Pentoxifylline Improves Short-term Survival in Severe Acute Alcoholic Hepatitis: A Double-Blind, Placebo-Controlled Trial

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See editorial on page 1787.

Background & Aims: **An earlier pilot study from our liver unit suggested benefit from treatment with pentoxifylline (PTX), an inhibitor of tumor necrosis factor (TNF), in severe acute alcoholic hepatitis. The aim of the present study was to evaluate this treatment in a larger cohort of patients.** ***Methods:*** **One hundred one patients with severe alcoholic hepatitis (Maddrey discriminant factor ≥ 32) entered a 4-week double-blind randomized trial of PTX (400 mg orally 3 times daily) vs. placebo. Primary endpoints of the study were the effect of PTX on (1) short-term survival and (2) progression to hepatorenal syndrome. On randomization, there were no differences in demographic and clinical characteristics or laboratory values (including TNF) between the 2 groups.** ***Results:*** **Twelve (24.5%) of the 49 patients who received PTX and 24 (46.1%) of the 52 patients who received placebo died during the index hospitalization ($P = 0.037$; relative risk, 0.59; 95% confidence interval, 0.35–0.97). Hepatorenal syndrome was the cause of death in 6 (50%) and 22 (91.7%) patients ($P = 0.009$; relative risk, 0.29; 95% confidence interval, 0.13–0.65). Three variables (age, creatinine level on randomization, and treatment with PTX) were independently associated with survival. TNF values on randomization were not predictive of survival; however, during the study period they increased markedly in nonsurvivors compared with survivors in both groups.** ***Conclusions:*** **Treatment with PTX improves short-term survival in patients with severe alcoholic hepatitis. The benefit appears to be related to a significant decrease in the risk of developing hepatorenal syndrome. Increasing TNF levels during the hospital course are associated with an increase in mortality rate.**

Acute alcoholic hepatitis can lead to profound impairment of liver function, and in severe cases it has a high morbidity and mortality rate.[1–4] It is often superimposed on chronic liver disease,[5] and its pathologic characteristics include development of Mallory "alcoholic" hyaline, prominent intrasinusoidal collagen deposition, and infiltration with polymorphonuclear leukocytes of the hepatic parenchyma, usually at the perivenular area. This intrahepatic infiltration with polymorphonuclear leukocytes is commonly associated with marked peripheral leukocytosis, fever, and signs of hepatic inflammation, including hepatic pain and tenderness. The pathogenesis of liver injury in acute alcoholic hepatitis remains elusive. A direct hepatotoxic effect of alcohol cannot explain the fact that the syndrome of acute alcoholic hepatitis develops in only a minority of patients with alcoholic liver disease. Therefore, genetic factors and immune-mediated mechanisms have been postulated.[6] Recently, a cytokine-induced acute inflammatory response has been proposed,[7–11] and increased tumor necrosis factor (TNF) levels have been found in sera of patients with acute alcoholic hepatitis,[7,8,12] particularly in more severe cases.[7,8] In liver tissue specimens, TNF has been detected by immunohistochemical analysis predominantly in ballooned hepatocytes, frequently containing alcoholic hyaline.[13] An earlier pilot study from our unit[14] showed that in patients with acute alcoholic hepatitis, the increase in plasma TNF levels could be prevented by the use of pentoxifylline (PTX), an inhibitor of TNF synthesis.[15–18] In the same study, treatment with PTX was also associated with less renal impairment and a tendency for improved survival.[14]

The present prospective short-term study was begun after the initial report to evaluate the efficacy and safety of PTX in patients with severe acute alcoholic hepatitis.

Patients and Methods

Patient Selection

The study was performed on patients hospitalized between August 1992 and May 1997 in the Liver Unit of the

Abbreviations used in this paper: BUN, blood urea nitrogen; CI, confidence interval; DF, discriminant factor; PT, prothrombin time; PTX, pentoxifylline; T_3, triiodothyronine; TNF, tumor necrosis factor; WBC, white blood cell.

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University of Southern California at Rancho Los Amigos Medical Center, in Downey, California. The study was approved by the Institutional Review Board before its initiation and periodically thereafter during the 5-year period of its conductance. Informed consent was obtained from all participating patients. Each patient had a history of heavy ethanol abuse and an admission diagnosis of acute alcoholic hepatitis. Inclusion criteria for patients in the study were (1) jaundice, (2) Maddrey discriminant factor (DF)[1] $\geq$ 32, and (3) 1 or more of the following clinical or laboratory findings: palpable tender hepatomegaly, fever, leukocytosis (white blood cell [WBC] count $>$ 12,000/mm^3 with predominantly neutrophilic differentiation), hepatic encephalopathy, and hepatic systolic bruit. Enrollment into the trial was attempted within the first 10 days after admission.

Patients were excluded if they had concomitant bacterial infections, active gastrointestinal hemorrhage, or severe cardiovascular or pulmonary disease. An attempt was made to obtain a homogeneous patient population. Patients with decreasing serum bilirubin values or rapid improvement of other liver test results over the first postadmission days were excluded. Patients with clinical evidence of advanced alcoholic cirrhosis were excluded. All patients were screened by one of the investigators and by a senior staff member of the liver unit (T.B.R.) before they were enrolled in the study.

Therapy

All patients who fulfilled the above criteria and gave written informed consent were randomly placed into 2 treatment groups: one group received 400-mg PTX tablets orally 3 times daily enclosed in opaque capsules, and the other group received identical capsules containing placebo (tablets of vitamin B_{12}, 500 or 1000 μg). Vitamin B_{12} tablets were chosen as placebo because their size and appearance are similar to those of PTX tablets, thus facilitating identical filling of the capsules. It was believed that this would protect against unmasking of randomization to active medication or placebo in case of accidental opening of the capsules. The study was double-blinded. A coordinator who was not an investigator randomly selected sealed envelopes for treatment decisions, and drugs were coded and distributed by the hospital pharmacy. An ombudsman who was not an investigator was appointed to resolve potential issues arising from possible life-threatening complications of therapy. The duration of therapy was 28 days. The randomization was stratified for serum creatinine levels above and below 2.5 mg/dL to provide balanced randomization of patients with renal impairment between the 2 groups. Criteria for discontinuation of the trial were withdrawal of consent and side effects thought to be related to possible drug toxicity, including persistent vomiting or diarrhea, abdominal pain, headache, and skin rash. Infection was not considered an indication to terminate the trial. In patients who developed gastrointestinal bleeding after enrollment, therapy was withheld temporarily and resumed after control of hemorrhage.

All patients were offered a standard ward diet (2100–2700 kcal, 2 g NaCl). Medical management was individualized according to each patient's condition. The patients were examined at least weekly by one of the investigators with regard to the development of possible complications (gastrointestinal bleeding or other bleeding complications, infection, abdominal pain, dyspepsia, diarrhea, leukopenia, thrombocytopenia, renal impairment, skin rash, and hepatic encephalopathy). Laboratory assessment, including measurements of complete blood count, liver biochemistry, electrolytes, blood urea nitrogen (BUN), serum creatinine, fasting blood glucose, and prothrombin time (PT), was performed at least twice weekly. At the time of enrollment in the study, serum was tested for the presence of antibodies against hepatitis C virus, hepatitis B surface antigen, cholesterol, α-fetoprotein, and triiodothyronine (T_3). Blood was also drawn in EDTA tubes containing the protease inhibitor aprotinin for measurement of TNF. These tubes were kept refrigerated before blood drawing. Plasma was separated not later than 30 minutes after blood drawing and kept frozen at -70°C for measurement of TNF levels using the Quantikine HS human TNF-α immunoassay (R&D Systems, Minneapolis, MN). According to manufacturers' data, plasma TNF concentrations of normal donors should range from nondetectable to 4.12 pg/mL.

Patients were hospitalized as long as medically indicated. If they were discharged before completion of the 4-week treatment period, capsules were given to be continued on an outpatient basis. Patients were asked to return to the liver unit 1 week after discharge, at which time blood tests were repeated and the remaining capsules were counted.

A histologic diagnosis of acute alcoholic hepatitis was not required for inclusion in the study, because we wanted to enroll severely ill patients whose coagulopathy frequently prohibited the performance of transcutaneous liver biopsy. The presence of esophageal varices was assessed by endoscopy or injection studies of the inverted esophagus at autopsy. A ^{99m}Tc–sulfur colloid liver spleen scan with scintigraphic assessment of hepatic blood flow pattern[19] was obtained in each patient during the index hospitalization.

Statistical Analysis

The data were analyzed for differences between the 2 treatment groups and also between survivors and nonsurvivors within and between the 2 groups. The categorical variables were tested using the Fisher exact test. Continuous data were tested using either *t* tests or repeated-measures analysis of variance (ANOVA) as required. Multiple comparisons were done using the Student–Newman–Keuls method. Comparisons between the 2 groups were done both for absolute values and for changes from baseline values. The Pearson correlation coefficient was used to examine associations between continuous variables. A significance level of 0.05 was used for all testing. Differences in outcome measures were calculated with *P* values and 95% confidence intervals (CIs). Continuous variables are expressed as means $\pm$ SD. The survival curves were estimated by Kaplan–Meier estimates. Differences in the survival curves of the 2 groups were tested using the log-rank test, which is a test for differences between the curves that does not

test overall survival. All analyses were done on an intention-to-treat basis.

Endpoints

The endpoints of the study were predetermined. The 2 primary endpoints were the effect of PTX on (1) short-term survival (during index hospitalization or over the 28-day study period) and (2) progression to hepatorenal syndrome. Secondary endpoints were the effect of PTX on (1) course of laboratory parameters, including serum TNF levels, and (2) development of clinical complications of liver disease.

Results

Patient Characteristics

One hundred two patients were enrolled. There was 1 dropout: a patient from the PTX group left the hospital against medical advice 1 day after randomization. He received only 3 capsules of PTX and therefore was excluded from analysis. Of the remaining 101 patients, 49 (35 men and 14 women) received PTX and 52 (40 men and 12 women) received placebo. Mean age was 42.4 ± 8.2 years for the PTX group and 40.8 ± 8.7 years for the control group ($P = 0.36$; Table 1).

Demographic and clinical characteristics of the 2 treatment groups are summarized in Table 1. There were no significant differences between groups for any of the demographic variables (Table 1). The mean period from hospital admission to randomization was ≤6 days in both groups. Twelve patients from the PTX group and 10 from the control group had 1 or more previous episodes of decompensation of alcoholic liver disease requiring hospitalization. These patients were included because they did not appear to have irreversible end-stage liver disease and their physicians thought that they might benefit from receiving a potentially therapeutic agent. Nine patients, 3 from the PTX group and 6 from the control group, had serum creatinine levels ≥ 2.4 mg/dL when treatment was started. Hepatic encephalopathy was present in 10 patients (4 in the PTX group and 6 in the control group) at the time of randomization. Other prominent clinical features for both groups were ascites, edema, esophageal varices, fever (temperature > 100°F) without evidence of infection, palpable hepatomegaly, and a systolic bruit over the liver. There were no significant differences in the frequency of these clinical features between the groups (Table 1).

Table 1. Duration of Treatment and Demographic and Clinical Characteristics of Patients at Randomization

	PTX-treated (n = 49)	Controls (n = 52)	*P*
Days of treatment [mean (SD)]	21.5 (9.5)	23 (7.4)	0.39
Male	35 (71%)	40 (77%)	0.65
Age (*yr*) [mean (SD)]	42.4 (8.2)	40.8 (8.7)	0.36
Hospital days to randomization [mean (SD)]	5.8 (3.9)	6.0 (3.8)	0.81
Patients with previous decompensation	12 (24%)	10 (19%)	0.32
Hepatic encephalopathy	4 (8%)	6 (12%)	0.41
Renal impairment[a]	3 (6.1%)	6 (11.5%)	0.22
Ascites	76%	69%	0.51
Edema	59%	54%	0.69
Varices	80%	73%	0.73
Splenomegaly	21%	15%	0.60
Temperature ≥ 100°F	13%	13%	>0.95
Palpable hepatomegaly	92%	92%	1.00
Hepatic bruit	59%	58%	1.00

[a]Serum creatinine level ≥ 2.4 mg/dL; progressed to hepatorenal syndrome in 2 PTX-treated and 4 control patients.

The mean duration of treatment in the PTX group was 21.5 ± 9.5 days (22.9 ± 9.3 days for survivors and 17.2 ± 9.3 days for nonsurvivors); in the control group the mean duration of treatment was 23 ± 7.4 days (26.8 ± 3.7 days for survivors and 18.5 ± 8.1 days for nonsurvivors) ($P > 0.05$ for all comparisons between the PTX and control groups). The mean period from study entry to discharge was 39.4 ± 17.1 days for the PTX group and 38.2 ± 15.0 days for the control group ($P > 0.05$). Among the PTX patients, 38 (77.6%) received PTX until completion of 28 days (n = 31) or until death (n = 7), 5–24 days after randomization. Of the remaining 11 PTX patients, 2 of whom died, treatment was discontinued 4–9 days after enrollment because of adverse effects in 7. Reasons for early discontinuation were severe gastrointestinal symptoms and headache (n = 3), gastrointestinal symptoms (n = 2), severe headache (n = 1), and generalized skin rash (n = 1). In 1 patient, capsules were given for only 16 days because of a miscalculation by the pharmacy. One patient left the hospital against medical advice without medication 15 days after enrollment. He was readmitted 6 days later in terminal liver failure. The remaining 2 patients were discharged between 9 and 12 days after enrollment in the trial and did not return for their scheduled appointments (therefore it could not be determined whether they completed the 28-day course). In the control group, 48 patients (92.3%) received the placebo capsules for 28 days (n = 32) or until death (n = 16), 7–26 days after randomization. Of the remaining 4 patients, treatment was discontinued after 10 days of treatment because of severe gastrointestinal symptoms and headaches in 1. This patient died 2 weeks later. The remaining 3 patients were discharged 11–22 days after entering the study and did not return for their scheduled appoint-

ments. The 5 patients from both groups who missed follow-up appointments were later contacted by phone or were seen at a later date in the clinic, and their survival status was ascertained. Survival status was also assessed after discharge from the hospital, over a 6-month follow-up period, for all patients from both groups who survived the index hospitalization. No further deaths occurred over this period.

Laboratory Values

No differences were observed between the 2 treatment groups in terms of laboratory findings on hospital admission (data not shown) and at the time of entry into the trial (Table 2). Laboratory values did not improve between admission and entry into the study in either of the 2 treatment groups (Figure 1). The effects of PTX and placebo on the course of DF, BUN, creatinine, prothrombin time (PT) prolongation, bilirubin, and TNF for all patients of the 2 groups are depicted in Figure 1.

There were no differences between the 2 groups at any time during the treatment period in absolute values or magnitude of changes from baseline for the course of DF. BUN levels increased significantly from admission to randomization in both groups ($P = 0.001$ for PTX and 0.0006 for control group). They continued to increase after randomization in both groups, but in the control group absolute values were higher at week 2 ($P = 0.0001$; Figure 1) and changes from baseline were greater at week 4 ($P = 0.003$). Similarly, serum creatinine values increased from admission to randomization in both groups ($P = 0.04$ for PTX and 0.053 for control). These values continued to increase after randomization in both groups, but in the control group absolute values were higher at week 2 ($P = 0.0001$; Figure 1) and changes from baseline were greater at week 4 ($P = 0.002$). Compared with baseline values, the magnitude of decrease in PT prolongation was greater in the PTX group at week 4 ($P = 0.007$; Figure 1). Absolute values of bilirubin were higher in the control group at week 2 ($P = 0.008$; Figure 1).

Table 2. Mean Values of Laboratory Parameters of the 2 Groups of Patients at Randomization

	PTX-treated (n = 49)	Controls (n = 52)	*P*
Bilirubin (*mg/dL*)	18.5 (5.5)	20.5 (6.7)	0.11
PT prolongation (*s*)	6.0 (2.4)	5.4 (1.9)	0.22
DF	45.9 (12.0)	45.3 (11.1)	0.80
AST (*IU/L*)	161.2 (86.6)	145.1 (71.7)	0.24
ALT (*IU/L*)	51.5 (44.3)	54.1 (31.1)	0.23
Albumin (*g/L*)	26.4 (3.4)	26.5 (4.8)	0.88
WBC (K/mm^3)	16.0 (9.6)	16.9 (12.0)	0.97
Platelets (1000/mm^3)	197.2 (101.6)	195.6 (111)	0.87
BUN (*mg/dL*)	15.4 (12.4)	18.5 (17.4)	0.3
Creatinine (*mg/dL*)	1.2 (0.9)	1.3 (0.8)	0.53
Serum sodium (*mEq/L*)	131.4 (5)	131.4 (4.3)	0.96
Cholesterol (*mg/dL*)	114.5 (48.9)	112.2 (40.7)	0.82
T_3 (*ng/dL*)	0.63 (0.21)	0.61 (0.25)	0.77
TNF (*pg/mL*)	12.0 (5.4)	11.4 (4.8)	0.65
Positive anti-HCV	11%	21%	0.26

NOTE. Values represent mean (SD).
AST, aspartate aminotransferase; ALT, alanine aminotransferase; anti-HCV, antibody to hepatitis C virus.

Plasma specimens for measurement of TNF were available for only 60 patients (29 in the PTX and 31 in the control group; Figure 1). Baseline TNF levels were above the normal range in all patients from both groups. There were no differences between the 2 groups at randomization ($P = 0.65$) or at any time during the treatment period in absolute values or in changes from baseline when all patients (Figure 1) or only the survivors of the 2 groups (Figure 2*A*) were compared. When only the nonsurvivors were compared, however, control patients had higher TNF values than PTX-treated patients at week 1 ($P = 0.04$ for comparison with baseline; Figure 2*B*). Moreover, when comparisons were made within each group, nonsurvivors had higher TNF levels than survivors at week 2 ($P = 0.0001$) and week 4 ($P = 0.05$) in the control but not in the PTX group (Figure 3).

WBC counts increased compared with baseline at weeks 1, 2, and 3 in both groups. However, there were no differences in absolute values or in changes from baseline between the 2 groups at any time during the treatment period. Serum sodium levels decreased significantly from admission to randomization in both groups ($P = 0.005$ for the PTX and 0.04 for the control group). There were no differences in absolute values or in changes from baseline between the 2 groups at any time during the treatment period.

Mortality

Twelve (24.5%) PTX-treated and 24 (46.1%) control patients died ($P = 0.037$; relative risk, 0.59; 95% CI, 0.35–0.97) after a mean of 29 ± 15.7 (range, 5–54) and 33.1 ± 27.3 (range, 7–139) days, respectively ($P = 0.63$; Table 3). Eleven of the deaths in the PTX-treated group occurred during the index hospitalization; 1 patient left the hospital against medical advice, was readmitted 6 days later, and died in the hospital with terminal liver failure and hepatorenal syndrome. Among the 24 deaths in the control group, 22 occurred during the index hospitalization; 2 patients left the hospital because they wanted to die at home. Death occurred 3 and 7 days after discharge in these 2 patients, as confirmed by telephone calls to the families. The probability of survival was significantly higher for patients random-

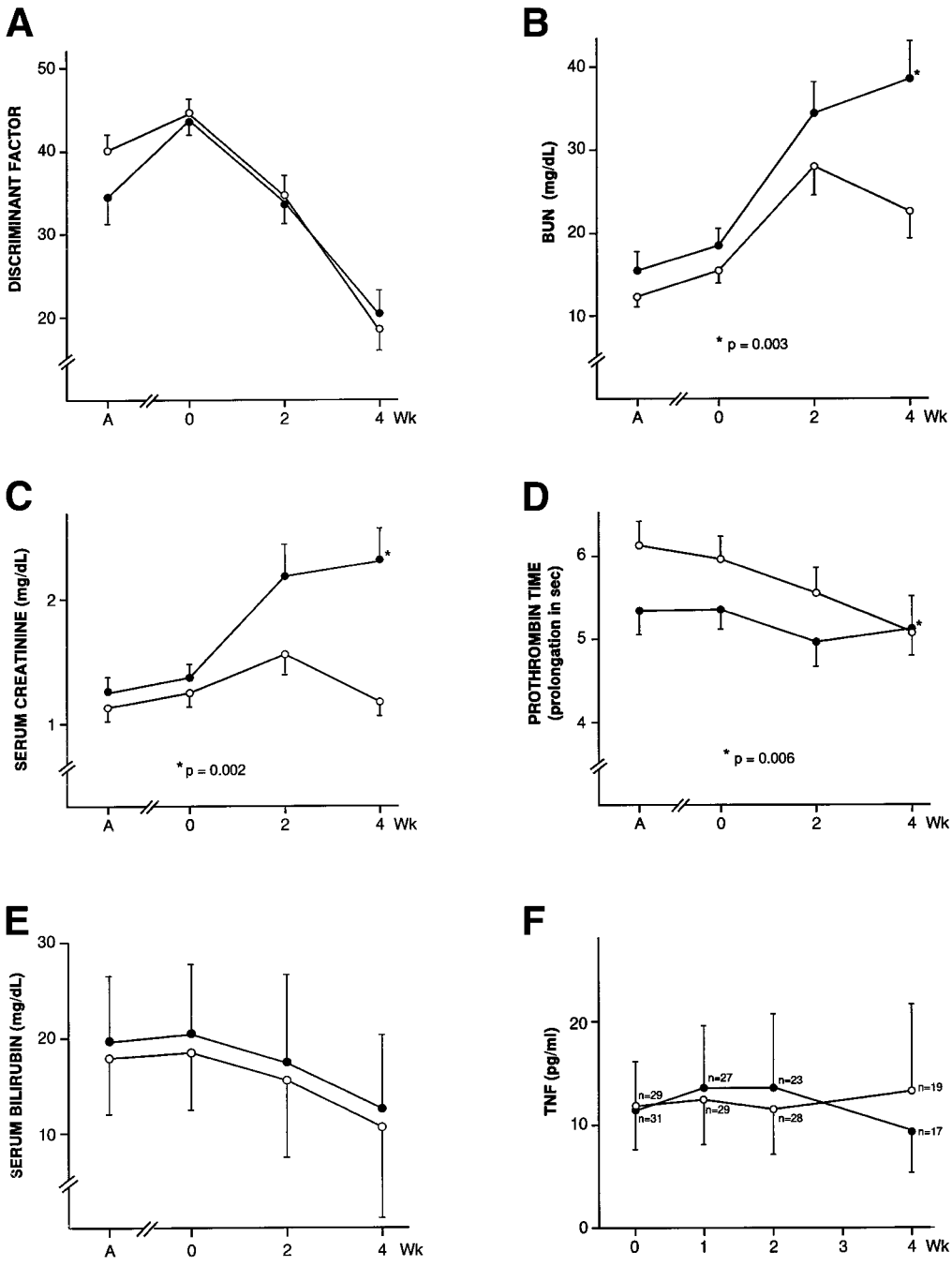

Figure 1. Course of (*A*) DF, (*B*) BUN, (*C*) serum creatinine, (*D*) PT prolongation, (*E*) serum bilirubin, and (*F*) tumor necrosis factor values in all patients in the PTX-treated (○) and control (●) groups. A, admission.

ized to receive PTX (Figure 4). It is clear from looking at the curves that the PTX group was more likely to survive. Of the patients who died, hepatic failure with hepatorenal syndrome had developed in 6 (50%) PTX-treated and 22 (91.7%) control patients ($P = 0.009$; relative risk, 0.29; 95% CI, 0.13–0.65). In the other 6 PTX-treated patients who died, the causes of death were variceal hemorrhage (n = 2), rectal bleeding (n = 1), cryptococcal sepsis (n = 1), posttraumatic epidural hematoma (n = 1), and bronchopneumonia (with normal renal function; n = 1). In the 2 control patients who died without hepatorenal syndrome, the cause of death was variceal hemorrhage in 1 and necrotizing pancreatitis in 1 patient who died after a long hospital course, 139 days after enrollment in the study.

Morbidity

The frequency of symptoms considered to be attributable to drug-induced adverse effects is shown in Table 3. Overall, adverse effects were recorded in 18 PTX-treated and 11 control patients ($P = 0.12$). Transient diarrhea developed in 4 PTX-treated and 2 control

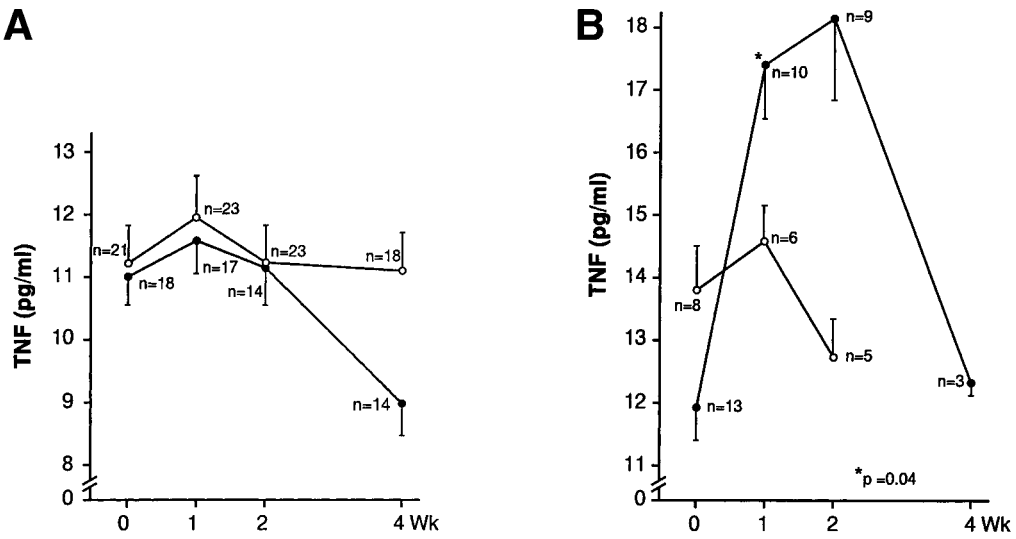

Figure 2. Comparison of TNF values between the PTX-treated (○) and control (●) groups for (*A*) survivors and (*B*) nonsurvivors in each group.

patients and, in most cases, was easily controlled with loperamide. Epigastric discomfort/pain, vomiting, or both developed in 13 PTX-treated and 5 control patients ($P = 0.037$; relative risk, 1.67; 95% CI, 1.14–2.43). Treatment was withdrawn because of presumed adverse effects in 7 PTX patients (severe gastrointestinal symptoms and headache, n = 3; diarrhea, n = 1; epigastric pain, n = 1; severe headache, n = 1; generalized skin rash, n = 1) and in 1 control patient (headache and gastrointestinal symptoms; $P = 0.028$; relative risk, 1.97; 95% CI, 1.37–2.73).

One episode of urinary tract infection, 3 episodes of spontaneous bacterial peritonitis, 1 episode of cryptococcal septicemia, and 1 episode of bronchopneumonia occurred in the PTX group. In the control group, there were 4 episodes of spontaneous bacterial peritonitis, 1 episode of pneumonia, 1 episode of staphylococcal bacteremia, and 1 episode of necrotizing pancreatitis leading to pulmonary and renal failure. Upper gastrointestinal hemorrhage occurred in 6 patients from the PTX group and 10 from the control group ($P = 0.42$). There were 4 additional bleeding episodes in the PTX group (intracranial bleeding, n = 1; severe epistaxis, n = 1; vaginal bleeding, n = 1; rectal bleeding, n = 1) and 3 in the control group (rectal bleeding, n = 2; epistaxis, n = 1).

Renal impairment (serum creatinine level ≥ 2.4 mg/dL) was present in 3 patients from the PTX group and 6 control patients at the time of entry into the study ($P =$

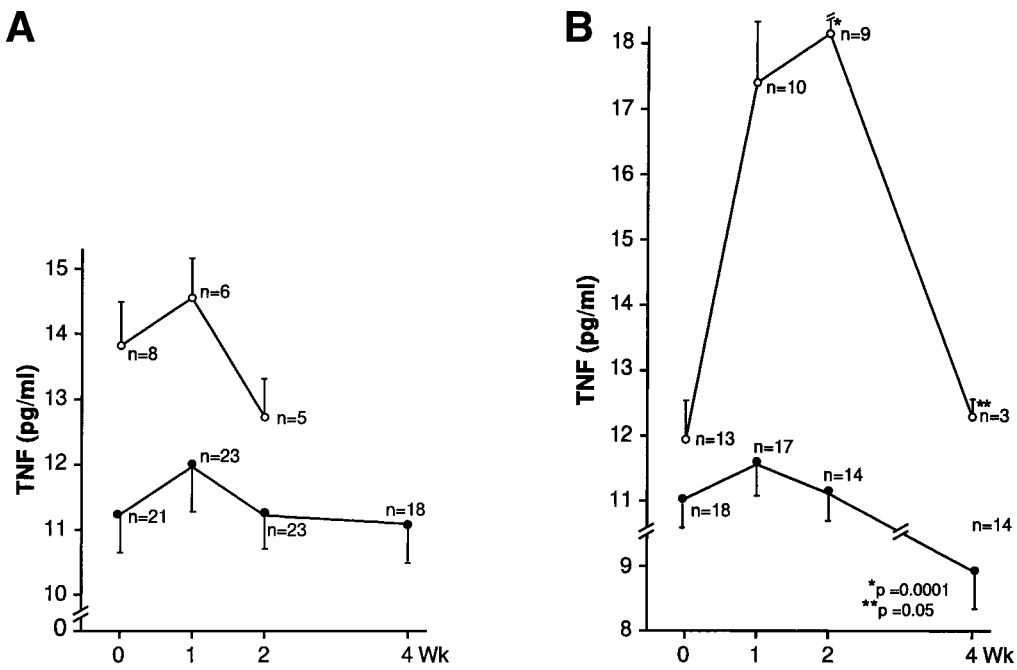

Figure 3. Comparison of TNF values between survivors (●) and nonsurvivors (○) in the (*A*) PTX-treated and (*B*) control groups.

Table 3. Mortality and Morbidity in the 2 Treatment Groups

	PTX-treated (n = 49)	Controls (n = 52)	*P*	RR (95% CI)
Mortality				
Hospital deaths [n (%)]	12 (24.5)	24 (46.1)	0.037	0.59 (0.35–0.97)
Deaths with HRS[a] [n (%)]	6 (50)	22 (91.7)	0.009	0.29 (0.13–0.65)
Days to death after randomization (mean ± SD)	29 ± 15.7	33.1 ± 27.3	0.63	
Morbidity				
Diarrhea [n (%)]	4 (8.2)	2 (3.8)	0.31	
Epigastric pain/vomiting [n (%)]	13 (26.5)	5 (9.6)	0.037	1.67 (1.14–2.43)
GI bleeding [n (%)]	6 (12.2)	8 (15.4)	0.43	
Skin rash [n (%)]	1 (2)	0 (0)	0.49	
Headache [n (%)]	4 (8.2)	2 (3.8)	0.31	
Dyspepsia [n (%)]	4 (8.2)	0 (0)	0.052	
Dizziness [n (%)]	4 (8.2)	1 (1.9)	0.16	
HRS after randomization	4 (8.2)	18 (34.6)	0.0015	0.32 (0.13–0.79)
HE after randomization [n (%)]	9 (18.4)	13 (25.0)	0.48	
Days to HE (mean ± SD)	12.8 (6.8)	12.5 (6.0)	0.91	
Withdrawals due to adverse effects [n (%)]	7 (14)	1 (2)	0.028	1.94 (1.37–2.73)

RR, relative risk; HRS, hepatorenal syndrome; GI, gastrointestinal; HE, hepatic encephalopathy.
[a]Includes both patients who were enrolled with and those who subsequently developed irreversible renal impairment.

0.22). It progressed to irreversible renal failure (hepatorenal syndrome) in 2 PTX-treated and 4 control patients (Table 1). Renal impairment of new onset developed in 5 PTX-treated and 20 control patients ($P = 0.001$; relative risk, 0.35; 95% CI, 0.15–0.77) after a mean of 15.4 ± 9.1 and 15.1 ± 12.8 days ($P = 0.95$) and progressed to hepatorenal syndrome in 4 and 18 patients, respectively ($P = 0.0015$; relative risk, 0.32; 95% CI, 0.13–0.79; Table 3). Renal impairment eventually resolved in all PTX-treated and control patients who survived.

Hepatic encephalopathy was present in 4 PTX-treated and 6 control patients at the time of entry into the study ($P = 0.41$; Table 1). New-onset encephalopathy developed in 9 PTX-treated and 13 control patients ($P = 0.26$; Table 3) after a mean of 12.8 ± 6.8 and 12.5 ± 6.0 days, respectively ($P = 0.91$), and was reversible in 4 and 1 patients, respectively ($P = 0.12$).

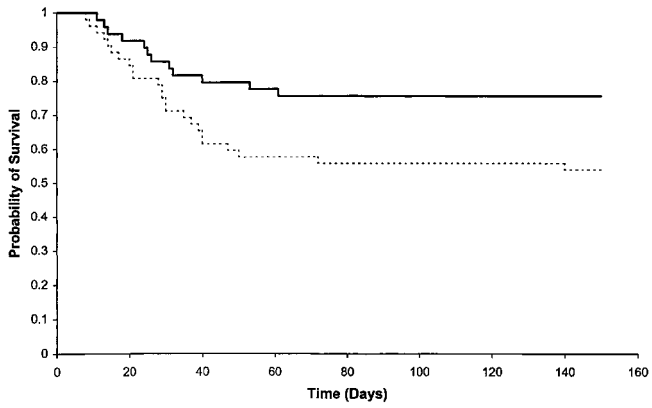

Figure 4. Survival curves for the PTX-treated (*solid line*) and control (*dotted line*) groups.

Comparison Between Survivors and Nonsurvivors

Table 4 shows a comparison of the clinical and laboratory characteristics of the survivors and nonsurvivors at the time of enrollment in the study independent of treatment group. In addition to treatment with PTX, 7 variables (DF, BUN, serum creatinine, PT prolongation, bilirubin, albumin, and age) were associated with survival when analysis included all patients from both groups (Table 4). When univariate analysis was done separately for the 2 treatment groups, 3 variables (BUN, creatinine, and bilirubin) in the PTX group and 8 variables (DF, BUN, serum creatinine, PT prolongation, albumin, age, cholesterol, and T_3) in the control group were significantly associated with survival (Table 5). In the multiple logistic regression analysis model, 2 variables (DF and age) were independently associated with survival in the control group, 1 variable (creatinine) in the PTX group, and 3 variables (creatinine, age, and treatment with PTX) were independently associated with survival in the 2 groups combined (Table 6).

When TNF values in survivors of both groups were compared with those in nonsurvivors, there were no differences at randomization ($P = 0.35$). However, at weeks 1, 2, and 4, TNF levels were higher in nonsurvivors than in survivors of both groups combined (Figure

Table 4. Clinical and Laboratory Characteristics at Randomization of Survivors and Nonsurvivors, Independent of Treatment Group

	Survivors (n = 65)	Nonsurvivors (n = 36)	*P*	95% CI
DF[a]	41.9 (12.2)	48.4 (13.3)	0.002	2.70–12.26
BUN (*mg/dL*)[a]	12.8 (8.9)	24.3 (20.5)	0.001	5.28–17.66
Creatinine (*mg/dL*)[a]	1.04 (0.44)	1.72 (1.18)	0.002	0.31–1.01
PT prolongation (*s*)[a]	5.34 (2.22)	6.36 (1.96)	0.01	0.10–1.94
Bilirubin (*mg/dL*)[a]	18.4 (5.5)	21.6 (6.9)	0.04	0.49–5.53
Albumin (*g/L*)[a]	27.1 (4.1)	25.2 (4.0)	0.03	−3.9 to −0.5
Age (*yr*)[a]	40.3 (8.5)	43.9 (7.9)	0.042	0.17–6.96
Cholesterol (*mg/dL*)[a]	120.2 (47.2)	101.3 (37.4)	0.056	
Positive for anti-HCV[b]	9 (15%)	6 (20%)	0.71	
Males[b]	48 (74%)	27 (75%)	0.98	
Varices[b]	20 (69%)	16 (89%)	0.62	
Ascites[b]	44 (68%)	29 (81%)	0.12	
Hepatic encephalopathy[b]	5 (8%)	5 (14%)	0.38	
Systolic bruit[b]	34 (52%)	25 (69%)	0.08	
T_3 (*ng/dL*)[a]	0.67 (0.23)	0.51 (0.20)	0.06	
ALT (*IU/L*)[a]	52.8 (39.9)	52.9 (35.0)	0.95	
AST (*IU/L*)[a]	152.1 (81.7)	154.8 (76.3)	0.68	
WBC (1000/mm^3)[a]	15.1 (11.3)	18.8 (9.4)	0.13	
Na^+ (*mEq/L*)[a]	131.8 (4.2)	130.8 (5.3)	0.31	
Platelets (1000/mm^3)[a]	195.5 (104.4)	198.7 (110.7)	0.9	
TNF (*pg/mL*)[a]	11.2 (4.7)	12.7 (5.7)	0.37	

[a]Mean (SD).
[b]n (%).

5). A similar course of deterioration of other laboratory parameters in nonsurvivors from both groups was also observed over the treatment period (Figure 5).

Correlations

At randomization, significant correlations were found between TNF and serum creatinine levels (correlation coefficient [*R*] = 0.43, *P* = 0.0006)] and TNF and BUN (*R* = 0.44, *P* = 0.0005). Serum creatinine levels were also correlated at randomization with values of DF, bilirubin, and PT; furthermore, a weak inverse correlation was observed between DF and platelet counts. These correlations were maintained at week 2 and were even stronger at week 4 after randomization for TNF and creatinine (*R* = 0.72, *P* = 0.0001) and for TNF and BUN (*R* = 0.87, *P* = 0.001).

Discussion

Increased production of TNF by monocytes[12] and Kupffer cells[20] has been reported in patients with acute alcoholic hepatitis, and levels of TNF correlated with mortality in some studies.[7] Predisposition for alcohol-induced steatohepatitis appears to be genetically determined through increased TNF gene expression.[21] TNF can cause hepatocyte injury either directly by binding to cytokine receptors or indirectly by attracting and activating neutrophils.[22–24] Administration of human recombinant TNF has been linked with reversible hepatotoxicity.[25] Therefore, agents with anticytokine effects could be of benefit in the treatment of severe acute alcoholic hepatitis. A previous pilot study from our unit showed that PTX prevents renal impairment in patients with severe alcoholic hepatitis; this effect was associated with stabilization of TNF levels.[14] Increased TNF levels have also been described in patients with hepatorenal syndrome.[26] PTX is a suppressor of TNF production.[15,16,18,27] PTX has been used in the treatment of Behçet disease,[28] a disorder also associated with enhanced TNF production.[29]

The present study was initiated to test the hypothesis that PTX, by inhibiting TNF production, might decrease both the occurrence of progressive renal failure and the mortality rate associated with severe alcoholic hepatitis. We decided to compare PTX with placebo and not prednisolone (which has been reported in some studies to have a beneficial effect on patients with acute alcoholic hepatitis[3,30–33]) because our experience with severely decompensated patients (3 trials, 2 published[34,35] and 1 unpublished) failed to show any benefit from the use of glucocorticosteroids. Moreover, the role of glucocorticosteroids in alcoholic hepatitis has been questioned in a recent meta-analysis.[36] Randomization resulted in evenly matched cohorts in the PTX and control groups. The 2 primary endpoints of this study were development of renal impairment and mortality over the 4-week treatment period or during hospitalization. We enrolled only

Table 5. Variables at Randomization Associated With Survival Separately in the 2 Treatment Groups

	PTX-treated (n = 49)	Control (n = 52)	*P*
DF			
All patients	45.9 (12.0)	45.3 (16.1)	0.8
Survivors	44.4 (12.5)	37.9 (12.2)	0.24
Nonsurvivors	51.1 (8.3)	53.0 (16.5)	0.83
P[a]	0.1	0.001	
BUN (*mg/dL*)			
All patients	15.37 (12.40)	18.49 (17.40)	0.3
Survivors	13.22 (10.01)	12.26 (7.18)	0.58
Nonsurvivors	21.83 (16.68)	25.50 (22.44)	0.63
P[a]	0.05	0.001	
Creatinine (*mg/dL*)			
All patients	1.23 (0.86)	1.34 (0.84)	0.53
Survivors	1.04 (0.35)	1.05 (0.54)	0.94
Nonsurvivors	1.82 (1.52)	1.68 (0.99)	0.69
P[a]	0.008	0.004	
PT prolongation (*s*)			
All patients	5.97 (2.39)	5.42 (1.94)	0.22
Survivors	5.83 (2.63)	4.68 (1.29)	0.03
Nonsurvivors	6.42 (1.37)	6.33 (2.22)	0.88
P[a]	0.47	0.001	
Bilirubin (*mg/dL*)			
All patients	18.5 (5.5)	20.5 (6.7)	0.11
Survivors	17.5 (4.9)	19.6 (6.2)	0.12
Nonsurvivors	21.7 (6.4)	21.6 (7.3)	0.88
P[a]	0.02	0.29	
Albumin (*g/L*)			
All patients	26.3 (3.3)	26.5 (4.8)	0.88
Survivors	26.5 (3.6)	27.9 (4.7)	0.10
Nonsurvivors	25.9 (2.5)	24.8 (4.6)	0.37
P[a]	0.59	0.02	
Age (*yr*)			
All patients	42.4 (8.2)	40.8 (8.7)	0.36
Survivors	42.2 (8.6)	37.7 (7.8)	0.037
Nonsurvivors	43.0 (7.1)	44.3 (8.4)	0.62
P[a]	0.78	0.005	
Cholesterol (*mg/dL*)			
All patients	114.5 (48.9)	112.2 (40.7)	0.82
Survivors	116.5 (53.1)	125.2 (38.6)	0.50
Nonsurvivors	108.6 (35.4)	97.5 (38.8)	0.43
P[a]	0.64	0.02	
T_3 (*mg/dL*)			
All patients	0.63 (0.21)	0.61 (0.25)	0.77
Survivors	0.64 (0.22)	0.70 (0.24)	0.48
Nonsurvivors	0.60 (0.22)	0.46 (0.18)	0.17
P[a]	0.66	0.012	

[a]Comparisons between survivors and nonsurvivors within each group.

patients with the more severe forms of acute alcoholic hepatitis, with a Maddrey disciminant factor of ≥32. Inclusion of patients with rapidly improving liver tests was avoided by repeated clinical and laboratory assessment over the first few days of hospitalization (Figure 1). Results were analyzed on an intention-to-treat basis. Statistical analysis regarding the 2 primary endpoints was performed using "group A" and "group B" and was completed before the treatment allocation code was broken.

This trial showed a clinically and statistically significant effect of PTX in severe acute alcoholic hepatitis. Twelve (24%) PTX-treated and 24 (46%) control patients died ($P = 0.037$; relative risk, 0.59; 95% CI, 0.35–0.97; Table 3). This improved survival rate was associated with a dramatic decrease in the development of progressive renal failure. Among the patients who died, hepatorenal syndrome had developed in only 6 (50%) of the 12 PTX-treated patients compared with 22 (91.7%) of the 24 in the control group ($P = 0.009$; relative risk, 0.29; 95% CI, 0.13–0.65; Table 3). The mortality rate of the control group (46.1%) is similar to previously reported figures from studies that included severely ill patients,[32,34,35] particularly patients with DF ≥ 32.[32] The mean period of treatment was >21 days for both groups (Table 1). Therefore, active treatment was probably provided for a sufficient period, although PTX was discontinued because of presumed adverse effects in 7 (14%) patients. Adverse effects were minor, were commonly manifested by gastrointestinal symptoms, and resolved soon after discontinuation of treatment.

TNF levels were correlated with serum creatinine and BUN levels at randomization and even more strongly during the hospital course, suggesting that increased cytokine levels were implicated in the pathogenesis of functional renal failure. Patients with active infection

Table 6. Results of Multiple Logistic Regression Analysis of Variables at Randomization Associated With Survival Within and Between the 2 Groups of Patients

	Mean ± SD	*P*	OR	95% CI
Placebo-treated patients (n = 52)				
DF				
Survivors (n = 28)	39.6 ± 10.5	0.006	1.12	10.2–1.22
Nonsurvivors (n = 24)	48.3 ± 14.5			
Age (*yr*)				
Survivors (n = 28)	37.7 ± 7.8	0.01	1.10	1.01–1.20
Nonsurvivors (n = 24)	44.3 ± 8.4			
PTX-treated patients (n = 49)				
Creatinine (*mg/dL*)				
Survivors (n = 37)	1.04 ± 0.35	0.008	3.46	1.0–11.92
Nonsurvivors (n = 12)	1.82 ± 1.52			
Both groups (n = 101)				
Creatinine (*mg/dL*)				
Survivors (n = 65)	1.04 ± 0.44	0.003	3.25	1.48–7.13
Nonsurvivors (n = 36)	1.72 ± 1.18			
Age (*yr*)				
Survivors (n = 65)	40.3 ± 8.5	0.03	1.06	1.01–1.13
Nonsurvivors (n = 36)	43.9 ± 7.8			
Treatment with PTX				
Survivors [n (%)]	37 (56.9)	0.02	0.33	0.12–0.86
Nonsurvivors [n (%)]	12 (33.3)			

OR, odds ratio.

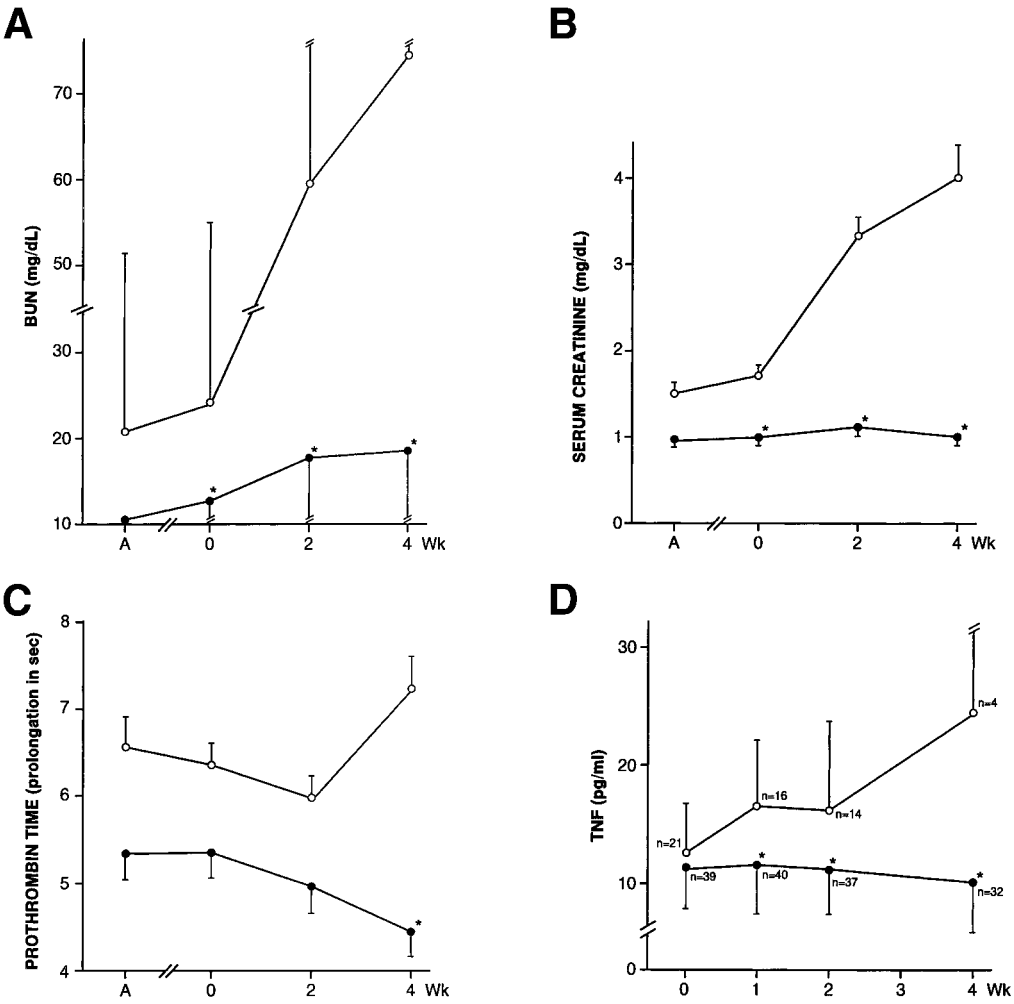

Figure 5. Course of (*A*) BUN, (*B*) serum creatinine, (*C*) PT prolongation, and (*D*) TNF values in survivors (●) and nonsurvivors (○) in both groups combined. $*P < 0.05$ for comparisons between the 2 groups at different time intervals. A, admission.

were not enrolled in the present study. During the study period, there were 12 episodes of infection (7 in the PTX and 5 in the control group). Therefore, it is unlikely that infection (which can induce TNF overproduction through endotoxin release) could play a role in the initial levels of TNF or in possible differences between the 2 groups thereafter. The decrease in mortality rate attributed to treatment with PTX was not associated with an overall appreciable difference in the course of TNF levels between the 2 groups (Figure 1). However, when comparisons were made separately between the subgroups of nonsurvivors of the 2 groups, the increase in TNF levels was less pronounced over the course of treatment in the PTX compared with the control group (Figure 2*B*). Half of the deaths in the PTX group were not accompanied by development of the hepatorenal syndrome. Furthermore, although TNF levels at randomization were not predictive of survival, they increased significantly during the course of the disease in the nonsurvivors of both groups combined (Figure 5). These data clearly show that increasing TNF levels during the hospital course were associated with a higher mortality rate. A trend for a PTX-induced inhibition of TNF overproduction is also suggested; this effect was clearly evident in the subgroup of most severely ill patients (Figure 2*B*). Increased TNF levels have been previously reported to predict decreased short-term[37] and long-term[38] survival in patients with alcoholic hepatitis.

It is possible that PTX prevented renal impairment through mechanisms not related to its effect on TNF synthesis. PTX was introduced as a hemorrheologic agent to treat claudication putatively by decreasing blood viscosity through enhancing deformability of erythrocytes.[39] It has also been used for the treatment and prophylaxis of chemotherapy-induced organ toxicity[40,41] through mechanisms that are not well defined. It is conceivable that the reported beneficial properties of PTX on microcirculation[39] play a role in the prevention of functional renal failure. However, our study was not designed to test for such an effect on microcirculation; therefore, this possible mechanism remains an untested hypothesis.

In conclusion, a substantial decrease in mortality was achieved in this study with the use of PTX in severely ill patients with acute alcoholic hepatitis. This beneficial effect was associated with a decrease of the risk for development of hepatorenal syndrome. Although baseline values of TNF overall were not predictive of survival, increasing levels during the hospital course were clearly associated with a higher mortality rate. Treatment with PTX overall did not lead to an appreciable change in the evolution of TNF levels during the hospital course. Nevertheless, a significant PTX-induced decrease of TNF levels was observed in the subgroup of patients with the more severe form of disease.

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