Transplantation for Acute Alcoholic Hepatitis

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Acute alcoholic hepatitis (AAH) is a clinical syndrome characterized by jaundice, ascites, hypoalbuminemia, hyperbilirubinemia, prothrombin time (PT) prolongation, and mild-to-moderate increase of transaminases.¹ Usually it presents with fatigue, anorexia, nausea, and elevation of neutrophils reflecting the systemic involvement of the disease. An increasing incidence of hospitalization for AAH has been seen both in the United States² and in Europe, as shown by a Danish nationwide population-based cohort study, with a parallel increase in mortality rate in recent years compared with the past.³

Severe alcoholic hepatitis is defined by a Maddrey discriminant function >32 and is associated with a high risk for early mortality.⁴ The role of medical therapies, especially corticosteroids, in patients with severe alcoholic hepatitis is still controversial, with studies showing efficacy in reducing mortality⁵⁻⁷ and others showing a small or no effect on improving survival.^{8,9} In patients not responding to medical therapy the prognosis is very poor, with a 6-month mortality rate of 75%.¹⁰

Until recently, despite the lack of other effective therapies, severe alcoholic hepatitis was considered an absolute contraindication to liver transplantation (LT) in most transplant centers. Indeed, according to a recent survey to assess the use of LT for severe alcoholic hepatitis among US LT centers, only 12 of 45 responding centers (27%) reported listing patients with alcoholic hepatitis for LT.¹¹ In contrast, in 2011, Mathurin et al.¹² performed a multicenter pilot study of early “rescue” LT in 26 patients with severe alcoholic hepatitis not responding to steroids. All selected patients fulfilled four stringent criteria: alcoholic hepatitis presenting in the first episode, no response to steroid therapy, excellent psychosocial support, and unanimity for selection among all professionals involved. The authors found that the 6-month survival rate was significantly higher in these carefully selected patients with severe alcoholic hepatitis compared with matched historical control patients who were denied LT (77% versus 23%; $P = 0.001$). This benefit was also evident at 2 years after transplant, with an overall survival rate of 71% in transplanted patients. Furthermore, no patient relapsed at 6 months after surgery,

Abbreviations: AAH, acute alcoholic hepatitis; LT, liver transplantation; PT, prothrombin time.

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although 3 of 26 (11.5%) later resumed drinking alcohol. This percentage of alcohol relapse is comparable with that observed in patients transplanted for alcoholic-related cirrhosis after the required period of 6 months of abstinence before LT.

Since then, two small single-center US studies have shown an impact of LT in patients with severe alcoholic hepatitis, while mimicking the methodology adopted by Mathurin et al.¹² In the study by Im et al.,¹³ 9 patients with favorable psychosocial profiles, selected from 111 patients with severe alcoholic hepatitis assessed for transplantation between January 2012 and January 2015, underwent early LT. The 6-month survival rate was higher among those receiving early LT compared with matched control patients (89% versus 11%; $P < 0.001$). Alcohol relapse was diagnosed in one patient. A second study compared the outcome of LT in 17 patients with severe alcoholic hepatitis, presenting in the first decompensation, with outcomes in 26 patients with decompensated alcoholic cirrhosis and at least 6 months of abstinence from alcohol.¹⁴ The 6-month survival rate was 100% in the alcoholic hepatitis patients, compared with 89% in the control population. Alcohol relapse, defined as any evidence of alcohol consumption after LT, was similar in both groups (23.5% versus 29.2%; $P > 0.99$). When harmful drinking was evaluated, there was a trend toward a higher incidence in the alcoholic hepatitis group compared with cirrhotic recipients, albeit without reaching statistical significance (23.5% versus 11.5%; $P = 0.42$).

We started a prospective program of early LT for AAH in our unit in Padua in 2013. Since then, nine patients with severe alcoholic hepatitis, not responding to corticosteroid therapy, were evaluated for LT. Among these, five patients were considered suitable for selection criteria for LT. Of four patients who were excluded because of psychosocial contraindications, two died within 28 days, whereas the remaining two are still alive. Four of the five selected patients underwent LT, whereas the remaining patient died during the evaluation process. All four patients are alive with no alcohol relapse at a median follow-up of 17 months (range 9-41 months).

Thus, the role of LT in treating severe alcoholic hepatitis, unresponsive to treatment, seems to be changing on both sides of the Atlantic. Considerable ethical quandaries remain, however. We believe in an ethical approach

that holds that any given therapy should be made available to patients likely to benefit according to best scientific knowledge of the moment, and that a deliberate exclusion from treatment should not be based on prejudice, lack of evidence, or presumed lack of resource.¹⁵ In the case of LT for the treatment of alcoholic liver disease, we have to balance the needs of the individual patient, the claims of other potential recipients for each donated organ, and the potential for a public backlash against transplantation of people who were drinking recently, which in turn could harm organ donation. In this regard, we are encouraged by a recent online survey in which the majority of respondents (81.5%) were neutral toward early transplantation for these patients, with a most favorable view toward middle-aged patients with good social support and financial stability.¹⁶ Mathurin et al.'s study¹² offers a template for LT programs to follow to bring consistency, transparency, and consensus to these difficult decisions.

In conclusion, transplanting patients with severe alcoholic hepatitis within strict criteria can allow equity and justice to be applied to these patients¹⁷; however, a new consensus, involving transplant hepatologists, surgeons, an addiction specialist, a psychologist, and the public, is needed to ensure the best clinical outcome and to overcome potential ethical barriers.¹⁸

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