Prednisolone or Pentoxifylline for Alcoholic Hepatitis

TO THE EDITOR: In their article on the Steroids or Pentoxifylline for Alcoholic Hepatitis (STOPAH) trial, Thursz et al. (April 23 issue) explain their choice not to select patients on the basis of liver-biopsy results because such procedures are “uncommon” in this group of patients and the goal was to replicate the typical conditions of clinical practice. However, by basing their diagnosis on clinical factors, they misclassified a considerable number of patients, given that a Maddrey’s discriminant function (MDF) score of 32 or more alone for diagnosis lacks specificity. In a prospective study conducted in our center between 2005 and 2014, we evaluated 114 patients with a similar clinical definition of severe alcoholic hepatitis and an MDF score of 32 or more. All the patients underwent transjugular liver biopsy within 72 hours after hospital admission. Of these patients, 38 (33%) did not have histologic features of severe alcoholic hepatitis and were thus misdiagnosed on clinical grounds. Therefore, the authors incorporated a 30% chance of erroneous diagnosis and probably included patients who were unlikely to benefit from prednisolone treatment. In future trials involving patients with alcoholic hepatitis, histologic confirmation should be pursued, as recommended by international guidelines.

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TO THE EDITOR: As a matter of practical necessity, interventional trials often test a reasonable dose and duration of a drug regimen and so leave unanswered the most effective dose for the condition under investigation. Thursz and colleagues
appropriately conclude that prednisolone as used in their study may have had a modest but fleeting survival benefit in patients with alcoholic hepatitis. The rate of death was decreased by a borderline-significant 28% at the primary 28-day end point; after adjustment in the multivariate analysis, the reduction was a significant 39%. In stark contrast, this survival benefit was completely lost by day 90, indicating that mortality among prednisolone recipients (predominantly attributed to liver injury) had caught up with the control rate during the 2 months after prednisolone was discontinued.1,2 Since tapering doses are not described, a speculative concern is that patients may have been harmed by an inflammatory reconstitution reaction to the abrupt withdrawal of prednisolone.2-5 Accordingly, it may be premature to abandon the use of glucocorticoids for severe alcoholic hepatitis just yet, given the early survival benefit in the face of a clinically plausible explanation for the catch-up mortality.

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The views expressed in this letter are the those of the author and do not necessarily reflect the viewpoint of Merck.

DiNubile reports being employed by Merck and having an equity interest in the company. No other potential conflict of interest relevant to this letter was reported.


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THE AUTHORS REPLY: The role of liver biopsy in the diagnosis of alcoholic hepatitis remains controversial, with the guidelines of the American Association for the Study of Liver Diseases being less didactic regarding its necessity.1 It is fair to state that the routine use of biopsy is uncommon, as indicated in a recent clinician survey.2 The diagnosis of alcoholic hepatitis should never rely simply on an arithmetic calculation of a discriminant function. Cardinal to the clinical diagnosis of alcoholic hepatitis in our study was the recognition of a minimal threshold of serum bilirubin (>80 µmol per liter), a recent onset of jaundice (<3 months), and a clear recent history of alcohol excess (≤2 months). The abstract cited by Verbeke et al. describes patients with a discriminant function of 32 or more without reference to these clinical criteria.3 Their results seem to be at variance with a previous report from the same group, which describes patients presenting with alcoholic acute-on-chronic liver failure with a recent onset of hyperbilirubinemia (bilirubin level, >85 µmol per liter).4 In that study, 96% of patients had some features of alcoholic steatohepatitis.

We have recently reported an analysis of liver-biopsy samples that were obtained from the patients in our study.5 Only 93 of 208 biopsy samples were of adequate quality and obtained within 5 days after randomization; the overall rate of alcoholic steatohepatitis on histologic analysis was 88%. This rate rose to 91% in centers where biopsy was routine and fell to 83% when the biopsy was performed only on account of diagnostic uncertainty. We would advocate liver biopsy in situations of clinical uncertainty, but future studies that insist on the use of biopsy results may exclude many patients and further distance the observations from the routine clinical management of this florid manifestation of alcoholic liver disease.

DiNubile raises an interesting question regarding whether the abrupt cessation of glucocorticoids led to an inflammatory reconstitution reaction. Such a reaction has not previously been recognized in the context of prednisolone treatment of alcoholic hepatitis. The regimen that was used reflects the one that is described in published studies of prednisolone therapy in alcoholic hepatitis; to our knowledge, no studies have investigated the role of a tapering dose. Thus, although we cannot rule out such a reaction, we think that infection and progressive liver failure explain most of the catch-up mortality after 28 days.
More on the Age of Transfused Red Cells

TO THE EDITOR: The report by Steiner et al. (April 9 issue)\(^1\) concerns one of three recent trials addressing the effects of red-cell storage duration on transfusion outcome.\(^2,3\) All three trials compared “fresh blood,” stored for approximately 7 days, with storage for 2 to 4 weeks and concluded that fresher blood afforded no advantage to critically ill adults, patients undergoing cardiac surgery, or premature infants. These trials reassure us that most patients receive safe, effective transfusions and will not benefit from fresher-than-usual blood. The studies do not address storage for 35 to 42 days and are not powered to examine certain subpopulations, such as patients with infections. Preclinical data suggest that very old blood increases intra-vascular levels of iron and may present additional risk during established infection.\(^4,5\) For ethical reasons, clinical trials cannot randomly assign patients to receive only the oldest blood, yet units that are in the last week of approved storage are transfused daily. Given the absence of need and the possible increased risk, we at the National Institutes of Health restrict transfusion of very old blood, as do the national blood services of the United Kingdom and the Netherlands. It is important to emphasize these limitations of the clinical trials.

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THE AUTHORS REPLY: We agree that the three published randomized, controlled trials investigating the clinical effects of red-cell storage duration (the Red-Cell Storage Duration Study [RECESS],\(^1\) the Age of Blood Evaluation trial,\(^2\) and the Age of Red Blood Cells in Premature Infants trial\(^3\)) were not specifically designed to evaluate the oldest units — that is, those stored 35 to 42 days. We cited this limitation in the Discussion section of our report on RECESS. Owing to the clinical demand for red-cell units before they reach 35 days of storage, few participants in RECESS received only red-cell units stored this long, and these participants may have been a biased subset of all study participants.

We also acknowledged in the Discussion sec-