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Treatment of alcoholic hepatitis: is this a "dead-end"?

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Title: Prednisolone or pentoxifylline for alcoholic hepatitis

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Summary

Alcoholic hepatitis (AH) is a clinical syndrome characterized by jaundice and liver failure that develops in subjects with chronic and active alcohol abuse [1]. The short-term mortality in patients with severe disease, as defined by the Maddrey's discriminant function, exceeds 30% [2]. Up to now, only two drugs, prednisolone and pentoxifylline, have shown some efficacy for the treatment of this condition. In a Cochrane meta-analysis published in 2008, glucocorticoids showed a non-significant trend toward a benefit in mortality [3]. However, a later reanalysis of the five largest studies that evaluated glucocorticoids indicated a significant benefit [4]. On the other hand, pentoxifylline has been shown to significantly increase survival in patients with severe AH, without any serious adverse effects [5]. This favorable outcome is mediated through a decrease in the rate of hepatorenal syndrome. Controversy over the treatment of choice for AH persists for many years as neither drug has convincingly shown superiority. This trial -the STOPAH trial- evaluating the effect of treatment of AH with prednisolone or pentoxifylline has long been awaited with eagerness as it was expected to answer the question which drug is more efficient [6].

STOPAH trial was a large (1103 patients), multicenter, double-blind, randomized trial using a 2-by-2 factorial design. Four arms (placebo, prednisolone, pentoxifylline and prednisolone plus pentoxifylline) were incorporated. All drugs were prescribed for 28 days at doses of 40 mg daily for prednisolone and 400 mg three times daily for pentoxifylline. Patients with renal failure (serum creatinine >5.7 mg/dL or requiring renal replacement therapy) or other dismal characteristics such as untreated sepsis were excluded from the trial. All patients were followed for 12 months or until their death with the exception of patients enrolled at the end of the trial. The primary endpoint was mortality at 28 days and secondary endpoints included mortality or liver transplantation at 90 days and after 1 year.

Neither drug showed mid- (90 days) or long-term (12 months) survival benefit. However, prednisolone was associated with an improvement in 28-day mortality with an odds ratio of 0.72 (95%CI 0.52-1.01; P=0.06). In multivariate analysis, baseline age, encephalopathy, white cell count, prothrombin ratio and levels of bilirubin, creatinine and urea were found to be additional significant factors for mortality. In a secondary analysis adjusting for these prognostic variables the odds ratio for 28-day mortality among the patients who received prednisolone compared with those who did not was 0.61 (95%CI 0.41-0.91; P=0.02). Serious adverse events were reported in 42% of the patients with approximately half of them resulting in death. No significant differences in the rate of adverse events were noted between treatment groups. However, infection occurred more frequently in patients who received prednisolone compared with those who did not (13% vs. 7%, P=0.002). Of note, infections were the main reason for death in this trial (24% of deaths). Finally, pentoxifylline was associated with numerically fewer cases of acute kidney injury.

Opinion

Contrary to what was expected from the trial, the results left uncertainties in the field as neither drug showed a long-term survival benefit. Clinicians should interpret cautiously the findings of STOPAH trial and weigh the possible benefit of prednisolone therapy against its adverse events, notably infectious complications.

Patients were included in the study based solely on a clinical diagnosis of AH. According to the authors, this was elected because liver biopsy is not usually used in this setting in clinical practice. Although strict clinical criteria are thought to accurate diagnose AH, distinction from decompensated

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cirrhosis in the setting of sepsis remains challenging. Thus, some enrolled patients in the STOPAH trial could have been incorrectly diagnosed with AH. It is conceivable that histological confirmation instead of clinical diagnosis would have been the optimal inclusion criterion in such a significant study in order to ensure correct patient disposition.

A score of 32 or higher for Maddrey's discriminant function was used as an inclusion criterion in this trial, as in most previous trials. Nonetheless, some baseline characteristics of the patients known to influence mortality were favorable in the STOPAH trial. No patients with renal failure -as defined in the study- or hepatic encephalopathy grade 4 and few patients with sepsis were included. Subsequently, the overall death rate at day 28 (15.2%) was remarkably low compared with previous studies using steroids (26.3%) or pentoxifylline (40%) [4,5]. The difference in mortality is more striking when compared to the pivotal pentoxifylline study where the death rate was 24.5% in the pentoxifylline group and 46.1% in the placebo group [5]. These differences in patient characteristics could have masked the protective role of pentoxifylline in renal function as this agent was shown to improve survival in patients with far worse characteristics.

As already outlined, prednisolone treatment increased the rate of infectious complications in the STOPAH trial. This adverse effect paired with the absence of long-term benefit should make clinicians use prednisolone with vigilance. The Lille model, using common baseline variables and the evolution of bilirubin after one week of treatment, can identify patients at risk of death early in the course of prednisolone treatment thus providing a tool for adjusting treatment [7]. In contrast, use of pentoxifylline can be completed uneventfully and without enhanced monitoring.

Overall, we believe that prednisolone did not show adequate effectiveness to be generally recommended and pentoxifylline may have been tested in a population that did not allow its beneficial effect on renal function to be exerted. A recent systematic review and network meta-analysis showed that prednisolone is not the only effective pharmacological agent for AH. Pentoxifylline was also shown to be effective although its use is supported by weaker evidence than prednisolone [8]. We propose that the use of each agent in clinical practice should be tailored to each individual patient's characteristics. Careful selection of drug, close monitoring and early assessment of response (when prednisolone is used) can increase success rates in the treatment of this dreadful condition.

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