

Long-term ursodeoxycholic acid therapy for primary biliary cirrhosis: a follow-up to 12 years

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SUMMARY

Background: It is uncertain whether ursodeoxycholic acid therapy slows down the progression of primary biliary cirrhosis, according to two meta-analyses. However, the randomized trials evaluated had only a median of 24 months of follow-up.

Aim: To evaluate long-term ursodeoxycholic acid therapy in primary biliary cirrhosis.

Methods: We evaluated 209 consecutive primary biliary cirrhosis patients, 69 compliant with ursodeoxycholic acid and 140 untreated [mean follow-up 5.79 (s.d. = 4.73) and 4.87 (s.d. = 5.21) years, respectively] with onset of all complications documented. Comparison was made following adjustment for baseline differences according to Cox modelling, Mayo and Royal Free prognostic models.

Results: Bilirubin and alkaline phosphatase concentrations improved with ursodeoxycholic acid (at 36 months, $P = 0.007$ and 0.018 , respectively). Unadjusted Kaplan–Meier analysis showed benefit ($P = 0.028$), as 44 (31%) untreated and 15 (22%) ursodeoxycholic acid patients died or had liver transplantation. However, there was no difference when adjusted by Cox modelling ($P = 0.267$), Mayo ($P = 0.698$) and Royal Free models ($P = 0.559$). New pruritus or fatigue or other complications were not different, either before or after adjustment for baseline characteristics.

Conclusions: Long-term ursodeoxycholic acid therapy did not alter disease progression in primary biliary cirrhosis patients despite a significant improvement in serum bilirubin and alkaline phosphatase consistent with, and similar to, those seen in ursodeoxycholic acid cohorts in randomized trials.

INTRODUCTION

Primary biliary cirrhosis (PBC) is a chronic inflammatory liver disease with cholestasis, a positive antimitochondrial antibody, lymphocytic portal inflammation and bile duct loss with variable fibrosis.¹ Progression results in biliary cirrhosis, and eventually liver failure in many cases. Ursodeoxycholic acid (UDCA) is the only approved drug for this disease. However, the beneficial effect of UDCA in PBC patients is uncertain. Two independent

meta-analyses, examining both the randomized and open-label phases (placebo patients subsequently given UDCA), failed to show benefit in terms of survival, transplantation rates or complications of disease.^{2, 3} The major shortcoming has been that the follow-up time in the randomized treatment arms was too short to make useful conclusions as the median follow-up was only 24 months as non-UDCA-treated patients were crossed over to UDCA.⁴ Since the publication of the meta-analyses, a prolonged follow-up to 4 years of one double-blind placebo-controlled study in the USA⁵ has shown no benefit of UDCA, although again interpretation is difficult as for the period between 2 and 4 years all patients were taking UDCA.

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Current guidelines in the USA recommend UDCA 13–15 mg/kg/day for up to 4 years with the expectation of delaying liver transplant or death.⁶ Unfortunately, new trials of UDCA with a prolonged follow-up are not practical because of the long natural history of the disease and UDCA is usually administered anyway as it is a very safe drug in other liver diseases also.⁷ Therefore, further data on the benefit of UDCA can only be obtained by evaluating patients with prospectively collected information who have had prolonged UDCA therapy, or no UDCA, adjusting for the known and well-validated prognostic variables in PBC.^{8, 9} We set up this study to evaluate this comparison, assessing whether long-term UDCA treatment has any effect on clinical and biochemical features, survival and liver transplantation rates.

PATIENTS AND METHODS

Primary biliary cirrhosis was diagnosed by positive antimitochondrial antibodies and/or alkaline phosphatase (ALP) >1.5 times the upper limit of normal, and/or compatible liver histology. The UDCA-treated cohort was 69 consecutive patients seen at our centre from April 1989 to August 2001 who did not stop taking the drug even if they had side-effects. The untreated group was 140 consecutive patients seen at our centre in the same period. This cohort does not overlap with our previously published Royal Free prognostic model of 289 patients.⁹ The choice of using, or not using UDCA, was determined by the patient's physician. All information had been prospectively collected in a database set up for PBC studies, which recorded symptoms, signs and biochemical data (liver and renal function, prothrombin time, full blood count, immunological tests and histological grading) at date of referral, presentation and/or diagnosis, and then every 3–6 months or whenever attending or admitted to hospital. Dates of occurrence of the following, if clinically detected, were always recorded: ascites, ankle oedema, encephalopathy, pruritus, fatigue and gastrointestinal bleeding. Liver biopsies were evaluated if performed within 12 months of entry in the study; Scheuer's classification system was used: 120 (57%) had valuable baseline liver biopsies, of a total of 160 of 209 (77%) patients who had a liver biopsy at any time.

The UDCA starting date was either at Royal Free Hospital or before referral whichever was earlier. The mean UDCA dosage was 14 mg/kg/day (s.d. = 4), ranging from 7 to 22 mg/kg/day: 25 patients received

low-dose UDCA (mean 10 mg/kg/day; range 7–12) and 44 patients received standard/high dose (mean 16 mg/kg/day; range 13–22). The starting date of the untreated group was the time when patients were first seen at Royal Free Hospital. These patients remained without UDCA therapy, either because they presented and were followed up in the pre-UDCA era, or because of physician preference.

Death was classified as liver-related if it resulted from a complication of liver disease or non-liver-related. Liver transplantation was censored at the date of transplantation whereas all patients alive without transplantation at the end of the study were censored at the date of last follow-up. The follow-up period in UDCA-treated group was a mean of 5.8 (s.d. = 4.73) years when compared with the untreated group of 4.9 (s.d. = 5.21) years.

We evaluated the occurrence of liver transplantation or death as the main endpoint. The indications for liver transplantation were defined as those due to progressive liver disease, i.e. development of refractory or resistant ascites, repeated variceal bleeding, intractable hepatic encephalopathy, spontaneous bacterial peritonitis and/or increase in serum bilirubin concentrations to >170 $\mu\text{mol/L}$ or hepatocellular carcinoma, or for control of symptoms. Other endpoints were the advent of fatigue or pruritus, or their worsening, development of varices (diagnosed endoscopically in all but 4% of patients), variceal or nonvariceal bleeding, ascites, occurrence of urinary tract infection (UTI), spontaneous bacterial peritonitis or other sepsis. For each patient, the changes from baseline (start of therapy for UDCA group, and first visit at Royal Free Hospital for untreated group) of serum bilirubin, ALP and albumin values were evaluated at each time interval, and between groups, median values were compared. For those who died or were transplanted, the values closest to death or on the day before transplantation were used.

Statistical analysis

Data were analysed using the SAS package version 8.2 (SAS, Cary, NC, USA), comparing baseline variables by chi-square tests or Fisher exact tests and Student's *t*-tests for quantitative or qualitative data, as appropriate. Within the UDCA-treated and -untreated groups, Wilcoxon signed rank test was used for changes in biochemical profile, whereas between these groups, Mann–Whitney *U*-test was used for comparisons. Time-to-event analyses were evaluated by the Kaplan–Meier

method using log-rank tests to assess differences between groups. Cox proportional hazards regression was used to adjust for differences in baseline characteristics, affecting death or transplantation. These were identified initially using unadjusted analyses and then adjusted in multivariate analyses. Survival free from liver transplantation was further examined after adjusting for survival predicted by the Mayo risk score⁸ and the Royal Free risk score⁹ as the covariate. Both scores do not have histology stage as an independent predictor. Sensitivity analyses for the major endpoints were performed by separately comparing the untreated group with the standard/high (13–22 mg/kg/day) or low-dose UDCA groups. A two-tailed *P* value <0.05 was considered to be statistically significant.

RESULTS

Baseline characteristics

The two groups were broadly similar with respect to sex distribution, clinical and biochemical characteristics

(Tables 1 and 2). However, regarding the known prognostic factors in PBC, the mean age was higher in the untreated group at 55.6 (s.d. = 11.9) years vs. 52.4 (s.d. = 10.3) years in the UDCA group (*P* = 0.06), and mean baseline bilirubin level was higher in the untreated 47.6 (s.d. = 7.0) $\mu\text{mol/L}$ vs. 31.0 (s.d. = 6.4) $\mu\text{mol/L}$ in the UDCA group (*P* = 0.08). The mean baseline albumin level was lower at 39.9 (S.E. = 0.5) g/L in the untreated group vs. 41.8 (S.E. = 0.6) g/L in the UDCA group (*P* = 0.03). Ascites at baseline: 23 (16%) untreated vs. 4 (6%) UDCA (*P* = 0.05). Baseline bilirubin $\geq 34 \mu\text{mol/L}$ was more frequent in the untreated group 43 (31%) vs. 11 (16%) in the UDCA group (*P* = 0.03). The mean Royal Free risk score was significantly higher, i.e. worse prognosis, in the untreated (-3.51; s.d. = 1.86) compared with the UDCA group (-4.11; s.d. = 1.39) (*P* = 0.013). The Mayo risk score was also higher in untreated (5.32; s.d. = 1.92) when compared with UDCA (4.86; s.d. = 1.34) but was not significantly different. The histological stages were similar in two groups (stage I–II 50.7% untreated and 63.9% UDCA group).

Table 1. Baseline characteristics of 209 consecutive PBC patients

	Untreated group	UCDA group	UCDA group (13–22 mg/kg/day)
No. of patients (<i>n</i>)	140	69	44
Mean age (s.d.)	55.6 (11.9)	52.4 (10.3)	50.7 (10.5)
Sex (male : female)	13 : 127	4 : 65	2 : 42
Pruritus (%)	75 (54)	30 (44)	22 (50)
Fatigue (%)	65 (46)	29 (42)	19 (43)
Bone pain (%)	36 (26)	16 (23)	9 (21)
Hyperpigmentation (%)	23 (16)	11 (16)	9 (21)
Spider naevi (%)	30 (21)	11 (16)	8 (18)
Muscle wasting (%)	12 (9)	3 (4)	3 (7)
Hepatomegaly (%)	64 (46)	36 (52)	22 (50)
Splenomegaly (%)	37 (26)	16 (23)	10 (23)
Oesophageal varices (%)	22 (16)	14 (20)	8 (18)
History of gastrointestinal bleeding (%)	18 (13)	6 (9)	3 (7)
Ankle oedema (%)	19 (14)	7 (10)	4 (9)
Ascites (%)	23 (16)	4 (6)	2 (5)
Hepatic encephalopathy (%)	13 (9)	3 (4)	1 (2)
Histology staging (<i>n</i> = 120) (%)	<i>n</i> = 73	<i>n</i> = 47	<i>n</i> = 29
I	20 (27.4)	20 (42.6)	12 (41)
II	17 (23.3)	10 (21.3)	5 (17)
III	20 (27.4)	9 (19.1)	6 (21)
IV	16 (21.9)	8 (17.0)	6 (21)
Risk scores			
Mayo risk score ⁸	5.32 (1.92)*	4.86 (1.34)*	4.72 (1.29)*
Royal Free risk score ⁹	-3.51(1.86)*	-4.11(1.39)*	-4.27(1.35)*

* Mean (standard deviation).

Table 2. Baseline laboratory data of 209 consecutive PBC patients

	Reference range	Untreated group (n = 140)	UDCA group (n = 69)	UDCA group (13–22 mg/kg/day) (n = 44)
Median bilirubin ($\mu\text{mol/L}$)	5–17	14 (9–27)†	13 (8–25)†	13 (8–27)†
Mean bilirubin ($\mu\text{mol/L}$)	5–17	47.6 (7.03)*	31.0 (6.4)*	25.0 (5.3)*
Bilirubin ($\geq 34 \mu\text{mol/L}$) (%)		43 (31)	11 (16)	7 (16)
Albumin (g/L)	35–50	39.9 (0.5)*	41.8 (0.6)*	42.1 (0.8)*
ALP (U/L)	42–128	408.0 (28.9)*	464.3 (41.5)*	482 (56.7)*
AST (U/L)	5–40	91.6 (9.7)*	90.1 (8.9)*	95.2 (12.2)*
Prothrombin time (s)	12–16	14.8 (1.1)*	13.0 (0.2)*	12.9 (0.3)*
INR	0.9–1.2	1.09 (0.03)*	1.31 (3.19)*	0.97 (0.02)*
Cholesterol (mmol/L)	3.0–6.0	6.3 (0.2)*	10.7 (3.3)*	6.4 (0.3)*
Urea (mmol/L)	3.0–6.5	5.4 (0.2)*	5.2 (0.26)*	5.1 (0.2)*
Creatinine ($\mu\text{mol/L}$)	60–97	83.8 (1.80)*	79.7 (1.6)*	78.8 (1.7)*
IgG (g/L)	7.0–16.0	16.9 (0.7)*	16.3 (0.9)*	16.9 (0.7)*
IgA (g/L)	0.7–4.0	3.4 (0.2)*	3.2 (0.4)*	3.3 (0.4)*
IgM (g/L)	0.4–2.3	5.2 (0.58)*	3.5 (0.26)*	3.5 (0.31)*
AMA positive		94%	91%	89%
ANA positive		35%	39%	44%
SMA positive		9%	6%	5%
Haemoglobin (g/dL)	11.5–15.5	12.4 (0.2)*	12.5 (0.2)*	12.6 (0.2)*
Platelet ($\times 10^3/\text{L}$)	140–400	222 (9)*	242 (14)*	240 (15.2)*

ALP, alkaline phosphatase; AMA, antimitochondrial antibody; ANA, antinuclear antibody; AST, aspartate aminotransferase; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; INR, international normalized ratio; SMA, smooth muscle antibody; UDCA, ursodeoxycholic acid.

* Mean (standard error).

† Median (inter-quartile range).

Comparison of baseline characteristics with those in randomized studies

The baseline prognostic factors were comparable with those of the randomized UDCA trials evaluated meta-analytically.^{2, 3} This cohort's mean age of 52.4 years in UDCA and 55.6 years in untreated arms vs. the trials' range of mean ages of 49–57.5 years in UDCA and 48.9–57 years in non-UDCA arms; median bilirubin: 13 $\mu\text{mol/L}$ UDCA vs. 14 $\mu\text{mol/L}$ untreated, compared with 17–19 $\mu\text{mol/L}$ UDCA and 17–18 $\mu\text{mol/L}$ non-UDCA arms in two studies giving the median.^{10, 11} In the other studies, the mean bilirubin ranged between 18.9–39.1 $\mu\text{mol/L}$ in UDCA and 18.2–34.2 $\mu\text{mol/L}$ in non-UDCA, compared with 31 $\mu\text{mol/L}$ in UDCA group and 47.6 $\mu\text{mol/L}$ in untreated group. Patients with bilirubin $\geq 34 \mu\text{mol/L}$ were similar in the UDCA (16%) group and in the untreated group (31%) when compared with meta-analysed trials (10–34%) vs. (6–32%). The mean albumin was 41.8 g/L in UDCA and 39.9 g/L in untreated group compared with a mean of 34–42 g/L (UDCA) and 33–41 g/L (non-UDCA) in meta-analysis trials. Ascites present at randomization was mentioned in only two trials (1.8 and 3% UDCA vs. 4 and 4.3%

placebo); our patients had a higher proportion of ascites at baseline in both UDCA (6%) and untreated groups (16%). Our mean Mayo prognostic score was 4.86 (s.d. = 1.34) in UDCA and 5.32 (s.d. = 1.92) in the untreated group, compared with 1.89–5.2 in UDCA and 2.07–5.1 in non-UDCA arms in the five trials that evaluated it.

Similarly, the known prognostic factors in the standard/high-dose UDCA-treated cohort were better, compared with the untreated cohort (Tables 1 and 2), and similar to UDCA groups in the randomized trials.

Changes in bilirubin, albumin, alkaline phosphatase and prothrombin time

Comparing changes from the baseline bilirubin concentration for each patient within each group, there was a significant increase in median bilirubin concentration in the untreated group from 6 months onwards, whereas in UDCA treatment group, the median concentration remained stable (Figure 1 and Table 3). Comparing groups, the bilirubin concentration in the UDCA group was significantly lower than the untreated group at 6 months ($P = 0.008$) and 36 months ($P = 0.007$).

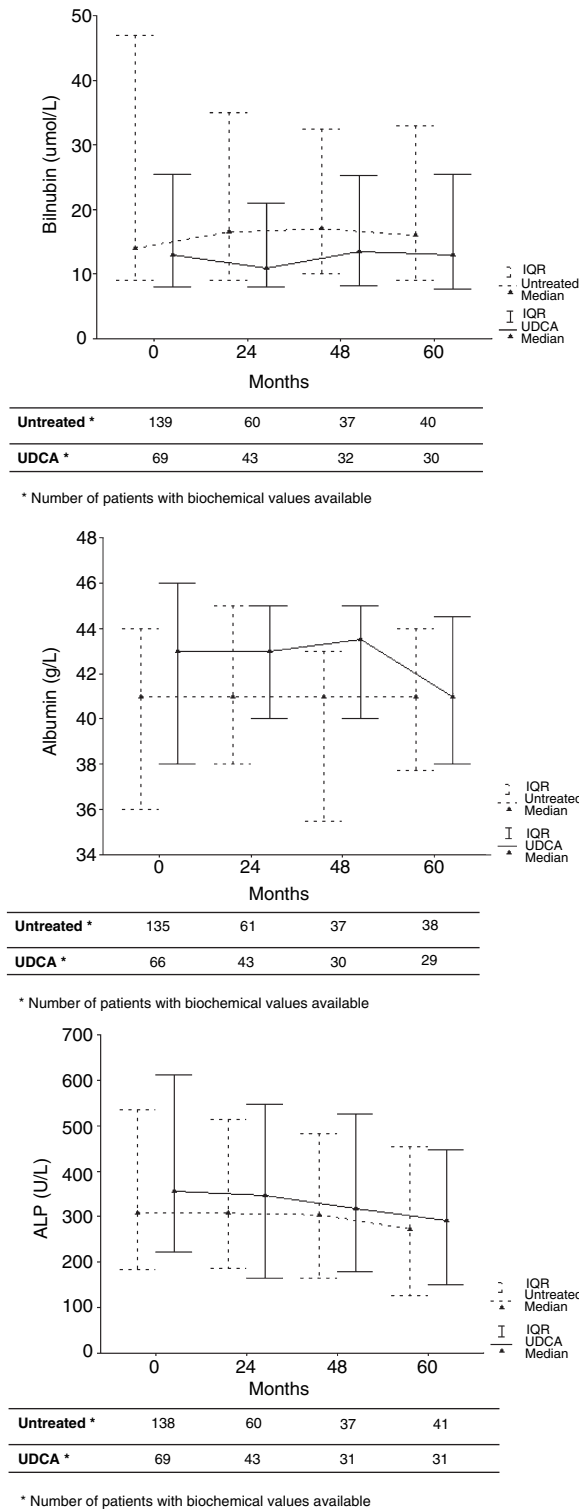


Figure 1. Changes of serum bilirubin, albumin and alkaline phosphatase concentrations in the study (median and IQR, interquartile range).

Similarly, there was a significant reduction the serum ALP in the UDCA group from 6 months onwards when compared with the untreated group in which the median serum ALP concentration did not change significantly, so that there were significant differences at 6 months ($P = 0.044$), 12 months ($P = 0.017$) and at the last available biochemistry values ($P < 0.001$). There were no significant effects in UDCA-treated patients with respect to the serum albumin concentration and prothrombin time.

Changes in serum bilirubin and ALP concentration in the standard/high UDCA dose group were similar to the low-dose group. Compared with baseline, median change per patient of bilirubin was $-0.5 \mu\text{mol/L}$ [interquartile range (IQR) -11 to $+6.25 \mu\text{mol/L}$] in high-dose vs. $1 \mu\text{mol/L}$ (IQR 0 – $6 \mu\text{mol/L}$ in low dose) at 36 months ($P = 0.365$) and median ALP was -102 U/L (IQR -307 to -4.25 U/L) high dose vs. -16 U/L (IQR -132 to 62 U/L) in low dose ($P = 0.214$).

Death or liver transplantation

There were 19 (9%) deaths without transplantation (Table 4): 12 in the untreated group and seven in the UDCA group. Liver-related death occurred in 14 (6.7%) (eight untreated and six UDCA group). Five patients died of non-liver-related causes (2%) (three cardiac deaths and one chronic chest disease in untreated vs. one cardiac death in UDCA group). Liver transplantation occurred in 40 (19%) (32 untreated and eight treatment group). Liver decompensation was the indication for liver transplantation in 36 (90%) (eight UDCA, bilirubin range 11 – $302 \mu\text{mol/L}$; and 28 untreated group, bilirubin range 7 – $481 \mu\text{mol/L}$); four (10%) were transplanted for refractory pruritus, all in the non-UDCA group (bilirubin range 12 – $78 \mu\text{mol/L}$).

The unadjusted analysis of baseline variables with respect to death or transplantation showed that the following were associated with decreased survival: a history of gastrointestinal bleeding ($P < 0.001$), bilirubin concentration ($P < 0.001$), albumin concentration ($P < 0.001$), presence of pruritus ($P = 0.01$), fatigue ($P = 0.04$), hepatomegaly ($P < 0.001$), splenomegaly ($P < 0.001$), oesophageal varices ($P < 0.001$), ascites ($P < 0.001$), hepatic encephalopathy ($P = 0.01$), high Mayo risk score ($P < 0.001$) or Royal Free risk score ($P < 0.001$). In the multivariate analysis, only baseline bilirubin concentration ($P = 0.002$) and the presence of ascites ($P = 0.009$) remained significant predictors of liver transplantation or death (Table 5).

	Untreated group [median (IQR)]	UDCA group [median (IQR)]	Untreated vs. UDCA group (<i>P</i> -value*)
Bilirubin ($\mu\text{mol/L}$)			
Baseline	14.0 (9.0–47.0)	13.0 (8.0–25.5)	0.32
36 months	21.0 (10.2–43.0)†	12 (8–20)	0.007
Last data	22.0 (10.0–81.0)†	14.0 (10.0–32.0)‡	0.724
Albumin (g/L)			
Baseline	41 (36–44)	43 (38–46)	0.034
36 months	40 (38–43)	43 (41–44)	0.387
Last data	38 (32–41)†	40 (36.9–43)†	0.659
ALP (U/L)			
Baseline	307 (183–536)	355 (223–612)	0.25
36 months	350 (169–568)	278 (129–485)§	0.275
Last data	314 (175–474)	260 (142–417)†	<0.001
Prothrombin time (s)			
Baseline	13.0 (12.0–14.8)	12.9 (12.0–13.8)	0.24
36 months	12.9 (12.5–14.2)	12.0 (12.0–13.0)	0.063
Last data	14.4 (13.0–17.0)†	14.1 (13.0–16.0)†	0.460

IQR, inter-quartile range.

* Mann–Whitney *U*-test comparing untreated and UDCA treatment group.

† Significant difference compared with baseline values $P < 0.001$.

‡ Significant increase of bilirubin concentration compared to its baseline $P = 0.030$; Wilcoxon signed rank test.

§ Significant reduction of ALP compared with its baseline $P = 0.018$; Wilcoxon signed rank test.

Table 4. Death or liver transplantation in the cohort of 209 consecutive PBC patients

	Untreated group (<i>n</i> = 140)	UDCA group (<i>n</i> = 69)
Death (%)	12 (9)	7 (10)
Liver-related deaths (%)	8 (6)	6 (9)
Non-liver-related deaths (%)	4 (3)	1 (1)
Liver transplantation (%)	32 (23)	8 (12)

Table 5. Significant baseline predictive factors for liver transplant or death in the PBC cohort with or without UDCA treatment

Covariates	Regression Coefficient	Standard error	<i>P</i> -value
Log ₁₀ (bilirubin)	1.530	0.506	0.002
Ascites*	1.352	0.515	0.009

* Ascites absent, 0; ascites present, 1.

The 5-year probability of survival free from liver transplantation or death was 78.3% (S.E. = 7.4%) in the untreated group and 77.1% (S.E. = 10.6%) in the UDCA group.

Before adjustment for baseline characteristics, survival was longer in the UDCA group vs. untreated group

Table 3. Changes of biochemical parameters (comparison of groups at baseline and median of changes from baseline per patient at other time points)

($P = 0.028$ log-rank test) (Figure 2). However, because of the poorer baseline characteristics of the untreated cohort, the difference disappeared after adjustment for the baseline covariates using Cox regression modelling ($P = 0.267$) (Figure 3).

To test the robustness of this result, we also used the Mayo model and the Royal Free model to adjust for baseline characteristics.^{8, 9} There were no differences in the probability of transplantation or death comparing the untreated and UDCA groups ($P = 0.698$ Mayo model, $P = 0.559$ Royal Free model) (Figures 4 and 5).

Without adjustment for baseline covariates, the difference was far less if death and only transplantation caused by liver decompensation was evaluated (excluding the four patients transplanted for refractory pruritus; $P = 0.056$, log-rank test).

To evaluate the effect of UDCA dosage, a standard sensitivity analysis was performed comparing 140 untreated with 44 patients treated with standard/high-dose UDCA treatment (13–22 mg/kg/day); nine (21%) died or had liver transplantation. There was no significant difference in time to transplantation or death, before adjustment ($P = 0.120$ log-rank test), nor after adjustment by all three models: either the cohort Cox model with baseline characteristics ($P =$

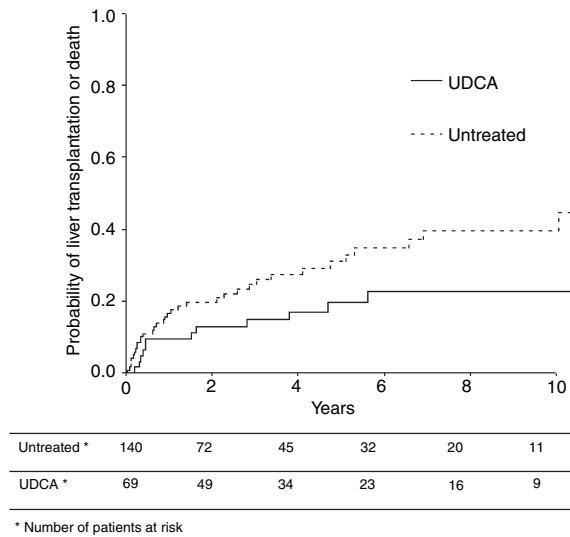


Figure 2. Probability of death or liver transplantation in UDCA-treated or -untreated primary biliary cirrhosis patients without adjustment for baseline variables ($P = 0.028$).

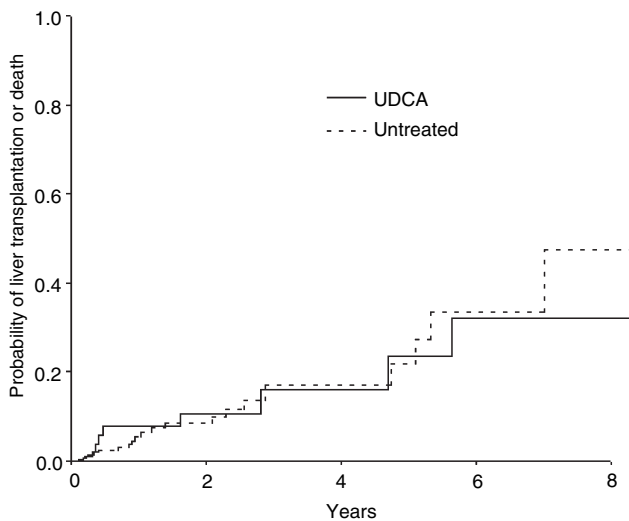


Figure 3. Probability of liver transplantation or death of UDCA-treated or -untreated primary biliary cirrhosis patients after adjustment of baseline characteristics by Cox regression ($P = 0.267$).

0.653), Mayo model ($P = 0.326$), or the Royal Free model ($P = 0.778$).

Changes in clinical characteristics and complications

The changes in clinical characteristics and complications are summarized in Table 6, excluding those patients who had the complications at baseline in

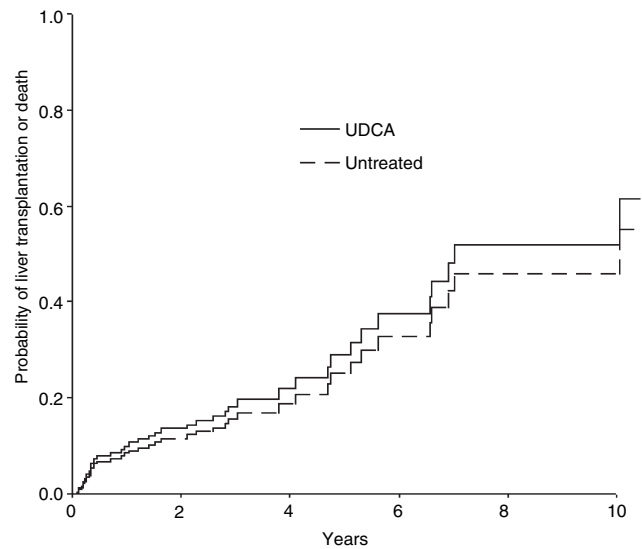


Figure 4. Probability of liver transplantation or death in UDCA-treated or -untreated PBC patients after adjustment using the Mayo prognostic index ($P = 0.698$).

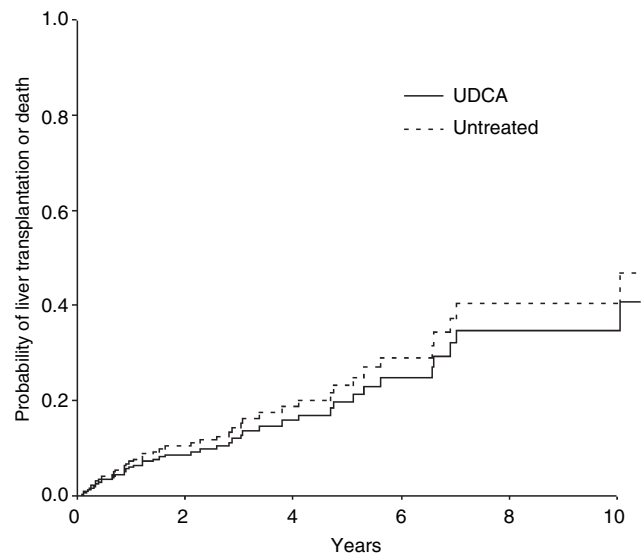


Figure 5. Probability of liver transplantation or death in UDCA-treated or -untreated PBC patients after adjustment using the Royal Free prognostic index ($P = 0.559$).

untreated and UDCA groups. There were no significant differences in the proportions of patients in the two groups developing the complications shown.

Analysis of time-to-event showed no significant differences between UDCA and untreated groups, using log-rank test or after adjustment using Cox proportional hazards modelling, using the baseline independently significant associated variables (Table 6).

Table 6. Changes in clinical characteristics and occurrence of new complications throughout the study*

	Untreated group	UDCA group	P-value		
			Differences in occurrence†	Differences in time to event§	Differences in time to event¶
Worsening pruritus	38 (13%)	13 (43%)	0.64	0.269	0.086
New pruritus	19 (29%)	12 (31%)	1.00	0.250	0.489
Worsening fatigue	31 (48%)	14 (48%)	1.00	0.798	0.697
New fatigue	26 (35%)	17 (43%)	0.53	0.904	0.203
Development of varices	22 (19%)	6 (10%)	0.27	0.109	0.769
Development of variceal bleeding	7 (25%)	4 (14%)	0.78	0.875	0.267
Development of upper gastrointestinal bleeding‡	23 (20%)	9 (16%)	0.55	0.976	0.218
Development of ascites	35 (31%)	15 (25%)	0.35	0.976	0.218
Hepatic encephalopathy	2 (1%)	0 (0%)	0.55		
Significant clinical sepsis	25 (24%)	12 (23%)	0.94	0.06	0.49
Urinary tract infection	11 (11%)	3 (6%)	0.33	0.217	0.218
Septicaemia	4 (6%)	2 (4%)	0.98	0.199	0.327

* Patients with these complications at baseline were excluded.

† Chi-square test or Fischer's exact test.

‡ It refers to variceal bleeding including unknown sources as well as known nonvariceal sources.

§ Log rank test.

¶ Adjusted using Cox proportional hazards modelling.

DISCUSSION

Ursodeoxycholic acid-treated patients, when compared with untreated patients, had a significant reduction over time for both serum bilirubin and ALP (median reduction of 43% and 21% at 36 months, respectively), similar to the magnitude seen in randomized studies.^{2, 3} Despite the similarity in baseline prognostic characteristics, as well as similar reduction in serum bilirubin and ALP, with respect to UDCA cohorts in randomized trials, our UDCA-treated group did not have a significant reduced risk of liver transplantation or death when adjusted for same prognostic factors using validated prognostic models in PBC. There were sufficient events (59, 28%) to give sufficient power to fit a Cox model with two regressors, UDCA treatment and prognostic score, as well as all the known prognostic factors individually. Moreover, the UDCA-treated group did not have any improvement in the time of occurrence of new or worsening of fatigue or pruritus, nor delay in the occurrence of complications of advanced liver disease. This is consistent with the conclusions of two independent meta-analyses^{2, 3} which evaluated 1444 patients, only 12% of whom died or had liver transplantation. Furthermore, no significant improvement was observed in serum albumin and prothrombin time, both established prognostic predictors in PBC, similar to the randomized studies^{2, 3} despite a longer follow-up interval.

As the major shortcoming of the two meta-analyses^{2, 3} was the short follow-up of the UDCA-treated patients and the inclusion of trials with short follow-up times, our evaluation has the advantage of an average follow-up time of 5.79 years in UDCA group, longer than all randomized trials except one.¹² This potentially gives better power to detect differences between UDCA-treated and untreated groups as a higher event rate was observed – 28% vs. 12% in the randomized trials died or underwent liver transplantation. Based on our event rate and sample size (140 untreated and 69 UDCA-treated), we should have been able to detect a 20% reduction in death and transplantation in the UDCA group with a power of 87% (assuming UDCA to be effective, i.e. a one-tail alpha level of 0.05). The 5-year probability of survival free of transplantation in our untreated group was 78.3% (S.E. = 7.4%). It was predicted well by both the Mayo model⁸ (predicted 5-year probability 72%) and Royal Free model⁹ (predicted 5-year probability 77.5%) indicating that the PBC cohort which we studied did not have different prognostic characteristics to others published, including those in randomized trials.

Evaluating indications for liver transplantation is an important, yet unaddressed issue in many randomized trials in PBC. It may be the reason for uncertainty regarding the benefit of UDCA as some patients with good prognostic indices are transplanted for intractable

pruritus alone. In one centre,¹³ serum bilirubin ranged from 6 to 966 $\mu\text{mol/L}$ at transplantation. Excluding our four patients transplanted for pruritus alone (all in the non-UDCA group), an unadjusted comparison between untreated and UDCA groups found a non-significant difference in survival (censoring patients at date of transplantation).

Given the long natural history of PBC, evaluation of clinical endpoints other than death or transplantation is relevant. We had prospectively collected the date of onset of complications using 3–6-month observations on all patients. Time to occurrence of complications has not been extensively evaluated in UDCA studies. In our study, UDCA used for a mean of just over 5 years did not confer significant benefit in either reducing the occurrence nor delaying worsening of fatigue and pruritus.

There has been controversy as to whether UDCA delays the development of varices, recognizing that varices can occur before cirrhosis in PBC.¹⁴ One trial did not find any effect of UDCA,¹⁵ while another reported delayed development of varices.¹⁶ There was no evaluation in the other nine randomized UDCA trials.^{10–12, 17–22} In our study, the rate of endoscopically diagnosed varices was not delayed by UDCA and neither was the occurrence of upper gastrointestinal bleeding nor ascites.

Increased susceptibility to bacterial infection is associated with increasing severity of liver disease, particularly cirrhosis^{23–25} and was not evaluated in the randomized UDCA trials. Our cohort had an overall rate of significant clinical sepsis of 24%, but UDCA did not confer any protection. In a previous PBC cohort, recurrent UTI had prognostic significance.²⁴ In this cohort, symptomatic UTI was similar in the untreated and UDCA group.

In conclusion, in this study, PBC patients treated with UDCA had no changes in the progression of their disease, the occurrence of complications and neither was death nor transplantation delayed compared with untreated patients, adjusting for baseline prognostic factors for PBC. Although UDCA may be effective only in patients with early-stage PBC or those with normal serum bilirubin concentrations,²⁶ we did observe improvement in serum bilirubin and ALP, consistent with, and similar to, the published randomized trials. As a result of our sample size, we were not able to evaluate the effect of UDCA or no UDCA in those with normal serum bilirubin. Our evaluation with a much longer

follow-up period of up to 12 years with a mean of 5.8 years, supports the evidence from the published meta-analyses^{2, 3} that UDCA does not change the natural course of PBC. New therapeutic strategies are needed for treating patients with PBC.²⁷

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