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Pentoxifylline and prednisolone in severe alcoholic hepatitis

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Article commented:

De BK, Gangopadhyay S, Dutta D, Baksi SD, Pani A, Ghosh P. Pentoxifylline versus prednisolone for severe alcoholic hepatitis: A randomized controlled trial. *World J Gastroenterol* 2009; 15: 1613-9.

Original Abstract

Aim. To compare the efficacy of pentoxifylline and prednisolone in the treatment of severe alcoholic hepatitis and to evaluate the role of different liver function scores in predicting prognosis. **Methods.** Sixty-eight patients with severe alcoholic hepatitis (Maddrey score ³ 32) received pentoxifylline (n = 34, group I) or prednisolone (n = 34, group II) for 28 d in a randomized double-blind controlled study, and subsequently in an open study (with a tapering dose of prednisolone) for a total of 3 mo, and were followed up over a period of 12 mo. **Results.** Twelve patients in group II died at the end of 3 mo in contrast to five patients in group I. The probability of dying at the end of 3 mo was higher in group II as compared to group I (35.29% *vs.* 14.71%, p = 0.04; log rank test). Six patients in group II developed hepatorenal syndrome as compared to none in group I. Pentoxifylline was associated with a significantly lower model for end-stage liver disease (MELD) score at the end of 28 d of therapy (15.53 ± 3.63 *vs* 17.78 ± 4.56, p = 0.04). Higher baseline Maddrey score was associated with increased mortality. **Conclusion.** Reduced mortality, improved risk-benefit profile and renoprotective effects of pentoxifylline compared with prednisolone suggest that pentoxifylline is superior to prednisolone for treatment of severe alcoholic hepatitis.

Key words. Alcoholic hepatitis. Pentoxifylline. Prednisolone. Maddrey discriminant function score. Model for end-stage liver disease score. Glasgow alcoholic hepatitis score.

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Comment

We have read a very interesting study by De, *et al.*,[1] on the treatment of alcoholic hepatitis (AH), in which they compared the use of pentoxifilline (PTX) vs. prednisolone (PDS) in 68 subjects with AH. They found a reduced mortality within the pentoxifilline group (14.71% *vs.* 35.29%, p = 0.04), as well as a lower frequency of hepatorrenal syndrome, therefore suggesting that pentoxifilline should be used instead of prednisolone in subjects with severe AH.

Severe AH is a life-threatening condition that is observed in approximately 20% of heavy drinkers which lacks an effective therapy.[2] This condition has been defined by a discriminant function of the Maddrey score ≥ 32.[3] Experimental data has demonstrated that AH pathogenesis is multi-factorial and involves metabolism of ethanol into toxic substrates-such as acetaldehyde - leading to hepatocyte injury;[4] increased gut permeability (causing endotoxemia and further Kupffer cell activation);[5] oxidative stress (promoting stellate cell activation)[6, 7] as well as nutritional impairment.[8] Several of these processes are thought to be mediated by tumor necrosis factor-α (TNF- α),[9] secreted mainly by activated Ku-

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pffer cells.[10] Elevated levels of TNF-α have been found to be a marker of poor survival in AH,[11, 12] and its decrease in animal experimental models was associated to attenuation of liver injury. Therefore, anti-TNF-α therapy is one of the most attractive approaches for severe AH.[13] Several anti-TNF therapies have been tested, including the monoclonal antibodies Infliximab[14] and Etanercept[15] as well as PTX. Unfortunately, despite initial promising pilot studies,[16,17] monoclonal anti-TNF-α has shown either only a modest benefit, with increase of infection rate[14] and mortality,[15] and therefore they cannot be currently recommended for treating AH. Furthermore, only PTX has been proved of benefit in reducing mortality, possibly explained by its reno-protective and hemorheological effect[18-20] as well as attenuation of inflammatory response.[21-25] PTX decreases production of pro-inflammatory chemokines/cytokines including TNF-α[26] and it seems to exert an antifibrogenic effect.[27] Current evidence consistently shows that short-term use of PTX significantly reduces both the overt proteinuria and microalbuminuria in subjects with diabetes.[28] In spite of these results, patients with AH refractory to steroids do not benefit from PTX use, as demonstrated by a recent cohort study by Louvet, *et al.*[29] This finding corresponds to a set of non-responding patients, a group first described by Mathurin, *et al.*[30] This study found that in a steroid-treated group, an early change in bilirrubin levels (ECBL) at 7 days has the most important prognostic value for identifying a non-responding patient, a finding that could be also useful in the use of PTX but needs to be confirmed.

In conclusion, although the treatment of AH remains one of the main challenges for clinicians involved in the management of severe alcoholic liver disease, early identification of subjects with substantial risk of death according to the prognostic models will improve management of patients suffering from severe AH and will aid in designing future studies for alternative therapies. With the current evidence, we support the use of PTX in AH as a reasonably alternative in the management of AH. It is our knowledge that since the study by Akiridavidis, *et al.* the present research is the only assay that compares both PDS and PTX in AH and demonstrates a benefit from PTX use. This effect on mortality seems not to be explained by TNF-α inhibition *per se,* and is though to be explained by the renal effects of PTX; therefore, PTX could have an indication for prevention of hepatorrenal syndrome in AH. Further randomized controlled trials are needed to support this recommendation.

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