

URSODIOL FOR PRIMARY SCLEROSING CHOLANGITIS

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ABSTRACT

Background There is no satisfactory medical therapy for patients with primary sclerosing cholangitis. Ursodiol (ursodeoxycholic acid) benefits patients with primary biliary cirrhosis, another cholestatic liver disease.

Methods From May 1989 to July 1995, we enrolled 105 patients with well-documented primary sclerosing cholangitis in a randomized, double-blind study comparing ursodiol (13 to 15 mg per kilogram of body weight per day in divided doses) with placebo. The primary outcome was the time to treatment failure, defined as death; liver transplantation; histologic progression by two stages (of four) or progression to cirrhosis; the development of varices, ascites, or encephalopathy; sustained quadrupling of the serum bilirubin concentration; marked worsening of fatigue or pruritus; inability to tolerate the drug; or voluntary withdrawal from the study.

Results We analyzed data on the 51 patients in each group with at least 3 months of follow-up; the median follow-up was 2.2 years. There was no significant difference between the groups in time to treatment failure (relative risk of treatment failure in the ursodiol group, 1.01; 95 percent confidence interval, 0.6 to 1.7). During the first two years of follow-up, treatment was unsuccessful in 17 of 32 patients (53 percent) in the placebo group and 16 of 31 (52 percent) in the ursodiol group. There were also no differences in time to treatment failure for patients with early-stage disease or in time to liver transplantation. Ursodiol, but not placebo, was associated with improvement in serum alkaline phosphatase, aspartate aminotransferase, bilirubin, and albumin levels at one and two years.

Conclusions In a group of patients with well-defined primary sclerosing cholangitis, ursodiol provided no clinical benefit. (N Engl J Med 1997;336:691-5.)

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P RIMARY sclerosing cholangitis is a progressive cholestatic liver disease characterized by intrahepatic and extrahepatic biliary-duct fibrosis as well as associated inflammatory changes involving the portal and periportal regions of the liver.¹ The cause is unknown, although immunologic abnormalities have been described.^{2,3} Deleterious effects of retained toxic bile acids from progressive cholestasis may also be important. Currently, there is no effective treatment. A number of medications have been evaluated, but frequently in small, uncontrolled trials of short duration.⁴⁻⁷ Random-

ized, controlled trials have found no benefit from penicillamine, methotrexate, or colchicine.⁸⁻¹⁰

Ursodiol (ursodeoxycholic acid) is beneficial for patients with primary biliary cirrhosis, another cholestatic liver disease that has some features in common with primary sclerosing cholangitis.¹¹⁻¹³ In small or uncontrolled trials, ursodiol has shown benefit for some patients with primary sclerosing cholangitis.¹⁴⁻¹⁷ We evaluated the efficacy of ursodiol in patients with this disorder.

METHODS**Patients**

We conducted a multicenter, randomized, double-blind, placebo-controlled trial. The diagnosis of primary sclerosing cholangitis required a chronic cholestatic liver disease of at least six months' duration; a serum alkaline phosphatase level at least 1.5 times the upper limit of normal; retrograde, operative, or percutaneous cholangiographic findings of intrahepatic or extrahepatic biliary-duct obstruction, beading, or narrowing consistent with primary sclerosing cholangitis; and a liver biopsy in the previous three months with compatible findings.

Patients were excluded for the following reasons: treatment with ursodiol, colchicine, corticosteroids, cyclosporine, methotrexate, or penicillamine in the preceding three months; anticipated need for liver transplantation within one year (estimated one-year survival of 50 percent or less) on the basis of the Mayo survival model (Mayo risk score), which takes into account age, bilirubin level, presence of splenomegaly, and histologic stage¹⁸; recurrent variceal hemorrhage, spontaneous uncontrolled encephalopathy, or ascites resistant to diuretic agents; pregnancy; an age of less than 18 years or more than 70 years; features suggestive of coexisting liver diseases, including primary biliary cirrhosis, chronic alcoholic liver disease, autoimmune hepatitis, chronic hepatitis B or C, or cholangiocarcinoma; a history of intrahepatic stones or biliary tract operations aside from cholecystectomy; and recurrent ascending cholangitis requiring hospitalization more than twice a year.

Most of the participants were referred specifically because the referring physician knew about this study. A small number of patients were excluded because they did not meet the criteria with respect to elevation of serum alkaline phosphatase levels. Toward the end of the study, some patients were referred who had already begun to receive ursodiol in the form of Actigall (Summit, Ciba-Geigy, Summit, N.J.), which had become available by prescription. Such patients were not eligible for enrollment. We did not keep specific information about the number of patients not enrolled. We estimate that more than 90 percent of eligible patients were enrolled.

Patients were included regardless of the duration of disease, whether or not they were symptomatic, and whether, aside from the exclusion criteria, they had received previous therapy for their liver disease. Informed written consent was obtained from each

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*The members of the study group are listed in the Appendix.

patient before the study; the trial was approved by the institutional review board of the Mayo Foundation.

The study was designed to compare the effects of ursodiol and placebo with respect to the time to treatment failure. Treatment failure was defined as death; liver transplantation; histologic progression by two stages (of four) or progression to cirrhosis; the development of varices, ascites, or encephalopathy; quadrupling of the serum bilirubin level for at least three months (with the second measurement during this period greater than 1.5 mg per deciliter [$26 \mu\text{mol}$ per liter]) without evidence of bacterial cholangitis, dominant stricture, or obstruction by a biliary-tract stone; marked worsening of fatigue or pruritus; inability to tolerate the drug; or voluntary withdrawal for any reason consistent with an intention-to-treat analysis. Patients in whom the treatment failed continued to receive their assigned treatment unless liver transplantation or drug toxicity necessitated withdrawal.

The grading system for pruritus was as follows: grade 0, none; grade 1, mild; grade 2, some interference with sleep; and grade 3, excoriation and substantial sleep disturbance. For fatigue, the grading system was as follows: grade 0, none; grade 1, present, but no interference with activity; grade 2, extra rest required and activity limited but patient able to work; and grade 3, patient unable to work a full day. Worsening of symptoms as a component of treatment failure was defined as progression by two grades or the development of disabling pruritus or fatigue.

Liver-biopsy specimens were compared sequentially. For histologic staging, the criteria of Ludwig et al.¹⁹ were applied, in which stage I represents inflammation confined to the portal tracts; stage II, inflammation in the periportal region; stage III, fibrosis; and stage IV, established cirrhosis. The slides were read with coded identification by the pathologist.

Experimental Design

Patients were enrolled from the Mayo Clinics in Jacksonville, Florida; Scottsdale, Arizona; and Rochester, Minnesota, which served as the coordinating center. Patient groups were stratified according to histologic stage (stage I or II vs. stage III or IV), serum bilirubin level (≤ 1.8 mg per deciliter [$31 \mu\text{mol}$ per liter] vs. >1.8 mg per deciliter), and the presence or absence of esophageal varices. Randomization was carried out separately for each of the eight strata (combinations of variables) with a computer-generated, blocked, randomized drug-assignment schedule.

Ursodiol was administered in the form of 250-mg tablets (URSO, Axcan Pharma, Mont St. Hilaire, Quebec, Canada) at a dose of 13 to 15 mg per kilogram of body weight per day in four divided doses, given with meals and a bedtime snack. The placebo was an identical-appearing tablet given in the same way. Patients receiving cholestyramine were asked to take that drug two hours before or after their study medication. The patients, physicians, nurses, and study coordinators were blinded as to whether active drug or placebo was being administered.

At entry, a complete history was taken and a complete physical examination was performed, and serum levels of alkaline phosphatase, aspartate aminotransferase, bilirubin, and albumin and the prothrombin time were measured. A serum sample from each patient was stored. Abdominal ultrasonography, esophagogastroduodenoscopy, and liver biopsy were performed. At the time of esophagogastroduodenoscopy, bile samples were obtained after stimulation with cholecystokinin (40 ng per kilogram intravenously) to measure biliary bile acid composition.

Serum biochemical values were determined at three-month intervals. Annual evaluations included a complete history and physical examination, and determination of liver biochemical values and the prothrombin time. Liver biopsy, abdominal ultrasound examination, and esophagogastroduodenoscopy were repeated biannually. Additional ultrasound examinations and esophagogastroduodenoscopy were performed when clinically indicated. All patients had undergone diagnostic cholangiography at some time before entry. In 100 of the 105 patients, this had been performed endoscopically. Endoscopic retrograde cholangiopancreatography

was repeated only as clinically indicated. Duodenal bile acid levels were measured at entry and at two years. Samples were stored at -70°C and analyzed for ursodeoxycholic acid by high-performance liquid chromatography in the laboratory of Dr. Alan Hofmann at the University of California, San Diego, with previously validated methods.²⁰

The protocol originally called for three years of recruitment and a minimum of two years of follow-up. Recruitment declined after the first year, and the accrual period was extended, with the approval of the institutional review board, to six years.

Statistical Analysis

In the primary analysis we compared the time to treatment failure using methods for censored survival data.²¹ Data on patients in whom treatment failure did not occur were censored at the time of the last follow-up visit. Event-free survival in the two groups was estimated by the Kaplan-Meier method and compared between groups with use of the two-sample log-rank test. We also adjusted for potential imbalances in the stratification variables by estimating treatment effect in a Cox proportional-hazards regression model that included the strata as covariates.

Two-sample *t*-tests or Wilcoxon rank-sum tests were used to examine differences between treatment groups with respect to changes in biochemical values from base line to one and two years. Statistical tests were conducted at a two-sided alpha level of 0.05.

With the observed accrual rates and an estimated survival free of treatment failure of 3.3 years in the placebo group, the study had approximately 70 percent power to detect a hazard ratio of 2.0 (placebo:ursodiol) with 51 subjects per group and approximately 90 percent power to detect a hazard ratio of 2.5.

RESULTS

Between the middle of 1989 and the middle of 1995, 105 patients were enrolled: 91 from Rochester, 10 from Scottsdale, and 4 from Jacksonville. Fifty-three received ursodiol, and 52 placebo. Two patients assigned to ursodiol and one assigned to placebo did not have follow-up data beyond three months. Our analyses are based on the 51 patients in each group who had at least three months of follow-up.

The groups were well matched at entry with respect to age, sex, histologic stage, base-line biochemical values, the presence of esophageal varices, Mayo risk score, and the presence of inflammatory bowel disease (Table 1). The mean age was 42 years; 58 percent of the patients were men. Eighty-one percent had a history of inflammatory bowel disease. The median follow-up was 2.2 years (range, 0.5 to 72 months). Ursodiol was well tolerated. Two patients in the placebo group stopped therapy, one because of a flare of chronic ulcerative colitis and the second because of diarrhea.

The main results are shown in Figure 1. Ursodiol treatment had no effect on time to treatment failure (relative risk of treatment failure in the ursodiol group, 1.01; 95 percent confidence interval, 0.6 to 1.7) (Fig. 1A). During the first two years of follow-up, treatment failure occurred in 17 of 32 patients in the placebo group (53 percent) and in 16 of 31 in the ursodiol group (52 percent). Similarly, there were no significant differences between the groups in time to treatment failure among patients with an

TABLE 1. CLINICAL AND LABORATORY CHARACTERISTICS OF THE STUDY PATIENTS AT ENTRY.*

CHARACTERISTIC†	URSODIOL (N = 53)	PLACEBO (N = 52)
Age — yr	41.7±1.8	43.8±1.6
Female sex — %	40	44
Histologic stage — no. (%)		
I	13 (25)	6 (12)
II	16 (30)	16 (31)
III	17 (32)	18 (35)
IV	7 (13)	12 (23)
Alkaline phosphatase — U/liter	1103±106	1260±129
Aspartate aminotransferase — U/liter	117±11	111±10
Bilirubin — mg/dl	1.6±0.2	1.6±0.2
Bilirubin level >1.8 mg/dl — no. (%)	13 (25)	11 (21)
Albumin — g/dl	4.0±0.1	3.9±0.1
Varices — no. (%)	18 (34)	14 (27)
Previous variceal bleeding — no. (%)	3 (6)	1 (2)
Mayo risk score‡	4.0±0.1	4.1±0.2
Inflammatory bowel disease — no. (%)	41 (77)	44 (85)

*Plus-minus values are means ±SD.

†For alkaline phosphatase the normal range is 90 to 234 U per liter; for aspartate aminotransferase, 12 to 31 U per liter; for bilirubin, 0.1 to 1.1 mg per deciliter (1.7 to 18.8 μmol per liter); and for albumin, 3.5 to 5.0 g per deciliter. To convert values for bilirubin to micromoles per liter, multiply by 17.1.

‡The Mayo risk score is based on age, bilirubin level, histologic stage, and the presence or absence of splenomegaly; values range from 2.3 to 7.1, with higher values indicating more severe disease.¹⁸

early histologic stage of disease (relative risk, 0.7; 95 percent confidence interval, 0.3 to 1.8) (Fig. 1B) or in time to liver transplantation (relative risk, 1.5; 95 percent confidence interval, 0.6 to 3.5) (Fig. 1C). When the individual components of the definition of treatment failure were assessed, no significant differences between groups were found (Table 2). The presence or absence of colitis did not influence the response to treatment.

Ursodiol, but not placebo, was associated with improvement in serum alkaline phosphatase, aspartate aminotransferase, bilirubin, and albumin levels at one and two years (Table 3).

Ursodiol was not associated with significant changes in histologic findings in the liver or changes in symptoms after two years. There was a significant increase in the percentage of ursodeoxycholic acid in bile among treated patients (48±20 percent, as compared with 4±5 percent in the placebo group; P<0.001). There were no significant differences between the groups with respect to changes in serum lipids (cholesterol, triglycerides, and high-density lipoprotein cholesterol) at one or at two years (data not shown).

Cholangiocarcinoma developed in three patients, all in the placebo group. The first had the diagnosis

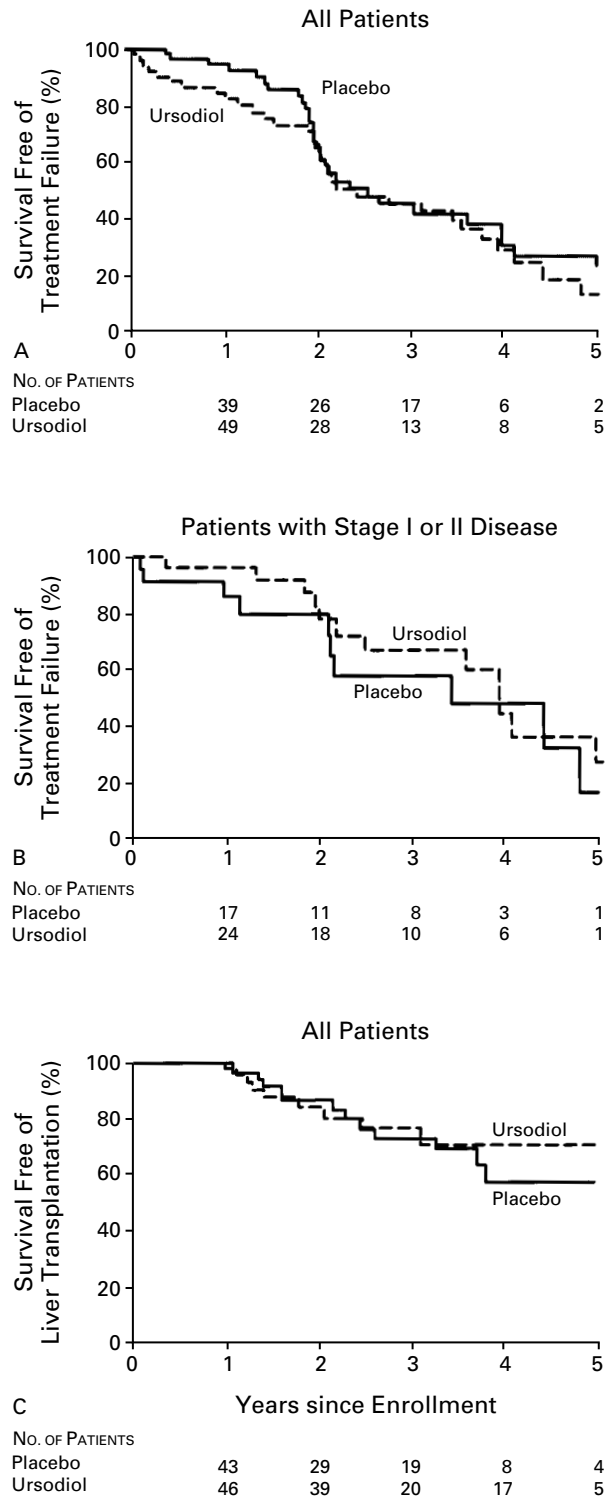


Figure 1. Kaplan-Meier Analysis of Survival Free of Treatment Failure among All Study Patients (Panel A) and Patients in Histologic Stage I or II (Panel B) and Survival Free of Liver Transplantation (Panel C).

TABLE 2. REASONS FOR FIRST TREATMENT FAILURE.*

REASON FOR FAILURE	PLACEBO (N=51)	URSODIOL (N=51)
	no. in whom responsible for failure/total no.	
Drug toxicity	2/2	0/0
Withdrawal from study	13/13	9/9
Liver transplantation	8/8	6/9
Quadrupling of bilirubin concentration†	2/2	2/3
Worsening of symptoms	2/3	3/3
Varices	6/7	8/8
Ascites	8/8	3/3
Encephalopathy	0/0	3/5
Histologic progression	3/3	7/8
Death‡	0/3	0/4
Other	2/2	3/3

*The three patients without follow-up (see the Results section) were excluded. Values shown are the numbers of patients in whom treatment failure was ascribed to a particular factor and the total numbers in whom the factor was present.

†In these patients the serum bilirubin concentration quadrupled and remained at that level for at least three months (with the second value measured during this period ≥ 1.5 mg per deciliter [$26 \mu\text{mol}$ per liter]) without acute cholangitis, dominant stricture, or obstruction by stones.

‡Causes of death included cholangiocarcinoma or gall-bladder cancer in three patients (two in the placebo group) and liver failure or complications of portal hypertension in four patients (one in the placebo group).

established two months after entry and almost certainly had an unrecognized tumor when she was initially evaluated. In the second, the cancer was diagnosed 18 months after entry, and the patient died 15 months later. The third had marked deterioration of liver-test results 15 months after entry and was found to have cholangiocarcinoma at the time of transplantation.

DISCUSSION

We found no obvious benefit of ursodiol treatment for patients with primary sclerosing cholangitis with respect to time to treatment failure. In contrast, ursodiol was associated with improved laboratory results, as in previous reports.¹⁴⁻¹⁷ Other trials have been shorter (three months to one year) and smaller (12 to 15 patients)¹⁴⁻¹⁷ and thus could not meaningfully evaluate the long-term efficacy of ursodiol with respect to clinically relevant end points.

In patients with primary biliary cirrhosis, ursodiol has been associated with improved survival and decreased need for transplantation, but there has been no evidence of similar effects in patients with primary sclerosing cholangitis.^{11,12} One possibility is that ursodiol is simply not effective in primary sclerosing cholangitis. The improvement in biochemical values may argue against this, but caution should be exercised to avoid overinterpreting biochemical improvement without detectable clinical improvement.

TABLE 3. COMPARISON OF LABORATORY FINDINGS BETWEEN STUDY GROUPS.*

BIOCHEMICAL VALUES	PLACEBO			URSODIOL		
	BASE LINE	12 MO	24 MO	BASE LINE	12 MO	24 MO
Bilirubin (mg/dl)††	1.6±1.6	2.2±3.3	2.6±3.7	1.6±1.6	1.3±1.4	1.5±2.1
Alkaline phosphatase (U/liter)‡§	1262±934	1194±818	1185±852	1102±762	592±462	655±481
Aspartate aminotrans- ferase (U/liter)§¶	111±73	120±86	132±122	120±78	70±71	68±47
Albumin (g/liter)‡	3.9±0.4	3.9±0.4	3.9±0.6	3.9±0.4	3.9±0.6	3.7±0.7

*The observations were based on 51 patients in each treatment group. In the placebo group, biochemical values were not available for 8 and 22 of the patients at one and two years, respectively. In the ursodiol group, values were not available for 4 and 14 patients at one and two years, respectively. The last available values for these patients were carried forward to avoid the confounding effect of the most ill patients' dropping out of the study.

†P<0.05 for the comparison of changes from base line to one year between groups. To convert values for bilirubin to micromoles per liter, multiply by 17.1.

‡P<0.05 for the comparison of changes from base line to two years between groups.

§P<0.001 for the comparison of changes from base line to one year between groups.

¶P<0.001 for the comparison of changes from base line to two years between groups.

||P>0.05 for the comparison of changes from base line to one year between groups.

Another possibility is that ursodiol is not sufficiently well absorbed to be able to exert a beneficial effect. However, a comparison of the percentages of ursodeoxycholic acid in the bile of patients with primary biliary cirrhosis and patients with primary sclerosing cholangitis (both groups received ursodiol) showed greater enrichment of biliary bile acids with ursodeoxycholic acid in the patients with primary sclerosing cholangitis (48 percent vs. 39 percent).¹¹

The lack of clinical effect may also be related to patient selection. A large percentage of the patients in this study, as in most studies of patients with primary sclerosing cholangitis, had an advanced histologic stage with substantial fibrosis. Given the patients' characteristics and the criteria for treatment failure, the disease may have been too advanced in many patients to respond to medical therapy. Moreover, the duration of the study was too short to detect differences in clinically relevant end points in patients with less advanced disease.

A randomized comparison of ursodiol and placebo might be conducted in patients in the earlier stages of the disease. They would need to be followed for a considerably longer period to assess the effect of therapy on the development of clinically important end points. Such a study, although theoretically desirable, would be very difficult to perform. The majority of patients with primary sclerosing cholangitis do not present with early disease, and even if they did, it is difficult to retain patients in placebo-controlled randomized trials for more than a few years.

To address further the question of the long-term effects of ursodiol in patients with primary sclerosing cholangitis, we are continuing to treat participants in this study who wish to receive the medication for a prolonged period. We plan to follow them and compare their course with that expected from natural-history models.¹⁸ Although not as rigorous a test as a randomized trial, this approach is more practical. On the basis of current data, however, we would not recommend empirical therapy with ursodiol for patients with primary sclerosing cholangitis.

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APPENDIX

The members of the Mayo Primary Sclerosing Cholangitis-Ursodeoxycholic Acid Study Group were as follows: *Mayo Clinic, Rochester*: K.D. Lindor, C. DeSotel, E.R. Dickson, G.J. Gores, J.B. Gross, Jr., R.A. Jorgensen, N.F. LaRusso, J. Ludwig, R.L. MacCarty, D.W. Mahoney, R.H. Wiesner, and A.R. Zinsmeister; *Mayo Clinic, Jacksonville*: C.R. Fleming, S.M. Lange, and J.R. Cangemi; *Mayo Clinic, Scottsdale*: M.L. Anderson; and *University of California, San Diego*: A.F. Hofmann.

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