

Cost and health consequences of treatment of primary biliary cirrhosis with ursodeoxycholic acid

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SUMMARY

Background

Long-term use of ursodeoxycholic acid (UDCA) is the recommended therapy in primary biliary cirrhosis (PBC). The lifetime effectiveness and cost-effectiveness of UDCA in PBC have, however, not been assessed.

Aim

To estimate the health outcomes and lifetime costs of a Norwegian cohort of PBC patients on UDCA.

Methods

Norwegian PBC patients ($n = 182$) (90% females; mean age 56.3 ± 8.9 years; Mayo risk score 4.38) who were included in a 5-year open-label study of UDCA therapy were subsequently followed up for up to 11.5 years. The lifetime survival was estimated using a Weibull survival model. The survival benefit from UDCA was based on a randomised clinical trial from Canada, comparing the effect of non-UDCA and UDCA. Survival and costs of standard care vs. standard care plus UDCA were simulated in a Markov model with death and liver transplantation as major events, invoking transition of a patient's state in the model.

Results

The gain in life expectancy for a PBC patient on UDCA compared with standard care was 2.24 years (1.19 years discounted). The lifetime treatment costs were EUR 151 403 and EUR 157 741 (EUR 102 912 and EUR 115 031 discounted) for patients with and without UDCA respectively. A probabilistic sensitivity analysis indicated an 82% probability that UDCA entails both greater life expectancy and lower costs than standard care.

Conclusions

The results of this study indicate that UDCA therapy is a dominant strategy as it confers reduced morbidity and mortality, as well as cost savings, compared with standard therapy.

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INTRODUCTION

Primary biliary cirrhosis (PBC) is characterised by non-suppurative destruction of interlobular bile ducts, resulting in progressive ductopenia and liver fibrosis.¹ The liver injury eventually progresses to cirrhosis and liver failure, and patient survival is reduced as compared with control populations.² No curative medical therapy for PBC has been identified. In large clinical trials, ursodeoxycholic acid (UDCA) treatment consistently improves biochemical parameters in PBC.^{3–6} The effect of UDCA on the clinical course is more uncertain. A combined analysis of three placebo-controlled trials suggested that UDCA improved survival free of liver transplantation in PBC patients.⁷ Two meta-analyses^{8, 9} and one systematic review of published trials¹⁰ found, however, that any hard evidence of therapeutic benefits of UDCA is lacking. On the other hand, another meta-analysis that included the extended follow-up of randomised controlled trials concluded that long-term treatment with UDCA can delay histological progression and improve survival free of liver transplantation.¹¹ The inconclusive meta-analyses have, however, been criticised for the inclusion of studies of only 2-year duration and studies using low doses of UDCA.¹² The effect of UDCA on survival in PBC thus remains controversial. Nevertheless, UDCA is currently recommended as standard therapy in PBC^{13, 14} and it is the only drug approved by the Food and Drug Administration for treatment of this disease. As additional randomised, placebo-controlled trials of sufficient size and duration are unlikely to be performed, it is important to prospectively collect results of ongoing UDCA treatment in PBC.

PBC is one of the most frequent indications for liver transplantation in the Scandinavian countries (www.Scandiatransplant.org), and it has become an important disease in terms of healthcare cost. UDCA seems to reduce the cost of medical care of PBC as judged from the combined US and Canadian data.¹⁵ The time span of this previous study of cost-effectiveness of UDCA in PBC was, however, limited to 4 years, and the effect of UDCA therapy in a lifetime perspective has until now not been assessed. In this study, we used a Markov model to estimate the long-term outcomes and costs of UDCA treatment of Norwegian PBC patients.

MATERIALS AND METHODS

To estimate lifetime costs and health outcomes of cohorts of PBC patients with and without UDCA treatment, we first estimated life expectancy of Norwegian UDCA-treated patients. This was carried out on the

basis of up to 11.5 years of actual follow-up. We subsequently estimated the excess mortality if patients were not on UDCA on the basis of the relative risk of death and liver transplantation in the placebo- and UDCA-treated groups in a randomised clinical trial from Canada. We thus assumed that the relative gain in survival due to UDCA treatment was comparable between Canadian and Norwegian patients. Using all these data, we simulated the lifetime course of patients with and without UDCA in a Markov model.

UDCA-treated Norwegian PBC patients

A total of 205 PBC patients were recruited from 37 hospitals in Norway during the period September 1997–October 1998 into a national cohort for treatment with UDCA for 5 years. All patients had been diagnosed with PBC according to accepted criteria. Inclusion criteria were duration of cholestatic liver disease of longer than 6 months without evidence of extrahepatic bile duct obstruction, serum alkaline phosphatase (ALP) activity above upper limit of normal, positive antimitochondrial antibody (AMA) titre, age 18–80 years, weight ≤ 115 kg and anticipated survival of at least 1 year. Exclusion criteria were pregnancy or planned pregnancy within the next 5 years, alcoholism or other misuse, positive HBsAg or anti-HCV, or the presence of other causes of liver disease. Upon review of the patient records, six patients proved to have ALP values within reference limits at treatment start. AMA was positive in all of these, while five had a liver biopsy available, all compatible with PBC. The patient with no biopsy was excluded. In another five patients, AMA analysed at inclusion was negative, but had previously been positive in all but one patient, who was excluded. We also chose to exclude 21 patients who were older than 70 years at start of UDCA therapy. This report is based on the remaining 182 PBC patients. The Mayo risk score for PBC was calculated for each patient at study entry.¹⁶

The patients received 20 mg/kg/day (17–23 mg/kg/day) of UDCA, divided into two doses. Follow-up visits were scheduled at 3 months, 6 months and every 6 months thereafter until 5 years. We registered major events, including episodes of oesophageal variceal bleeding, development of ascites or encephalopathy, liver transplantation and death. Blood samples were drawn and a clinical examination carried out at each visit. The patients were initially followed up until death or dropout of the study for other reasons, or until study termination at 5 years. In an extension of the study, we extended follow-up of mortality and (re)transplantation

until 1 March 2009 among those who survived the first 5 years.

The study was approved by the regional ethics committees, and all patients gave informed consent.

Survival analysis

On the basis of data from the Norwegian UDCA cohort, we estimated survival time free of liver transplantation using a competing risk approach. Specifically, we first fitted a Weibull model to each of the two outcomes, death and liver transplantation, regarding the other as a censoring event before we used numerical integration to compute the cumulative mortality and incidence of liver transplantation, respectively, as well as the combined cumulative risk of experiencing either of the two.

Mortality rates from the Weibull model were used directly for the first 10 years of the age range of interest (age 56–65). Because this model would overestimate later survival, we used mortality in the general population and adjusted it upwards. Specifically, we assumed that patients in years 11–45 (age 66–100 years) had the same relative increase of 2.9 in mortality compared with the background population, as patients had during years 6–10 (age 61–65 years). Mortality rates for the Norwegian population were obtained from Statistics Norway (<http://statbank.ssb.no/statistikkbanken/>).

Survival and risk of re-transplantation after liver transplantation in PBC patients were obtained from the Nordic Liver Transplant Registry (NLTR) (www.scandia-transplant.org). The relative mortality rate (3.4) after the first liver transplantation compared with the background population was based on that of 255 PBC patients transplanted during the period 1995–2009. The risk of a second liver transplantation was estimated at 1.7% per year, and we used the same risk for a potential third transplantation. The risk of death after the second liver transplantation was based on that of 34 patients who were re-transplanted during the years 1985–2009 (relative mortality risk 2.27 after the second transplantation relative to that after the first transplantation).

Survival in non-UDCA patients

To estimate the health benefits of UDCA vs. no-UDCA in Norway, we used the relative risk of mortality and transplantation of UDCA- and non-UDCA-treated patients observed in a double-blind randomised controlled trial in Canada.³ These patients were included in the study during the period 1988–1990 and initially followed up for 2 years. The trial was continued for 2 more years in an open-label phase.^{3, 15}

The effect of non-UDCA- compared with UDCA treatment was based on a Cox proportional hazard model. Effect on mortality from the Cox model was 1.54 with liver transplantation regarded as a censoring factor. Hence, not treating with UDCA increases the mortality rate by 54%. Likewise, the effect on risk of need for liver transplantation was also based on Cox regression of the non-UDCA- compared with UDCA-treated patients. The relative risk of transplantation was 2.03, this time considering death as censoring factor, indicating a 103% increased transplantation rate by not treating with UDCA.

Incidence of major events

The incidence of major events (oesophageal variceal bleeding, development of ascites or encephalopathy, liver transplantation, death) was used to calculate morbidity costs. For the control group, the overall annual incidence of major events, except for liver transplantation (see above), was obtained from the study of Pasha *et al.*,¹⁵ based on the combined placebo groups from the Canadian ($n = 111$)³ and Mayo ($n = 91$)⁴ UDCA-PBC trials. The annual incidence of major complications was relatively constant over the four-year follow-up period, so only overall incidence rates were reported. These included episodes of oesophageal variceal bleeding (1.64/100 person-years), development of ascites (2.66/100 person-years), varices (11.21/100 person-years) and encephalopathy (1.81/100 person-years).¹⁵ In the UDCA-treated Norwegian PBC patients, we calculated the incidence of major events for each study year (number of events/number of patients under study).

Markov model

We developed a Markov model for the disease course of the PBC patients in TreeAge Pro.¹⁷ The model had three states: alive without liver transplantation, alive after liver transplantation, and death (Figure 1). Starting age was set at 56 years, based on the average age in the patient population (Table 1). The probability of change from one state to another (i.e. to liver transplantation or death) was estimated as explained above. The patient starts in the state 'Alive without liver transplantation' and may then, on an annual basis, have transplantation or die, depending on the probabilities of these events. These transitions are subsequently used to estimate survival time. The model captures the costs of staying in the states alive without/with transplantation together with the costs of major events. All these costs are used to estimate lifetime costs.

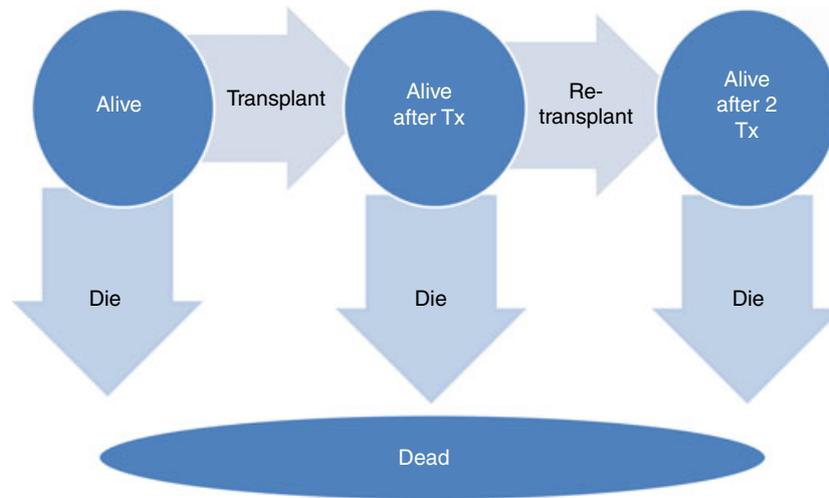


Figure 1 | Markov model for the disease course in PBC. Patients are at a constant risk of variceal bleeding, ascites and encephalopathy in the model. These risks incur costs as described in Table 3. Patients may also be transplanted, which results in costs, but also in adjusted risk of dying. All patients are always at risk of dying from any cause.

Table 1 | Characteristics of PBC patients at start of UDCA- or non-UDCA treatment

Variable	UDCA Norwegian patients (n = 182)	UDCA Canadian patients* (n = 111)	Placebo Canadian patients* (n = 111)	Placebo patients from Mayo study† (n = 91)
Gender; females, n (%)	163 (90)	101 (91)	105 (95)	79 (87)
Age; years, mean (s.d.)	56.3 (8.9)	57.3	55.4	52.0 (9)
Body weight; kg, mean (s.d.)	66.3 (11.9)			
Dose UDCA; mg/kg/day, median (range)	20.2 (17–23)		0	0
Symptoms before start, n (%)				
Pruritus, n (%)	91 (50)	87 (78)	79 (71)	
Fatigue, n (%)	99 (54)	87 (78)	83 (75)	
Jaundice, n (%)	12 (7)			
Ascites (clinical finding), n (%)	3 (2)	2 (1.8)	4 (3.6)	
Pruritus + fatigue, n (%)	65 (36)			
Encephalopathy, n (%)	3 (2)			
Asymptomatic, n (%)	56 (31)	13 (12)	14 (13)	
AMA titre, median (range)‡	1024 (0–2048)			
Bilirubin, mean (s.d.) (3–26 µmol/L)	19.4 (18.3)	40 (64)	31 (39)	31 (39)
ALP, mean (s.d.) (70–230 U/L)	980 (636)	588 (418)	549 (339)	1252 (712)
ALT, mean (s.d.) (10–50 U/L)	110 (70)	110 (63)	109 (62)	
Albumin, mean (s.d.) (35–45 g/L)	40.0 (3.6)			33 (4.0)
INR, mean (s.d.) (0.8–1.2)	1.2 (0.2)			
IgM, mean (s.d.) (0.4–2.1 g/L)	5.23 (3.72)	5.9 (4.5)	5.9 (3.5)	
Hepatomegaly, n (%)	54 (30)			
Splenomegaly, n (%)	14 (8)			
Mayo risk score at inclusion§, mean (s.d.)	4.38 (0.88)	4.6 (1.3)	4.4 (1.2)	5.1 (1.1)

ALT, amino transaminase.

* Data obtained from Heathcote *et al.* and Pasha *et al.*^{3, 15}

† Data obtained from Lindor *et al.* and Pasha *et al.*^{4, 15}

‡ Titre available in 150 patients.

§ Based on 173 patients with complete set of variables in the Mayo risk score at inclusion.

Costs

For each year a patient was alive, we included the estimated costs of regular physician visits, the costs of major events including transplantation and the cost of UDCA, if appropriate.

For each major event, we estimated costs based on clinical experience of the project participants. A typical management profile for each event was developed, including the annual numbers of hospitalisations, outpatient physician visits, specific interventions, laboratory use and medications. The hospital costing model for Rikshospitalet University Hospital was used to estimate unit costs for these services. Liver transplantation represents a major cost in the treatment of PBC. We derived the unit cost from hospital accounts for 36 adult patients who underwent liver transplantation in 2005. The cost of donor organ harvesting was also based on hospital accounts. For a patient who was expected to die within 1 year and who was not a transplant candidate due to age (>73 years), cost of the last year of life was estimated to be fivefold increased. Rikshospitalet University Hospital is a tertiary referral centre with higher average costs than local hospitals that will treat most complications of chronic liver disease. The cost of hospital admissions other than for transplantation was therefore adjusted for the average costs per diagnostic group (DRG) in other Norwegian hospitals (http://www.sintef.no/project/Samdata/rapporter/SAMDATA_Sykehus_tabeller_2001.pdf). Costs were captured in Norwegian kroner (NOK) and adjusted to year 2005 NOK according to the consumer price index. A discount rate of 0.04 was used to discount future costs and life-years. Costs were expressed in EUR (EUR 1.00 = NOK 8.00). Further details on cost estimates are available from the first author.

Probabilistic sensitivity analysis

All uncertain model parameters were incorporated in the model as probability distributions. Distributions were created based on common accepted principles.¹⁸ We used beta distributions for probabilities, log-normal for relative risks and gamma distributions for costs. The model was run with 10 000 iterations and mean cost and effects presented are based on these. Incremental cost of UDCA compared with no treatment was evaluated against the incremental effects based on the proposed Norwegian cost-effectiveness threshold of NOK 500 000 (EUR 62 500) per life-year gained. This threshold has been suggested by the Norwegian Directorate of Health (<http://helsedirektoratet.no/publikasjoner/helseeffekter-i-samfunnsokonomiske-analyser>).

RESULTS

Patient characteristics

The PBC patients were typically middle-aged women (Table 1). Approximately 2/3 of the patients were symptomatic at study entry. Only 12 (7%) patients were jaundiced. The Canadian UDCA- and placebo-treated patients were quite comparable to the Norwegian patients regarding gender distribution, age at study start and severity of disease (Mayo risk score)³ (Table 1). The Mayo placebo group that was used along with the Canadian controls for data on incidence of events had a slightly higher Mayo risk score.^{4, 15}

The mean follow-up of the patients in the primary study was 4.50 (± 1.41) years. Sixteen (8.8%) patients died and 3 (1.6%) patients underwent liver transplantation (after 0.7 years, 2.9 years and 4.5 years respectively). Another 17 (9.3%) patients withdrew during follow-up. Liver failure was the main cause of death, and UDCA side effects caused the majority of withdrawals. The patients were subsequently followed up with respect to the end points, death and liver transplantation, until a total follow-up of median 10.85 (range 0.66–11.47) years.

Incidence of major events and survival

The incidence of the major events was fairly evenly distributed over time in the primary study, except for death that occurred with a higher incidence rate in the fifth year (Table 2). The observed survival of the UDCA-treated Norwegian PBC patients was compared with the modelled survival for both UDCA-treated and placebo-treated patients (Figure 2). The Markov model predicted that expected remaining lifetime for a patient who does not receive UDCA is 15.39 years (10.78 discounted), while it is 17.63 years (11.97 discounted) for those on UDCA.

Costs

The cost of a patient in the UDCA strategy was EUR 2329/year and that of an untreated patient was EUR 1188/year (Table 3). The cost of a liver transplantation, including donor organ harvesting and the initial hospital stay, was EUR 132 903.

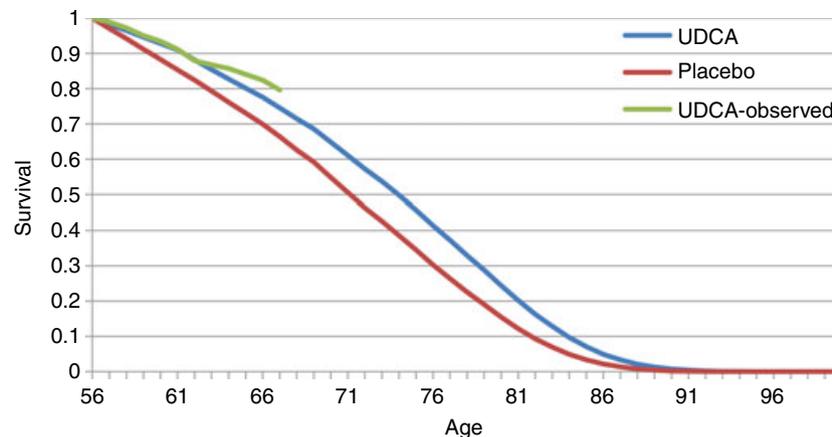
Lifetime results

The total lifetime costs were EUR 151 403 (EUR 102 912 discounted) and EUR 157 741 (EUR 115 031 discounted) for the UDCA and the control group respectively. The cost saving for a patient on UDCA was EUR

Table 2 | Incidence (per 100 person-years) of major events over time among Norwegian PBC patients ($n = 182$) treated with UDCA during the first 5 years

Total number of events	First year	Second year	Third year	Fourth year	Fifth year
Variceal bleeding ($n = 16$)	1.72	1.20	3.13*	1.94	1.82*
Ascites (<i>de novo</i>) ($n = 9$)	1.15	1.20	1.88	0	1.21
Encephalopathy (<i>de novo</i>) ($n = 4$)	0.57	0.60	0.63	0.65	0
Liver transplantation ($n = 3$)	0.57	0	0.63	0	0.61
Death ($n = 16$)	1.10	1.81	1.88	1.30	3.64

* Including 1 death.

**Figure 2** | Survival curves. Survival in UDCA-treated Norwegian PBC patients as estimated from observed data (green line). Survival in UDCA-treated patients based on Weibull model first 10 years and later survival based on mortality in the general population and excess mortality in PBC patients (blue line). Survival in patients not treated with UDCA as estimated from excess mortality in Canadian PBC patients³ (red line).

6338 (EUR 12 119 discounted), which, along with the incremental gain in life expectancy of 2.24 years (1.19 years discounted), makes UDCA a dominant strategy.

Probabilistic sensitivity analysis

In 10 000 runs of the model, 82% resulted in UDCA increasing health effects and decreasing costs (Figure 3). Hence, the probability of UDCA being a dominant strategy is 82%. While there remains an 18% probability that UDCA increased both costs and effects in a lifetime perspective, UDCA treatment was less effective than standard care in only 0.18% of the simulations. In 99.9% of the simulations, UDCA was either dominant or cost-effective, if a threshold of EUR 62 500 per life-year gained was adopted. Altering the threshold did not change the results noticeably (Figure 4). Distributions on

parameters for probabilities and relative risks are given in Table S1 (published online).

DISCUSSION

In this study, we estimated lifetime costs and health outcomes of PBC patients with and without UDCA treatment by modelling the disease course. To our knowledge, this is the first time that the effect of UDCA in a lifetime perspective has been assessed. The results indicate that UDCA therapy in PBC entails lower costs and better health outcomes than standard care. The incremental gain in life expectancy for a PBC patient on UDCA was 2.24 years (1.19 years discounted), which is a considerable benefit.¹⁹ Along with lifetime cost savings of EUR 6338 (EUR 12 119 discounted), UDCA therapy was the dominant strategy in our analysis.

Table 3 | Cost estimates (2005 EUR) for treating major events in PBC patients. A typical management profile for each event was developed. The hospital costing model for Rikshospitalet University Hospital was used to estimate unit costs for these services. The unit cost for liver transplantation was derived from hospital accounts for 36 adult patients who underwent liver transplantation in 2005. The cost of donor organ harvesting was also based on hospital accounts

Event	Cost (EUR)
Variceal bleeding	
Initial hospital admittance + first 2 controls	8156
Follow-up per year	2343
Ascites (<i>de novo</i>)	
Initial hospital admittance	3059
Follow-up per year	2254
Encephalopathy (<i>de novo</i>)	
Initial hospital admittance	3059
Follow-up per year	2329
Liver transplantation	
Donor organ harvesting	
- costs allocated transplant centre	8347
- costs allocated donor hospital	8070
Initial hospital admittance for liver transplantation	116 490
Follow-up after liver transplantation	
Year 1	28 818
Year 2	18 601
Year 3	18 601
Year 4	17 133
Year 5	18 601
Year 6	17 133
Year 7	18 601
Year 8	17 133
Year 9	17 133
Year 10	18 601
Cost of UDCA per year	1373
Cost per year for a patient on UDCA*	2329
Cost per year for a control patient*	1188

For each major event, we estimated costs based on clinical experience of the project participants.

* Costs without liver transplantation. Average of the first 5 years. For control patients, it is assumed that cost for the fifth year equals the average cost per year for the first 4 years.

With the extension of our initial study, we obtained a rather long actual follow-up (up to 11.5 years) of the PBC patients with respect to the major events, death and liver transplantation. We do not have data on UDCA compliance for the extended follow-up, but in general, PBC patients continue on UDCA once they have started on this therapy. A true gain in life expectancy by the UDCA treatment can be assessed only after complete

follow-up when all patients have reached an end point. In effect, this will not be the case until approximately 2050. As an alternative approach, we estimated lifetime survival by use of a Weibull model that computed the combined cumulative risk of mortality and liver transplantation.

The ideal situation would have been to perform a randomised placebo-controlled clinical trial in Norway, but at the time when this study was initiated, the opinion of internationally leading hepatologists indeed favoured UDCA therapy, and performing another placebo-controlled study was not feasible. As an alternative strategy, we used the relative risks of mortality and transplantation of UDCA- and non-UDCA-treated patients observed in a double-blind randomised controlled trial in Canada³ to estimate the survival benefit of the UDCA-treated Norwegian PBC patients. Thus, we did not compare survival in our patients directly with the Canadian placebo group, but rather assumed that the relative gain in survival was comparable between Canadian and Norwegian UDCA-treated patients. The age and disease severity of the Canadian and Norwegian patients were quite comparable.³ These are major prognostic factors in PBC¹ and we considered the Canadian patients to represent comparable patients, although we cannot completely rule out differences in prognosis due to geographical or time factors. On the other hand, we find it rather unlikely that there should have been a shift in the relative survival between UDCA- and non-UDCA-treated patients between the studies during this time period. Two years after randomisation, the Canadian trial was continued in an open-label phase for an additional 2 years.¹⁵ As some patients in the placebo group converted to UDCA, our estimate of the survival benefit of the Norwegian cohort is expected to be rather conservative. Also, our survival gain estimate was somewhat lower than in other placebo-controlled trials.^{6, 20}

We used Canadian and Mayo data to estimate the risk of major events for placebo patients. The Mayo placebo patients had a higher Mayo risk score than both the Canadian placebo group and the Norwegian UDCA-treated patients. As survival in the combined placebo groups was even slightly better than in the Canadian group alone,^{3, 15} a comparison with the combined groups is considered conservative. Moreover, the major cost-driving event proved to be liver transplantation, and in the Markov model, the risk of this event was based on the Canadian placebo data only.

The choice of the UDCA dose of 17–23 mg/kg/day was adapted from the concomitant Scandinavian study

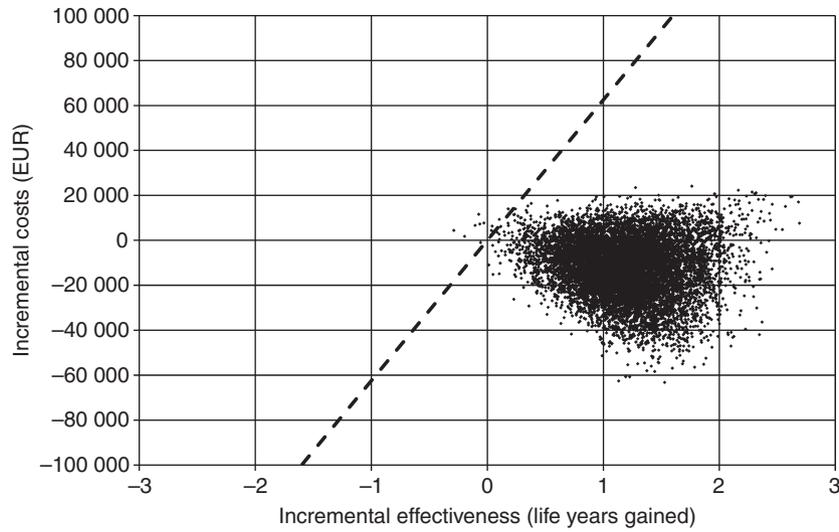


Figure 3 | Scatter plot of 10 000 simulations of incremental costs and incremental effects of UDCA compared with placebo (based on probabilistic analyses). The dotted line represents the assumed Norwegian cost-effectiveness threshold of EUR 62 500 per life-year gained.

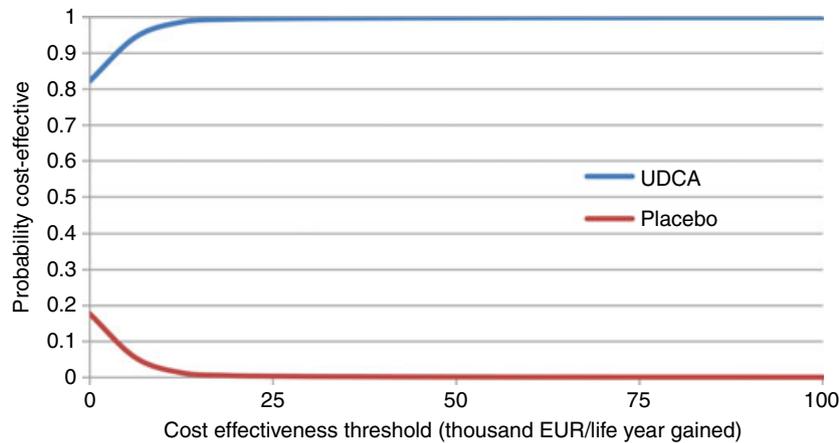


Figure 4 | Cost-effectiveness acceptability curve indicating probability of UDCA being cost-effective compared with placebo for different cost-effectiveness thresholds. Regardless of cost-effectiveness threshold, the probability of UDCA being cost-effective is above 80% (probability of placebo being cost-effective is always 100% minus the probability of UDCA being cost-effective).

of UDCA in primary sclerosing cholangitis²¹ and was somewhat higher than the regular dose of 13–15 mg/kg/day in PBC. As there were no statistically significant differences in the improvement of serum ALP and aspartate aminotransferase activities or the Mayo risk score in PBC patients treated with UDCA in doses of 13–15 mg/kg/day and 23–25 mg/kg/day in a dose comparison study,²² we do not consider this UDCA dose to significantly influence the results, although the latter study was of shorter duration than ours.

The costs of transplantation were based on real hospital accounts and should be valid. Even though the other cost estimates are not based on actual patients, this uncertainty is unlikely to invalidate the conclusion because any bias will be present in both treatment arms, i.e. if a cost is overestimated in one arm of the model, it will be overestimated in the other too.

In principle, all major events recorded in the clinical study could have been entered into a multistate Markov model. We chose to limit the states to death and liver

transplantation as these states can be more reliably predicted and as the cost of transplantation predominates over costs of any other event. Data on survival and risk of re-transplantation in liver transplanted PBC patients were based on actual observations in the Nordic Liver Transplant Registry from the same time period and are therefore adequate. A Markov model has also previously been used to describe the disease course in PBC patients on UDCA, but without comparison with a placebo group and without inclusion of costs.^{23, 24}

The sensitivity analyses indicate that our findings of reduced morbidity and mortality as well as cost savings from UDCA therapy are robust. To our knowledge, only a single study has previously estimated the cost-effectiveness of UDCA in PBC.¹⁵ Based on the combined Canadian and Mayo Clinic trials, that study concluded that UDCA for 4 years was cost-effective.¹⁵ The gain in life expectancy at 4 years was 0.18 years, with a concomitant cost saving of USD 1372. Our results not only support this finding, but also extend the concept of cost-effectiveness of UDCA to a lifetime perspective, which is recommended for economic evaluations of interventions that affect mortality.²⁵ In 99.9% of the simulations, UDCA was either dominant or cost-effective, if a threshold for cost-effectiveness was assumed to be EUR 62 500 per life-year gained. There is no universally accepted value for a gain of 1 year of life, but the analysis was robust to alterations of the threshold. Models to differentiate between responders and nonresponders to UDCA by assessing patient characteristics after 1 year of therapy have been suggested.^{26, 27} We did not stratify the patients for response to UDCA, but the impact on cost-effectiveness in a lifetime perspective by stopping UDCA treatment in patients defined as nonresponders after 1 year could be an aim of future studies.

UDCA is currently the only drug approved for PBC, and international guidelines recommend that UDCA therapy is initiated at an early disease stage.^{13, 14} The low prevalence and slow disease progression of PBC have, however, contributed to difficulties in conducting studies of sufficient size and duration to definitely show a beneficial effect of UDCA on survival and need for liver transplantation.²⁸ In medical therapy, it is important to assess long-term effects and costs. Although this study was based on costs from a single country, we have demonstrated that it is possible to model a lifelong disease course along with lifetime costs when adopting a limited set of conservative assumptions. By indicating that UDCA therapy in PBC confers reduced morbidity and mortality

as well as cost savings compared with non-UDCA in a lifetime perspective, our results support the international guidelines. Norway has a public healthcare system in which most drugs that are deemed to be cost-effective are reimbursed. The results of this study indicate that UDCA should be funded by the healthcare system.

We conclude that UDCA therapy in PBC seems to confer reduced morbidity and a gain in life expectancy as well as cost savings compared with non-UDCA treatment and hence represents a dominant strategy.

AUTHORSHIP

Guarantor of the article: K. M. Boberg.

Author contributions: Boberg, Wisløff and Sønbo Kristiansen designed the study. Boberg collected the data on the Norwegian UDCA-treated PBC patients. Boberg and Kjøllesdal carried out the cost analyses. Støvring fitted the Weibull model and computed the cumulative mortality and incidence of liver transplantation. Wisløff made the Markov model and performed the analysis of the data. All authors contributed to the interpretation of the data. All authors approved the final version of the article including the authorship list.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Distributions on parameters for probabilities and relative risks.

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