A MULTICENTER, CONTROLLED TRIAL OF URSODIOL FOR THE TREATMENT OF PRIMARY BILIARY CIRRHOSIS

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Abstract *Background.* In primary biliary cirrhosis the hepatic lesions may result, at least in part, from the intracellular accumulation of potentially toxic endogenous bile acids. Preliminary work suggests that the administration of ursodiol (also called ursodeoxycholic acid), a hydrophilic bile acid without hepatotoxicity, leads to improvement in the condition of patients with primary biliary cirrhosis.

Methods. We conducted a two-year, multicenter, double-blind trial to compare the efficacy of ursodiol with that of placebo. Patients with biopsy-proved primary biliary cirrhosis were randomly assigned to receive either ursodiol (13 to 15 mg per kilogram of body weight per day) (n = 73) or placebo (n = 73). Treatment failure was defined as a doubling of bilirubin levels to more than 70 μmol per liter or the occurrence of a severe complication (ascites or variceal bleeding) or an adverse reaction.

Results. Treatment failed in 6 patients in the ursodiol group, as compared with 13 in the placebo group ($P<0.01$ by Cox regression model). A single patient in each group withdrew because of minor adverse effects. After two years of treatment, the proportion of patients with clinically overt disease decreased only in the ursodiol group ($P<0.02$). The patients treated with ursodiol had significant improvements in serum levels of bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, cholesterol, and IgM (all $P<0.001$); the antimitochondrial-antibody titer ($P<0.01$); and the Mayo risk score ($P<0.001$). Follow-up analysis of 95 liver-biopsy specimens showed a significant improvement in the mean histologic score ($P<0.002$) and in all the characteristic histologic features except fibrosis only in the group given ursodiol.

Conclusions. Ursodiol is a safe and effective treatment for primary biliary cirrhosis. (N Engl J Med 1991; 324:1548-54.)

PRIMARY biliary cirrhosis is a chronic cholestatic liver disease of unknown cause, most often diagnosed in middle-aged women. Morphologically, primary biliary cirrhosis is characterized by portal inflammation and necrosis of biliary cells in the small and medium-sized bile ducts. These lesions result in the focal destruction of the interlobular and septal bile ducts, with progressive cholestasis. As in other forms of chronic obstructive cholestasis, lobular lesions and cirrhosis can occur. Although primary biliary cirrhosis is generally a progressive disease, the rate of progression varies greatly from one patient to another.[1] The terminal phase is characterized by hyperbilirubinemia (>100 μmol per liter), a major decrease in the number of intrahepatic bile ducts, and extensive fibrosis or cirrhosis. Orthotopic liver transplantation is currently the treatment of choice for patients with end-stage disease, with a two-year survival rate as high as 80 percent.[2]

Most of the drugs so far evaluated in controlled trials have been chosen for their immunosuppressive properties, with the aim of reducing portal inflammation and thereby limiting destruction of the bile ducts.[2-17] Colchicine has been used for its antifibrotic and antiinflammatory properties.[18-20] Most of these drugs, particularly cyclosporine, show some degree of efficacy, but major side effects make their long-term use hazardous.[16,17]

In 1987, we proposed ursodiol (also called ursodeoxycholic acid) as a novel therapeutic approach to primary biliary cirrhosis,[21] on the basis of evidence that hepatic lesions in chronic cholestatic diseases can result from intracellular accumulation of potentially toxic bile acids. Ursodiol is a hydrophilic bile acid devoid of cytotoxicity in humans and in vitro.[22] We postulated that long-term administration of ursodiol, by modifying the composition of the endogenous bile acid pool, might be beneficial to patients with primary biliary cirrhosis. This hypothesis was supported by the results of an uncontrolled prospective pilot study[21] and an interim analysis of the present trial.[23]

We now report the final results of a two-year, double-blind, multicenter, controlled trial that compared the efficacy and tolerance of ursodiol with those of a placebo in patients with primary biliary cirrhosis.

METHODS

This study was a multicenter, double-blind trial comparing the effects of ursodiol and a placebo in patients with primary biliary cirrhosis. A placebo was used, in the absence of a reference treat-

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ment, to provide a comparison with the natural history of primary biliary cirrhosis. The end points chosen to assess the efficacy of ursodiol during the two-year treatment period were as follows: a doubling of bilirubin concentrations to more than 70 μmol per liter or a value of more than 200 μmol per liter on two consecutive measurements three months apart; the occurrence of a serious complication, such as gastrointestinal bleeding from esophageal varices, ascites, or encephalopathy; and the occurrence of an adverse effect. When either treatment failed according to these criteria, the study design allowed patients whose clinical status was worsening to receive another treatment, including ursodiol. The sample size was calculated to allow a difference to be detected between the rates of treatment failure, estimated to be 30 percent in the placebo group and 5 percent in the ursodiol group, with an α level of 5 percent and a β level of 10 percent. After applying correction factors allowing an interim analysis after six months and taking into account the likelihood that we would not be able to evaluate 10 percent of the patients for various reasons, we determined that 100 patients were necessary for analysis.

Selection of Patients

Criteria for entry into the trial were the presence of clinical and histologic features compatible with a diagnosis of primary biliary cirrhosis, serum alkaline phosphatase activity more than twice the upper limit of normal, and a positive test (titer >1:100) for antimitochondrial antibodies. Patients were admitted to the trial regardless of the duration of symptoms or the histologic stage. Patients who had received any of the following drugs during the previous six months were excluded: ursodiol, azathioprine, chlorambucil, colchicine, corticosteroids, D-penicillamine, and cyclosporine. Other exclusion criteria were a serum bilirubin concentration above 150 μmol per liter, a serum albumin concentration below 25 g per liter, past or active gastrointestinal bleeding from esophageal varices, evidence of past or present extrahepatic obstruction of the bile ducts, excessive alcohol consumption (>50 g per day), and a positive test for hepatitis B surface antigen. Informed consent was obtained from each patient before the study, and the trial design was approved by the ethics committee of the Hôpital Saint-Antoine.

Study Design

Patients were randomly assigned by each center to receive either ursodiol, 13 to 15 mg per kilogram of body weight per day, or placebo in identical 200-mg capsules. At entry to the trial, in addition to a clinical examination, serum levels of bilirubin, alkaline phosphatase, alanine and aspartate aminotransferases, γ-glutamyltransferase, cholesterol, albumin, gamma globulins, immunoglobulins (IgG, IgA, and IgM), antimitochondrial antibodies, and total and individual serum bile acids (analyzed by capillary gas chromatography[24]) and prothrombin time were determined. A percutaneous liver biopsy was performed unless one had been done in the previous 12 months. The clinical examination was repeated and serum levels of bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and γ-glutamyltransferase were determined every three months. The other laboratory tests were repeated every six months. The progression of disease was assessed by histologic examination of liver-biopsy specimens obtained at the end of the two-year study period.

The trial started in June 1987 and ended in April 1990. The 22 participating clinical centers[23] were individually responsible for patient care and for the performance of standard liver-function tests. All assays of serum bile acids were performed in the same laboratory in the interests of standardization and the double-blind design. At the end of the trial, liver-biopsy specimens were reassessed by three pathologists who knew the sequence in which the specimens were obtained but not the treatment status of patients. A steering committee addressed all scientific, methodologic, and ethical problems arising during the trial.

Statistical Analysis

Quantitative data are expressed as means ±SE. To minimize variations between centers, enzyme activities and immunoglobulin data were standardized according to the reference values of each laboratory and are expressed as multiples of the upper limit of normal values. Pruritus was graded as follows: absent (a score of 0), occasional (1), or permanent (2). Similarly, fatigue was graded as absent (a score of 0), hindering normal activity (1), or preventing normal activity (2). Improvement and disease progression were defined as changes of one or two grades. Clinically overt disease was defined by the presence of at least one of the following signs or symptoms: jaundice, fatigue, pruritus, hepatomegaly, and splenomegaly. The Mayo risk score, based on a combination of five variables (bilirubinemia, age, albuminemia, prothrombin time, and severity of edema) was calculated as previously described.[25]

Liver-biopsy specimens obtained at entry and after two years were paired and reassessed at the end of the trial. Histologic stage was determined according to accepted criteria.[26] The stage was determined in terms of the most advanced lesions in each specimen. The main histologic features were graded as follows: fibrosis, 0 to 3; portal and periportal inflammation, 0 to 3; piecemeal necrosis, 0 to 2; ductular proliferation, 0 to 2; parenchymal lobular necrosis, 0 to 2, and inflammation, 0 to 3; and cholestasis, 0 to 3. The degree of bile-duct paucity was calculated as the number of interlobular bile ducts divided by the number of portal tracts. These values were used to calculate a liver-histology score for each liver-biopsy specimen. Histologic progression was analyzed according to changes in the grade and was deemed to be improving, unchanged, or worsening.

Quantitative data were compared with the Wilcoxon rank-sum test, and clinical and histologic variables were compared with the Wilcoxon rank-sum exact test for ordered categorical variables.[27] Treatment efficacy was assessed at various points over the two-year period; for each patient, at each point analyzed, the difference between the last value recorded and the initial value was computed, and comparisons were then made between treatment groups. Data are shown for the entire population (the intention-to-treat cohort) and for subjects who completed the study. The rates of treatment failure were estimated from survival curves based on the Kaplan–Meier method[28] and compared by the log-rank test.[29] Multivariate Cox analysis[30] was used to adjust for possible differences in prognostic factors between the two groups at entry. Variables predictive of treatment failure (bilirubin and albumin levels, age, and the presence of cirrhosis) were included with the treatment in the model; bilirubin level, albumin level, and age were expressed both as two value classes, with cutoff points of 16 μmol per liter, 37.4 g per liter, and 56 years, respectively, and as continuous variables. Bilirubin concentrations were expressed as log values. The proportional-hazards assumption for these variables was satisfied. One-sided tests were used to compare the two treatment groups, since ursodiol was tested against a placebo. Statistical calculations were performed with BMDP and Cytel software[27,31] on a VAX 8530 at the INSERM computing center.

Results

Eligibility and Base-Line Characteristics

The data for 146 patients were analyzed. After randomization, 73 patients were assigned to receive

Table 1. General and Histologic Characteristics at Entry in the Ursodiol and Placebo Groups.*

Characteristic	Ursodiol (N = 73)	Placebo (N = 73)
Age (yr)	55±1	57±1
No. of women (%)	69 (95)	65 (89)
Time since diagnosis — mo (range)	39±4 (1–132)	43±5 (0–240)
Histologic stage — no. of patients (%)		
I	15 (21)	16 (22)
II	21 (29)	26 (36)
III	23 (31)	20 (27)
IV	14 (19)	11 (15)

*Plus–minus values are means ±SE.

ursodiol and 73 to receive placebo. Three additional patients who were randomized (two in the ursodiol group and one in the placebo group) were excluded from the analysis for the following reasons: one had a bilirubin level of more than 300 μmol per liter, one was being treated for ascites, and one had intercurrent disease likely to compromise follow-up. Eight patients who entered the study after the deadline for inclusion but who completed the two-year treatment period were included in the analysis. The two groups were well matched for age, sex, time since initial diagnosis, and histologic severity (Table 1).

Treatment Failures and Withdrawals

During the two-year study period, there were 6 treatment failures in the ursodiol group and 13 in the placebo group. The reasons for failure in the ursodiol group were a doubling of bilirubin levels to more than 70 μmol per liter or an increase to more than 200 μmol per liter in three patients, ascites in one, gastrointestinal bleeding from esophageal varices in one, and side effects in one. The reasons for failure in the placebo group were a doubling of bilirubin levels to more than 70 μmol per liter or an increase to more than 200 μmol per liter in seven patients, ascites in three, gastrointestinal bleeding from esophageal varices in two, and side effects in one.

Five patients in the ursodiol group were withdrawn from the study: two for noncompliance and one each because of glomerulopathy and renal insufficiency, bone cancer, and cytolytic autoimmune (type 1) hepatitis. Six patients in the placebo group were withdrawn: four for noncompliance, one because of meningeal hemorrhage, and one because of liver metastases.

The failure rates were significantly different between the two groups, according to the log-rank test ($P<0.05$) (Fig. 1). To take into account the base-line characteristics of the patients, the failure rates were further compared in a Cox regression model, which included known prognostic variables. The treatment effect was significant ($P<0.01$), and the patients in the ursodiol group had a risk of failure of 0.32 (95 percent confidence interval, 0.11 to 0.88) relative to those receiving placebo.

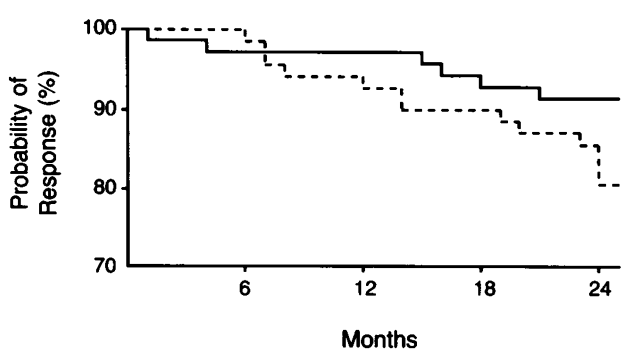

Figure 1. Probability of Responding to Treatment with Ursodiol (Solid Line) or Placebo (Dotted Line).

Kaplan–Meier estimates were used. The rates of treatment failure in the two groups were significantly different ($P<0.01$ by Cox regression model).

Table 2. Clinical Characteristics of the Ursodiol and Placebo Groups during the Two-Year Study.

Characteristic	Cohort at Entry	Intention-to-Treat Cohort	Cohort Completing Study*
		no. of patients (%)	
Jaundice			
Ursodiol	6 (8)	4 (5)†	0‡
Placebo	8 (11)	15 (21)	5 (9)
Pruritus§			
Ursodiol	39 (53)	22 (30)‡	14 (23)¶
Placebo	35 (48)	25 (34)	16 (28)
Fatigue§			
Ursodiol	28 (38)	22 (30)	15 (24)
Placebo	36 (49)	35 (48)	22 (39)
Hepatomegaly			
Ursodiol	18 (25)	17 (23)	13 (21)
Placebo	20 (28)	20 (27)	12 (21)
Splenomegaly			
Ursodiol	12 (16)	12 (16)	7 (11)
Placebo	15 (21)	17 (23)	9 (16)
Clinically overt disease			
Ursodiol	48 (66)	37 (51)¶	27 (44)‖
Placebo	44 (60)	44 (60)	30 (53)

*There were 73 patients in each group at the beginning of the study and 62 patients in the ursodiol group and 54 patients in the placebo group at the end of the study. The Wilcoxon rank-sum exact test was used for comparisons.

†$P<0.006$ for the comparison with values in the placebo group.

‡$P<0.07$ for the comparison with values in the placebo group.

§Graded according to a three-point scale.

¶$P<0.02$ for the comparison with values in the placebo group.

‖$P<0.03$ for the comparison with values in the placebo group.

Changes in Clinical and Biochemical Variables

Changes in the main clinical variables after treatment are shown in Table 2. The prevalence of hyperpigmentation, xanthoma, arthritis, Sjögren's syndrome, Raynaud's phenomenon, and CREST syndrome did not change significantly. The proportion of patients with clinically overt disease was significantly reduced in the ursodiol group after two years, as compared with the variations in the placebo group.

The time course of the changes in biologic variables is shown in Figure 2. After two years, the levels of the following were markedly reduced in the ursodiol group relative to the placebo group: bilirubin, alkaline phosphatase, aminotransferases, γ-glutamyltransferase, cholesterol, and IgM (Table 3). Finally, the mean Mayo risk score, reflecting the overall severity of the disease, was significantly reduced after two years of treatment with ursodiol (Table 3).

Changes in Histologic Features

The histologic analysis did not include the 19 patients in whom treatment failed or the 11 patients who withdrew from the trial. Among the 116 patients who completed the two-year treatment, paired liver-biopsy specimens were not available for 21, either because the patient refused to have a second biopsy or because the

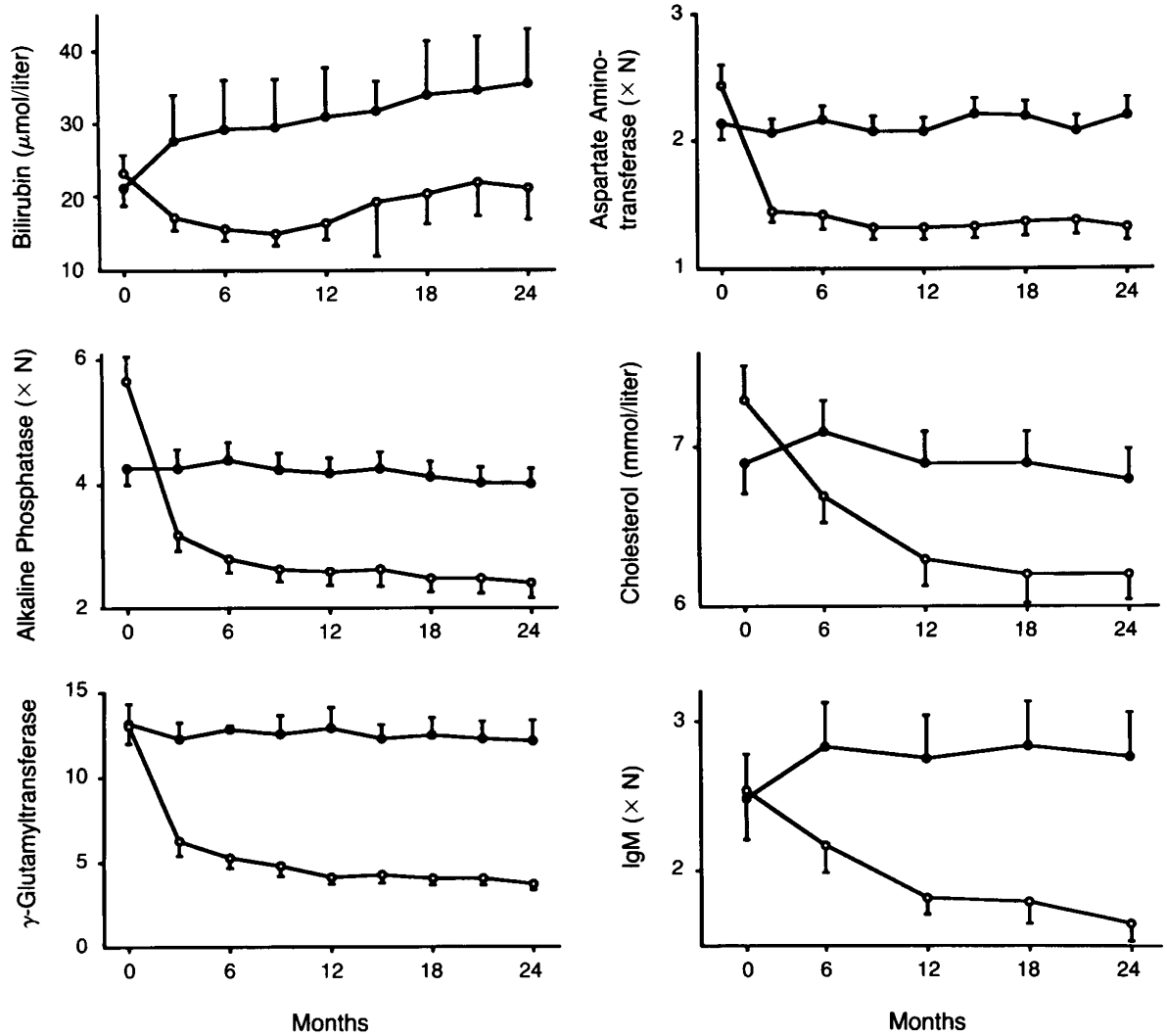

Figure 2. Changes in Mean Serum Bilirubin, Alkaline Phosphatase, γ-Glutamyltransferase, Aspartate Aminotransferase, Cholesterol, and IgM Concentrations in the Ursodiol (Open Circles) and Placebo (Solid Circles) Groups during the Two-Year Study.
Enzyme activities and IgM levels are expressed as multiples of the upper limit of normal (× N). All differences between the two groups were significant at every time studied except base line ($P<0.001$). Error bars indicate SE.

specimens were considered inadequate for analysis. The histologic analysis is therefore based on the results for 95 patients (50 in the ursodiol group and 45 in the placebo group). There was a significant improvement in the ursodiol group relative to the placebo group in the following characteristics: degree of bile-duct paucity ($P<0.05$), degree of ductular proliferation ($P<0.001$), degree of portal mononuclear-cell infiltration ($P<0.06$), degree of polymorphonuclear-cell infiltration ($P<0.02$), degree of piecemeal necrosis ($P<0.002$), degree of lobular inflammation ($P<0.03$), degree of parenchymal necrosis ($P<0.03$), and severity of cholestasis ($P<0.07$). The degree of fibrosis was not significantly different between groups ($P = 0.3$). At entry, the mean histologic scores were 11.0±0.5 and 10.0±0.6 in the ursodiol and placebo groups, respectively; after two years, the corresponding scores were 9.5±0.6 and 11.4±0.6 ($P<0.002$). Further details of the changes in the histologic score are given in Table 4.

Compliance with Treatment

Compliance was assessed by measuring the amount of serum ursodiol relative to the total level of bile acids in serum after an overnight fast. In the placebo group, if the proportion of ursodiol was higher than 30 percent, patients were considered to have taken ursodiol. Similarly, in the ursodiol group, patients were considered to have stopped treatment if the proportion of ursodiol was less than 30 percent. The mean percentages of ursodiol in the ursodiol and placebo groups were 3 percent in both groups at entry, 56 percent in the ursodiol group and 3 percent in the placebo group after one year, and 53 percent in the ursodiol group and 9 percent in the placebo group after two years. Five patients in the placebo group had evidence of

episodic ingestion of ursodiol. Twelve patients in the ursodiol group appeared to have discontinued treatment for periods of three to nine months. None of the patients in the placebo group in whom treatment failed had taken ursodiol, whereas one patient in the ursodiol group in whom treatment failed after 21 months had stopped taking the drug for nine months. If treatment compliance were taken into account in the analysis of the results, this patient would be excluded.

Discussion

The results of this double-blind, controlled trial show that ursodiol is a safe and effective treatment for patients with primary biliary cirrhosis. The two-year treatment with ursodiol markedly reduced the occurrence of events considered to be indicators of entry into the terminal phase of the disease. In addition, the Mayo risk score, a cross-validated index predictive of survival in primary biliary cirrhosis, was significantly reduced by such treatment. Moreover, there was a clear improvement in terms of the severity of pruritus, biochemical indicators of liver and immune function, and most of the characteristic histologic features; there was no effect on fibrosis. There were no major side effects; one patient in each group withdrew because of minor side effects. These findings confirm and extend the results of our pilot study[21] and the interim analysis performed after six months of the present trial.[23] The beneficial effect of ursodiol in terms of the biochemical features of primary biliary cirrhosis has previously been suggested in other controlled and uncontrolled trials involving small numbers of patients and shorter treatment periods.[32-35]

The results of this trial were analyzed on an intention-to-treat basis. Only three patients were excluded from the analysis, because they did not meet the inclusion criteria. Although compliance with treatment was not taken into account in the analysis, one patient in the ursodiol group in whom treatment was considered to have failed (doubling of the bilirubin level) had stopped taking ursodiol. It is also noteworthy that five patients assigned to the placebo group had serum ursodiol levels representing more than 30 percent of the total level of bile acids in serum, suggesting temporary or continuous ingestion of ursodiol.

Most of the patients in this study were symptomatic but did not have advanced disease. The number of subjects studied was too small to determine whether the beneficial effect of ursodiol in primary biliary

Table 4. Progression of Disease in the Ursodiol and Placebo Groups during the Two-Year Study, According to Histologic Analysis of Liver-Biopsy Specimens.*

Group	Improvement		No Change	Worsening	
	≤−5	−4 to −2	−1 to 1	2 to 4	≥5
Ursodiol	10	18	12	6	4
Placebo	5	8	10	13	9

*The specimens were graded according to changes in histologic scores: ≤−2 indicated improvement, −1 to 1 no change, and ≥2 worsening. Further details are given in the Methods section. Overall, the changes were significant (P<0.002).

Table 3. Laboratory Findings in the Ursodiol and Placebo Groups during the Two-Year Study.*

Variable	Cohort at Entry	Intention-to-Treat-Cohort	P Value†	Cohort Completing Study	P Value†
Bilirubin (μmol/liter)					
Ursodiol	23.2±2.6	21.2±4.3	<0.001	12.3±0.9	<0.001
Placebo	21.2±2.5	35.6±7.5		17.9±2.2	
Alkaline phosphatase (× N)*					
Ursodiol	5.68±0.40	2.41±0.24	<0.001	2.04±0.19	<0.001
Placebo	4.26±0.27	4.02±0.24		4.01±0.28	
Alanine aminotransferase (× N)					
Ursodiol	2.69±0.18	1.29±0.11	<0.001	1.16±0.10	<0.001
Placebo	2.25±0.13	2.32±0.12		2.23±0.19	
Aspartate aminotransferase (× N)					
Ursodiol	2.44±0.16	1.32±0.10	<0.001	1.14±0.09	<0.001
Placebo	2.14±0.13	2.19±0.15		2.08±0.18	
γ-Glutamyltransferase (× N)					
Ursodiol	13.04±1.07	3.72±0.33	<0.001	3.47±0.35	<0.001
Placebo	13.17±1.14	12.15±1.20		13.40±1.49	
Cholesterol (mmol/liter)					
Ursodiol	7.3±0.2	6.2±0.2	<0.001	6.2±0.2	<0.001
Placebo	6.9±0.2	6.8±0.2		7.0±0.2	
Albumin (g/liter)					
Ursodiol	38.9±0.5	38.9±0.6	NS	39.8±0.6	<0.05
Placebo	40.1±0.5	38.9±0.6		39.8±0.7	
Prothrombin time (%)					
Ursodiol	95.9±1.0	95.8±1.0	NS	97.0±0.9	NS
Placebo	95.4±1.1	94.5±1.2		93.7±1.8	
IgG (× N)					
Ursodiol	1.21±0.04	1.11±0.04	<0.01	1.10±0.05	<0.01
Placebo	1.15±0.05	1.20±0.05		1.14±0.05	
IgA (× N)					
Ursodiol	1.14±0.09	1.11±0.08	<0.07	1.01±0.08	<0.02
Placebo	0.94±0.06	1.03±0.08		0.92±0.09	
IgM (× N)					
Ursodiol	2.54±0.24	1.67±0.12	<0.001	1.65±0.13	<0.001
Placebo	2.49±0.27	2.77±0.30		2.50±0.31	
Gamma globulins (g/liter)					
Ursodiol	18.2±0.6	16.6±0.7	<0.04	15.9±0.8	<0.04
Placebo	18.1±0.7	17.7±0.7		16.1±0.8	
Antimitochondrial antibodies (1:titer)					
Ursodiol	1800±330	730±140	<0.01	730±140	<0.02
Placebo	1800±360	1700±300		1400±300	
Mayo risk score					
Ursodiol	4.90±0.12	4.59±0.13	<0.001	4.37±0.11	<0.001
Placebo	4.80±0.12	5.01±0.13		4.72±0.13	

*Plus–minus values are means ±SE. There were 73 patients in each group at the beginning of the study and 62 patients in the ursodiol group and 54 patients in the placebo group at the end of the study. Enzyme activities and immunoglobulin levels were standardized by dividing the measured value by the reference value of the laboratory, so that values are expressed as multiples of the upper limit of normal values (× N).

†NS denotes not significant (P>0.10). The Wilcoxon rank-sum test was used for comparisons.

cirrhosis depends on the severity of the disease. A meta-analysis of the results of this and other controlled studies now under way may provide an answer to this question. Nonetheless, since the probable mode of action of ursodiol is to reduce intestinal reabsorption of endogenous bile acids, it seems reasonable to think that the greater the degree of residual enterohepatic bile-acid circulation, the greater the potential beneficial effect. Thus, patients with severe bile-duct paucity or severe cholestasis are unlikely to benefit from treatment with ursodiol.

Drugs previously used for the treatment of primary biliary cirrhosis have had either only moderate efficacy or side effects that make their long-term use hazardous. Corticosteroids lead to improvements in liver function and in histologic features, but their long-term administration causes severe osteopenia.[15] Azathioprine, an immunosuppressive drug evaluated in two double-blind studies, has no beneficial effect on clinical symptoms, biochemical variables, or histologic progression.[11,12] Further analysis of the second trial, however, indicated that there might be a beneficial effect on survival.[13] In eight controlled clinical trials, D-penicillamine had no beneficial effect on primary biliary cirrhosis.[3-10] Chlorambucil leads to an improvement in biochemical variables, IgM concentrations, and some histologic features of primary biliary cirrhosis, but its long-term administration is limited by potentially severe side effects.[14] Colchicine improves biochemical variables but has no effect on clinical or histologic features.[18-20] Recently, promising results have been reported with cyclosporine.[16,17] In both studies there was an improvement in biologic variables, and in one there was also an improvement in clinical and histologic features. However, there was a very high incidence of side effects (particularly renal toxicity), thus establishing that prolonged administration requires careful evaluation. Moreover, these side effects compromised the double-blind nature of the latter trial and introduced a potential bias into the evaluation, particularly with regard to symptoms.[36] Thus, although ursodiol and cyclosporine appear to have comparable efficacy, ursodiol has the important advantage of being virtually free of side effects. Indeed, only one patient in our trial had a side effect (a transitory increase in the severity of pruritus early in the treatment) that required cessation of treatment with ursodiol. A similar phenomenon has previously been observed in patients with advanced disease,[21] and we now recommend that a lower dose of ursodiol be used at the outset of treatment.

When we originally proposed the use of ursodiol for the treatment of primary biliary cirrhosis,[21] we postulated that it might reduce the concentration of endogenous, hydrophobic bile acids in the liver, thereby hindering progression to the terminal phase. The results of this trial appear to support this hypothesis. Ursodiol probably modifies the composition of the bile-acid pool by inhibiting the ileal absorption of endogenous bile acids.[37,38] It has also been suggested that ursodiol may itself have a cytoprotective effect.[22,39]

Two unexpected effects of ursodiol in the present study are worthy of note. First, there was a strong decrease in serum cholesterol levels, with a gradual return to normal values after two years of treatment. Since ursodiol has little action on 3-hydroxy-3-methylglutaryl coenzyme A reductase, this effect is probably due to the reduced intestinal absorption of cholesterol,[40] together with an increase in its clearance from the blood or an increase in the number or activity of receptors for low-density lipoprotein cholesterol.[41] Second, some immunologic features of primary biliary cirrhosis improved markedly in the patients receiving ursodiol, suggesting that either ursodiol or the endogenous bile acids interfere with basic immune regulation in this disease. Our data do not indicate whether these effects were due to the overall improvement in liver function or were directly related to the presence of ursodiol or the reduction in endogenous bile acids in the blood and liver. However, we have recently found that bile acids have major effects on components of the immune system. The expression of HLA antigens in the liver, which is induced by cholestasis,[42] is reduced by treatment with ursodiol.[43] Decreased expression of HLA antigens in biliary cells after ursodiol therapy has also been reported in patients with primary biliary cirrhosis.[44] Such a reduction in the expression of HLA Class I antigens might, by suppressing the target of cytotoxic T cells, block the destruction of bile ducts and prevent periportal or lobular necrosis, thereby slowing the progression of the disease.

In conclusion, given its efficacy and absence of side effects, ursodiol would now appear to be the medical treatment of choice for patients with primary biliary cirrhosis.

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