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Ethical considerations regarding early liver transplantation in patients with severe alcoholic hepatitis not responding to medical therapy

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Summary

A recent study proposed that liver transplantation may represent life-saving treatment in patients with severe alcoholic hepatitis not responding to medical therapy. In this pilot experience, stringent patient selection resulted in major improvement of short-term survival with low rates of post-transplant alcohol relapse. In the context of organ shortage, which imposes a need for strict selection of transplant candidates, these results raise major ethical questions. Reluctance to perform liver transplantation in alcoholics is based on the fact that alcoholism is frequently considered to be self-inflicted and on fears of harmful post-transplant alcoholism recurrence. A minimal interval of sobriety lasting at least 6 months is a widely adopted criterion for the selection of patients with alcoholic liver disease for liver transplantation. In severe alcoholic hepatitis, the disastrous short-term prognosis in patients not responding to medical therapy does not allow one to reasonably impose an arbitrary period of 6-months of abstinence. This means that these patients must be either systematically excluded from transplantation or selected according to other criteria. Without significant pre-transplant abstinence, it might be argued that these patients do not merit a graft as they have not demonstrated their ability to gain control over their disease through durable modification of their behaviour. Consequently, this procedure could have a negative impact in the public, affecting organ donation and confidence in the fairness of transplant programs. In contrast, ethical principles recommend active treatment of patients, without discrimination, according to the best scientific knowledge. At this stage, we propose that there are no major ethical barriers for further evaluation of this new therapeutic option. The next steps should include transparent communication with the public and further studies to reproduce these results and identify the selection criteria that provide the best long-term outcomes.

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Introduction

The lack of available organs for transplantation imposes a need to define priorities for graft allocation and creates a situation in which the objectives of equity, justice, utility, and benefit are frequently in conflict and impossible to fully reconcile. As transplantation is, in many cases, a life-saving procedure, the selection of transplant recipients is a crucial question, integrating major ethical aspects. Such dilemmas, where optimal individual treatment cannot be provided to each patient, are not unique in modern medical practice. These choices are made in similar cases where financial limitations exist in many parts of the world, such as in cases where patients lack medical insurance or do not have the ability to pay for the costs of medical care. It is therefore a primary necessity for the transplant community to establish a fair system for organ allocation and to define the selection criteria for admission to transplantation waiting lists. This will require regular re-evaluation of the criteria used for selection and prioritization of organ recipients, and verification of the adequacy of the system based on patient outcomes. There is also a need for clear definition of the desirable end-points, which may vary from the evaluation of primary disease recurrence, to graft and patient survival, or to social re-integration. In addition, these reflections must be shared with the public who are central actors in the success of transplantation programs as organ donors and providers of the health care system. It is in this context that a pilot study recently evaluated the role of early liver transplantation (LT) in treatment of patients with severe alcoholic hepatitis (SAH) not responding to medical therapy [1]. In this indication, LT was performed rapidly after the diagnosis of alcohol-induced life-threatening liver failure, without respect to the broadly-accepted rule that 6 months of alcohol sobriety must be achieved before a patient is accepted onto a waiting list for LT. As might be expected, this new therapeutic proposal created vigorous discussions within the institutions involved in the study and in the transplantation community. The central point of controversy is the question of the fairness of the allocation of scarce transplantation resources to patients who have not demonstrated a period

of abstinence from alcohol. Reluctance to adopt these programs is, in part, related to concerns about the risk of harmful alcohol relapse after LT, potentially leading to the waste of a precious organ. Further, some people believe that these patients do not deserve a transplant, as their condition is often considered to be self-inflicted and patients at this advanced stage have not convincingly shown repentance for their behaviour by demonstrating an ability to gain control over their disease. These debates, concerning patients with SAH, and the broader group of patients with alcoholic liver disease (ALD), trigger fundamental ethical questions about the selection of patients for transplantation. These include a necessity to respect the right of each individual to be treated without discrimination, the interpretation of notions such as the merit to be treated, the responsibilities of the medical community to the public, the relationship between public opinion and medical decisions, and finally, the potential conflicts between moral and ethical positions in the context of medicine.

Patients with severe alcoholic hepatitis not responding to medical therapy as potential candidates for liver transplantation

SAH is a well-defined entity, corresponding to clear clinical, biological, and histological criteria [2]. Alcoholic hepatitis (AH) is a clinical syndrome associated with recent onset of jaundice and/or ascites in a patient with ongoing alcohol abuse, and characterized, at the histological level, by the presence of steatosis, hepatocyte balonization, and inflammatory infiltrate [3]. Severity of AH can be objectively graded, on the basis of laboratory data, using the Maddrey function [4]. SAH is defined by a Maddrey discriminant function $\geqslant$32 and is associated with a high risk of early mortality [4]. Among patients with SAH, medical therapies, particularly corticosteroids, have proven effective in reducing mortality [5–7]. However, the prognosis remains very poor for patients not responding to medical therapy with 6-month mortality rates of 75% [8]. The majority of these deaths occur in the first 3 months [8]. A major step forward for the management of SAH has been the development of the Lille Model, which allows rapid evaluation of the response to treatment on the basis of bilirubin level evolution at day 7 [8]. It is in the subgroup of patients, identified by the Lille Model as presenting with SAH not responding to medical therapy, that LT was first advocated [9] and then evaluated [1]. Not surprisingly, in these patients, LT provided a highly significant short-term survival advantage as compared with a matched group of non-transplanted patients [1]. In transplanted patients, the 6-month survival rate was 77% as compared with 23% in control patients and 90% of deaths in this last group occurred within 2 months after the identification of the non-response to medical therapy. This benefit was maintained at 2 years in transplanted patients, with overall survival reaching 71%. Certainly, longer follow-up is required to recommend LT as an option in these patients but these results serve as a proof of concept for further evaluations. Importantly from an ethical point of view, this also means that LT was performed in approximately 25% of the SAH cohort who would have recovered despite failing medical therapy, raising the issue of providing a liver graft to someone who was destined to recover and underlining the need for other predictive markers of early mortality in this setting.

The 6-month rule and other potential selection criteria for liver transplantation in patients with severe alcoholic hepatitis not responding to medical therapy

In current practice, compliance in patients with ALD who are candidates for LT is predominantly evaluated by their presumed capacity to remain abstinent after transplant. In the selection process, a patient's adhesion to this principle can be considered to be part of a contract with his treatment team. The rule that 6 months of alcohol abstinence is required before acceptance to the LT list is broadly applied worldwide and has two main objectives: First, to challenge a patient's motivation and to identify those that will remain abstinent after LT, and second, to evaluate the possibility for stabilization or improvement of liver function, which may eventually obviate the need for further LT. The validity of the 6-month rule has been recently debated in the literature [10]. Several weaknesses of this criterion have been shown, including its arbitrary duration, limited specificity [11], limited predictive value [11–13], and the fact that it does not consider the presence of other predictive factors associated with alcohol relapse, such as drug dependence, tobacco use, or depression [12]. Still, on a consensual basis, 6 months of abstinence remains accepted as obligatory for listing ALD patients for LT. In addition, some may argue that the ability to respect the 6-month abstinence period is a necessary step toward reassuring the community that the patient merits a transplant [14]. While this concept is debatable, it widely exists in the medical community and in the public, influencing, at least subliminally, the entire discussion about the fairness of LT in patients with ALD. For patients with SAH not responding to medical therapy, however, the question relies more on the applicability of the 6-month rule than on its validity. In these patients, both objectives of an observational period before transplant decision are essentially elusive when one takes into account the nearly 70% mortality rate at 3 months and the very small chance for spontaneous clinical improvement. Realistic options are, therefore, either to systematically deny these patients for transplantation or to evaluate other potential selection criteria that can be obtained in a time period compatible with rapid therapeutic decision. In the first prospective study in patients with SAH not responding to medical therapy, strict selection criteria were applied, including first liver decompensation, strong familial support, absence of psychiatric disorders, and expressed adherence to lifelong complete alcohol abstinence programs [1]. The selection was based on meetings of multidisciplinary groups that included physicians, specialists in addiction, patients, and family members. In these patients, after a follow-up ranging from 2 to 3 years, alcohol relapse after LT was 11%. Importantly, none of these recurrences occurred in the first 6 months, corresponding to the period classically used to select LT candidates [1]. These selection criteria were extremely restrictive, taking into account the fact that this was a pilot study and, at this point, additional work is needed to assess their reproducibility. Restricting inclusion to patients in their first episode of decompensation is based on the concept that patients who had previous episodes of liver failure deliberately chose to ignore a warning. This is ethically questionable as it introduces a judgmental aspect to the therapeutic decision, leading to distinct treatments for patients with the same disease based on their different behaviours. In addition, group decision making itself carries its own limitations, as it may be influenced by individual authorities, potentially leading to some form of subjectivity [15].