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Editorial

Steroids or cocktails for alcoholic hepatitis

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Alcoholic hepatitis (AH) is a clinico-pathologic syndrome; the therapy of which remains a much discussed and controversial area of clinical hepatology. Corticosteroids (CS) have been used in the treatment of this disorder for five decades and are, thus, the most extensively studied treatment modality [1].

There have been 13 published trials in the English literature which used CS for AH. Five of these studies showed benefit, while the other eight found no benefit [1]. However, the results of one of these trials [2] and a meta-analysis [3] suggested that steroids should be targeted to the specific subset of AH patients with severe disease, which was not done in all of the 13 studies.

The importance of this observation has been substantiated by the fact that the two randomized placebo controlled double-blind prospective studies [4,5] which included only patients with severe AH, both showed a significant benefit of CS in terms of 30 day hospital survival. In addition, a subsequent study [6] demonstrated that 1 month of CS improved survival up to 1 year. Based largely on these treatment trials, published guidelines recommend the use of CS for severe AH [7].

However, their efficacy remains debated and many hepatologists are hesitant to use CS in patients with AH. This hesitancy is due to a number of factors. First, the personal experience of many clinicians is that patients with severe AH still die despite the use of CS. This is in fact the case for a number of reasons. Some patients with severe AH are too sick to respond to CS. In a large VA cooperative study [8], when patients were stratified by disease severity (quantified by Maddrey Discriminant Function—MDF score), patients with a score of >54 did not respond to CS while those with ≤ 54 did. Another reason for hesitancy is that approximately five patients with severe AH need to be treated with CS to save one patient [9]. However, the survival curves from the combined data of the last three randomized placebo controlled double-blind trials of CS in severe AH demonstrated clearly that CS significantly improved 30-day survival in these patients [9]. The final reason for hesitancy is that histologically confirmed AH may correlate poorly with the clinical impression of AH [1,6] and as many as 28% of patients with a clinical diagnosis of AH do not have histologic features of AH on liver biopsy. Therefore, many clinicians choose pentoxifylline, which is the only other treatment with demonstrated clinical efficacy [10]. Since there are virtually no significant side effects caused by pentoxifylline, clinicians are not concerned using this therapy even if their clinical diagnosis might be wrong.

The second factor often quoted for the justification not to use CS is the fact that the largest trial was negative [8]. However, as mentioned above, when the patients in the trial were stratified according to disease severity, CS were effective in the patients with severe disease. The final factor is the well-known side effects of CS and the co-morbidities that occur in these diseases (such as GI bleeding, infection and pancreatitis), which discourage CS use. Subsequently, there is clearly a need for a treatment strategy in addition to CS in severe AH.

In the current issue of the Journal, Phillips et al. [11] compare a cocktail of eight different anti-oxidants with CS in AH. The anti-oxidants included in the cocktail are B-carotene, Vitamin C, Vitamin E, selenium, methionine, allopurinol, desferrioxamine and *n*-acetylcysteine. The rationale for this strategy is well justified [12,13]. However, perhaps somewhat surprisingly and contrary to the authors' hypothesis, survival in the anti-oxidant group was less than in the CS group. Before the implications of this observation are discussed, it is important to address the study design and

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outcome measures used in the study performed by Phillips et al.

Regarding the study design, it is important to consider disease severity for enrollment in a clinical trial of AH. The mortality rate of hospitalized patients with AH varies widely ranging from 0 to 100%. Based on clinical experience and many clinical trials, it is clear that patients with mild disease do not need to be treated with extraordinary measures. It is also likely that patients with severe disease in extremis may be too ill for any form of drug treatment to be effective. Consequently, it is important to identify those patients who might benefit from aggressive intervention, as well as those patients for whom the therapeutic benefit risk ratio is favorable. Although other scoring systems are currently being evaluated [6,14–16], the MDF (as calculated by Phillips et al.) is the most widely used method for calculating disease severity and its prognostic value has been prospectively confirmed in clinical trials. However, none of these scoring systems were used as inclusion criteria in the paper under discussion. Although the patients clearly had severe AH as demonstrated by a mean MDF of 61 in both the antioxidant and the CS group, the range of MDF scores were wide; 7–163 and 15–200 in these two groups, respectively. These discriminant function scores at both extremes suggest that at least a percentage (not given) of these patients had either mild disease not needing treatment or disease in extremis and not likely to respond for reasons stated above. Therefore, it would have been of interest to see the results displayed according to the MDF scoring of <32 (mild disease and not needing treatment), 32–54, and >54. If this were done, the investigators might have noticed a different therapeutic response dependant on the discriminant function. More information also would have been helpful regarding the histologic comparison between the two groups and how histologic severity was defined.

Another issue regarding the study design is the fact that it is unclear what triggered cessation of treatment. Some patients completed 28 days of treatment as stated in the Methods section, while other patients had premature termination of therapy based on a favorable clinical response; the definition of which was not provided and would have been helpful. This latter point is important since the study using pentoxifylline demonstrated similar improvement in the MDF in both the treatment and placebo group over the entire course of the 30-day study despite improved survival in the treatment group [10].

Regarding outcome measures, survival is certainly the most important clinical outcome measure as recognized by Phillips et al. However, although the concentrations of three of the antioxidants in the cocktail were measured in blood, it would have been useful to measure the effect anti-oxidant treatment on some measure of oxidative stress since antioxidants were the new therapy in the study. This limitation is not restricted to this current paper under discussion, but it also pertains to many of the clinical trials that have been performed in the area of clinical hepatology. Nonetheless, these investigators are to be commended for performing a hypothesis driven study evaluating an important new therapeutic strategy in these patients.

We assume the reason that the current study employed a cocktail consisting of eight different anti-oxidants is that previous studies using a single anti-oxidant have been uniformly disappointing for liver disease [17–19], as well as for most other disease states [20] and healthy controls [21]. Therefore, Phillips et al.'s rationale for taking the cocktail approach is that the sum may be greater than the parts, and that a combination of these anti-oxidants may be more effective together than singly. Each of the eight anti-oxidants used in the cocktail are well recognized and have been studied for their anti-oxidative effects. Therefore, we need to ask the question why did not this approach work. Is it possible that the sum was less than its parts? Is it possible that perhaps a significant anti-oxidant effect was not achieved? Unfortunately, these questions cannot be answered by the present study. Vitamin A has the potential for hepatotoxicity and Vitamin E and Vitamin C may both become pro-oxidants [22,23]. While it is unlikely that any one of the anti-oxidants used in the cocktail were harmful at the doses employed, it might be possible that the cocktail produced a pro-oxidant state and a positive effect of any single agent might have been neutralized by the mix of the anti-oxidants.

The lack of efficacy of this anti-oxidant cocktail also is discouraging because there is an enormous body of evidence implicating oxidative stress in the pathophysiology of AH [11,12]. However, there are still a number of aspects of oxidative stress that are poorly understood. Studying pro-oxidants in vivo is difficult due to their inherent reactivity. Consequently, they cannot be measured directly, but rather the products of the reaction of these molecules with endogenous and exogenous targets are measured. However, there are relatively clear data supporting the involvement of two pro-oxidant species in ALD. These species generally fall under the categories of reactive oxygen species (ROS) derived from superoxide anion ($O_2^{-}\cdot$) and reactive nitrogen species (RNS) derived from nitric oxide (NO). These reactive species are produced in both parenchymal and non-parenchymal cells within the liver and by different organelles within these cells. In addition, different anti-oxidants have different kinetics which are not usually considered in therapeutic trials [13]. Therefore, the site and source of ROS and RNS are unclear and there are many enzymes in vivo capable of inducing these pro-oxidants [12]. Much of the data regarding the efficacy of anti-oxidants and alcohol are derived from animal studies in which the alcohol and anti-oxidant are administered concomitantly. This is in contrast to the pattern of alcohol injury in a patient in whom anti-oxidants are employed after