

Selected summary

Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial.

Akriviadis E, Bolta R, Briggs W, Han S, Reynolds T, Shakil O

Gastroenterology 2000,119:1637-1648

Severe alcoholic hepatitis has a high mortality and morbidity rate, but its exact pathogenetic mechanisms have not been completely clarified. According to recent studies, tumor necrosis factor- α (TNF- α) may play a key role in the development of alcoholic hepatitis. In this large, prospective, double-blind, randomized clinical trial, the efficacy of pentoxifylline (PTX), a TNF- α inhibitor was evaluated in the management of severe alcoholic hepatitis. One hundred and one patients were randomized to receive 400 mg PTX three times daily ($n=49$) or vitamin B12 (placebo, $n=52$), both given for four weeks. All patients had severe alcoholic hepatitis, as defined by Maddrey discriminate function (DF) ≥ 32 (DF = $4.6 \times \{\text{prothrombin time above control in seconds}\} + \text{bilirubin in mg/dl}$). Patients with evidence of bacterial infection, active gastrointestinal bleeding, advanced cirrhosis, or severe cardiovascular or pulmonary disease were excluded. Primary end points of the study were: a) death and b) development of hepatorenal syndrome. The follow-up period was six months. Twelve (24,5%) of the 49 PTX and 24 (46%) of the 52 placebo treated patients died during the study period ($p=0,037$). Among the patients who died, hepatorenal syndrome developed in 6 (50%) of 12 PTX and in 22 (92%) of the 24 placebo treated patients ($p=0,009$). Baseline serum

creatinine was $\geq 2,4$ mg/dl in three PTX and six placebo treated patients, while new onset renal dysfunction developed in four and 18 patients respectively. Baseline TNF levels were elevated in all patients; they did not differ between survivors and nonsurvivors in each group. However, nonsurvivors compared to survivors had higher TNF- α levels over the study period. Baseline creatinine levels, age and PTX treatment were the only variables that were independently associated with survival in both groups. Adverse events were usually minor, mainly involving the gastrointestinal tract (nausea, vomiting, diarrhea); they caused early discontinuation in seven PTX treated patients. The mean period of treatment was 21,5 days in the PTX and 23 days in the placebo group.

In conclusion, PTX treatment was found to significantly improve survival in patients with severe alcoholic hepatitis. This benefit seems to be mainly associated with the reduction in the incidence of hepatorenal syndrome.

COMMENTS

Alcoholic liver disease results from prolonged and heavy alcohol intake. Alcohol is responsible for about 100.000 deaths per year in USA (N Engl J Med 1995; 333:1058-65) and may result in a wide spectrum of liver lesions, ranging from fatty liver to hepatitis, fibrosis, cirrhosis and hepatocellular carcinoma. Alcoholic hepatitis is characterized by fever, elevated white blood cell count, elevation of transaminases and/or bilirubin levels, and hepatic tenderness; histology usually shows polymorphonuclear infiltration, Mallory bodies and collagen deposition (Am J Gastroenterol 1993; 88:1822-31). The pathogenetic mechanisms by which alcohol causes liver damage constitute the basis for development of therapeutic strategies for alcoholic liver disease. Despite intensive investigations, these mechanisms remain not fully elucidated. The fact that only 20% of heavy drinkers develop serious liver disease (alcoholic hepatitis and/or cirrhosis) (J Hepatol 1995; 23 (Suppl. 1): 7-15) shows that environment and genetic factors may play an important role (J Hepatol 2000; 32 (Suppl 1):113-28). However, direct ethanol toxicity, acetaldehyde adducts, free radicals formations and nutritional deficiencies also appear to be involved in the pathogenesis of alcoholic liver disease (Gastroenterology 1994; 106:1085-1105).

Evangelos Cholongitas, George V. Papatheodoridis

Address for correspondence: George V. Papatheodoridis.

1 Ath. Diakou street, 152 35 -Vrilissia. Tel: 0946-330639, Fax: 6138036

Cytokines production, mainly TNF- α , is currently thought to represent a key factor, not only in the early stage of fatty liver, but also in the more advanced stages as well (N Engl J Med 2000; 343:1467-76). TNF- α is a central proinflammatory cytokine, with a molecular weight of 17300 and with 30% homology to lymphotoxin. It is mainly secreted by the monocytes/macrophages system (or Kupffer cells in liver) and triggers the production of other cytokines. TNF- α acts on the polymorphonuclear cells enhancing their adhesion to endothelial cells (J Immunol 1986; 136:4220-5) as well as their phagocytic capacity, degranulation and cytotoxic activity (J Immunol 1985; 135:2069-73). Activated polymorphonuclear cells in the liver parenchyma produce oxygen-derived metabolic products, which can cause liver damage. On the other hands, TNF- α is also important in fibrogenesis, regulation of proliferation (Science 1996; 274:1379-83) and apoptosis of hepatocytes (J Immunol 1994; 153:1778-88). All these mean that TNF- α may have both detrimental and protective activities for the liver.

Several models of alcoholic liver disease in rats have supported the important roles of endotoxemia, Kupffer cells and TNF- α in liver damage (Hepatology 1999; 29:1680-9). Moreover, studies in knockout TNF-R1 (p55) mice offer the best evidence for the key role of TNF- α in alcoholic liver disease (Gastroenterology 1999; 117:942-52). In chronic alcohol consumption, increases of bacteria in the intestine and changes in gut permeability (leaky gut) have been observed (Am J Gastroenterol 1999; 94:200-207). Endotoxins derived by Gram negative bacteria activate Kupffer cells (via endotoxin membrane-receptor CD14 and elevation of intracellular Ca⁺⁺). Activated Kupffer cells release free radicals species, prostanoids and cytokines (TNF- α may be the most important). The release of these mediators trigger inflammatory events and finally lead to liver injury. This hypothesis is supported by several experiments: (a) administration of antibodies against TNF- α reduce inflammation and necrosis in early liver injury (Hepatology 1994; 26:1530-7); (b) destruction of Kupffer cells by intravenous injections of Gadolinium chloride, a specific Kupffer cell toxicant, diminishes steatosis (Hepatology 1994; 20:453-60); (c) intestinal sterilization with antibiotics (e.g. polymixin B, neomycin) prevents the induction of alcoholic liver disease (Gastroenterology 1995; 108:218-24); (d) serum TNF- α and soluble TNF- α receptors (sRp75/sRp55 and plasma level of sRp55) levels correlate with the severity and mortality of alcoholic hepatitis (J Hepatol 1998; 28:778-84).

PTX is a xanthine derivative drug, FDA-approved for

the treatment of claudication (PTX increase red blood cell deformability). PTX (as a phosphodiesterase inhibitor) inhibit TNF- α gene transcription, possibly via elevation of intracellular adenosine 3,5-cyclic monophosphate (cAMP) and guanosine 3,5-cyclic monophosphate (cGMP) (Surgery 1991; 110:192-8). It has been also used: a) in patients with haematology malignancies undergoing bone marrow transplantation, to decrease transplant-related toxicities (PTX reduces TNF- α and enhances PGI₂ and PGE₂ production) (Blood 1991; 78: 1205-11); b) in Behcet's disease (PTX seems to reduce superoxide anion production by neutrophils) (Ann Intern Med 1996; 124:891-3); c) in inflammatory bowel disease (via inhibition of TNF- α synthesis by peripheral mononuclear cells and by inflamed intestinal mucosa) (Gut 1997; 40:475-80); d) in chronic liver disease, to reduce the accumulation of collagen fibers {via inhibition of Platelet-Derived Growth Factor (Hepatology 1993; 17:486-93) and Myofibroblast-like cells (MFLC) (Hepatology 1997; 26:315-21)}; e) in primary sclerosing cholangitis (in a pilot study, without effect on symptoms or liver enzymes) (Am J Gastroenterol 2000; 95:2338-42).

Based on the pharmacological properties of PTX, Akriviadis et al., from the University of California Liver Unit, evaluated its efficacy in severe alcoholic hepatitis in this large (101 patients), double-blind, placebo-controlled clinical trial. Randomization was stratified to serum creatinine levels. There was no significant difference between the two groups in any of the demographic, clinical or biochemical baseline characteristic.

The results of this study are quite impressive. PTX was found to reduce mortality by 40%, mainly due to prevention of development of hepatorenal syndrome. The first comment coming to mind reading this study is the choice for the control group. The investigators decided to use vitamin B12 as placebo, and not prednisolone, because their previous experience with corticosteroids in severe alcoholic hepatitis showed no benefit in both morbidity and mortality. It should be noted, however, that the American College of Gastroenterology recently recommended the use of prednisolone (40mg daily for 4 weeks, followed by a tapering dosage) for severe alcoholic hepatitis (Am J Gastroenterol 1998, 93:2022-36). According to this trial, PTX decreased mortality more than the reported reduction with prednisolone (40% vs 25%). In addition, there are several reasons for caution in using corticosteroids in alcoholic hepatitis. First, use of prednisolone frequently has several and potentially severe effects, such as osteoporosis, diabetes mellitus, opportunistic infections and life-threatening

sepsis. In particular, in patients with severe alcoholic hepatitis, prednisolone must be used with great caution because of their sensitivity to bacterial infections. Second, alcoholic hepatitis is usually accompanied by fever and elevated neutrophil cell count, which make exclusion of bacterial infections uncertain in clinical practice. Thus, selection of patients who might benefit from prednisolone can be difficult and not always certain. On the contrary, PTX did not appear to have serious side effects (eleven of 38 PTX patients discontinued therapy due to gastrointestinal symptoms, headache or skin rash), and may be given more easily than corticosteroids. Since patients with bacterial infections were excluded from the commented study, an established infection remains a problem even for PTX therapy. It should be noted, however, that, in the present study, PTX therapy was not found to increase the incidence of bacterial infections compared with placebo.

Until the pathogenesis of alcoholic liver disease (ALD) has been unravelled, treatment for patients with this disease will remain an elusive goal. TNF- α may play an important role in pathogenesis of ALD. PTX may reduce TNF- α levels, which is why Akriviadis et al. tried this substance in patients with severe alcoholic hepatitis. TNF- α levels did not differ between the two groups at baseline as expected for a randomised study, but their changes were also not found to be influenced by the PTX during the study period. If all findings are correct, PTX may improve survival via other unknown mechanisms and not via TNF- α inhibition. Thus, further investigation is needed to reveal the mechanisms of action of PTX on ALD. PTX (in contrast to prednisolone) was found to

reduce the incidence of hepatorenal syndrome, the major cause of death in severely ill alcoholic patients. Such a benefit in renal function was probably associated with both prevention of renal failure and improvement of liver function. Plasma TNF- α levels were significantly associated with serum creatinine levels. Thus, prevention of renal failure might result from the beneficial role of PTX on plasma TNF- α levels, which was mainly observed in the subgroup of patients with the more severe course, and/or on renal microcirculation. A beneficial effect of PTX on microcirculation may be due to changes of erythrocytes deformability or to other unknown mechanisms. The role of nitric oxide or of endothelins which are very important molecules in the regulation of renal blood flow was not evaluated in this study.

This study was well designed but it seems early to recommend PTX as a standard therapy for severe alcoholic hepatitis. Further large clinical trials are needed to confirm the beneficial effect of PTX and to clarify the exact mechanisms by which PTX reduces hepatorenal syndrome and mortality in such patients. When the pathogenesis of ALD is clarified, then we will be able to give specific therapy to the several settings of ALD patients. Until then, our main efforts should focus on abstinence and primary or secondary prevention of ALD. However, since abstinence is an almost impossible target to achieve for all alcoholics, efforts to establish therapies that improve survival in this difficult setting are always welcome.

EVANGELOS CHOLONGITAS
GEORGE V. PAPTAEODORIDIS