Original Investigation

Prednisolone With vs Without Pentoxifylline and Survival of Patients With Severe Alcoholic Hepatitis
A Randomized Clinical Trial

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IMPORTANCE Prednisolone or pentoxifylline is recommended for severe alcoholic hepatitis, a life-threatening disease. The benefit of their combination is unknown.

OBJECTIVE To determine whether the addition of pentoxifylline to prednisolone is more effective than prednisolone alone.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, randomized, double-blind clinical trial conducted between December 2007 and March 2010 in 1 Belgian and 23 French hospitals of 270 patients aged 18 to 70 years who were heavy drinkers with severe biopsy-proven alcoholic hepatitis, as indicated by recent onset of jaundice in the prior 3 months and a Maddrey score of at least 32. Duration of follow-up was 6 months. The last included patient completed the study in October 2010. None of the patients were lost to follow-up for the main outcome.

INTERVENTION Patients were randomly assigned to receive either a combination of 40 mg of prednisolone once a day and 400 mg of pentoxifylline 3 times a day (n=133) for 28 days, or 40 mg of prednisolone and matching placebo (n=137) for 28 days.

MAIN OUTCOMES AND MEASURES Six-month survival, with secondary end points of development of hepatorenal syndrome and response to therapy based on the Lille model, which defines treatment nonresponders after 7 days of initiation of treatment.

RESULTS In intention-to-treat analysis, 6-month survival was not different in the pentoxifylline-prednisolone and placebo-prednisolone groups (69.9% [95% CI, 62.1%-77.7%] vs 69.2% [95% CI; 61.4%-76.9%], $P = .91$), corresponding to 40 vs 42 deaths, respectively. In multivariable analysis, only the Lille model and the Model for End-Stage Liver Disease score were independently associated with 6-month survival. At 7 days, response to therapy assessed by the Lille model was not significantly different between the 2 groups (Lille model score, 0.41 [95% CI, 0.36-0.46] vs 0.40 [95% CI, 0.35-0.45], $P = .80$). The probability of being a responder was not different in both groups (62.6% [95% CI, 53.9%-71.3%] vs 61.9% [95% CI, 53.7%-70.3%], $P = .91$). The cumulative incidence of hepatorenal syndrome at 6 months was not significantly different in the pentoxifylline-prednisolone and the placebo-prednisolone groups (8.4% [95% CI, 4.8%-14.8%] vs 15.3% [95% CI, 10.3%-22.7%], $P = .07$).

CONCLUSION AND RELEVANCE In patients with alcoholic hepatitis, 4-week treatment with pentoxifylline and prednisolone, compared with prednisolone alone, did not result in improved 6-month survival. The study may have been underpowered to detect a significant difference in incidence of hepatorenal syndrome, which was less frequent in the group receiving pentoxifylline.

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Treatment of severe forms of alcoholic hepatitis, as defined by a Maddrey discriminant function of at least 32, is extremely challenging because of the poor outcome.[1,2] Compelling data have shown that corticosteroids improve short-term survival compared with placebo,[2-6] while pentoxifylline has been shown to be more effective than placebo in a double-blind, randomized clinical trial.[7] Two other studies have evaluated pentoxifylline in alcoholic hepatitis, in smaller cohorts, and without histological confirmation of alcoholic hepatitis. In a study of a comparison of pentoxifylline with corticosteroids,[8] a benefit in survival in the pentoxifylline group was observed. In that study, although the primary end point was 3-month survival, treatment allocation was revealed after 4 weeks. In a second study,[9] in which a combination of pentoxifylline and corticosteroids was compared with corticosteroids alone, no difference in survival was found; however, this study was not double-blind in design. European and US guidelines for alcoholic liver disease recommend the use of prednisolone or pentoxifylline in patients with severe alcoholic hepatitis.[10,11] Nevertheless, a substantial proportion of patients continue to die at 6 months regardless of first-line therapy.[1,2]

The mechanisms involved in the effects of corticosteroids and pentoxifylline seem to differ under experimental conditions. In vitro, pentoxifylline and corticosteroids are known to be anti-inflammatory molecules.[12,13] On the other hand, in humans, pentoxifylline seems to have a protective effect against the hepatorenal syndrome, but with no significant effect on proinflammatory cytokines or liver tests.[7] Prednisolone improves liver function and inhibits proinflammatory cytokines and polymorphonuclear neutrophil activation.[14] Because of the potential synergistic action of these 2 compounds, a randomized clinical trial comparing their combination with prednisolone alone or pentoxifylline alone may be warranted.

Early improvement in liver function with prednisolone is highly predictive of short-term survival. After 7 days of treatment, physicians can identify responders to medical therapy using the Lille model.[15] The Lille model is highly predictive of death at 6 months, and a score of more than 0.45 predicted 75% of deaths. At present, it is necessary to evaluate the effect of new strategies on the improvement of liver function with specific tools targeting severe alcoholic hepatitis.

To improve the management of patients with severe alcoholic hepatitis, therapeutic strategies must be developed that address the main mechanisms involved in the death of patients, and early improvement in liver injury is an important goal in this regard. The work presented herein is original because it assumes that the assessment of the efficacy of a new therapeutic strategy must include an evaluation of its early effect on liver injury. Based on this approach, the goal of this randomized clinical trial was to evaluate the efficacy of a combination of prednisolone and pentoxifylline compared with prednisolone alone in patients with severe alcoholic hepatitis.

Methods

Patient Selection

This multicenter, randomized, double-blind placebo-controlled clinical trial was performed in 1 Belgian hospital and 23 French hospitals between December 2007 and September 2010 (last patient randomized in March 2010). Patients were eligible for the study if they were aged 18 to 70 years and were heavy drinkers (>40 g/d of alcohol for women and >50 g/d of alcohol for men) with severe biopsy-proven alcoholic hepatitis, as indicated by the recent onset of jaundice within the past 3 months and a Maddrey score of at least 32. The definition for alcoholic hepatitis described by Lucey et al[2] was used. Alcohol intake was estimated based on a discussion between the physician and the patient. Transjugular liver biopsy was performed in all patients according to routine French and Belgian diagnostic practices for diagnosis and histological confirmation of alcoholic hepatitis was based on the following findings: ballooned hepatocytes, Mallory bodies, and infiltration of polymorphonuclear neutrophils.

Exclusion criteria included the presence of hepatitis B surface antigen, hepatitis C virus or human immunodeficiency virus antibodies, pregnancy, breastfeeding, concomitant or previous history of hepatocellular carcinoma, evolutive neoplasia likely to threaten 1-year outcome, uncontrolled bacterial infection within 7 days, concomitant or previous history of fungal, viral, or parasitic infection, severe associated disease (cardiac failure, severe pulmonary disease, neoplastic disease, severe psychiatric disorders), portal thrombosis, acute pancreatitis, type 1 hepatorenal syndrome, and serum creatinine at randomization of more than 2.5 mg/dL (>221 µmol/L).

At admission, systematic screening for infection included chest radiograph, blood and urine cultures, and culture of ascites fluid. Before randomization, antibiotics were administered to patients with sepsis in relation to the site of infection (ie, spontaneous bacterial peritonitis, urinary tract infection, or bacteremia, excluding other types of infection). Antibiotic treatment was considered to be effective based on international and French guidelines, and patients could be included in the study once the infection was under control.[16] In the case of gastrointestinal bleeding, patients were excluded from the study in the presence of shock, transfusion of more than 3 units of blood, or if the Maddrey function was less than 32 at admission and increased to 32 or more due to the severity of bleeding. Patients who had been treated with corticosteroids, immunosuppressants, budesonide, pentoxifylline, or thalidomide in the year before the study were also excluded.

Written informed consent was obtained from all participants. Approval was given by a relative in the case of severe encephalopathy. Encephalopathy was measured by a routine clinical examination for confusion and asterixis. The study was approved by the institutional review board or ethics committee and adhered to Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws. The study was registered under European policy number EudraCT 2006-006944-78.

Study Design

Eligible patients were randomly assigned at a 1:1 ratio to receive either 40 mg of prednisolone once a day and 400 mg of pentoxifylline 3 times a day or 40 mg of prednisolone and a matching placebo 3 times a day. All patients were scheduled to receive the allocated treatment for 28 days, regardless of treatment response evaluated by the Lille model on day 7. Ran-

domization was centralized and patients were assigned in blocks of 6 by a computerized procedure to achieve a balance between the 2 groups, with stratification according to center.

In the case of drug-related adverse effects, treatment was interrupted or reduced by up to 2 doses, as decided by a physician. Adherence was assessed by pill count and patients' diary entries.

The following variables were assessed at baseline: age, sex, alcohol intake, presence of encephalopathy, ascites, serum bilirubin level, prothrombin time, international normalized ratio (INR), serum albumin, aspartate aminotransferase, sodium, creatinine and urea, blood cell count, and C-reactive protein. Clinical follow-up and laboratory tests were performed weekly from day 0 to day 28, then monthly for the next 5 months.

Maddrey discriminant function[4,17] and the Model for End-Stage Liver Disease (MELD) score[18,19] were calculated at baseline, and the Lille model[15] was calculated 7 days after treatment had begun. The formulas for the scores were as follows: Maddrey discriminant function = {4.6 × [patient prothrombin time −control prothrombin time (in seconds)] + serum bilirubin (in mg/dL)}; MELD score = [9.57 × $\log_e$ creatinine (in mg/dL) + 3.78 × $\log_e$ bilirubin (in mg/dL) + 11.20 × $\log_e$ INR + 6.43]; Lille score = {Exp(−R)/[1+Exp(−R)]}, where R = [3.19 −0.101 × age (in years) + 0.147 × albumin (in g/L) + 0.0165 × evolution (in bilirubin, µmol/L) −0.206 × renal insufficiency −0.0065 × bilirubin (in µmol/L) −0.0096 × prothrombin time (in seconds)].

Study Outcome Measures

The primary outcome was survival at 6 months after the initiation of allocated treatment. Secondary outcomes included response to therapy and the incidence of the hepatorenal syndrome. Response to therapy was based on the results of the Lille model after 7 days of allocated treatment. Hepatorenal syndrome was defined according to recommended international criteria.[20]

Statistical Analysis

Assumption of normality was assessed by the Shapiro-Wilk test. Comparisons were made with the Wilcoxon or *t* test for continuous variables according to the normality of distribution, and the χ^2 test or Fisher exact test for qualitative variables. All results of continuous variables were expressed as means and 95% CIs for continuous variables and as the frequencies, percentages, and 95% CIs for categorical variables. The primary results presented for all analyses were unadjusted. Follow-up time was defined as the period from the first day of treatment to 180 days after initiation of the assigned treatment. Data for patients without events of interest were censored at the date of the last follow-up visit. The status (alive or dead) of patients lost to follow-up was assessed by telephoning a family member, general practitioner, or both, or by contacting the death registry at the patient's birthplace.

The cumulative incidence of death was estimated by the Kaplan-Meier method in each treatment group. The statistical significance of hazard ratio (HR) for treatment allocation was tested using the Cox proportional hazards regression model. The potential heterogeneity in the treatment effect according to different study centers was tested by adding an interaction center × treatment in the Cox proportional hazards regression model. Potential risk factors were first tested by the Cox proportional hazards regression model in bivariable analysis. The linearity assumption for quantitative variables was checked by the martingale residual. When this assumption was not verified, the variable was dichotomized according to the median value. The proportional hazards assumption was checked by Schoenfeld residuals and the test proposed by Therneau and Grambsch.[21] Prognostic variables with a significance level of less than .10 in bivariable analyses were included in a multivariable Cox proportional hazards regression model. The variables included in the Cox proportional hazards regression model analyses were treatment allocation, male sex, age, prothrombin time, bilirubin at day 0, Maddrey score at day 0, MELD score at day 0, serum creatinine at day 0, serum sodium, albumin at day 0, aspartate aminotransferase at day 0, white blood cell count at day 0, Lille model, presence of ascites, and presence of encephalopathy. Factors included in a composite score were not included in multivariable analysis to avoid bias related to the effect of colinearity. A complete case analysis was performed because missing data did not exceed 10%.[22]

The hepatorenal syndrome was defined as such if it occurred within 180 days. Death without hepatorenal syndrome was considered to be a competing event. The cumulative incidence of the hepatorenal syndrome was calculated by using the Kalbfleisch and Prentice method, and was compared using the Gray test.[23]

All statistical analyses were performed in the intention-to-treat population. The sample size was calculated based on the following hypotheses. With an expected survival rate of 64% at 6 months in the placebo-prednisolone group,[15] an improvement in survival of 78% in the pentoxifylline-prednisolone group,[7] a type I error rate of 5%, and a power of 80%, at least 242 patients were required for the study using a 2-sided test. All statistical analyses were performed by using NCSS 2007 (version 07) and SAS version 9.2 (SAS Institute). The significance level was set at .05 with a 2-sided test.

Results

Patients

A total of 278 patients were randomized between December 2007 and March 2010. An independent committee including 2 external experts not involved in the study recommended that 7 patients who did not meet criteria for the definition of severe alcoholic hepatitis be excluded from the statistical analysis (ie, absence of jaundice despite histological lesions suggesting alcoholic hepatitis [n = 4], absence of histological confirmation of the diagnosis of alcoholic hepatitis [n = 2], and Maddrey discriminant function <32 [n = 1]). One patient was also excluded from analysis because of withdrawal of informed consent after randomization. Thus, a total of 270 randomized patients were analyzed, 133 in the pentoxifylline-prednisolone group and 137 in the placebo-prednisolone group

Table 1. Baseline Characteristics of Patients Included in Intention-to-Treat Analysis

Characteristics	Pentoxifylline-Prednisolone Group (n = 133)	Missing Data, No. (%)	Placebo-Prednisolone Group (n = 137)	Missing Data, No. (%)
Age, mean (95% CI), y	51.5 (49.9-53.1)	0	51.8 (50.4-53.2)	0
Male sex, No./Total No. (%) [95% CI]	83/133 (62.4) [54.1-70.8]	0	80/137 (58.4) [50.0-56.8]	0
Ascites, No./Total No. (%) [95% CI]	88/131 (67.2) [59.0-75.3]	2 (1.5)	104/136 (76.5) [69.2-83.7]	1 (0.7)
Encephalopathy, No./Total No. (%) [95% CI]	9/132 (6.8) [2.5-11.2]	1 (0.7)	18/135 (13.3) [7.5-19.1]	2 (1.5)
Leukocytes, mean (95% CI), /μL	11 562 (10 375-12 749)	2 (1.5)	12 169 (11 110-13 228)	1 (0.7)
Neutrophil count, mean (95% CI), /μL[a]	9521 (7830-11 212)	31 (23.3)	8147 (7136-9157)	39 (29.3)
Prothrombin time, mean (95% CI), s	20.5 (19.8-21.2)	0	21.2 (20.1-22.3)	1 (0.7)
INR, mean (95% CI)	1.9 (1.8-2.0)	0	2.0 (1.9-2.1)	1 (0.7)
Bilirubin, mean (95% CI), mg/dL	15.3 (13.4-17.2)	0	16.1 (14.3-17.9)	0
Urea, mean (95% CI), mg/dL	12.0 (10.6-13.2)	5 (3.8)	12.9 (11.2-14.8)	3 (2.2)
Serum creatinine, mean (95% CI), mg/dL	0.81 (0.75-0.87)	0	0.85 (0.78-0.91)	0
Serum sodium, mean (95% CI), mEq/L	133.3 (132.4-134.1)	2 (1.5)	132.7 (131.9-133.4)	2 (1.5)
Albumin, mean (95% CI), g/dL	2.55 (2.45-2.65)	0	2.52 (2.42-2.62)	0
AST, mean (95% CI), U/L	118 (108-128)	3 (2.3)	120 (111-129)	4 (2.9)
Maddrey function, mean (95% CI)	54.4 (50.8-58.1)	0	58.6 (53.1-64.2)	1 (0.7)
MELD score, mean (95% CI)	23.2 (22.4-24.0)	0	23.9 (23.0-24.7)	1 (0.7)
Biopsy-proven cirrhosis, No./Total No. (%) [95% CI]	122/133 (91.7) [87.0-96.5]	0	129/137 (94.2) [90.2-98.1]	0

Abbreviations: AST, aspartate aminotransferase; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease.

SI conversion factors: To convert albumin to g/L, multiply by 10; to convert bilirubin to μmol/L, multiply by 17.104; to convert creatinine to μmol/L, multiply by 88.4; to convert urea nitrogen to mmol/L, multiply by 0.357.

[a] Twenty-six percent of the data for the neutrophil count was missing (23.3% and 29.3%, respectively), a variable that represents a percentage of the leukocytes and therefore cannot be dissociated from leukocytes. Only leukocytes were considered in the statistical plan.

(see eFigure in the Supplement). Baseline characteristics of the 270 patients are shown in **Table 1**. The time between the date of screening and the start of treatment was 4.5 days (95% CI, 2.2-6.7 days). Overall, 25.8% of patients relapsed regarding alcohol use within 6 months of follow-up and 74.2% did not relapse. However, the percentage of alcohol relapse was not significantly different between the pentoxifylline-prednisolone group and the placebo-prednisolone group (30.7% vs 21.3%, respectively; $P = .11$).

Efficacy

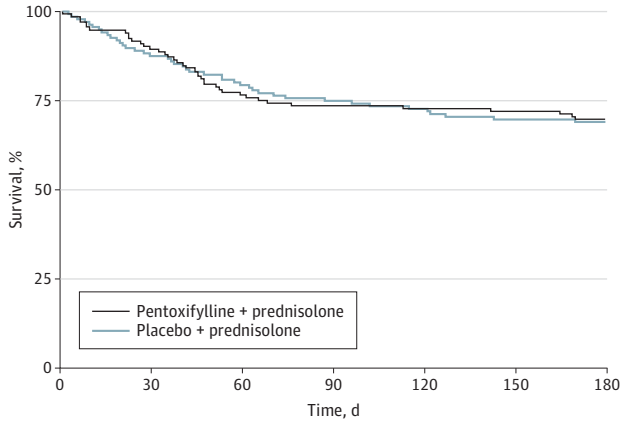
Overall 6-Month Survival

Assessment of mortality was 100% at 6 months. Eighty-two deaths occurred in the 2 groups during the 6-month follow-up, due to complications from liver failure in 67 cases (81.7%) and other causes including gastrointestinal bleeding in 15 cases (18.3%). There was no significant difference in causes of death between the 2 groups (see eTable in the Supplement). There was no difference in 6-month survival between the 2 groups according to intention-to-treat analysis and with a bivariable Cox proportional hazards regression model (69.9% [95% CI, 62.1%-77.7%] in the pentoxifylline-prednisolone group [corresponding to 40 deaths] vs 69.2% [95% CI, 61.4%-76.9%] in the placebo-prednisolone group [corresponding to 42 deaths]; $P = .91$) (**Figure 1**). There was no significant difference in treatment effect by center as assessed by the center × treatment interaction test ($P = .59$). One patient in the placebo-prednisolone group received liver transplantation for nonresponse to medical treatment after 31 days (Lille score of 0.982).[24] Data for this patient were censored at transplantation. Mean time until death was 49.7 (95% CI, 35.6-63.7) days and 51.4 (95% CI, 38.2-64.7) days in each group, respectively ($P = .85$).

Ten variables were significantly associated with 6-month survival in bivariable Cox proportional hazards regression analysis (**Table 2**). Exploratory multivariable analysis using a Cox proportional hazards regression model identified the MELD and Lille scores as independent prognostic variables of overall 6-month survival (Table 2). After adjustment for treatment allocation in the multivariable Cox proportional hazards regression model, the Lille score (HR, 12.55; 95% CI, 5.19-30.34) and MELD score (HR, 1.11; 95% CI, 1.03-1.19) remained independent factors.

Per-protocol analysis was performed after exclusion of 9 patients (6 patients who did not meet inclusion criteria [ie, aged >70 years {n = 2}, treatment with corticosteroids in the previous year {n = 1}, type 1 hepatorenal syndrome {n = 1}, and jaundice evolving for >3 months {n = 2}]; nonblinded administration of pentoxifylline by the general practitioner during the treatment period [n = 1]; treatment with anticoagulants making it impossible to calculate the Maddrey discriminant function [n = 1]; or complete lack of adherence [n = 1]). Per-protocol analysis did not show any significant difference in 6-month survival between the pentoxifylline-prednisolone and

Figure 1. Probability of 6-Month Survival According to Treatment Allocation



No. at risk							
Pentoxifylline + prednisolone	133	119	102	98	96	96	93
Placebo+ prednisolone	137	120	108	102	99	95	94

There was no difference in 6-month survival between the pentoxifylline+prednisolone and placebo+prednisolone groups according to intention-to-treat analysis (69.9% [95% CI, 62.1%-77.7%] vs 69.2% [95% CI, 61.4%-76.9%], $P = .91$). Comparison of hazard ratio using the Cox proportional hazards regression model was 0.98 (95% CI, 0.63-1.51; $P = .91$). The combination therapy lasted 28 days.

Table 2. Factors Predicting 6-Month Survival in Bivariable and Multivariable Analyses[a]

	Bivariable Analysis		Multivariable Analysis	
Covariate[b]	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Treatment allocation	0.98 (0.63-1.51)	.91		
Male sex	0.94 (0.60-1.46)	.76		
Age, y[c]	1.03 (1.00-1.05)	.03		
Prothrombin time at day 0, s[c]	1.06 (1.03-1.08)	<.001		
Bilirubin at day 0, mg/dL[c]	1.05 (1.03-1.07)	<.001		
Maddrey score at day 0	1.01 (1.01-1.02)	<.001	1.00 (0.99-1.01)	.81
MELD score at day 0	1.19 (1.14-1.24)	<.001	1.10 (1.03-1.18)	<.001
Serum creatinine at day 0, mg/dL[c]	4.95 (3.17-7.72)	<.001		
Serum sodium, mEq/L	0.93 (0.89-0.98)	<.001	0.98 (0.93-1.03)	.42
Albumin at day 0 > 2.5 g/dL[c,d]	0.63 (0.41-0.99)	.04		
AST at day 0 > 107 U/L[d]	1.18 (0.75-1.84)	.47		
White blood cells at day 0, /μL	1.03 (1.00-1.06)	.07	0.99 (0.95-1.03)	.72
Lille model	24.45 (10.94-54.64)	<.001	12.86 (5.31-31.14)	<.001
Presence of ascites, %	1.38 (0.83-2.31)	.22		
Presence of encephalopathy, %	2.23 (1.23-4.04)	<.001	1.80 (0.89-3.61)	.10

Abbreviations: AST, aspartate aminotransferase; MELD, model for end-stage liver disease.

SI conversion factors: To convert albumin to g/L, multiply by 10; to convert bilirubin to μmol/L, multiply by 17.104; to convert serum creatinine to μmol/L, multiply by 88.4.

[a] Bivariable analysis used Cox proportional hazards regression model. Multivariable analysis used Cox proportional hazards regression model, with 19 missing data (13 Lille model [among which not calculable for 7 patients who died before day 7] and 6 other missing variables). Multivariable analysis was performed on 251 of 270 patients (92.9%) using complete case analysis.

[b] All available variables included intention-to-treat analysis. See the Methods section for definitions of the Lille model, the Maddrey score, and the MELD score.

[c] To avoid bias related to the effect of colinearity, when composite scores (Lille, Maddrey, and MELD) were tested, factors included in them were not included in multivariable analysis comprising these scores.

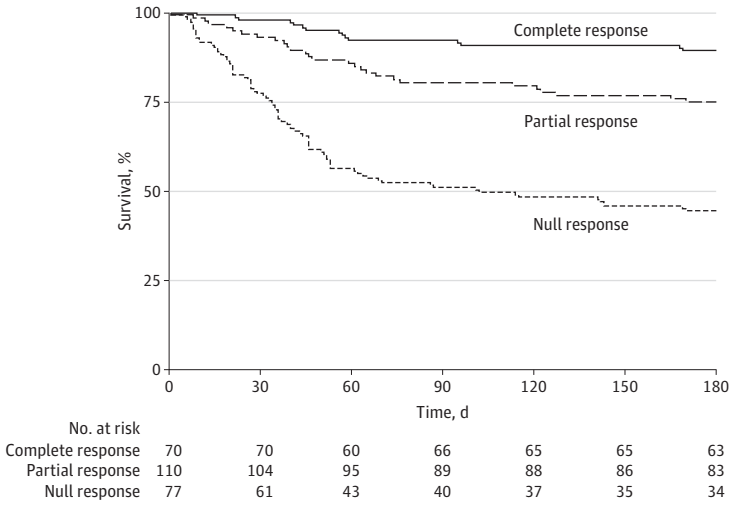
[d] Variables were dichotomized according to median values (see Statistical Methods).

placebo-prednisolone groups (72.4% [95% CI, 64.7%-80.2%] vs 70.0% [95% CI, 62.2%-77.8%], $P = .69$). In a subgroup analysis restricted to responders to treatment (ie, those patients with a Lille model score of <0.45), it was observed that alcohol relapse within 6-month follow-up had no effect on short-term survival (6-month survival of responders with alcohol relapse was not significantly different than that of responders who remained abstinent [88.9% vs 81.7%, respectively; $P = .23$]).

Response to Therapy According to the Lille Model

Patients classified as responders (ie, Lille score of <0.45) had better 6-month survival than nonresponders (ie, Lille score of ≥0.45) in both groups (85.0% [95% CI, 79.5%-90.5%] vs 46.0% [95% CI, 36.0%-55.9%], $P < .001$). There was no significant difference in the cumulative incidence of infection at 6 months in the pentoxifylline-prednisolone group compared with the placebo-prednisolone group (33.1% [95% CI, 25.2%-41.1%] vs 32.2% [95% CI, 24.5%-40.2%], $P = .88$). In the overall popula-

Figure 2. Probability of 6-Month Survival According to the Pattern of Response to Treatment in the Pentoxifylline+Prednisolone and Placebo+Prednisolone Groups



No. at risk							
Complete response	70	70	60	66	65	65	63
Partial response	110	104	95	89	88	86	83
Null response	77	61	43	40	37	35	34

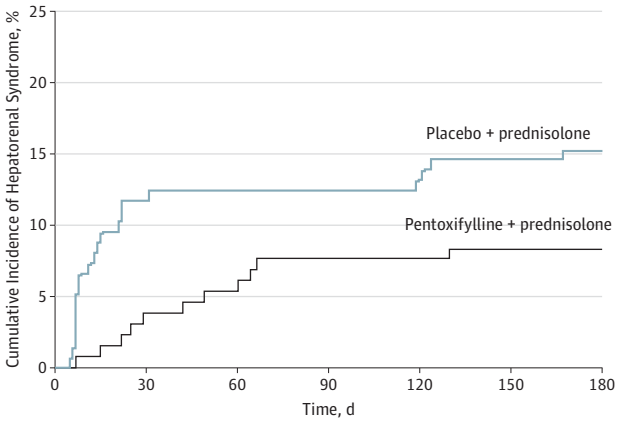
Pattern of response was based on previously proposed cutoffs that classified patients as complete (Lille score of ≤0.16), partial (0.16<Lille score<0.56), or null (Lille score of ≥0.56) responders.[25] In all patients, survival gradually decreased from 90% (95% CI, 83%-97%) in complete responders to 75.4% (95% CI, 67.4%-83.5%) in partial responders and 44.9% (95% CI, 33.7%-56.1%) in null responders (P < .001). Six-month survival in the 3 patterns of response did not significantly differ between the pentoxifylline-prednisolone and placebo-prednisolone groups (89.3% [95% CI, 77.8%-100%] vs 90.5% [95% CI, 81.6%-99.3%], P = .86 for complete responders; 70.0% [95% CI, 58.4%-81.6%] vs 82.0% [95% CI, 71.3%-92.6%], P = .15 for partial responders; and 54.3% [95% CI, 37.8%-70.8%] vs 36.9% [95% CI, 22.1%-51.6%], P = .21 for null responders). The combination therapy lasted 28 days.

tion, treatment nonresponders (ie, Lille score of ≥0.45) had a higher cumulative incidence of infection at 6 months than responders (48.9% [95% CI, 38.4%-58.3%] vs 22.5% [95% CI, 16.4%-29.2%], P < .001). This difference was observed in the 2 treatment groups as well (pentoxifylline-prednisolone group: 54.3% [95% CI, 38.7%-67.6%] vs 20.8% [95% CI, 12.5%-30.5%], P < .001; and placebo-prednisolone group: 43.7% [95% CI, 29.6%-56.9%] vs 24.1% [95% CI, 15.5%-33.7%], P = .02). Treatment response was no different between the pentoxifylline-prednisolone and placebo-prednisolone groups in terms of Lille score or the probability of being a responder (0.41 [95% CI, 0.36-0.46] vs 0.40 [95% CI, 0.35-0.45], P = .80; and 62.6% [95% CI, 53.9%-71.3%] vs 61.9% [95% CI, 53.7%-70.3%], P = .91, respectively). Based on previously proposed cutoffs that classified patients as complete (Lille score of ≤0.16), partial (0.16<Lille score<0.56), or null (Lille score of ≥0.56) responders,[25] the response patterns of the pentoxifylline-prednisolone and placebo-prednisolone groups still did not significantly differ (22.8%, 48.8%, and 28.5% vs 31.3%, 37.3%, and 31.3%, respectively; P = .14). In all patients, survival gradually decreased from 90% (95% CI, 83%-97%) in complete responders to 75.4% (95% CI, 67.4%-83.5%) in partial responders and 44.9% (95% CI, 33.7%-56.1%) in null responders (P < .001) (**Figure 2**). Six-month survival in these 3 patterns of response did not significantly differ between the pentoxifylline-prednisolone and placebo-prednisolone groups (89.3% [95% CI, 77.8%-100%] vs 90.5% [95% CI, 81.6%-99.3%], P = .86; 70.0% [95% CI, 58.4%-81.6%] vs 82.0% [95% CI, 71.3%-92.6%], P = .15; and 54.3% [95% CI, 37.8%-70.8%] vs 36.9% [95% CI, 22.1%-51.6%], P = .21).

Hepatorenal Syndrome

Two patients were excluded from the analysis for occurrence of hepatorenal syndrome. During the 6-month follow-up, in relation to the end point of renal failure, a significantly lower cumulative risk of hepatorenal syndrome at 1 month (end of the treatment period) was observed in patients treated with a combination of pentoxifylline and prednisolone (3.1% [95% CI, 1.2%-8.0%] vs 11.7% [95% CI, 7.4%-18.5%], P = .007), although this difference was no longer significant at 6 months (8.4% [95% CI, 4.8%-14.8%] vs 15.3% [95% CI, 10.3%-22.7%], corresponding to 11 vs 21 occurrences, respectively; P = .07) (**Figure 3**). Baseline disease severity was not significantly different between patients who developed hepatorenal syndrome in the pentoxifylline-prednisolone and placebo-prednisolone groups (serum creatinine: 0.90 [95% CI, 0.72-1.08] vs 1.03 [95% CI, 0.81-1.24] mg/dL, respectively; P = .44; prothrombin time: 22.5 [95% CI, 19.3-25.8] vs 23.5 [95% CI, 21.2-25.8] seconds, respectively; P = .61; serum bilirubin: 20.9 [95% CI, 13.7-28.1] vs 21.6 [95% CI, 16.1-27.1] mg/dL, respectively; P = .88; Maddrey's discriminant function: 67.0 [95% CI, 53.8-80.3] vs 74.4 [95% CI, 62.3-86.6], respectively; P = .42; and the MELD score: 25.9 [95% CI, 23-28.7] vs 27.7 [95% CI, 25.5-29.9], respectively; P = .29). There was no significant difference in 6-month survival between these 2 groups (36.4% [95% CI, 7.9%-64.8%] vs 21.0% [95% CI, 2.9%-39.0%], P = .27). A total of 26 of 32 patients (81.3%) who developed hepatorenal syndrome were nonresponders according to the Lille model; therefore, these patients had a higher Lille score (0.78 [95% CI, 0.71-0.85] vs 0.22 [95% CI, 0.06-0.37], P < .001). There were no significant differences in the Lille model for patients who devel-

Figure 3. Cumulative Incidence of Hepatorenal Syndrome in the Pentoxifylline+Prednisolone and Placebo+Prednisolone Groups Estimated by the Kalbfleisch and Prentice Method



At the 6-month follow-up, the difference in cumulative risk of hepatorenal syndrome was not observed in patients treated with a combination of pentoxifylline and prednisolone (8.4% [95% CI, 4.8%-14.8%] in the pentoxifylline+prednisolone group vs 15.3% [95% CI, 10.3%-22.7%] in the placebo+prednisolone group, corresponding with 11 vs 21 occurrences, respectively; $P = .07$). Comparison of cumulative incidence was performed by using the Gray test. The combination therapy lasted 28 days.

oped hepatorenal syndrome between the pentoxifylline-prednisolone and placebo-prednisolone groups (0.62 [95% CI, 0.41-0.82] vs 0.71 [95% CI, 0.59-0.83], $P = .37$). Patients who developed hepatorenal syndrome had more severe liver disease at day 1 of therapy than those who did not develop hepatorenal syndrome (serum creatinine levels: 0.99 [95% CI, 0.83-1.14] vs 0.79 [95% CI, 0.76-0.84] mg/dL, $P = .005$; prothrombin time: 23.2 [95% CI, 21.4-24.9] vs 20.5 [95% CI, 19.8-21.2] seconds, $P = .01$; INR: 2.2 [95% CI, 2.0-2.5] vs 1.9 [95% CI, 1.8-2.0], $P = .002$; serum sodium: 129.9 [95% CI, 127.6-132.2] vs 133.4 [95% CI, 132.8-133.9] mEq/L, $P < .001$; serum bilirubin: 21.3 [95% CI, 17.2-25.5] vs 14.9 [95% CI, 13.6-16.2] mg/dL, $P = .001$; Maddrey score: 71.9 [95% CI, 63.1-80.7] vs 54.4 [95% CI, 50.8-57.9], $P < .001$; and MELD score: 27.1 [95% CI, 25.4-28.8] vs 23.0 [95% CI, 22.4-23.6], $P < .001$).

Safety

No deaths were considered to be attributable to treatment allocation by clinicians. Temporary (13 vs 13 cases) and definite (3 vs 6 cases) treatment withdrawal was not significantly more frequent in the pentoxifylline-prednisolone or placebo-prednisolone groups, respectively. In the pentoxifylline-prednisolone group, definite withdrawal was related to infection (2 cases) and the patient's decision (1 case). Definite treatment withdrawal was related to infection (4 cases) and neurological disorders (2 cases) in the placebo-prednisolone group. In the pentoxifylline-prednisolone group, temporary withdrawal was related to infection (8 cases), gastrointestinal bleeding (2 cases), pruritus (1 case), and other causes (2 cases). Temporary treatment withdrawal was related to infection in 13 cases in the placebo-prednisolone group. Adherence was considered to be inadequate in 18 and 11 cases in the pentoxifylline-prednisolone and placebo-prednisolone groups, respectively. Pruritus, diarrhea, and nausea were reported in 6, 8, and 10 cases, respectively, in the pentoxifylline-prednisolone group, and in 3, 4, and 5 cases, respectively, in the placebo-prednisolone group. These adverse events led to a decrease in treatment dose in 3 patients in the pentoxifylline-prednisolone group because of pruritus, diarrhea, and nausea. One patient randomized in the placebo-prednisolone group took only 2 pills per day of the experimental treatment because the patient misunderstood the directions from the investigator.

Discussion

This double-blind, randomized clinical trial in 270 patients with biopsy-proven, severe alcoholic hepatitis showed that the addition of pentoxifylline with prednisolone did not improve survival compared with prednisolone alone. As assessed using the Lille model, the 2 groups demonstrated the same magnitude of response to treatment. Because of the lack of difference in survival, our study does not support the use of a combination of pentoxifylline and prednisolone for severe alcoholic hepatitis.

The pathways involved in severe alcoholic hepatitis appear to be more complex than originally believed.[1] The rationale behind our study was to combine the 2 molecules that target different mechanisms that cause death in severe alcoholic hepatitis. The main protective pathway of pentoxifylline is the prevention of the hepatorenal syndrome,[7] although prednisolone induces early improvement in liver function, the main factor contributing to short-term survival.[14,26] Our data do not support this strategy. However, these results cannot be considered as evidence that pentoxifylline is not effective for severe alcoholic hepatitis. Indeed, the study supporting the use of pentoxifylline compared this drug with a placebo.[7] Our study design did not include a study group receiving pentoxifylline treatment alone. Future molecules that target other important pathways such as those involved in liver regeneration should be explored.

A recent randomized study in patients with liver disease classified as Child-Pugh C reported that pentoxifylline reduced the risk of renal failure with no significant difference in 6-month survival between the pentoxifylline and placebo groups.[27] Sensitivity analysis restricted to patients with alcoholic hepatitis led to the same conclusions. Nevertheless, this

improvement in renal function did not lead to an improvement in survival at 1 or 6 months.

Our results should be interpreted in light of the study limitations. Assessment of response to therapy at 1 week may be less suitable in patients treated with pentoxifylline and prednisolone than in those treated with prednisolone alone. It may be more effective to continue pentoxifylline therapy beyond 28 days, depending on the mean time until death, and because the effect of pentoxifylline may depend on the pattern of response. Moreover, our study was powered to detect survival as the primary outcome; therefore, it was probably underpowered to detect a difference in secondary outcomes related to the occurrence of the hepatorenal syndrome. Indeed, 345 patients would have been needed per group to show a 50% decrease in the incidence of the hepatorenal syndrome in patients treated with pentoxifylline in relation to an incidence of 15% in patients receiving the standard of care (with a type I error of 5% and a power of 80%). Therefore, the difference in the incidence of the hepatorenal syndrome in our study should not be interpreted as being null and a larger study is necessary to evaluate this issue.

In our study, there was an effect on short-term survival due to early improvement in liver function as assessed by the Lille model. The importance of early improvement was confirmed because the Lille model was the strongest predictor of outcome in multivariable analysis. The treatment effect on this end point was not significantly different in either study group, which may partially explain the lack of difference in 6-month survival. Our results are somewhat disappointing regarding the probability of response, because only 62.3% of the patients were classified as responders. Because of the strong link between response to therapy and short-term outcome, the goal of future treatments should be to improve liver function early on in these patients. Shifting the pattern of response from a partial to a complete response might be another strategy to decrease short-term mortality.

Our study design integrates recent insights in the management of patients with severe alcoholic hepatitis, and the findings are applicable to patients observed in clinical practice. The results may be useful in helping physicians rationally evaluate the therapeutic strategy of combining pentoxifylline and prednisolone, and adapt their management of patients based on reliable tools.

Conclusion

Four weeks of treatment with a combination of pentoxifylline and prednisolone did not improve 6-month survival compared with prednisolone alone in patients with alcoholic hepatitis. The study may have been underpowered to detect a significant difference in the incidence of the hepatorenal syndrome, which was numerically less frequent in the pentoxifylline group. Future studies with an appropriate design are needed to provide robust data for developing new strategies to improve the outcome of patients with this life-threatening disease.[1,2]

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