Ursodeoxycholic Acid for Treatment of Nonalcoholic Steatohepatitis: Results of a Randomized Trial

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No effective medical therapy is available for all patients with nonalcoholic steatohepatitis (NASH). Ursodeoxycholic acid (UDCA) has been suggested to be of benefit based on open label clinical studies. We randomized 166 patients with liver biopsy–proven NASH to receive between 13 and 15 mg/kg/d of UDCA or placebo for 2 years. End points included changes in liver test results and liver histology at 2 years of therapy. The treatment groups were comparable at entry with regard to age, gender, risk factors for NASH, serum liver biochemistries, and baseline liver histology. A total of 126 patients completed 2 years of therapy. Pre- and posttreatment liver biopsies were available in 107 patients for review at the end of the study. UDCA was well tolerated and body weight was stable during the study duration. Serum liver biochemistries were stable or improved in both the UDCA and placebo-treated groups. Changes in the degree of steatosis, necroinflammation, or fibrosis that occurred with therapy were not significantly different between the UDCA and placebo groups. In conclusion, 2 years of therapy with UDCA at a dose of 13 to 15 mg/kg/d, although safe and well tolerated, is not better than placebo for patients with NASH. (HEPATOLOGY 2004; 39:770–778.)

Nonalcoholic steatohepatitis (NASH), an increasingly recognized cause of chronic liver disease, is histologically indistinguishable from alcohol-induced liver injury but occurs in patients who deny alcohol abuse.[1] NASH represents only one stage within the spectrum of nonalcoholic fatty liver disease,[2] which may be the most common cause of chronic liver disease in the United States[3,4] and other countries.[5,6] Most patients with NASH have some degree of liver fibrosis[7]; in a subset of patients the disease progresses to cirrhosis[8] and liver cancer,[9] and in some patients it may lead to liver transplantation.[10] There are no proven treatments for NASH. Treatment of associated conditions such as obesity, diabetes mellitus, and dyslipidemia is frequently attempted but seldom effective in reversing NASH.[11] Pharmacologic therapy with insulin-sensitizing medications[12–14] and antioxidants[15,16] holds promise, but only small pilot studies lasting 1 year or less have been reported to date.

Ursodeoxycholic acid (UDCA), a naturally occurring bile acid with multiple hepatoprotective activities, improves liver condition in patients with a wide range of chronic liver diseases.[17] In an open-label pilot study,[18] we previously reported that in patients with NASH, 1 year of treatment with UDCA (13–15 mg/kg/d) improves liver enzymes and degree of steatosis evaluated by way of liver biopsy. Based on those results, we conducted a large-scale, placebo-controlled trial aimed at determining the efficacy of UDCA for the treatment of patients with NASH.

Methods

Study Design. Between 1994 and 2000, a total of 174 patients with liver biopsy–proven NASH were entered into this prospective, randomized, double-blind, placebo-controlled trial. Patients were enrolled from 13 medical centers in the United States and Canada. The study was conducted in compliance with the Declaration of Hel-

Abbreviations: NASH, nonalcoholic steatohepatitis; UDCA, ursodeoxycholic acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TNF-α, tumor necrosis factor-α.

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sinki and approved by appropriate regulatory bodies at all centers. All patients gave written informed consent for participation.

Male and female patients 18 to 75 years of age with NASH were eligible. Inclusion criteria consisted of:

1. persistent elevation of serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) at least 1.5 times the upper limits of normal for at least 3 months;
2. weekly ethanol consumption of less than 40 g as confirmed through an interview with the patient and a family member and completion of the Self-Administered Alcoholism Screening Test by the patient and someone close to the patient (*e.g.*, a spouse, family member, relative); and
3. a liver biopsy within the previous 6 months showing greater than 10% steatosis along with lobular necroinflammatory changes.

Patients were excluded for the following reasons:

1. treatment with UDCA or chenodeoxycholic acid in the 3 months prior to the study;
2. anticipated need for transplantation within 1 year or recurrent variceal bleeding, spontaneous portosystemic encephalopathy, diuretic-resistant ascites, or bacterial peritonitis;
3. pregnancy or lactation;
4. treatment with any drugs associated with steatohepatitis (*e.g.*, corticosteroids, high-dose estrogens, methotrexate, amiodarone, calcium channel blockers, spironolactone, sulfasalazine, naproxen, or oxacillin) in the 6 months prior to the study;
5. laboratory or histologic findings highly suggestive of liver disease of another etiology, such as chronic viral hepatitis, autoimmune hepatitis, primary biliary cirrhosis, biliary obstruction, or genetic liver diseases such as hemochromatosis, alpha-1-antitrypsin deficiency, or Wilson's disease; and
6. age less than 18 years or more than 75 years.

A complete history, physical examination, and laboratory assessment including height and weight and measurement of serum liver biochemistries (including ALT, AST, alkaline phosphatase, γ-glutamyl-transferase, and total and direct serum bilirubin), fasting blood glucose, and lipid profile (cholesterol, triglycerides, high-density lipoprotein cholesterol) was performed prior to entry. Abdominal Doppler ultrasonography was performed at entry to assess liver echotexture, biliary tree, vascular patency, presence of ascites, and evidence of portal hypertension. An upper endoscopy was performed to assess for esophageal varices and hypertensive portal gastropathy in patients with advanced fibrosis (septal fibrosis or cirrhosis) on initial liver biopsy.

Patients were randomly assigned in a double-blind manner to receive 13 to 15 mg/kg/d of oral UDCA or an identical-appearing placebo for 2 years. Patients were stratified for presence or absence of diabetes (fasting blood glucose $>$150 mg/dL on at least two occasions or use of an oral hypoglycemic agent or insulin), obesity (weight $>$20% above ideal body weight), and hypertriglyceridemia (serum fasting triglycerides $\geq$200 mg/dL). The study pharmacy at each participating site was provided with a randomized list for each strata. The patients brought their entry forms to the pharmacy. Each patient's name and clinic or medical record number was recorded, and each patient was assigned a study number. Patients were then given their study drug based on the previously randomized list. UDCA and placebo tablets were provided by Axcan Pharma US (Mont Saint-Hilaire, Canada) and administered in four divided doses daily given with meals and a bedtime snack. The investigators, study coordinators, and patients were blinded as to the treatment administered.

At the time of initial administration of the study drug, the treatment regimen was reviewed with the patient. Enough UDCA (or placebo) tablets for 15 weeks was given to each randomized patient. Because the subjects were only seen each year, further drug supplies were shipped to them every 3 months by mail. Patients returned all unused drug supplies to the study coordinator as soon as they received the new 3-month supply. Patients recorded the dates at which they started and stopped taking tablets of a specific drug shipment. This information allowed for calculation of patient compliance. Patients were discouraged from using over-the-counter medications and were asked to report any new prescription drugs they were using.

Weight loss was encouraged in all overweight or obese patients. Patients recorded their weight in pounds on the first day of each month and reported this reading to the investigator or coordinator at each site each quarter. Samples for serum AST, ALT, alkaline phosphatase, bilirubin, and albumin were collected using mailed containers every 3 months. Patients were re-evaluated at 1 and 2 years with complete history and physical examination and measurement of serum liver biochemical values. Following 2 years of drug therapy, repeat percutaneous liver biopsy was performed.

Baseline and posttreatment liver biopsies were reviewed at the end of the study by a single pathologist in a central location to better ensure consistency. This pathologist was blinded to the sequence of the biopsy and assigned treatment. The severity of fatty infiltration, necroinflammation and fibrosis on liver biopsy was

Table 1. Baseline Values

Variable	UDCA	Placebo	*P* Value
Age (y) N	80	86	
Mean (S.D.)	45.4 ± 12.0	48.5 ± 11.6	.12
Median (minimum, maximum)	47.5 (19.0, 70.0)	49.0 (25.0, 74.0)	
Gender (%) N	80	86	.80
Male	36 (45%)	37 (43%)	
Female	44 (55%)	49 (57%)	
Weight (pounds) N	80	86	
Mean (S.D.)	207.0 ± 52.0	202.9 ± 45.4	.79
Median (minimum, maximum)	202.5 (115.0, 446.7)	199.3 (124.0, 390.0)	
Body mass index (kg/m^2) N	79	84	
Mean (S.D.)	32.3 ± 6.4	31.7 ± 5.5	.76
Median (minimum, maximum)	31.0 (21.0, 58.0)	31.0 (22.0, 47.0)	
AST (12–31 IU/L) N	78	86	
Mean (S.D.)	71.4 ± 42.4	70.6 ± 41.4	.85
Median (minimum, maximum)	60.0 (8.0, 263.0)	59.5 (25.0, 267.0)	
ALT (9–29 IU/L) N	79	86	
Mean (S.D.)	104.6 ± 56.3	108.0 ± 73.4	.92
Median (minimum, maximum)	90.0 (32.0, 302.0)	95.0 (32.0, 521.0)	
Alkaline phosphatase (81–213 IU/L) N	79	86	
Mean (S.D.)	154.7 ± 102.9	154.4 ± 103.1	.94
Median (minimum, maximum)	146.0 (42.0, 679.0)	124.0 (48.0, 572.0)	
GGT (10–39 IU/L, M; 6–29 IU/L, F) N	50	56	
Mean (S.D.)	100.6 ± 113.4	108.9 ± 99.1	.43
Median (minimum, maximum)	73.5 (19.0, 704.0)	78.5 (17.0, 515.0)	
Prothrombin (8.4–12.0 s) N	70	75	
Mean (S.D.)	11.6 ± 1.6	11.9 ± 1.7	.41
Median (minimum, maximum)	11.6 (8.4, 14.7)	11.9 (8.7, 15.5)	
Total bilirubin (0.1–1.0 mg/dL) N	79	86	
Mean (S.D.)	0.8 ± 0.5	0.9 ± 0.7	.71
Median (minimum, maximum)	0.7 (0.2, 4.3)	0.7 (0.0, 4.7)	
Direct bilirubin (0.0–0.3 mg/dL) N	68	66	
Mean (S.D.)	0.2 ± 0.1	0.2 ± 0.1	.37
Median (minimum, maximum)	0.1 (0.0, 0.7)	0.2 (0.0, 0.7)	
Albumin (3.5–5 g/dL) N	78	86	
Mean (S.D.)	4.4 ± 0.4	4.3 ± 0.5	.78
Median (minimum, maximum)	4.4 (3.1, 5.7)	4.3 (3.2, 5.5)	

Abbreviations: GGT, γ-glutamyltransferase; M, male; F, female.

graded on a 0–3+ scale (0 = none; 1+ = mild; 2+ = moderate; 3+ = severe). Information about presence of Mallory's hyaline and ballooning of hepatocytes was also collected based on the scoring system developed by Brunt and colleagues.[19] Twelve patients had biopsies; however, their slides could not be retrieved at the conclusion of the study, so they were not included in the histologic data.

Statistical Analysis. Comparison of serum biochemical parameters and liver histology before and after drug therapy was performed. Wilcoxon signed-rank tests were used for comparisons of baseline to follow-up overall and within treatment groups. Wilcoxon rank-sum tests were used between treatment group comparisons. Spearman's rank correlation coefficient was used as a measure of association. A χ^2 test was used for gender comparison.

The sample size was based on our previous experience with patients with NASH. We estimated that 5% or fewer of patients would spontaneously improve in the placebo group. To detect at least a 25% response rate among the treatment patients, using a two-sample test for proportions at an alpha level of 0.05 with 90% power, we estimated that we needed to include 65 patients per group (130 patients total) to detect a difference of 20% between success rates. Adjusting for an estimated drop-out rate of 20%, and a failure to acquire biopsy tissue in some, a total of 174 patients were entered to be followed over a 2-year period.

Results

Characteristics of the Patients. Of the 174 subjects randomized, eight (six randomized to UDCA, one randomized to placebo, one with unknown randomization) were not included in the analysis data set for various rea-

Table 2. Baseline Histology

Variable	UDCA	Placebo	*P* Value
Overall steatosis (stage) N	70	74	
Mean (S.D.)	2.2 ± 0.7	2.1 ± 0.7	.29
Median (minimum, maximum)	2.0 (0.0, 3.0)	2.0 (1.0, 3.0)	
Overall steatosis (%) N			
0	1 (1%)	0 (0%)	
1	7 (10%)	16 (22%)	
2	39 (56%)	36 (49%)	
3	23 (33%)	22 (30%)	
Overall inflammation (stage) N	70	73	
Mean (S.D.)	1.7 ± 0.8	1.8 ± 0.8	.79
Median (minimum, maximum)	1.0 (1.0, 3.0)	2.0 (0.0, 3.0)	
Overall inflammation (%) N			
0	0 (0%)	1 (1%)	
1	36 (51%)	33 (45%)	
2	16 (23%)	21 (29%)	
3	18 (26%)	18 (25%)	
Overall fibrosis (stage) N	70	73	
Mean (S.D.)	1.5 ± 1.1	1.4 ± 1.2	.84
Median (minimum, maximum)	1.0 (0.0, 3.0)	1.0 (0.0, 3.0)	
Overall fibrosis (%) N			
0	16 (23%)	21 (29%)	
1	21 (30%)	17 (23%)	
2	17 (24%)	17 (23%)	
3	16 (23%)	18 (25%)	
Hepatocell balloon (stage) N	70	74	
Mean (S.D.)	1.4 ± 0.6	1.4 ± 0.6	.78
Median (minimum, maximum)	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	
Hepatocell balloon (%) N			
0	3 (4%)	2 (3%)	
1	35 (50%)	37 (50%)	
2	32 (46%)	35 (47%)	
Mallory's hyaline (stage) N	70	74	
Mean (S.D.)	0.5 ± 0.7	0.6 ± 0.8	.31
Median (minimum, maximum)	0.0 (0.0, 2.0)	0.0 (0.0, 2.0)	
Mallory's hyaline (%) N			
0	48 (61%)	40 (54%)	
1	18 (26%)	20 (27%)	
2	9 (13%)	14 (19%)	

sons. Data were lost for one subject. One subject was withdrawn before receiving the drug for not meeting study criteria based on the baseline liver biopsy (<10% steatosis). One subject declined postrandomization before receiving the drug. Two subjects declined postrandomization and returned all received drugs. Two subjects were given open-label placebo instead of randomized treatment. One subject, after a hospitalization, was rerandomized and all data from the initial randomization were lost.

The 166 patients included in the analysis, including 73 men and 93 women, had a median age of 47 years (range: 19–74). Eighty patients were randomized to UDCA; 86 were randomized to placebo. The two treatment groups were comparable at entry with regard to age, gender, risk factors for NASH, serum liver biochemistries, and liver histology (Tables 1 and 2). Forty patients were withdrawn for various reasons (Table 3). There was no significant change in body weight over the course of the study, and this was consistent among the two treatment groups (Fig. 1, Table 4). The baseline characteristics of these patients at entry were comparable to the patients who completed the study (data not shown). One patient died of a myocardial infarction.

Table 3. Reasons for Discontinuation

Reason	N
Completed	126
Had follow-up liver biopsy	119
No follow-up liver biopsy due to medical reason	2
No follow-up liver biopsy due to refusal	5
Reasons for discontinuation	
Adverse event	20
Death	1
Personal reason	
Financial/no insurance	3
Moved	3
Family	3
No perceived benefit	1
Lost to follow-up	2
Other, noncompliant	7

Biochemical Response. A significant improvement in serum levels of AST and ALT occurred with therapy in both the UDCA and placebo groups when compared with pretreatment values (Fig. 2); however, the degree of

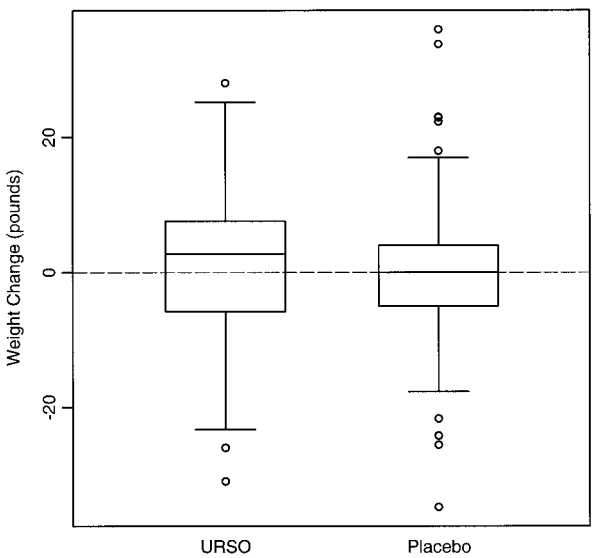

Fig. 1. Comparison of body weight change between both treatment groups.

Table 4. Differences at 24 Months From Baseline

Variable	UDCA	Placebo	*P* Value
Weight difference (pounds) N	56	65	
Mean (S.D.)	1.0 ± 12.4	0.2 ± 12.3	.33
Median (minimum, maximum)	2.4 (−31.0, 28.0)	0.0 (−34.8, 36.0)	
BMI difference (kg/m^2) N	53	60	
Mean (S.D.)	0.1 ± 2.0	−0.1 ± 2.6	.52
Median (minimum, maximum)	0.0 (−4.0, 4.0)	0.0 (−10.0, 7.0)	
AST difference (12–31 IU/L) N	55	64	
Mean (S.D.)	−21.7 ± 53.2	−20.7 ± 43.8	.37
Median (minimum, maximum)	−19.0 (−217.0, 121.0)	−9.0 (−167.0, 115.0)	
ALT difference (9–29 IU/L) N	56	61	
Mean (S.D.)	−32.7 ± 69.8	−31.6 ± 67.3	.60
Median (minimum, maximum)	−30.0 (−246.0, 133.0)	−24.0 (−243.0, 227.0)	
Alkaline phosphatase difference (81–213 IU/L) N	57	63	
Mean (S.D.)	−8.1 ± 54.2	−8.2 ± 47.5	.44
Median (minimum, maximum)	−1.0 (−268.0, 87.0)	−6.0 (−225.0, 143.0)	
GGT (10–39 IU/L, M; 6–29 IU/L, F) N	30	34	
Mean (S.D.)	−41.5 ± 117.5	−25.0 ± 46.3	.28
Median (minimum, maximum)	−19.5 (−628.0, 100.0)	−11.5 (−167.0, 40.0)	
Prothrombin difference (8.4–12.0 s) N	47	49	
Mean (S.D.)	0.1 ± 0.9	0.3 ± 1.3	.80
Median (minimum, maximum)	0.2 (−1.9, 2.4)	0.0 (−2.2, 3.7)	
Total bilirubin difference (0.1–1.0 mg/dL) N	55	63	
Mean (S.D.)	−0.0 ± 0.3	0.0 ± 0.6	.46
Median (minimum, maximum)	0.0 (−1.0, 0.7)	0.0 (−3.0, 1.5)	
Direct bilirubin difference (0.0–0.3 mg/dL) N	34	40	
Mean (S.D.)	0.0 ± 0.1	0.0 ± 0.1	.86
Median (minimum, maximum)	0.0 (−0.1, 0.2)	0.0 (−0.4, 0.6)	
Albumin difference (3.5–5 g/dL) N	54	62	
Mean (S.D.)	−0.1 ± 0.4	−0.2 ± 0.4	.32
Median (minimum, maximum)	−0.1 (−1.0, 1.0)	−0.2 (−1.1, 1.1)	

Abbreviation: GGT, γ-glutamyltransferase.

improvement between groups was not significantly different (Table 4). Similarly, changes in serum levels of other liver enzymes were similar between the two treatment groups (Table 4). There was a weak association between serum liver biochemistries and changes in weight among individual patients [AST: r = 0.22 (P = .02); ALT: r = 0.25 (P = .01)]. Similarly, in subgroups selected by the presence or absence of obesity, diabetes mellitus, hyperlipidemia, or severity of initial histology (presence or absence of severe fibrosis), there was no difference in treatment response between UDCA and placebo groups.

Histological Response. Of the 166 patients, pre- and posttreatment histologic material was available for re-review in 107 patients because 40 patients withdrew from the study, 7 patients refused repeat biopsy, and 12 patients had outside material that could not be retrieved for additional review. When compared with baseline, a significant improvement in the degree of steatosis occurred in the UDCA ($P < .0001$) and placebo ($P < 0.0001$) groups without significant changes in the degree of inflammation (P = .84 and 0.64, respectively) or severity of fibrosis (P = .75 and .86, respectively). Changes in the degree of steatosis, inflammation, or fibrosis were not significantly different between the two treatment groups (Table 5). Similarly, the changes in ballooning of hepatocytes and Mallory hyaline were not significantly different between the two treatment groups (Table 5). Subgroup analysis to assess the histologic response in patients by randomization strata—as well as by baseline histologic severity of the disease—failed to disclose any effect in these subgroups.

Adverse Events. Table 6 summarizes the number of patients who developed adverse events possibly related to UDCA or placebo. There was a trend for more gastrointestinal adverse events in the UDCA than in the placebo group, but the rate of clinical adverse events was similar in both groups. Twenty patients were withdrawn because of intolerance of the drug (11 in the UDCA group, nine in the placebo group); the reasons for withdrawal are shown in Table 7.

Natural History of Histology. Because there were no histologic differences between the UDCA-treated patients and the placebo-treated patients, the results were pooled to provide information regarding the natural his-

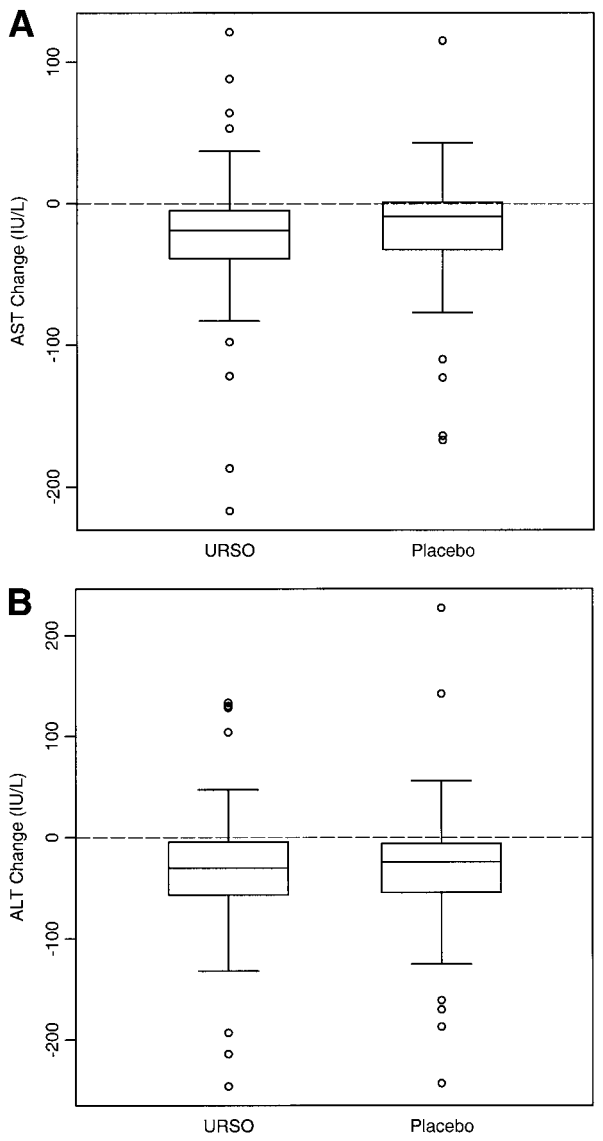

Fig. 2. Changes in (A) AST and (B) ALT in the UDCA and placebo groups. Two years of therapy led to a significant improvement in AST values in the UDCA ($P = .0001$) and placebo ($P < .0001$) groups when compared with baseline. However, this degree of improvement of AST ($P = .37$) and ALT ($P = .60$) was not significantly different between the two groups.

tory of NASH. Notably, the degree of steatosis was unchanged in 57 patients. More importantly, steatosis seemed to improve spontaneously in 44 patients (approximately 40%) and was noted to worsen in only six patients over the 2-year period. Furthermore, the degree of inflammation was stable in 59 patients. The number of patients with a decrease in necroinflammation was similar to the number with an increase in new inflammation over 2 years. Moreover, the degree of fibrosis appeared stable in 56 patients and regressed in 22 patients. Progression was noticed in 27 patients.

Discussion

The data from this study suggest that UDCA at 13 to 15 mg/kg/d is not of value as a sole agent in the treatment of patients with NASH. UDCA was not associated with an improvement in serum liver biochemistries or histology when compared with placebo. Furthermore, subgroup analyses did not suggest a benefit of UDCA therapy for patients with less or more severe disease. Previous uncontrolled studies in adult patients with NASH have used an UDCA dosage of 10 to 15 mg/kg/d, and all suggested a benefit.[11] The current study shows that when compared with baseline, UDCA leads to a significant improvement in serum aminotransferase levels as well as some histological features, which is in agreement with our previous study.[18] However, an equal improvement was seen in the placebo group. Thus the results of this larger placebo-controlled trial do no support a benefit of UDCA. Without a placebo (control) group, we would have wrongly concluded that UDCA therapy is associated with substantial biochemical and histologic improvement in patients with NASH. The spontaneous biochemical and histologic improvements in the placebo group further emphasize the importance of including a control group in future treatment studies of NASH.

UDCA improves liver enzymes and liver histology in patients with a wide range of hepatobiliary diseases, with most data derived from patients with chronic cholestasis. For example, in patients with primary biliary cirrhosis, UDCA is a cost-effective therapy and has proven beneficial by delaying the progression of liver fibrosis and the development of cirrhosis and esophageal varices and improving transplant-free survival.[17] UDCA has been used in patients with cholestasis for almost two decades, and thus many data on the long-term safety of UDCA in patients with liver disease have been accumulated over time.

The mechanisms responsible for the development of necroinflammation and progressive fibrosis in patients with NASH are unknown, but differences in antioxidant systems and the degree of insulin resistance may be among the explanations.[2] Steatotic hepatocytes are more susceptible to necrosis when exposed to hydrophobic bile acids.[20] Steatotic hepatocytes also generate increased quantities of hydroperoxides when exposed to hydrophobic bile acids, resulting in increased oxidative stress within the liver.[20] A mechanistic link between oxidants, insulin resistance, and tumor necrosis factor-α (TNF-α) has been identified in animal models of fatty liver.[21] TNF-α seems to play a key role in the development of insulin resistance contributing to the pathogenesis of NASH.[22] At least in

Table 5. Differences in Histology at 24 Months From Baseline

Variable	UDCA	Placebo	*P* Value
Overall steatosis difference (stage) N	50	57	
Mean (S.D.)	−0.4 ± 0.6	−0.3 ± 0.7	.41
Median (minimum, maximum)	0.0 (−2.0, 1.0)	0.0 (−2.0, 2.0)	
Overall steatosis difference (%) N			
−2	1 (2%)	1 (2%)	
−1	22 (44%)	20 (35%)	
0	24 (48%)	33 (58%)	
1	3 (6%)	2 (4%)	
2	0 (0%)	1 (2%)	
Overall inflammation difference (stage) N	50	55	
Mean (S.D.)	0.0 ± 0.9	−0.1 ± 0.8	.43
Median (minimum, maximum)	0.0 (−2.0, 2.0)	0.0 (−2.0, 2.0)	
Overall inflammation difference (%) N			
−2	4 (8%)	3 (5%)	
−1	5 (10%)	10 (18%)	
0	28 (56%)	31 (56%)	
1	11 (22%)	9 (16%)	
2	2 (4%)	2 (4%)	
Overall fibrosis difference (stage) N	50	55	
Mean (S.D.)	0.0 ± 1.0	−0.0 ± 0.8	.50
Median (minimum, maximum)	0.0 (−3.0, 2.0)	0.0 (−2.0, 2.0)	
Overall fibrosis difference (%) N			
−3	1 (2%)	0 (0%)	
−2	3 (6%)	2 (4%)	
−1	6 (12%)	10 (18%)	
0	25 (50%)	31 (56%)	
1	13 (26%)	11 (20%)	
2	2 (4%)	1 (2%)	
Hepatocell balloon difference (stage) N	50	57	
Mean (S.D.)	0.0 ± 0.7	−0.1 ± 0.5	.62
Median (minimum, maximum)	0.0 (−2.0, 1.0)	0.0 (−2.0, 1.0)	
Hepatocell balloon difference (%) N			
−2	1 (2%)	1 (2%)	
−1	9 (18%)	7 (12%)	
0	29 (58%)	43 (75%)	
1	11 (22%)	6 (11%)	
Mallory's hyaline difference (stage) N	50	57	
Mean (S.D.)	−0.1 ± 0.7	−0.2 ± 0.8	.54
Median (minimum, maximum)	0.0 (−2.0, 2.0)	0.0 (−2.0, 2.0)	
Mallory's hyaline difference (%) N			
−2	2 (4%)	4 (7%)	
−1	7 (14%)	10 (18%)	
0	34 (68%)	35 (61%)	
1	6 (12%)	7 (12%)	
2	1 (2%)	1 (2%)	

patients with chronic cholestasis, long-term therapy with UDCA diminishes production of TNF-α which is associated with biochemical and histologic improvement.[23] Thus UDCA, by decreasing hydrophobic bile acids, is expected to improve oxidative stress and prevent cellular damage in patients with NASH. In addition, the decreased production of TNF-α accomplished during long-term therapy with UDCA is expected to improve the underlying insulin resistance in patients with this condition.

It is possible that UDCA is simply not effective in patients with NASH. However, we cannot ignore the fact that the dosage of UDCA used in this study was too low to demonstrate a benefit. In patients with primary biliary cirrhosis, a higher dosage does not seem to provide extra benefit than the standard dosage of 13 to 15 mg/kg/d.[24] However, in patients with primary sclerosing cholangitis,[25,26] and in patients with liver disease associated with cystic fibrosis,[27] it has been shown that a higher dosage of UDCA is equally well tolerated but is associated with a

greater benefit. Therefore, it may be worth investigating the potential benefit of a higher dosage of UDCA in patients with NASH.

The data from this study provide important insights into the natural history of NASH, as we have collected prospective histologic data on more than 100 patients with NASH. This study demonstrates that spontaneous improvement in serum aminotransferase levels can occur despite stable body weight, and—more importantly—that the degree of steatosis may spontaneously improve over a 2-year period in a substantial number of NASH patients. It is possible that the natural history of NASH is associated with spontaneous resolution of steatosis over time. Documented case reports of patients with NASH who exhibit disappearance of steatosis with development of cirrhosis is consistent with the hypothesis that steatosis may disappear in the late stages of disease.[28] Alternatively, the finding that 20% of patients had apparent spontaneous improvement in hepatic fibrosis may be attributable to sampling variability within the liver biopsy; however, it may also indicate that liver fibrosis in patients with NASH is not static but may worsen or improve spontaneously over time. Our experience suggests that future studies that include histologic findings in patients with NASH should have adequate sample size to accommodate this expected spontaneous variability in fibrosis in subsequent liver biopsies.

In conclusion, UDCA at a dose of 13 to 15 mg/kg/d was not effective in patients with NASH. Based on our findings, the natural history of steatohepatitis may be characterized by spontaneous regression of steatosis and slow progression of necroinflammation and fibrosis.

Table 6. Number of Patients With Adverse Events by Treatment Group for Active Treatment Period

	UDCA (N = 83)		Placebo (N = 86)		
System	N	%	N	%	*P* Value
Any	79	95	79	92	0.54
Cardiovascular	16	19	23	27	0.28
Cutaneous	24	29	24	28	1.00
Endocrine	21	25	20	23	0.86
Ear, nose, and throat	22	27	22	26	1.00
Gastrointestinal	64	77	54	63	0.05
Gastrointestinal/Liver	8	10	3	3	0.13
Genitourinary	30	36	26	30	0.51
Gynecologic	1	1	0	0	0.49
Hematologic	2	2	7	8	0.17
Musculoskeletal	26	31	32	37	0.52
Neoplasia	4	5	5	6	1.00
Neurologic	35	42	36	42	1.00
Ocular	8	10	7	8	0.79
Other	7	8	7	8	1.00
Psychiatric	13	16	11	13	0.66
Renal	3	4	3	3	1.00
Respiratory	12	14	11	13	0.82
Systemic	60	72	55	64	0.25

Table 7. Reasons for Withdrawal Due to Intolerance of the Drug

	UDCA	Placebo
Gastrointestinal intolerance	7	5
Rash	2	1
Miscellaneous		
Cardiac arrest	1	2
Paraesthesia	1	
Renal failure		1

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