High-Dose Ursodeoxycholic Acid in Primary Sclerosing Cholangitis: A 5-Year Multicenter, Randomized, Controlled Study

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Background & Aims: **There is no medical treatment of proven benefit for primary sclerosing cholangitis. This study aimed at studying the effect of a higher dose of ursodeoxycholic acid than previously used on survival, symptoms, biochemistry, and quality of life in this disease.** ***Methods:*** **A randomized placebo-controlled study was performed in tertiary and secondary gastroenterology units. A total of 219 patients were randomized to 17 to 23 mg/kg body weight per day of ursodeoxycholic acid (n = 110) or placebo (n = 109) for 5 years. Follow-up data are available from 97 patients randomized to ursodeoxycholic acid and for 101 randomized to placebo. Quality of life was assessed by using the Medical Outcomes Study 36-item Short-Form Health Survey.** ***Results:*** **The combined end point "death or liver transplantation" occurred in 7 of 97 (7.2%) patients in the ursodeoxycholic acid group vs 11 of 101 (10.9%) patients in the placebo group (*P* = .368; 95% confidence interval, −12.2% to 4.7%). The occurrence of liver transplantation as a single end point showed a similar positive trend for ursodeoxycholic acid treatment (5/97 [5.2%] vs 8/101 [7.9%]; 95% confidence interval, −10.4% to 4.6%). Three ursodeoxycholic acid and 4 placebo patients died from cholangiocarcinoma, and 1 placebo patient died from liver failure. Alkaline phosphatase and alanine aminotransferase tended to decrease during the first 6 months. There were no differences between the 2 groups in symptoms or quality of life. Analyses of serum ursodeoxycholic acid concentration gave no evidence that noncompliance may have influenced the results.** ***Conclusions:*** **This study found no statistically significant beneficial effect of a higher dose of ursodeoxycholic acid than previously used on survival or prevention of cholangiocarcinoma in primary sclerosing cholangitis.**

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease that mainly affects patients with chronic inflammatory bowel disease.[1,2] The median survival from diagnosis to death or liver transplantation is reported to be 12–16 years[3,4] and is significantly longer in asymptomatic than in symptomatic patients.[3] The main cause of death is liver failure, followed by death from cholangiocarcinoma.[3] Approximately every third hepatobiliary malignancy is diagnosed within 1 year after the diagnosis of PSC; thereafter, the annual rate is approximately 1.5%.[5]

Different forms of medical treatment have been tried, but until now, no treatment has been proven efficient in randomized controlled studies. One of the most recent drugs suggested as treatment of PSC is ursodeoxycholic

†Deceased.

Abbreviations used in this paper: ALP, alkaline phosphatase; PSC, primary sclerosing cholangitis; SF-36, Medical Outcomes Study 36-item Short-Form Health Survey.

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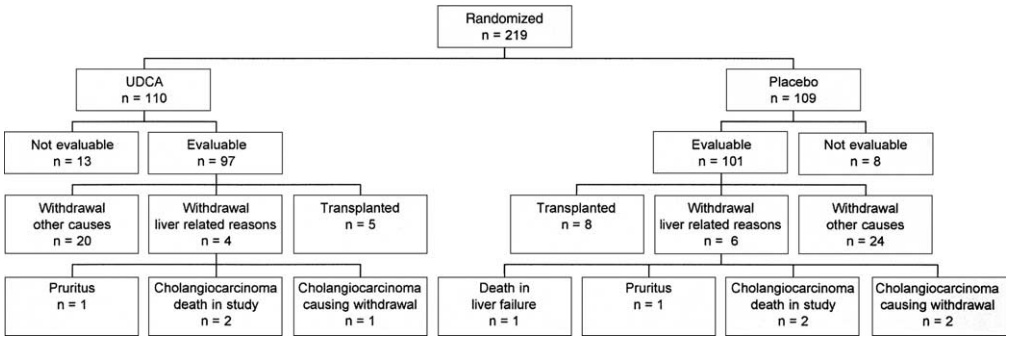

Figure 1. Number of patients in the study.

acid (UDCA). In a randomized controlled study with 102 patients treated for a median of 2.2 years, no significant effect on survival was observed.[6] Before that study was published, we had already started a randomized controlled trial designed to run for 5 years with a higher dose of UDCA. This study primarily aimed to investigate the effect of UDCA on survival without liver transplantation.

Materials and Methods

We conducted a randomized, double-blind, placebo-controlled, multicenter, Swedish–Norwegian (main investigator K.M.B.)–Danish (main investigator O.S.d.M.) study that was initiated by the Swedish Internal Medicine Liver Club and comprised hepatologists from all Swedish university hospitals. Inclusion criteria were a diagnosis of PSC based on cholangiography with conventional radiological criteria, age 18–70 years, body weight $\leq$115 kg, and expected survival $>$1 year. Exclusion criteria were earlier treatment with UDCA, planned pregnancy within the forthcoming 5 years, alcohol abuse and other forms of abuse, positive tests for hepatitis B surface antigen or anti–hepatitis C virus, or another concomitant cause of liver disease.

The study design was approved by the committees of human ethics in Gothenburg, Oslo, and Odense and by the local committees, as well as by the Medical Products Agencies in Sweden, Norway, and Denmark. Altogether, 34 centers with 48 investigators from secondary and tertiary referral centers participated in the study. All patients were informed of the nature, purpose, and possible risks involved in the study before giving their consent to participate.

The primary end point was death or liver transplantation. Secondary end points were measurements of changes in the frequency of PSC-associated symptoms (itching, right upper quadrant abdominal pain, fever, and jaundice), changes in self-estimated quality of life, and changes in liver laboratory tests. A third objective was to investigate whether UDCA has an effect on the intestinal symptoms, eg, stool frequency, in patients with concomitant inflammatory bowel disease.

For the estimation of the number of patients required for the study, the median survival time was assumed to be 144 months.[3] The response to UDCA treatment was assumed to reduce the rate of events (ie, death or liver transplantation) by 50% compared with the placebo treatment. Assuming a constant rate of events (hazard function) as a function of time and a mean observation period of 5 years, 346 patients were needed to detect a significant difference in the primary end point (death and liver transplantation) at a power of 80% with a 2-tailed test and a 5% level of significance.

Recruitment of PSC patients into the study was limited to 15 months (until the end of 1997). At that time we had recruited 219 patients (121 from Sweden, 77 from Norway, and 21 from Denmark) who were randomized to either UDCA (in a daily dose of 17–23 mg/kg of body weight divided in 2 doses) or placebo in identical 250-mg gelatin capsules containing microcrystalline cellulose (Avicel PH200; Ebulon Ag, Allschwil, Switzerland), cornstarch, and magnesium stearate. In case of troublesome diarrhea, the patients were instructed to reduce the dose to the highest tolerable dose or, in severe cases, to stop treatment temporarily and to restart treatment at a lower, but increasing, dose. If a patient for some reason had to stop treatment for more than 10 weeks during the course of a year, the patient was excluded.

The patients were stratified before randomization as symptomatic or asymptomatic according to the course of the disease and randomized by a hospital pharmacist into blocks of 4 patients. The trial code was kept at the pharmacies in the hospitals. The code was not broken until data from all patients had been collected.

Data on the presence and severity (on a 10-point scale) of PSC-related symptoms, adverse events, intercurrent diseases, and so on, as well as on results of clinical examinations and laboratory tests, were collected at entry and every 6 months until the end of the trial. The blood tests included serum bilirubin, alkaline phosphatase (ALP), alanine aminotransferase, albumin, and immunoglobulin G, A, and M. At the start and after 2 and 5 years, the patients were asked to complete a Medical Outcomes Study 36-item Short-Form Health Survey (SF-36).

From earlier studies, a decrease in liver laboratory tests in the UDCA-treated patients was expected. Because this was not the case, we decided after the study to analyze serum UDCA concentrations in serum samples from the 6 months of fol-

Table 1. Demographics of the Patients Included in the Study as Well as Serum Laboratory Values at Randomization: In Total, 38 UDCA Patients and 40 Placebo Patients Were on IBD Treatment With Monotherapy or Combination Therapy

Variable	UDCA (n = 97)	Placebo (n = 101)
Sex (M/F)	70/26	69/32
Age, mean (SD)	43.6 (12.7)	43.1 (11.2)
Body weight, mean (SD)	75.8 (13.2)	74.5 (12.9)
Duration of PSC, y, mean (SD)	6.1 (5.8)	5.6 (5.3)
IBD (n)		
Ulcerative colitis	70	69
Crohn's disease	10	13
Nonspecified colitis	1	5
IBD treatment (n)		
Corticosteroids	5	6
Sulfasalazine	21	22
Mesalamine	14	13
Azathioprine	3	2
Prevalence of symptoms before start, n (%)		
Pruritus	33 (34)	38 (38)
RUQ abdominal pain	32 (33)	29 (29)
Fever	18 (19)	16 (16)
Jaundice	24 (25)	27 (27)
Ascites	2 (2)	0
Asymptomatic	45 (46)	51 (50)
Bilirubin, mean (SD), ref. values, 3.4–21 μmol/L	18.2 (15.2)	19.0 (20.7)
ALP, mean (SD), ref. value <5 μkat/L	11.8 (9.5)	12.5 (11.4)
ALT, mean (SD), ref. value <0.7 μkat/L	2.3 (4.2)	1.9 (1.6)
Albumin, mean (SD), ref. values 36–50 g/L	41.2 (3.9)	41.2 (4.8)
IgG, mean (SD), ref. values 7–14 g/L	14.1 (4.0)	15.9 (11.4)
IgA, mean (SD), ref. values 0.5–3.0 g/L	2.8 (1.3)	2.7 (1.1)
IgM, mean (SD), ref. values 0.7–2.0 g/L	1.7 (2.4)	1.4 (0.7)

IBD, inflammatory bowel disease; RUQ, right upper quadrant; ALT, alanine aminotransferase; Ig, immunoglobulin, ref., reference.

low-up in the 26 patients randomized to UDCA but not displaying a ≥10% decrease in ALP after 6 months and from the 35 patients randomized to placebo but nonetheless displaying a ≥10% decrease in ALP after 6 months. According to the protocol, extra serum and plasma samples should be collected and deep-frozen at each follow-up. It was possible to retrieve 24 and 28, respectively, of the serum samples. These samples were analyzed for serum UDCA concentration.[7]

Time to death or liver transplantation was evaluated by using life-table survival analyses and Cox proportional hazards models. Standard descriptive sample statistics were applied to summarize continuous variables. Categorical data were described by using absolute and relative frequencies. PSC symptoms during the last 6 months were compared between enrollment and the last observation under medication by using cross tables. For PSC symptoms last week, remission, and improvement rates for the last observation under medication were calculated. For the analysis of SF-36 questionnaire data, the standardized 8 single and 2 global scales of the SF-36 questionnaire model according to Ware's standard method[8] were calculated. The Wilcoxon rank sum test was used to compare the UDCA- and placebo-treated patients regarding change from enrollment for each scale in the SF-36.

Results

A total of 110 patients were assigned to UDCA treatment and 109 to placebo. Twenty-one of these patients were excluded from further analysis because they either did not come to any follow-up appointments or never started taking the test capsules. Thus, 97 UDCA-treated and 101 placebo-treated patients were available for statistical analysis (Figure 1). The groups were well matched regarding demographic and clinical data (Table 1).

The combined end point "death or liver transplantation" occurred in 7 of 97 (7.2%) patients in the UDCA group vs 11 of 101 (10.9%) patients in the placebo group ($P = .368$; 2 sided; normal approximation). The occurrence of liver transplantation as a single end point showed a similar positive trend for UDCA treatment (5/97 [5.2%] vs 8/101 [7.9%]). Moreover, Kaplan–Meier analysis showed a corresponding trend toward a shorter time to event with placebo compared with UDCA ($P = .3069$; Figure 2). Kaplan–Meier analysis according to intention to treat yielded the same result ($P = .3069$).

Endoscopic therapeutic procedures were performed in 5 UDCA-treated and in 8 placebo-treated patients during the study. Three patients in each group were subjected to both dilation and stenting procedures.

There was no difference between the groups in the incidence of cholangiocarcinoma. The cholangiocarcinomas were diagnosed at 1, 5, and 45 months in the UDCA-treated patients and at 13, 36, 48, and 54 months in the placebo-treated patients.

A total of 44 patients discontinued treatment (20 UDCA and 24 placebo) for non–liver-related reasons;

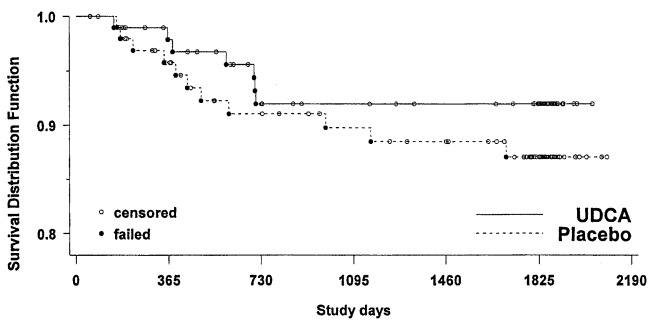

Figure 2. Kaplan–Meier analysis of survival without liver transplantation in UDCA and placebo-treated patients. ●, uncensored patients.

Table 2. Causes of Withdrawal From the Study

Variable	UDCA-treated	Placebo-treated
Noncompliance	13	14
Liver transplantation	5	8
Diarrhea	1	5
Pregnancy	2	2
Death from liver failure	0	1
Cholangiocarcinoma causing discontinuation	1	2
Death in cholangiocarcinoma	2	2
Pruritus	1	1
Indigestion	2	0
Urticaria	1	0
Mammary carcinoma	1	0
Urinary bladder carcinoma	0	1
Headache	0	1
Unknown	0	1

itching was regarded as a liver-related reason (Table 2). There was no trend to more drug-related problems as the cause of withdrawal in the UDCA-treated group. As for reported adverse events not leading to discontinuation of treatment, there was no evidence for a higher rate of any type of event in UDCA-treated vs placebo-treated patients.

The reported incidence of pruritus and abdominal pain during the 6 months preceding each follow-up decreased during the study without any difference between groups (Figure 3). There was no change in the incidence of fever during the course of the study. There was also no difference between the groups regarding the severity of PSC-related symptoms during the last week preceding every 6-month follow-up, nor was there any general change in severity during the course of the study (data not shown).

ALP and alanine aminotransferase tended to decrease in the UDCA-treated patients during the first 6 months, but this decrease was not statistically significant (Figure 4). Likewise, there was a nonsignificant trend to decreased bilirubin values during the study in the UDCA-treated patients (Figure 4). Serum albumin and immunoglobulins G, A, and M did not change during the course of the study, with no differences between groups (data not shown).

Bile acid analyses of deep-frozen serum samples from 24 of the 26 patients randomized to UDCA but not displaying a ≥10% decrease in ALP after 6 months and from 28 of the 35 patients randomized to placebo but nonetheless displaying a ≥10% decrease in ALP after 6 months showed that in no patient randomized to placebo did the UDCA amount to >10% of total serum bile acids. In 3 of the patients randomized to UDCA but not displaying a ≥10% decrease in ALP after 6 months, UDCA amounted to <10% of their serum bile acids. These 3 patients had declared at the first follow-up at 6 months that they did not want to continue in the study, so they probably had not taken the capsules. One of them was shortly afterward diagnosed to have a cholangiocarcinoma. Kaplan–Meier analysis comparing time to death or liver transplantation in patients randomized to UDCA treatment showed no difference between patients who showed a decrease of ALP and those who displayed no

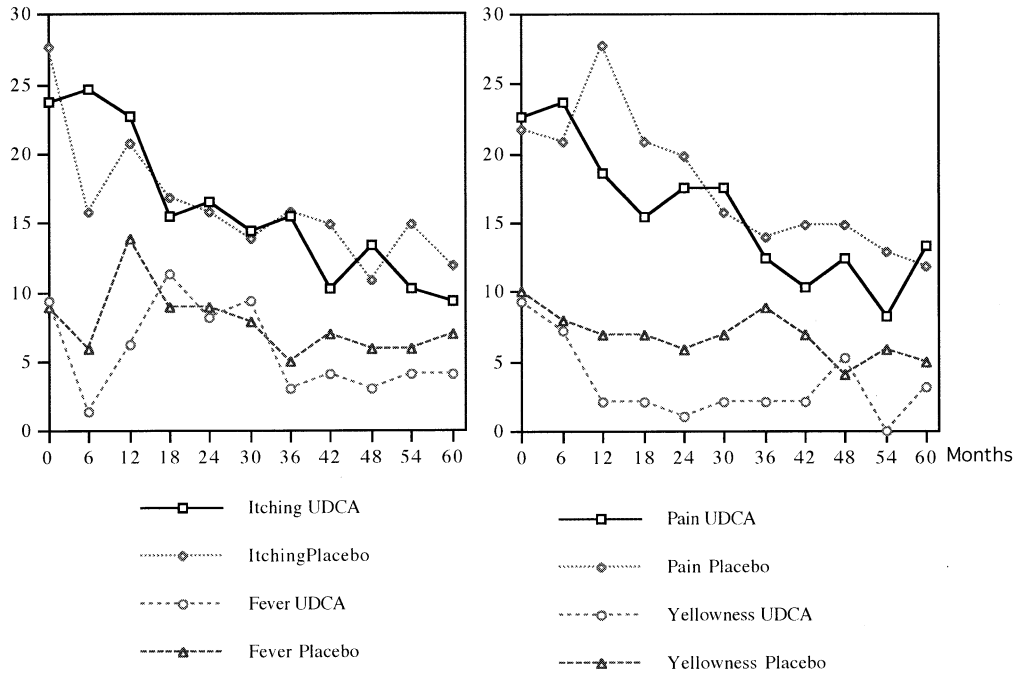

Figure 3. Incidence (%) of PSC-related symptoms during the past 6 months, reported at each 6-month follow-up.

such decrease (data not shown). UDCA responders had significantly higher mean immunoglobulin G (15.0 g/L [SD, 4.0] vs 12.6 g/L [SD, 3.1]; $P = .009$) than UDCA nonresponders. There was no significant difference related to age, sex, extension of PSC, presence or not of symptoms at start, or initial laboratory values besides immunoglobulin G. The single UDCA-treated patient with cholangiocarcinoma who had a follow-up of at least 6 months showed a 47% decrease in ALP. Four of the 6 UDCA-treated patients who underwent a dilation procedure after the first 6 months belonged to the nonresponders. However, 3 of the 4 patients who underwent a stenting procedure after 1, 28, and 45 months in the study were responders.

The scores for self-estimated quality of life were remarkably constant during the course of the study, with no differences between groups (Table 3). Physical functioning, role-physical, bodily pain, social functioning, and role-emotional define health status as the absence of limitation or disability. For these items, the highest possible score of 100 is achieved when no limitations or disabilities are observed. General health, vitality, and mental health are bipolar in nature. For these items, a score in the mid range is obtained when no limitations or disabilities are reported. A score of 100 on these bipolar scales is earned only when respondents report positive states and evaluate their health favorably. The physical and mental health summary scores express health conditions in comparison to a standard population. A score of 50 indicates an average health condition. Values below and above 50 denote health conditions inferior and superior to the mean. No statistically significant differences between UDCA and placebo patients were detected regarding changes from enrollment.

The number of daily stools did not show any changes from baseline (UDCA, 2.4 ± 2.2; placebo, 2.6 ± 2.1) to last observation carried forward (UDCA, 2.2 ± 1.7; placebo, 2.6 ± 2.7), and no difference between the treatment groups could be observed. Eight patients in each group had flares of either their colitis or pouchitis. None of these deteriorations seemed to have had any effect on the serum enzymes or bilirubin.

There seemed to be no difference between the 2 groups in the overall frequency of reported side effects attributed to the capsules (UDCA, 38.1%; placebo, 33.7%), as well as in the frequency of the prevailing adverse events: diarrhea (UDCA, 10.3%; placebo, 13.9%) and loose stools (UDCA, 10.3%; placebo, 4.0%). Diarrhea and loose stools seemed to be less severe in the UDCA than in the placebo group (not scored). Temporary withdrawal of medication because of diarrhea occurred only rarely and then for only a few days. The overall frequency of

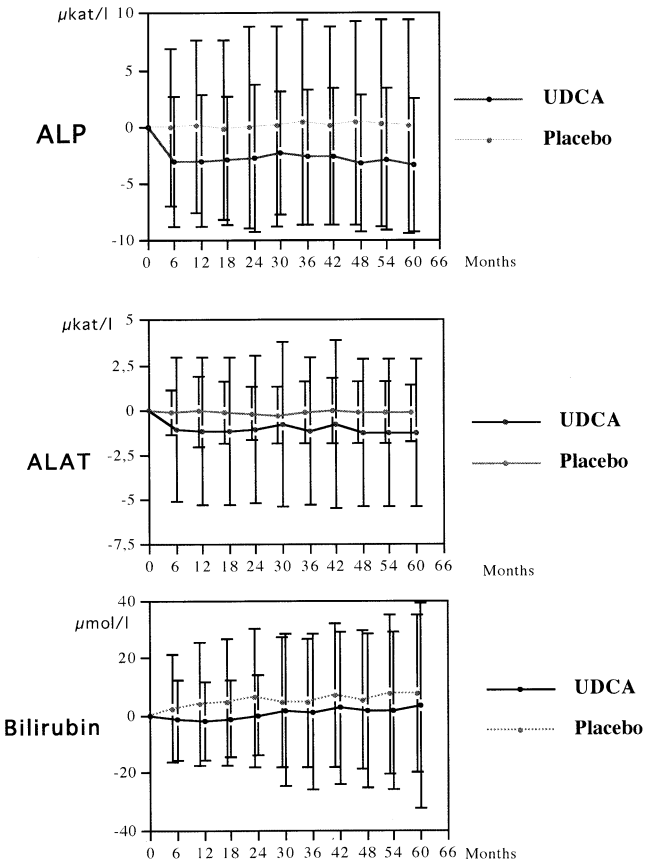

Figure 4. Changes from start in serum ALP, ALT, and bilirubin. Mean with SD.

pruritus (UDCA, 7.2%; placebo, 2.0%), anorexia (7.2% in the UDCA group only), and flatulence (4.1% in the UDCA group only) seemed to be higher in the UDCA group than in the placebo group. Upper abdominal pain (UDCA, 2.1%; placebo, 10.9%) and arthralgia (UDCA, 4.1%; placebo, 8.9%) seemed to be slightly more frequent in the placebo group than in the UDCA group. Back pain, abdominal pain, and pyrexia were also frequently observed but seemed to be equally distributed among the treatment groups. Other adverse events occurred more seldom and were equally distributed among the treatment groups.

Discussion

Since the first demonstration that UDCA may be an effective treatment of primary biliary cirrhosis,[9] several studies have been published investigating the potential role of this drug for the treatment of PSC. UDCA has been used as a single treatment[6,10–20] or in combination with immunosuppressive,[20,21] antibiotic,[22] or endoscopic[23] treatment (Table 4). The design of the studies varies considerably. Thus, the number of UDCA-treated patients varies between 1[10] and 51,[6] and the doses vary

Table 3. Self-Estimated Quality of Life According to the Medical Outcome Study 36-Item Short-Form Health Survey

	At enrollment		Change to last observation under medication	
Variable	UDCA	Placebo	UDCA	Placebo
Physical functioning	90.0 (17.5)	90.8 (14.0)	1.6 (13.5)	−1.0 (12.9)
Role-physical	78.2 (36.0)	78.4 (33.7)	3.1 (34.6)	3.7 (37.5)
Bodily pain	76.0 (27.5)	77.6 (25.8)	5.7 (26.1)	0.2 (22.9)
General health	62.4 (25.8)	61.1 (23.7)	4.2 (17.6)	−0.8 (21.2)
Vitality	64.3 (24.0)	65.1 (25.3)	4.4 (18.3)	−2.6 (20.5)
Social functioning	86.3 (19.4)	85.2 (21.1)	3.5 (20.0)	3.7 (18.7)
Role-emotional	86.1 (30.9)	86.7 (29.1)	−2.8 (32.0)	−4.8 (35.1)
Mental health	82.0 (14.9)	81.3 (18.7)	1.9 (13.6)	−1.7 (15.0)
Physical component, summary	48.3 (9.7)	49.1 (8.3)	1.7 (8.4)	−0.1 (7.5)
Mental component, summary	52.8 (9.1)	53.0 (9.7)	0.5 (9.3)	−1.6 (9.7)

Data are mean (SD).

between approximately 8 mg/kg body weight[10,15,19] and 30 mg/kg body weight.[18] Six of the studies were randomized controlled studies,[6,13–15,17,22] with study periods ranging from 3 months[14] to 3 years.[22] The uncontrolled studies lasted for 6 months[11] to 41 months.[20] In this study, we choose not to include changes in histology and in the cholangiographic appearance of the bile ducts as end points. One reason for this was that we judged it highly probable that inclusion of these procedures in the protocol should considerably reduce the number of patients willing to participate in the study. Furthermore, the high sampling variability of percutaneous liver biopsy in PSC[24] reduces the value of liver histological characteristics for assessment of the effect of treatment on this disease.

No statistically significant benefit from 20 mg/kg body weight UDCA on survival without liver transplantation in PSC was shown in this study. However, there was a tendency to improved survival in the UDCA-treated patients. To detect a 50% reduction of primary events (death or liver transplantation) during the 5-year period of treatment, we needed at least 346 patients—a goal we did not reach within the predetermined recruitment time of 15 months. We considered it unrealistic to prolong the inclusion period until we had reached the desired 346 patients in view of the fact that the included 219 patients originated from our composite patient materials, as well as the known low incidence of newly diagnosed PSC. Hence, the study was undernumbered to exclude a significant beneficial effect on survival. Therefore, our study cannot exclude a beneficial effect of high-dose UDCA on survival without liver transplantation, even though the effect might not be very pronounced. It may be pointed out that our data are in accordance with experiences from the Nordic Transplant Register, in which previous UDCA treatment was associated with a better prognosis on the waiting list for liver transplantation.[25]

In contrast to most previous experiences, including those in which high UDCA doses were used,[17,18] as in this study, we did not observe any significant decrease of serum ALP in the UDCA-treated patients. With arbitrary definition of a decrease of ALP of $<10\%$ after 6 months as nonresponse to treatment, whatever the cause, no fewer than 28 of the 97 UDCA-treated patients could be regarded as nonresponders. Conversely, 35 of the 101 placebo-treated patients could be regarded as responders. To evaluate both whether nonresponders in the UDCA-treated group were really compliant and whether there could have been some mistake in the distribution or production of the test capsules, we analyzed serum UDCA concentrations in the 6-month follow-up deep-frozen serum sample in UDCA nonresponders and placebo responders. In the samples from 24 UDCA nonresponders and 28 placebo responders, we found no evidence that erroneous distribution of the drug or noncompliance influenced the assessment of the potential effectiveness of UDCA, because the only 3 UDCA patients showing low serum UDCA (S-UDCA) levels and, thus, noncompliance dropped out of the study within 6 months. We can of course never exclude that the patients without a substantial decrease in serum ALP despite high UDCA concentrations in serum had taken their capsules only in association with the follow-up visits. The possibility of noncompliance for psychological reasons, eg, doubts about the meaningfulness of taking tablets with unknown content for years for a disease without symptoms or maybe progressing symptoms despite the tablets, cannot be totally excluded. With the usually long-term personal knowledge of the patients that most of us have, however, we judge this highly unlikely. The virtually identical time to death or liver transplantation in

Table 4. Review of Previous Studies on UDCA in PSC

Study	n	RCT	Duration (*y*)	Dose (*mg/day*)	Laboratory tests	Histology	Symptoms	ERC	Survival
Hayashi[10]	1	−	2	600	+	0	NE	−	NE
Chazouillers[11]	15	−	0.5	750–1250	+	NE	0	NE	NE
O'Brien[12]	12	−	1.5	10/kg	+	NE	+	NE	NE
Beuers[13]	14	+	1	13–15/kg	+	+	0	NE	−
Stiehl[14]	27	−	1	750	+	NE	+	NE	NE
	20	+	0.25	750	+	NE	0	NE	−
	12	−	1	750	+	+	+	[a]	NE
De Maria[15]	40	+	2	600	0	NE	0	0	0
Lindor[6]	102	+	2.2	13–15/kg	+	0	0	NE	0
Van Hoogstraten[16]	48	−	2	10/kg	+	0	0	0	0
Mitchell[17]	26	+	2	20/kg	+	+	0	NE	NE
Harnois[18]	30	−	1	25–30/kg	+	NE	NE	NE	+[b]
Okolicsanyi[19]	86	−	≈4	8–13/kg	+	+	NE	NE	NE
Schramm[20c]	15	−	4.5	500–750	−	+	NE	[d]	[b]
Färkkilä[22e]	80	+	3	15/kg	+	+	NE	0	0
Stiehl[23f]	65	−	≈4	750	+	NE	NE	0	+[b]
Sterling[21g]	25	−	2	13–15/kg	0	0	0	0	0

+, improvement; 0, no effect; ERC, endoscopic retrograde cholangiography; NE, not evaluated; RCT, randomized controlled trial.
[a]Deterioration in only 1/20.
[b]Compared with expected survival according to Mayo score.
[c]Combined with prednisolone and azathioprine.
[d]Deterioration in only 1/10.
[e]Comparison with UDCA + metronidazole.
[f]Combined with endoscopic dilations.
[g]Compared with mycophenolate mofetil.

UDCA responders and UDCA nonresponders, with a trend to better survival in the UDCA group compared with the placebo group, also argues against noncompliance in nonresponders. Notably, we were not able to identify any predictors of non-UDCA response but for the higher S-immunoglobulin G in responders—a difference probably without biological significance. The question may arise whether there may be individual PSC patients who may, indeed, benefit from UDCA in view of the heterogeneity of PSC. We do not think that this is likely, because the commonly used definition of "incomplete response" to UDCA is a persistent increase of ALP, and we did not find any difference in survival between nonresponders and responders.

It may be important to remember, in this context, that PSC is a very heterogeneous disease with an unpredictable course in the individual patient and with changes in liver tests that cannot be explained on the basis of present-day knowledge of the pathophysiology of the disease. Nonresponse to UDCA in liver tests may be just another expression of the heterogeneity of the disease population. It may also be important to underscore that the patients included in this study had not taken UDCA before and that in our countries this drug is almost certainly used only in gastroenterology units. We therefore consider it unlikely that placebo patients received UDCA from another physician. It may also be pertinent to mention that in our countries, interventional endoscopic therapy is seldom used unless there is dominant stenosis associated with severe cholestasis,[26] which is reflected in the low number of such procedures in this study and which makes it easier to assess the effect of UDCA.

Three studies report a lower prevalence of colon neoplasia in patients with ulcerative colitis and PSC on UDCA,[27–29] as well as a reduced rate of recurrence of colorectal adenomas after removal in primary biliary cirrhosis patients on UDCA.[30] There is also experimental evidence for reduction of hepatocarcinogenesis by UDCA.[31] However, such an effect was not evident in 1 human long-term study of UDCA in primary biliary cirrhosis.[32] In this study there was also no significant difference in the number of patients with a diagnosis of cholangiocarcinoma during the study. However, it is worth noticing that 2 of the 3 cholangiocarcinomas in the UDCA-treated patients were diagnosed within the first 5 months, whereas in the placebo group, 3 of the 4 carcinomas were diagnosed after 3–4.5 years. The 2 early cases in the UDCA-treated patients had their PSC diagnosed within 1 year before the start of the study, whereas the other patients who developed cholangiocarcinomas had a history of PSC ranging from 5 to 13 years. Taking into consideration that approximately every third hepatobiliary malignancy is diagnosed within 1 year after the diagnosis of PSC and that the annual incidence of cholangiocarcinoma thereafter is approximately 1.5%,[5] we

judge that our data still could be compatible with a cholangiocarcinoma-preventive effect of UDCA in PSC.

The Cochrane Database analysis of the effect of UDCA in primary biliary cirrhosis concluded that there was no significant antipruritic effect of the drug[33] in this disease. In conformity with this, we observed effects neither on pruritus nor on abdominal pain or fever in this study. An observation difficult to explain was the decreasing rate of days with pruritus and pain during the course of the study in both study groups. A possible explanation could be that with time, more and more of the symptomatic patients died or underwent transplantation. However, there was the same clear trend to decreasing symptom load when the analysis was restricted to patients who completed the study. Another hypothetical explanation is that the decreased rate is a sort of exhaustion phenomenon or accommodation phenomenon in the patients. It may be mentioned that fatigue was not analyzed as a symptom, because at the time when this study was started, there were no data that suggested that fatigue should be a specific PSC-related symptom.

The physical and mental health summary scores in our patients differed very little from those in a standard population. This is consistent with data obtained in a small group of PSC patients from the Mayo Clinic.[34] However, they are at variance with SF-36 data obtained in a bigger sample of patients with cholestatic liver disease, who were found to have significantly lower scores for all domains of SF-36 compared with controls.[35] However, that study group included both PSC and primary biliary cirrhosis patients, and no differentiation of the results to the 2 diseases was performed. Anyhow, in view of the fairly normal scores at the start of the study in this cohort of patients, it is not surprising that no difference between the 2 groups in self-estimated quality of life was observed until the last observation under medication.

There was a similar and rather lower incidence of diarrhea in UDCA-treated patients as compared with placebo-treated patients. Troublesome diarrhea causing withdrawal or dose reduction of UDCA was reported in 2 early studies of UDCA in PSC,[13,14] whereas improvement of diarrhea was observed in a third.[12] As mentioned, temporary withdrawal of medication because of diarrhea occurred only rarely and only for a few days. No patient had to continue the study on a reduced dose.

To conclude, this study, being the biggest controlled prospective study in PSC ever performed, could not show a beneficial effect of UDCA on survival or prevention of cholangiocarcinoma. Although the study was underpowered to show a possible positive effect, it included a large number of patients carefully followed up over 5 years. We therefore believe that in clinical practice, the effect of UDCA on disease progression in PSC, if any, is limited.

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