

# Ursodeoxycholic Acid or Clofibrate in the Treatment of Non - Alcohol-Induced Steatohepatitis: A Pilot Study

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Non-alcohol-induced steatohepatitis (NASH) is characterized by elevated serum aminotransferase activities with hepatic steatosis, inflammation, and occasionally fibrosis that may progress to cirrhosis. No established treatment exists for this potentially serious disorder. Our aim was to conduct a pilot study to evaluate the safety and estimate the efficacy of ursodeoxycholic acid (UDCA) and clofibrate in the treatment of NASH. Forty patients were diagnosed with NASH based on a compatible liver biopsy with other causes of liver disease, including alcohol abuse, excluded by history, serum tests, and use of ultrasound. Twenty-four patients received 13 to 15 mg/kg/d of UDCA for 12 months. Sixteen patients with hypertriglyceridemia were placed on clofibrate, 2 g/day for 12 months. Twenty-five women and 15 men entered the study. Six of 40 patients (15%) withdrew because of side effects. Four additional patients were withdrawn because of noncompliance; one of them later required liver transplantation. In the UDCA group, the decreases in mean serum levels of alkaline phosphatase, alanine transaminase (ALT), and  $\gamma$ -glutamyl transpeptidase (GGT) as well as histological grade of steatosis were significant. Among the patients treated with clofibrate, no change from baseline was found in mean ALT, aspartate transaminase (AST), GGT, bilirubin, triglycerides, and cholesterol, or in histological grade of steatosis, inflammation, or fibrosis after 12 months of treatment as compared with entry. Alkaline phosphatase activities decreased significantly from baseline. Despite the known lipid-lowering effects of clofibrate, it did not appear to be of clinical benefit in the treatment of NASH in this 1-year pilot study. However, treatment of NASH with UDCA for 12 months resulted in significant improvement in alkaline phosphatase, ALT, GGT, and hepatic steatosis. The possible benefit of UDCA therapy should be further investigated in the context of a randomized, controlled trial. (HEPATOLOGY 1996; 23:1464-1467.)

Non-alcohol-induced steatohepatitis (NASH) is incompletely defined but may result in progressive liver disease with cirrhosis. NASH is a disease characterized by the development of histopathological features comparable to those findings induced by excessive alcohol intake, without clinical evidence of alcohol abuse. Macrovesicular steatosis, lobular and portal inflammation, and often Mallory bodies with fibrosis and occasionally cirrhosis characterize NASH. Other clinical conditions that may lead to comparable pathological features include jejunoileal bypass, total parental nutrition, chronic hepatitis C, Wilson's disease, and use of drugs such as calcium channel blockers, high-dose synthetic estrogens, methotrexate, and amiodarone. Classically, NASH has been associated with obesity, type II diabetes mellitus, and hypertriglyceridemia, although not in all series.

The pathogenesis of NASH is unknown but may relate to excessive accumulation of lipids in the liver. Steatotic livers secondary to alcohol abuse or associated with type II diabetes mellitus contain predominantly triglycerides and to a lesser extent cholesterol esters.<sup>9</sup> Elevated hepatic free fatty acids, products of triglyceride hydrolysis, have been identified in fatty liver of pregnancy,<sup>10</sup> alcohol-induced hepatitis,<sup>11</sup> and morbid obesity<sup>11-12</sup> and have been shown to cause cellular injury.<sup>13</sup>

There is no proved treatment for NASH. Ursodeoxycholic acid (UDCA) is a potentially cytoprotective agent<sup>14-15</sup> and, by preventing membrane injury may improve liver injury in NASH. Clofibrate, a lipid-lowering agent, has been demonstrated to decrease the amount of hepatic triglycerides in animal studies<sup>16</sup> and, on this basis, may be useful in the treatment of NASH. Here we report the results of 12 months of therapy with ursodeoxycholic acid or clofibrate in the treatment of NASH.

## PATIENTS AND METHODS

Forty patients were diagnosed with NASH, based on liver biopsy showing hepatic steatosis and lobular inflammation in the 6 months before study entry and compatible liver biochemical tests. Other causes of liver disease, including alcohol abuse, had been excluded by history, family interview, serum tests, liver biopsy, and hepatobiliary ultrasound in all patients. Patients were excluded if age was younger than 18 years or if serum pregnancy testing was positive. No patient

TABLE 1. Biochemical and Clinical Data at Entry

Measurement (Normal Values)	UDCA Group (mean = SD)	Clofibrate Group (mean = SD)	Comparison Between Groups
AST (12 - 31 U/L)	70.8 = 35.1	88.8 = 77.7	NS
ALT (9-45 U/L)	113.4 = 62.7	93.0 = 44.7	NS

Alkaline phosphatase (114-309 U/L)	234.5 = 106.1	298.4 = 236.0	NS
Total serum bilirubin (0.1-1.1 mg/dL)	0.7 = 0.3	0.6 = 0.2	NS
GOT (9-48 U/L)	77.3 = 52.8	174.1 = 197.3	NS
Cholesterol (185-265 Mg/dL)	193.7 = 32.8	227.2 = 52.8	NS
Triglyceride (137-198 Mg/dL)	158.4 = 58.1	352.9 = 176.6	P = .00
Weight (kg)	90.5 = 17.4	90.0 = 19.4	NS

Abbreviation: NS, not significant.

had a history of treatment with lipid-lowering agents or UDCA in the 6 months before study entry. Informed consent was obtained from each patient.

Laboratory evaluation included serum liver tests (total protein, albumin, aspartate transaminase (AST), alanine transaminase (ALT),  $\gamma$ -glutamyl transpeptidase [GGT], alkaline phosphatase, and total serum bilirubin), hepatitis B serology (hepatitis B surface antigen, antibody to hepatitis B surface antigen, antibody to hepatitis B core antigen), antibody to hepatitis C virus, hepatitis C RNA polymerase chain reaction, auto-antibodies (antinuclear antibody, antismooth muscle antibody, and antimitochondrial antibody), iron profile (serum iron, transferrin saturation, and ferritin), ceruloplasmin and  $\alpha$ -antitrypsin phenotype. Serum electrolytes, urea, creatinine, fasting glucose, complete blood count, cholesterol, and triglyceride levels were also obtained.

Patients were assigned to treatment groups according to the presence of gallstones and triglyceride level. Patients with cholelithiasis demonstrated on biliary ultrasound or serum triglyceride level less than 200 mg/dL were placed on UDCA because of UDCA's known beneficial effects in treating gallstones (n = 24). Patients with serum triglyceride level greater than 200 mg/dL and no gallstones were treated with clofibrate because of this agent's lipid-lowering effects (n = 16). A single patient had mild hypertriglyceridemia with a history of gallstones and was therefore assigned to the UDCA group. UDCA (supplied by Interfalk, now Axcan, Mount-Saint Hilaire, Quebec, Canada) was given in a dose of 13 to 15 mg/kg/d in divided doses with meals and a bedtime snack. Clofibrate (supplied by Wyeth-Ayerst, Philadelphia, PA) was given in a dose of 1 g twice daily. All obese patients were strongly encouraged to lose weight.

In the UDCA group, there were 14 women and 10 men. Their mean age was 46 years. Obesity (>20% above ideal body weight) was present in 19 of 24 (79%) patients. Five patients were taking an oral hypoglycemic agent or insulin, with adequate glucose control in all patients. The clofibrate Group comprised 11 women and 5 men. Their mean age was 50 years. Obesity was present in 10 of 16 (62%) patients. Six patients were taking oral hypoglycemic agents or had a fasting glucose >150 mg/dL. No patients required insulin or had diabetes that was difficult to control.

Serum biochemistries, lipid profile, and measurement of body weight were performed at entry and every 3 months. Patients were instructed to lose weight, offered referral to a dietitian for instruction in weight reduction, and expected to monitor and record their weight weekly during the study.

TABLE 2. Liver Histological Features at Entry

Grade*	UDCA Group (mean -- SD)	Clofibrate Group (mean -- SD)	Comparison Between Groups
Steatosis	2.2 = 0.8	2.3 = 0.5	NS
Inflammation	1.0 = 0.5	1.1 = 0.6	NS
Fibrosis	0.8 = 0.7	1.5 = 1.0	P < .015

Abbreviation: NS, not significant.

\*(0 = none; 1 = mild; 2 = moderate; 3 = severe)

period. Entry clinical and biochemical data by patient group (UDCA vs. clofibrate) are listed in Table 1. Liver biopsy was performed at entry and after 1 year of therapy. An experienced hepatopathologist evaluated all liver biopsy specimens and graded hepatic steatosis, inflammation, and fibrosis on a scale of 0 (none) to 3 (severe). Entry liver biopsy histology results are listed in Table 2. Although the mean grade of fibrosis at entry was 1.1 or mild, patients ranged from having no fibrosis to cirrhosis.

T tests were used to compare the treatment groups at entry if normally distributed; otherwise, the Wilcoxon rank sum test was used.

Confidence intervals (CI) were used to estimate the change of biochemical and histological parameters after 12 months of therapy in each group.

## RESULTS

In the UDCA treatment group, the changes from entry to 12 months in alkaline phosphatase, ALT, GGT, and hepatic steatosis were significant. Hepatic steatosis was decreased in 12 of the 19 patients. After 12 months of UDCA therapy, there was no significant change in mean AST, total serum bilirubin in, or histological grade of inflammation or fibrosis.

There was no significant change in mean weight after 12 months of therapy with UDCA. We correlated change in liver biochemical tests, cholesterol level, triglyceride level, and histological features with weight change. The mean change in ALT correlated weakly with weight loss in the UDCA group ( $r = .49$ ,  $P = .03$ ). No other parameters that improved significantly over 12 months correlated with weight loss.

In the clofibrate group, there was no significant change from baseline in mean ALT, AST, GGT, total serum bilirubin, cholesterol, or triglyceride level after 12 months of therapy. The alkaline phosphatase level was significantly reduced from baseline. (95% CI, -46 to -108). The change in alkaline phosphatase did not correlate with weight loss (data not shown). There was no evidence of histological improvement with respect to steatosis, fibrosis, or inflammation after 12 months of clofibrate therapy. The clofibrate group did not have significant mean weight loss after 12 months.

Five patients in the UDCA group and two patients in the clofibrate group had normal liver biochemical tests after 12 months of therapy. No patient had normal histological features after 12 months of therapy.

Thirty of the 40 patients completed the study. Six of 40 (15%) withdrew because of side effects. Side effects in the 3 patients in the UDCA treatment group included tinnitus, diarrhea, and abdominal pain. In the clofibrate treatment group, side effects were an elevated creatinine phosphokinase in two patients (one who also experienced tachycardia) and an undefined systemic disorder in the third. Four of 40 patients (10%) were withdrawn because of noncompliance (2 patients from each treatment group). One of these patient had cirrhosis at entry and eventually underwent liver transplantation.

## DISCUSSION

NASH describes the development of hepatic histopathological features that are comparable to those induced by excessive alcohol intake. The condition can be progressive, leading to cirrhosis and end-stage liver disease. NASH is commonly associated with obesity and type II diabetes mellitus.<sup>1</sup> Most of our patients were middle-aged, female, and obese, but a minority had diabetes. Steatosis is not always associated with inflammation and fibrosis, and fatty liver may be a secondary change in the pathogenesis of NASH rather than a primary instigating factor.<sup>15</sup> However, there does seem to be a correlation between the degree of steatosis and the degree of fibrosis in some studies.

Treatment of NASH has generally consisted of weight reduction. Maintenance of substantial weight loss has been shown to lead to marked improvement in liver histology in some patients. However, adverse effects on liver histology, such as progression of fibrosis, have been noted as well.<sup>20-22</sup> Furthermore, most obese patients find it virtually impossible to maintain weight loss.<sup>23</sup>

UDCA has been used in the treatment of other chronic liver diseases with symptomatic and biochemical improvement demonstrated in patients with primary biliary cirrhosis,<sup>24</sup> primary sclerosing cholangitis,<sup>2</sup> and autoimmune hepatitis.<sup>26</sup> UDCA may have a membrane-stabilizing or cytoprotective effect, either of which may lead to improvement in biochemical and histologic parameters in NASH.<sup>14,15</sup> In this study, we noted a significant decrease in mean alkaline phosphatase, ALT, GGT, and grade of hepatic steatosis after 1 year of therapy with UDCA at a dose of 13 to 15 mg/kg/d. UDCA was safe, with mild potential side effects noted in three patients. UDCA, when used in the treatment of other liver diseases, has an excellent safety profile with minimal reported side effects.

Clofibrate has been shown to decrease hepatic triglycerides in animals and, hence, was a theoretically attractive drug to test in this condition characterized by excessive accumulation of lipids in the liver. Unfortunately, there was no significant change from baseline in mean ALT, AST, GGT, bilirubin, or cholesterol after 12 months of clofibrate therapy when compared with entry. Furthermore, no evidence of histological improvement with respect to steatosis, fibrosis, or inflammation was identified. Despite the known lipid-lowering effects of clofibrate, it did not appear to provide clinical benefit to patients with NASH in this 1-year pilot study.

From our experience in this pilot study, we conclude that treatment of NASH for 12 months with UDCA results in significant improvement in alkaline phosphatase, ALT, GGT, and hepatic steatosis. Because no proven treatment for nonalcoholic steatohepatitis exists, the possible benefit of UDCA will be investigated further by us in the context of a randomized, controlled trial.

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