

Liver transplantation for severe alcoholic hepatitis saves lives

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COMMENTARY ON:

Early Liver Transplantation for Severe Alcoholic Hepatitis. Mathurin P, Moreno C, Samuel D, Dumortier J, Salleron J, Durand F, Castel H, Duhamel A, Pageaux GP, Leroy V, Dharancy S, Louvet A, Boleslawski E, Lucidi V, Gustot T, Francoz C, Letoublon C, Castaing D, Belghiti J, Donckier V, Pruvot FR, Duclos-Valleé JC. *N Engl J Med* 2011 November 10;365:1790–1800. Copyright (2011). Abstract reprinted with permission from the Massachusetts Medical Society.

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Abstract: Background: A 6-month abstinence from alcohol is usually required before patients with severe alcoholic hepatitis are considered for liver transplantation. Patients whose hepatitis is not responding to medical therapy have a 6-month survival rate of approximately 30%. Since most alcoholic hepatitis deaths occur within 2 months, early liver transplantation is attractive but controversial.

Methods: We selected patients from seven centers for early liver transplantation. The patients had no prior episodes of alcoholic hepatitis and had scores of 0.45 or higher according to the Lille model (which calculates scores ranging from 0 to 1, with a score ≥ 0.45 indicating nonresponse to medical therapy and an increased risk of death in the absence of transplantation) or rapid worsening of liver function despite medical therapy. Selected patients also had supportive family members, no severe coexisting conditions, and a commitment to alcohol abstinence. Survival was compared between patients who underwent early liver transplantation and matched patients who did not.

Results: In all, 26 patients with severe alcoholic hepatitis at high risk of death (median Lille score, 0.88) were selected and placed on the list for a liver transplant within a median of 13 days after nonresponse to medical therapy. Fewer than 2% of patients admitted for an episode of severe alcoholic hepatitis were selected. The centers used 2.9% of available grafts for this indication. The cumulative 6-month survival rate (\pm SE) was higher among patients who received early transplantation than among those who did not ($77 \pm 8\%$ vs.

$23 \pm 8\%$, $P < 0.001$). This benefit of early transplantation was maintained through 2 years of follow-up (hazard ratio, 6.08; $P = 0.004$). Three patients resumed drinking alcohol: one at 720 days, one at 740 days, and one at 1140 days after transplantation.

Conclusions: Early liver transplantation can improve survival in patients with a first episode of severe alcoholic hepatitis not responding to medical therapy. (Funded by Société Nationale Française de Gastroentérologie.)

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Severe alcoholic hepatitis (SAH), if there is no response to supportive and steroid therapy, has a mortality rate of 70% within 6 months [1,2], exceeding that of other acute conditions, such as severe pneumonia. Is there further therapy? There is liver transplantation used successfully for end stage cirrhosis, including alcoholic cirrhosis, and acute liver failure [3] which shares several clinical features with SAH: renal failure, sepsis and poor outcomes [3]. Thus, it is a paradox that transplantation has rarely been used for SAH. The reason is a transposition of current clinical practice for selecting patients with alcoholic cirrhosis for transplantation, which in many centres requires 6 months of abstinence. A critically important point is that evidence that this criterion correlates with survival has no documentation [4]. However, it is associated with a return to drinking alcohol [5], although disputed by some [4], but which in any case reflects a risk for alcoholism, and not necessarily alcoholic liver disease. The disassociation may be because the transplanted liver changes the genetic susceptibility to damage by alcohol [6].

The focus on recidivism due to alcohol, rather than survival as the primary outcome after transplantation for alcoholic cirrhosis has been challenged [7], and this would be even more so for SAH. Indeed, the latter consideration is only valid if there is time for recovery, avoiding transplantation in some patients. Thus, this landmark paper [8], which documents a 77% ($\pm 8\%$) survival at 6 months in 26 patients with SAH not responding to steroid therapy followed by liver transplantation, vs. 23% ($\pm 8\%$) in matched controls ($p < 0.001$) without transplantation, challenges current medical practice, because it demonstrates a dramatic survival benefit (also extended to 2 years), and the incongruity of the “6-month rule”, for SAH. Franco-Belgian clinicians in seven centres initiated this study [8], following a consensus [9], applying strict selection criteria, sensitive to the risk of recidivism, but also to “natural justice”, given the increasing shortage of donor organs. Thus, they considered patients with SAH for early liver

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transplantation if there was, histological confirmation (23/3 by explant histology), non-response to corticosteroids after 7 days ($n = 25$), or increasing disease severity ($n = 1$). In addition, the admission had to be the first liver decompensating event, the patient had to have close and supportive family, no medical or psychiatric co-morbidity, and a life-long commitment to abstinence (already the case for transplantation of alcoholic cirrhosis). Furthermore, all nursing and medical team members had to agree to listing without exception – this degree of unanimity is not necessarily achieved for alcoholic cirrhosis – so this was a very stringent criterion. Two centres had prospective data bases on alcoholic hepatitis, used for case controls (matched age, gender, disease severity); another 69 patients were randomly matched: they had a $30 \pm 6\%$ month survival. Outcomes after transplantation were compared to 92 randomly selected responders to medical therapy: survival was $75 \pm 4\%$ at 6 months. The decision to list for liver transplantation took place at a median of 13 days after diagnosing non-response to steroids, and transplantation occurred at a median of 9 days after listing.

After transplantation, five of six deaths were related to infection, invasive aspergillosis accounting for 4. Thus, antifungal prophylaxis could have further increased survival. The patients had very close follow-up (median of 11 visits in 6 months). Three patients resumed drinking at 720, 740, and 1140 days after transplantation – two remained daily consumers (30 g and >50 g/day) – 1 imbibed 10 g/week. This recidivism rate is similar to that for alcoholic cirrhosis with 6-month pretransplant abstinence [4,5]. The 26 transplanted patients, represented 1.8% of patients with alcoholic hepatitis, 2.9% of all transplants, and 8.3% of transplants for alcoholic liver disease [8].

Thus, patients with SAH with non-response to steroids can be selected for liver transplantation, have good survival (potentially improved by prophylactic antifungals), and have a low rate of recidivism with close follow-up. The medical aspects have been addressed in this study [8]. What needs to change is the abolition of the “6-month rule”, which also needs to be rescinded in severe alcoholic cirrhosis, with a focus on survival, rather than a return to drinking *per se* as the main outcome, still the focus of the accompanying editorial [10]. The important distinction is a return to harmful drinking for the graft, family or society. What is also needed is a transparent and consistent system of allocation of organs that does not favour, but most importantly does not discriminate against, patients with SAH, thus denying the chance of survival.

At a societal level, education is needed to explain that alcoholic liver disease does have a genetic basis [6], and that liver transplantation is already widely used in other situations of either deliberate or unknowing self harm: paracetamol and

ecstasy induced acute liver failure, previous intravenous drug misuse or unprotected sex, in some with hepatitis B and C. Thus, action is needed from national transplant policy committees, to promote such education, and to establish that liver transplantation for SAH is not a subject for research, as to whether it should take place or not, but only relevant for improving outcomes. Service development needs to encompass this group of patients, ensuring access to liver transplantation to save lives, and reinforcing follow-up protocols already in use for alcoholic cirrhosis, that give adequate support to minimize the risk of damaging the new liver and society.

This ground breaking clinical result [8] demonstrates that survival outcomes must justifiably trump recidivism in considering patients with SAH for liver transplantation, and thus, selection and allocation criteria need to change.

Conflict of interest

The author declared that he does not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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