Treatment of Severe Alcoholic Hepatitis With Corticosteroids and Pentoxifylline
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Despite being the most frequently abused drug for centuries, alcohol was not recognized as a direct hepatotoxin until the 1960s. Alcohol abuse accounts for the third leading preventable cause of death and the second most common cause of cirrhosis after hepatitis C virus infection in the United States. Alcoholic hepatitis is a common complication of alcohol abuse; its severity can range from mild to severe liver inflammation and can lead to the development of jaundice, prolonged prothrombin time, and liver failure. When left untreated in its severe form, alcoholic hepatitis has an extremely high mortality rate of up to 40% within 6 months after onset of clinical symptoms.

In addition to abstinence and nutritional support, corticosteroids have been the cornerstone of treatment for severe alcoholic hepatitis based on more than 3 decades of clinical data, although sometimes divergent, including clinical trials and meta-analyses. However, alcoholic hepatitis is responsive to corticosteroids in only approximately 40% of patients, and many patients have contraindications to corticosteroid therapy, such as active infection. For patients with contraindications to corticosteroids, use of pentoxifylline, a phosphodiesterase inhibitor and xanthine derivative, has shown reduced short-term mortality in several small studies among patients with severe alcoholic hepatitis. Use of other treatments beyond corticosteroids and pentoxifylline, including anti-tumor necrosis factor (TNF) agents and S-adenosyl-L-methionine, has been disappointing, resulting in an important need for more effective therapies due to the persistently high mortality rate associated with severe alcoholic hepatitis.

In this issue of JAMA, Mathurin and colleagues report the main findings of a randomized, multicenter, double-blind, placebo-controlled study comparing the logical combination of prednisolone and pentoxifylline with prednisolone alone for the treatment of patients with severe alcoholic hepatitis. In this well-designed study spanning 2 countries and 24 hospitals, data were collected with the objective of determining whether the addition of pentoxifylline with prednisolone was more effective than prednisolone alone. Between 2007 and 2010, patients aged 18 to 70 years who were heavy drinkers (>40 g/d of alcohol for women and >50 g/d of alcohol for men) with biopsy-proven severe acute alcoholic hepatitis and a Maddrey discriminant function of at least 32 were enrolled. Patients (n = 270) were randomized to receive the allocated treatment (prednisolone and pentoxifylline vs prednisolone alone) for 28 days, regardless of treatment response evaluated by the Lille model on day 7, a well-accepted and validated tool to prognosticate response to corticosteroids in severe alcoholic hepatitis. The primary end point was 6-month survival. The secondary end points were the development of hepatorenal syndrome and response to therapy based on the Lille model, which defined treatment nonresponders after 7 days.

The proposed mechanisms of the effects of corticosteroids and pentoxifylline in alcoholic hepatitis are thought to differ. Corticosteroids are thought to reverse hepatic inflammation by reducing the circulating levels of the proinflammatory cytokines, including IL-8 and TNF. Pentoxifylline, although its exact mechanism of action is not completely understood, is thought to benefit patients with severe alcoholic hepatitis due to a protective effect against hepatorenal syndrome, possibly by modulation of TNF transcription. Combination therapy with pentoxifylline and corticosteroids in severe alcoholic hepatitis is often used in clinical practice with the hope of synergistic action leading to improved patient survival. Although often prescribed, the combined use of corticosteroid and pentoxifylline has never been studied in a double-blind, placebo-controlled setting until this study by Mathurin and colleagues.

Contrary to expected outcomes, Mathurin and colleagues reported the outcomes of a 4-week treatment with a combination of pentoxifylline and prednisolone, which did not improve 6-month survival compared with prednisolone treatment alone in patients with severe alcoholic hepatitis; both the pentoxifylline-prednisolone and placebo-prednisolone groups had a 6-month survival rate of approximately 69%. At day 7 of therapy, response to therapy was not significantly different as assessed by the Lille model. Of additional interest was the finding that the incidence of hepatorenal syndrome at 6 months was less in the pentoxifylline-prednisolone group than in the placebo-prednisolone group (8.4% vs 15.3%, P = .07), but failed to reach statistical significance.

The study by Mathurin and colleagues is not the first study unable to demonstrate increased efficacy with the use of pentoxifylline in severe alcoholic hepatitis, but it is the largest and first fully randomized, placebo-controlled study of its kind. Although significant renal preservation was not observed in the pentoxifylline-prednisolone group, this study was only powered to detect survival as a primary outcome and may have been underpowered to detect a difference in the occurrence of hepatorenal syndrome. Nonetheless, an effect on early markers of recovery or decreased mortality from presumed pre-
vention of renal dysfunction would be expected in the pentoxifylline-placebo group as described in smaller studies.9-11 A potential reason no mortality benefit was found in the combination group, despite lower incidence of hepatorenal syndrome, is that 6-month mortality in patients with decompensated cirrhosis and a Model for End-Stage Liver Disease (MELD) score of 20 to 29 is reported to be more than 25% alone, even in the absence of severe alcoholic hepatitis.18 Because the mean MELD score in the study by Mathurin and colleagues was 23, causes of liver-related mortality other than hepatorenal syndrome, including hepatic encephalopathy and spontaneous bacterial peritonitis, may predominate by 6 months.

The data presented by Mathurin and colleagues are valuable and long awaited. Overall, the study does not support the simultaneous use of pentoxifylline and prednisolone to improve survival compared with prednisolone use alone. However, the results of this study should not be interpreted by clinicians as meaning that pentoxifylline is an ineffective therapy for patients with severe alcoholic hepatitis, because this study did not include a pentoxifylline-placebo group. In the study by Akriviasis et al,9 which supported pentoxifylline use in severe alcoholic hepatitis, pentoxifylline alone was compared with placebo. For patients in whom clinicians are reluctant to prescribe corticosteroids, pentoxifylline still appears to be useful in preventing the hepatorenal syndrome, which can often lead to death.9-11 Additionally, due to the current lack of effective treatments and mostly benign adverse effects associated with pentoxifylline, including gastrointestinal symptoms, headache, and rash,9 this medication should remain a treatment option for selected patients with severe alcoholic hepatitis.

In conclusion, corticosteroids and pentoxifylline are currently the only and most successful medical treatments available for severe alcoholic hepatitis despite providing only modest improvements in mortality. The results reported by Mathurin and colleagues demonstrate that the sum (corticosteroids and pentoxifylline) is no greater than the individual parts for preventing mortality in well-characterized patients with severe alcoholic hepatitis. Pentoxifylline may remain a useful option for patients who have contraindications to receiving corticosteroids; however, this group was not studied by Mathurin and colleagues. The study also emphasizes the importance of developing new treatments for severe alcoholic hepatitis. These future studies also should include well-conducted evaluations of liver transplantation for carefully selected patients with severe alcoholic hepatitis not responding to medical management.

ARTICLE INFORMATION

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REFERENCES


