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Editorial

Alcoholic hepatitis – glucocorticosteriods or not?

Erik Christensen*

Clinic of Internal Medicine I, Bispebjerg University Hospital, Bispebjerg Bakke 23, DK-2400 Copenhagen NV, Denmark

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In alcoholic hepatitis, the question of whether glucocorticosteroid therapy is more effective than placebo or no specific treatment has been debated for many years [1]. As recently reviewed by Gluud [2] a total of 17 controlled trials including more than 900 patients have been identified. Analysis of the total evidence presented in these trials does not reveal a significant survival benefit of glucocorticosteroids (relative risk (RR) 0.85, 95% confidence interval (CI) 0.67–1.07) [2]. Only seven of the 17 trials were explicitly analyzed according to the intention-to-treat principle and for these trials the result was RR 1.06 (95% CI 0.87–1.31). Furthermore, there was strong evidence of publication bias since a funnel plot showed a significant overrepresentation of positive results among the smaller trials [2]. This suggests that a number of negative trials have not been published, and that glucocorticosteroids may therefore be less effective.

A negative overall result does not preclude that glucocorticosteroids might be effective in selected patients. A meta-analysis adjusting for confounding variables [3] (which used a standard inverse variance weighting assigning relative weights, similar to the method by Peto) suggested performing further analyses of individual patient data from the largest trial [4] and testing the resultant hypotheses in new randomized clinical trials (RCTs).

In this issue of the Journal, Mathurin et al. [5] present an analysis based on 215 individual patients included in three RCTs [4,6,7]. The authors should be commended for performing a more comprehensive analysis of existing data. Unfortunately, the sample analyzed comprises less than 25% of the identified data and therefore one cannot exclude a selection bias. Although the authors tried to acquire more individual data from other trials, this was apparently no longer available.

It has been suggested that the survival benefit of corticosteroids is mainly confined to patients with hepatic encephalopathy. However, a lack of treatment effect can be noted in the three largest trials that included encephalopathic patients (Fig. 2 of Ref. [8]).

It has also been suggested that patients with a high Maddrey discriminant function (DF) score (≥32) (high bilirubin combined with marked prothrombin time prolongation) may particularly benefit from glucocorticosteroids. Mathurin et al. [5] identified 96 patients (44 placebo and 52 glucocorticosteroid) with DF ≥ 32 in the largest RCT [4] which showed a negative overall result. Importantly, Mathurin et al. show that in this RCT, even when selecting patients with DF ≥ 32, there was still no significant effect of glucocorticosteroids, the 4 week survival being 78.1% for glucocorticosteroid-treated and 67.6% for placebo-treated patients ($P = 0.17$).

It is not surprising that by combining this data with that of the two other positive trials of patients with a high DF score [6,7], the overall result of the analysis turns out to be positive showing a significant beneficial effect of glucocorticosteroids on 4-week survival. The effect is maintained in a Cox regression analysis adjusting for imbalance in prognostic variables.

What is the explanation of the apparent difference in therapeutic effect between the three RCTs in patients with DF ≥ 32? A possible explanation may be that the negative RCT [4] allowed the inclusion of patients with gastrointestinal (GI) bleeding, which may negatively affect survival, while the other two trials [6,7] excluded such patients. Thus, the beneficial effect seems confined to a highly selected minority group in which the inhibitory effect of glucocorticosteroids on liver inflammation is not outweighed by side-effects such as weakened defense against infections, anti-anabolic effects, and possible ulcer-promoting effects causing GI bleeding, which may be deleterious in these very ill patients.

For these reasons glucocorticosteroid therapy is not the ideal option. We need effective therapies which can be offered to the full spectrum of patients with alcoholic hepatitis.

* Tel.: +45-3531-2854; fax: +45-3531-3556.
Email address: e.chr@email.dk (E. Christensen).

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In recent years a somewhat better understanding of the pathophysiology of the disease has been obtained although the picture is not yet very clear. Factors such as nutritional abnormalities, oxidative stress, free radical generation, lipid peroxidation, dysregulated cytokine metabolism, acetaldehyde adduct formation, and an impaired immunological response seem to be involved. Alcohol interferes with nutrient activation resulting in changes in nutritional requirements [9] such as an increased need for S-adenosylmethionine (SAMe) and polyenylphosphatidylcholine (PPC) that, if supplemented, may decrease the liver injury [9].

Lately, interest has focused on cytokines such as tumor necrosis factor (TNF). TNF in serum is elevated and correlates with the severity of the disease. Furthermore, TNF can cause liver injury and can account for many of the findings observed in alcoholic hepatitis such as anorexia, neutrophilia, fever, and muscle wasting [10]. Antioxidants or glutathione enhancing agents such as SAMe may inhibit TNF production [10].

Pentoxyfylline, an inhibitor of TNF synthesis, has been found in an RCT to increase short-term survival significantly [11]. In particular, the risk of developing hepatorenal syndrome was reduced (an effect not described for glucocorticosteroids). These first results are promising, but many more large, high quality placebo-controlled multicentre trials conducted for longer periods of time are needed to further evaluate the potential of these new promising therapeutic avenues and to define their role in the treatment of alcoholic hepatitis.

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