Early liver transplantation for acute alcoholic hepatitis: we can't say no

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ABSTRACT

In patients with severe alcoholic hepatitis not responding to medical therapy, it is detrimental to postpone the decision to list a patient in this context of therapeutic dead end. The last decade has seen the place of early transplantation in the therapeutic arsenal in patients with severe alcoholic hepatitis using a restricted selection process of candidates resulting in an acceptable relapse rate. Early transplantation procedure seems to win the support of a growing number of experts from different countries as shown by the European, American and Latin American recommendations. However, there is still a great heterogeneity between countries and even between the centers of a country to list or not a patient with severe alcoholic hepatitis.

EARLY LIVER TRANSPLANTATION: HOW CAN WE SAY NO?

In most countries transplant procedures performed for patients with alcohol-related liver disease are on the rise. This is largely related to advances in antiviral treatments for hepatitis C leading to a sharp decline liver-related morbidity and mortality thanks to the extended use of direct-acting antivirals. Accordingly in the next decade, the proportion of patients listed with the primary diagnosis of hepatitis C will decrease and at a same time those listed for alcohol related liver disease or nonalcoholic fatty liver disease will steadily increase. These reversed trends have already been observed [1].

Due to the prerequisite of abstinence, patients with alcoholic hepatitis have long been excluded from liver transplantation programs [2]. However progress in the early identification of non-responders to medical therapy who are unlikely to survive [3-7] led the French consensus on liver transplantation to strongly recommend innovative approaches including transplantation in patients with severe alcoholic hepatitis not responding medical therapy [8]. This statement was mainly based on three ethical dilemma: a/ unlike other presentations of alcohol related liver disease, abstinence does not allow patients with severe alcoholic hepatitis not responding to medical therapy to recover from their liver disease and obviate the need for LT; b/ the use of the length of abstinence and of the 6-month rule as decision-making tools to predict alcohol relapse is associated with methodological shortcomings; c/ requesting a period of abstinence while knowing that the postponement of a decision to list a patient is detrimental in a context of therapeutic dead end.

The use of prognostic scores such as Lille model [4], early worsening of liver function [3] or combination of MELD and Lille models [9] allows rigorous identification of patients with severe alcoholic hepatitis not responding to medical therapy who have a 6-month mortality rate of approximately 70-80% [10]. Before referring a patient to a transplant center for early liver transplantation, clinicians should stop corticosteroid therapy as soon as a poor response to

treatment is identified on day 7 with a Lille score greater than 0.45. In addition, the detection and early treatment of fungal or bacterial infection is an important component of therapeutic management. The use of 6-month rule excludes patients at low risk of alcohol relapse from prompt listing for liver transplantation while the length of abstinence prior to listing appears to be a relatively poor indicator [11]. The United Network for Organ Sharing (UNOS) [11] and the French Conference Consensus on Liver Transplantation [8] do not strictly recommend the use of the 6 month rule due to its deficiencies.

The first study evaluating the impact of early transplantation in patients with severe alcoholic hepatitis not responding to medical therapy was performed using a very strict selection (table 1) with the following criteria: a process of meetings with members of the medical and surgical teams and nursing staff, absence of co-morbidities or psychiatric disorders, no history of liver decompensating event, patient ignorance of underlying cirrhosis, supportive family members, patient's commitment to stay sober after transplantation, approval of the liver transplant selection committee [12]. Mortality was reduced by 3 times in early transplanted patients in comparison to non-transplanted patients and alcohol relapse rate was low during the follow-up. Once listed, if a transplant is not obtained within a period of less than 30 days, the probability of death on the waiting list is close to 80%. Early liver transplantation transformed the fate of these non-responder patients, initially at a therapeutic impasse, into an evolution similar to those responding to medical treatment. The percentage of patients resuming alcohol consumption was less than 15% during the follow-up period [12]. The first replicative study with an almost similar selection protocol confirmed the higher survival of early transplanted patients compared to non-transplanted matched controls (89% vs 11%) with an acceptable risk of relapse (25%) compared to that usually observed in the setting of transplantation for patients selected with the 6-month rule [13]. An overview of practice of early transplantation for severe alcoholic hepatitis in the US was carried out by means of a retrospective analysis of the activity of 12 liver transplant programs in 8 UNOS regions [14]. One and 3-year survival was excellent, 94% and 84% respectively, which is comparable to survival rates for other transplant indications. There were significant differences in patient selection between the American and European experiences. The American experts did not require a histological diagnosis of alcoholic hepatitis. Such approach is associated 30–50% risk of including patients without disease explaining that only 59% of the American patients had alcoholic hepatitis on explant. French and Belgian patients were selected during hospitalization while American patients were selected after a median period of abstinence of 2 months. It is therefore likely that the American patients were less severe because only those surviving a short period of abstinence could be selected. After liver transplantation, relapse in alcohol consumption and sustained alcohol use occurred in around 30%

and 20% of cases and alcohol consumption was the leading cause of post-transplant death [14]. Younger age was an independent risk factor of relapse in alcohol use. In fact, although convincing, these data were not enough to persuade skeptical experts who are waiting for additional data. They suggested that this procedure could be analyzed as a questioning of utility, justice and respect for persons, the tripod of principles erected by the UNOS [15] although the authors should have recognized that these principles had been considered as achieved by several ethics committees and scientific societies [16-20].

Some experts fear that any modification in the selection process of candidates for liver transplantation with alcohol related liver disease could lead to increase the organ shortage. However, the imbalance between number of organs and patients on the waiting list cannot in itself consist of an argument prohibiting the adaptation of practices based on scientific data and the need to improve the prognosis of patients with severe forms of liver injury regardless of the cause. This organ allocation dilemma cannot be resolved without taking into account several ethical issues. In a context of scarce life-sustaining resources, framework models have been proposed to assist medical decision-making. in patients in life-threatening medical situations, two ethical principles appear to be essential as recommended by expert consensus [21]. The first one is whether the patient can undergo the medical procedure without a significant risk of death surrounding this medical intervention procedure. The second one is the long-term survival prospect after discharge from the hospital [14]. In the setting of severe alcoholic hepatitis, all studies evaluating early transplantation have found a low risk of transplantation-related death similar to that previously reported after this procedure. In terms of long-term survival, a mathematical model showed that early liver transplantation is associated with approximately a 4.5-fold increase in comparison to delayed transplantation [22]. The survival benefit at long term has been recently confirmed in a French study presented at the 2020 EASL Congress. However, those ethical principles are sufficient only for catastrophic public health emergencies requiring a rapid decision-making process for the allocation of scarce mechanical ventilation.

In a context unrelated to a health disaster, it is obvious that many additional criteria, both ethical and medical, need to be consider to achieve expert consensus [19]. Among other things, public opinion is very attached to a deliberative democracy which can only be achieved through the existence of committee selection. To avoid heterogeneity of access to transplantation, the notion of procedural justice could be integrated with a standardized approach. It can be noted that the selection as proposed in early liver transplantation already uses a standardized approach integrating the identification of non-response and of candidates with low risk of relapse into alcohol consumption.

Other ethical concerns have been raised such as the fear of uncontrolled access to transplantation could increase the graft shortage for other etiologies because each graft taken for early liver transplantation is one removed from the pool [15]. This fear is not appropriate because early liver transplantation accounts for less than 5-10% of grafts. Unethical prioritization of other etiologies ahead of severe alcoholic hepatitis in the MELD allocation as recently proposed by some experts cannot be retained because it amounts to a stigmatization of patients with alcohol related liver disease [15]. The authors do not come up with similar proposals for obese patients with diabetes who did not take into account the recommendations on weight control and glycemic balance and did not comply with hygiene and dietary rules [15]. In addition, the authors made such proposal by anticipating a potential risk of misconduct of transplant centers in order to increase their own activity in a context of competition while neglecting the common good of organ sharing. It is surprising that such a fear is targeted at patients with severe alcoholic hepatitis when the risks of abusively listing candidates can be observed regardless of the etiology [23]. The authors should acknowledged that ethical committees have already ruled on the fact patients with self-inflicted diseases should have the same access to medical resources [19, 24]. Even in the situation of transplantation for fulminant failure, it has never been proposed to penalize patients with acetaminophen overdose after suicidal attempt of active drug abusers with acute hepatitis B virus.

There is a great heterogeneity between countries and even between the centers of a country to list or not a patient with severe alcoholic hepatitis. In Germany, early liver transplant procedure is framed by a procedure unsuitable for a rapid decision-making process as the authorization to list can only be obtained by a center after having questioned the office of the Federal Medical Association [23]. In Canada, all transplant centers still require the 6-month rule of abstinence before listing patients with alcohol related liver disease and none had performed early liver transplantation [25]. However, the directors of the Canadian transplant centers recognized the value of a discussion about a possible change in Canadian policy towards patients with alcoholic hepatitis [25]. Conversely in other countries whose experts have endorsed early transplantation [24, 26, 27], a growing number of centers list patients with severe alcoholic hepatitis through a very strict selection process explaining why the burden of this indication remains low. The selection process developed by the French investigators leads to put on the waiting list less than 5% of patients with severe AH. The percentage of transplant centers performing this procedure has increased from 31% to 100% in France [28] and from 0% to 50% in US [29]. In US, the three main reasons raised by centers not performing the procedure were the belief that the 6-month rule was beneficial in terms of improving liver function and reducing the risk of alcohol relapse and the fear of a negative impact on public opinion [29].

One of the obstacles that seems the most difficult to grasp is the possible impact of the program on the public's willingness to donate organs. In order to obtain quantitative data on this issue, an online survey was carried out using a representative sample of the donor public [30]. Among the 503 respondents, two-thirds were considering donating their organs, 21% were unsure and 11% were unwilling. Respondents who were completely abstinent were less likely to donate than the others. Almost 86% of the respondents found that early transplantation was consistent with a rational use of grafts while the remaining 14% did not share this opinion. Middle-age, good social support and financial stability were the patient characteristics considered as the most relevant by respondents for selecting candidates for early transplantation [30]. Consequently, public opinion seems to approve early transplantation in patients with severe alcoholic hepatitis, even if this entity is partly self-inflicted. Moreover, it is important to stress that organ donation has not weakened in France, a country where early liver transplantation has been integrated into routine practice. [19].

The concept of early transplantation raises several issues that remain unsettled [24]. Among others, exclusion of patients with a history of liver decompensations is based on the concept that such patients chose to ignore a warning [19]. This criterion is questionable as it introduces a judgmental aspect to therapeutic decision [19]. Such a criterion should be re-evaluated in more rational terms such as utility, impact on waiting list mortality and risk of alcohol relapse compared to those currently selected. It is likely that, for example, a patient who had a single relapse after 10 years of follow-up after a first decompensation probably does not have the same risk of relapse as compared to another patient without prolonged periods of abstinence during similar follow-up. Some experts suggest shortening the period of abstinence from 6 months to 1 to 3 months. In terms of gain in life expectancy, a modeling approach showed that delayed transplantation at 1 and 3 months led to higher life expectancy as compared to transplantation performed using the 6-month rule [22]. However, shortening the period of abstinence was still an inferior strategy in terms of survival benefit as compared to early transplantation [22].

In summary, the last decade has seen the place of early transplantation in the therapeutic arsenal in patients with severe alcoholic hepatitis using a restricted selection process of candidates resulting in an acceptable relapse rate. Early transplantation procedure seems to win the support of a growing number of experts from different countries as shown by the European, American and Latin American recommendations [16, 17, 20]. A selection approach based on the use of a dedicated score based on social and addiction parameters seems to be an interesting approach as shown in the first prospective controlled trial conducted by the Lille Team (NCT01756794).

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Table 1: Selection criteria for Early Transplantation in patients with severe alcoholic hepatitis (i.e Maddrey ≥ 32) not responding to medical therapy

Assessment of lack of Response to medical therapy Lille Score Join-Effect Model (Lille + MELD)	 > 0,45 ≥1.45 for high risk of mortality or ≥2.82 for very high risk of mortality
First liver-decompensating event	☑
Patient ignorance of underlying cirrhosis	☑
Absence of medical comorbidities	☑
Decision-making parties to reach a consensus Nurse Resident, Fellow Specialist in Addiction Senior Hepatologist Surgeon, Anesthesist	 ☑ ☑ ☑ ☑ ☑
Evaluation of the addictological profile of the patient Absence of severe coexisting or psychiatric disorders Supportive family members who do not have alcohol use disorders Patients's commitment to adhere to lifelong total abstinence No episode of violence upon alcohol Aware of the need to build up new life Fully involved in the selection process of early TH	 ☑ ☑ ☑ ☑ ☑ ☑

The selection process required meeting of four decision-making parties to reach a consensus about the suitability of the candidate for transplantation