Ursodeoxycholic Acid for Liver Disease Associated With Cystic Fibrosis: A Double-Blind Multicenter Trial

CARLA COLOMBO,[1] PIER MARIA BATTEZZATI,[2] MAURO PODDA,[2] NORA BETTINARDI,[3] ANNAMARIA GIUNTA,[3] AND THE ITALIAN GROUP FOR THE STUDY OF URSODEOXYCHOLIC ACID IN CYSTIC FIBROSIS*

Liver disease is increasingly recognized as a major cause of morbidity in cystic fibrosis (CF). Preliminary data suggest that ursodeoxycholic acid (UDCA) may be beneficial for treatment of this manifestation. We performed a double-blind, multicenter trial in these patients to establish efficacy and safety of UDCA in terms of the improvement of clinical and nutritional indicators besides standard liver function tests. We also intended to establish whether taurine supplementation has a beneficial effect in patients receiving UDCA. From June to December 1990, we enrolled in 12 centers 55 CF patients with liver disease (39 male subjects; median age, 13.8 years). They were randomly assigned to receive for 1 year one of the following treatments: UDCA (15 mg/kg body weight daily) plus taurine (30 mg/kg body weight daily), UDCA plus placebo, placebo plus taurine, or double placebo. Clinical and laboratory evaluations were performed every 3 months. After 1 year, deterioration of overall clinical conditions, as indicated by the Shwachman-Kulczycki score (SKS), occurred in patients who received placebo but not in those who received UDCA (P = .025). Patients treated with UDCA also showed an improvement in γ-glutamyl transpeptidase (GGT) (P = .004) and 5′-nucleotidase (P = .006) levels. Treatment with taurine was followed by a significant increase in serum prealbumin levels (P = .053), a trend toward a reduction in fat malabsorption, and no effect on the biochemical profile. No severe side effects occurred with any treatment. Thus, we concluded that UDCA administration improves clinical and biochemical parameters in CF patients with liver disease. Taurine supplementation may be indicated in patients with severe pancreatic insufficiency and poor nutritional status. (HEPATOLOGY 1996;23:1484-1490.)

It has been speculated that chronic liver disease develops in patients with cystic fibrosis (CF) as a consequence of the plugging of intrahepatic bile ducts with inspissated bile.[1-3] The lack of CF transmembrane regulator in the apical membrane of bile duct cells, recently documented in CF,[4] may lead to abnormalities in biliary drainage, with chronic cholestasis and the development of multilobular biliary cirrhosis. According to data from the American CF registry in 1990, liver disease is increasingly recognized as a cause of morbidity.[5,6] This probably reflects an increased prevalence of hepatobiliary complications because CF patients live longer.[5,6] A negative prognostic impact of liver disease is thus to be expected in CF, as also suggested by the recent identification of hepatomegaly as an independent risk factor for early death in affected patients.[7]

Over the last few years, we and others have found in open studies that treatment with ursodeoxycholic acid (UDCA) can improve serum liver enzyme levels, hepatic function, and nutritional status in patients with CF and liver disease.[8-17] UDCA is a hydrophilic bile acid with choleretic properties.[18] In patients with CF-associated liver disease, UDCA may decrease bile viscosity, thus preventing obstruction of bile ductules by abnomal secretions. It has been suggested that, by displacing potentially toxic endogenous bile acids from the enterohepatic circulation, UDCA may also prevent further liver damage during chronic cholestasis.[18] An effect on the immune response in adult patients with chronic cholestatic liver diseases has also been advocated.[18] Confirmation of the beneficial effects of UDCA by placebo-controlled, double-blind studies was obtained on standard liver function tests as the only outcome measure.[11] Moreover, no study addressed the issue of the need for taurine supplementation, which was recommended by some authors during concomitant UDCA treatment in the assumption that chronic administration of unconjugated UDCA may aggravate the degree of taurine deficiency in CF.[8,12,19]

Abbreviations: CF, cystic fibrosis; UDCA, ursodeoxycholic acid; GGT, γ-glutamyl transpeptidase; SKS, Shwachman-Kulczycki score.

From the [1]Department of Pediatrics, University of Sassari, Sassari, the [2]Department of Internal Medicine, San Paolo Hospital, University of Milan, and the [3]Department of Pediatrics, University of Milan, Milan, Italy.

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* The Italian Group for the Study of Ursodeoxycholic Acid in Cystic Fibrosis consists of the following investigators and CF centers: L. Iapichino (Ospedale dei Bambini G. De Cristina, Palermo), S. Quattrucci (University of Rome), B. Santini (University of Turin), V. Lucidi (Bambin Gesù Hospital, Rome), R. Ferrari (University of Florence), S. Scotta (University of Pavia), L. Minicucci (University of Genoa), M. Candusso (University of Trieste), E. Valletta (Ospedale Civile Maggiore, Verona), R. Gagliardini (Ospedale dei Bambini G. Salesi, Ancona), F. Santamaria (University of Naples), and F. Battistini (Ospedale Bufalini, Cesena).

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Address reprint requests to: Carla Colombo, M.D., Department of Pediatrics, University of Sassari, Viale San Pietro 12, 07100 Sassari, Italy.

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We designed a multicenter, double-blind, controlled trial in CF patients with associated liver disease to evaluate efficacy and safety of treatment with UDCA on an extended spectrum of outcome measures, including nutritional and other clinically relevant parameters. In addition, we evaluated for the first time the effects of taurine supplementation, which was administered randomly in a double-blind fashion to patients taking UDCA or placebo.

PATIENTS AND METHODS

Patients and Study Design. Patients with a diagnosis of CF and chronic liver disease with persistent alterations of serum liver enzymes were considered for admission into the study at 12 centers in Italy. Diagnosis of CF had been previously established on the basis of increased sweat chloride concentrations and typical symptoms of pulmonary and pancreatic involvement. Chronic liver disease was defined on the basis of: presence of hepatomegaly, confirmed by abnormal ultrasonographic findings (increased liver size, nonhomogeneous echogenic pattern, and irregular surface), and the presence of abnormal liver biochemistries (serum transaminases, γ-glutamyl transpeptidase [GGT]) of at least 1 year's duration. To ensure that an effect of UDCA on serum liver enzymes could be detected, presence of serum transaminase and GGT levels exceeding 1.5 times the upper limit of normal reference values on at least three determinations over the year before entry into the study was also required for admission.

Patients were excluded if they were less than 3 years old, if they had serum bilirubin >3 mg/dL, ascites, chronic viral hepatitis, concomitant severe pulmonary disease, previous episodes of variceal bleeding or encephalopathy, or portosystemic shunting. Patients who had been treated with corticosteroids or other immunosuppressant agents in the previous 6 months, as well as those previously included in other clinical studies on UDCA, were also excluded.

Diagnosis of multilobular biliary cirrhosis was based on histological criteria when recent liver biopsy specimens were available (five cases). The remaining patients were considered as having cirrhosis if one of the following indicators of portal hypertension were present: enlarged portal vein in the absence of respiratory variation on ultrasound and platelet count $<100 \times 10^9$/L; or esophageal varices at endoscopy.

Patients who fulfilled the criteria for enrollment were randomly assigned by a centrally computer-generated list to receive, on a weight basis, either UDCA or placebo at the daily dose of one to three 300-mg capsules for 1 year. Taurine or a second placebo at the dose of one to three 500-mg capsules daily were randomly added double-blind to patients in either group. Accordingly, patients received one of the following four treatment combinations: UDCA plus taurine (UDCA + T); UDCA plus placebo (UDCA + P); placebo plus taurine (P + T); double placebo (P + P).

The sample size determination was based on the results of a dose-response study of the effects of UDCA administration to CF patients with liver disease.[16] In those patients, an improvement in GGT levels corresponding to approximately 0.90 standard deviations had been achieved during daily administration of 15 to 20 mg/kg body weight of UDCA. Assuming no improvement in the two placebo groups (P + T and P + P), we calculated that an overall sample size of 54 patients would yield a probability of a type II error of 0.90, at the 5% level of significance, in detecting such a difference between patients receiving UDCA (UDCA + T and UDCA + P) and the remaining patients.

Patients and/or parents were informed of the nature, purpose, and requirements of the study before giving written consent. The study was performed according to the principles of the Helsinki declaration for research in human subjects. The protocol was approved by the review institutional boards of the participating centers.

Criteria for Evaluation. The primary objective of the study was to compare treatment groups with respect to changes in clinically relevant and nutritional parameters (Shwachman-Kulczycki score [SKS], fecal fat excretion, serum prealbumin and lipid levels, prothrombin time, and urinary creatinine) besides improvements in serum liver enzymes (serum transaminases, GGTP, and 5′-nucleotidase). The SKS encompasses four categories: general activity, physical examination, nutrition, and chest radiographic findings.[20,21]

Clinical and standard laboratory evaluations were performed at the time of enrollment and every 3 months thereafter. Blood samples were obtained for determination of serum liver enzyme levels (alanine and aspartate aminotransferases, GGT, and alkaline phosphatase), total and conjugated bilirubin, cholinesterase, total and high-density lipoprotein cholesterol, triglycerides, glucose, albumin, gamma globulins, immunoglobulins, prothrombin time, complete blood counts, urea, and creatinine. Urine samples were obtained from 24-hour collection for determination of urinary creatinine excretion. These tests were performed in the clinical laboratory of each participating center by routine automated techniques.

Blood samples for determination of fasting serum bile acid levels (conjugated cholic acid, chenodeoxycholic acid, and UDCA, by solid-phase immunoenzymatic assays),[22] serum 5′-nucleotidase (by enzymatic method), and prealbumin concentrations (by radial immunodiffusion) were obtained at baseline and after 6 and 12 months of treatment. Their determination was performed centrally in the same laboratory, in the interest of standardization and double-blind design.

The SKS, abdominal ultrasound scanning, upper digestive endoscopy (to be performed only in patients with splenomegaly and/or suspected portal hypertension), and fecal fat excretion[23] were evaluated at baseline and at the end of the study.

Compliance to treatment was assessed by counting the capsules returned to the clinic by the patient.

Analysis of Data. Serum liver enzyme values were standardized according to reference values for each laboratory and expressed as multiples of the upper limit of reference values. Height and weight were expressed as z scores.

Changes in SKS, height, weight, fecal fat excretion, and in serum bile acid levels were expressed as differences between values at the last determination and those at baseline. Changes over time in the remaining laboratory variables were expressed as percentage difference.

ANOVA for factorial designs was used for estimation of the effects of UDCA, of taurine, and of their interaction.[24] Bartlett's test was used for testing of homogeneity of variances. When nonhomogeneity of variances or departures from normality were detected, data were analyzed using a logarithmic transformation or the rank transformation approach.[25] According to the latter method, the usual ANOVA is applied to the ranks of the data instead of to the data themselves. The association between changes in serum liver enzyme levels and UDCA dosage, expressed on a weight basis, was studied by multiple-regression analysis. In this analysis, the final values of serum liver enzymes were included as the independent variable, the logarithm of the dose, and

TABLE 1. Characteristics of Patients

	UDCA		Placebo	
	With Taurine (n = 15)	Without Taurine (n = 15)	With Taurine (n = 12)	Without Taurine (n = 13)
Mean age (yr)	14.2 ± 4.2	11.3 ± 3.6	14.8 ± 3.7	12.8 ± 3.8
Male subjects (%)	73	60	83	69
Height (*z* score)	−0.65 ± 0.72	−0.75 ± 1.00	−0.93 ± 0.86	−0.85 ± 1.32
Weight (*z* score)	−1.03 ± 0.66	−0.83 ± 0.91	−0.80 ± 0.99	−0.65 ± 1.93
With multilobular cirrhosis (%)	8	8	6	6
With esophageal varices (%)	4	1	0	0

NOTE. Plus-minus values are means ± SD.

baseline serum liver enzyme values as independent variables.

The total period of observation was used in the analysis of data for each patient, according to the "intention-to-treat" principle.

All the analyses were two-sided, and .05 was the level of statistical significance.

RESULTS

From June 1 to December 31, 1990, 55 patients (39 male subjects) with a median age of 13.8 years (range, 4 to 22 years) were enrolled in 12 Italian centers. On the whole, 214 patients had been considered for admission. Of the 159 of these patients who could not be enrolled, 55% had to be excluded for nonconformity to biochemical criteria for admission, 13% for previous occurrence of major complications of cirrhosis, 9% for severe pulmonary involvement, and 23% for other reasons, mainly for lack of consensus or previous inclusion in other clinical trials. CF had been diagnosed at a median age of 1 year (range, 1 month to 13 years), and liver disease had been diagnosed at a median age of 9 years (range, 2 months to 18 years). All but 2 patients had pancreatic insufficiency, which was partially corrected by enzymatic therapy.

Fifteen patients were assigned to the UDCA + T group, 15 to the UDCA + P group, 12 to the P + T group, and 13 to the P + P group. The main characteristics of patients at the time of entry into the study are shown in Tables 1 and 2. By chance, all 5 patients with esophageal varices and 7 out of 8 patients with abnormal serum bilirubin levels at entry had been assigned to receive UDCA.

Patients in the two groups who received UDCA assumed an average daily dose of 15 ± 3 mg/kg body weight (range, 10 to 20 mg) of this bile acid, whereas the average dose of taurine in the two taurine-supplemented groups was 24 ± 5 mg/kg b.w (range, 17 to 33 mg).

Withdrawals and Side Effects. During the study period, one patient in the UDCA + T group and another in the P + P group left the study for personal choice. Two other patients, both in the UDCA + P group, were withdrawn for deterioration of clinical conditions, involving pulmonary disease in one case and liver disease in the other. The latter patient then became a candidate for liver transplantation, which was performed successfully. All remaining subjects took more than 80% of the prescribed dose, as assessed from the count of unused capsules at each visit.

No severe side effects were reported. Four patients, two in the UDCA + P group and two in the P + P group, transiently complained of diarrhea and/or mild and transient abdominal pain. One patient in the UDCA + P group experienced an episode of fever and abdominal pain. None of these patients required any specific treatment or any modifications of the treatment schedule.

Efficacy of Treatments. One patient developed jaundice and deterioration of liver function after 7 months of treatment with UDCA and placebo. As indicated above, she was withdrawn from the study and shortly after she underwent successful transplantation. Another patient experienced an episode of melena after 4 months of treatment with UDCA and taurine, but treatment was not interrupted. Both patients had advanced liver disease on entry into the study. No patient developed ascites.

During the study period, changes of the SKS and of serum levels of GGT and 5′-nucleotidase differed significantly in the two groups that were treated with UDCA compared with the two other groups (Table 2). Among the components of the SKS, the score relative to clinical conditions significantly worsened in the patients who did not receive UDCA compared with patients who did receive it ($P = .020$).

Substantial improvements also occurred for aspartate transaminase and alanine transaminase in the two UDCA groups, but the difference with patients not receiving UDCA did not attain significance. No relationship was found between changes in serum liver enzyme levels and UDCA dosage expressed on a weight basis. Serum prealbumin improved in patients who received taurine supplementation but not in the remaining patients with a significant difference between taurine-supplemented patients and the other patients. A similar trend was observed for fecal fat excretion, although, in this case, that difference did not attain significance (Fig. 1). Serum cholesterol levels were within the normal range in basal conditions and did not change substantially during treatment. No significant

TABLE 2. Initial Values of Biochemical and Nutritional Variables and Changes During Treatment

	UDCA		Placebo	
	With Taurine (n = 15)	Without Taurine (n = 15)	With Taurine (n = 12)	Without Taurine (n = 13)
SKS				
Baseline	73 ± 12	79 ± 10	79 ± 11	76 ± 14
Change*	−0.14 ± 4.75¶	0.00 ± 2.65¶	−2.92 ± 4.17	−3.00 ± 4.26
GGT†				
Baseline	4.4 ± 3.5	2.4 ± 1.6	3.0 ± 2.5	2.8 ± 2.6
Change	−31 ± 28§	−26 ± 35§	31 ± 68	−15 ± 33
5′-nucleotidase (IU/L) (n.v. <5)				
Baseline	13.0 ± 22.6	5.4 ± 4.7	5.2 ± 5.1	5.5 ± 3.8
Change	−21 ± 34‖	−23 ± 40‖	26 ± 43	42 ± 126
AST†				
Baseline	2.3 ± 1.2	2.1 ± 1.3	2.2 ± 1.0	2.1 ± 1.8
Change	−29 ± 49	−24 ± 25	−13 ± 32	−10 ± 40
ALT†				
Baseline	3.2 ± 2.2	2.2 ± 1.0	2.8 ± 1.7	3.6 ± 4.3
Change	−37 ± 38	−30 ± 32	−17 ± 46	−17 ± 41
Prealbumin (mg/dL) (n.v. >20)				
Baseline	18.0 ± 3.4	19.1 ± 6.4	18.4 ± 7.4	18.0 ± 4.6
Change	25 ± 40#	−3 ± 14	36 ± 69#	16 ± 26
Daily fecal fat excretion (g) (n.v. <7)‡				
Baseline	17 ± 11	11 ± 4	13 ± 6	12 ± 8
Change	−4 ± 12	3 ± 16	−4 ± 4	−3 ± 10

NOTE. Values are means ± SD.

Abbreviations: AST, aspartate transaminase; ALT, alanine transaminase; n.v., normal reference value.

* Changes are expressed as the difference between values at 12 months and basal values for the SKS, and for fecal fat excretion, and as the percentage differences between values at 12 months and basal values for the remaining variables. Negative values indicate that a decrease occurred during treatment.

† Data reported as multiples of the upper limit of normal reference values.

‡ Data for 7 and 9 patients who received UDCA with and without taurine, respectively, and for 8 and 6 patients who received placebo with and without taurine, respectively.

§,‖,¶ Significant difference between the two groups who received UDCA and the two other groups, $P = .025$, $P = .006$, and $P = .004$, respectively.

Significant difference between the two groups who received taurine and the two other groups ($P = .053$).

differences were found among patients concerning the other variables under study. Urinary creatinine increased in the patients in the UDCA + T group (30 ± 56%) and in those in the UDCA + P group (57 ± 229%), whereas it remained unchanged in the two other groups. The difference between patients who received UDCA and the remaining patients did not reach the significance level. In the patients with more advanced liver disease, i.e., those with varices and/or elevated serum bilirubin levels, no significant changes in liver synthetic data (serum albumin, prealbumin, or prothrombin time) were observed.

Baseline levels and changes during the study in serum UDCA and primary bile acids are reported in Table 3. Data showed a high variability, and, with the exclusion of serum UDCA, no difference was found among treatment groups.

At baseline ultrasound examination, eight patients were found to have gallstones. One of these patients, belonging to the UDCA + T group, showed dissolution of a 3-mm stone at the end of the study.

DISCUSSION

The aim of the present study was to establish if UDCA administration improves clinically relevant variables in patients with CF complicated by liver disease. Only patients with persistent alterations of serum liver enzyme levels were admitted into the study to base evaluation of the efficacy of UDCA on objective measurements. The design of the study also enabled us to establish whether taurine supplementation is beneficial to patients on chronic UDCA treatment, in view of the well-documented predisposition of CF patients to develop a deficiency of this amino acid.[19]

We chose not to include histological assessment among the study variables because the interpretation of serial biopsies is potentially misleading due to the heterogeneous distribution of hepatic lesions in CF, and performing repeat liver biopsies in our patients was considered unethical.

Much of the interest initially raised by UDCA in the treatment of chronic cholestatic diseases comes from its ability to improve serum liver enzymes. An effect of the same magnitude as that reported in the literature, i.e., an improvement of approximately 20 to 40%,[9,12,16,26-28] was consistently observed in our patients, with no relationship to UDCA dose, expressed on a weight basis. UDCA apparently did not influence the liver inflammatory profile of our patients. Serum

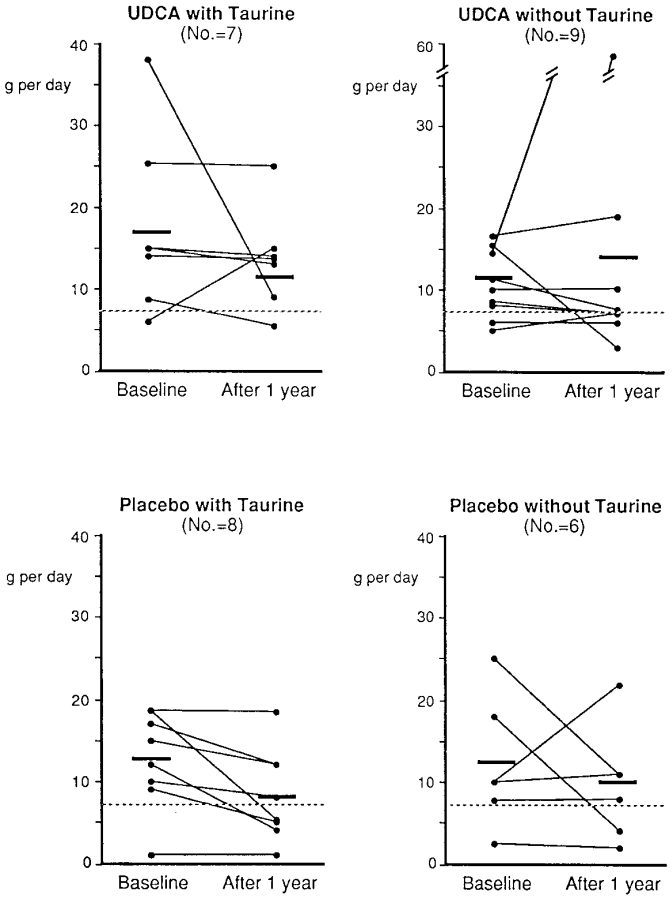

FIG. 1. Changes in fecal fat excretion during the study. The dotted lines represent the upper normal limits for fecal fat excretion. Mean values are represented by boldface lines.

liver enzyme levels were standardized according to reference values for each laboratory, and no relationship was observed between their changes and patient centers. It seems unlikely that differences among laboratories may have affected the results of the study. Although a decrease in serum liver enzyme levels in CF patients has been associated with concomitant improvement of bile secretory function,[14] changes in biochemical indicators do not necessarily reflect diminished liver damage or halting of disease progression. Other clinically relevant outcome measures for liver disease, such as liver transplantation or decompensation of cirrhosis, are hardly attainable by clinical studies on CF patients because these events are a late manifestation of the disease and occur infrequently.[2,6]

Thus far, only the effects on standard liver function tests have been evaluated by a double-blind study,[11] whereas the efficacy of UDCA has yet to be established on other relevant end-points, including those of clinical and nutritional interest. In patients with CF, it has been reported that liver disease, regardless of its severity, may be associated with poor nutritional status, and that patients with this complication may be predisposed to a higher mortality risk for causes other than liver disease.[2,6] To establish whether the beneficial effects of treatment also extended to overall clinical conditions, we included the SKS[20] as well as some indices of nutritional status among the primary outcome measures. The SKS takes into account the severity of pulmonary involvement, nutritional status, and general patient's conditions, and is widely used in the clinical evaluation of CF patients. Its inclusion as an outcome measure in clinical trials on CF patients has been recently suggested.[21] This score remained stable in the patients who received UDCA and worsened in the remaining patients. We also observed a trend toward an increased urinary excretion of creatinine, which is considered an index of muscle mass. A significant increase in this parameter during UDCA administration was reported by Cotting et al. in adult CF patients with major nutritional problems.[9,15] These findings suggest that UDCA administration may favorably affect clinical and nutritional status of CF patients with associated liver disease. This issue is still controversial be-

TABLE 3. Changes in Serum Conjugated Bile Acids

	UDCA		Placebo	
	With Taurine (n = 10)	Without Taurine (n = 11)	With Taurine (n = 10)	Without Taurine (n = 10)
UDCA				
Baseline	1.1 ± 1.9	0.5 ± 1.6	0.4 ± 0.6	1.0 ± 2.6
Change*	3.4 ± 6.8	5.8 ± 6.4	−0.1 ± 0.5	0.5 ± 1.9
CA (μmol/L)				
Baseline	5.8 ± 7.7	6.2 ± 8.7	5.0 ± 4.9	6.9 ± 13.0
Change	−1.6 ± 6.4	−0.7 ± 4.0	−1.1 ± 3.1	−4.1 ± 9.6
CDCA (μmol/L)				
Baseline	5.2 ± 6.0	7.1 ± 9.8	4.0 ± 6.4	3.8 ± 6.0
Change	−1.6 ± 5.3	−1.7 ± 3.4	−1.0 ± 1.7	−0.4 ± 7.2

NOTE. Data are expressed as means ± SD.

Abbreviations: UDCA, ; CA, colic acid; CDCA, chenodeoxycholic acid.

* Changes are expressed as difference between values at 12 months and basal values. Negative values indicate that a decrease occurred during treatment.

cause a recent report indicated that 6 months of treatment with UDCA, either alone or with taurine, did not affect the nutritional status of young, malnourished CF patients.[29] It should be noted, however, that UDCA was given for a short period and at a lower dosage, and that only 20% of the patients had overt liver disease.

The increase in UDCA serum levels during its administration was highly variable among patients, as we previously showed in a dose-response study in CF patients with liver disease.[16]

During the study, in one patient who initially had multilobular biliary cirrhosis and esophageal varices and was allocated to treatment with UDCA, further deterioration of liver function occurred and liver transplantation was required. This suggests that, especially in patients with portal hypertension, UDCA treatment is ineffective in preventing the occurrence of major complications of cirrhosis, as it has been observed in adults with primary biliary cirrhosis.[30]

Taurine deficiency is frequently found in CF patients[19] as a result of bile acid malabsorption,[31] and it has also been shown to negatively affect the lipolytic phase of fat digestion.[32] Previous studies have shown that taurine can improve the efficiency of micellar solubilization of lipolytic products, and its use has been suggested as an effective adjuvant in CF patients with severe steatorrhea.[33-36] Moreover, long-term administration of unconjugated UDCA may critically increase taurine need for bile acid conjugation. Our study provides a double-blind evaluation of the effects of taurine supplementation, either alone or during UDCA therapy. Treatment with taurine had no effect on the biochemical expression of liver damage nor on the SKS. Conversely, patients who were administered taurine showed a significant improvement in serum prealbumin levels—a sensitive indicator of nutritional status[37]—and a trend toward a reduction in the degree of fat malabsorption.

In conclusion, data from our double-blind study confirm that UDCA administration improves biochemical indicators of liver damage in CF patients with liver disease and is free of relevant side effects. The favorable effect we observed on the overall clinical status of patients is promising, suggesting that UDCA may also affect the natural history of the disease, and warrants the evaluation of this bile acid in CF patients before development of overt liver disease. Taurine supplementation is advisable in CF patients with severe pancreatic insufficiency and poor nutritional status during chronic administration of UDCA.

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