Can We Reliably Predict Response to Corticosteroid Treatment in Severe Alcoholic Hepatitis?

SEE ARTICLE ON PAGE 628

Severe alcoholic hepatitis (SAH), as defined by Maddrey's discriminant function ≥32, is the most serious clinical manifestation of alcohol-related liver disease. This increasingly common condition is associated with poor survival, and a recent meta-analysis of 77 studies, which included data from a total of 8,184 patients, showed mortality rates from SAH as 26% at 28 days, 29% at 90 days, and 44% at 180 days.[1] Even after decades of debate and research, SAH continues to be a treatment enigma, and abstinence remains the only independent predictor of long-term survival.[2] The shortage of novel therapeutic strategies in SAH is attributable to being clinically understudied in comparison with other liver diseases, the lack of significant research funding historically, and the inability of recapitulating this complex, inflammatory yet immunodeficient, multifactorial disease in animal models.

Current guidelines recommend the use of corticosteroids in the absence of contraindications, such as uncontrolled infection, active gastrointestinal bleeding, or hepatorenal syndrome, and they remain the mainstay of treatment for SAH.[3] However, the widespread utility of prednisolone, a corticosteroid with broad anti-inflammatory and immunosuppressive actions, in improving survival outcomes in SAH remains controversial. From 1971 to 2014, there have been 13 randomized trials and four meta-analyses that have investigated the use of corticosteroids in SAH.[4,5] In the main, these studies have indicated that steroids significantly increased the short-term survival of patients with SAH, but concerns have revolved around the risk of sepsis and gastrointestinal hemorrhage. The Steroids or Pentoxifylline for Alcoholic Hepatitis (STOPAH) trial, conducted between 2011 and 2014, reported a reduction in mortality at 28 days for patients given prednisolone compared with control patients but did not reach significance, and survival curves converged after 28 days.[6] Moreover, there was no survival benefit from corticosteroids at 90 days or 1 year, and the incidence of infections was almost doubled in subjects given prednisolone.[7] Overall, the unpredictability of a favorable response to corticosteroids combined with the risk of life-threatening infections continues to limit the widespread use of this drug in SAH.

There are, however, large numbers of patients with SAH who would benefit from steroid treatment, and their early identification would be a substantial step forward in the management of these patients; but to date, prognosticators of response have been difficult to identify, partly due to the lack of understanding regarding the mechanisms by which corticosteroids impart their beneficial effects. Studies have shown that while this treatment can effectively suppress injurious, inflammatory, and immune-mediated liver injury, corticosteroids concomitantly dampen antipathogen immunity, resulting in an immunodeficient state that renders patients with SAH with a further heightened

Abbreviation: SAH, severe alcohol hepatitis.

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susceptibility to bacterial infection. Moreover, the potent anti-anabolic effects of corticosteroids may in parallel suppress liver regeneration and repair. Further mechanistic work is urgently required to assess the impact of corticosteroids during different phases of SAH and during systemic inflammatory response syndrome and compensatory anti-inflammatory response syndrome, and these studies may pave the way for more targeted treatment protocols.

The Lille score for assessing the response after 4 days of corticosteroid treatment offers a pathway for identifying this subgroup of patients who would benefit from a 28-day corticosteroid treatment[8] compared to the classic 7-day model. However, any period of unnecessary high-dose corticosteroid treatment may exacerbate disease severity, infection risk, and mortality. As such, there is a clear unmet need for biomarkers to predict response to corticosteroids at the time of clinical presentation.

In this issue of *Hepatology Communications*, Maras et al.[9] provide convincing evidence for the ability of urinary metabolome signatures to predict steroid response in patients with SAH prior to starting therapy. In this unique pilot study, Maras et al. use ultra-high-performance liquid chromatographic and high-resolution mass spectrometry to perform metabonomic analysis of urine samples from patients with biopsy-proven SAH prior to initiation of corticosteroid treatment to identify noninvasive predictive markers of response. The authors initially used a discovery cohort of 60 patients and used the Lille score to stratify SAH patients as responders or nonresponders at treatment day 7 and then used this stratified cohort for the identification of potential biomarkers. These biomarkers were then subsequently tested on a validation cohort of 80 patients with SAH. From a pool of 212 signatures detected in the discovery cohort, a total of nine urinary metabolites linked to mitochondrial functionality were identified and found to significantly discriminate nonresponders to corticosteroid treatment from responders. There were significantly increased levels of acetyl-L-carnitine, octanoylcarnitine, decanoylcarnitine, decenedioic acid, and alpha-ketoglutaric acid in the nonresponder group. Further to this, Maras et al. show that acetyl-L-carnitine could strongly predict nonresponse and mortality in SAH with levels of >2,500 ng/mL, reliably differentiating survivors from nonsurvivors. Interestingly, these metabolites were found to correlate closely with transcriptomic data obtained in a subset of patients, indicating a direct link between regulation of metabolic genes in the liver, immune-related genes in peripheral blood mononuclear cells, and detectable urine metabolic profiles in the same patients.

Acetyl-L-carnitine is an essential component of the inner mitochondrial membrane and is an ester of the trimethylated amino acid L-carnitine, which is synthesized in the brain, liver, and kidneys and is excreted in the urine. Both acetyl-L-carnitine and its derivative L-carnitine have been shown to have wide clinical applications in various neurologic disorders, including hepatic encephalopathy.[10] Interestingly, studies have also found that L-carnitine administration can improve liver function, plasma glucose levels, and lipid profiles in patients with nonalcoholic steatohepatitis.[11] Why high levels are found in the urine of patients with SAH and the mechanisms underlying this phenomenon require in-depth analysis and further attention.

Although the study by Maras et al. is well designed and reveals a potentially novel noninvasive tool to tailor steroid treatment at clinical presentation of SAH to those who are likely to benefit, it does have some limitations. First, the study is monocentric and needs to be confirmed and replicated with patients from different centers worldwide. Second, the difference in response rates between the discovery and validation cohorts is of some concern. Third, the proportion of nonresponders in this study is much lower compared to reported studies; this may indeed be due to genetic and environmental differences but certainly requires further consideration.

This study by Maras et al. is the first demonstration of the utility of urine to determine treatment responsiveness in SAH. These findings could form the basis for the development of a cost-effective dipstick screening test for restricting steroid use to patients with a good likelihood of responding. Such a urine test for SAH could provide a practical point of care assessment that may delineate metabolic changes, predict mortality, and potentially personalize treatment strategies.

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