Cost and health consequences of treatment of primary biliary cirrhosis with ursodeoxycholic acid in a Norwegian patient population

Kirsten Muri Boberg

Thesis for the degree Master of Health Management and Health Economics

UNIVERSITY OF OSLO

January 2009

Table of Contents

Supervisor: Ivar Sønbø Kristiansen, Institute of Health Management and Health Economics, University of Oslo, Oslo, Norway

Correspondence: Kirsten Muri Boberg, Medical Dept., Rikshospitalet, 0027 Oslo, Norway, e-mail: kirsten.boberg@rikshospitalet.no, Phone: + 47 23 07 00 00

Keywords: cost-effectiveness, life expectancy, liver transplantation, primary biliary cirrhosis, survival, ursodeoxycholic acid

Abbreviations: alkaline phosphatase (ALP); antimitochondrial antibody (AMA); confidence interval (CI); international normalized ratio (INR); Norwegian kroner (NOK); primary biliary cirrhosis (PBC); ursodeoxycholic acid (UDCA); standard deviation (SD); standard error of the mean (SEM)

Funding: The study was financed by Rikshospitalet and Meda AS. Meda AS was not involved in design, data collection, or reporting of findings.

Preface

In 1997 Norwegian gastroenterologists were invited to treat primary biliary cirrhosis (PBC) patients with ursodeoxycholic acid (UDCA) according to a common protocol for 5 years, with the intention to gain experience from treatment of a large cohort of patients. The study was initiated, designed and executed by the author. A number of colleagues from hospitals all over the country started their PBC patients on UDCA and provided clinical and laboratory data from patient visits throughout the study period. Ishtiaq Kushi, Dept. of Research Services, Rikshospitalet, supported the Access database. Marte Olstad, Rikshospitalet, assisted with statistical analyses and Karl Sæbjørn Kjøllesdal, Rikshospitalet, with retrieval of cost data. Professor, dr. med. Erik Schrumpf, Medical Dept., Rikshospitalet, participated with medical advice during the planning and implementation of the study. Survival data for the placebo group of a previous Canadian study of UDCA in PBC were kindly provided by prof. Jenny Heathcote, Division of Gastroenterology, The Toronto Hospital, University of Toronto, Canada. This thesis for the degree Master of Health Management and Health Economics, University of Oslo, has been written under the supervision of professor Ivar Sønbø Kristiansen, Institute of Health Management and Health Economics, University of Oslo. I am grateful to all participants for their valuable support and advice.

Abstract

Background/aims: Primary biliary cirrhosis (PBC) is a chronic, cholestatic liver disease that progresses to liver cirrhosis. Patients who develop end-stage liver disease are candidates for liver transplantation. Several studies have supported the view that ursodeoxycholic acid (UDCA) prolongs survival in PBC, but results have been challenged in other reports. Nevertheless, UDCA is currently recommended as standard therapy in PBC. The aims of this study were to 1) evaluate the effect of UDCA on the clinical course in a Norwegian cohort of PBC patients and to 2) estimate cost-effectiveness of UDCA therapy in the perspective of public health service.

Patients and methods: 180 Norwegian PBC patients (90% females; mean age 56.2 ± 8.9 years; Mayo risk score 4.38) were included in a five-year open-label study of UDCA therapy. The observed survival of the UDCA-treated patients was compared with survival predicted from the Mayo prognostic model for PBC and with survival (at four years) of the placebo group in a previous Canadian trial of UDCA in PBC (n = 111; 95% females; mean age 55.4 years; Mayo risk score 4.4). The frequencies of major events in the UDCA group were compared with those of the combined placebo groups in the Canadian trial and a previous study from the Mayo Clinic (n = 91; 87% females; Mayo risk score 5.2). The hospital costing model for Rikshospitalet University Hospital was applied to estimate average annual costs (2005 NOK) of major events. A spread sheet model was constructed for the calculations of costs. Cost-effectiveness was expressed as the ratio of incremental cost of UDCA therapy as compared with standard therapy, to the incremental gain in life expectancy during the four years of study.

Results: The observed survival of the UDCA-treated patients was significantly higher than that of the control group ($P < 0.001$; log-rank test). Within the four-year perspective, the life

expectancy was 3.92 years in patients on UDCA therapy and 3.54 years in those receiving standard treatment (discounted, 3.57 years and 3.22 years, respectively). The life expectancey of the UDCA-treated patients according to the Mayo prognostic model was 3.79 years (discounted 3.45 years). The net total discounted cost per patient of the UDCA strategy was NOK 73 000 as compared with NOK 302 000 of standard treatment. Thus, the incremental discounted cost of UDCA therapy as compared with standard therapy was minus NOK 229 000, and the incremental discounted gain in life expectancy was 0.35 years. One-way sensitivity analysis revealed that even the upper bound cost estimate in the UDCA group (NOK 205 000) was slightly less that the lower bound estimate in the control group (NOK 210 000).

Conclusions: The results of this study indicate that UDCA therapy in PBC confers reduced morbidity, gain in life expectancy as well as cost savings compared with standard therapy and thus represents a dominant strategy.

1. Introduction

Primary biliary cirrhosis (PBC) is characterized 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 (2-5). No curative medical therapy for PBC has been identified (6). Ursodeoxycholic acid (UDCA) treatment consistently improves biochemical parameters in PBC, as has been demonstrated in several large randomized, placebo-controlled trials (7-12). The effect of UDCA on the clinical course has however been uncertain. A combined study of liver histologic findings from four clinical trials concluded that UDCA delays the progression of histologic stage of PBC when initiated during early stage disease (13). A combined analysis of three placebo-controlled trials suggested that UDCA improved survival free of liver transplantation in PBC patients (14). Two meta-analyses (15, 16) and one systematic review of published trials (17), however, concluded that evidence of therapeutic benefits of UDCA is lacking. Another meta-analysis that included the extended follow-up of randomized controlled trials, concluded on the other hand that long-term treatment with UDCA can delay histological progression, significantly reduce the incidence of liver transplantation and cause a marginally significant improvemet of survival free of liver transplantation (18). The meta-analyses with negative results have been critized for the inclusion of many studies of only two-year duration and studies using low doses of UDCA (19, 20). The effect of UDCA on survival in PBC thus remains controversial. Nevertheless, UDCA is currently recommended as standard therapy in PBC (21, 22), and it is the only drug approved by the Food and Drug Administration for treatment of this disease (19). Since additional randomized, placebo-controlled trials of sufficient size and duration

are unlikely to be performed (23), it is important to prospectively collect results of ongoing UDCA treatment in PBC (24).

Although a relatively rare disease, PBC is one of the most frequent indications for liver transplantation in the Scandinavian countries (www.Scandiatransplant.org), and it has become an important disorder from a health economic point of view. UDCA seems to reduce the cost of medical care of PBC as judged from trials in the United States (Mayo Clinic) and Canada (25), but this conclusion has been challenged (15). The economic impact of UDCA therapy in the Nordic countries has not been assessed.

The aim of this study was twofold: 1) to evaluate the effect of UDCA on the clinical course of PBC in a Norwegian cohort of patients and 2) to estimate cost-effectiveness of this therapy in the perspective of public health service. At the time when this study was planned, UDCA was increasingly world-wide used for PBC on the basis of favourable results from available studies. We therefore considered it unethical to start another placebo-controlled trial. We chose to compare the course of UDCA-treated Norwegian PBC patients with that predicted for this group of patients by the Mayo prognostic model (26, 27) as well as with that of placebo groups from previous placebo-controlled trials (8, 9, 25).

2. Materials and methods

This study was based on clinical data from a cohort of UDCA-treated Norwegian PBC patients and the placebo groups in previous Canadian- and Mayo Clinic double-blind randomized, placebo-controlled trials of UDCA in PBC (8, 9) and an economic model that was developed to assess the cost-effectiveness of UDCA therapy in PBC. The analytic perspective is that of the health care system.

2.1 Patients

2.1.1 UDCA-treated Norwegian PBC-patients

A total of 205 PBC patients were recruited by physicians at 37 different hospitals in Norway during the period September 1997 – October 1998 to join a national protocol for UDCA treatment for five years. All patients had been diagnosed with PBC according to accepted criteria and were considered candidates for UDCA therapy. Criteria for inclusion in the study were cholestatic liver disease of >6 months` duration without evidence of extrahepatic bile duct obstruction by ultrasonography or cholangiography, 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 >1 year. A liver biopsy compatible with PBC obtained at some time previous to the study start was considered preferable, but was not required (21). Patients were excluded from the study in cases of pregnancy or planned pregnancy within the next five 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 normal ALP values at treatment start. AMA was positive in all of these cases and a liver biopsy compatible with PBC available in five. The patient

lacking biopsy was excluded from the current analysis. In another five patients, AMA analyzed at inclusion was negative, but had previously been positive in all but one patient, who was excluded. We also chose to exclude from this analysis 21 patients who were older than 70 years at start of UDCA treatment and two patients who died within 6 months of treatment start. The current report is based on the remaining 180 PBC patients (Figure 1). A liver biopsy had been carried out in 158 (88%) among these.

The Mayo risk score for PBC is based on the variables age, serum bilirubin concentration, serum albumin level, prothrombin time, and the presence or absence of edema. The score was calculated for each patient at study entry (26, 27).

The study was approved by the regional ethics committees, and the patients gave their informed consent to participate. UDCA had not been accepted for reimbursement in Norway, but public coverage of the study medication was approved by the Norwegian Medicines Agency.

2.1.2 Placebo-treated PBC patients from Canada and Mayo Clinic (US)

Survival data up to four years for the placebo-treated patients (n = 111) enrolled in the Canadian multicenter double-blind randomized controlled trial were kindly made available to us (8, 25). These patients were entered into the study during the period 1988 – 1990 and initially followed for two years. The trial was continued for an additional two years in an open-labeled phase (25). We also obtained survival data for the combined placebo groups from the Canadian study and a corresponding study carried out at the Mayo Clinic, US (9, 25). The Canadian patients were quite comparable to the Norwegian patients regarding gender distribution, age at study start, and severity of disease.

2.2 UDCA therapy and follow-up visits

The patients received 20 mg/kg/day (17 – 23 mg/kg/day) of UDCA, divided in two doses. Follow-up visits were scheduled at 3 months, 6 months and every 6 months thereafter until five years. At each visit, the local physician recorded PBC-related symptoms during the previous 6 months, potential side-effects of the medication, as well as other intercurrent medical events. We registered major complications, including episodes of esophageal variceal bleeding and development of ascites or encephalopathy. Blood samples were drawn and a clinical examination carried out. The patients were followed until death or liver transplantation, drop-out of the study for other reasons, or until study termination at five years.

2.3 Survival analyses

The observed survival with (end-point death) or without liver transplantation (end-points death and liver transplantation) for the Norwegian UDCA-treated PBC patients and placebo-treated patients from the Canadian PBC-UDCA trial was computed by the Kaplan-Meier method (28). The predicted survival curve (end-point death) for the Norwegian patients was obtained from the Mayo prognostic model, based on the calculated Mayo risk scores (27). The updated Mayo model was used to predict survival without liver transplantation (end-points death and liver transplantation) (26, 29). Survival curves were compared using the one-sample log-rank test (28). P-values ≤ 0.05 were considered statistically significant. 95% confidence intervals (CI) for small numbers were calculated based on the Poisson distribution (Geigy Scientific Tables). The statistical analyses were performed using the statistical package SPSS 16.0 (SPSS 16.0, standard version, SPSS Inc.).

2.4 Cost-effectiveness analysis

The cost-effectiveness of UDCA therapy was expressed as the ratio of incremental cost of four-year UDCA therapy as compared with standard therapy, to the incremental gain in life expectancy during four years of study:

$$\text{Cost-effectiveness ratio} = \frac{(\text{Cost}_{\text{UDCA-group}} + \text{drug cost}) - \text{Cost}_{\text{control group}}}{\text{Life expectancy}_{\text{UDCA group}} - \text{Life expectancy}_{\text{control group}}}$$

The methods used to calculate gain in life expectancy and to estimate costs are described below.

2.4.1 Gain in life expectancy in the UDCA-treated patients

The gain in life expectancy was determined by estimating the difference between the observed survival of the UDCA-treated patients and a) survival predicted from the Mayo prognostic model for the same group of patients and b) survival calculated for placebo-treated patients from the Canadian study. The differences in survival were calculated as the differences between the areas under the survival curves at four years, since this was the observation period for the historical controls (25). Survival beyond four years was disregarded. In the cost-effectiveness analysis, we used the gain in life expectancy derived from survival with transplantation and assumed that liver transplanted patients stayed alive for the duration of the study. A discount rate of 0.04 was used to discount life expectancy.

2.4.2 Probability of major events

In the UDCA treated group of PBC patients, we calculated the probability of major events for each study year (number of events/number of patients under study). For the control group, the overall annual incidence of major events was obtained from the study of Pasha et al. (25),

based on the combined placebo groups from the Canadian- (n = 111) and Mayo- (n = 91) UDCA-PBC trials. In that study, the annual incidence of major complications was noted to be relatively constant over the follow-up period of four years, so only the overall incidence rates were reported. The major events recorded included episodes of esophageal variceal bleeding, development of ascites or encephalopathy, and liver transplantation, since the management of these events accounts for the majority of resourses used in PBC patients (25). Development of esophageal varices (regardless of episodes of bleeding) was not assessed in our study since regular gastroscopies were not part of the protocol.

2.4.3 Estimation of costs

Net incremental cost of treatment was calculated as the difference between estimated costs among patients on UDCA therapy (cost of hospitalization, physician visits, treatment of major events, and cost of UDCA) and the anticipated cost in patients on standard treatment (cost of hospitalization, physician visits, and treatment of major events). For the UDCA-treated group, the average cost for each year was calculated from the probability of each event and their respective costs, with addition of the cost of UDCA. For the control group, the overall incidence of events was used. In calculation of total costs for each group during the four-year period, it was assumed that the patients stayed in the study also after major events (except for death). All costs were expressed in 2005 Norwegian kroner (NOK).

2.4.4 Morbidity costs

For each major event (episode of esophageal variceal bleeding, development of ascites or encephalopathy, and liver transplantation), annual resources used were estimated based on clinical experience of the project participants, combined with expert opinion. A typical management profile for each event was developed. The profiles included estimated annual

numbers of hospitalizations, outpatient physician visits, specific interventions, laboratory use, and medications (see the spread sheet models in Appendix, Tables 1 - 3, for details). The hospital costing model for Rikshospitalet University Hospital was used to estimate costs for both inpatient services and outpatient visits. The model uses a full-costing approach, calculating the costs of the various services provided to the individual patient. These include clinical, laboratory, radiology, anestesiology, operation, and intensive care services (30). Costs related to research and development and other external activities (e.g. kindergarten for the personell) are not included. Allocation of the internal service costs (administration, housing, etc.) to the chosen activities have been carried out using a top-down approach. Liver transplantation represents the major cost related to the treatment of PBC. This cost was derived from a mean of liver transplantations carried out in adult patients (n = 36) in 2005. For other events, costs were based on those of a typical patient course. Rikshospitalet University Hospital is a tertiary referral center with higher average costs than local hospitals that will normally treat most complications of chronic liver disease. Costs were therefore adjusted for the average costs per diagnostic group (DRG) in other Norwegian hospitals (Samdata sykehus, Tabeller, Sintef Unimed NIS SAMDATA), except for costs of liver transplantation since Rikshospitalet is the only liver transplant center in Norway. For liver transplantation, only costs of ordinary visits were included, and those related to admittance for potential complications were not taken into account. Costs for visits with a general practitioner were obtained from the Norwegian Medical Association. For all patient services, only direct costs were included, not accounting for indirect costs like those related to transportation, loss of working capacity etc.. Costs were captured in NOK and adjusted to year 2005 NOK according to the consume price index. A discount rate of 0.04 was used to discount costs.

2.5 Sensitivity analysis

To test the robustness of model results, we carried out sensitivity analyses. We explored the consequences of parameter uncertainties in one-way sensitivity analyses, where one parameter at a time was varied up and down within the pre-specified uncertainty bounds, while maintaining the others at their base-case values. In this way, we compared the costs of UDCA- and standard treatment in PBC patients. For the incidence of major events, the 95% confidence limits were used as upper and lower bounds. For costs, we used base-case values ± 20%.

3. Results

3.1 Patient characteristics

Characteristics of the UDCA-treated Norwegian PBC patients at study start are given in Table 1, that also shows the available information on the controls. Typically, the patients were middle-aged women. Approximately 2/3 of the patients were symptomatic. The main symptoms were pruritus and fatigue, reported by 50% and 54% of patients, respectively. Only 11 (6%) patients were jaundiced. The mean Mayo risk score for the group was 4.38 (± 0.88), which is quite similar to that of the Canadian placebo group (4.4 ± 1.2) that was used for comparison of survival, but lower than that of the Mayo placebo group (5.2 ± 1.1) that was used along with the Canadian controls for comparison of incidence of events (25). Mean follow-up of the patients was 4.55 (± 1.35) years. Fourteen (7.8%) patients died and 3 (1.7%) patients underwent liver transplantation (after 0.7 years, 2.9 years, and 4.5 years, respectively). Another 17 (9.4%) patients withdrew from the study at various points in time during follow-up. Among the UDCA-treated patients, liver failure was the main cause of death, and side effects caused the majority of withdrawals (Table 2).

As expected, serum ALP levels decreased significantly during the first year of treatment, with mean levels 980 (SEM 47.5) U/l at inclusion, 469 (SEM 21.9) U/l at 3 months, 438 (SEM21.5) U/l at 6 months, and 391 (SEM 18.7) U/l at 12 months ($P < 0.0001$ for all values compared with initial measurement). Bilirubin concentration decreased from mean 18.9 (SEM 1.3) μmol/l at inclusion to 13.3 (SEM 0.8) μmol/l at 6 months ($P < 0.0001$) and remained at 13.7 (SEM 0.8) μmol/l at 12 months.

3.2 Survival

Figure 2 illustrates the survival with liver transplantation (end-point death) of the UDCA-treated Norwegian PBC patients compared with the Canadian placebo-group. The observed survival among the UDCA-treated patients was significantly better than that of the controls ($P = 0.001$ based on all data and $P < 0.001$ based on data up to four years). Survival with liver transplantation (end-point death) for the treated Norwegian patients was 95.2% and 93.2% at four years and five years, respectively. Survival free of liver transplantation (combined end-point death and liver transplantation) was also significantly better among UDCA-treated patients compared with the Canadian placebo-group ($P < 0.001$ based on all data as well as data up to four years) (figure not shown). Survival free of liver transplantation was 94.0% at 4 years and 91.5% at study end after five years. Figure 3 shows the survival with liver transplantation (end-point death) and the calculated areas under the survival curves for the UDCA-treated Norwegian patients, the Canadian placebo patients, the placebo patients from the combined Canadian and Mayo trials, and the survival of the UDCA-treated patients as predicted by the Mayo model.

3.3 Gain in life expectancy

Within the four-year perspective, the gain in life expectancy for the UDCA-treated patients was 0.13 years per patient when compared with the Mayo model and 0.38 years when compared with the Canadian placebo group (Figure 3). This means that treating 100 PBC patients with UDCA for four years would result in a gain of 13 years of life compared with calculated expected survival and a gain of 38 years compared with survival of the Canadian placebo group. The gain in life expectancy of the UDCA group compared with the combined control group was 0.27 years per patient. The gain in transplant free life expectancy at four

years was 0.13 years per UDCA-treated patient relative to the prognostic model and 0.75 years relative to the Canadian placebo group.

3.4 Survival in subgroups of UDCA-treated PBC patients

Among the UDCA-treated patients, survival was not significantly different between asymptomatic (n = 56) and symptomatic (n = 124) patients at study start (P = 0.781 for end-point death (Figure 4) and P = 0.811 for combined end-points death and liver transplantation). On the other hand, patients who had bilirubin levels above normal at inclusion (n = 30) had a significantly reduced survival as compared with those with normal bilirubin (n = 149) (P < 0.001 both for end-point death (Figure 5) and for the combined end-points death and liver transplantation). A decrease in ALP greater than 40% of baseline levels or normal ALP levels after one year of treatment has been suggested to define response to UDCA-treatment in PBC (31). In the current study, survival among biochemical responders in this regard (n = 145) was significantly better than that of non-responders (n = 23) (P = 0.038 for end-point death (Figure 6) and P = 0.083 for end-points death and liver transplantation).

3.5 Incidence of major events

The patients were followed for a total of 818.4 person-years. During the five-year period, there were 16 episodes of esophageal variceal bleeding, nine cases of *de novo* ascites, four incidents of *de novo* encephalopathy, and three cases of liver transplantation (Table 3 A). The annual incidence rates of the major events were fairly evenly distributed over time, except for death, that occurred with a higher incidence rate in the fifth year (Table 3 B). Comparing the overall incidence rates of each major event, liver transplantation and death

occurred less frequently in the UDCA-treated patients than in the combined placebo groups in the study by Pahsa (Table 4) (25). The risks of developing ascites and encephalopathy were also reduced in patients subjected to UDCA therapy compared with controls. On the contrary, the overall annual incidence of variceal bleeding was slightly increased in the UDCA group versus patients on standard treatment.

3.6 Cost-effectiveness

Cost estimates for the treatment of major events are listed in Table 5. The total cost of management was estimated to be NOK 79 529 per patient in the UDCA group and NOK 331 341 in the control group (discounted at 4%, NOK 72 629 and NOK 302 170, respectively) (Table 6). The net incremental cost per patient in the UDCA group was minus NOK 251 812 (discounted at 4%, minus NOK 229 541). Within the four-year perspective, the incremental gain in life expectancy of the UDCA therapy was 0.38 years (discounted at 4%, 0.35 years) compared with standard therapy and 0.13 years (discounted, 0.12 years) compared with the Mayo prognostic model. In other words, UDCA therapy represented a dominant strategy in that it resulted not only in reduced morbidity and a gain in life expectancy, but also in cost savings.

3.7 Sensitivity analysis

Lower and upper bound of total costs for four-year of UDCA treatment were NOK 47 505 and NOK 205 244, respectively (Table 7). The lower and upper bound of total costs of standard treatment for the same period of time were NOK 209 885 and NOK 497 282, respectively (Table 8). Thus, even the highest cost estimates for UDCA therapy was slightly lower than the lowest cost estimates for standard treatment. Liver transplantation was the

dominating factor responsible for the cost difference between the groups. The lower bound of the cost difference between UDCA- and standard treatment was minus NOK 162 380 and the corresponding upper bound was minus NOK 292 038 (Table 9).

Sensitivity analysis of various cost components also showed that the cost of liver transplantation was the most important factor (Table 10). The upper bound cost of liver transplantation in the UDCA group was considerably less that the lower bound cost of this component in the control group.

4. Discussion

The results of this study indicate that UDCA treatment in PBC reduces costs and increases life expectancy within a four year perspective. These results should be seen against the limitations of the study.

4.1 Study limitations

4.1.1 Use of the Mayo prognostic model

The Mayo survival model is a Cox proportional hazards model that was developed from characteristics of a set of PBC patients and validated in a second patient cohort (27). Based on a computed risk score, the survival probability of a patient for up to seven years can be derived from the underlying survival function. Individual survival curves can then be averaged to get an overall predicted survival curve for a group of patients (32). The original Mayo model predicted survival in the absence of liver transplantation as an effective therapy, and it has later been updated to predict survival using death or liver transplantation as a combined end-point (26). An improvement in the general care of PBC patients during the years since the Mayo model was introduced would result in a better survival than that predicted by the model, even in the absence of UDCA therapy (29). A variable reliability of the Mayo model with respect to low-risk and high-risk patients has been discussed (33), but an early cross-validation of the model suggested that it performs well across different risk groups (34). Any prognostic model is hampered by a limited predictive ability (35). Models based on baseline data without follow-up information are moreover not very precise in long-term prognostication (35). Despite the limitations, the Mayo natural history model generally is considered to accurately predict prognosis in groups of PBC patients (4, 5, 33, 36). The

model has been widely used, also in recent studies of European cohorts of patients (5, 31-33, 36). We therefore chose to consider the difference between observed and predicted survival in our group of patients as gain in life expectancy caused by UDCA.

4.1.2 Control groups

As a second strategy to estimate the efficacy of UDCA therapy, we compared survival of our treated PBC patients with that of the placebo group in a previous Canadian study (8, 25). In that study, the UDCA- and placebo-treated patients were followed for two years after randomization (8), but thereafter the trial was continued in an open-labeled phase for an additional two years (25). Since some patients in the placebo group thus had received UDCA therapy that could contribute to improved survival, our estimate of gain in life expectancy in the Norwegian patients is expected to be rather conservative. On the other hand, the survival of the placebo group was less than that predicted in our group of UDCA treated patients, despite comparable mean Mayo risk scores. Differences in geographical regions and time periods of study might contribute to this observation, but it cannot be excluded that the controls actually had more advanced disease.

Since we did not have access to the specific incidence rates of major events for the Canadian placebo patients, we compared the observed annual incidences of major events in the UDCA treated patients with those of the combined placebo groups of the Canadian- and Mayo trials published by Pasha et al. (25). The Mayo placebo patients had a higher Mayo risk score than both the Canadian placebo group and the Norwegian UDCA treated patients. The incidence rates of events of the combined placebo groups consequently are likely to be higher than those of the Canadian placebo group alone, causing an overestimation of costs for the control patients in the present analysis. However, survival with liver transplantation in the combined

placebo groups was even slightly better than in the Canadian group alone (area under the survival curve after four years being 3.64 and 3.54, respectively), so a comparison with the combined groups still might be acceptable.

4.1.3 The study time span

The cost-effectiveness analysis was limited to comprise the first four years of treatment, since this was the observation period for the Canadian placebo group. The UDCA-treated patients were followed for approximately five years. Compared with predicted survival by the Mayo model, a survival benefit was still apparent at that time (Figure 3). Ideally, a potential gain in life expectancy by the UDCA treatment should have been assessed only after a complete follow-up, until all patients had reached an end-point. In reality, this situation will never be achieved. If a positive effect of UDCA persists, which we find most likely, our analysis has underestimated the gain in life expectancy.

Our model was based on the assumption that patients stayed alive for the entire study period of four years after experiencing one of the pre-defined events. Survival after liver transplantation for PBC is very good, with one-year survival around 90% and four-year survival close to this rate (www.scandiatransplant.org). Since the cases of liver transplantation not all occurred the first year, but were distributed over the four years, an average of around 90% of patients are expected to survive throughout the study. The other major events (esophageal variceal bleeding, ascites, and encephalopathy) are all signs of advanced liver disease. Two patients actually died in relation to an episode of variceal bleeding (in the third and fifth year, respectively) (Table 3 A), but patients may also stay alive for some years after development of these complications. If we consider the risk of not

surviving until study end after one of these complications to be equal in the UDCA- and placebo groups, the potential error in our assumption will affect both groups.

4.1.4 Reliability of the frequency of events

The model accounts for costs of each major event from the time it occurs until the end of the four-year period, assuming that the events are independent and do not occur in the same patient. Patients who progress to decompensated liver cirrhosis may experience one or more of the events esophageal variceal bleeding, ascites, and encephalopathy. To the extent that these events might have coincided in patients, parts of the costs attributed to one specific event may also cover costs related to another. The consequence would be lower total costs of follow-up, but again this would apply to both UDCA- and control cases.

Overall, the risks of major events were lower in the UDCA-treated patients than in the historical controls (Table 4). In particular, the considerable higher risk of liver transplantation in control patients contributed to the higher cost of medical care in this group. PBC-patients are good candidates for liver transplantation and should be timely referred for this treatment (21). Only three patients in our study were transplanted whereas as many as nine patients died from liver-related causes. It could be speculated that at least some patients in the latter group could have been transplant candidates. These patients proved to be mostly elderly (mean age 65.9 years) at the time of death, so both age and other potential complicating factors could have influenced on a decision not to refer them for liver transplantation. Four patients died from non-liver-related causes and in one case there was no information of a specific cause. These cases were treated along with the liver-related deaths in the survival analyses. If we had chosen to select only liver-related deaths as end-point, the survival of the UDCA-treated patients would have been even better.

4.1.5 Cost estimates

We used the costing model developed at Rikshospitalet University Hospital as a basis to estimate costs for hospital stays. For the event of liver transplantation, our data were derived from 2005, comprising a total of 36 transplantations. The primary cost of the event requiring most resources thus is quite realistic. Costs of treatment of follow-up of liver transplanted patients and costs of handling other major complications of chronic liver disease are not readily available. Based on our routine follow-up of liver transplanted patients, we estimated costs for the first and subsequent post-transplant years. For other major events, we estimated costs based on selected patients who represented a typical course for each condition in question. We judged this approach to give more accurate estimates than to make a general search for costs related to specific ICD-10 diagnostic groups. We did not assign any costs to death, which also underestimates the beneficial effect of UDCA (25). For the follow-up management, we constructed typical profiles for each major event from our clinical experience. Deviations from the observed frequencies of major events and from the profiles may affect the cost estimates in either a positive or negative direction. The uncertainties were explored by sensitivity analyses.

4.2 Findings of this study

Within the four-year perspective of the study, the net total discounted cost per patient of the UDCA strategy was NOK 73 000 as compared with NOK 302 000 of standard treatment. The incremental discounted gain in life expectancy of UDCA therapy compared with usual care within the same time frame was 0.35 years. In the sensitivity analyses, we used wide ranges to account for uncertainties in incidence rates of events (95% CI`s), and we varied costs by ± 20%. By varying the incidence rates in the UDCA group within these pre-

specified uncertainty bounds, the cost per patient ranged from NOK 48 000 to NOK 205 000. The drug cost was fixed and amounted to NOK 44 000 of each of these sums. At the upper bound, liver transplantation was the single most expensive event, priced at NOK 107 000. In the control group, the cost per patient ranged from NOK 210 000 up to NOK 497 000, with liver transplantation being responsible for the major cost in both cases. Since UDCA therapy conferred a gain in life expectancy and even the upper bound cost of this therapy was slightly lower than the lower bound cost of standard care, UDCA therapy appeared to be a dominant strategy. The sensitivity analysis made by varying the costs of each event did not change this conclusion. Our results are also in accordance with those of the previous cost-effectiveness assessment of the combined Canadian and Mayo Clinic trials that concluded that UDCA was a highly cost-effective therapy for patients with PBC (25). The gain in life expectancy by UDCA therapy for four years in that study was 0.18 years per patient.

It has been pointed out that most cost-effectiveness analyses use decision analytic methods primarily because of lack of data from studies and thus necessitate the use of many assumptions (25). An advantage our analysis was the availability of actual data from a five-year UDCA treatment study in PBC. The most ideal situation would have been to have access also to data of a parallel placebo group. At the time when this study was initiated, the opinion of internationally leading hepatologists indeed favoured UDCA therapy, and we could not defend performing another placebo-controlled study. As a subsidiary strategy, we used survival data and incidence rates for major events from placebo-groups treated elsewhere. With the assumptions discussed above, we consider this a relevant strategy, and it proved to be robust to the one-way sensitivity analyses carried out.

4.3 Policy implications

Norway has a system for public coverage of costs of specific drugs for specific diseases. Cost-effectiveness estimates are relevant, but not always obtainable, before public coverage of drug costs is accepted. In the lack of a concomitantly treated placebo group, we consider this analysis of cost-effectiveness of UDCA in PBC the best currently available evidence for decision-making in the perspective of public health services.

4.4 Conclusion

We conclude that UDCA therapy in PBC confers reduced morbidity and a gain in life expectancy as well as cost savings compared with standard treatment within the first four years.

5. Tables

Table 1. Characteristics of PBC patients at start of UDCA- or standard treatment

Variable	UDCA Norwegian patients (n = 180)	Placebo Canadian patients* (n = 111)	Placebo patients from Mayo study§ (n = 91)
Gender; females, n (%)	162 (90)	105 (95)	79 (87)
Age; years, mean (SD)	56.2 (8.9)	55.4	52.0 (9)
Body weight; kg, mean (SD)	66.4 (11.9)		
Dose UDCA; mg/kg/day, median (range)	20 (17 – 22)	0	0
Symptoms before start, n (%)			
Pruritus, n (%)	90 (50)	79 (71)	
Fatigue, n (%)	97 (54)	97 (87)	
Jaundice, n (%)	11 (6)		
Ascites (clinical finding), n (%)	2 (1)	4 (3.6)	
Combined pruritus and fatigue, n (%)	64 (36)		
Encephalopathy, n (%)	2 (1)		
Asymptomatic, n (%)	56 (31)		
AMA titre, median (range)¤	1024 (0 – 2048)		
Bilirubin, mean (SD) (3 – 26 μmol/l)	18.9 (17.6)	31 (39)	31 (39)
ALP, mean (SD) (70 – 230 U/l)	981 (637)	549 (339)	1252 (712)
ALT, mean (SD) (10 – 50 U/l)	111 (70)	109 (62)	
Albumin, mean (SD) (35 – 45 g/l)	40.1 (3.5)		33 (4.0)
INR, mean (SD) (0.8 – 1.2)	1.2 (0.2)		
IgM, mean (SD) (0.4 – 2.1 g/l)	5.24 (3.74)	5.9 (3.5)	
Hepatomegaly, n (%)	53 (29%)		
Splenomegaly, n (%)	13 (7%)		
Mayo risk score at inclusion#, mean (SD)	4.38 (0.88)	4.4 (1.2)	5.1 (1.1)

*Data obtained from Heathcote et al and Pasha et al (8, 25)

§Data obtained from Lindor et al and Pasha et al (9, 25)

¤Titre available in 150 patients. In four cases, AMA-titre at inclusion was 0 but had previously been positive

#Based on 173 patients with results from complete set of variables in the Mayo risk score formula at inclusion. Values for international normalized ratios (INR) were converted to prothrombin time before calculations

Table 2. Causes of death (n = 14) and withdrawal from the study (n = 17) among Norwegian PBC patients (n = 180) treated with UDCA

Cause of death	**n**
Liver failure*	8
Hepatocellular carcinoma*	1
Heart failure	2
Myelomatosis	1
Cancer of the urinary bladder	1
Unknown	1
Cause of withdrawal	
Side effects¤	7
Patient`s decision to withdraw	5
Lost to follow-up	2
Other cause	3

*Median age at death from liver failure or hepatocellular carcinoma was 70 years (range 53 – 74 years)

¤Side effects:

- Right upper abdominal pain and nausea after one week of therapy. Planned cholecystectomy
- Diarrhoea
- Pain and swelling in fingers, knees and feet as well as dyspnoea
- Nausea
- Skin problem (tendency to acne)
- Pruritus
- Diarrhoea and pruritus

Table 3 A. Distribution of major events over time among Norwegian PBC patients (n = 180) treated with UDCA

Event	**First year**	**Second year**	**Third year**	**Fourth year**	**Fifth year**
Variceal bleeding (n = 16)	3	2	5*	3	3*
Ascites (*de novo*) (n = 9)	2	2	3	0	2
Encephalopathy (*de novo*) (n = 4)	1	1	1	1	0
Liver transplantation (n = 3)	1	0	1	0	1
Death (n = 14)	0	3	3	2	6

*Including 1 death

Table 3 B. Annual incidence per 100 person-years of major events over time among Norwegian PBC patients (n = 180) treated with UDCA

Event	**First year (n = 180)***	**Second year (n = 170)***	**Third year (n = 163)***	**Fourth year (n = 156)***	**Fifth year (n = 153)***
Variceal bleeding (n = 16)	1.67	1.18	3.07¤	1.92	1.96¤
Ascites (*de novo*) (n = 9)	1.1	1.18	1.84	0	1.31
Encephalopathy (*de novo*) (n = 4)	0.56	0.59	0.61	0.64	0
Liver transplantation (n = 3)	0.56	0	0.61	0	0.65
Death (n = 14)	0	1.76	1.84	1.28	3.92

*Number of patients at risk at the beginning of each time period

¤Including 1 death

Table 4. Overall annual incidence per 100 person-years of major events in Norwegian PBC patients treated with UDCA (during five years) and relative risk of each event compared with results from placebo patients in Canada/Mayo-study (25) (during four years)

Event	Norwegian UDCA-treated PBC patients* Event per 100/year (95% CI)	Canada/Mayo placebo group Event per 100/year (95% CI)	Relative risk (UDCA vs placebo)	Relative risk (placebo vs UDCA)
Variceal bleeding	1.96¤ (1.12 – 3.17)	1.64 (0.71 – 3.22)	1.20	0.84
Ascites (*de novo*)	1.10 (0.50 – 2.09)	2.66 (1.42 – 4.55)	0.41	2.42
Encephalopathy (*de novo*)	0.49 (0.13 – 1.25)	1.81 (0.69 – 3.18)	0.27	3.69
Liver transplantation	0.37 (0.08 – 1.07)	5.02 (3.25 – 7.41)	0.07	13.57
Death	1.71 (0.94 – 2.87)	4.40 (2.76 – 6.66)	0.39	2.57

95% CIs were calculated based on Poisson distribution (Geigy Scientific Tables)

*Average numbers from table 3 B

¤Represents 16 events among 11 patients, since all events are counted

Table 5. Cost estimates (2005 NOK) for treating major events in Norwegian PBC patients. Costs are calculated for district hospitals (not referral centers). See Appendix, Table 1, for a detailed description of how cost estimates were derived. No cost was attributed to the event of death

Event	**Cost, 2005 NOK**
Variceal bleeding	
Initial hospital admittance + first 2 controls	65 247
Follow-up per year	18 744
Ascites (*de novo*)	
Initial hospital admittance	24 468
Follow-up per year	18 035
Encephalopathy (*de novo*)	
Initial hospital admittance	24 468
Follow-up per year	18 635
Liver transplantation	
Initial hospital admittance	931 917
Follow-up first year	230 542
Follow-up subsequent years*	148 807

*Except for year four when there is no visit at Rikshospitalet and the cost is NOK 137 063

Table 6. Total cost (2005 NOK) and life expectancy per patient in the UDCA-treated and control groups of PBC patients and differences in these parameters between the groups after four years of follow-up. See Appendix, Table 2, for a detailed description of how total cost estimates were derived. No cost was attributed to the event of death

	UDCA-treated patient	**Control patient**	**Difference UDCA –control**
Costs			
UDCA	43 940	0	43 940
Variceal bleeding*	10 240	8 584	1 656
Ascites*	3 962	9 320	-5 358
Encephalopathy*	2 178	6 494	-4 316
Liver transplantation	19 210	306 944	-287 734
Total costs	79 529	331 341	-251 812
Total costs discounted#	72 629	302 170	-229 541
Life expectancy (years)	3.92	3.54	0.38
Life expectance discounted (years)#	3.57	3.22	0.35

*Includes costs of the initial hospital admittance for treatment of the respective major events and costs of follow-up until study termination at four years after inclusion. Costs of regular check-up visits are not included because these are considered to be identical in the UDCA- and control groups

#Discount rates 4%

Table 7. Sensitivity analysis of incidence of major events and cost estimates for UDCA-treated PBC patients

Event	Probability of event Lower bound	Probability of event Upper bound	Cost (2005 NOK) per patient Lower bound	Cost (2005 NOK) per patient Upper bound
First year				
Variceal bleeding	0,0036	0,0505	567	8 032
Ascites	0,0014	0,0416	160	4 773
Encephalopathy	0,0001	0,0321	17	3 777
Liver transplantation	0,0001	0,0321	255	56 058
Second year				
Variceal bleeding	0,0015	0,0435	204	6 100
Ascites	0,0015	0,0435	141	4 202
Encephalopathy	0,0002	0,0335	15	3 321
Liver transplantation	0,0000	0,0000	0	0
Third year				
Variceal bleeding	0,0102	0,0731	1 236	8 881
Ascites	0,0039	0,0549	305	4 316
Encephalopathy	0,0002	0,0349	13	2 806
Liver transplantation	0,0002	0,0349	231	50 971
Fourth year				
Variceal bleeding	0,0040	0,0568	412	5 838
Ascites	0,0000	0,0000	0	0
Encephalopathy	0,0002	0,0361	10	2 229
Liver transplantation	0,0000	0,0000	0	0
Year 1 - 4				
UDCA			43 940	43 940
Variceal bleeding			2 419	28 850
Ascites			605	13 291
Encephalopathy			55	12 134
Liver transplantation			486	107 029
Total costs UDCA-treated patients, year 1 - 4			**47 505**	**205 244**

Table 8. Sensitivity analysis of incidence of major events and cost estimates for the control group of PBC patients

Event	Probability of event Lower bound	Probability of event Upper bound	Cost (2005 NOK) per patient Lower bound	Cost (2005 NOK) per patient Upper bound
First year				
Variceal bleeding	0,0071	0,0322	1 129	5 119
Ascites	0,0142	0,0455	1 628	5 216
Encephalopathy	0,0069	0,0318	812	3 741
Liver transplantation	0,0325	0,0741	56 743	129 374
Second year				
Variceal bleeding	0,0071	0,0322	996	4 515
Ascites	0,0142	0,0455	1 372	4 396
Encephalopathy	0,0069	0,0318	683	3 148
Liver transplantation	0,0325	0,0741	51 907	118 348
Third year				
Variceal bleeding	0,0071	0,0322	863	3 912
Ascites	0,0142	0,0455	1 116	3 575
Encephalopathy	0,0069	0,0318	555	2 556
Liver transplantation	0,0325	0,0741	47 452	108 191
Fourth year				
Variceal bleeding	0,0071	0,0322	729	3 308
Ascites	0,0142	0,0455	860	2 754
Encephalopathy	0,0069	0,0318	426	1 963
Liver transplantation	0,0325	0,0741	42 616	97 165
Year 1 - 4				
UDCA			0	0
Variceal bleeding			3 716	16 854
Ascites			4 975	15 941
Encephalopathy			2 475	11 409
Liver transplantation			198 719	453 078
Total costs placebo-treated patients, year 1 - 4			**209 885**	**497 282**

Table 9. Sensitivity analysis of estimates of cost difference (2005 NOK) between UDCA-treated PBC patients and controls (i.e. cost of UDCA therapy minus cost of standard therapy)

Event	Cost difference per patient Lower bound	Cost difference per patient Upper bound
UDCA	43 940	43 940
Variceal bleeding	-1 297	11 996
Ascites	-4 370	-2 650
Encephalopathy	-2 420	725
Liver transplantation	-198 233	-346 050
Total	**-162 380**	**-292 038**

Table 10. Sensitivity analysis of costs (2005 NOK) of major events among UDCA-treated PBC patients and controls (base-case costs ± 20%). Base-case costs are listed in Table 6

Event	Cost UDCA Lower bound	Cost UDCA Upper bound	Cost controls Lower bound	Cost controls Upper bound
UDCA	43 940	43 940	0	0
Variceal bleeding	8 192	12 288	6 867	10 301
Ascites	3 170	4 754	7 456	11 184
Encephalopathy	1 742	2 614	5 195	7 793
Liver transplantation	15 368	23 052	245 555	368 333
Total	**72 412**	**86 657**	**265 073**	**397 611**

6. Figures

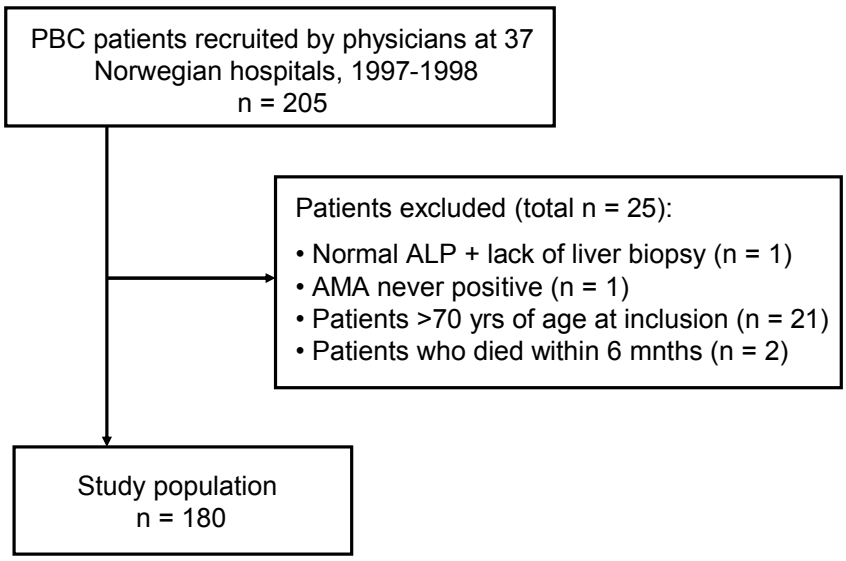

Figure 1. Flow-chart of inclusion of Norwegian PBC patients into study of UDCA therapy

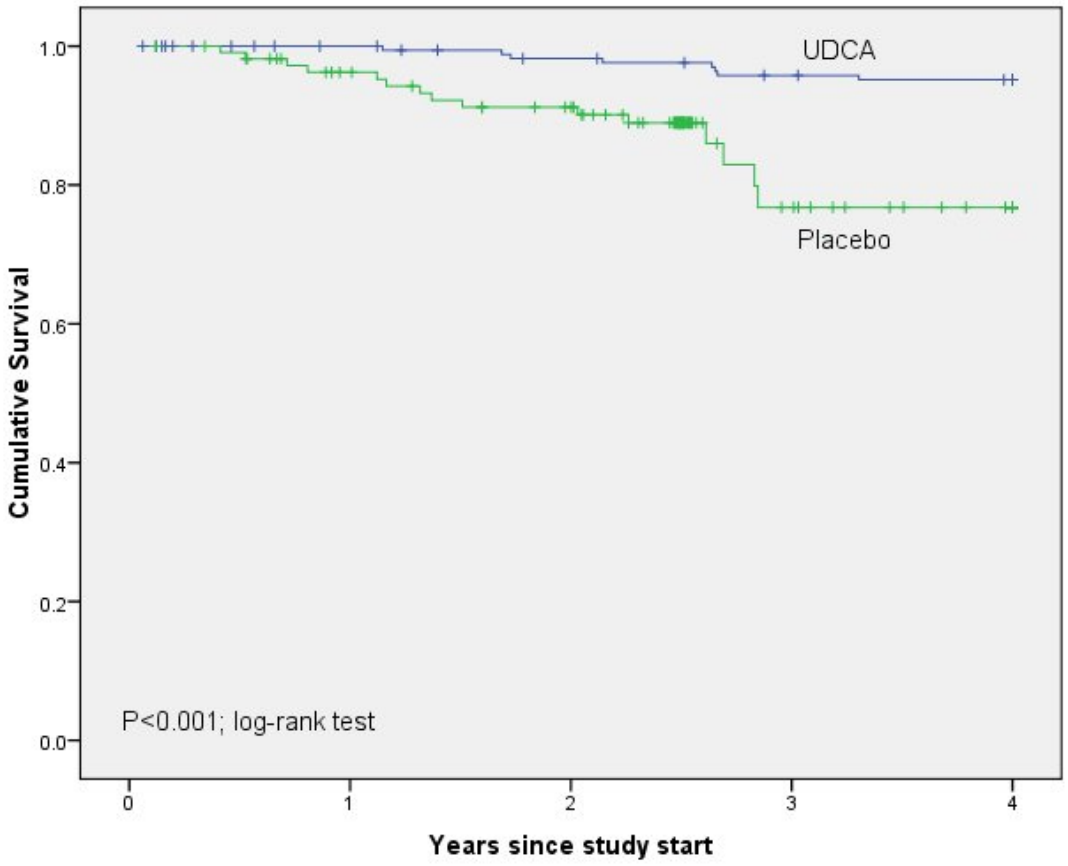

Figure 2. Survival (end-point death) (Kaplan-Meier curves) during four years of follow-up for UDCA-treated Norwegian PBC patients (n = 180) and placebo-treated Canadian PBC patients (n = 111)

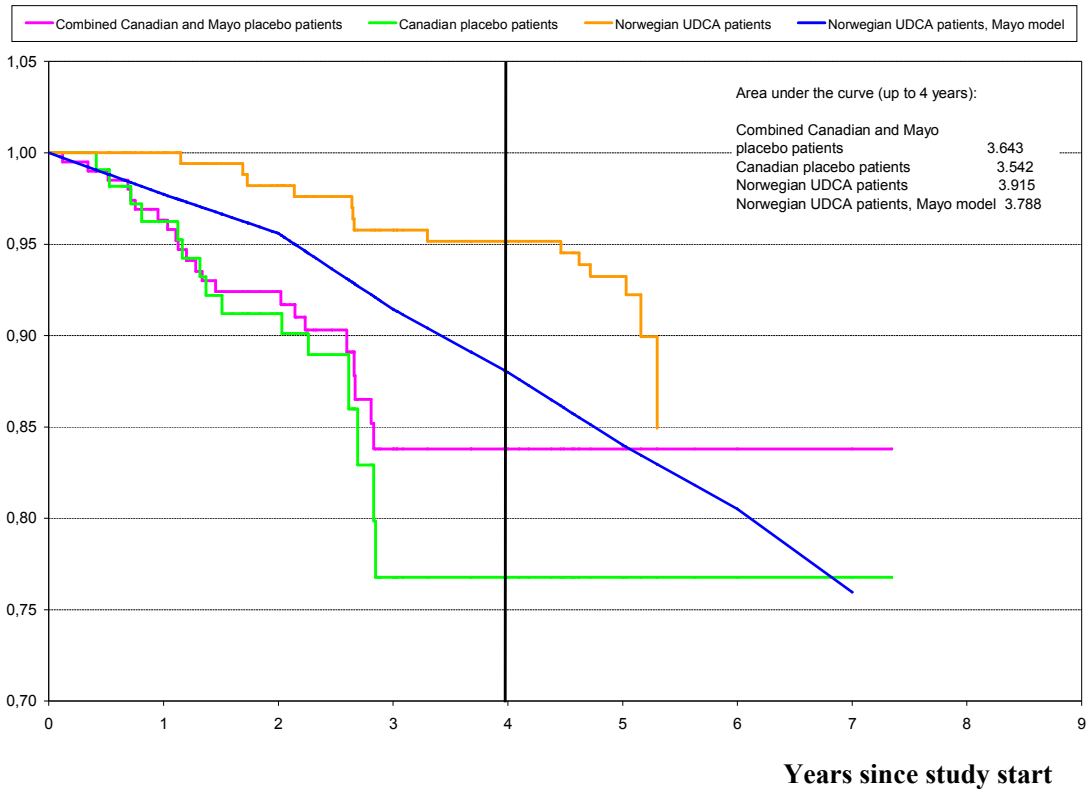

Figure 3. Observed survival (end-point death) for UDCA-treated Norwegian PBC patients (orange line; n = 180), the combined placebo groups of the Canadian- and Mayo trials (pink line; n = 202), and placebo-treated Canadian patients (green line; n = 111), as well as survival of the Norwegian UDCA-treated patients as predicted by the Mayo model (blue line)

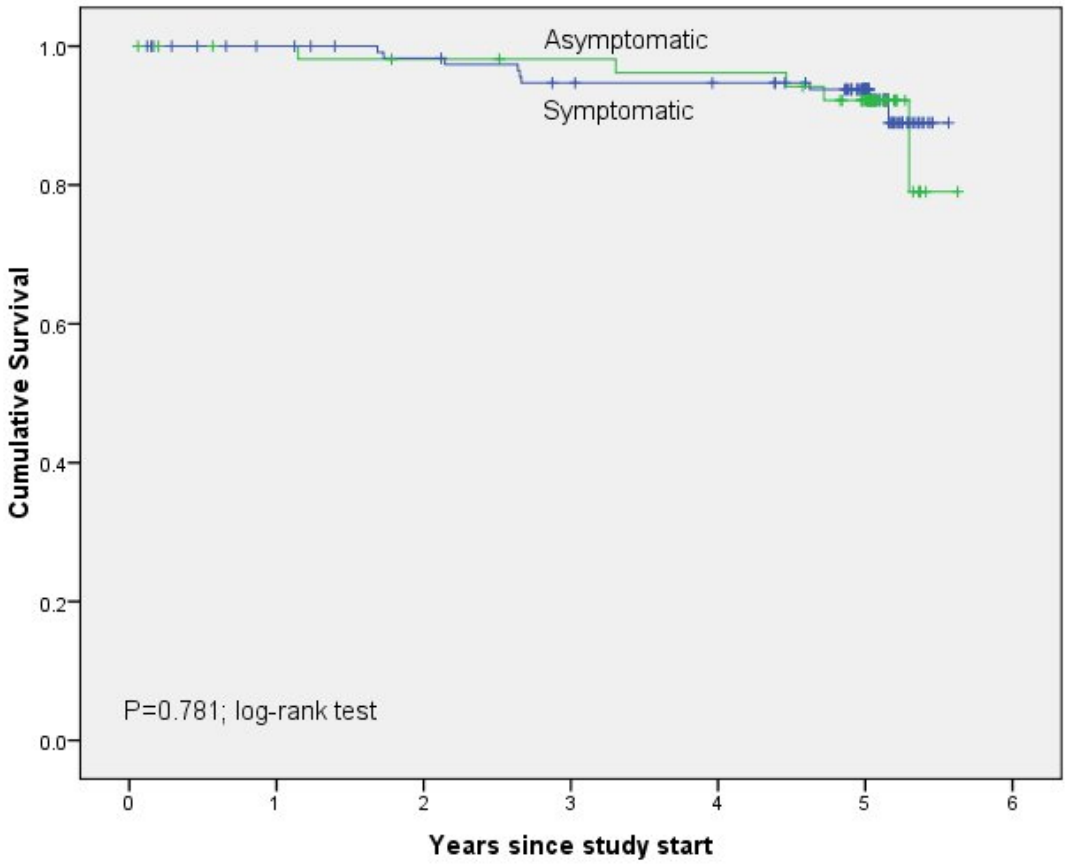

Figure 4. Survival (end-point death) for UDCA-treated Norwegian PBC patients who were asymptomatic (n = 56) and symptomatic (n = 124) at study start (P = 0.781; log-rank test)

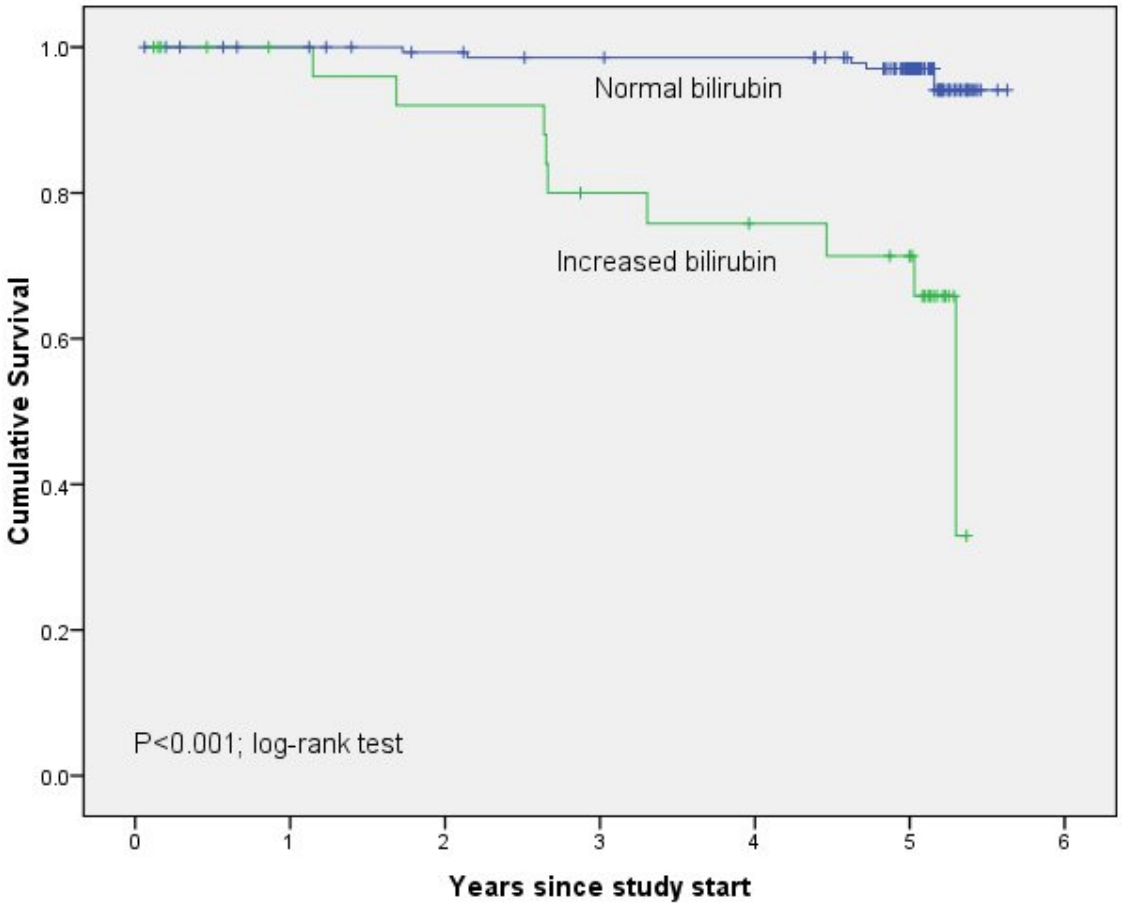

Figure 5. Survival (end-point death) for UDCA-treated Norwegian PBC patients who had bilirubin levels above normal (n = 30) and within normal limits (n = 149) at study start (P < 0.001; log-rank test)

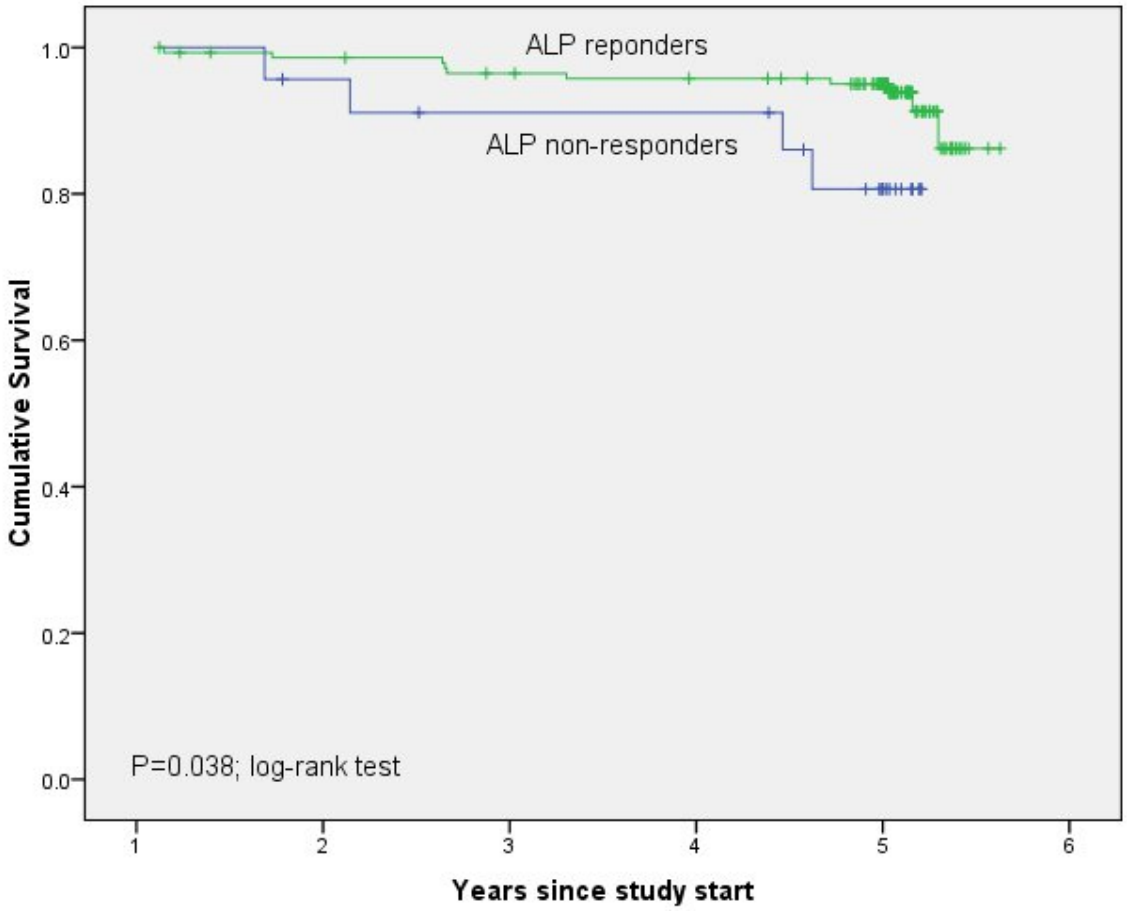

Figure 6. Survival (end-point death) for UDCA-treated Norwegian PBC patients who experienced a decrease in serum ALP levels greater than 40% of baseline levels or had a normal ALP after one year of treatment (n = 145) compared with those who were ALP "non-responders" (n = 23) (P = 0.038; log-rank test)

7. References

1. Kaplan MM. Primary biliary cirrhosis. N Engl J Med 1996;335:1570-1580.

2. Mahl TC, Shockcor W, Boyer JL. Primary biliary cirrhosis: survival of a large cohort of symptomatic and asymptomatic patients followed for 24 years. J Hepatol 1994;20:707-713.

3. Springer J, Cauch-Dudek K, O'Rourke K, Wanless IR, Heathcote EJ. Asymptomatic primary biliary cirrhosis: a study of its natural history and prognosis. Am J Gastroenterol 1999;94:47-53.

4. Kim WR, Lindor KD, Locke GR, III, Therneau TM, Homburger HA, Batts KP, et al. Epidemiology and natural history of primary biliary cirrhosis in a US community. Gastroenterology 2000;119:1631-1636.

5. Prince M, Chetwynd A, Newman W, Metcalf JV, James OF. Survival and symptom progression in a geographically based cohort of patients with primary biliary cirrhosis: follow-up for up to 28 years. Gastroenterology 2002;123:1044-1051.

6. Vierling JM. Future Treatment Options in PBC. Semin Liver Dis 2005;25:347-363.

7. Combes B, Carithers RL, Jr., Maddrey WC, Lin D, McDonald MF, Wheeler DE, et al. A randomized, double-blind, placebo-controlled trial of ursodeoxycholic acid in primary biliary cirrhosis. Hepatology 1995;22:759-766.

8. Heathcote EJ, Cauch-Dudek K, Walker V, Bailey RJ, Blendis LM, Ghent CN, et al. The Canadian Multicenter Double-blind Randomized Controlled Trial of ursodeoxycholic acid in primary biliary cirrhosis. Hepatology 1994;19:1149-1156.

9. Lindor KD, Dickson ER, Baldus WP, Jorgensen RA, Ludwig J, Murtaugh PA, et al. Ursodeoxycholic acid in the treatment of primary biliary cirrhosis. Gastroenterology 1994;106:1284-1290.

10. Pares A, Caballeria L, Rodes J, Bruguera M, Rodrigo L, Garcia-Plaza A, et al. Long-term effects of ursodeoxycholic acid in primary biliary cirrhosis: results of a double-blind controlled multicentric trial. UDCA-Cooperative Group from the Spanish Association for the Study of the Liver. J Hepatol 2000;32:561-566.

11. Poupon RE, Balkau B, Eschwege E, Poupon R. A multicenter, controlled trial of ursodiol for the treatment of primary biliary cirrhosis. UDCA-PBC Study Group. N Engl J Med 1991;324:1548-1554.

12. Poupon RE, Poupon R, Balkau B. Ursodiol for the long-term treatment of primary biliary cirrhosis. The UDCA-PBC Study Group. N Engl J Med 1994;330:1342-1347.

13. Poupon RE, Lindor KD, Pares A, Chazouilleres O, Poupon R, Heathcote EJ. Combined analysis of the effect of treatment with ursodeoxycholic acid on histologic progression in primary biliary cirrhosis. J Hepatol 2003;39:12-16.

14. Poupon RE, Lindor KD, Cauch-Dudek K, Dickson ER, Poupon R, Heathcote EJ. Combined analysis of randomized controlled trials of ursodeoxycholic acid in primary biliary cirrhosis. Gastroenterology 1997;113:884-890.

15. Gong Y, Huang Z, Christensen E, Gluud C. Ursodeoxycholic acid for patients with primary biliary cirrhosis: an updated systematic review and meta-analysis of randomized clinical trials using Bayesian approach as sensitivity analyses. Am J Gastroenterol 2007;102:1799-1807.

16. Goulis J, Leandro G, Burroughs AK. Randomised controlled trials of ursodeoxycholic-acid therapy for primary biliary cirrhosis: a meta-analysis. Lancet 1999;354:1053-1060.

17. Gluud C, Christensen E. Ursodeoxycholic acid for primary biliary cirrhosis. Cochrane Database Syst Rev 2002;CD000551.

18. Shi J, Wu C, Lin Y, Chen YX, Zhu L, Xie WF. Long-term effects of mid-dose ursodeoxycholic acid in primary biliary cirrhosis: a meta-analysis of randomized controlled trials. Am J Gastroenterol 2006;101:1529-1538.

19. Kaplan MM, Gershwin ME. Primary biliary cirrhosis. N Engl J Med 2005;353:1261-1273.

20. Poupon RE. Ursodeoxycholic acid for primary biliary cirrhosis: lessons from the past--issues for the future. J Hepatol 2000;32:685-688.

21. Heathcote EJ. Management of primary biliary cirrhosis. The American Association for the Study of Liver Diseases practice guidelines. Hepatology 2000;31:1005-1013.

22. Levy C, Lindor KD. Current management of primary biliary cirrhosis and primary sclerosing cholangitis. J Hepatol 2003;38 Suppl 1:S24-S37.

23. Paumgartner G. Ursodeoxycholic acid for primary biliary cirrhosis: treat early to slow progression. J Hepatol 2003;39:112-114.

24. Chan CW, Gunsar F, Feudjo M, Rigamonti C, Vlachogiannakos J, Carpenter JR, et al. Long-term ursodeoxycholic acid therapy for primary biliary cirrhosis: a follow-up to 12 years. Aliment Pharmacol Ther 2005;21:217-226.

25. Pasha T, Heathcote J, Gabriel S, Cauch-Dudek K, Jorgensen R, Therneau T, et al. Cost-effectiveness of ursodeoxycholic acid therapy in primary biliary cirrhosis. Hepatology 1999;29:21-26.

26. Angulo P, Lindor KD, Therneau TM, Jorgensen RA, Malinchoc M, Kamath PS, et al. Utilization of the Mayo risk score in patients with primary biliary cirrhosis receiving ursodeoxycholic acid. Liver 1999;19:115-121.

27. Dickson ER, Grambsch PM, Fleming TR, Fisher LD, Langworthy A. Prognosis in primary biliary cirrhosis: model for decision making. Hepatology 1989;10:1-7.

28. Altman D. Practical statistics for medical research. 1st ed. London: Chapman and Hall, 1991.

29. Lindor KD, Therneau TM, Jorgensen RA, Malinchoc M, Dickson ER. Effects of ursodeoxycholic acid on survival in patients with primary biliary cirrhosis. Gastroenterology 1996;110:1515-1518.

30. Larsen B-I. Activity-based funding of health services in Norway. An assessment and suggested measures. Oslo, Norway: Norwegian Directorate for Health and Social Affairs; 2007 Jul.

31. Pares A, Caballeria L, Rodes J. Excellent long-term survival in patients with primary biliary cirrhosis and biochemical response to ursodeoxycholic Acid. Gastroenterology 2006;130:715-720.

32. Poupon RE, Bonnand AM, Chretien Y, Poupon R. Ten-year survival in ursodeoxycholic acid-treated patients with primary biliary cirrhosis. The UDCA-PBC Study Group. Hepatology 1999;29:1668-1671.

33. ter Borg PC, Schalm SW, Hansen BE, van Buuren HR. Prognosis of ursodeoxycholic Acid-treated patients with primary biliary cirrhosis. Results of a 10-yr cohort study involving 297 patients. Am J Gastroenterol 2006;101:2044-2050.

34. Grambsch PM, Dickson ER, Kaplan M, LeSage G, Fleming TR, Langworthy AL. Extramural cross-validation of the Mayo primary biliary cirrhosis survival model establishes its generalizability. Hepatology 1989;10:846-850.

35. Christensen E. Prognostic models including the Child-Pugh, MELD and Mayo risk scores--where are we and where should we go? J Hepatol 2004;41:344-350.

36. Corpechot C, Carrat F, Bahr A, Chretien Y, Poupon RE, Poupon R. The effect of ursodeoxycholic acid therapy on the natural course of primary biliary cirrhosis. Gastroenterology 2005;128:297-303.

Appendix, Table 1. Various cost components (2005 NOK)

		Rikshospitalet	Other hospital
Outpatient visit, Rikshospitalet (RH) and other hospitals			
Consultation, gastroenterologist, 30 min		287	
Lab tests (liver-related), RH		1,670	
Total		1,957	
Total incl. additional 20% overhead		**2,348**	**2,348**
Relative cost, Rikshospitalet	1.20		
Ordinary visit with general practitioner (GP)			
Patient pay (60% are specialists: plus NOK 60)		161	
GP funding (NOK 311.50/patient/yr; accounts for 3 visits)		104	
Patient pay for lab tests		47	
Lab tests (same as RH price)		1670	
Total		**1982**	
Visit with GP for liver transplanted patient			
Sum ordinary visit (above)		1,982	
Tacrolimus analysis		785	
Total		**2,767**	
Lab tests - analysis incl Tacrolimus		2,455	
Management of ascites			
1) Initial hospitalization		**29,361**	**24,468**
2) Follow-up per year			
Outpatient visit, gastroenterologist: x 2/yr		4,697	
Ordinary visit with GP x 6/yr		11,892	
Spironolactone 100 mg/day		1,205	
Furosemid 40 mg/day		241	
Total follow-up per year		**18,035**	**18,035**
Cost of ascites first year + 4 years			**114,642**
Cost of ascites first year + 3 years			**96,607**
Cost of ascites first year + 2 years			**78,572**
Cost of ascites first year + 1 years			**60,537**
Cost of ascites first year			**42,502**
Management of variceal bleeding			
1) Initial hospitalization with endoscopy w/therapy		48,935	40,779
Follow-up endoscopy w/therapy, hospital 1 night:x 2		29,361	24,468
Total initial hospitalization(s)		**78,296**	**65,247**
2) Follow-up per year			
Outpatient visit, gastroenterologist: x1/yr		2,348	2,348
Outpatient visit, with endoscopy: x1/yr (estimate)		4,404	3,670
Ordinary visit with GP x 6/yr		11,892	11,892

Inderal Retard 80 mg/d		834	834
Total follow-up per year		**19,478**	**18,744**
Cost of variceal bleed first year + 4 years			**158,969**
Cost of variceal bleed first year + 3 years			**140,224**
Cost of variceal bleed first year + 2 years			**121,480**
Cost of variceal bleed first year + 1 years			**102,735**
Cost of variceal bleed first year			**83,991**
Management of encephalopathy			
1) Initial hospitalization as for ascites		**29,361**	**24,468**
2) Follow-up per year			
Outpatient visit, gastroenterologist: x 2/yr		4,697	4,697
Ordinary visit with GP x 6/yr		11,892	11,892
Lactulose 40 ml/d		2,046	2,046
Total follow-up per year		**18,635**	**18,635**
Cost of encephalopathy first year + 4 years			**117,642**
Cost of encephalopathy first year + 3 years			**99,007**
Cost of encephalopathy first year + 2 years			**80,372**
Cost of encephalopathy first year + 1 years			**61,737**
Cost of encephalopathy first year			**43,102**
Management of liver transplantation			
1) Initial hospitalization		**931,917**	
2) Follow-up first year			
Follow-up visits at RH with ordinary investigations: x 3		35,233	
Ordinary visit with GP every 2. week: visit x 24		47,568	
Lab test incl tacrolimus: x 1/week first 3 months: x 8		19,640	
Lab test incl tacrolimus: x 1 per 3 weeks: x 12		29,460	
Prograf 6 mg/d		54,102	
Prednisolon 7.5 mg/d		514	
Mycophenolate 2 g/d		42,238	
AlbylE 75 mg/d		341	
Calcigran Forte 1 g/d		1,123	
Bactrim 1/d for 6 months		323	
Total follow-up first year		**230,542**	
3) Follow-up subsequent years			
Follow-up visit at RH with ordinary investigations: x 1		11,744	
Ordinary visit with GP every month: visit x 12		23,784	
Lab test incl tacrolimus: x 1/3 weeks: x 17		41,735	
Prograf 4 mg/d		48,811	
Prednisolon 5 mg/d to 50% of patients		152	
Mycophenolate 1 g/d		21,117	
AlbylE 75 mg/d		341	
Calcigran Forte 1 g/d		1,123	

Total follow-up subsequent years		**148,807**	
Cost OLT first year + 4 more years (no visit at RH 4th year)		**1,745,943**	
Cost OLT first year + 3 more years (no visit at RH 4th year)		**1,597,136**	
Cost OLT first year + 2 more years		**1,460,073**	
Cost OLT first year + 1 more year		**1,311,266**	
Cost OLT first year		**1,162,459**	

Appendix, Table 2. Annual morbidity cost estimates in UDCA-treated PBC patients and controls (2005 NOK)

Remaining patients	Event	Number	Probability of event UDCA	Cost per event per event	Cost per year UDCA	Probability of event controls	Cost per year controls	Cost difference UDCA-controls
Year 1	Treated with UDCA			10,985	10,985	0	0	
At year	Variceal bleeding	3	0.0173	158,969	2,748	0.0164	2,607	
start: 180	Ascites	2	0.0115	114,642	1,321	0.0266	3,049	
Patient	Encephalopathy	1	0.0058	117,642	678	0.0181	2,129	
years:	Liver tx	1	0.0058	1,745,943	10,061	0.0502	87,646	
173.53	Death	0	0.0000	0	0	0.044	0	
	Censored (drop-out)	9						
					25,794		**95,432**	**-69,638**
Year 2	Treated with UDCA			10,985	10,985	0	0	
At year	Variceal bleeding	2	0.0120	140,224	1,689	0.0164	2,300	
start: 170	Ascites	2	0.0120	96,607	1,163	0.0266	2,570	
Patient	Encephalopathy	1	0.0060	99,007	596	0.0181	1,792	
years:	Liver tx	0	0.0000	1,597,136	0	0.0502	80,176	
166.09	Death	3	0.0181	0	0	0.044	0	
	Censored (drop-out)	4						
					14,433		**86,838**	**-72,405**
Year 3	Treated with UDCA			10,985	10,985	0	0	
At year	Variceal bleeding	5	0.0313	121,480	3,806	0.0164	1,992	
start: 163	Ascites	3	0.0188	78,572	1,477	0.0266	2,090	
Patient	Encephalopathy	1	0.0063	80,372	504	0.0181	1,455	
years:	Liver tx	1	0.0063	1,460,073	9,148	0.0502	73,296	
159.6	Death	3	0.0188	0	0	0.044	0	
	Censored (drop-out)	3						
					25,920		**78,833**	**-52,913**
Year 4	Treated with UDCA			10,985	10,985	0	0	
At year	Variceal bleeding	3	0.0194	102,735	1,998	0.0164	1,685	
start: 156	Ascites	0	0.0000	60,537	0	0.0266	1,610	
Patient	Encephalopathy	1	0.0065	61,737	400	0.0181	1,117	
years:	Liver tx	0	0.0000	1,311,266	0	0.0502	65,826	

154.29	Death	2	0.0130	0	0	0.044	0	
	Censored (drop-out)	1						
					13,383		**70,238**	**-56,855**

Year 5	Treated with UDCA			10,985	10,985	0	0	
At year	Variceal bleeding	3	0.0182	83,991	1,528	0.0164	1,377	
start: 153	Ascites	2	0.0121	42,502	516	0.0266	1,131	
Patient	Encephalopathy	0	0.0000	43,102	0	0.0181	780	
years:	Liver tx	1	0.0061	1,162,459	7,051	0.0502	58,355	
164.87	Death	6	0.0364	0	0	0.044	0	
OBS	(some followed>5yrs)				**20,080**		**61,644**	**-41,564**

Sum cost UDCA	**Sum cost controls**	**Sum difference**
Year 1 - 5:	Year 1 - 5:	
99,609	**392,984**	**-293,376**
Year 1 - 4:	Year 1 - 4:	
79,529	**331,341**	**-251,812**

TOTAL, year 1 - 4

Treated with UDCA				43,940		0	43,940
Variceal bleeding				10,240		8,584	1,656
Ascites				3,962		9,320	-5,358
Encephalopathy				2,178		6,494	-4,316
Liver tx				19,210		306,944	-287,734
Total				**79,529**		**331,341**	**-251,812**

Appendix, Table 3. One-way sensitivity analysis of annual morbidity cost estimates in UDCA-treated PBC patients and controls (2005 NOK)

Remaining patients	Event	Number	95% lower no.	95% upper no.	Probability of event UDCA	Probability UDCA Lower bound	Probability UDCA Upper bound	Cost per event	Cost per year UDCA	Cost per year UDCA Lower bound	Cost per year UDCA Upper bound	Probability of event controls	Probability controls Lower bound	Probability controls Upper bound	Cost per year controls	Cost per year controls Lower bound	Cost per year controls Upper bound	Cost difference UDCA-controls	Cost difference Lower bound	Cost difference Upper bound
Year 1	Treated with UDCA							10,985	10,985	10,985	10,985	0			0	0	0			
At year	Variceal bleeding	3	0.6187	8.7673	0.0173	0.0036	0.0505	158,969	2,748	567	8,032	0.0164	0.0071	0.0322	2,607	1,129	5,119			
start: 180	Ascites	2	0.2422	7.2247	0.0115	0.0014	0.0416	114,642	1,321	160	4,773	0.0266	0.0142	0.0455	3,049	1,628	5,216			
Patient	Encephalopathy	1	0.0253	5.5716	0.0058	0.0001	0.0321	117,642	678	17	3,777	0.0181	0.0069	0.0318	2,129	812	3,741			
years:	Liver tx	1	0.0253	5.5716	0.0058	0.0001	0.0321	1,745,943	10,061	255	56,058	0.0502	0.0325	0.0741	87,646	56,743	129,374			
173.53	Death	0						0	0	0	0	0.044	0.0276	0.0666	0	0	0			
	Censored (drop-out)	9	4.1154	17.085																
									25,794	**11,983**	**83,625**				**95,432**	**60,311**	**143,450**	**-69,638**	**-48,328**	**-59,826**
Year 2	Treated with UDCA							10,985	10,985	10,985	10,985	0			0	0	0			
At year	Variceal bleeding	2	0.2422	7.2247	0.0120	0.0015	0.0435	140,224	1,689	204	6,100	0.0164	0.0071	0.0322	2,300	996	4,515			
start: 170	Ascites	2	0.2422	7.2247	0.0120	0.0015	0.0435	96,607	1,163	141	4,202	0.0266	0.0142	0.0455	2,570	1,372	4,396			
Patient	Encephalopathy	1	0.0253	5.5716	0.0060	0.0002	0.0335	99,007	596	15	3,321	0.0181	0.0069	0.0318	1,792	683	3,148			
years:	Liver tx	0						1,597,136	0	0	0	0.0502	0.0325	0.0741	80,176	51,907	118,348			
166.09	Death	3	0.6187	8.7673	0.0181	0.0037	0.0528	0	0	0	0	0.044	0.0276	0.0666	0	0	0			
	Censored (drop-out)	4	1.0899	10.242																
									14,433	**11,345**	**24,608**				**86,838**	**54,957**	**130,407**	**-72,405**	**-43,612**	**-105,799**
Year 3	Treated with UDCA							10,985	10,985	10,985	10,985	0			0	0	0			
At year	Variceal bleeding	5	1.6234	11.668	0.0313	0.0102	0.0731	121,480	3,806	1,236	8,881	0.0164	0.0071	0.0322	1,992	863	3,912			
start: 163	Ascites	3	0.6187	8.7673	0.0188	0.0039	0.0549	78,572	1,477	305	4,316	0.0266	0.0142	0.0455	2,090	1,116	3,575			
Patient	Encephalopathy	1	0.0253	5.5716	0.0063	0.0002	0.0349	80,372	504	13	2,806	0.0181	0.0069	0.0318	1,455	555	2,556			
years:	Liver tx	1	0.0253	5.5716	0.0063	0.0002	0.0349	1,460,073	9,148	231	50,971	0.0502	0.0325	0.0741	73,296	47,452	108,191			
159.6	Death	3	0.6187	8.7673	0.0188	0.0039	0.0549	0	0	0	0	0.044	0.0276	0.0666	0	0	0			
	Censored (drop-out)	3	0.6187	8.7673																
									25,920	**12,769**	**77,959**				**78,833**	**49,985**	**118,234**	**-52,913**	**-37,216**	**-40,275**
Year 4	Treated with UDCA							10,985	10,985	10,985	10,985	0			0	0	0			
At year	Variceal bleeding	3	0.6187	8.7673	0.0194	0.0040	0.0568	102,735	1,998	412	5,838	0.0164	0.0071	0.0322	1,685	729	3,308			
start: 156	Ascites	0						60,537	0	0	0	0.0266	0.0142	0.0455	1,610	860	2,754			
Patient	Encephalopathy	1	0.0253	5.5716	0.0065	0.0002	0.0361	61,737	400	10	2,229	0.0181	0.0069	0.0318	1,117	426	1,963			
years:	Liver tx	0						1,311,266	0	0	0	0.0502	0.0325	0.0741	65,826	42,616	97,165			
154.29	Death	2	0.2422	7.2247	0.0130	0.0016	0.0468	0	0	0	0	0.044	0.0276	0.0666	0	0	0			
	Censored (drop-out)	1	0.0253	5.5716																
									13,383	**11,407**	**19,052**				**70,238**	**44,631**	**105,191**	**-56,855**	**-33,224**	**-86,138**
Year 5	Treated with UDCA							10,985	10,985	10,985	10,985	0			0	0	0			
At year	Variceal bleeding	3	0.6187	8.7673	0.0182	0.0038	0.0532	83,991	1,528	315	4,466	0.0164	0.0071	0.0322	1,377	596	2,705			
start: 153	Ascites	2	0.2422	7.2247	0.0121	0.0015	0.0438	42,502	516	62	1,862	0.0266	0.0142	0.0455	1,131	604	1,934			
Patient	Encephalopathy	0						43,102	0	0	0	0.0181	0.0069	0.0318	780	297	1,371			
years:	Liver tx	1	0.0253	5.5716	0.0061	0.0002	0.0338	1,162,459	7,051	178	39,284	0.0502	0.0325	0.0741	58,355	37,780	86,138			
164.87	Death	6	2.2019	13.059	0.0364	0.0134	0.0134	0	0	0	0	0.044	0.0276	0.0666	0	0	0			
OBS	(some followed>5yrs)								**20,080**	**11,541**	**56,598**				**61,644**	**39,277**	**92,147**	**-41,564**	**-27,736**	**-35,549**

Sum cost UDCA
Year 1 - 5:
99,609

Year 1 - 4:
79,529

Sum cost placebo
Year 1 - 5:
392,984

Year 1 - 4:
331,341

Sum difference
Year 1 - 5:
-293,376

Year 1 - 4:
-251,812

TOTAL, year 1 - 4									Cost year 1 - 4 UDCA	Cost year 1 - 4 UDCA Lower bound	Cost year 1 - 4 UDCA Upper bound				Cost year 1 - 4 controls	Cost year 1 - 4 controls Lower bound	Cost year 1 - 4 controls Upper bound	Cost difference UDCA-controls	Cost difference Lower bound	Cost difference upper bound
UDCA									43,940	43,940	43,940				0	0	0	43,940	43,940	43,940
Variceal bleeding									10,240	2,419	28,850				8,584	3,716	16,854	1,656	-1,297	11,996
Ascites									3,962	605	13,291				9,320	4,975	15,941	-5,358	-4,370	-2,650
Encephalopathy									2,178	55	12,134				6,494	2,475	11,409	-4,316	-2,420	725
Liver tx									19,210	486	107,029				306,944	198,719	453,078	-287,734	-198,233	-346,050
Total									**79,529**	**47,505**	**205,244**				**331,341**	**209,885**	**497,282**	**-251,812**	**-162,380**	**-292,038**