Outcomes After Early Liver Transplantation for Patients With Severe Alcoholic Hepatitis: Additional Evidence From a Meta-analysis

Dear Editors:

We read with interest the article from Lee et al1 about early liver transplantation for severe alcoholic hepatitis. We compliment them for their exhaustive collection of data on patients transplanted for alcoholic hepatitis across the United States in the retrospective ACCELERATE-AH study. We would like to add some comments that may contribute to the debate on this hot topic.

First, in this study, a liver biopsy was not systematically performed, as it should preferably have been.2 The fact that alcoholic hepatitis was observed on the liver explant in only 59% of the cases (vs 100% in the landmark study from Mathurin et al3) strongly suggests that a significant proportion of patients were transplanted for decompensated cirrhosis without alcoholic hepatitis, which made the study population heterogeneous. Whether this heterogeneity in the study population explains the surprisingly high rates of survival is a matter of debate.

Second, as the authors acknowledged, the rate of any alcohol relapse was higher in their study than in Mathurin et al study,2 as well as in other studies using stringent criteria for patient selection. This observation was also made in a recent meta-analysis of trials evaluating alcohol relapse after liver transplantation among patients with alcoholic hepatitis.4 This meta-analysis (which also included some patients from the Lee et al study) observed a substantial decrease in rates of alcohol relapse when only studies that used a stringent selection process for deciding which patients should be transplanted were selected. In the subgroup analysis that included only patients transplanted for clinically severe alcoholic hepatitis and that did not include studies that did not use stringent criteria for selecting candidates for liver transplantation (patients motivated to stay abstinent from alcohol after liver transplantation, good psychosocial support, and/or a favorable patient psychological profile), only 14% of patients had alcohol relapse after liver transplantation (95% confidence interval, 0.08–0.23). No heterogeneity was identified in this analysis ($P = .6; I^2 = 0\%$), which is a strong indicator of confidence in these results. Thus, these stringent criteria should be used to select patients with a low risk of alcohol relapse after liver transplantation. Avoiding alcohol relapse after liver transplantation is a major issue because patients who relapse after liver transplantation usually return to harmful drinking patterns (pooled estimate rate in the recent meta-analysis, 0.15; 95% confidence interval, 0.07–0.27; $I^2 = 3\%$) and, as Lee et al1 and others5 have highlighted, patients with significant alcohol relapse have decreased survival rates. Furthermore, as the use of liver transplantation for patients with severe alcoholic hepatitis is gaining interest, the application of a strict selection process will help to avoid any problems of equity in liver graft allocation.6 This conservative strategy for patient selection will contribute to the continued adoption of severe alcoholic hepatitis not responsive to medical therapy as a new indication for liver transplantation by public opinion and healthcare providers.7

Overall, Lee et al provide additional evidence that prospective studies aimed at identifying factors predicting alcohol relapse after liver transplantation are urgently needed. The first results of an ongoing prospective trial with the primary goal of assessing alcohol relapse after liver transplantation (NCT01756794) are expected at the end of 2018 and will be of interest.

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References
Both letters highlight the importance of alcohol use after liver transplantation (LT). Although complete post-LT abstinence is the goal, distinguishing clinically harmful patterns of drinking is essential. Although sustained alcohol use after LT was associated with increased risk for post-LT death, slips were not consistent with other studies. Our retrospective data likely underestimate slips; however, these carefully selected LT recipients were followed closely after LT, with alcohol questioning at every visit, and routine biochemical testing with ethylglucuronide or phosphatidyethanol by the majority of ACCELERATE-AH sites. Thus, our ability to capture harmful patterns of drinking was relatively high. We also note, in this regard, the contradictory criticism of Deltenre et al, that our study accentuates “the rate of any relapse.” We do, however, acknowledge that a prospective study with protocolled monitoring is essential to better understand drinking behavior by LT recipients with alcoholic hepatitis (AH).

Deltenre et al highlight that liver biopsy was not performed to diagnose AH and that the population may have included patients with acutely decompensated cirrhosis rather than AH. A strength of our study is its reflection of US real-world practice, where liver biopsy is rarely done to diagnose AH. We hypothesize that the reason for only 59% of explants having evidence of histologic steatohepatitis relates to the interval from active drinking to histologic evaluation (at LT) and does not exclude the possibility of AH at initial presentation. Ultimately, although we agree that confirmation of steatohepatitis is important for studies of pharmacotherapies in AH targeting active steatohepatitis, this is tangential to addressing LT for life-threatening alcohol-associated liver disease (ALD).

Solga et al assert that our report “overlooks” the 3 ethical principles of utility, justice, and respect for persons. They state that LT for AH may lead to increased morbidity and mortality of patients listed for LT for other conditions with lower Model for End-stage Liver Disease (MELD) scores. Indeed, the ongoing organ shortage makes this likely, but is also true for any new or expanded indication for LT, including the recent changing MELD exception thresholds for hepatocellular carcinoma. In addition, ALD has long been disadvantaged in access for LT, although it accounts for 48% of liver-related deaths in the United States, with higher post-LT survival than most other indications for LT; only 24% of LT recipients in 2016 had ALD. The AH subpopulation has been further marginalized and historically denied any access to LT by mandated sobriety periods that were admittedly arbitrary and with limited scientific validity. Furthermore, the desire to deny appropriate therapy to patients with life-threatening ALD is part of a more general failure to acknowledge that this is a medical condition, as shown by Dr Solga’s use of the term recidivism to describe relapse.

By asserting that it is unethical to provide a life-saving procedure purely based on etiology of disease and preconceived stigma, Solga et al are reviving the discredited theory that patients with alcohol use disorder are less deserving of medical and surgical care, which violates other well-known ethical consensus statements. Their concerns about the “liberal expansion” of early LT and ALD patients being “deincentivized” falls just short of fear mongering, while omitting that our study is consistent with previous literature and guidelines in offering early LT to a highly selected population of patients with AH. The authors highlight the demographic landscape of our cohort, which was predominantly white, male, and privately insured. Indeed, the majority of the general LT population fit into these categories and whether LT for AH contributes to a disparity should be assessed in the context of an accurate measurement of national AH prevalence.

Finally, Solga et al argue that early LT for AH violates respect for persons, citing the severity of illness and acuity of disease. This scenario is no different from patients with acute liver failure, the most common etiology being self-administered acetaminophen overdose, which is a well-accepted indication for LT, and prioritized above all LT candidates by status 1A priority. To deny access to patients with AH with “encephalopathy and imminent threat of life” is contradictory to current well-accepted practice and in direct violation of the federally mandated final rule, which prioritizes those who are sickest and would derive the most benefit from LT.

In summary, our study shows that salvage LT for AH is life saving and should be explored as an option for appropriate candidates. How patient selection should be conducted, how this will affect LT candidates with other liver diseases, and how to best prevent and treat alcohol use disorder after LT requires further study and discussion, and we thank the authors for highlighting issues that should frame this ongoing dialogue.

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References