A RANDOMIZED TRIAL OF PREDNISOLONE IN PATIENTS WITH SEVERE ALCOHOLIC HEPATITIS

MARIE-JOSÉ RAMOND, M.D., THIERRY POYNARD, M.D., BERNARD RUEFF, M.D., PHILIPPE MATHURIN, M.D., CHRISTIAN THÉODORE, M.D., JEAN-CLAUDE CHAPUT, M.D., AND JEAN-PIERRE BENHAMOU, M.D.

Abstract *Background.* Controlled trials have yielded inconsistent results with regard to the efficacy of corticosteroids in the treatment of alcoholic hepatitis. Three meta-analyses suggest that they may be effective in patients with encephalopathy who have severe liver disease.

Methods. We conducted a randomized, double-blind trial comparing 28 days of prednisolone treatment (40 mg per day) with placebo in 61 patients with biopsy-proved alcoholic hepatitis and either spontaneous hepatic encephalopathy (n = 19) or a discriminant-function value higher than 32. The discriminant function used was as follows: 4.6 (prothrombin time − control time [in seconds]) + serum bilirubin (in micromoles per liter)/17. Fifty-seven of the patients had evidence of cirrhosis on biopsy. The primary end point was death within two months.

Results. One patient was lost to follow-up after 56 days. Treatment was discontinued in two patients because of drug toxicity. By the 66th day after randomization, 16 of 29 placebo recipients had died (mean [±SE] survival, 45±8 percent), as compared with 4 of 32 prednisolone recipients (survival, 88±5 percent) (log-rank test, 10.9; P = 0.001). The survival advantage for prednisolone persisted after stratification according to center and the presence of encephalopathy, and after adjustment for prognostic factors in a proportional-hazards model.

Conclusions. Treatment with prednisolone improves the short-term survival of patients with severe biopsy-proved alcoholic hepatitis. (N Engl J Med 1992;326: 507-12.)

ALCOHOLIC hepatitis is a serious form of acute liver injury, with mortality in the hospital as high as 65 percent.[1] Conventional management consists of abstinence from alcohol, the correction of dietary deficiencies, and general support. Corticosteroid therapy has been studied extensively, but randomized clinical trials have yielded inconsistent results.[2-4] In the most recently published randomized trial, therapy with methylprednisolone decreased short-term mortality in patients with severe alcoholic hepatitis manifested by either spontaneous hepatic encephalopathy or a markedly abnormal discriminant-function value based on measurements of prothrombin time and serum bilirubin.[5] In an unpublished retrospective analysis of patients with biopsy-proved alcoholic hepatitis, we found that this discriminant-function value was a valid index of the severity of disease: it identified patients with a 50 percent risk of dying within two months. Our objective in the present study was to assess the hypothesis that corticosteroid therapy could improve short-term survival in patients with the severe form of alcoholic hepatitis as defined by this discriminant function.

METHODS

Patients

Patients admitted to either Hôpital Beaujon or Hôpital Béclère who had a longstanding history of alcoholism and clinical features of alcoholic hepatitis were evaluated clinically and biochemically at admission and at weekly intervals until all data required for inclusion or exclusion were obtained. The period of observation was limited to one month. Tests for hepatitis B surface antigen and antibodies to the human immunodeficiency virus (HIV), gastroscopy, and percutaneous or transvenous liver biopsy were carried out. All the patients included in the study had biopsy-proved alcoholic hepatitis (characterized by hyaline necrosis and infiltration of polymorphonuclear leukocytes) and spontaneous hepatic encephalopathy or a discriminant-function value higher than 32 (or both). The discriminant function used[5] was as follows: 4.6(prothrombin time − control time [in seconds]) + serum bilirubin (in micromoles per liter)/17. Patients with gastrointestinal bleeding or bacterial infection were excluded from the study unless they could be effectively treated within 48 hours.

From March 1987 through June 1990, 124 alcoholic patients with a discriminant-function value above 32, spontaneous hepatic encephalopathy, or both were admitted to the two participating centers. Eight patients died before they could be included in the study — i.e., before liver biopsy could be performed or before gastrointestinal bleeding or infection could be controlled. Six other patients refused liver biopsy and were excluded from the study. In the remaining 110 patients, liver biopsy was performed. It showed alcoholic hepatitis in 93 patients; the other 17 patients were excluded. Twenty-eight patients were excluded for various other reasons: a decision not to participate (10 patients), gastric or duodenal ulcer or ulcerated esophagitis at endoscopy (5 patients) (patients with hypertensive gastropathy or superficial ulcerations were not excluded), persistent bacterial infection one month after admission (5 patients), the fulfillment of the criteria for inclusion a period of more than one month before (3 patients), neoplastic disease (2 patients), and the presence of hepatitis B surface antigen, presence of HIV antibodies, and anticoagulation therapy (1 patient each). Diabetes mellitus was not a criterion for exclusion, but glycemia was encountered frequently, and insulin therapy was instituted or increased. In all, 65 patients were included in the study (24 at Hôpital Béclère and 41 at Hôpital Beaujon).

Study Design

The study was approved by the hospital ethics committees. Informed consent was obtained from each patient or, if encephalopathy was present, from a family member. Follow-up data were collected weekly for two months after enrollment. Data obtained at admission, during the evaluation period, at randomization, and during the follow-up period were recorded on standardized data-collection forms.

Randomization

The study was conducted in a randomized, double-blind fashion. A random code was prepared by computer for each participating center. There was a different code for men and women in each center, so that within each group of six patients (male or female),

From the Service d'Hépatologie (M.-J.R., J.-P.B.) and the Service de Traitement Ambulatoire des Maladies Alcooliques, Hôpital Beaujon, Clichy (B.R.); the Service de Gastroentérologie, Hôpital A. Béclère, Clamart (T.P., P.M., J.-C.C.); and the Service de Gastroentérologie, Hôpital de Forcilles, Ferolles-Attilly (C.T.); all in France. Address reprint requests to Dr. Rueff at the Service de Traitement Ambulatoire des Maladies Alcooliques, Hôpital Beaujon, 92118 Clichy, France.

three patients received prednisolone and three patients placebo. Prednisolone (Solupred) in 20-mg tablets and identical placebo tablets were provided by the Laboratoire Houdé (Paris). Random sequences of drug or placebo were prepared by the pharmacist at each hospital.

Prednisolone or an identical placebo was given in a single dose of two pills (i.e., 40 mg of prednisolone, equivalent to 32 mg of methylprednisolone) each morning for 28 days. Patients unable to take oral medication received intravenous infusions of prednisolone (Hydrocortancyl) or placebo prepared by the pharmacist and administered in a blinded fashion by the attending physician. Drug therapy was interrupted by the attending physician if there was severe bacterial infection or gastrointestinal bleeding, or if a corticosteroid-related complication was suspected. In patients with such complications the remaining tablets of the study drug were replaced with placebo tablets provided by the pharmacist (the only person who knew which regimen the patient had received first). The principal investigators and their associates were not aware of the randomization procedure or of the medication that the patients were receiving throughout the trial.

Treatment Regimens

All the patients were provided with a 3000-kcal diet containing 1 g of protein per kilogram of body weight. Patients with hepatic encephalopathy received lactulose therapy. Ascites was managed with sodium restriction or by the addition of spironolactone to the treatment regimen. Fluid intake was restricted in patients with hyponatremia. B-complex multivitamins, folic acid, and antacids were given each day. Antacids were administered at least two hours after the study tablets.

Statistical Analysis

According to an unpublished retrospective study at one center, the predicted two-month mortality rate was 50 percent in the placebo group. We calculated that 65 patients were needed in each group to show a 50 percent reduction in mortality in the steroid group as compared with the placebo group (25 percent vs. 50 percent, respectively) with an alpha error of 5 percent and a beta error of 10 percent. However, since Maddrey et al. had found a significant difference with only 33 patients per group in 1986,[6] we arranged for an intermediate analysis with 30 patients per group and decided to discontinue the study if the level of significance (alpha error) was below 0.025.

The statistical analysis was performed according to the intention-to-treat method. Both parametric tests (t-test and Fisher's exact test) and nonparametric tests (Mann–Whitney test) were used to compare the characteristics of the patients. Survival percentages were estimated by the Kaplan–Meier method and compared by the log-rank test. An adjusted log-rank test was used to compare percentages in subgroups. To estimate the treatment effect adjusted for prognostic factors, a multidimensional Cox proportional-hazards model was used. For quantitative prognostic factors (prothrombin time, serum bilirubin, serum albumin, and serum creatinine levels), the differences between the values at admission and at enrollment in the study were also included in the Cox model to adjust the treatment effect for the evolution of prognostic factors before randomization. The comparison between quantitative prognostic factors during treatment used the last available measurement for each patient with the Mann–Whitney test to avoid bias due to death.

Results

Sixty-five patients were randomly assigned to treatment groups between March 19, 1987, and June 8, 1990. Four patients were excluded from the analysis. Of these, one patient assigned to receive prednisolone was found to have anguilluliasis, and her treatment was stopped one day after her inclusion in the study. Three patients assigned to placebo were found not to have satisfied the criteria for inclusion before treatment was instituted (two patients had discriminant-function values below 32 and no encephalopathy, and in the third patient a liver biopsy showed no alcoholic hepatitis). These four patients were alive at the end of the study. Liver biopsy was performed in the remaining 61 patients (percutaneous in 7 and transvenous in 54), and it revealed alcoholic hepatitis and cirrhosis in 57. Four patients had alcoholic hepatitis and fibrosis. At the time of randomization, 57 patients had discriminant-function values higher than 32. Fifteen of these also had hepatic encephalopathy. Only four patients had spontaneous hepatic encephalopathy and discriminant-function values below 32 (20, 21, 22, and 27).

Demographic, clinical, and biochemical characteristics of the 61 patients at admission and at randomization are shown in Table 1. The 32 recipients of prednisolone and the 29 recipients of placebo did not differ with respect to sex, age, duration of hospitalization before entry into the study, and the presence of ascites, spontaneous hepatic encephalopathy, or esophageal varices. Between admission and randomization, three prednisolone recipients had bacterial infections, and one placebo recipient had gastrointestinal bleeding. There was no statistically significant difference between the groups at admission or randomization in any of the biochemical values. Drug

Table 1. Characteristics of 61 Patients with Alcoholic Hepatitis at Admission and at Randomization.*

Characteristic†	Prednisolone		Placebo	
	Admission	Randomization	Admission	Randomization
No. of patients	32		29	
No. male/female	10/22		9/20	
Age (yr)	48.1±1.3		48.2±1.6	
Days from admission to randomization	13.7±1.3 (2–25)		16.8±1.2 (4–32)	
Ascites (no. of patients)	25	24	25	25
Spontaneous hepatic encephalopathy (no. of patients)	14	9	9	10
Esophageal varices, medium or large (no. of patients)	17		14	
Hepatic venous pressure gradient (mm Hg)‡	18.1±1.6		21.0±1.3	
Serum bilirubin (μmol/liter)	222.6±21.0	213.0±25.0	239.0±34.0	284.0±34.0
Prothrombin time (% of normal)	43.3±1.9	38.6±2.4	40.2±3.1	37.4±4.2
Serum aspartate aminotransferase (no. of times upper limit of normal)	4.0±0.3	3.7±0.3	3.7±0.3	3.3±0.1
Serum albumin (μmol/liter)	416±17	414±17	381±24	388±11
Serum creatinine (μmol/liter)	70.8±4.9	83.3±10.5	88.3±12.7	103.1±12.6
Hemoglobin (mmol/liter)	6.7±0.2	6.4±0.2	6.5±0.2	6.4±0.2
Discriminant function§	42±3	51±4	41±3	60±5

*Plus–minus values are means ±SE. Ranges are shown in parentheses.

†Normal ranges for clinical measures are as follows: serum bilirubin, 0 to 17 μmol per liter; serum albumin, 507 to 739 μmol per liter; serum creatinine, 65 to 105 μmol per liter; and hemoglobin, 7.4 to 10.5 mmol per liter.

‡Measured in 46 patients.

§See the Methods section for an explanation of the derivation of this value.

therapy was discontinued in four patients. In two patients treated with prednisolone, treatment was stopped 8 and 12 days after enrollment because of psychological disturbance and bacterial meningitis, respectively. Both patients were alive at the end of the study. In one placebo recipient, treatment was stopped after nine days because of bacterial infection and gastrointestinal bleeding. This patient died three days later. One patient treated with prednisolone left the hospital 10 days after enrollment. She was rehospitalized 56 days after enrollment and left again the following day. She was the only patient lost to follow-up. The other 60 patients were hospitalized at the initial center for one month after randomization or until they died. Twenty-four patients remained hospitalized for at least one more month, either at the initial center or in a specialized medical department of a participating rest home. Seventeen patients were discharged and then seen regularly by their attending physicians or one of the principal investigators of the study. Insulin therapy was begun in one diabetic patient during the trial and was discontinued afterward.

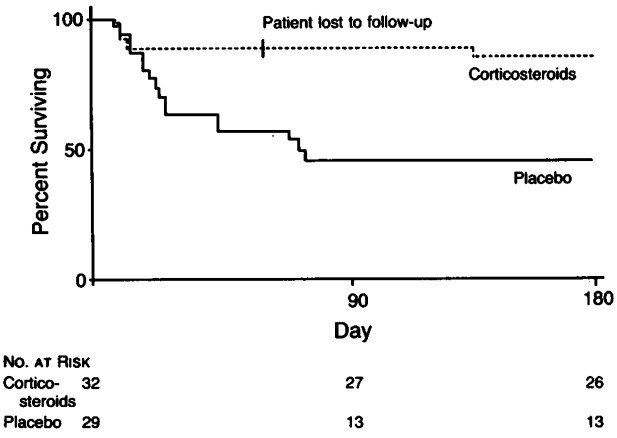


Figure 1. Survival in 61 Patients Randomly Assigned to Receive Corticosteroid Therapy or Placebo.

Survival rates at six months were 84±6 percent in the corticosteroid group and 45±9 percent in the placebo group (P = 0.002).

Survival

During the study, 16 of the 29 placebo recipients died, as compared with 4 of the 32 prednisolone recipients (log-rank test, 10.9; P = 0.001). All the deaths occurred during hospitalization. The mean (±SE) cumulative rates of survival at one and two months were 88±5 percent and 88±5 percent, respectively, in the prednisolone group and 62±9 percent and 45±8 percent in the placebo group (Fig. 1).

The intervals from the time of randomization to death, causes of death, and associated biochemical factors at death in the 4 prednisolone recipients and the 16 placebo recipients who died are shown in Table 2. It should be noted that hepatocellular failure was severe in most patients.

Stratification analysis showed that survival was

Table 2. Length of Time from Randomization to Death, Causes of Death, and Associated Biochemical Disorders at Death in the 4 Prednisolone and 16 Placebo Recipients Who Died during the Study.*

Patient No.	Days from Randomization to Death	Associated Disorders					Prothrombin Time	Factor V	Serum Bilirubin	Serum Creatinine
		Encephalopathy	Gastrointestinal Bleeding	Infection	ARDS*	Other				
		grade					*% of normal*		*μmol/liter*	
Prednisolone										
1	8	3					24	18	352	96
2	9	2	Gastritis				16	21	622	494
3	9	2		Septicemia			13	28	266	331
4	11	3		Lung			20	20	415	215
Placebo										
1	7	1			Present		32	—	125	133
2	9	0				Rupture of peritoneal varices	35	35	111	54
3	12	3	Undetermined origin	Ascites			12	10	174	402
4	12	2	Undetermined origin	Urinary			10	10	248	226
5	16	0				Pancreatitis†	51	41	508	370
6	16	3		Ascites and lung		Pancreatitis†	5	5	236	294
7	18	3		Lung			17	—	282	239
8	20	1			Present		14	15	54	285
9	21	1			Present		10	10	257	130
10	23	0	Variceal rupture				47	—	133	143
11	23	1		Ascites			13	—	633	260
12	39	1		Septicemia			44	65	259	104
13	39	3	Undetermined origin				32	26	779	140
14	61	0	Variceal rupture				23	32	230	88
15	64	2		Ascites and lung			12	18	115	331
16	66	3		Lung			14	19	381	455

*ARDS denotes acute respiratory distress syndrome.

†Autopsy-proved acute pancreatitis.

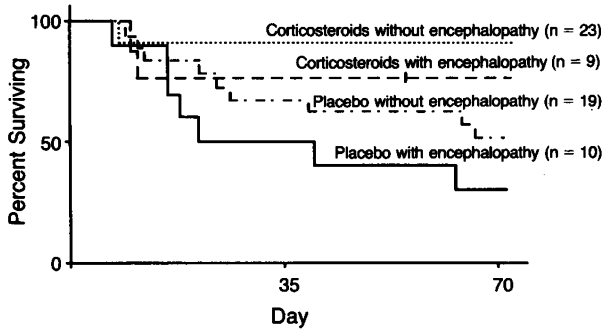


Figure 2. Survival in 61 Patients Randomly Assigned to Receive Corticosteroid Therapy or Placebo, According to the Presence or Absence of Encephalopathy.

Survival was significantly better in corticosteroid recipients than in placebo recipients, regardless of the presence or absence of encephalopathy (P = 0.0017).

significantly better in the corticosteroid-treated patients than in the patients given placebo at both centers (adjusted log-rank test, 10.8; P = 0.001) and whether encephalopathy was present or absent (adjusted log-rank test, 9.9; P = 0.0017) (Fig. 2). Among the patients with no encephalopathy, 9 of 19 placebo recipients had died two months after entry, as compared with 2 of 23 prednisolone recipients. Although it was not the aim of the present study, patients were followed as long as possible, and survival curves were constructed for periods up to six months. The cumulative six-month survival rates were 84±6 percent in the prednisolone group and 45±9 percent in the placebo group (log-rank test, 9.5; P = 0.002) (Fig. 1).

Factors Associated with a Fatal Outcome

The following variables in the Cox model were considered potential covariates with prognostic importance for survival: treatment, age, sex, presence of ascites and encephalopathy, prothrombin time, and serum concentrations of bilirubin, creatinine, and albumin. For quantitative prognostic factors (prothrombin time and serum bilirubin, albumin, and creatinine concentrations), the differences between the values at hospital admission and enrollment in the study were also included in the Cox model to adjust any treatment effect for the evolution of prognostic factors before randomization. The only variables that correlated with survival during the study were treatment (P = 0.02), the presence of ascites (P = 0.06), and the serum bilirubin concentration (P = 0.07).

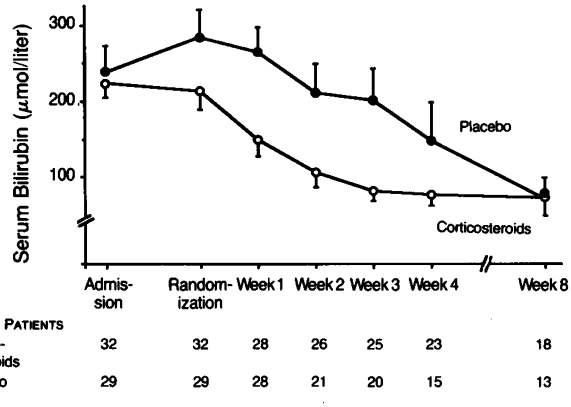


Figure 3. Mean (±SE) Serum Bilirubin Concentrations in 61 Patients Randomly Assigned to Receive Corticosteroid Therapy or Placebo.

Serum bilirubin levels were significantly decreased in corticosteroid recipients during treatment (P<0.002 by the Mann–Whitney test for the last available measurement for each patient).

Liver Function

Changes in the prothrombin time and the serum bilirubin, albumin, and creatinine concentrations are shown in Figures 3, 4, 5, and 6, respectively. All these indexes improved significantly in the prednisolone group during treatment.

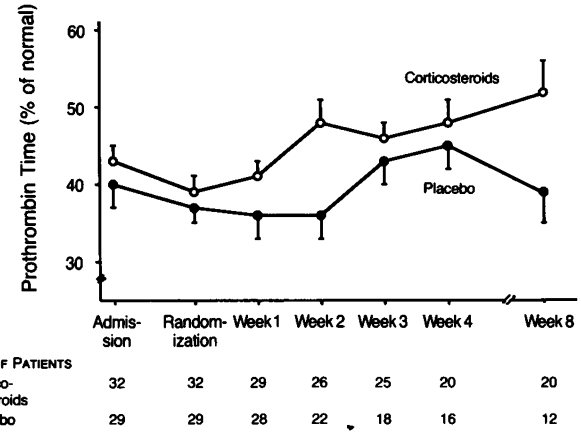


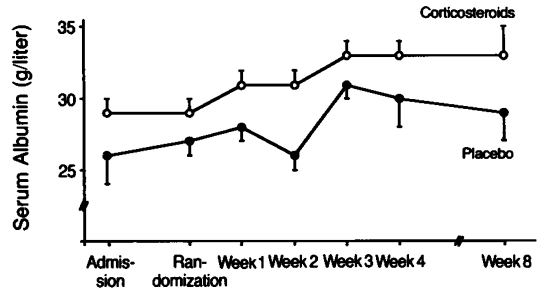
Figure 4. Mean (±SE) Prothrombin Time in 61 Patients Randomly Assigned to Receive Corticosteroid Therapy or Placebo.

Prothrombin time was significantly increased in corticosteroid recipients during treatment (P<0.007 by the Mann–Whitney test for the last available measurement for each patient).

Discussion

Three meta-analyses published since the initiation of the present trial have shown that corticosteroid therapy significantly improved the short-term survival of patients with severe alcoholic hepatitis. These studies also concluded that further studies were needed, because of the conflicting results of published trials and persistent uncertainties about the subgroup of patients who could best benefit from corticosteroid treatment, although it appeared that patients with spontaneous hepatic encephalopathy could probably benefit most.[2-4]

The results of our study confirm that corticosteroid therapy is efficacious in patients with severe alcoholic hepatitis. The results are remarkably similar to those of Carithers et al.,[5] who reported a 28-day mortality



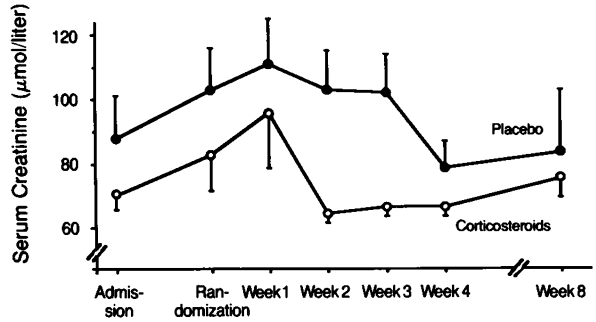
No. of Patients							
Corticosteroids	32	32	24	25	21	21	13
Placebo	29	29	24	14	16	14	8

Figure 5. Mean (±SE) Serum Albumin Concentrations in 61 Patients Randomly Assigned to Receive Corticosteroid Therapy or Placebo.

Serum albumin levels were significantly increased in corticosteroid recipients during treatment ($P<0.01$ by the Mann–Whitney test for the last available measurement for each patient).

rate of 6 percent in corticosteroid recipients as compared with 35 percent in placebo recipients. Conflicting results in other previously published trials may be due to type II errors related to insufficient numbers of patients or variations in the clinical condition of the patients studied; if there is a high percentage of subjects with mild-to-moderate disease, the mortality will be low whatever the treatment.[2-5,7] Conflicting results may also be due to the inclusion of patients who did not have alcoholic hepatitis, since liver biopsy was not performed in most of them.

The selection of patients appears to be critical. The discriminant function,[5,8] which identified 57 of our 61 patients as having severe disease, appears to be a better index of severity than the presence of hepatic encephalopathy. This trial shows an improvement in survival for patients without and those with encephalopathy, possibly because the liver disease in the patients without encephalopathy was more severe in our study than in previous studies. In the trial of Carithers et al.,[5] which used the same methods to evaluate the severity of disease, 2 of 13 placebo recipients without encephalopathy died, as compared with 9 of 19 in our trial. We included only patients with biopsy-proved alcoholic hepatitis; in the only other study in which histologic diagnosis was required, there was also a significant improvement in survival for the treated patients.[9]



No. of Patients							
Corticosteroids	32	32	30	24	23	21	15
Placebo	29	29	27	21	19	16	14

Figure 6. Mean (±SE) Serum Creatinine Concentration in 61 Patients Randomly Assigned to Receive Corticosteroid Therapy or Placebo.

Serum creatinine concentrations were significantly decreased in corticosteroid recipients during treatment ($P<0.05$ by the Mann–Whitney test for the last available measurement for each patient).

The fact that death occurred early in the corticosteroid group suggests that some patients were too ill to benefit from corticosteroid treatment. The delay from admission to randomization was relatively long in our study (15 days on average), mainly because of the delay in obtaining the results of liver biopsy. Because a delay may have been responsible for the death of some patients, we suggest that corticosteroid therapy should be initiated in severely ill patients before the results of liver biopsy are available, and should be discontinued if the diagnosis is not histologically confirmed.

The pathogenesis of alcoholic hepatitis and the mechanisms of the favorable effects of corticosteroids are not well understood.[10] Corticosteroids stimulate the appetite, increase the production of albumin, and inhibit the production of collagen Types I and IV.[11,12] They may also affect immune processes of possible importance in the initiation or perpetuation of alcoholic hepatitis. The persistence of the hepatic injury is probably important, because hepatic failure may progress despite the discontinuation of alcohol intake. Some patients in the placebo group died two to three months after hospitalization. Acetaldehyde is known to form adducts with macromolecules in the hepatocyte, with the adducts serving as neoantigens and eliciting an immune response.[13] Corticosteroids decrease cytokine production, which may also play a part in the pathogenesis of alcoholic hepatitis.[14]

No serious adverse effects of corticosteroid therapy were encountered in our study. Infection and gastrointestinal bleeding were more common in placebo recipients than in corticosteroid recipients (Table 2). Exacerbation of psychiatric disorders and glucose intolerance were each observed in one corticosteroid recipient. The abrupt discontinuation of corticosteroid therapy did not lead to any adverse effects.

We are indebted to the following, without whose dedicated assistance the completion of this study would not have been possible: Hôpital Beaujon — Gérard Babany, Jacques Bernuau, Françoise Degos, Serge Erlinger, Antoine Hadengue, and Patrick Marcellin (Service d'Hépatologie); Patrick Chiche, Jocelyne Crnac, Roselyne Elbaz, Jane Languepin, Véronique Peuchet, Isabelle Zeggane, and Florence Zembra (Service de Traitement Ambulatoire des Maladies Alcooliques); Didier Lebrec (Laboratoire d'Hémodynamique Splanchnique, INSERM U 24); Claude Degott and Jean-François Mosnier (Service d'Anatomie et de Cytologie Pathologiques); Cath-

erine Montagnier and Jeanick Stocco (Pharmacie); and Martine Landié (Service Social); Hôpital Antoine Béclère — Sylvie Naveau (Service de Gastroentérologie); Dominique Musset (Service d'Hémodynamique); Pierre Bedossa (Service d'Anatomie Pathologique); and Nicole Préaux (Pharmacie); Laboratoire Houdé — Michel Bodin; and Quanta Medical — Othar Zourabichvili. We are also indebted to the nurses of Hôpital Beaujon (Service d'Hépatologie), Hôpital Béclère (Service de Gastroentérologie), and Hôpital de Forcilles; to Alain Truskolaski for drawing figures; and to Suzanne Devoto for assistance in the preparation of the manuscript.

References

1. Hardison WG, Lee FI. Prognosis in the acute liver disease of the alcoholic patient. N Engl J Med 1966;275:61-6.
2. Reynolds TB, Benhamou JP, Blake J, Naccarato R, Orrego H. Treatment of acute alcoholic hepatitis. Gastroenterol Int 1989;2:208-16.
3. Imperiale TF, McCullough AJ. Do corticosteroids reduce mortality from alcoholic hepatitis? A meta-analysis of the randomized trials. Ann Intern Med 1990;113:299-307.
4. Daures JP, Peray P, Bories P, et al. Place de la corticothérapie dans le traitement des hépatites alcooliques aiguës: résultats d'une métaanalyse. Gastroenterol Clin Biol 1991;15:223-8.
5. Carithers RL Jr, Herlong HF, Diehl AM, et al. Methylprednisolone therapy in patients with severe alcoholic hepatitis: a randomized multicenter trial. Ann Intern Med 1989;110:685-90.
6. Maddrey WC, Carithers RL, Herlong HF, et al. Prednisolone therapy in patients with severe alcoholic hepatitis: results of a multicenter trial. Hepatology 1986;6:1202. abstract.
7. Conn HO. Steroid treatment of alcoholic hepatitis: the yeas and the nays. Gastroenterology 1978;74:319-26.
8. Maddrey WC, Boitnott JK, Bedine MS, Weber FL Jr, Mezey E, White RI Jr. Corticosteroid therapy of alcoholic hepatitis. Gastroenterology 1978; 75:193-9.
9. Helman RA, Temko MH, Nye SW, Fallon HJ. Alcoholic hepatitis: natural history and evaluation of prednisolone therapy. Ann Intern Med 1971;74: 311-21.
10. Maddrey WC. Alcoholic hepatitis: pathogenesis and approaches to treatment. Scand J Gastroenterol Suppl 1990;175:118-30.
11. Jefferson DM, Reid LM, Giambrone MA, Shafritz DA, Zern MA. Effects of dexamethasone on albumin and collagen gene expression in primary cultures of adult rat hepatocytes. Hepatology 1985;5:14-20.
12. Weiner FR, Czaja MJ, Jefferson DM, et al. The effects of dexamethasone on in vitro collagen gene expression. J Biol Chem 1987;262:6955-8.
13. Zetterman RK, Sorrell MF. Immunologic aspects of alcoholic liver disease. Gastroenterology 1981;81:616-24.
14. Nolan JP. Intestinal endotoxins as mediators of hepatic injury — an idea whose time has come again. Hepatology 1989;10:887-91.