length of sobriety, family history of alcohol consumption and the use of other substances identified patients with a major risk of relapse (DiMartini et al., 2010). Despite that there are studies showing that pre-LT behavior is a poor predictor of relapse, or that other variables such as demographic, family and social ones come into play (De Gottardi et al., 2007; Foster et al., 1997; Kelly et al., 2006; Pfitzmann et al., 2007). Overall, this multitude of often competing possible predictors of recidivism, further stresses the need for an accurate stratification of potential candidates to identify those most likely to remain abstinent, and thus benefit the most from a LT.

2.2 Comorbidities associated with ALD

There is a significant number of comorbidities among patients with ALD which ultimately may limit their suitability for LT, unless properly addressed. Some of these comorbidities may be a direct effect of alcoholism, or they may be medical conditions commonly occurring in alcoholics. Patients with alcoholic cirrhosis may have alcohol related heart disease, such as alcoholic cardiomyopathy, in addition to the cirrhotic cardiomyopathy that is attributed to cirrhosis itself, and this may be related to the total lifetime use of alcohol (Urbano-Marquez et al., 1989). Alcoholic cardiomyopathy has specific diagnostic criteria and is associated with active alcohol intake. For that reason interventions that would lead to alcohol cessation would also prevent progression to cardiac failure. Additional medical comorbidities include neurologic disease ranging from myopathy to fixed deficits, with the latter being at times hard to differentiate from the hepatic encephalopathy that is associated with cirrhosis and can be reversible following LT (Keefe, 1997). Chronic pancreatitis and malnutrition are other problems commonly seen in these patients, whereas one cannot ignore the coexistence of other liver disease, such as chronic hepatitis C virus (HCV) infection or hepatocellular carcinoma (HCC), which can affect the urgency of LT, and especially the overall prognosis.

2.3 Acute alcoholic hepatitis

Acute alcoholic hepatitis (AH) represents a treatment dilemma for the medical team, as it may occur in patients with previously normal liver or with established cirrhosis. Patients with a previously normal liver present an opportunity, from a technical standpoint, as the

liver transplantation is significantly easier with the absence of the trademarks of end-stage liver disease, such as portal hypertension (Figure 1 a, b).
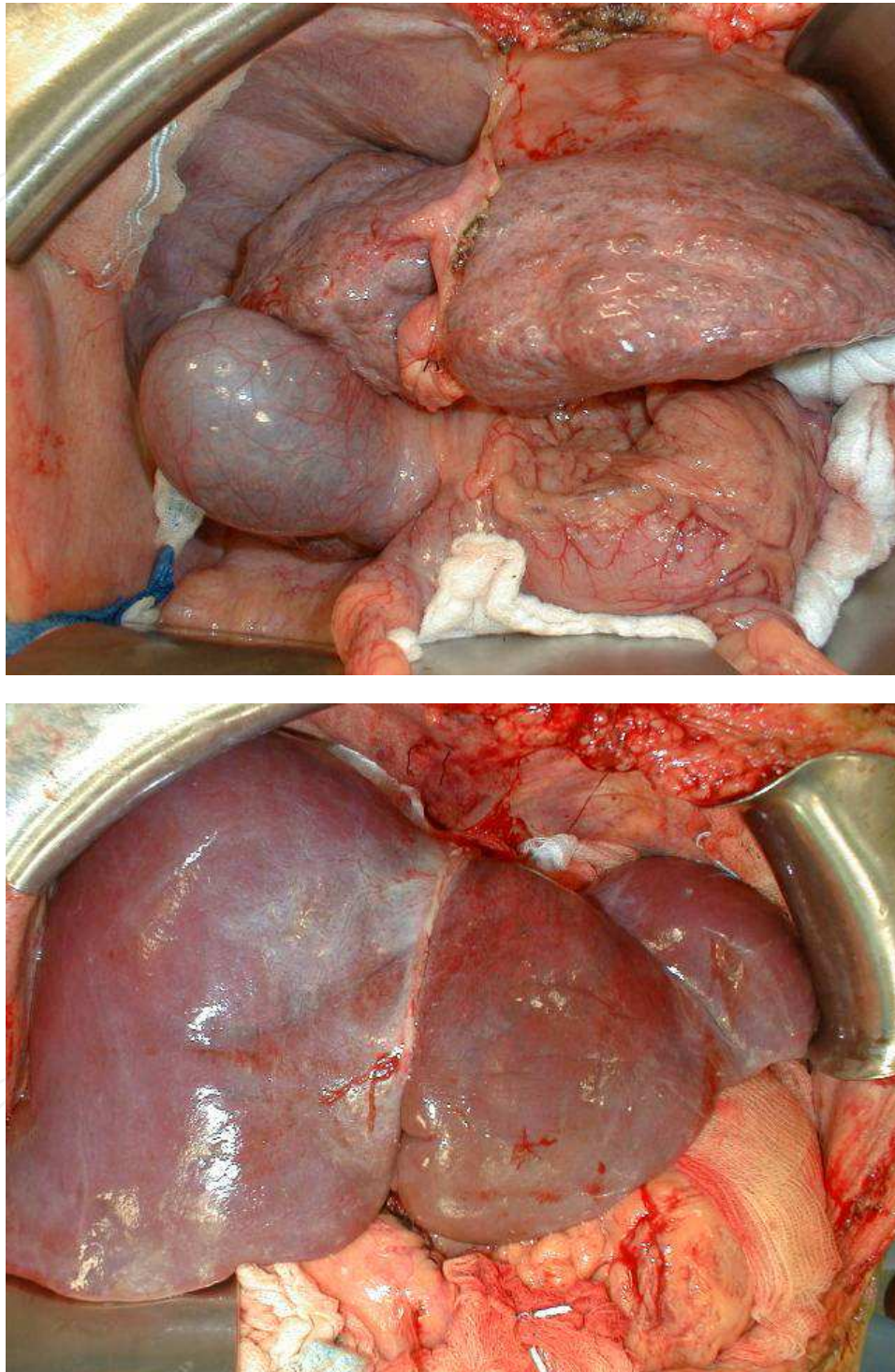

Fig. 1. a, b: Different types of livers encountered in patients with alcoholic liver disease. (a) This patient has acute alcoholic hepatitis on top of previously established cirrhosis. The hepatectomy stage of the LT is much more challenging in this patient. (b) This patient has acute alcoholic hepatitis without any previous evidence of cirrhosis, with the liver revealing some edema, but no cirrhosis.

Unfortunately, in the severe form, even with maximal medical treatment, there is a 40-50% mortality within 1 month after diagnosis (Dureja & Lucey, 2010). This very high mortality, despite the organ shortage, has led to many advocating LT for that subset of patients who have failed medical treatment. To date, only corticosteroids and pentoxifylline are considered to potentially improve short-term survival, although the results of meta-analysis remain controversial (Imperiale et al., 1990; Mathurin et al., 2011). Currently, the majority of transplant centers are reluctant to offer LT for patients with acute AH, although there is an effort to identify that subset of patients that will fail medical treatment with corticosteroids and likely benefit the most from LT. Experience has been mixed regarding transplantation for these patients, although there are some encouraging new studies, where strict selection can lead to favorable results, both in terms of survival, as well as in terms of relapse (Castel et al., 2009; Tome & Lucey, 2003). One of these studies was a European multicenter study about a carefully selected group of patients suffering from their first episode of severe AH and for whom medical treatment had failed. They had received a favorable psychosocial assessment and had excellent intermediate survival and low frequency of significant drinking after LT (Castel et al., 2009). Based on these results, transplant groups on both sides of the Atlantic have argued in favor of placement on the LT waiting list of patients with life-threatening AH who meet criteria.

3. Outcome of LT for ALD and ethical issues

3.1 Outcome of LT for ALD

The overall survival of patients who underwent LT for ALD is statistically comparable to that of patients who underwent LT for other indications. Data from the European Liver Transplant Registry 2008 revealed 1-, 5-, and 10-year patient survival rates for ALD of 96%, 88% and 76% respectively, as compared to 97%, 80% and 72% for patients with other indications (European Liver Transplantation Registry [ELTR], 2008). Similar survival rates have been reported for ALD patients in the US after LT: 92% at 1 year, 86% at 3 and 5 years and 76% at 9 years (Bhagat et al., 2009). It has been shown that patients with ALD had similar patient and graft survival rates, if not better in some cases, compared to those of patients undergoing LT for other indications (Dumortier et al., 2007; Mutimer et al., 2006; Romano et al., 1999). In a "perfect" world patients would have a single aetiology for their end-stage liver disease, unfortunately in the real world patients may undergo LT for ALD in the presence of other comorbidities, which can significantly affect the result. The most common is HCV, where there have been data of a more rapid progression of the liver disease in immunocompetent patients with the combination of ALD and HCV (Cromie et al., 1996; Pessione et al., 1998). However, other, more recent studies have shown that patients transplanted for ALD plus HCV had a better survival than patients with HCV alone and similar survival to those with ALD alone (Aguilera et al., 2009). This could be partly explained by the greater use of antiviral treatment in patients with HCV and ALD, as they were younger than the HCV alone patients. Furthermore, data from the European Liver Transplantation Registry have shown similar post-LT survival rates between patients with ALD and ALD plus a viral etiology (HCV and HBV), although patients with ALD plus HCV had a significantly shorter survival compared to those with ALD plus HBV infection (Burra et al., 2010). These data support the notion that ALD represents a good indication for LT, even in the presence of hepatitis virus infection.

Regarding long-term morbidity and survival in patients with ALD, there appears to be an effect from a high prevalence of medical comorbidities, including de novo cancers. In one study of a group of patients undergoing LT for ALD, 5 year graft and patient survival were significantly lower than non-alcoholics undergoing LT, mainly due to cardiorespiratory, cerebrovascular and neoplastic problems (Jain et al., 2000). When compared to patients receiving LT for other indications, those transplanted for ALD are at a greater risk of de novo malignancy, and especially aerodigestive cancers possibly due to the chronic alcohol use (Oo et al., 2005; Watt et al., 2009). These comorbidities are associated with worse survival (Bellamy et al., 2001; Duvoux et al., 1999). These studies do not show an association between new-onset cancers and alcoholic relapse. An important factor may be the high prevalence of chronic heavy tobacco use in this population, in combination with the immunosuppression. This presents the question of whether patients with ALD require specific surveillance programs for de novo tumours after LT. Also, if the link between tobacco use and death from either cancer or cardiovascular disease holds true, then an obvious way to improve post-transplant health is through the promotion of smoking cessation, especially in LT recipients with alcoholism.

3.2 Impact of recidivism on survival after LT for ALD

Not unexpectedly, better survival rates were observed for patients that remained abstinent after LT than those who returned to alcohol use. Still in trying to identify the impact of recidivism on survival after LT, first we have to overcome the problem of a lack of a commonly accepted definition and the fact that the reported rates of recidivism vary widely at different follow-up periods post-LT. In one of the better prospective studies, DiMartini et al., showed that 22% of patients had used some alcohol by the first year after LT and 42% had a drink by 5 years (DiMartini et al., 2006). By 5 years, 26% drank at a heavier use pattern and 20% in a frequent pattern. In another prospective study by DiMartini et al., there were five different patterns of alcohol consumption identified, based on the time of relapse and the subsequent pattern (DiMartini et al., 2010). Approximately 80% of the patients either did not drink or consumed only small amounts rarely. Among the remaining 20%, there were 3 patterns of harmful drinking, varied according to the time of relapse and the consumption of alcohol (sustained, heavy use or subsequently modified drinking). These data were similar to the retrospective data from Tang et al., who found harmful drinking in 16% of the patients (Tang et al., 1998). The problem of identifying a commonly-accepted definition for recidivism and the prevailing rates is made more difficult by the fact that most of these studies are based on data obtained through self-report questionnaires, interviews with patients and/or family members, or even retrospective analysis of routine screening tests. In all of this there is an apparent risk of underestimation.

However, there is disagreement on the impact of recidivism on post-transplant survival. Specifically, there have been studies showing no significant impact on survival rates (Burra et al., 2003; Gerhardt et al., 1996). These have been contradicted by other studies reporting 5- and 10-year survivals of 69% and 20% respectively in patients with alcohol relapse following LT, and the argument that attention needs to be paid to the different patterns of relapse, rather than the overall rate (DiMartini et al., 2006). It does appear that the long-term survival of patients who resume heavy drinking is lower compared to those

who remain abstinent or have minor slips (Cuadrado et al., 2005; Pfitzmann et al., 2007). Interestingly enough, a significant factor for the decreased survival appears to be an association with developing malignancies, rather than recurrent end-stage liver disease. The influence of slips on LT outcome remains unclear, but there is the general perception that, although a slip should be considered an adverse event, it is unlikely to cause harm if it does not lead to a full-blown relapse (Cuadrado et al., 2005; Pfitzmann et al., 2007). One area where clinicians should pay particular attention to alcohol recidivism is when it is combined with concomitant HCV infection, since it may exacerbate the liver damage with rapid progression to cirrhosis and graft loss (Bellamy et al., 2001; Neuberger et al., 2002; Tome & Lucey, 2003). This can often lead to a late onset of acute or chronic rejection, whose management can be a nightmare in the patient with HCV recurrence (which is the vast majority of patients).

A question closely related to the effect of recidivism on survival after LT for ALD, is that of the quality of life after the LT. In a study in the UK of patients undergoing LT for ALD over a 10-year period, it was seen that overall in the long term at least 50% of the patients will drink again at some time post-LT, although at lower levels of alcohol intake than before the transplant (Perreira et al., 2000). The group at greatest risk for harmful drinking appears to be the patients with the most predictive factors for relapse, and thus the group that would benefit the most from professional counselling. Even so, the overall quality of life after LT for ALD, based on three different questionnaires, is high and in general similar to the level expected in the general population. When everything is put together regarding the issue of recidivism after LT for ALD, the challenge is the need for improved methodology and tools in monitoring post-transplantation abstinence, in order to better evaluate the effect of relapse. Ultimately, the question is critical, as it raises the issue of proper stewardship of a limited resource for society.

3.3 Cost-effectiveness of LT for ALD

As liver transplantation has not really been the subject of a randomized controlled trial, there is some uncertainty regarding the magnitude of the benefit and cost-effectiveness for specific patient groups. In an attempt to answer this question a study from England and Wales attempted an economic evaluation of liver transplantation in that area (Longworth et al., 2003). Cost-effectiveness was measured using incremental cost per quality-adjusted life years (QALY; commonly referred to as cost-utility analysis). The results of a comparison group, representing experience in the absence of LT, are estimated using a combination of observed data from patients waiting for transplant and published prognostic models. The analysis was limited to three disease groups for which prognostic models were available at the beginning of the study, one of which was the group of patients with ALD. Overall, a higher proportion of patients with ALD were assessed for a transplant but not placed on the waiting list. The estimated gain in quality-adjusted life-years from transplantation was positive for each of the disease groups. The mean incremental cost per quality-adjusted life-year from time of listing to 27 months was €54,000 (€13,500 to €93,500). The study showed that LT increases survival and health-related quality of life of ALD patients, although the cost-effectiveness estimates within that 27 month period were poorer for patients with ALD than for patients with PBC or

PSC. The authors suggested that this may reflect the cost of the higher number of ALD patients assessed for each transplant.

3.4 Ethical issues

The indication of ALD for LT is unlike many of the others as it involves the proper use of a scarce resource for patients with a potentially "self-inflicted" disease. Some have argued that since alcohol dependence as an "addiction" carries a neurobiological and a genetic component, then it may be more appropriate to treat it more as a medical condition. This does not answer the problem fully, as what matters is the outcome and if we accept that self-control has no role in the management of alcoholism then relapse would be all but a certainty. Others have challenged the ethics of the "6-month abstinence" rule, based on lack of evidence making it an arbitrary decision (Everhart & Beresford, 1997). Studies have found that although neither the presence of histological alcoholic hepatitis in the explant, nor any history of drinking within 6 months correlated with subsequent relapses (Tome et al., 2002; Wells et al., 2007). Against this background of conflicting data, there is a lack of consensus from country to country regarding the timing and suitability of patients with ALD for LT. One has to consider whether rules such as the "6-month" one represent an attempt towards an ethical approach to patient selection for LT, or whether they are a matter of practicality. For example, in the United States, the evaluation process usually results in the presentation of a comprehensive clinical and psychosocial assessment to the transplant program's selection committee. When the selection committee decides to recommend transplantation, the approval of the third party payer is necessary before the patient is placed on the waiting list. The 6-month rule has been widely adopted by the US insurance industry, without adequate data, leading to anecdotal reports of the difficult decisions involved (Boren, 1994). There are certain lessons that can be drawn regarding sobriety and prognosis after LT for ALD, which may have more validity than simply following the 6-month rule. Specifically, no single measure is a reliable prognosticator for future relapses into harmful drinking after transplantation, and although the duration of abstinence has been associated with subsequent drinking, it is an imprecise prognostic tool. Furthermore, there is more value in a careful evaluation by a trained addiction specialist with a special interest in transplant medicine, with such a psychosocial assessment helping determine the risk of relapse into significant alcohol abuse, but not with an absolute certainty. Finally, when all is said and done, the severely ill patient who has been drinking recently, but has other favorable prognostic indicators with respect to post-transplant behavior, represents a very difficult question for any transplant program.

Another issue is that since the need to restrict access to LT for patients with ALD is based on the donor shortage, then it could be argued that these recipients should be held to different standards when there is the possibility of a living donor. The answer to this question should still relate to the outcome and long-term results of LT for this group of patients, as no matter how willing the living donor may be, it must be made certain that the benefit to the recipient is worth the risk to the donor. Consideration of ALD patients as recipients for Living Donor Liver Transplantation (LDLT) has raised similar issues as those seen with cadaveric donation for these patients. Since most living donors are closely related to the recipient, they have watched the progression of ALD in the recipients over time and many may not regard

the pathogenesis of ALD as totally unavoidable. This would result to donors seeing recipient relapses with alcohol, no matter how frequent or clinically significant, as ingratitude. Thus, for every patient with ALD being considered for LDLT there are individual conditions and relationships, which dictate significant less tolerance with alcohol relapse in LDLT compared to cadaveric donation.

The answer to many of these concerns has been the utilization of the 6 month abstinence rule by most programs. Notwithstanding the shortcomings of this rule regarding its predictive capacity that have been described elsewhere in this chapter, there are also certain issues unique to LDLT that may limit its use. Specifically, with a cadaveric LT there is the "luxury" of waiting given the organ shortage, and so that period can be used to test the abstinence and intervene; in LDLT the biggest advantage is the short preparative period and waiting time needed, something which would be negated by the strict use of the 6 month rule. Additionally, there are several Asian countries where, because of religious considerations, LDLT is the main type of LT, as cadaveric donation is limited or nonexistent. Thus, in these countries patients with ALD may have limited options. These two points are not meant to suggest that patients with ALD should be able to proceed with LDLT without addressing the issue of alcohol abuse and the possibility of recidivism, as that would be a disservice to the gift of the donor. A study by Hwang et al. from the Asan Medical Center in Korea of patients with ALD undergoing LDLT concluded that the pretransplant abstinence seemed to be beneficial and that for ethical reasons the 6 month abstinence rule should be strictly observed in LDLT (Hwang et al., 2006). When considering the ethical aspects of living organ donation, it is certainly reasonable to exclude recipients with significant factors for relapse. Also, we need to consider the unique aspects of the donor-recipient relationship, similar to those seen in the case of LDLT for patients with HCC. Along these lines a factor that may help is that a very close relationship between the donor and the recipient may be critical in preventing alcohol relapse or at least an escalation to significant alcohol abuse. The same study from South Korea found 3- and 5-year relapse rates of 20% in these patients undergoing LDLT for ALD, lower than many of the studies with cadaveric LT (Hwang et al., 2006). This issue cannot be simply ignored as in Korea, for example, at the Asan Medical Center 134 LDLTs had been performed by 2003, of which only four were for ALD (Moon & Lee, 2004). Although the actual prevalence of ALD in S. Korea may not be known, it is thought that 6% of patients with cirrhosis have ALD. This means that the trends are changing, as the 20-year vaccination program for Hepatitis B virus has reduced the incidence of the disease in the population, there is a gradual increase in alcohol consumption which will eventually lead to a higher need for LDLT for patients with ALD.

4. Future challenges

4.1 Psychosocial assessment

Evaluating the role of LT in the treatment of patients with ALD is a work in progress as significant challenges remain. Chief among them is the need for improved psychometric tools and assessments that would be able to predict with greater accuracy the pattern of alcohol use after transplant and the effect of that on the liver graft. This could lead to

more targeted interventions with higher likelihood of success. A number of predictive tools have been considered as part of the assessment. The University of Michigan Alcoholism Prognosis Scale examines a number of psychosocial domains with a higher score suggesting increased stability leading to improved prognosis and Lucey et al. have suggested this broad-based tool as a useful alternative to the fixed pre-LT abstinence period (Lucey et al., 1997). Other tools include the alcohol abstinence self-Efficacy Scale which rates an individual's ability to self-determine in the context of relapse precipitants (DiClemente et al., 1994). Although it has shown good reliability and validity in alcohol treatment settings, it has yet to be proven in the liver transplant setting. Beresford, an addiction psychiatrist from the University of Michigan, who introduced the concept of psychosocial assessment of ALD transplant candidates, alerted the transplant community to the clinical insights into the factors involved in maintaining sobriety reported in the addiction literature (Beresford, 1994). Based on the studies of Vaillant and of Strauss and Bacon, he constructed a panel of negative prognostic factors that he used to assess prospective ALD patients as candidates for LT (Strauss & Bacon, 1951; Vaillant, 1995). These included psychiatric comorbid conditions, such as uncontrolled polysubstance abuse or unstable character disorder, a history of many failed rehabilitation attempts, social isolation as shown by lack of a fixed employment and living alone without a spouse or companion.

All of this has led to psychosocial assessment becoming part of the norm in liver transplant centers, where the use of agreed clinical guidelines and candidate selection criteria offer the assessment team a framework upon which to base complex decisions and an opportunity to explain the assessment and decision to the patient. It also allows transplant centers the opportunity to audit their selections and outcomes against accepted listing criteria. These observations, together with those by DiMartini documenting the five patterns of alcohol use, need validation in a large prospective cohort, and if successful can help clinicians identify tailored monitoring and interventions. Behavioral and pharmacological therapies may be necessary and helpful, but it is essential that they are individualized and that the support required is discussed and agreed upon with the candidate and their support system (DiMartini et al., 2010).

4.2 Genetic element of ALD

Also, further data are needed to clarify the element of genetic predisposition in alcohol abuse, as this too could help identify people at greater risk. Recent high-throughput technologies, such as micro arrays, genomics and proteomics have led to novel concepts in our understanding of several liver pathologies (Decaciuc et al., 2004; Seth et al., 2006). Application of these technologies has identified novel pathways that could not have been discovered using traditional methods and opened up several lines of investigation for understanding the mechanism involved in alcohol-mediated liver injury. Hepatic gene profiling using DNA micro arrays are reported from animal models of ALD and human ALD (Decaciuc et al., 2004; Seth et al., 2006). The ALD transcriptome profile is dominated by alcohol metabolism and inflammation related molecules, thus differing from other liver diseases (Seth et al., 2003). Additionally, several functional groups of genes showed similar qualitative and quantitative changes also in rodents as a result of chronic alcohol exposure

regardless of the type of array platform (Decaciuc et al., 2004). This finding shows the existence of common mechanisms of alcohol effect on the liver across species.

In the past, genetic studies in ALD have focused on genes involved in alcohol metabolism (ADH, ALDH, CYP2E1), oxidative stress (GST, superoxide dismutase), endotoxin (TNF-a, CD14, TLR4), cytokines (IL-10), immune (cytotoxic T-lymphocyte antigen-4) and fibrosis (collagen, MMPs, osteopontin, TGF-b) and have been extensively reviewed (Stickel & Osterreicher, 2006). All appear to have an effect, but to date the search for single nucleotide polymorphisms (SNPs) in a hypothesis-driven candidate gene approach has been rather disappointing in identifying risk factors for ALD. Some of the reasons have been that most of the studies involved have either lacked statistical power due to small sample size, or investigated polymorphisms in a single or a few candidate genes or were subject to population stratification, Type 1 and 2 errors, or have failed to account for factors such as obesity and the confounding effect of Non-alcoholic steatohepatitis (NASH). Susceptibility to ALD, like most other multifactorial complex diseases, is controlled by a number of genes, each of which makes its own contribution. Therefore, what is needed is a genome-wide approach, in carefully designed large studies in order to identify various degree of risk genetic variants associated with ALD. The lack of an a priori hypothesis has helped Genome Wide Association (GWA) technologies yield successful outcomes in a variety of several common liver diseases (Karlsen et al., 2010; Kolleritis et al., 2009; Romeo et al., 2008). Advantage should also be taken of the understanding gained from research in other liver diseases, such as NASH, that show increasing parallels with ALD development. Recent advances in newer technologies enabling genome wide search for millions of SNPs, whole genome sequencing, global epigenetic profiles, and non-coding regulatory elements (miRNA) are the future research areas to construct the architecture of ALD and identify ways to predict and intervene in its progression. In these times of financial turmoil, a global well-coordinated effort is required to invest in future research to provide answers for a problem common in all different countries.

5. Conclusion

Liver transplantation has become over the last few decades one of the main treatments for advanced ALD. However, in order to optimize the results of this treatment, as well as fully establish its societal acceptance, it is imperative that careful patient selection takes place and that attention is paid not only to the peri-operative but also to the pre- and post-transplant periods. We need to stratify ALD potential transplant candidates according to the risk of relapse. Unfortunately, as we have seen in this chapter, to date the results reported from different studies are mostly inconclusive regarding the evaluation of predictive factors for alcoholic relapse after LT. Also, a defined pre-LT abstinence period for ALD candidates for transplantation appears to be justified, both as a way to ensure compliance, as well as an opportunity to effect some interventions to possibly recover liver function to the extent that a LT might not be needed. Even so, there are no strong data supporting the 6 month abstinence rule, and that means that we need to reach a consensus on this specific issue by conducting longitudinal, prospective studies. Just as important is the need to avoid the ease that strict "yes or no" rules and regulations offer (such as the 6 month rule) and concentrate more on creating and using improved psychomotor tools and assessments that will allow us

to better evaluate and help these patients. The question of the definition of alcohol relapse is another area where further studies are needed. The reason is that although a number of patients return to some degree of alcohol use after LT, recidivism leading to liver disease threatening the graft is uncommon. Additionally, post-LT surveillance programs for the early detection of cardiovascular problems and de novo malignancies are also needed, given the apparent higher prevalence in this population. To fully achieve this, patients with ALD need to be evaluated and followed by a team of professionals, including internists, surgeons, hepatologists, psychiatrists and social workers who will be able to fully address their complicated needs.

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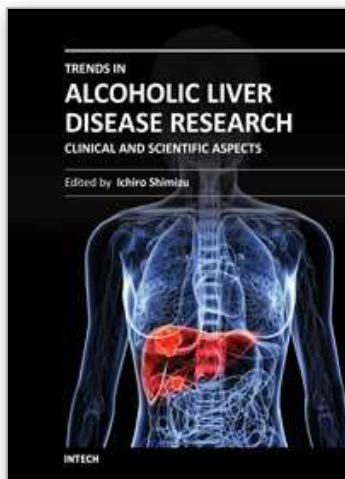
Trends in Alcoholic Liver Disease Research - Clinical and Scientific Aspects

Edited by Dr. Ichiro Shimizu

Alcoholic liver disease occurs after prolonged heavy drinking. Not everyone who drinks alcohol in excess develops serious forms of alcoholic liver disease. It is likely that genetic factors determine this individual susceptibility, and a family history of chronic liver disease may indicate a higher risk. Other factors include being overweight and iron overload. This book presents state-of-the-art information summarizing the current understanding of a range of alcoholic liver diseases. It is hoped that the target readers - hepatologists, clinicians, researchers and academicians - will be afforded new ideas and exposed to subjects well beyond their own scientific disciplines. Additionally, students and those who wish to increase their knowledge will find this book a valuable source of information.

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