A Randomized, Double-Blind, Placebo-Controlled Trial of Ursodeoxycholic Acid in Primary Biliary Cirrhosis

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One hundred fifty-one patients with primary biliary cirrhosis (PBC) grouped into four strata based on entry serum bilirubin (<2 mg/dL vs. 2 mg/dL or greater) and liver histology (stages I, II vs. stages III, IV—Ludwig criteria) were randomized within each stratum to ursodiol or placebo given in a single dose of 10 to 12 mg/kg at bedtime for 2 years. Placebo- (n = 74) and ursodiol-treated (n = 77) patients were well matched at baseline for demographic and prognostic factors. Ursodiol induced major improvements in biochemical tests of the liver in strata 1 and 2 (entry bilirubin <2), but had less effect on laboratory tests in patients with entry serum bilirubin of ≥2 (strata 3 and 4). Histology was favorably affected by ursodiol in patients in strata 1 and 2 but not in strata 3 and 4. Ursodiol enrichment in fasting bile obtained at the conclusion of the trial was approximately 40% and comparable in all strata. Thus, differences in ursodiol enrichment of the bile acid pool do not explain better responses of laboratory tests and histology found in patients with less advanced PBC. Patients treated with ursodiol tended to develop a treatment failure less frequently than those who received placebo, particularly in strata 1 and 2 (ursodiol 42%, placebo 60%, $P = .078$). Development of severe symptoms (fatigue/pruritus) and doubling of serum bilirubin were reduced significantly in ursodiol-treated patients. Major complications of liver disease, progression to liver transplantation or death, occurred in 10.5% and 76.6%, respectively, in patients who had an entry serum bilirubin of <2 or ≥2 mg/dL. The incidence of these complications was comparable in ursodiol- and placebo-treated patients. Treatment failure occurred sooner in placebo than in ursodiol-treated patients in strata 1 and 2 but at the same rate in similarly treated patients in strata 3 and 4. Patients with advanced disease are unlikely to benefit from ursodiol. Trials longer than 2 years will likely be needed to determine whether ursodiol reduces major complications of liver disease in patients with milder disease. (HEPATOLOGY 1995;22:759-766.)

Stimulated by the report of Poupon and associates in 1987[1] that ursodeoxycholic acid (ursodiol) improved results of liver tests and ameliorated symptoms in 15 patients with primary biliary cirrhosis (PBC), and by the earlier observations of Leuschner and colleagues in 1985[2] that ursodiol improved liver tests in a smaller number of patients with PBC, we organized a multicenter, randomized, double-blind, 2-year clinical trial of ursodiol versus placebo in the treatment of this disease. At the initiation of our trial, we did not know which patients might benefit from therapy, i.e., patients with early or late or both stages of PBC. As a result, we stratified for variables generally accepted to be markers of earlier and later stages of PBC. The current report presents the results of our clinical trial. Major improvements, particularly in results of biochemical tests of the liver, were observed in ursodiol-treated patients who had earlier phases of the disease, as defined by an entry serum bilirubin level of less than 2 mg/dL. By contrast, patients whose entry serum bilirubin was equal to or greater than 2 mg/dL (mean value of 5.1 mg/dL) had modest or no improvement in laboratory tests that are markers of cholestasis and liver inflammation. Histology was also favorably affected by ursodiol in patients with an entry serum bilirubin less than 2 mg/dL.

MATERIALS AND METHODS

Entry inclusion criteria consisted of (1) the presence of evidence of PBC with manifestations of cholestatic liver dis-

Abbreviations: PBC, primary biliary cirrhosis; M-W, Mann-Whitney.

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ease of at least 6 months' duration; (2) a serum alkaline phosphatase level at least one and a half times the upper limit of normal; (3) a positive antimitochondrial antibody test; (4) exclusion of biliary obstruction by ultrasonography, computed tomography, or by endoscopic cholangiography; and (5) a liver biopsy specimen within the previous 6 months judged compatible with the diagnosis of PBC. Exclusion criteria consisted of (1) treatment in the 3 months before entry with immunosuppressive, antiinflammatory agents such as azathioprine, colchicine, corticosteroids, cyclosporine, methotrexate, and d-penicillamine; or with ursodiol; (2) recurrent bleeds from esophagogastric varices, spontaneous encephalopathy, or diuretic-resistant ascites; (3) a serum bilirubin of 20 mg/dL or greater; (4) pregnancy; (5) age younger than 19 years; and (6) findings of other causes of liver disease. Patients with a negative antimitochondrial antibody were accepted if they met all other criteria for the diagnosis of PBC and had no evidence of extrahepatic obstruction.

Patients satisfying both inclusion and exclusion criteria and providing written informed consent were stratified into four groups on the basis of (1) a serum bilirubin of less than 2 mg/dL, or 2 mg/dL and greater; and (2) liver histology, either stages I and II or stages III and IV as defined by Ludwig et al.[3] Three antimitochondrial antibody-negative patients satisfying all other criteria were accepted for this trial. Patients in stratum 1 had a serum bilirubin less than 2 and stage I or II histology; stratum 2, a bilirubin less than 2 and stage III or IV histology; stratum 3, a bilirubin of 2 or greater and stage I or II histology; stratum 4, a bilirubin of 2 or greater and stage III or IV histology. Patients were randomized separately at each of our six treatment centers in blocks of four for each of the four stratification groups. It was planned that 50% of the patients were to receive ursodiol, 10 to 12 mg/kg/day administered in a single dose at bedtime. The other 50% received a comparable-appearing placebo. Coded medications were provided in 300-mg capsules by the Ciba-Geigy Corporation. Patients taking cholestyramine or colestipol were asked to take the medication at least 2 hours before intake of ursodiol or its placebo.

Patients underwent an initial assessment including upper endoscopy and abdominal ultrasonography, then laboratory testing at 3-monthly intervals and a final assessment at 2 years, including repeat ultrasonography and upper endoscopy. A liver biopsy was performed within 6 months before starting the trial, and again after 2 years on trial medication. The protocol was approved by the institutional review boards at each of our six treatment centers.

Recognizing that PBC is a chronic disease, and that even in a 2-year placebo-controlled treatment trial, patients with early disease might not develop severe complications of their liver illness, a series of efficacy measures were established in the study protocol. Specifically, it was planned to compare the effects of the two treatments, ursodiol and placebo, on symptoms; changes in biochemical parameters; liver histology; development of esophagogastric varices if not present on entry; bleeding from esophagogastric varices; development of ascites; development of hepatic encephalopathy; liver transplantation; and death. Treatment failure was defined as any of the following: (1) death before liver transplantation; (2) liver transplantation; (3) development of bleeding esophagogastric varices, ascites, or hepatic encephalopathy in those without at entry; (4) development of esophagogastric varices; (5) histologic progression by two stages or to cirrhosis; (6) doubling of serum bilirubin with the second value $\geq$1.5 mg/dL; (7) marked worsening of fatigue or pruritus defined by progression or two grades of development of disabling fatigue or pruritus; (8) inability to tolerate the drug regimen; or (9) voluntary discontinuation of drug for any reason. Differences in the proportion of failures as well as the time to treatment failure were also assessed. Patients failing treatment continued on assigned trial medication unless death, liver transplantation, drug toxicity, or voluntary withdrawal ensued.

The grading system for fatigue was 0 for none; 1 for present but not interfering with activity; 2 for requiring extra rest and limiting activity but allowing the patient to work; and 3 for patient unable to work. Pruritus was graded 0 for none; 1, mild; 2, more severe with some interference with sleep; 3, excoriations and marked disturbance with sleep.

Liver biopsy specimens were reviewed by a panel of five hepatopathologists. At a pretrial meeting, the pathologists simultaneously reviewed 35 biopsy specimens obtained from patients with documented PBC, using a multiheaded microscope. They standardized a grading system for assessing stage because this was a criterion used for stratification of patients at entry into the trial. They characterized florid duct lesions. In addition, they arrived at a grading system for four parameters, i.e., piecemeal necrosis, portal inflammation, fibrosis, and cholate injury with 0 = not present; 1 = mild; 2 = moderate; and 3 = severe. Biopsy specimens were staged at each center. Unstained slides were sent to our pathology center at Nebraska where they were stained and coded. The trial biopsies were then assessed blindly and mostly simultaneously by the five pathologists, each of whom assigned a score for the above four parameters. The average of the five scores for each parameter was used for statistical analysis. Highlights of the analysis are presented in this publication. A more detailed description of the hepatic pathology is reported in a separate communication.

Fasting duodenal bile samples were obtained at entry and at 2 years, at the time of upper endoscopy (after stimulation with intravenously administered cholecystokinin). Samples were stored frozen at −20°C. Bile acid composition was measured in the laboratory of A. F. Hofmann and S. S. Rossi by a high-pressure liquid chromatography method,[4] which was validated against gas chromatography (GC).[5]

Sample Size. Before initiating the trial, it was assumed that roughly one-half of the control patients would experience treatment failures during the 2-year protocol. We wanted sufficient power to detect significant departures in either direction because it was possible that ursodiol might make PBC worse. Therefore, a two-sided test was planned. To detect a change in proportion failing of 25 percentage points (i.e., from 50% to 25% or from 50% to 75%) with 80% power, testing at alpha = 0.05 would require that a total of 130 patients be randomized (65 placebo, 65 ursodiol). Controlling for an estimated dropout rate of 0.05, we estimated a sample size of 144 patients. Actually, 151 patients were recruited for the trial in slightly over 2 years.

Interim Analysis. A planned interim analysis was performed on the 93 patients recruited in year 1.[6] The primary rationale was to assure justification for continuing the trial. If toxicity was acceptable and no clearcut improvement in survival or need for transplantation was found ($P > .01$), the trial was to be continued. The data analyzed at our statistical center were presented to our data monitoring committee (Peter Gregory, MD, Leonard Seeff, MD), who recommended that the trial be completed. All investigators remained blinded throughout the trial as to the treatment allocation for each patient. This information was only made available to the statistical center.

Statistical Methods. This study was planned as a multicenter trial. Data from all centers were pooled for analy-

sis. Statistical analyses were performed on all randomized patients who were enrolled in the trial and who either completed 24 months of therapy or were discontinued from the trial. Analyses followed the intention-to-treat rule. Between-treatment statistical comparisons were performed for each efficacy variable. For baseline comparability, frequency tables were developed for patient demographics at baseline (visit 1). Treatment comparability was examined using *t*-test, Pearson's chi-Square tests or Fisher's exact tests, as appropriate, for all efficacy measurements and the demographics. Measurements made at entry (visit 1) were used as baseline values in the analyses. Analyses were performed for the 6-, 12-, 18-, and 24-month visits. The analyses for immunoglobulin M were done only for the 12- and 24-month visits. Two-sided tests were performed for all between-treatment comparisons. It was anticipated that the effects of ursodiol might be different among the four strata. Thus, we decided *a priori* to analyze the data on all patients as well as on each stratum, even though it was not possible to accrue enough patients to ensure adequate power for stratum-specific tests. The .05 level of significance was used to declare statistical significance. No adjustments were made for the interim analysis or multiple comparisons. The change from baseline for each biochemical measurement at each analysis time was compared using the two-sample *t*-test and the Mann-Whitney nonparametric test. The same analyses were performed for histological variables at the 24-month visit. The proportions of treatment failures were analyzed by Pearson's chi-square tests or Fisher's exact tests, and times to treatment failure were analyzed by log rank tests.

RESULTS

Accounting of Patients. A total of 151 patients was randomized, 74 to placebo, 77 to ursodiol (Table 1). Recruitment was well distributed among the six treatment centers. (UT Southwestern, 31; Thomas Jefferson, 32; Yale, 24; Medical College of Virginia, 23; Nebraska, 18; Washington University at St. Louis, 23). Fourteen patients in each treatment arm were discontinued prematurely from the trial. Treatment failures were the major reason. There were two protocol violators, one in each treatment group.

Demographic, Laboratory, and Histological Characteristics at Entry. (Table 2) The patients, as is characteristic of PBC, were predominantly female. Most of the patients were white. Age and the above features were comparable in the two treatment arms (Table 2).

The results of entry laboratory tests were comparable in the two groups of patients. Further evidence of good balance and reflecting the value of stratification at entry before randomization is the comparable distribution into the two treatment arms of patients with a serum bilirubin of <2 mg/dL, or 2 mg/dL or greater and with stage I, II or III, IV histology. Moreover, the average Mayo Risk (R) Score, a prognostic marker of survival,[7] was virtually identical in the two groups.

Duration of Exposure to Trial Medication. Approximately 80% of the patients completed the 2-year trial. The frequency and rate at which patients discontinued either placebo or ursodiol were comparable in the two groups (Table 3).

Effects of Ursodiol Therapy on Symptoms and Laboratory Tests. Mean scores for pruritus and fatigue were not affected by treatment (data not shown). By contrast, in ursodiol-treated patients, statistically significant improvements in markers of cholestasis (serum bilirubin, alkaline phosphatase, gamma-glutamyl-transferase) and of inflammation (aspartate transaminase, alanine transaminase) were observed by 6

TABLE 1. Accounting of Patients

	No. of Patients		
	Placebo	Ursodiol	Total
Randomized at visit 1	74	77	151
Completing the trial	60	63	123
Discontinuing prematurely from the trial			
Caused by			
Intractable diarrhea	0	1	1
Severe nausea or vomiting	1*	0	1
Voluntary discontinuation of drug	3	1	4
Treatment failure	10	12	22
Total	14	14	28
Protocol violators	1	1	2

* This patient subsequently proceeded to transplantation.

TABLE 2. Demographic, Laboratory, and Histological Characteristics at Entry

	Placebo (n = 74)	Ursodiol (n = 77)
Age (yrs)		
Mean ± SD	48.9 ± 10.6	49.5 ± 8.6
	n (%)	
Sex		
Female	68 (92)	66 (86)
Male	6 (8)	11 (14)
Race		
White	67 (91)	71 (92)
Black	2 (3)	2 (3)
Hispanic	4 (5)	1 (1)
Oriental	1 (1)	2 (3)
Other	0 (0)	1 (1)
	Mean ± SE	
Serum bilirubin (mg/dL)	2.0 ± 0.3	2.3 ± 0.4
Alkaline phosphatase (U/L)	623 ± 41	598 ± 47
GGT (U/L)	578 ± 52	618 ± 53
AST (U/L)	116 ± 7	118 ± 10
ALT (U/L)	141 ± 11	129 ± 11
IgM (mg/dL)	622 ± 52	651 ± 41
Albumin (g/dL)	3.9 ± 0.05	3.8 ± 0.05
Prothrombin time (sec)	12 ± 0.1	12 ± 0.1
Mayo R score	4.7 ± 0.1	4.7 ± 0.1
	n (%)	
Serum bilirubin		
<2 mg/dL	52 (70)	52 (68)
≥2 mg/dL	22 (30)	25 (32)
Histological staging		
I, II	22 (31)	28 (34)
III, IV	52 (69)	49 (66)

Abbreviations: GGT, gamma-glutamyltransferase; AST, aspartate transaminase; ALT, alanine transaminase; IgM, immunoglobulin M.

TABLE 3. Duration of Exposure to Trial Medication

Extent of Exposure (mos)	Placebo	Ursodiol
	n (%)	
0-≤6	4 (5)	4 (5)
6-≤12	3 (4)	1 (1)
12-≤18	6 (8)	9 (12)
18-≤24	61 (82)	63 (82)
	74	77

months (most by 3 months) and persisted for the 2 years of the trial. Immunoglobulin M levels decreased significantly at 12 and 24 months, and serum albumin was maintained better at 2 years.

Biochemical tests were improved to a greater extent in ursodiol-treated patients in strata 1 and 2 (entry bilirubin <2 mg/dL) than in those in strata 3 and 4 (entry bilirubin ≥2 mg/dL). This is evident in Figs. 1 and 2. Parenthetically, entry characteristics for the placebo- and ursodiol-treated patients in strata 1 and 2 and in strata 3 and 4 were well balanced (data not shown).

Histology. A total of 122 paired liver biopsy specimens were available for analysis; 38 (16 placebo, 22 ursodiol) from patients in stratum 1; 48 (28 placebo, 20 ursodiol) in stratum 2; 5 (2 placebo, 3 ursodiol) in stratum 3; and 31 (16 placebo, 15 ursodiol) in stratum 4. Data are provided separately for findings in stratum 1 (stage I, II lesions) and stratum 2 (stage III, IV lesions)—both strata had an entry serum bilirubin <2 mg/dL; and collectively for strata 3 and 4 with entry serum bilirubin ≥2 mg/dL). The number of patients in stratum 3 is too small to permit separate analyses. The statistical significance of differences from initial biopsies for the parameters assessed is detailed in Fig. 3. Significant treatment effects were observed as follows: In stratum 1, scores for all four parameters increased in the second biopsy in the placebo-treated group, but did not change in ursodiol-treated patients for piecemeal necrosis (t-test $P = .002$; Mann-Whitney [M-W] $P = .038$), and tended not to change for portal inflammation (t-test $P = .059$, M-W $P = .073$), and for cholate injury (t-test $P = .068$). The average score, a mean of the values for the four individual parameters, which rose significantly in the placebo-treated group, did not change in ursodiol-treated patients (t-test $P = .01$; M-W $P = .048$). In ursodiol-treated patients in stratum 2, fibrosis was less in the second biopsy (t-test $P = .007$; M-W $P = .003$), and cholate injury, which worsened in the placebo group, was prevented (t-test $P = .061$; M-W $P = .052$). The average score tended to fall (t-test $P = .063$, M-W $P = .098$). No significant treatment effects were observed in any histological category for patients in strata 3 and 4.

Treatment Failures. A series of end points was assessed (Table 4). Placebo-treated patients appeared to develop treatment failure more frequently than did ursodiol-treated patients (placebo 69%, ursodiol 56%, $P = .098$). This was particularly evident in patients in strata 1 and 2 (placebo 60%, ursodiol 42%, $P = .078$). Patient withdrawal was infrequent in either treatment group. Neither the development of major complications of liver disease (bleeding esophagogastric varices, ascites, hepatic encephalopathy), progression to death without transplantation, nor progression to liver transplantation were significantly different between the two treatment arms. Development of severe symptoms (fatigue, pruritus) and doubling of the serum bilirubin were reduced significantly in ursodiol-treated patients. Histological progression and development of varices (not present at entry) occurred with similar frequency in both groups. The time to treatment failure occurred sooner in placebo than in ursodiol-treated patients in strata 1

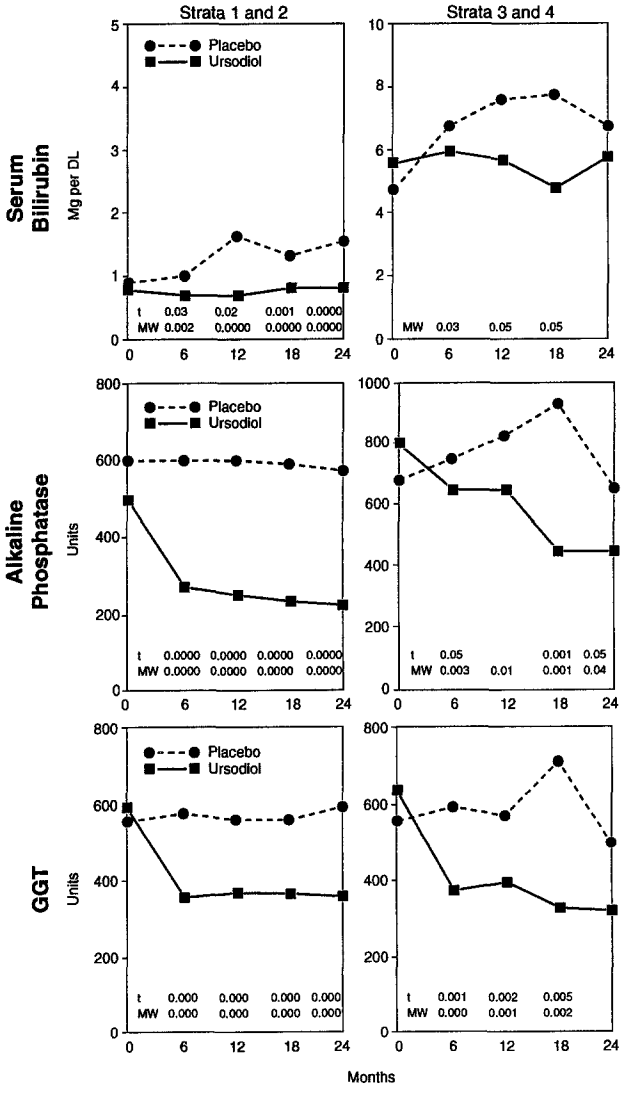

FIG. 1. A comparison of treatment effects (ursodiol or placebo) on the results of serum bilirubin, alkaline phosphatase, and gamma-glutamyltransferase in patients with an entry serum bilirubin of <2 mg/dL (strata 1 and 2) or ≥2 mg/dL (strata 3 and 4). Between-treatment P values for t-tests and Mann-Whitney tests are indicated when statistically significant.

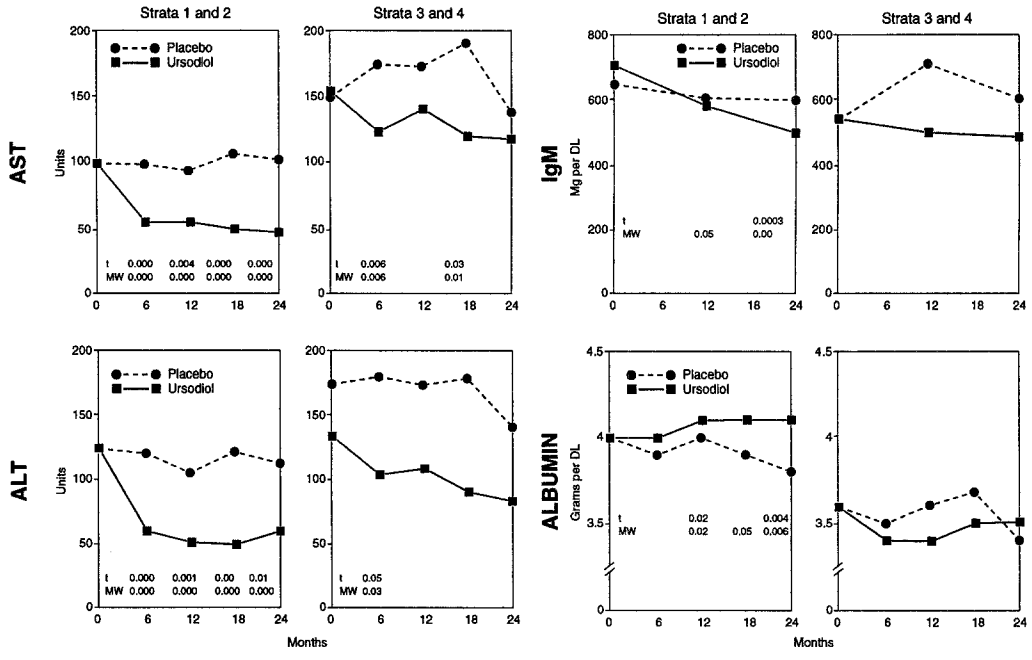

FIG. 2. A comparison of treatment effects (ursodiol or placebo) on the results of aspartate transaminase, alanine transaminase, immunoglobulin M, and serum albumin in patients in strata 1 and 2 and in strata 3 and 4. Statistically significant P values shown as in Fig. 1.

and 2, the log rank $P = .057$, but was comparable in strata 3 and 4, log rank $P = .868$ (Fig. 4).

Ursodeoxycholic Acid Enrichment in Bile. Approximately 40% of the bile acids in fasting bile collected at the end of the trial were accounted for by ursodeoxycholic acid in ursodiol-treated patients. The range of values and coefficients of variation were comparable for the various strata (Fig. 5). All patients randomized to receive ursodiol had at least 10.3% ursodeoxycholic acid in bile. In placebo-treated patients, ursodiol represented only 0.4% of the biliary bile acids.

Three patients randomized to receive placebo had detectable ursodeoxycholic acid in bile, confirmed by mass spectrometry. The percent enrichment and strata for these patients were 16.2% and 37.9%, both in stratum 2; and 10.6% in stratum 4. In none of these patients had laboratory tests improved while in the trial. Unfortunately, capsules they had been taking were not available for analysis. It is likely then that these patients had ingested ursodiol, but it is not clear for how long or in what dose. Other data for these patients were included in the respective efficacy analyses for placebo-treated patients.

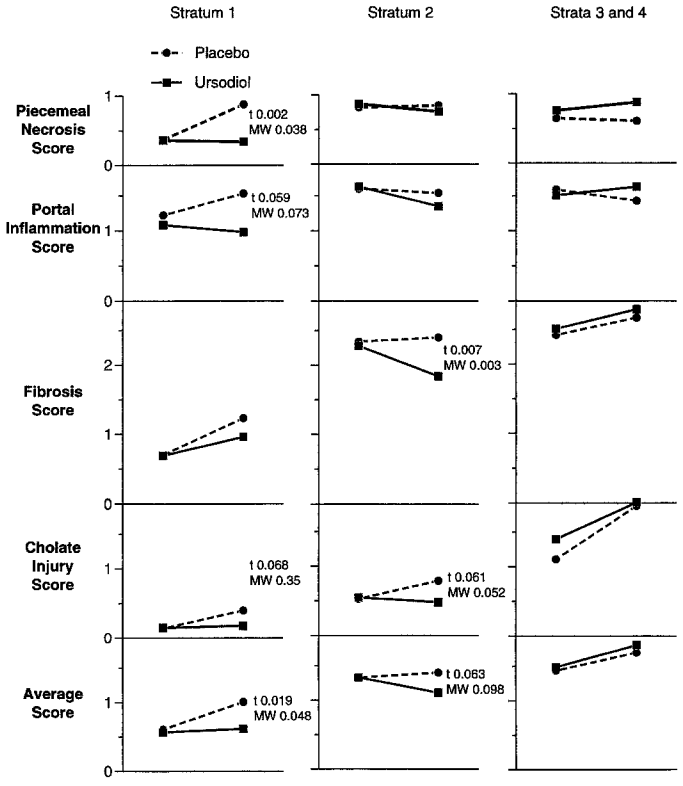

FIG. 3. A comparison of treatment effects (ursodiol or placebo) on changes in histological parameters in patients in stratum 1, stratum 2, and in strata 3 and 4. Shown are scores at entry and at 2 years. Between-treatment relevant P values shown for t-tests and Mann-Whitney tests.

DISCUSSION

The current trial demonstrates a marked improvement in results of liver tests that serve as markers of cholestasis and inflammation in PBC patients treated with ursodiol for 2 years. This was particularly evident in patients with an entry serum bilirubin less than 2 mg/dL (strata 1 and 2). Ursodiol also prevented worsening of piecemeal necrosis, portal inflammation, and of cholate injury (i.e., ballooning of hepatocytes adjacent to portal tracts and septa) in stratum 1 (serum bilirubin <2, stage I, II histology); and improved fibrosis and prevented worsening of cholate injury in stratum 2 (bilirubin <2, stage III, IV histology).

Severe treatment failures, i.e., bleeding esophagogastric varices, ascites, hepatic encephalopathy, liver transplantation, and death without transplantation,

TABLE 4. Treatment Failures

	Stratum 1		Stratum 2		Strata 3-4		All Patients		
	Placebo	Ursodiol	Placebo	Ursodiol	Placebo	Ursodiol	Placebo	Ursodiol	P*
No. of patients	19	26	33	26	22	25	74	77	
Patients withdrawn	1	1	2	1	0	0	3 (4)†	2 (3)†	.677
Bleeding varices, ascites, encephalopathy	1	2	2	2	5	11	8 (11)	15 (19)	.138
Transplantation/death	0	0	1	2	10	10	11 (15)	12 (16)	.902
Severe fatigue/pruritus	6	5	9	3	6	3	21 (28)	11 (14)	.034
Doubling of bilirubin	4	1	11	1	9	6	24 (32)	8 (10)	.001
Histological progression	2	2	5	3	8	4	15 (20)	9 (12)	.149
Development of varices	1	1	1	3	1	2	3 (4)	6 (8)	.496
No. of patients with any failure	12	11	19	11	20	21	51 (69)	43 (56)	.098

* P values are based on Pearson's χ^2 tests or Fisher's exact tests. The log rank P values are similar and omitted.
† Values in parentheses are percentages.

were comparable in ursodiol- and placebo-treated patients. The incidence of these severe events was much greater in patients whose entry serum bilirubin was ≥2 mg/dL (mean value, 5.1 mg/dL). Histologic progression by at least two stages or to cirrhosis and development of varices occurred to a similar extent in both treatment arms. Doubling of serum bilirubin occurred much more frequently in placebo-treated patients. Although mean scores for fatigue and pruritus were not favorably affected by ursodiol, severe worsening of these symptoms was noted less frequently in ursodiol-treated patients. Time to treatment failure occurred sooner in placebo as compared with ursodiol-treated patients in strata 1 and 2, but not in strata 3 and 4.

The major findings in the current trial are remarkably similar to those reported in similar recently completed trials conducted by three other groups[8-10] using generically comparable ursodiol at a somewhat higher dose than that used in the current study. The salient features of all four trials are summarized in Table 5.

All published trials demonstrate impressive improvements in results of laboratory tests, and in some histologic features (not yet reported for Lindor et al[10]). Few treatment effects were observed for symptoms. At 2 years, all trials observed trends toward fewer treatment failures in ursodiol-treated patients. Prevention of or slowing the increase in serum bilirubin is a major contributor to these findings. When observations are extended beyond 2 years (ursodiol vs. placebo for

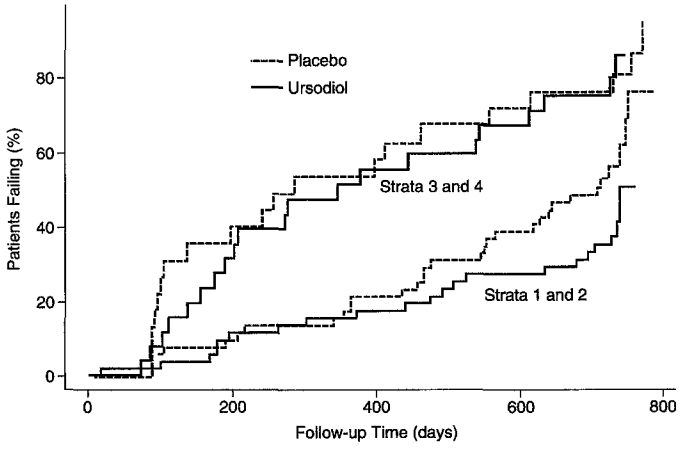

FIG. 4. Time to treatment failure for patients on ursodiol (solid lines) versus placebo (dashed lines). For patients in strata 3 and 4 (upper two lines), the log rank P = .868 and for patients in strata 1 and 2 (lower two lines), the log rank P = .057. For all patients, the log rank P = .168.

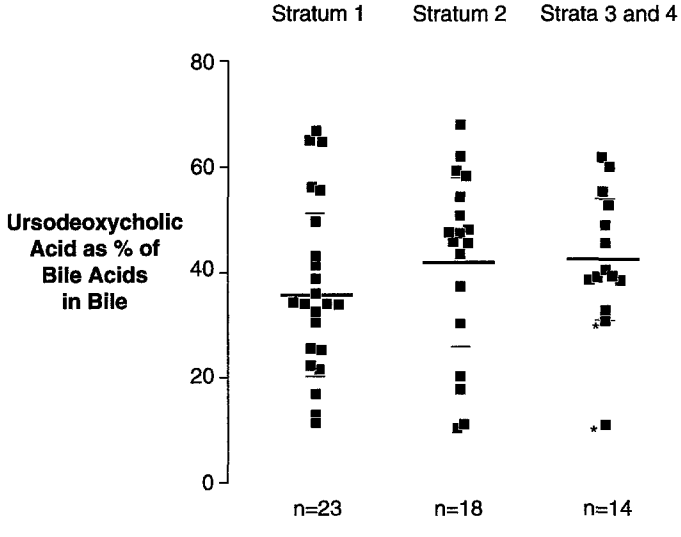

FIG. 5. Ursodiol as percent of bile acids in fasting bile, sampled at conclusion of trial by stratum. Mean percent ± SD for stratum 1, 37.0 ± 16.3; for stratum 2, 42.1 ± 17.4; for strata 3 and 4, 42.7 ± 12.9. Values for two patients in stratum 3 indicated by *. Mean percent for 51 placebo-treated patients (16 stratum 1, 26 stratum 2, 9 strata 3 and 4) was 0.4 ± SD, 0.6; range, 0 to 2.4%. Excluded are data for three such patients found to have significant amounts of ursodiol in the final bile sample (see text).

TABLE 5. Features of the Four Major Randomized, Double-Blind, Controlled Trials of Ursodiol Versus Placebo in the Treatment of Primary Biliary Cirrhosis

	Poupon et al[8]		Heathcote et al[9]		Lindor et al[10]		Combes et al	
	Placebo	Ursodiol	Placebo	Ursodiol	Placebo	Ursodiol	Placebo	Ursodiol
No. of patients	73	73	111	111	91	89	74	77
Percent women	89	95	95	91	87	91	92	86
Mean age (yrs)	52	54	55	57	52	54	49	49
Histological stage:								
I, II (%)	58	50	44	47	29	35	28	36
III, IV (%)	42	50	56	53	71	65	72	64
Mayo risk score	4.8	4.9	—	—	5.1	5.2	4.7	4.7
Duration of controlled trial	24 months		24 months		Up to 48 months Mean follow-up 24 months		24 months	
Daily dose (mg/kg)	13-15 in 2 doses		14 with evening meal		13-15 with meals and at bedtime		10-12 at bedtime	
Withdrawals	6 (8%)	5 (7%)	15 (14%)	10 (9%)	13 (14%)	5 (6%)	3 (4%)	2 (3%)
Completed 2-year trial	54 (74%)	62 (85%)	77 (69%)	89 (80%)	Uncertain		60 (80%)	63 (82%)
End point failures at 2 years:								
Death/transplantation	5* (7%)	5* (7%)	19 (17%)	12 (11%)	6† (7%)	6† (7%)	11 (15%)	12 (16%)
Developed cirrhosis	Not stated		Not stated		No difference		No difference	
Developed varices	Not stated		Not stated		No difference		No difference	
Ursodiol effects on:								
Symptoms	Not stated		No treatment effect		No treatment effect		No treatment effect on overall mean values, but significant decrease in development of severe fatigue/pruritus	
Laboratory tests	Improvements in bilirubin, alkaline phosphatase, GGT, AST, ALT, IgM, cholesterol		Improvements in bilirubin, alkaline phosphatase, GGT, AST, ALT, IgM, cholesterol		Improvements in bilirubin, alkaline phosphatase, AST		Improvements in bilirubin, alkaline phosphatase, GGT, AST, ALT, IgM, albumin, particularly in patients with entry serum bilirubin <2 mg/dL	
Histology	Better for piecemeal necrosis, parenchymal necrosis, portal and lobular inflammation, cholestasis, bile duct paucity and proliferation		Better for periportal ballooning and bile duct paucity		No effect on stage. Other features not yet reported.		Better for piecemeal necrosis, portal inflammation, and cholestasis in stratum 1; for fibrosis and cholestasis in stratum 2.	

Abbreviations: GGT, gamma-glutamyltransferase; AST, aspartate transaminase; ALT, alanine transaminase; IgM, immunoglobulin M.
* Estimated from Fig. 2, Reference 11.
† Estimated from Fig. 3.

Lindor et al,[10] although the number of patients assessed beyond 2 years is not clear); (placebo 2 years, then ursodiol 2 years vs. ursodiol for 4 years for Poupon et al[11]), fewer treatment failures, including death and transplantation, are recorded in favor of ursodiol. All trials demonstrate that ursodiol is well tolerated and safe, with a notable absence of drug-related toxicity.

The current trial demonstrates that patients with less advanced disease (bilirubin less than 2 mg/dL) derive the most benefit from ursodiol treatment. Test results improve the most, certain features of histologic progression are prevented, and time to treatment failure is slowed. Clearly, longer comparisons of ursodiol versus placebo are needed to determine whether and to what extent severe complications of liver disease will be prevented or delayed. The observations of Poupon et al[11] and of Lindor et al[10] suggest that ursodiol will impact favorably with long-term use, but it seems unlikely that ursodiol will be compared with placebo in a sufficient number of patients with earlier stages of primary biliary cirrhosis for the time required to demonstrate such effects.

The current trial also demonstrates that patients with more advanced disease (bilirubin 2 mg/dL or greater) are unlikely to benefit from ursodiol treatment. This group already has severe ductopenia, fibrosis, and cirrhosis. The incidence of treatment failures was very high in such patients. In our trial, the Mayo R score averaged 6.0 and 6.1, respectively, for the placebo and ursodiol-treated patients in strata 3 and 4, compared with the scores of 3.9 and 3.8 for those in stratum 1, and 4.2 and 4.4 for the placebo- and ursodiol-treated patients in stratum 2.

Assessment of enrichment of the bile acid pool with ursodiol as reflected in the bile analyses carried out at the end of the trial showed that ursodiol accounted for approximately 40% of the bile acids excreted into bile. This value was achieved in each of the strata, suggesting that differences in degrees of enrichment do not account for the differences in extent of response to ursodiol treatment. A comparable mean value of 39.5% was reported for the ursodiol-treated patients of Lindor et al.[10] Bile acid analyses for both trials were carried out in the same laboratory. Of interest, the comparable degree of enrichment was achieved even though our patients ingested a lower dose of ursodiol (10 to 12 vs. 13 to 15 mg/kg) and took it once at bedtime rather than in divided doses.

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