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LETTERS TO THE EDITOR

Pentoxifylline: A first line treatment option for severe alcoholic hepatitis and hepatorenal syndrome?

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Abstract

Although favourable results of pentoxifylline (PTX) used in treatment of severe alcoholic hepatitis patients with a Maddrey discriminant function score $\geqslant$ 32 have been previously reported, it is not currently recommended as a first line treatment for alcoholic hepatitis owing to lack of evidence for its efficacy as compared to the standard treatment with corticosteroids. In a very recent issue of *World Journal of Gastroenterology*, Dr. De BK and colleagues compared for the first time the two treatment modalities head to head in a randomized controlled study, demonstrating the advantage of PTX over corticosteroids in terms of patients' survival and risk-benefit profile. The advantage of PTX over corticosteroids in survival of patients with severe alcoholic hepatitis was found to be related to the prevention of hepatorenal syndrome in their study. This study raises the question of the use of PTX as a standard treatment for severe alcoholic hepatitis. Considering the fact that PTX presented a spectacular efficiency in prevention of hepatorenal syndrome in their study as well as that previous studies have shown that this effect is possibly related to a primary renoprotective action because it is irrelevant of tumor necrosis factor-α synthesis inhibition or improved liver function, we tempted to speculate that PXT might be an effective option for prevention and/or treatment of hepatorenal syndrome complicating other forms of advanced liver disease. This attractive theory remains to be elucidated by pressing future studies in view of the lack of effective treatment modalities for hepatorenal syndrome.

TO THE EDITOR

We read with great interest the article recently published by Dr. De and colleagues in *World Journal of Gastroenterology*[1], who evaluated in a randomized double-blind controlled study the advantage of pentoxifylline (PTX) over prednisolone in treatment of severe alcoholic hepatitis [Maddrey discriminant function (DF) score $\geqslant$ 32]. The most important observation was the significantly reduced mortality of patients after treatment with PTX (14.71%) as compared to those after treatment with prednisolone (35.29%, $P = 0.04$). Reduced mortality in patients after treatment with PTX was found to be related to a significant reduction in the development of hepatorenal syndrome. Among patients who died, hepatorenal syndrome developed in 50% of prednisolone-treated patients but in none of PTX-treated patients.

Current guidelines of the American College of Gastroenterology recommend the use of glucocorticosteroids in treatment of patients with severe alcoholic hepatitis as defined by the Maddrey score (DF $\geqslant$ 32)[2,3]. Primary use of PTX in treatment of severe alcoholic hepatitis patients is not recommended due to the lack of evidence for improvement in patient-oriented outcomes[2]. Also, the early switch of corticosteroids to PTX, if no improvement in bilirubin is seen after 7 d of treatment, has been proved to be an inefficient treatment strategy[4]. However, a number of French experts in the field consider PTX a reasonable alternative to corticosteroids for severe acute alcoholic hepatitis based on the

favourable results of previous studies comparing PTX with placebo[5,6].

Specifically, up to now, the use of PTX in treatment of severe alcoholic hepatitis has been supported by two clinical studies[5,6]. The first one was conducted in 1991 by McHutchison *et al*[5], in patients with severe alcoholic hepatitis (defined as DF score ⩾ 32), which showed that PTX could reduce the development of hepatorenal syndrome and the mortality, in comparison to those receiving placebo. These findings were confirmed in 2000 by Akriviadis *et al*[6] in a double-blind placebo-controlled trial, which showed that 24% of PTX-treated patients and 46.1% of control patients died during hospitalization. The survival benefit of PTX was found to be related to a significant reduction in the development of hepatorenal syndrome. Among the patients who died, hepatorenal syndrome developed in 50% of PTX-treated patients and in 91.7% of placebo-treated patients. The study by De *et al*[1] is the first to compare PTX and corticosteroids head to head in a randomized controlled manner. The results of this study, demonstrating the advantage of PTX over corticosteroids, raise the question of the use of PTX as a standard treatment modality for severe alcoholic hepatitis.

A second issue we would like to comment on is the fact that the advantage of PTX in survival of patients with severe alcoholic hepatitis is clearly related to the prevention of hepatorenal syndrome[1,5,6]. The available data do not show the evident mechanism underlying this beneficial effect of PTX and only speculations could be made on this matter. The use of PTX in treatment of alcoholic hepatitis is based on its ability to inhibit the synthesis of tumor necrosis factor (TNF)-α, which is considered a pivotal mediator of alcohol-induced liver injury[6,7]. Although the authors did not assess in this study the immunological and inflammatory status (e.g. TNF-α) of their patients, it has been previously reported that the prevention of hepatorenal syndrome and survival advantage in patients with severe alcoholic hepatitis after treatment with PTX are not associated with decreased circulating TNF-α levels or improved liver function[6]. These findings give an alternative explanation for the positive effect of PTX on renal function of alcoholic hepatitis patients, which is the beneficial action of PTX on renal microcirculation and hemodynamics. This potential primary protective effect of PTX on renal function and its repeatedly confirmed efficacy on prevention of hepatorenal syndrome in severe alcoholic hepatitis patients (in this study, PTX prevented the development of hepatorenal syndrome) tempt us to speculate that it could potentially be used in the prevention and/or treatment of hepatorenal syndrome complicating other forms of advanced liver disease. To the best of our knowledge, this possibility has not been investigated up to now and appears to be an attractive new field for experimental and clinical research, given the current difficulties in the management of patients with hepatorenal syndrome.

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