Ursodeoxycholic acid for primary biliary cirrhosis (Review)

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[Intervention Review]

Ursodeoxycholic acid for primary biliary cirrhosis

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Editorial group: Cochrane Hepato-Biliary Group.
Publication status and date: Edited (no change to conclusions), published in Issue 4, 2008.
Review content assessed as up-to-date: 10 January 2008.

Citation: Gong Y, Huang ZB, Christensen E, Gluud C. Ursodeoxycholic acid for primary biliary cirrhosis. *Cochrane Database of Systematic Reviews* 2008, Issue 3. Art. No.: CD000551. DOI: 10.1002/14651858.CD000551.pub2.

ABSTRACT

Background

Primary biliary cirrhosis is an uncommon autoimmune liver disease with unknown aetiology. Ursodeoxycholic acid (UDCA) has been used for primary biliary cirrhosis, but the effects remain controversial.

Objectives

To evaluate the benefits and harms of UDCA on patients with primary biliary cirrhosis against placebo or no intervention.

Search methods

We searched *The Cochrane Hepato-Biliary Group Controlled Trials Register, The Cochrane Central Register of Controlled Trials* on *The Cochrane Library, MEDLINE, EMBASE, SCI-EXPANDED, The Chinese Biomedical CD Database, LILACS*, and the references of identified studies. The last search was performed in January 2007.

Selection criteria

Randomised clinical trials evaluating UDCA versus placebo or no intervention in patients with primary biliary cirrhosis.

Data collection and analysis

The primary outcomes were mortality and mortality or liver transplantation. Binary outcomes were reported as odds ratio (OR) or relative risk (RR) and continuous outcomes as weighted mean difference, all with 95% confidence intervals (CI). Meta-regression was used to investigate the associations between UDCA effects and quality of the trial, UDCA dose, trial duration, and patient's severity of primary biliary cirrhosis. We also used Bayesian meta-analytic approach to estimate the UDCA effect as sensitivity analysis.

Main results

Sixteen randomised clinical trials evaluating UDCA against placebo or no intervention were identified. Data from three trials have been updated. Nearly half of the trials had high risk of bias. The combined results demonstrated no significant effects favouring UDCA on mortality (OR 0.97, 95% CI 0.67 to 1.42) and mortality or liver transplantation (RR 0.92, 95% CI 0.71 to 1.21). The findings were supported by the Bayesian meta-analyses. UDCA did not improve pruritus, fatigue, autoimmune conditions, liver histology, or portal pressure. UDCA seemed to improve biochemical variables, like serum bilirubin, ascites, and jaundice, but the findings were based on few trials with sparse data. The use of UDCA is significantly associated with adverse events, mainly weight gain.

Authors' conclusions

This systematic review did not demonstrate any benefit of UDCA on mortality and mortality or liver transplantation of patients with primary biliary cirrhosis. The few observed beneficial effects could be due to random errors or outcome reporting bias.

PLAIN LANGUAGE SUMMARY

Ursodeoxycholic acid is not likely to yield a benefit on survival of patients with primary biliary cirrhosis

Primary biliary cirrhosis is an uncommon and slowly progressive autoimmune disease of the liver that primarily attacks middle-aged women. The cause of the disease is unknown. Over the last 30 years, substantial increases in the prevalence of primary biliary cirrhosis have been observed. Primary biliary cirrhosis is now a frequent cause of liver morbidity, and the patients are significant users of health resources, including liver transplantation.

Ursodeoxycholic acid (UDCA) is the only FDA approved drug to treat primary biliary cirrhosis, but the effects remain controversial. This review evaluates if UDCA has any beneficial role to play in relation to primary biliary cirrhosis patients. It includes 16 randomised clinical trials with a total of 1447 patients. The primary outcome measures were mortality and mortality or liver transplantation. Although UDCA showed a reduction in liver biochemistry, jaundice, and ascites, this review did not demonstrate any benefit of ursodeoxycholic acid on mortality and mortality or liver transplantation.The use of UDCA is associated with weight gain and costs. A number of the trials had risk of bias and the topic seems to have selective reporting of outcomes.

BACKGROUND

Primary biliary cirrhosis is an uncommon and slowly progressive autoimmune disease of the liver that primarily attacks middle-aged women. It was first comprehensively described around 1950 (MacMahon 1949; Ahrens 1950). Over the last 30 years, substantial increases in the prevalence of primary biliary cirrhosis have been observed (Kim 2000). Primary biliary cirrhosis is now a frequent cause of liver morbidity, and the patients are significant users of health resources, including liver transplantation (Prince 2003).

Histopathologically, a progressive granulomatous hepatitis destroys small septal and interlobular bile ducts. The loss of bile ducts leads to decreased bile secretion and the retention of toxic substances within the liver, resulting in further hepatic damage, fibrosis, cirrhosis, and eventually, liver failure (Kaplan 2005). Fatigue and pruritus are the most common presenting symptoms. Other findings include hyperlipidaemia, hypothyroidism, osteopaenia, and coexisting autoimmune diseases, including Sjögren's syndrome and scleroderma. The diagnosis of primary biliary cirrhosis is currently based on a triad: the presence of detectable antimitochondrial antibodies in serum; the elevation of liver enzymes (most commonly alkaline phosphatases) for more than six months; and the characteristic liver histological changes in the absence of extrahepatic biliary obstruction (Kaplan 1996).

Bile duct destruction leads to the retention of hydrophobic bile acids within the liver cell. This most likely contributes to the gradual deterioration in liver function observed in patients with primary biliary cirrhosis. Ursodeoxycholic acid (UDCA), the epimer of chenodeoxycholic acid, increases the rate of transport of intracellular bile acids across the liver cell and into the canaliculus in patients with primary biliary cirrhosis (Jazrawi 1994). UDCA treatment reduces intracellular hydrophobic bile acid levels and thereby may have a cytoprotective effect on cell membranes. UDCA may also act as an immunomodulatory agent (Calmus 1992).

UDCA is the only drug approved for primary biliary cirrhosis by the Food and Drug Administration. Doses of 13 mg/kg to 15 mg/kg/ day cause significant improvements in liver tests and immunoglobulin levels and reduce titers of antimitochondrial antibodies (TORONTO; BARCELONA). However, the effect of UDCA on mortality and histological progression remains controversial (Goulis 1999; Gluud 2001 b). Since 2001, several randomised clinical trials have been published with results of longer-term follow-up on patients' survivals (ATHENS; DALLAS; MAYO-I). We, therefore, re-evaluated the effects of UDCA in patients with primary biliary cirrhosis by updating our systematic review on the topic (Gluud 2001 b).

OBJECTIVES

The objective is to evaluate the beneficial and harmful effects of UDCA on patients with primary biliary cirrhosis.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised clinical trials irrespective of blinding, language, year of publication, and publication status. We excluded studies using quasi-randomisation (for example, allocation by date of birth).

Types of participants

Patients with primary biliary cirrhosis, ie, a positive result for serum mitochondrial antibody, and/or elevated serum activity of alkaline phosphatases (or other markers of intrahepatic cholestasis), and/or liver biopsy findings diagnostic for or compatible with primary biliary cirrhosis.

Types of interventions

Peroral administration of UDCA at any dose versus placebo or no intervention. Co-interventions were allowed as long as the intervention arms of the randomised clinical trial received similar co-interventions.

Types of outcome measures

The primary outcome measures were:

- Mortality.
- Mortality or liver transplantation.

The secondary outcome measures were:

- Liver transplantation.
- Pruritus: number of patients with pruritus or pruritus score.
- Fatigue: number of patients with fatigue.
- Other clinical symptoms: number of patients developing jaundice, portal pressure, oesophageal varices, gastric varices, ascites, hepatic encephalopathy, hepato-renal syndrome, sicca complex, scleroderma-like lesions.
- Liver biochemistry: serum (s-)bilirubin; s-alkaline phosphatases; s-gamma-glutamyltransferase; s-aspartate aminotransferase; s-alanine aminotransferase; s-albumin; s-cholesterol (total); plasma immunoglobulins. These data were extracted as close to the first half year, where applicable.
- Liver biopsy: worsening of liver histological stage or score.
- Quality of life: physical functioning (ability to carry out activities of daily living such as self-care and walking around), psychological functioning (emotional and mental well-being), social functioning (social relationships and participation in social activities), and perception of health, pain, and overall satisfaction with life.
- Adverse events (excluding mortality and liver transplantation): The adverse event is defined as any untoward medical occurrence in a patient in either of the two arms of the included randomised clinical trials, which did not necessarily have a causal relationship with the treatment, but did, however, result in a dose reduction, discontinuation of treatment, or registration of the advent as an adverse event/side effect (ICH-GCP 1997).
- Cost-effectiveness: the estimated costs connected with the interventions were weighed against any possible health gains.

Search methods for identification of studies

We searched for trials *The Cochrane Hepato-Biliary Group Controlled Trials Register* (Gluud 2005), *The Cochrane Central Register of Controlled Trials* on *The Cochrane Library*, *MEDLINE*, *EMBASE, SCI-EXPANDED, The Chinese Biomedical CD Database, LILACS*, and in references of identified studies. The detailed searching strategy is listed in Appendix 1. The last search was performed in January 2007.

Data collection and analysis

We conducted the meta-analysis following the protocol (Gluud 1999 a) and the recommendations given by the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2006).

Data extraction

Two authors (YG and EC) independently evaluated whether newly identified trials fulfilled the inclusion criteria. We listed the excluded trials in 'Characteristics of excluded studies' with the reasons for exclusion. YG extracted data and EC validated the data extraction. Disagreements were resolved by discussion with YG, EC, and CG.

Bias risk

We assessed the methodological quality of the randomised clinical trials using four components (Schulz 1995; Moher 1998; Kjaergard 2001) as follows. Trials with low risk of bias were the ones meeting the adequacy criteria of the first three components.

Generation of the allocation sequence

- Adequate, if the allocation sequence was generated by a computer or random number table. Drawing of lots, tossing of a

coin, shuffling of cards, or throwing dice are considered as adequate if a person who was not otherwise involved in the recruitment of participants performed the procedure;

- Unclear, if the trial was described as randomised, but the method used for the allocation sequence generation was not described.
- Inadequate, if a system involving dates, names, or admittance numbers were used for the allocation of patients.

Allocation concealment

- Adequate, if the allocation of patients involved a central independent unit, on-site locked computer, numbered drug bottles or containers with identical appearance prepared by an independent pharmacist or investigator, or sealed envelopes;
- Unclear, if the trial was described as randomised, but the method used to conceal the allocation was not described;
- Inadequate, if the allocation sequence was known to the investigators who assigned participants.

Blinding

- Adequate, if the trial was described as double blind and the method of blinding involved identical placebo or active drug;
- Unclear, if the trial was described as double blind, but the method of blinding was not described;
- Not performed, if the trial was not double blind.

Follow-up

- Adequate, if the numbers and reasons for dropouts and withdrawals in all intervention groups were described or if it was specified that there were no dropouts or withdrawals;
- Unclear, if the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated;
- Inadequate, if the number or reasons for dropouts and withdrawals were not described.

The following items were recorded from the individual trial: mean (or median) age, sex ratio, histological stage, other baseline characteristics including serum (s)-bilirubin concentration, dose of UDCA, and type of intervention in the control group.
In the protocol for this systematic review (Gluud 1999 a) we only intended to extract data from the time when patients were on UDCA versus placebo/no intervention in order to secure data from the most unbiased comparisons. However, due to comments raised by some of the peer-reviewers we also extracted data on mortality and/or liver transplantation at the maximal follow-up of each trial, including data from patients switched from blinded UDCA onto open label UDCA (UDCA→UDCA) versus patients switched from placebo onto open label UDCA (placebo→UDCA). The interpretation of these data, however, should be performed with caution (see Discussion).

Statistical methods

We performed meta-analyses with Review Manager 4.2. We analysed data by a random-effects model (DerSimonian 1986) and a fixed-effect model (DeMets 1987). If the results of both analyses gave the same overall results regarding significance, only the results of the fixed-effect model analysis were reported. We presented binary outcome measure as odds ratio (OR) or relative risk (RR) with 95% confidence interval (CI), and continuous outcome measure as weighted mean difference (WMD) with 95% CI. Heterogeneity was explored by chi-squared test with significance set at $P < 0.1$ and the quantity of heterogeneity was measured by I^2 (Higgins 2002) and the moment-based estimate (DerSimonian 1986). We had a number of secondary outcomes, so much caution is needed to interpret the results due to the multiple testing issue.
We performed a meta-regression analysis with STATA® on primary outcomes, ie, mortality and mortality or liver transplantation. Meta-regression analysis examined the effect size of UDCA in relation to methodological quality of trials, UDCA dosage, trial duration (treatment and follow-up), and disease severity of patients at entry. We applied a random-effects meta-regression (Thompson 2002).
We used funnel plot to provide a visual assessment of whether treatment estimates are associated with study size. We explored publication bias and other bias according to Begg's and Egger's methods (Begg 1994; Egger 1997) with STATA®.

Sensitivity analyses

We conducted sensitivity analyses to investigate the robustness of our main analyses. These sensitivity analyses were only performed on the primary outcomes, ie, mortality and mortality or liver transplantation.

- The influence of missing data: the missing data could be due to patient dropouts or lost to follow-up. We used an uncertainty method to allow for missing data in that it incorporates both sampling error and the potential impact of missing data by pooling uncertainty intervals (Gamble 2005);
- Bayesian meta-analytic approach with WINBUGS (version 1.4.1), in which Markov chain Monte Carlo with Gibbs sampling was applied. This approach is able to account for uncertainty of all relevant sources of variability in the random-effects model. The analogue of a classical estimate is the marginal posterior median and the analogue of a classical confidence interval is the credibility interval (CrI) (Whitehead 2002). We applied a commonly used non-informative prior in the analysis: gamma (0.001, 0.001). We used odds ratio (OR) as summary statistic. For the ease of comparison, we reported the Bayesian results together with results from the classical meta-analysis presented as OR;

- Bayesian meta-regression to estimate the UDCA effects adjusted for underlying risk. The underlying risk is a convenient and clinically relevant trial-level measure, which can be interpreted as a summary of a number of unmeasured patient characteristics (Sharp 2000). We also use this approach to investigate the relationship between one specific covariate (eg, UDCA dosage, trial duration, or disease severity of patients at entry) and the effects of UDCA adjusted for underlying risk.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

We identified 863 references through electronic and hand searches. We excluded 762 duplicates and clearly irrelevant references, non-randomised clinical studies, or observational studies. The remaining 101 references referred to 16 randomised clinical trials including 1447 patients. A summary of the 16 trials was listed in 'Characteristics in the included trials'. Two of the 16 randomised clinical trials were published as abstracts only (MANCHESTER; MEXICO CITY), and the MEXICO CITY trial provided no extractable data on the trial's characteristics and outcomes. The excluded studies are listed under 'Characteristics of excluded studies' and the reasons for exclusion are given there. Compared to the first version of this systematic review (Gluud 2001 b), we updated with new mortality and liver transplantation data from three trials (ATHENS; DALLAS; MAYO-I) and adverse events data from the MAYO-I trial.

UDCA dose varied from 7.7 to 15.5 mg/kg/day with a median of 10 mg/kg/day. The duration of the trials varied from 3 to 92 months with a median of 24 months. The percentage of patients with advanced primary biliary cirrhosis or presenting symptoms at entry varied from 15% to 83% with a median of 51%. The details are displayed in Table 1.

Following the stipulated follow-up in the UDCA-group and the placebo-group, six trials (GÖTEBORG; DALLAS; MAYO-I; MILAN; TORONTO; VILLEJUIF) continued UDCA treated patients on open label UDCA (UDCA→UDCA) and offered open label UDCA to the patients originally given placebo (placebo→UDCA). The ATHENS trial continued to administer UDCA to all patients randomised to the UDCA arm and switched 14/43 'no intervention' patients to UDCA after they had been followed for a mean duration of 3.5 years. It was not possible to separate the data of the original period (UDCA versus no intervention) from the total period (UDCA→UDCA versus no intervention→UDCA), as only data from the total period were given.

Risk of bias in included studies

The methods to generate the allocation schedule were considered to be adequate in nine trials (ATHENS; BARCELONA; FRANKFURT; GÖTEBORG; HELSINKI; MAYO-I; MILAN; NEWCASTLE; TAIPEI). The remainder of the trials did not describe the method to generate the randomisation schedule.

The methods to conceal allocation were considered to be adequate in ten trials (ATHENS; BARCELONA; FRANKFURT; GÖTEBORG; HELSINKI; MAYO-I; NEWCASTLE; TOKYO; TORONTO; VILLEJUIF). The other six trials had inadequate or unclear allocation of concealment.

All the trials employing placebo were described as double blind. However, the description of the placebo contained enough detail in five trials (BARCELONA; FRANKFURT; HELSINKI; MAYO-I; TORONTO), ie, the placebo was identical in appearance and smell (and to some extent taste) to UDCA. All of the remaining placebo-controlled trials gave insufficient description of the placebo; whether the identical placebo tablets have also the same smell and taste could not be understood from the published reports (DALLAS; GÖTEBORG; MILAN; NEWCASTLE; TAIPEI; TOKYO; VILLEJUIF). Therefore, these trials may have compromised the double blind character of the trials.

Six trials out of 16 have met the criteria for being trials with low risk of bias (BARCELONA; FRANKFURT; GÖTEBORG; HELSINKI; MAYO-I; NEWCASTLE); nine trials with high risk of bias (ATHENS; DALLAS; MANCHESTER; MILAN; NEWARK-II; TAIPEI; TOKYO; TORONTO; VILLEJUIF); one trial did not provide enough information about methodological quality (MEXICO CITY).

There was generally a fair description of follow-up and withdrawals/dropouts. Details are given in the 'Characteristics of included studies'. However, only eight trials stated that they used the intention-to-treat method in the evaluation of their data (ATHENS; BARCELONA; DALLAS; HELSINKI; NEWCASTLE; TAIPEI; TORONTO; VILLEJUIF).

Effects of interventions

Mortality

Combining the results of 14 trials with data on mortality demonstrated no significant effects of UDCA on mortality (RR 0.97, 95% confidence interval (CI) 0.67 to 1.42). In the UDCA group, 45/699 (6.4%) patients died versus 46/692 (6.6%) patients in the control group. The moment-based estimate of between trials variance is 0.042.

To take the missing data into account, we used the uncertainty method to estimate the UDCA effect on mortality (Gamble 2005). The result was consistent with the main finding above (OR 1.03, 95% CI 0.80 to 1.33). The Bayesian meta-analysis results (median OR 0.89, 95% credibility interval (CrI) 0.50 to 1.49) also supported the main analysis presented as OR with 95% CI (OR

0.97, 95% CI 0.62 to 1.51). When adjusted for underlying risks the median OR was 0.82 and 95% CrI was from 0.43 to 1.51.

In a meta-regression model, risk of bias of the trials, UDCA dose, trial duration, and severity of primary biliary cirrhosis at entry were included as covariates and the effects of UDCA on mortality as a dependent variable. The model identified trial duration and severity of primary biliary cirrhosis as two covariates, which might have associations with the effects of UDCA (Table 2). These associations indicated that the longer the duration of therapy the less effect (if any), and the more disease activity the more effect (if any). The moment-based estimate of between-trial variance changed from 0.042 to 0. Bayesian meta-regression was also used for sensitivity analysis to estimate the influence of the trial duration and disease severity on UDCA effect (see Table 3).

Analysis of data from the extended follow-up during UDCA→UDCA versus placebo→UDCA into the analyses demonstrated a RR of 0.97 with 95% CI 0.73 to 1.30. It compared 76 deaths in 699 patients (10.9%) originally randomised to UDCA with 78 deaths in 692 patients (11.3%) originally randomised to placebo or no intervention.

Mortality or liver transplantation

Combining the results of 15 trials with data on mortality or liver transplantation, demonstrated no significant effects on mortality or liver transplantation; nether UDCA nor placebo was favoured (RR 0.92, 95% CI 0.71 to 1.21). In the UDCA group, 83/713 (11.6%) patients died or were transplanted versus 89/706 (12.6%) patients in the control group.

Taking missing data into consideration, UDCA effect on the composite outcome was estimated as OR 0.89 with 95% CI 0.64 to 1.25. The Bayesian analysis (median OR 0.84, 95% CrI 0.53 to 1.30) supported the main analysis presented as OR with 95% CI (OR 0.90, 95% CI 0.65 to 1.26). When adjusted for underlying risks, the median OR is 0.77 with 95% CrI from 0.43 to 1.37.

In the classical meta-regression model and Bayesian meta-regression, no covariate seems to be significantly associated with the effect of UDCA on this outcome (see Table 4). Including data from the extended follow-up for UDCA→UDCA versus placebo/no intervention→UDCA demonstrated a RR of 0.86 with 95% CI from 0.71 to 1.03. It compared 146 deaths or liver transplantations in 713 patients (20.5%) originally randomised to UDCA with 169 deaths or liver transplantations in 706 patients (23.9%) originally randomised to placebo or no intervention.

Liver transplantation

Combining the results of the 14 trials, which provided data on liver transplantation, demonstrated no significant effects on liver transplantation favouring UDCA (RR 0.82, 95% CI 0.53 to 1.26). In the UDCA group 34/699 (5.0%) patients had liver transplantation versus 41/692 (5.9%) patients in the control group.

Including data from the extended follow-up during UDCA→UDCA versus placebo/no intervention→UDCA (now comprising 66 liver transplantations in 699 patients (9.4%) originally randomised to UDCA versus 89 deaths or liver transplantations in 692 patients (12.9%) originally randomised to placebo/no intervention) demonstrated an RR of 0.74 with 95% CI from 0.55 to 0.99 (Comparison 04-03).

Pruritus, fatigue, jaundice, and other clinical symptoms

UDCA did not significantly influence either the number of patients with pruritus (RR 0.97, 95% CI 0.78 to 1.19, 5 trials) or the pruritus score (WMD -0.20, 95% CI -0.44 to 0.05, 3 trials). Fatigue was not significantly improved by UDCA (RR 0.90, 95% CI 0.76 to 1.06, 3 trials). Two trials in which the number of patients with jaundice was reported led to a significant effect of UDCA (RR 0.35, 95% CI 0.14 to 0.90). In most trials information on autoimmune conditions was sparse. However, the MAYO-I trial evaluated the autoimmune conditions during UDCA and placebo period and did not find any significant effect of UDCA on associated sicca syndrome, Raynaud's phenomenon, arthritis, or Hashimoto's thyroiditis - neither on disappearance of conditions present at entry nor acquisition of new conditions.

Neither portal pressure (WMD 0.8 mmHg; 95% CI -2.2 to 3.8 mmHg, 1 trial), varices (RR 0.59, 95% CI 0.29 to 1.17, 3 trials), bleeding varices (RR 0.55, 95% CI 0.21 to 1.41, 4 trials) nor hepatic encephalopathy (RR 0.39, 95% CI 0.06 to 2.56, 2 trials) were significantly affected by UDCA treatment. The number of patients developing ascites was significantly lower in the UDCA group compared with the control group (RR 0.42, 95% CI 0.19 to 0.93, 4 trials).

Liver biochemistry

UDCA intervention led to a significant improvement in:

s-bilirubin WMD (95% CI) -10.3 µmol/l (15.5 to -5.1); P < 0.001, 6 trials - corresponding to a decrease compared to the control group of about 25%;

s-alkaline phosphatases WMD (95% CI Random) 359.1 international units (IU)/l (-525.1 to -193.1); P < 0.001, 6 trials - corresponding to a decrease of about 40%;

s-gamma-glutamyl transpeptidase WMD (95% CI) -257.8 IU/l (-318.3 to -197.4); P < 0.001, 4 trials - corresponding to a decrease of about 50%;

s-aspartate aminotransferase WMD (95% CI Random) -35.5 IU/L (-53.1 to -17.8); P < 0.001, 5 trials - corresponding to a decrease of about 33%;

s-alanine aminotransferase (WMD (95% CI Random) -47.7 IU/l (-76.9 to -18.4); P < 0.001, 5 trials - corresponding to a decrease of about 35%,

s-total cholesterol WMD (95% CI) -0.5 mmol/l (-0.8 to -0.2); P < 0.001, 5 trials - corresponding to a decrease of about 8%; and

plasma immunoglobulin M WMD (95% CI) -1.3 g/l (-1.9 to -0.6); P < 0.001, 4 trials - corresponding to a decrease of about 24%.

Only one trial reported s-albumin concentrations (MILAN) and one on prothrombin index (VILLEJUIF). These variables were not significantly affected by UDCA intervention.

Liver histology

There were no significant effects of UDCA on histological stage

(RR 0.78, 95% CI 0.57 to 1.06, random, 5 trials), fibrosis (RR 0.88, 95% CI 0.57 to 1.38, 1 trial), or florid duct lesions (RR 0.84, 95% CI 0.40 to 1.76, 1 trial). About half of the patients in the BARCELONA trial observed statistically significant improvements in histological stage, portal inflammation, and piecemeal necrosis in the UDCA group, but not regarding ductular proliferation or cholestasis. The placebo group had significantly fewer bile ducts per portal tract.

Quality of life

None of the trials examined specific quality-of-life scales. Two trials (NEWCASTLE; GÖTEBORG) evaluated symptoms using visual analogue scales. None of these showed any significant difference between the UDCA group and placebo group. However, significantly ($P < 0.01$) more patients felt better or much better following UDCA intervention than after placebo in the GÖTEBORG trial.

Adverse events

Only the MILAN trial reported one serious adverse event. Other trials reported non-serious adverse events. It seems that using UDCA led to a higher incidence of adverse events (OR 1.32, 95% CI 1.05 to 1.65, 11 trials) comparing to placebo or no intervention, mainly weight gain.

Publication bias and other biases

Neither the Egger's nor the Begg's graphs and their corresponding tests on mortality provided evidence for asymmetry (Egger's test, $P = 0.47$; Begg's test, $P = 0.83$)

DISCUSSION

This review included 16 randomised clinical trials assessing the effects of UDCA against placebo or no intervention for patients with primary biliary cirrhosis. With the inclusion of updated data from 2001 to January 2007, the present systematic review did not demonstrate any benefit of UDCA on mortality and mortality or liver transplantation. Thus, it supports and extends the main findings of Goulis et al meta-analyses (Goulis 1999) and our previous Cochrane review (Gluud 2001 b). Moreover, the potential effects of UDCA on mortality seem to be associated with trial duration and disease severity: the longer the trial duration, the less effects of UDCA may be found (if any); the more severely the patients are affected, the more effects of UDCA (if any). These findings are in direct contrast to the common claim that UDCA ought to be started early in less diseased patients in order to show its 'full effect' (Kaplan 2005). There have been no new data on liver biochemistry and clinical symptoms since 2001, and we confirm a reduction in liver biochemistry, jaundice, and ascites following UDCA intervention. However, these results are based on few trials with sparse data. Therefore, trial selection bias and outcome reporting bias should be considered. UDCA is generally well tolerated in patients with primary biliary cirrhosis.

There was no statistical signs of publication bias and other bias. However, this review pooled data (mortality or liver transplantation) from 15 trials involving 1447 patients. It is a low number of patients (Ioannidis 2001). The median length of trial duration was 24 months. This is not sufficiently long considering that the estimated median survival of a patient with primary biliary cirrhosis is 10 to 15 years (Prince 2002). Therefore, it is difficult to detect a significant difference on mortality based on the trials, most of which are under-powered. Furthermore, over half of the trials had high risk of bias in terms of methodological quality. Generally, high-risk trials overestimate intervention effects (Schulz 1995; Moher 1998; Kjaergard 2001). If the same overestimation is valid for the present sample of trials, the prospects for UDCA in primary biliary cirrhosis may even look worse.

This systematic review did not demonstrate a benefit of UDCA on our predefined primary outcomes: mortality and mortality or liver transplantation, neither in the period during which patients were treated with UDCA or placebo/no intervention nor during the later period in which all the patients were treated with open label UDCA. This observation is in contrast to some previous attempts to aggregate data from studies assessing UDCA interventions for primary biliary cirrhosis (Simko 1994; Poupon 1997; Poupon 2000). However, Simko et al (Simko 1994) included non-randomised studies in their meta-analysis that are more liable to bias. Poupon et al (Poupon 1997; Poupon 2000) only included 3 and 5 out of the 16 randomised clinical trials in their meta-analyses, respectively. Such meta-analyses largely run the risk of trial selection bias (Gluud 2001 a).

Our main findings using classical meta-analytic approach are consistent with the results using Bayesian approaches. In our review, the 95% Bayesian CrIs for both mortality and mortality or liver transplantation cover 1.0, indicating absence of significant intervention effect. Therefore, it strengthens the robustness of our main findings.

We used Bayesian approach to make predictive statements, conditional on the evidence from the 14 trials which provided mortality data. UDCA effects on mortality in a new trial has been predicted as OR 0.89 with 95% CrI from 0.27 to 2.69, meaning that UDCA may decrease or increase the risk of mortality in a new trial with 'average' size of the 14 trials. Given the evidence from the 15 trials, UDCA effects on mortality or liver transplantation in a new trial has also been predicted: OR 0.84 with 95% CrI from 0.29 to 2.42, meaning that UDCA may decrease or increase the risk of mortality or liver transplantation in a new trial with 'average' size of the 15 trials.

A common criticism about meta-analyses is that they combine information from trials with very different patient characteristics and designs. Therefore, it is justified to estimate the 'true' UDCA effect after adjusting for important trial-level covariates. One important trial-level covariate is 'underlying risk', ie, the average risk

of an event (eg, mortality) for a patient at randomisation. The 'true' UDCA effect on mortality after adjusting the different underlying risks, by using Bayesian approach, is estimated as median OR 0.82 with 95% CrI 0.43 to 1.51, and the 'true' UDCA effect on mortality or liver transplantation is estimated as median OR 0.77 with 95% CrI 0.43 to 1.37. These results, taking underlying risk into consideration, support our unadjusted main meta-analysis.

We also considered other important and pre-defined trial-level covariates, including trial risk of bias, UDCA dose, trial duration, and severity of primary biliary cirrhosis. The classical meta-regression model showed that UDCA effect on mortality may be associated with trial duration and patients' disease severity at entry: the longer the trial, the less effects of UDCA (if any); the more severe primary biliary cirrhosis, the more effects of UDCA (if any). The moment-based estimate of between-trial variance is zero when the covariates are included, a change from 0.042 when no covariates are included. So the heterogeneity across the included trials seems largely explained by these two characteristics. The relationship between UDCA effect and trial duration is also supported by Bayesian meta-regression, which included 'trial duration' as covariate.

The previous Lancet meta-analysis (Goulis 1999) and our Cochrane systematic review (Gluud 2001 b) were mainly criticised for including many trials of only two-year duration and with very heterogeneous lengths of follow-up (Talwalker 2003; Kaplan 2005). Given the updated evidence from randomised clinical trials and analyses on longer follow-up data, the main finding in our present review does not seem to support long-term UDCA intervention, which was suggested in observational studies (Rust 2005; Pares 2006). Furthermore, estimation of UDCA's effect on mortality by Bayesian meta-analyses, adjusting for different length of trial duration and the above-mentioned underlying risk (OR 0.71, 95% CrI 0.39 to 1.29), has been consistent with the estimation from unadjusted pooled results (OR 0.89, 95% CrI 0.50 to 1.49). Thus, neither of the results suggests any benefit of UDCA on mortality, even when assuming that the trials have the same duration and underlying risk.

The relationship between UDCA effect and patients' severity of primary biliary cirrhosis was indicated in the classical meta-regression, meaning that UDCA's effect on mortality (if any) is more likely to be observed in patients with more severe primary biliary cirrhosis. This indication is supported by an analysis combining the raw data of three large clinical trials, in which the survival benefit of UDCA was observed in patients with moderate-to-severe disease, but not in those with mild disease (Poupon 1997). However, this relationship was not supported by our Bayesian meta-regression, which included 'severity' as covariate. Therefore, whether the UDCA intervention effect (if any) is related to the severity of primary biliary cirrhosis or not should be further investigated. Despite the uncertainty, the UDCA effect adjusting for the primary biliary cirrhosis severity and the above-mentioned underlying risk (OR 0.80, 95% CrI 0.43 to 1.46) has been consistent with the unadjusted pooled results (OR 0.89, 95% CrI 0.50 to 1.49). Thus, neither of the results suggested any benefit of UDCA on mortality, even when assuming that the trials have the same percentage of advanced patients and same level of underlying risk of death at randomisation.

We observed a marginally significant effect of UDCA on liver transplantation only in the later period in which all the patients were treated with open label UDCA, but not in the original period in which patients were treated with UDCA or placebo/no intervention. The decision of whether and when to perform liver transplantation is influenced by many factors: the attitude of the patient, the attitude of the physician, the time of referral, the length of the waiting list, etc. Therefore, liver transplantation is an imprecise measure of the stage of progression of the disease and thus most likely a biased outcome. The fact that liver biochemical outcomes improved in the UDCA group compared to the placebo treated may lead to the observation of fewer liver transplants in the UDCA group. For example, s-bilirubin is one of the prognostic indices used for patients with primary biliary cirrhosis (Pasha 1997). A lower s-bilirubin will provide the clinicians with less impetus to transplant. Second, the referrals for liver transplantation occurred mainly after the blinding in randomised clinical trials had been removed. Unblinded comparisons may exaggerate intervention efficacy significantly (Schulz 1995; Kjaergard 2001). Therefore, whether UDCA decreases the risk of liver transplantation should be confirmed in future research.

We noticed that the number of patients with ascites was significantly less in the UDCA group than in the placebo group. This observation originates from only four trials, and one may fear risk of publication bias and other bias. This observation could also be due to a play of chance, considering that many comparisons have been made without correction of the significance level. Furthermore, the diagnosis of ascites was clinically based; hence more susceptible to bias. Moreover, in our review, UDCA has not been found to decrease portal pressure and s-albumin, which are important in the pathogenesis of ascites. Therefore, our observation needs to be further investigated.

It is interesting to know if UDCA could slow the histological progression. We were not able to identify any convincible benefits of UDCA on histology. The possibility that UDCA may still delay progression from early stage disease to late stage disease and then ultimately prolong survival cannot be proven or disproved with the trials completed. Only one trial found significant effects on liver histology (BARCELONA). It observed positive effects on a number of histological variables, eg, the histological stage. This finding may also be a spurious one. Only about half of the randomised patients had a follow-up liver biopsy. Furthermore, as the trial showed a trend towards a higher mortality and liver transplantation rate in the UDCA group, this could have led to removal

of some of the more seriously affected livers from the UDCA group, probably making those having a biopsy look relatively less affected. Such subgroup results should be interpreted cautiously (Yusuf 1991; Oxman 1992; Assmann 2000). On the other hand, the finding of the BARCELONA trial is interesting and should stimulate more clinical research into the effect of UDCA on progression of fibrosis in primary biliary cirrhosis and eventually cirrhosis development.

UDCA was generally well tolerated. We observed that UDCA was associated with non-serious adverse events, mostly weight gain. This finding ensued from new data from the MAYO-I trial. However, it is at present unclear if this weight gain should be considered a beneficial or a harmful effect and it needs further study. The effect ought to be mentioned to the patient before considering starting UDCA. Other non-serious adverse events included mild gastrointestinal disorders like diarrhoea, nausea, vomiting, etc.

It has been claimed that UDCA is a cost-effective therapy for primary biliary cirrhosis (Pasha 1999). However, this claim rests on extrapolation from the results of two selected randomised clinical trials (MAYO-I; TORONTO). It is evident that cost-effectiveness analyses ought to be performed on the basis of all available high-quality evidence and not just on the selected. Considering the annual cost of UDCA of about $2500 (Pasha 1999) and the findings of the present review, we challenge the conclusion drawn by Pasha et al that UDCA is cost-effective for primary biliary cirrhosis.

In consistency with previous meta-analyses and reviews (Goulis 1999; Gluud 2001 b), this updated systematic review did not demonstrate any benefit of UDCA on mortality and mortality or liver transplantation in patients with primary biliary cirrhosis. On the other hand, UDCA improved biochemical outcomes. This seems to place clinicians and researchers in a dilemma: if therapeutic decisions are based on clinical outcomes (eg, mortality), there is insufficient evidence to support the use of UDCA in primary biliary cirrhosis, but if based on non-validated 'surrogate' outcomes (eg, s-bilirubin level), there is evidence favouring the UDCA interventions for the disease (Gluud 2007). This dilemma was reflected in a survey regarding the use of UDCA for primary biliary cirrhosis among Danish doctors (Kürstein 2005), who had very different answers to the question why they prescribed UDCA for primary biliary cirrhosis patients. Sixteen per cent of the doctors thought UDCA reduced mortality, twenty-seven per cent thought UDCA reduced morbidity, and twenty-three per cent thought it benefited 'surrogate' outcomes (Kürstein 2005).

Mayo Risk Score Model has identified several prognostic biomarkers for primary biliary cirrhosis, eg, serum bilirubin. These biomarkers may respond to intervention and are predictive of survival. But they do not necessarily predict clinical benefit of the intervention in question because 'a perfect correlation does not a surrogate make' (Baker 2003). In the absence of validated surrogate outcomes in UDCA for primary biliary cirrhosis, confirmatory trials assessing the UDCA effect should only be based on clinical outcomes, eg, survival. We believe that evaluation based on such clinical outcomes based evaluation will benefit patients in the long run (Gluud 2007).

We also realize that the challenge of performing a new trial on intervention for primary biliary cirrhosis is high. The estimated median survival of primary biliary cirrhosis is 10 to 15 years. To spend 15 years planning and carrying out a trial for each new potential treatment of primary biliary cirrhosis would consume many patients' lifetimes, not to mention the expense and difficulty of retaining patients in such a long study (Mayo 2005). Nevertheless, there are at least an estimated one million patients with primary biliary cirrhosis world-wide. Therefore, it is possible to conduct large trials with appropriate statistical power if international groups of primary biliary cirrhosis investigators collaborate. Such large trials do not need to be conducted for more than two to four years.

AUTHORS' CONCLUSIONS

Implications for practice

This updated review confirms and extends previous observations showing no benefit of UDCA on patients' mortality and mortality or liver transplantation. Although based on a small number of trials, UDCA seems to improve liver biochemical variables, including s-bilirubin concentration, jaundice, and ascites. This review does not support long-term use of UDCA. UDCA has few serious adverse events, but it is associated with weight gain.

Implications for research

It is less likely to find any benefit of UDCA on patient's survival in a new trial with the average size of the trials included into this updated review. Integration of international groups of investigation for primary biliary cirrhosis will make large trial sizes feasible. Full validation of potential surrogate outcomes is justified. In the absence of validated surrogate outcome(s), trials assessing UDCA or any new potential treatment for primary biliary cirrhosis, should be mainly based on clinical outcomes, eg, survival. Such trials ought to be reported according to the recommendations of the CONSORT Group (http://www.consort-statement.org).

ACKNOWLEDGEMENTS

The chief acknowledgement goes to the patients who took part in the trials reviewed here and to the researchers who conducted the trials. Dimitrinka Nikolova and Nader Salas are thanked for expert assistance during the preparation of this systematic review. We also

thank the peer-reviewers' comments as well as helpful comments from the contact editors.

Peer Reviewers: V Siersma, Denmark; J Hilden, Denmark.

Contact Editor: R Koretz, USA.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

ATHENS

Methods	Generation of allocation schedule: adequate, random table numbers Allocation concealment: adequate, serially numbered sealed envelopes Blinding: no blinding. Follow-up: no patients lost to follow-up.
Participants	Patients with symptomatic PBC (n = 86) from one centre in Greece. PBC defined as: cholestatic liver disease, positive AMA, liver biopsy compatible with PBC. Exclusion criteria were: asymptomatic PBC, hepatic encephalopathy, sepsis, renal failure, or life-threatening disease
Interventions	Control: no intervention. Experimental: UDCA 12 to 15 mg/kg/day.
Outcomes	Liver decompensation. Mortality or liver transplantation. Symptoms. Liver biochemistry. Liver histology.
Notes	14/43 control patients were crossed-over to UDCA at their own request at a median of 3.5 years (range 2 to 8 years) after entry in the study. The authors did both intention-to-treat analysis and treatment-as-received analysis

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

BARCELONA

Methods	Generation of allocation schedule: adequate. Allocation concealment: serially numbered sealed and opaque envelopes Blinding: placebo - identical in appearance, smell, and taste Follow-up: 10 UDCA treated patients and 21 placebo treated patients discontinued
Participants	Consecutive patients with PBC (compatible liver biopsy, alkaline phosphatase > 2 upper normal limit and positive or negative antimitochondrial antibodies; n = 192) from 16 centres in Spain. Patients with negative antimitochondrial antibodies were accepted if there was no evidence of extrahepatic biliary obstruction
Interventions	Control: placebo. Experimental: UDCA 14 to 16 mg/kg/day in three divided doses

BARCELONA (*Continued*)

Outcomes	Mortality. Liver transplantation. Symptoms. Complications. Liver biochemistry. Liver histology.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

DALLAS

Methods	Generation of allocation schedule: no information provided. Allocation concealment: no data, but randomisation was separate at each of the six centres in four stratification groups, involving serum bilirubin level and liver histology stage Blinding: described as double blind, but placebo only described as 'comparable-appearing' and no mention on smell and taste Follow-up: 2 patients from the UDCA and 3 patients from the placebo groups withdrew from the trial during the placebo controlled period (0 to 2 year)
Participants	Patients with PBC (n = 151) from six USA centres. Entry criteria were: cholestatic liver disease for at least six months, serum alkaline phosphatase > 1.5 times upper normal limit, positive AMA, no biliary obstruction, and liver biopsy compatible with PBC Excluded were: PBC treatment during the last three months, recurrent bleeds from varices, spontaneous encephalopathy, or diuretic-resistant ascites, serum bilirubin > 20 mg/l, pregnancy, age < 19 years, or other liver disease
Interventions	Control: placebo (2 years) and open-label UDCA (4 years) Experimental: UDCA 10 to 12 mg/kg/day once at bedtime (Ciba-Geigy Corporation)
Outcomes	Mortality free of liver transplantation. Liver transplantation. Symptoms. Liver biochemistry. Liver histology. UDCA enrichment in bile.
Notes	Three patients randomised to receive placebo had high bile-UDCA concentrations, suggesting UDCA intake. All patients were offered open label UDCA following completion of the first 2-year of the trial

Risk of bias

DALLAS (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

FRANKFURT

Methods	Generation of allocation schedule: adequate. Allocation concealment: adequate. Blinding: placebo identical in appearance, smell, and taste. Follow-up:
Participants	Patients with PBC (n = 20) from Germany. PBC defined as at least three of the following: alkaline phosphatase > 1.7 times upper normal limit, gamma-glutamyl transferase > 5.0 times upper normal limit, immunoglobulin M > 2.0 times upper normal limit, positive AMA plus no obstruction of the extrahepatic biliary tract Exclusion criteria were: oesophageal varices, pancreatitis, cardiac failure, renal failure, pregnancy, age < 03 years, PBC treatment within the previous four weeks, and alcohol or drug abuse
Interventions	Control: placebo. Experimental: UDCA 10 mg/kg/day, divided into two doses.
Outcomes	Mortality. Symptoms. Liver biochemistry. Liver histology.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

GÖTEBORG

Methods	Generation of allocation schedule: adequate, a randomisation list Allocation concealment: adequate, sealed envelopes (no mention on serial numbering or opaqueness) Patients were stratified into symptomatic/asymptomatic Blinding: described as 'double-blind', and placebo looked identical to UDCA, but details on taste and smell not given Follow-up: 8 patients from the UDCA and 7 patients from the placebo withdrew
Participants	Patients with PBC (n = 116) from six centres in Sweden. PBC defined as: chronic cholestatic liver disease of more than six months' duration with histology typical of or compatible with PBC plus at least two of the following: positive anti-mitochondrial antibodies, alkaline phosphatase > 1.5 times the upper reference value, and/or IgM > 1.5 times the upper reference value during the year preceding the entry into the study

GÖTEBORG (*Continued*)

Interventions	Control: placebo. Experimental: 500 mg UDCA (~7.7 mg/kg/day).
Outcomes	Mortality. Liver transplantation. Symptoms - pruritus, fatigue, ascites, jaundice. Liver biochemistry and bile acids. Histology - portal inflammation, spill-over, interface hepatitis, bile duct proliferation, portal fibrosis. Quality of life.
Notes	At 24 months, 32 of 49 patients allocated to placebo and still remaining in the study were switched to UDCA and 42 of 52 patients allocated to UDCA and still remaining in the study continued with UDCA. Anti-hepatitis C virus tests not performed.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

HELSINKI

Methods	Generation of allocation schedule: adequate, random numbers in blocks of six Allocation concealment: adequate, central. Patients were 'randomly stratified according to bilirubin' to intervention arm Blinding: placebo identical looking and film-coated (considered adequate) Follow-up: 0 patients receiving UDCA and 8 placebo withdrew.
Participants	Patients with PBC (n = 90) from four centres in Finland. PBC defined as: elevated alkaline phosphatase, liver biopsy compatible with PBC, and positive AMA. End-stage PBC and patients treated with drugs that might affect prognosis were excluded
Interventions	Control: placebo. Experimental 1: UDCA 12 to 15 mg/kg/day in two doses. Experimental 2: colchicine 1 mg/day.
Outcomes	Death. Liver transplantation. Symptoms. Liver biochemistry. Liver histology.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**

HELSINKI (*Continued*)

Allocation concealment?	Yes	A - Adequate

MANCHESTER

Methods	Generation of allocation schedule: unclear, no information provided Allocation concealment: unclear. Blinding: 'placebo' employed, but it is not known if it was indeed double blind Follow-up: not described.
Participants	Patients with PBC (n = 28) form UK. Diagnostic criteria (data being sought).
Interventions	Control: placebo. Experimental 1: UDCA 10mg/kg/day. Experimental 2: colchicine 1 mg/day. Experimental 3: UDCA plus colchicine.
Outcomes	Mortality (being sought) Liver transplantation (being sought). Serum aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, bilirubin, and albumin. Serum alkaline phosphatase. Serum procollagen peptide. Galactose elimination capacity. Bromosulfophtalin excretion.
Notes	No exact data on number of patients randomised to each arm. Data on mortality and liver transplantation are not given separately

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	No	C - Inadequate

MAYO-I

Methods	Generation of allocation schedule: adequate, computer. Allocation concealment: considered adequate, patients stratified for centre, histological stage, serum bilirubin, and oesophageal varices using 'a blocked, randomised assignment schedule' Blinding: 'double-blind, and placebo looked and smelled identical to UDCA, but placebo was sweet and UDCA bitter. However, only one patient broke the code Follow-up: five voluntary withdrawals in UDCA arm and 13 voluntary withdrawals in the placebo arm
Participants	Patients with PBC (n = 180) enrolled from four USA centres. However, 162 patients (90%) came from one centre. PBC defined as: chronic cholestatic liver disease for at least six months, a serum alkaline phosphatase level > 1.5 times upper normal limit, antimitochondrial antibody positivity, absence of biliary

MAYO-I (*Continued*)

	obstruction, and liver biopsy compatible with PBC. Excluded were: PBC-drug treatment in preceding 3 months, anticipated need for liver transplantation within one year, recurrent variceal haemorrhage, spontaneous encephalopathy, or diuretic resistant ascites, pregnancy, age less than 18 or more than 70 years, or other co-existent liver disease
Interventions	Control: placebo. Experimental: UDCA at a dose of 13 to 15mg/kg/day in four divided doses
Outcomes	Composite end point consisting of death, transplant, toxicity, and voluntary withdrawal. Death. Liver transplantation. Symptoms. Autoimmune conditions. Liver biochemistry. Liver histology. Adverse events, including weight gain.
Notes	Patients originally receiving placebo switched to UDCA after four years and were followed for an additional eight years

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

MEXICO CITY

Methods	Generation of allocation schedule: no information provided. Allocation of concealment: unclear. Blinding: 'placebo' used. Follow-up:
Participants	Patients with PBC (n = 28) from one centre in Mexico.
Interventions	Control: placebo. Experimental: UDCA (details were not given).
Outcomes	Serum cholesterol.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

MILAN

Methods	Generation of allocation schedule: adequate, patients were randomised by each centre according to a computer generated list Allocation concealment: no data. Blinding: described as double-blind, and placebo was 'identical in appearance', but smell and taste not mentioned Follow-up: 5 patients receiving UDCA and 1 placebo dropped out
Participants	Patients with PBC (n = 88) from seven centres in Italy. PBC defined as: positive AMA and liver biopsy compatible with PBC. If one of these were missing, patients could enter provided they had three of the following: serum alkaline phosphatase > 2.0 times upper normal limit, immunoglobulin M > 280 mg/l, pruritus, serum bilirubin > 2 mg/l, and/or a positive Schyrimer's test plus absence of extrahepatic obstruction
Interventions	Control: placebo. Experimental: UDCA 500 mg daily in two dived doses at mealtime (~8.7 mg/kg/day; range 5.4-11-6 mg/kg/day)
Outcomes	Symptoms. Liver biochemistry. Serum bile acids. Serum cholesterol.
Notes	Patients switched onto UDCA at the end of the trial.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

NEWARK-II

Methods	Generation of allocation schedule: unclear, no information provided Allocation concealment: unclear, no data. Blinding: described as double-blind, but no mention of appearance, smell, and taste Follow-up: no patients withdrew.
Participants	Patients with PBC (n = 19) enrolled from one centre in USA. Inclusion criteria: PBC confirmed by liver biopsy and supporting clinical tests. Exclusion criteria: extrahepatic biliary obstruction
Interventions	Control: placebo. Experimental: UDCA 10 mg/kg/day.
Outcomes	Mortality. Symptoms. Liver biochemistry.
Notes	

NEWARK-II (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

NEWCASTLE

Methods	Generation of allocation schedule: adequate, based on a list of random numbers Allocation concealment: adequate, patients were entered into the trial in pairs according to clinical stratification. Sealed envelopes were kept and opened by the pharmacy once a pair of matching patients were identified indicating 'treatment A' for one patient and 'treatment B' for the other Blinding: placebo 'identical looking', but was neither matched for taste nor smell Follow up:
Participants	Patients with PBC (n = 46) from one centre in UK. PBC defined as: clinically and histologically compatible with PBC, positive AMA, abnormal liver function tests, and no medication within six months of study entry
Interventions	Control: placebo. Experimental: UDCA ~10mg/kg/day (mean actual dose (+/-SD): 11.4+/-0.9 mg/kg/day
Outcomes	Mortality. Liver transplantation. Symptoms. Liver biochemistry. Liver histology. Quality of life.
Notes	

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

TAIPEI

Methods	Generation of allocation schedule: adequate, table of random numbers Allocation concealment: unclear, no data. Blinding: described as double-blind, and placebo and UDCA were identical looking, but no data on smell and taste Follow-up: no patients withdrew.

TAIPEI (*Continued*)

Participants	Patients with PBC (n = 12) from one centre in Taiwan. PBC defined as: elevated serum alkaline phosphatase and gamma-glutamyl transferase with lack of large bile duct abnormalities, positive AMA, with elevated immunoglobulin M, G or A, and liver biopsy compatible with PBC. Exclusion criteria were: previous PBC treatment
Interventions	Control: placebo. Experimental 1: UDCA 12-15 mg/kg/day in two doses. Experimental 2: colchicine 1 mg/day.
Outcomes	Mortality. Symptoms. Liver biochemistry.
Notes	All patients switched to UDCA on completion of the six months cross-over trial

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

TOKYO

Methods	Generation of allocation schedule: unclear, no data. Allocation concealment: adequate, allocation by a single monitor according to a randomisation scheme (1:1) Blinding: UDCA and placebo with identical appearance (size and colour), but taste and smell not mentioned Follow-up: 4 patients receiving UDCA and 3 placebo dropped out
Participants	Patients with PBC (n = 49) from 13 departments in Japan. PBC was diagnosed clinically and histologically. Patients with severe symptoms or having received other medications for their PBC within the last three months were excluded. Placebo female/male: 20/4. UDCA female/male: 24/1.
Interventions	Control: placebo. Experimental: UDCA
Outcomes	Symptoms (itching). Complications (oesophageal varices). Liver biochemistry. Serum cholesterol. Serum bile acids.
Notes	

Risk of bias

TOKYO (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

TORONTO

Methods	Generation of allocation schedule: unclear, no data. Concealment of allocation: adequate, separately at each centre by the study pharmacist stratified for symptomatic/asymptomatic Blinding: described as double-blind, and the placebo tablets were identical and 'equally bitter tasting', this was confirmed by the research coordinator Follow-up: 13 patients receiving UDCA and 19 placebo withdrew
Participants	Of 408 patients assessed, 222 patients with PBC were randomised (1:1) during a 26 months period. Inclusion criteria were: positive AMA, serum alkaline phosphatase > 1.0 times upper normal limit, liver biopsy compatible with PBC, and age > 18 years Patients were excluded if they were on liver transplant list, needed to take enzyme-inducing drugs, were pregnant, or had a severe coexisting condition that was likely to affect survival within five years of study entry
Interventions	Control: placebo. Experimental: UDCA 14mg/kg/day swallowed with the evening meal
Outcomes	Mortality. Liver transplantation. Symptoms - pruritus, fatigue. Liver biochemistry and bile acids. Histology.
Notes	Patients offered UDCA at the end of the trial.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

VILLEJUIF

Methods	Generation of allocation schedule: unclear, no information provided Allocation concealment: adequate, patients were randomised by each centre in blocks of four to drug package containing UDCA or placebo capsules Blinding: described as double-blind, and placebo was 'identical in appearance', but smell and taste are not mentioned. Placebo was made of starch and lactose Follow-up: 5 patients receiving UDCA and 6 placebo withdrew.
Participants	Patients with PBC (n = 146) from 22 centres in France and Canada. PBC defined as: liver biopsy compatible with PBC, serum alkaline phosphatase > 2.0 upper normal limit, and positive AMA. Exclusion criteria were: PBC treatment within last six months, serum bilirubin > 150 µmol/l, serum albumin < 25 g/l, past or active bleeding oesophageal varices, extrahepatic obstruction, excessive alcohol consumption, or positive hepatitis B surface antigen
Interventions	Control: placebo. Experimental: UDCA 13 to 15 mg/kg/day.
Outcomes	Mortality. Liver transplantation. Symptoms. Liver biochemistry. Liver histology.
Notes	All patients treated for two years with placebo were offered UDCA and further followed-up for another two years together with patients continuing on UDCA One patient, included in the publications of the study up to 1993, was excluded from the 1994 publication due to a raised serum bilirubin at entry, which violated the entry criteria

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

PBC = primary biliary cirrhosis.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Angulo 1999	This is not a randomised trial, but a comparison of liver histology of 16 UDCA treated patients from one randomised trial to the liver histology of 51 patients from another randomised trial
Angulo 1999 a	There is no placebo or no intervention group in this randomised trial, which compares low- (5-7 mg/kg/day), standard- (13-15 mg/kg/day), and high- (23-25 mg/kg/day) doses of UDCA in 155 patients with

(*Continued*)

	PBC. The improvements in alkaline phosphatase, aspartate aminotransferase, Mayo risk score, and biliary UDCA enrichment were significantly greater in the standard- and high-dose groups compared to the low-dose group, but not between the standard- and high-dose group. No significant effects were noted on symptoms with any dose
Bateson 1998	This is a case series of 40 PBC patients with symptomatic disease treated with UDCA. The results were compared to 12 historic UDCA-untreated PBC patients
Brodanova 1997	This is a case series of 13 PBC patients treated with UDCA.
Cauch-Dudek 1998	This is a case series of 88 patients with PBC evaluating fatigue. A self rated fatigue. Severity score did not correlate with UDCA use
Crippa 1995	The study is not randomised, but compares 18 UDCA treated PBC patients to eight untreated PBC patients
Crosignani 1996	This is a dose-response study examining the effects of three doses of tauro-UDCA in 24 patients with PBC
Eisenburg 1988	This is a case series of 21 PBC patients during UDCA administration
Ferri 1993	This is a controlled comparison of UDCA with tauro-UDCA for PBC
Grippa 1995	This is a non-randomised study comparing 18 UDCA treated PBC patients to eight UDCA-untreated PBC patients
Ideo 1990	Out of three PBC patients treated with UDCA (600 mg/day), UDCA was stopped in one of these patiens 'randomly selected'
Ikeda 1996	This is a randomised trial comparing UDCA plus colchicine versus UDCA alone in 22 patients with PBC
Kehagioglou 1991	The study is not described as randomised, but compares 16 PBC patients treated with UDCA (14 mg/kg/day for a mean period of 22 months (range 3 months to 35 months) to a control group consisting of 10 PBC patients treated with placebo
Kim 1997	This is a case series of eight UDCA-treated PBC patiens who lacked antimitochondrial antibodies
Kneppelhout 1992	This is a case series of 19 patients with PBC during UDCA administration
Krzeski 1999	This is a case series of 60 PBC patients treated with UDCA.
Larghi 1997	This is a randomised trial with crossover design comparing UDCA versus tauro-UDCA
Leuschner 1996	This randomised trial compared UDCA plus prednisolone versus UDCA plus placebo for PBC
LONDON 1998	This trial compared placebo to different doses of URSO (300 mg/day, 600 mg/day, 900 mg/day and 1200 mg/day) in 23 biopsy proven early stage PBC patients. There is no mention of randomisation. Patients were followed for eight weeks with a four week washout period between doses. A significant trend toward normalising of abnormal liver function tests was observed together with a significant increase in lethargy, irrespective of UDCA dose, compared to placebo

(*Continued*)

Lotterer 1990	This is a case series of seven PBC patients during UDCA administration
Matsuzaka 1994	This is a case series of three PBC patients during UDCA administration
Matsuzaki 1990	This is a case series of ten PBC patients during UDCA administration
MAYO-II 1997	This trial randomised 150 PBC patients to three doses of UDCA (5-7 mg/kg/day; 13-15 mg/kg/day; 22-25 mg/kg/day) and followed the patients for one year. No differences were observed between the medium and the high dose with respect to liver biochemistry changes, but both these dose groups had significantly greater improvement of liver biochemistry compared to the low dose group. Clinical events such as death, transplantation, or complications of liver disease were rare and were not different between the three dose groups
NEWARK-I	The study is not randomised. The study included only four patients with PBC and apparently these were treated first with placebo for three months and then with UDCA (10-15 mg/kg/day) for three-six months. No major outcome variables are reported
NEWARK-III	This study investigated biochemical features, including biliary bile acids, in 14 patients with PBC using a paired design. First, all patients received placebo for three months. Then, the patients were treated with 900 mg UDCA (10-12 mg/kg/day) for six months (n = 11) to 12 months (n = 8). The latter patients were then treated with placebo for three months and restarted on UDCA for another 12 months. Due to the paired design, the observed improvements may be due to the fluctuating course of PBC
Ogino 1993	This is a case series of 28 PBC patients treated with UDCA and compared to seven PBC patiens not treated with UDCA
Okuyama 1988	This is a study of a single PBC patient during UDCA administration
Osuga 1989	This is a case series of eight PBC patients during UDCA administration
Peridigoto 1992	This is a study of three PBC patiens during UDCA administration
Podda 1989	This is a randomised trial examining three doses of UDCA in PBC patients and patients with primary sclerosing cholangitis and chronic hepatitis
Poupon 1987	This is a case series of 15 PBC patients during UDCA administration
Poupon 1989	This study is not randomised.
Poupon 1996	This is a randomised trial comparing UDCA plus colchicine versus UDCA in 74 patients with PBC
Schonfeld 1997	This is a case series of 15 PBC patients during UDCA administration
Shibata 1992	This is a case series of 12 PBC patients during UDCA administration
Stiehl 1990	This is a case series of 29 patients with PBC during UDCA administration

(*Continued*)

Taha 1994	This is a case series of patients with PBC during different drug administrations (cholestyramine, wash out, UDCA, and UDCA plus cholestyramine)
Takezaki 1991	This is a study of a single PBC patient during UDCA administration
Toda 1998	No placebo or no intervention group are included. The trial compares the efficacy of three doses of UDCA (150 mg/day; 600 mg/day; 900 mg/day) in 82 PBC patients for 24 months
Unoura 1990	Not a randomised trial, but compares 16 UDCA treated PBC-patients to eight patients without UDCA treatment
Van de Meeberg 1996	No placebo or no intervention group. Five patients treated 'in random order' with 10 mg UDCA/kg/day in either a single or in three divided doses - no difference in liver biochemistry improvement
Van Hoogstraten 1998	This RCT compares 10 versus 20 mg UDCA/kg/day during six months in 61 PBC patients. Liver biochemistry improved in PBC patients receiving 20 mg/kg/day compared to a dose of 10 mg/kg/day
Verma 1999	This cross-over RCT compares different doses of UDCA in twenty-four biopsy-proven early-stage PBC patients (one male, 23 female) who received five doses of UDCA (0, 300, 600, 900, 1200 mg/day) each for eight weeks with four-week washout periods between doses. Symptoms (pruritus, fatigue, diarrhoea) were assessed on a four-point scale (none, mild, moderate, severe). Liver function tests were performed using conventional methods, and serum bile acids were measured using gas liquid chromatography. The dose of 900 mg/day produced the greatest enrichment of UDCA in serum bile acids, although there was no difference in the enrichment of UDCA between the different doses. There was a trend towards normalization of the abnormal LFTs in a dose-dependent manner (for y-glutamyl transferase (yGT), alkaline phosphatase (ALP) , alanine transaminase (ALT) and IgM). Multi-factorial analysis showed that UDCA treatment, irrespective of dose, was significantly better than placebo for all the variables. The 900 mg and 1200 mg doses were better than both 300 mg and 600 mg using gamma-glutamyltranspeptidase and total bilirubin as variables, better than 300 mg using alkaline phosphatase and IgM as variables, and better than 600 mg using albumin as a variable. No variables showed a significant difference between 900 and 1200 mg. The study concluded that the optimum dose of UDCA is 900 mg/day (equivalent to 13.5 mg/kg/day). This trial is excluded due to the cross-over design and due to the fact that it did not provide any data on the primary outcome variables
Wirth 1994	This is a case series of 14 patients with PBC examined before and during UDCA administration
Wirth 1995	This is a case series of 22 patients with PBC, who have their subtypes of antimitochondrial antibodies examined and related to response to UDCA administration
Wolfhagen 1994	No randomisation, combination therapy with UDCA and prednisone in seven patients
Yamazaki 1992	This is a study of a single PBC patient with eosinophilic infiltration
Yamazaki 1996	This is a case series of 38 PBC patients, of which 55 per cent exhibited eosinophilia. The eosinophilia was reduced during UDCA treatment

(*Continued*)

Yokomori 1996	This is a study of a single patient with PBC and pruritus responding to treatment with UDCA and cholestyramine

PBC = primary biliary cirrhosis.
UDCA = ursodeoxycholic acid.

DATA AND ANALYSES

Comparison 1. UDCA versus placebo or no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	14	1391	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.67, 1.42]
2 Mortality or liver transplantation	15	1419	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.71, 1.21]
3 Liver transplantation	14	1391	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.53, 1.26]
4 Pruritus	5	438	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.78, 1.19]
5 Pruitus score	3	271	Std. Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.45, 0.03]
6 Fatigue	3	373	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.76, 1.06]
7 Jaundice	2	198	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.14, 0.90]
8 Portal pressure	1	30	Mean Difference (IV, Fixed, 95% CI)	0.80 [-2.18, 3.78]
9 Development of varices	3	318	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.29, 1.17]
10 Bleeding varices	4	451	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.21, 1.41]
11 Hepatic encephalopathy	2	302	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.06, 2.56]
12 Ascites	4	500	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.19, 0.93]
13 Variceal bleeding, ascites, and/or encephalopathy	1	56	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.37, 4.17]
14 S-bilirubin (µmol/l) - about six months	6	674	Mean Difference (IV, Fixed, 95% CI)	-10.30 [-15.48, -5.13]
15 S-alkaline phosphatase (IU/l) - about six months	6	595	Mean Difference (IV, Random, 95% CI)	-359.08 [-525.05, -193.11]
16 S-gamma-glutamyl transpeptidase (IU/l) - about six months	4	395	Mean Difference (IV, Fixed, 95% CI)	-257.82 [-318.28, -197.36]
17 S-aspartate aminotransferase (IU/l) - about six months	5	575	Mean Difference (IV, Random, 95% CI)	-35.45 [-53.08, -17.81]
18 S-alanine aminotransferase (IU/l) - about six months	5	325	Mean Difference (IV, Random, 95% CI)	-47.66 [-76.90, -18.42]
19 S-albumin (g/l) - about six months	2	280	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.14, 0.33]
20 S-cholesterol (total) (mmol/l) - about six months	5	461	Mean Difference (IV, Fixed, 95% CI)	-0.54 [-0.85, -0.24]
21 Plasma immunoglobulin M (g/l) - about six months	4	446	Mean Difference (IV, Fixed, 95% CI)	-1.25 [-1.85, -0.64]
22 Prothrombin index	2	338	Mean Difference (IV, Fixed, 95% CI)	1.18 [-1.15, 3.50]
23 Liver biopsy findings - dichotomous variables	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
23.1 Worsening of histological stage	5	351	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.57, 1.06]
23.2 Worsening of fibrosis	1	139	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.57, 1.38]
23.3 Florid duct lesion	1	115	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.40, 1.76]
24 Liver biopsy findings - continuous variables	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
24.1 Histological stage	1	84	Mean Difference (IV, Fixed, 95% CI)	-0.54 [-0.91, -0.17]
24.2 Portal inflammation	1	84	Mean Difference (IV, Fixed, 95% CI)	-0.57 [-0.95, -0.19]

24.3 Piecemeal necrosis	1	84	Mean Difference (IV, Fixed, 95% CI)	-0.56 [-0.98, -0.14]
24.4 Lobular necrosis	1	84	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-0.66, 0.06]
24.5 Ductular proliferation	1	489	Mean Difference (IV, Fixed, 95% CI)	-0.23 [-0.46, -0.00]
24.6 Cholestasis	1	84	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.28, 0.12]
25 Liver biopsy findings - continuous variables	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
25.1 Bile duct/portal tract	1	84	Mean Difference (IV, Fixed, 95% CI)	0.23 [0.10, 0.36]

Comparison 2. Adverse events - UDCA versus placebo or no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serious adverse events	10	990	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 71.70]
2 Non-serious adverse events	11	1149	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [1.05, 1.65]

Comparison 3. Influence of missing data - UDCA versus placebo or no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality - completed patient's course plus case scenarios	14		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Completed patient's course analysis	14	1247	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.66, 1.43]
1.2 Assuming bad outcome	14	1391	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.61, 1.09]
1.3 Assuming good outcome	14	1391	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.69, 1.49]
1.4 Extreme case scenario favouring UDCA	14	1391	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.17, 0.56]
1.5 Extreme case scenario favouring control	14	1391	Risk Ratio (M-H, Random, 95% CI)	2.08 [1.36, 3.19]
2 Mortality or liver transplantation - completed patient's course plus case scenarios	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Completed patient's course analysis	15	1275	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.69, 1.24]
2.2 Assuming bad outcome	15	1419	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.67, 1.14]
2.3 Assuming good outcome	15	1419	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.75, 1.29]
2.4 Extreme case scenario favouring UDCA	15	1419	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.30, 0.74]
2.5 Extreme case scenario favouring control	15	1419	Risk Ratio (M-H, Random, 95% CI)	1.58 [1.17, 2.11]
3 Mortality - uncertain interval	14		Odds ratio (Fixed, 95% CI)	1.03 [0.80, 1.33]
4 Mortality or liver transplantation - uncertain interval	15		Odds ratio (Fixed, 95% CI)	0.89 [0.64, 1.25]

Comparison 4. UDCA-UDCA versus placebo/no intervention-UDCA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	14	1391	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.73, 1.30]
2 Mortality or liver transplantation	15	1419	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.71, 1.03]
3 Liver transplantation	14	1391	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.55, 0.99]

Analysis 1.1. Comparison 1 UDCA versus placebo or no intervention, Outcome 1 Mortality.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

Comparison: 1 UDCA versus placebo or no intervention

Outcome: 1 Mortality

Study or subgroup	UDCA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
ATHENS	17/43	14/43		30.1 %	1.21 [0.69, 2.14]
BARCELONA	10/99	4/93		8.9 %	2.35 [0.76, 7.23]
DALLAS	4/77	3/74		6.6 %	1.28 [0.30, 5.53]
FRANKFURT	0/10	0/10			Not estimable
GÖTEBORG	1/60	1/56		2.2 %	0.93 [0.06, 14.57]
HELSINKI	0/30	2/31		5.3 %	0.21 [0.01, 4.13]
MAYO-I	4/89	7/91		14.9 %	0.58 [0.18, 1.93]
MILAN	0/44	0/44			Not estimable
NEWARK-II	0/9	0/10			Not estimable
NEWCASTLE	1/22	3/24		6.2 %	0.36 [0.04, 3.24]
TAIPEI	0/6	0/6			Not estimable
TOKYO	0/26	0/26			Not estimable
TORONTO	5/111	9/111		19.4 %	0.56 [0.19, 1.61]
VILLEJUIF	3/73	3/73		6.5 %	1.00 [0.21, 4.79]
Total (95% CI)	**699**	**692**		**100.0 %**	**0.97 [0.67, 1.42]**

Total events: 45 (UDCA), 46 (Control)

Heterogeneity: Chi^2 = 6.66, df = 8 (P = 0.57); I^2 =0.0%

Test for overall effect: Z = 0.15 (P = 0.88)

Analysis 1.2. Comparison 1 UDCA versus placebo or no intervention, Outcome 2 Mortality or liver transplantation.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

Comparison: 1 UDCA versus placebo or no intervention

Outcome: 2 Mortality or liver transplantation

Study or subgroup	UDCA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
ATHENS	21/43	17/43		18.9 %	1.24 [0.76, 2.00]
BARCELONA	17/99	11/93		12.6 %	1.45 [0.72, 2.93]
DALLAS	12/77	11/74		12.5 %	1.05 [0.49, 2.23]
FRANKFURT	0/10	0/10			Not estimable
GÖTEBORG	3/60	4/56		4.6 %	0.70 [0.16, 2.99]
HELSINKI	0/30	5/31		6.0 %	0.09 [0.01, 1.63]
MANCHESTER	4/14	2/14		2.2 %	2.00 [0.43, 9.21]
MAYO-I	7/89	12/91		13.2 %	0.60 [0.25, 1.45]
MILAN	0/44	0/44			Not estimable
NEWARK-II	0/9	0/10			Not estimable
NEWCASTLE	3/22	4/24		4.3 %	0.82 [0.21, 3.25]
TAIPEI	0/6	0/6			Not estimable
TOKYO	0/26	0/26			Not estimable
TORONTO	12/111	19/111		21.2 %	0.63 [0.32, 1.24]
VILLEJUIF	4/73	4/73		4.5 %	1.00 [0.26, 3.85]
Total (95% CI)	**713**	**706**		**100.0 %**	**0.92 [0.71, 1.21]**

Total events: 83 (UDCA), 89 (Control)

Heterogeneity: Chi^2 = 8.91, df = 9 (P = 0.45); I^2 =0.0%

Test for overall effect: Z = 0.59 (P = 0.56)

Analysis 1.3. Comparison 1 UDCA versus placebo or no intervention, Outcome 3 Liver transplantation.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

Comparison: 1 UDCA versus placebo or no intervention

Outcome: 3 Liver transplantation

Study or subgroup	UDCA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
ATHENS	4/43	3/43		7.2 %	1.33 [0.32, 5.61]
BARCELONA	7/99	7/93		17.3 %	0.94 [0.34, 2.58]
DALLAS	8/77	8/74		19.5 %	0.96 [0.38, 2.43]
FRANKFURT	0/10	0/10			Not estimable
GÖTEBORG	2/60	3/56		7.4 %	0.62 [0.11, 3.59]
HELSINKI	0/30	3/31		8.2 %	0.15 [0.01, 2.74]
MAYO-I	3/89	5/91		11.8 %	0.61 [0.15, 2.49]
MILAN	0/44	0/44			Not estimable
NEWARK-II	0/9	0/10			Not estimable
NEWCASTLE	2/22	1/24		2.3 %	2.18 [0.21, 22.42]
TAIPEI	0/6	0/6			Not estimable
TOKYO	0/26	0/26			Not estimable
TORONTO	7/111	10/111		23.9 %	0.70 [0.28, 1.77]
VILLEJUIF	1/73	1/73		2.4 %	1.00 [0.06, 15.69]
Total (95% CI)	**699**	**692**		**100.0 %**	**0.82 [0.53, 1.26]**

Total events: 34 (UDCA), 41 (Control)

Heterogeneity: $Chi^2 = 3.02$, df = 8 (P = 0.93); $I^2 = 0.0\%$

Test for overall effect: Z = 0.91 (P = 0.36)

Analysis 1.4. Comparison 1 UDCA versus placebo or no intervention, Outcome 4 Pruritus.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

Comparison: 1 UDCA versus placebo or no intervention

Outcome: 4 Pruritus

Study or subgroup	UDCA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
FRANKFURT	1/10	1/10		1.1 %	1.00 [0.07, 13.87]
HELSINKI	15/30	16/31		16.6 %	0.97 [0.59, 1.59]
TOKYO	5/22	5/23		5.2 %	1.05 [0.35, 3.12]
TORONTO	52/89	45/77		50.9 %	1.00 [0.77, 1.29]
VILLEJUIF	22/73	25/73		26.3 %	0.88 [0.55, 1.41]
Total (95% CI)	**224**	**214**		**100.0 %**	**0.97 [0.78, 1.19]**

Total events: 95 (UDCA), 92 (Control)

Heterogeneity: $Chi^2 = 0.24$, df = 4 (P = 0.99); $I^2 = 0.0\%$

Test for overall effect: Z = 0.33 (P = 0.74)

Analysis 1.5. Comparison 1 UDCA versus placebo or no intervention, Outcome 5 Pruitus score.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

Comparison: 1 UDCA versus placebo or no intervention

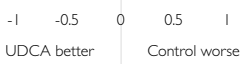
Outcome: 5 Pruitus score

Study or subgroup	UDCA N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
BARCELONA	99	1.5 (0.9)	93	1.7 (0.9)		70.8 %	-0.22 [-0.51, 0.06]
MILAN	17	1.3 (1.2)	16	1.45 (1.2)		12.2 %	-0.12 [-0.81, 0.56]
NEWCASTLE	22	62 (26.4)	24	68 (28.8)		17.0 %	-0.21 [-0.79, 0.37]
Total (95% CI)	**138**		**133**			**100.0 %**	**-0.21 [-0.45, 0.03]**

Heterogeneity: Chi² = 0.07, df = 2 (P = 0.97); I² =0.0%

Test for overall effect: Z = 1.70 (P = 0.088)

Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1 UDCA versus placebo or no intervention, Outcome 6 Fatigue.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

Comparison: 1 UDCA versus placebo or no intervention

Outcome: 6 Fatigue

Study or subgroup	UDCA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
HELSINKI	18/31	17/30		15.4 %	1.02 [0.66, 1.58]
TORONTO	66/89	56/77		53.5 %	1.02 [0.85, 1.23]
VILLEJUIF	22/73	35/73		31.2 %	0.63 [0.41, 0.96]
Total (95% CI)	**193**	**180**		**100.0 %**	**0.90 [0.76, 1.06]**

Total events: 106 (UDCA), 108 (Control)

Heterogeneity: Chi² = 4.91, df = 2 (P = 0.09); I² =59%

Test for overall effect: Z = 1.25 (P = 0.21)

Analysis 1.7. Comparison 1 UDCA versus placebo or no intervention, Outcome 7 Jaundice.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

Comparison: 1 UDCA versus placebo or no intervention

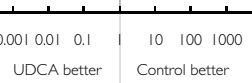
Outcome: 7 Jaundice

Study or subgroup	UDCA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
TOKYO	1/26	0/26		3.2 %	3.00 [0.13, 70.42]
VILLEJUIF	4/73	15/73		96.8 %	0.27 [0.09, 0.77]
Total (95% CI)	**99**	**99**		**100.0 %**	**0.35 [0.14, 0.90]**

Total events: 5 (UDCA), 15 (Control)

Heterogeneity: $Chi^2 = 2.04$, df = 1 (P = 0.15); $I^2 = 51\%$

Test for overall effect: Z = 2.18 (P = 0.029)



Analysis 1.8. Comparison 1 UDCA versus placebo or no intervention, Outcome 8 Portal pressure.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

Comparison: 1 UDCA versus placebo or no intervention

Outcome: 8 Portal pressure

Study or subgroup	UDCA N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
VILLEJUIF	15	10.3 (3.4)	15	9.5 (4.8)		100.0 %	0.80 [-2.18, 3.78]
Total (95% CI)	**15**		**15**			**100.0 %**	**0.80 [-2.18, 3.78]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.53 (P = 0.60)

Test for subgroup differences: Not applicable

Analysis 1.9. Comparison 1 UDCA versus placebo or no intervention, Outcome 9 Development of varices.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

Comparison: 1 UDCA versus placebo or no intervention

Outcome: 9 Development of varices

Study or subgroup	UDCA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
DALLAS	3/75	6/77		31.1 %	0.51 [0.13, 1.98]
MAYO-I	7/60	12/54		66.3 %	0.53 [0.22, 1.24]
TOKYO	1/26	0/26		2.6 %	3.00 [0.13, 70.42]
Total (95% CI)	**161**	**157**		**100.0 %**	**0.59 [0.29, 1.17]**

Total events: 11 (UDCA), 18 (Control)

Heterogeneity: Chi^2 = 1.13, df = 2 (P = 0.57); I^2 =0.0%

Test for overall effect: Z = 1.51 (P = 0.13)

Analysis 1.10. Comparison 1 UDCA versus placebo or no intervention, Outcome 10 Bleeding varices.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

Comparison: 1 UDCA versus placebo or no intervention

Outcome: 10 Bleeding varices

Study or subgroup	UDCA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
BARCELONA	4/99	6/93		53.1 %	0.63 [0.18, 2.15]
HELSINKI	0/30	2/31		21.1 %	0.21 [0.01, 4.13]
TOKYO	1/26	1/26		8.6 %	1.00 [0.07, 15.15]
VILLEJUIF	1/73	2/73		17.2 %	0.50 [0.05, 5.39]
Total (95% CI)	**228**	**223**		**100.0 %**	**0.55 [0.21, 1.41]**

Total events: 6 (UDCA), 11 (Control)

Heterogeneity: $Chi^2 = 0.65$, df = 3 (P = 0.89); $I^2 = 0.0\%$

Test for overall effect: Z = 1.25 (P = 0.21)

Analysis 1.11. Comparison 1 UDCA versus placebo or no intervention, Outcome 11 Hepatic encephalopathy.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

Comparison: 1 UDCA versus placebo or no intervention

Outcome: 11 Hepatic encephalopathy

Study or subgroup	UDCA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
BARCELONA	1/99	2/93		55.8 %	0.47 [0.04, 5.09]
MAYO-I	0/60	1/50		44.2 %	0.28 [0.01, 6.69]
Total (95% CI)	**159**	**143**		**100.0 %**	**0.39 [0.06, 2.56]**

Total events: 1 (UDCA), 3 (Control)

Heterogeneity: $Chi^2 = 0.07$, df = 1 (P = 0.80); $I^2 = 0.0\%$

Test for overall effect: Z = 0.99 (P = 0.32)

Analysis 1.12. Comparison 1 UDCA versus placebo or no intervention, Outcome 12 Ascites.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

Comparison: 1 UDCA versus placebo or no intervention

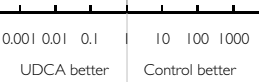
Outcome: 12 Ascites

Study or subgroup	UDCA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
BARCELONA	5/99	6/93		31.7 %	0.78 [0.25, 2.48]
MAYO-I	1/60	9/50		50.3 %	0.09 [0.01, 0.71]
TOKYO	1/26	0/26		2.6 %	3.00 [0.13, 70.42]
VILLEJUIF	1/73	3/73		15.4 %	0.33 [0.04, 3.13]
Total (95% CI)	**258**	**242**		**100.0 %**	**0.42 [0.19, 0.93]**

Total events: 8 (UDCA), 18 (Control)

Heterogeneity: $Chi^2 = 4.77$, df = 3 (P = 0.19); $I^2 = 37\%$

Test for overall effect: Z = 2.15 (P = 0.032)



Analysis 1.13. Comparison 1 UDCA versus placebo or no intervention, Outcome 13 Variceal bleeding, ascites, and/or encephalopathy.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

Comparison: 1 UDCA versus placebo or no intervention

Outcome: 13 Variceal bleeding, ascites, and/or encephalopathy

Study or subgroup	UDCA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
ATHENS	5/28	4/28		100.0 %	1.25 [0.37, 4.17]
Total (95% CI)	**28**	**28**		**100.0 %**	**1.25 [0.37, 4.17]**

Total events: 5 (UDCA), 4 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.36 (P = 0.72)

Analysis 1.14. Comparison 1 UDCA versus placebo or no intervention, Outcome 14 S-bilirubin (µmol/l) - about six months.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

Comparison: 1 UDCA versus placebo or no intervention

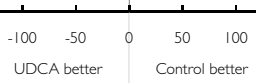
Outcome: 14 S-bilirubin (mol/l) - about six months

Study or subgroup	UDCA N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
ATHENS	28	32.5 (20.5)	28	33.2 (32.5)		13.2 %	-0.70 [-14.93, 13.53]
BARCELONA	99	24 (30.8)	93	35.9 (46.2)		21.4 %	-11.90 [-23.08, -0.72]
MAYO-I	89	35.9 (20.5)	91	51.3 (41)		30.0 %	-15.40 [-24.84, -5.96]
MILAN	44	27.4 (22.2)	44	33 (32.5)		19.8 %	-5.60 [-17.23, 6.03]
TAIPEI	6	33.2 (22.9)	6	78.8 (64.8)		0.9 %	-45.60 [-100.59, 9.39]
VILLEJUIF	73	17.2 (14.7)	73	27.6 (57)		14.7 %	-10.40 [-23.90, 3.10]
Total (95% CI)	**339**		**335**			**100.0 %**	**-10.30 [-15.48, -5.13]**

Heterogeneity: Chi² = 5.16, df = 5 (P = 0.40); I² =3%

Test for overall effect: Z = 3.90 (P = 0.000095)

Test for subgroup differences: Not applicable



Analysis 1.15. Comparison 1 UDCA versus placebo or no intervention, Outcome 15 S-alkaline phosphatase (IU/l) - about six months.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

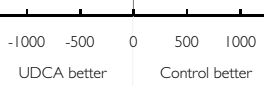
Comparison: 1 UDCA versus placebo or no intervention

Outcome: 15 S-alkaline phosphatase (IU/l) - about six months

Study or subgroup	UDCA N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
BARCELONA	99	517 (380)	93	917 (561)		23.0 %	-400.00 [-536.39, -263.61]
FRANKFURT	10	270 (104)	10	1100 (1265)		3.8 %	-830.00 [-1616.69, -43.31]
MAYO-I	89	643 (470)	91	1260 (710)		20.9 %	-617.00 [-792.54, -441.46]
TAIPEI	6	423 (122)	6	596 (370)		13.9 %	-173.00 [-484.73, 138.73]
TOKYO	22	332 (330)	23	576 (560)		16.0 %	-244.00 [-511.19, 23.19]
VILLEJUIF	73	633 (448)	73	827 (458)		22.4 %	-194.00 [-340.97, -47.03]
Total (95% CI)	**299**		**296**			**100.0 %**	**-359.08 [-525.05, -193.11]**

Heterogeneity: Tau² = 26329.48; Chi² = 16.94, df = 5 (P = 0.005); I² =70%

Test for overall effect: Z = 4.24 (P = 0.000022)



Analysis 1.16. Comparison 1 UDCA versus placebo or no intervention, Outcome 16 S-gamma-glutamyl transpeptidase (IU/l) - about six months.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

Comparison: 1 UDCA versus placebo or no intervention

Outcome: 16 S-gamma-glutamyl transpeptidase (IU/l) - about six months

Study or subgroup	UDCA N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
BARCELONA	99	172 (244)	93	426 (281)		65.6 %	-254.00 [-328.64, -179.36]
TAIPEI	6	355 (144)	6	400 (288)		5.5 %	-45.00 [-302.64, 212.64]
TOKYO	22	233 (254)	23	443 (419)		9.0 %	-210.00 [-411.46, -8.54]
VILLEJUIF	73	381 (444)	73	732 (390)		19.9 %	-351.00 [-486.56, -215.44]
Total (95% CI)	**200**		**195**			**100.0 %**	**-257.82 [-318.28, -197.36]**

Heterogeneity: $Chi^2 = 4.66$, df = 3 (P = 0.20); $I^2 = 36\%$

Test for overall effect: Z = 8.36 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.17. Comparison 1 UDCA versus placebo or no intervention, Outcome 17 S-aspartate aminotransferase (IU/l) - about six months.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

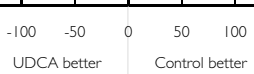
Comparison: 1 UDCA versus placebo or no intervention

Outcome: 17 S-aspartate aminotransferase (IU/l) - about six months

Study or subgroup	UDCA N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
BARCELONA	99	54 (36)	93	96 (72)		24.9 %	-42.00 [-58.26, -25.74]
MAYO-I	89	58 (34)	91	114 (61)		26.1 %	-56.00 [-70.39, -41.61]
TAIPEI	6	96 (48)	6	156 (97)		3.7 %	-60.00 [-146.60, 26.60]
TOKYO	22	67 (60)	23	74 (34)		17.2 %	-7.00 [-35.66, 21.66]
VILLEJUIF	73	57.6 (26)	73	82.4 (40)		28.1 %	-24.80 [-35.74, -13.86]
Total (95% CI)	**289**		**286**			**100.0 %**	**-35.45 [-53.08, -17.81]**

Heterogeneity: $Tau^2 = 256.53$; $Chi^2 = 16.19$, df = 4 (P = 0.003); $I^2 = 75\%$

Test for overall effect: Z = 3.94 (P = 0.000082)



Analysis 1.18. Comparison 1 UDCA versus placebo or no intervention, Outcome 18 S-alanine aminotransferase (IU/l) - about six months.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

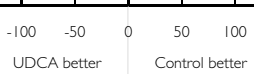
Comparison: 1 UDCA versus placebo or no intervention

Outcome: 18 S-alanine aminotransferase (IU/l) - about six months

Study or subgroup	UDCA N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
ATHENS	28	52 (35)	28	72 (42)		21.6 %	-20.00 [-40.25, 0.25]
BARCELONA	99	56 (45)	93	98 (63)		22.6 %	-42.00 [-57.57, -26.43]
FRANKFURT	10	17 (5.4)	10	74 (35)		21.3 %	-57.00 [-78.95, -35.05]
TAIPEI	6	79 (42)	6	211 (30.6)		16.2 %	-132.00 [-173.58, -90.42]
TOKYO	22	55.5 (70)	23	57.2 (41)		18.3 %	-1.70 [-35.41, 32.01]
Total (95% CI)	**165**		**160**			**100.0 %**	**-47.66 [-76.90, -18.42]**

Heterogeneity: $Tau^2 = 921.84$; $Chi^2 = 29.80$, df = 4 (P<0.00001); $I^2 = 87\%$

Test for overall effect: Z = 3.19 (P = 0.0014)



Analysis 1.19. Comparison 1 UDCA versus placebo or no intervention, Outcome 19 S-albumin (g/l) - about six months.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

Comparison: 1 UDCA versus placebo or no intervention

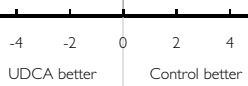
Outcome: 19 S-albumin (g/l) - about six months

Study or subgroup	UDCA N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
BARCELONA	99	40.3 (4.97)	93	40.3 (5.79)		2.3 %	0.0 [-1.53, 1.53]
MILAN	44	4.14 (0.6)	44	4.04 (0.53)		97.7 %	0.10 [-0.14, 0.34]
Total (95% CI)	**143**		**137**			**100.0 %**	**0.10 [-0.14, 0.33]**

Heterogeneity: Chi^2 = 0.02, df = 1 (P = 0.90); I^2 =0.0%

Test for overall effect: Z = 0.82 (P = 0.41)

Test for subgroup differences: Not applicable



Analysis 1.20. Comparison 1 UDCA versus placebo or no intervention, Outcome 20 S-cholesterol (total) (mmol/l) - about six months.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

Comparison: 1 UDCA versus placebo or no intervention

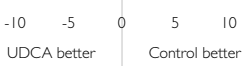
Outcome: 20 S-cholesterol (total) (mmol/l) - about six months

Study or subgroup	UDCA N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
BARCELONA	99	6.01 (1.4)	93	6.79 (1.66)		49.1 %	-0.78 [-1.22, -0.34]
MEXICO CITY	12	5.6 (2.15)	11	6.5 (2.36)		2.7 %	-0.90 [-2.75, 0.95]
MILAN	44	6.81 (2.41)	44	6.76 (1.89)		11.4 %	0.05 [-0.85, 0.95]
TAIPEI	6	7.28 (2.31)	6	6.45 (4.79)		0.5 %	0.83 [-3.43, 5.09]
VILLEJUIF	73	6.7 (1.4)	73	7.1 (1.71)		36.3 %	-0.40 [-0.91, 0.11]
Total (95% CI)	**234**		**227**			**100.0 %**	**-0.54 [-0.85, -0.24]**

Heterogeneity: $Chi^2 = 3.63$, df = 4 (P = 0.46); $I^2 = 0.0\%$

Test for overall effect: Z = 3.48 (P = 0.00050)

Test for subgroup differences: Not applicable



Analysis 1.21. Comparison 1 UDCA versus placebo or no intervention, Outcome 21 Plasma immunoglobulin M (g/l) - about six months.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

Comparison: 1 UDCA versus placebo or no intervention

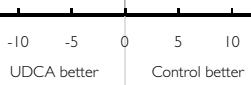
Outcome: 21 Plasma immunoglobulin M (g/l) - about six months

Study or subgroup	UDCA N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
BARCELONA	99	4.03 (2.62)	93	5.38 (3.89)		40.5 %	-1.35 [-2.29, -0.41]
FRANKFURT	10	3.62 (1.42)	10	5.12 (1.93)		16.4 %	-1.50 [-2.99, -0.01]
MILAN	44	5.04 (3.58)	44	6.07 (4.58)		12.2 %	-1.03 [-2.75, 0.69]
VILLEJUIF	73	3.47 (2.45)	73	4.53 (4.03)		30.9 %	-1.06 [-2.14, 0.02]
Total (95% CI)	**226**		**220**			**100.0 %**	**-1.25 [-1.85, -0.64]**

Heterogeneity: Chi² = 0.33, df = 3 (P = 0.95); I² =0.0%

Test for overall effect: Z = 4.06 (P = 0.000048)

Test for subgroup differences: Not applicable



Analysis 1.22. Comparison 1 UDCA versus placebo or no intervention, Outcome 22 Prothrombin index.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

Comparison: 1 UDCA versus placebo or no intervention

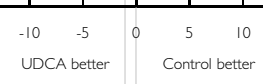
Outcome: 22 Prothrombin index

Study or subgroup	Control N	Mean(SD)	UDCA N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
BARCELONA	99	94 (11.94)	93	93 (13.51)		41.5 %	1.00 [-2.62, 4.62]
VILLEJUIF	73	95.8 (8.5)	73	94.5 (10.2)		58.5 %	1.30 [-1.75, 4.35]
Total (95% CI)	**172**		**166**			**100.0 %**	**1.18 [-1.15, 3.50]**

Heterogeneity: Chi² = 0.02, df = 1 (P = 0.90); I² =0.0%

Test for overall effect: Z = 0.99 (P = 0.32)

Test for subgroup differences: Not applicable



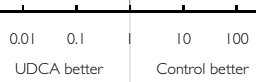
Analysis 1.23. Comparison 1 UDCA versus placebo or no intervention, Outcome 23 Liver biopsy findings - dichotomous variables.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

Comparison: 1 UDCA versus placebo or no intervention

Outcome: 23 Liver biopsy findings - dichotomous variables

Study or subgroup	UDCA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Worsening of histological stage					
ATHENS	9/20	10/19		16.1 %	0.86 [0.45, 1.63]
DALLAS	15/46	9/45		14.3 %	1.63 [0.80, 3.34]
MAYO-I	17/59	14/46		24.7 %	0.95 [0.52, 1.71]
NEWCASTLE	1/7	8/14		8.4 %	0.25 [0.04, 1.62]
VILLEJUIF	10/50	22/45		36.4 %	0.41 [0.22, 0.77]
Subtotal (95% CI)	**182**	**169**		**100.0 %**	**0.78 [0.57, 1.06]**
Total events: 52 (UDCA), 63 (Control)					
Heterogeneity: Chi^2 = 10.02, df = 4 (P = 0.04); I^2 =60%					
Test for overall effect: Z = 1.61 (P = 0.11)					
2 Worsening of fibrosis					
TORONTO	24/71	26/68		100.0 %	0.88 [0.57, 1.38]
Subtotal (95% CI)	**71**	**68**		**100.0 %**	**0.88 [0.57, 1.38]**
Total events: 24 (UDCA), 26 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.54 (P = 0.59)					
3 Florid duct lesion					
DALLAS	10/55	13/60		100.0 %	0.84 [0.40, 1.76]
Subtotal (95% CI)	**55**	**60**		**100.0 %**	**0.84 [0.40, 1.76]**
Total events: 10 (UDCA), 13 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.47 (P = 0.64)					

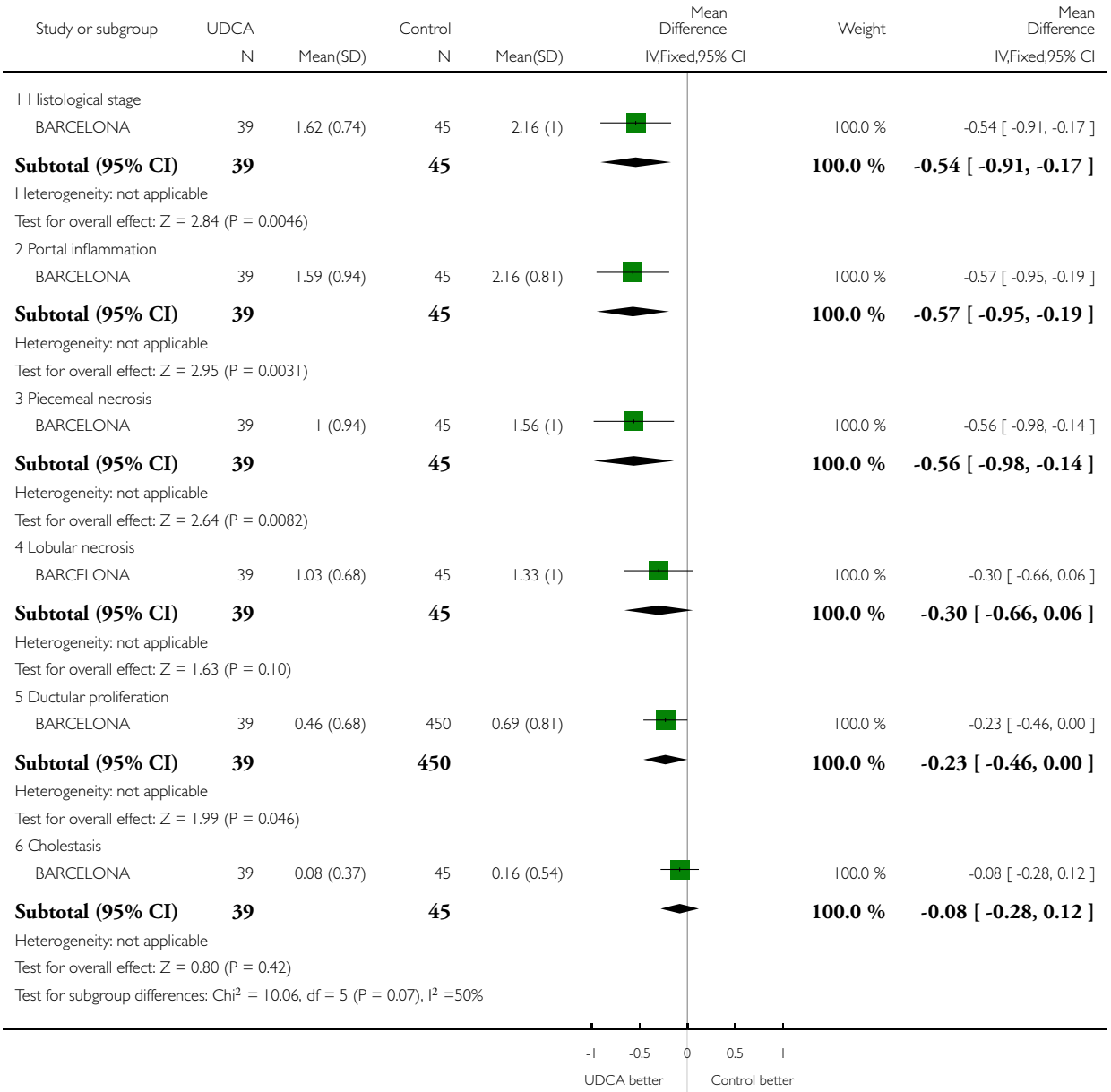


Analysis 1.24. Comparison 1 UDCA versus placebo or no intervention, Outcome 24 Liver biopsy findings - continuous variables.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

Comparison: 1 UDCA versus placebo or no intervention

Outcome: 24 Liver biopsy findings - continuous variables



Analysis 1.25. Comparison 1 UDCA versus placebo or no intervention, Outcome 25 Liver biopsy findings - continuous variables.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

Comparison: 1 UDCA versus placebo or no intervention

Outcome: 25 Liver biopsy findings - continuous variables

Study or subgroup	UDCA N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Bile duct/portal tract							
BARCELONA	39	0.48 (0.31)	45	0.25 (0.27)		100.0 %	0.23 [0.10, 0.36]
Subtotal (95% CI)	**39**		**45**			**100.0 %**	**0.23 [0.10, 0.36]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.60 (P = 0.00032)							
Test for subgroup differences: Not applicable							

Analysis 2.1. Comparison 2 Adverse events - UDCA versus placebo or no intervention, Outcome 1 Serious adverse events.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

Comparison: 2 Adverse events - UDCA versus placebo or no intervention

Outcome: 1 Serious adverse events

Study or subgroup	UDCA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
BARCELONA	0/99	0/93			Not estimable
DALLAS	0/77	0/74			Not estimable
FRANKFURT	0/10	0/10			Not estimable
HELSINKI	0/30	0/31			Not estimable
MILAN	1/44	0/44		100.0 %	3.00 [0.13, 71.70]
NEWCASTLE	0/22	0/24			Not estimable
TAIPEI	0/6	0/6			Not estimable
TOKYO	0/26	0/26			Not estimable
TORONTO	0/111	0/111			Not estimable
VILLEJUIF	0/73	0/73			Not estimable
Total (95% CI)	**498**	**492**		**100.0 %**	**3.00 [0.13, 71.70]**

Total events: 1 (UDCA), 0 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.68 (P = 0.50)

Analysis 2.2. Comparison 2 Adverse events - UDCA versus placebo or no intervention, Outcome 2 Non-serious adverse events.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

Comparison: 2 Adverse events - UDCA versus placebo or no intervention

Outcome: 2 Non-serious adverse events

Study or subgroup	UDCA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
BARCELONA	9/99	6/93		9.4 %	1.41 [0.52, 3.81]
DALLAS	1/77	1/74		1.5 %	0.96 [0.06, 15.08]
FRANKFURT	0/10	0/10			Not estimable
HELSINKI	0/30	0/31			Not estimable
MAYO-I	67/86	43/73		70.4 %	1.32 [1.06, 1.65]
MILAN	5/44	1/44		1.5 %	5.00 [0.61, 41.08]
NEWCASTLE	4/22	4/24		5.8 %	1.09 [0.31, 3.84]
TAIPEI	1/6	0/6		0.8 %	3.00 [0.15, 61.74]
TOKYO	0/26	0/26			Not estimable
TORONTO	4/111	6/111		9.1 %	0.67 [0.19, 2.30]
VILLEJUIF	1/73	1/73		1.5 %	1.00 [0.06, 15.69]
Total (95% CI)	**584**	**565**		**100.0 %**	**1.32 [1.05, 1.65]**

Total events: 92 (UDCA), 62 (Control)

Heterogeneity: $Chi^2 = 3.18$, df = 7 (P = 0.87); $I^2 = 0.0\%$

Test for overall effect: Z = 2.35 (P = 0.019)

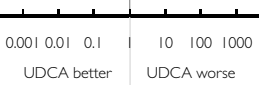
Analysis 3.1. Comparison 3 Influence of missing data - UDCA versus placebo or no intervention, Outcome 1 Mortality - completed patient's course plus case scenarios.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

Comparison: 3 Influence of missing data - UDCA versus placebo or no intervention

Outcome: 1 Mortality - completed patient's course plus case scenarios

Study or subgroup	UDCA n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Completed patient's course analysis					
ATHENS	17/43	14/43		23.7 %	1.21 [0.69, 2.14]
BARCELONA	10/89	4/72		14.4 %	2.02 [0.66, 6.18]
DALLAS	4/75	3/71		10.5 %	1.26 [0.29, 5.44]
FRANKFURT	0/10	0/8			Not estimable
GÖTEBORG	1/52	1/49		3.9 %	0.94 [0.06, 14.65]
HELSINKI	0/30	2/23		3.4 %	0.15 [0.01, 3.08]
MAYO-I	4/84	7/78		13.5 %	0.53 [0.16, 1.74]
MILAN	0/39	0/43			Not estimable
NEWARK-II	0/9	0/10			Not estimable
NEWCASTLE	1/17	3/20		5.8 %	0.39 [0.04, 3.43]
TAIPEI	0/6	0/6			Not estimable
TOKYO	0/22	0/23			Not estimable
TORONTO	5/98	9/92		15.3 %	0.52 [0.18, 1.50]
VILLEJUIF	3/68	3/67		9.6 %	0.99 [0.21, 4.71]
Subtotal (95% CI)	**642**	**605**		**100.0 %**	**0.97 [0.66, 1.43]**
Total events: 45 (UDCA), 46 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 6.90, df = 8 (P = 0.55); I² =0.0%					
Test for overall effect: Z = 0.13 (P = 0.89)					
2 Assuming bad outcome					
ATHENS	17/43	14/43		12.7 %	1.21 [0.69, 2.14]
BARCELONA	20/99	25/93		13.3 %	0.75 [0.45, 1.26]
DALLAS	6/77	6/74		8.0 %	0.96 [0.32, 2.85]
FRANKFURT	0/10	2/10		1.9 %	0.20 [0.01, 3.70]
GÖTEBORG	9/60	8/56		9.7 %	1.05 [0.44, 2.53]
HELSINKI	0/30	10/31		2.1 %	0.05 [0.00, 0.80]



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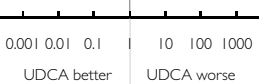
Study or subgroup	UDCA n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
MAYO-I	9/89	20/91		11.1 %	0.46 [0.22, 0.96]
MILAN	5/44	1/44		3.3 %	5.00 [0.61, 41.08]
NEWARK-II	0/9	0/10			Not estimable
NEWCASTLE	6/22	7/24		9.3 %	0.94 [0.37, 2.36]
TAIPEI	0/6	0/6			Not estimable
TOKYO	4/26	3/26		6.0 %	1.33 [0.33, 5.38]
TORONTO	18/111	28/111		13.1 %	0.64 [0.38, 1.09]
VILLEJUIF	8/73	9/73		9.6 %	0.89 [0.36, 2.18]
Subtotal (95% CI)	**699**	**692**		**100.0 %**	**0.82 [0.61, 1.09]**
Total events: 102 (UDCA), 133 (Control)					
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 14.01$, df = 11 (P = 0.23); $I^2 = 21\%$					
Test for overall effect: Z = 1.39 (P = 0.17)					
3 Assuming good outcome					
ATHENS	17/43	14/43		23.8 %	1.21 [0.69, 2.14]
BARCELONA	10/99	4/93		14.4 %	2.35 [0.76, 7.23]
DALLAS	4/77	3/74		10.5 %	1.28 [0.30, 5.53]
FRANKFURT	0/10	0/10			Not estimable
GÖTEBORG	1/60	1/56		3.9 %	0.93 [0.06, 14.57]
HELSINKI	0/30	2/31		3.4 %	0.21 [0.01, 4.13]
MAYO-I	4/89	7/91		13.5 %	0.58 [0.18, 1.93]
MILAN	0/44	0/44			Not estimable
NEWARK-II	0/9	0/10			Not estimable
NEWCASTLE	1/22	3/24		5.8 %	0.36 [0.04, 3.24]
TAIPEI	0/6	0/6			Not estimable
TOKYO	0/26	0/26			Not estimable
TORONTO	5/111	9/111		15.2 %	0.56 [0.19, 1.61]
VILLEJUIF	3/73	3/73		9.6 %	1.00 [0.21, 4.79]
Subtotal (95% CI)	**699**	**692**		**100.0 %**	**1.01 [0.69, 1.49]**
Total events: 45 (UDCA), 46 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.66$, df = 8 (P = 0.57); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.07 (P = 0.94)					
4 Extreme case scenario favouring UDCA					
ATHENS	17/43	14/43		18.1 %	1.21 [0.69, 2.14]
BARCELONA	10/99	25/93		16.5 %	0.38 [0.19, 0.74]



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Study or subgroup	UDCA n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
DALLAS	4/77	6/74		10.0 %	0.64 [0.19, 2.18]
FRANKFURT	0/10	2/10		2.7 %	0.20 [0.01, 3.70]
GÖTEBORG	1/60	8/56		4.9 %	0.12 [0.02, 0.90]
HELSINKI	0/30	10/31		2.9 %	0.05 [0.00, 0.80]
MAYO-I	4/89	20/91		11.9 %	0.20 [0.07, 0.57]
MILAN	0/44	1/44		2.3 %	0.33 [0.01, 7.97]
NEWARK-II	0/9	0/10			Not estimable
NEWCASTLE	1/22	7/24		5.0 %	0.16 [0.02, 1.17]
TAIPEI	0/6	0/6			Not estimable
TOKYO	0/26	3/26		2.7 %	0.14 [0.01, 2.63]
TORONTO	5/111	28/111		13.3 %	0.18 [0.07, 0.45]
VILLEJUIF	3/73	9/73		9.6 %	0.33 [0.09, 1.18]
Subtotal (95% CI)	**699**	**692**		**100.0 %**	**0.31 [0.17, 0.56]**
Total events: 45 (UDCA), 133 (Control)					
Heterogeneity: Tau^2 = 0.53; Chi^2 = 26.99, df = 11 (P = 0.005); I^2 =59%					
Test for overall effect: Z = 3.82 (P = 0.00013)					
5 Extreme case scenario favouring control					
ATHENS	17/43	14/43		18.2 %	1.21 [0.69, 2.14]
BARCELONA	20/99	4/93		12.0 %	4.70 [1.67, 13.23]
DALLAS	6/77	3/74		8.9 %	1.92 [0.50, 7.40]
FRANKFURT	0/10	0/10			Not estimable
GÖTEBORG	9/60	1/56		5.0 %	8.40 [1.10, 64.19]
HELSINKI	0/30	2/31		2.6 %	0.21 [0.01, 4.13]
MAYO-I	9/89	7/91		13.1 %	1.31 [0.51, 3.38]
MILAN	5/44	0/44		2.8 %	11.00 [0.63, 193.12]
NEWARK-II	0/9	0/10			Not estimable
NEWCASTLE	6/22	3/24		9.7 %	2.18 [0.62, 7.69]
TAIPEI	0/6	0/6			Not estimable
TOKYO	4/26	0/26		2.8 %	9.00 [0.51, 159.15]
TORONTO	18/111	9/111		15.5 %	2.00 [0.94, 4.26]
VILLEJUIF	8/73	3/73		9.4 %	2.67 [0.74, 9.65]
Subtotal (95% CI)	**699**	**692**		**100.0 %**	**2.08 [1.36, 3.19]**
Total events: 102 (UDCA), 46 (Control)					

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Study or subgroup	UDCA n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Heterogeneity: Tau^2 = 0.13; Chi^2 = 13.65, df = 10 (P = 0.19); I^2 =27%					
Test for overall effect: Z = 3.37 (P = 0.00075)					

Analysis 3.2. Comparison 3 Influence of missing data - UDCA versus placebo or no intervention, Outcome 2 Mortality or liver transplantation - completed patient's course plus case scenarios.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

Comparison: 3 Influence of missing data - UDCA versus placebo or no intervention

Outcome: 2 Mortality or liver transplantation - completed patient's course plus case scenarios

Study or subgroup	UDCA n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Completed patient's course analysis					
ATHENS	21/43	17/43		18.5 %	1.24 [0.76, 2.00]
BARCELONA	17/89	11/72		14.5 %	1.25 [0.63, 2.50]
DALLAS	12/75	11/71		13.5 %	1.03 [0.49, 2.19]
FRANKFURT	0/10	0/8			Not estimable
GÖTEBORG	3/52	4/49		6.0 %	0.71 [0.17, 3.00]
HELSINKI	0/30	5/23		1.9 %	0.07 [0.00, 1.21]
MANCHESTER	4/14	2/14		5.5 %	2.00 [0.43, 9.21]
MAYO-I	7/84	12/78		11.5 %	0.54 [0.22, 1.31]
MILAN	0/39	0/43			Not estimable
NEWARK-II	0/9	0/10			Not estimable
NEWCASTLE	3/17	4/20		6.7 %	0.88 [0.23, 3.40]
TAIPEI	0/6	0/6			Not estimable

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Study or subgroup	UDCA n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
TOKYO	0/22	0/23			Not estimable
TORONTO	12/98	19/92		15.0 %	0.59 [0.31, 1.15]
VILLEJUIF	4/68	4/67		6.7 %	0.99 [0.26, 3.78]
Subtotal (95% CI)	**656**	**619**		**100.0 %**	**0.93 [0.69, 1.24]**
Total events: 83 (UDCA), 89 (Control)					
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 9.92$, df = 9 (P = 0.36); $I^2 = 9\%$					
Test for overall effect: Z = 0.49 (P = 0.62)					
2 Assuming bad outcome					
ATHENS	21/43	17/43		12.7 %	1.24 [0.76, 2.00]
BARCELONA	30/99	32/93		13.6 %	0.88 [0.58, 1.33]
DALLAS	14/77	14/74		10.2 %	0.96 [0.49, 1.88]
FRANKFURT	0/10	2/10		1.2 %	0.20 [0.01, 3.70]
GÖTEBORG	11/60	11/56		9.2 %	0.93 [0.44, 1.98]
HELSINKI	0/30	13/31		1.4 %	0.04 [0.00, 0.62]
MANCHESTER	4/14	2/14		3.8 %	2.00 [0.43, 9.21]
MAYO-I	12/89	25/91		10.8 %	0.49 [0.26, 0.92]
MILAN	5/44	1/44		2.2 %	5.00 [0.61, 41.08]
NEWARK-II	0/9	0/10			Not estimable
NEWCASTLE	8/22	8/24		8.8 %	1.09 [0.49, 2.41]
TAIPEI	0/6	0/6			Not estimable
TOKYO	4/26	3/26		4.4 %	1.33 [0.33, 5.38]
TORONTO	25/111	38/111		13.4 %	0.66 [0.43, 1.01]
VILLEJUIF	9/73	10/73		8.3 %	0.90 [0.39, 2.08]
Subtotal (95% CI)	**713**	**706**		**100.0 %**	**0.87 [0.67, 1.14]**
Total events: 143 (UDCA), 176 (Control)					
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 17.84$, df = 12 (P = 0.12); $I^2 = 33\%$					
Test for overall effect: Z = 0.99 (P = 0.32)					
3 Assuming good outcome					
ATHENS	21/43	17/43		18.7 %	1.24 [0.76, 2.00]
BARCELONA	17/99	11/93		14.4 %	1.45 [0.72, 2.93]
DALLAS	12/77	11/74		13.6 %	1.05 [0.49, 2.23]
FRANKFURT	0/10	0/10			Not estimable
GÖTEBORG	3/60	4/56		6.0 %	0.70 [0.16, 2.99]
HELSINKI	0/30	5/31		1.9 %	0.09 [0.01, 1.63]

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Study or subgroup	UDCA n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
MANCHESTER	4/14	2/14		5.6 %	2.00 [0.43, 9.21]
MAYO-I	7/89	12/91		11.6 %	0.60 [0.25, 1.45]
MILAN	0/44	0/44			Not estimable
NEWARK-II	0/9	0/10			Not estimable
NEWCASTLE	3/22	4/24		6.5 %	0.82 [0.21, 3.25]
TAIPEI	0/6	0/6			Not estimable
TOKYO	0/26	0/26			Not estimable
TORONTO	12/111	19/111		15.0 %	0.63 [0.32, 1.24]
VILLEJUIF	4/73	4/73		6.8 %	1.00 [0.26, 3.85]
Subtotal (95% CI)	**713**	**706**		**100.0 %**	**0.99 [0.75, 1.29]**
Total events: 83 (UDCA), 89 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 8.91, df = 9 (P = 0.45); I² =0.0%					
Test for overall effect: Z = 0.10 (P = 0.92)					
4 Extreme case scenario favouring UDCA					
ATHENS	21/43	17/43		15.8 %	1.24 [0.76, 2.00]
BARCELONA	17/99	32/93		15.2 %	0.50 [0.30, 0.84]
DALLAS	12/77	14/74		12.3 %	0.82 [0.41, 1.66]
FRANKFURT	0/10	2/10		1.5 %	0.20 [0.01, 3.70]
GÖTEBORG	3/60	11/56		6.6 %	0.25 [0.07, 0.87]
HELSINKI	0/30	13/31		1.7 %	0.04 [0.00, 0.62]
MANCHESTER	4/14	2/14		4.7 %	2.00 [0.43, 9.21]
MAYO-I	7/89	25/91		11.1 %	0.29 [0.13, 0.63]
MILAN	0/44	1/44		1.3 %	0.33 [0.01, 7.97]
NEWARK-II	0/9	0/10			Not estimable
NEWCASTLE	3/22	8/24		6.8 %	0.41 [0.12, 1.35]
TAIPEI	0/6	0/6			Not estimable
TOKYO	0/26	3/26		1.6 %	0.14 [0.01, 2.63]
TORONTO	12/111	38/111		13.9 %	0.32 [0.17, 0.57]
VILLEJUIF	4/73	10/73		7.5 %	0.40 [0.13, 1.22]
Subtotal (95% CI)	**713**	**706**		**100.0 %**	**0.48 [0.30, 0.74]**
Total events: 83 (UDCA), 176 (Control)					
Heterogeneity: Tau² = 0.31; Chi² = 29.96, df = 12 (P = 0.003); I² =60%					
Test for overall effect: Z = 3.26 (P = 0.0011)					
5 Extreme case scenario favouring control					

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Study or subgroup	UDCA n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
ATHENS	21/43	17/43		15.8 %	1.24 [0.76, 2.00]
BARCELONA	30/99	11/93		13.3 %	2.56 [1.36, 4.81]
DALLAS	14/77	11/74		11.9 %	1.22 [0.59, 2.52]
FRANKFURT	0/10	0/10			Not estimable
GÖTEBORG	11/60	4/56		7.7 %	2.57 [0.87, 7.59]
HELSINKI	0/30	5/31		1.6 %	0.09 [0.01, 1.63]
MANCHESTER	4/14	2/14		4.7 %	2.00 [0.43, 9.21]
MAYO-I	12/89	12/91		11.6 %	1.02 [0.49, 2.15]
MILAN	5/44	0/44		1.6 %	11.00 [0.63, 193.12]
NEWARK-II	0/9	0/10			Not estimable
NEWCASTLE	8/22	4/24		8.0 %	2.18 [0.76, 6.24]
TAIPEI	0/6	0/6			Not estimable
TOKYO	4/26	0/26		1.6 %	9.00 [0.51, 159.15]
TORONTO	25/111	19/111		14.9 %	1.32 [0.77, 2.25]
VILLEJUIF	9/73	4/73		7.3 %	2.25 [0.73, 6.98]
Subtotal (95% CI)	**713**	**706**		**100.0 %**	**1.58 [1.17, 2.11]**
Total events: 143 (UDCA), 89 (Control)					
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 14.04$, df = 11 (P = 0.23); $I^2 = 22\%$					
Test for overall effect: Z = 3.03 (P = 0.0024)					

Analysis 3.3. Comparison 3 Influence of missing data - UDCA versus placebo or no intervention, Outcome 3 Mortality - uncertain interval.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

Comparison: 3 Influence of missing data - UDCA versus placebo or no intervention

Outcome: 3 Mortality - uncertain interval

Study or subgroup	log [Odds ratio] (SE)	Odds ratio IV,Fixed,95% CI	Weight	Odds ratio IV,Fixed,95% CI
ATHENS	0.2927 (0.1983)		43.0 %	1.34 [0.91, 1.98]
BARCELONA	0.6981 (0.3454)		14.2 %	2.01 [1.02, 3.96]
DALLAS	0.207 (0.5371)		5.9 %	1.23 [0.43, 3.52]
FRANKFURT	-0.2107 (3.2273)		0.2 %	0.81 [0.00, 452.46]
GÖTEBORG	-0.0619 (1.3891)		0.9 %	0.94 [0.06, 14.31]
HELSINKI	-1.9661 (2.5021)		0.3 %	0.14 [0.00, 18.88]
MAYO-I	-0.6349 (0.3848)		11.4 %	0.53 [0.25, 1.13]
MILAN	0.0953 (3.2235)		0.2 %	1.10 [0.00, 609.87]
NEWARK-II	0.1044 (3.3005)		0.2 %	1.11 [0.00, 715.70]
NEWCASTLE	-0.7985 (1.0515)		1.5 %	0.45 [0.06, 3.53]
TAIPEI	0 (3.3286)		0.2 %	1.00 [0.00, 681.25]
TOKYO	0.0392 (3.2293)		0.2 %	1.04 [0.00, 583.19]
TORONTO	-0.6539 (0.3117)		17.4 %	0.52 [0.28, 0.96]
VILLEJUIF	-0.0202 (0.6047)		4.6 %	0.98 [0.30, 3.21]
Total (95% CI)			**100.0 %**	**1.03 [0.80, 1.33]**

Heterogeneity: Chi^2 = 14.68, df = 13 (P = 0.33); I^2 =11%

Test for overall effect: Z = 0.24 (P = 0.81)

Test for subgroup differences: Not applicable

Analysis 3.4. Comparison 3 Influence of missing data - UDCA versus placebo or no intervention, Outcome 4 Mortality or liver transplantation - uncertain interval.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

Comparison: 3 Influence of missing data - UDCA versus placebo or no intervention

Outcome: 4 Mortality or liver transplantation - uncertain interval

Study or subgroup	log [Odds ratio] (SE)	Odds ratio IV,Fixed,95% CI	Weight	Odds ratio IV,Fixed,95% CI
ATHENS	0.3716 (0.4319)		15.3 %	1.45 [0.62, 3.38]
BARCELONA	0.2546 (0.4168)		16.5 %	1.29 [0.57, 2.92]
DALLAS	0.0392 (0.447)		14.3 %	1.04 [0.43, 2.50]
FRANKFURT	-0.2107 (2.1471)		0.6 %	0.81 [0.01, 54.46]
GÖTEBORG	-0.3425 (0.7373)		5.3 %	0.71 [0.17, 3.01]
HELSINKI	-2.8134 (1.777)		0.9 %	0.06 [0.00, 1.95]
MANCHESTER	0.7608 (0.8945)		3.6 %	2.14 [0.37, 12.35]
MAYO-I	-0.6733 (0.4871)		12.0 %	0.51 [0.20, 1.32]
MILAN	0.0953 (2.0286)		0.7 %	1.10 [0.02, 58.63]
NEWARK-II	0.1044 (2.0482)		0.7 %	1.11 [0.02, 61.49]
NEWCASTLE	-0.1165 (0.7916)		4.6 %	0.89 [0.19, 4.20]
TAIPEI	0 (2.0357)		0.7 %	1.00 [0.02, 54.05]
TOKYO	0.0392 (2.0199)		0.7 %	1.04 [0.02, 54.50]
TORONTO	-0.6162 (0.3959)		18.2 %	0.54 [0.25, 1.17]
VILLEJUIF	-0.0202 (0.6942)		5.9 %	0.98 [0.25, 3.82]
Total (95% CI)			**100.0 %**	**0.89 [0.64, 1.25]**

Heterogeneity: Chi² = 8.50, df = 14 (P = 0.86); I² =0.0%

Test for overall effect: Z = 0.66 (P = 0.51)

Test for subgroup differences: Not applicable

Analysis 4.1. Comparison 4 UDCA-UDCA versus placebo/no intervention-UDCA, Outcome 1 Mortality.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

Comparison: 4 UDCA-UDCA versus placebo/no intervention-UDCA

Outcome: 1 Mortality

Study or subgroup	UDCA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
ATHENS	17/43	14/43		17.9 %	1.21 [0.69, 2.14]
BARCELONA	10/99	4/93		5.3 %	2.35 [0.76, 7.23]
DALLAS	7/77	4/74		5.2 %	1.68 [0.51, 5.51]
FRANKFURT	0/10	0/10			Not estimable
GÖTEBORG	1/60	1/56		1.3 %	0.93 [0.06, 14.57]
HELSINKI	0/30	2/31		3.1 %	0.21 [0.01, 4.13]
MAYO-I	14/89	23/91		29.0 %	0.62 [0.34, 1.13]
MILAN	0/44	0/44			Not estimable
NEWARK-II	0/9	0/10			Not estimable
NEWCASTLE	1/22	3/24		3.7 %	0.36 [0.04, 3.24]
TAIPEI	0/6	0/6			Not estimable
TOKYO	0/26	0/26			Not estimable
TORONTO	20/111	17/111		21.7 %	1.18 [0.65, 2.12]
VILLEJUIF	6/73	10/73		12.8 %	0.60 [0.23, 1.57]
Total (95% CI)	**699**	**692**		**100.0 %**	**0.97 [0.73, 1.30]**

Total events: 76 (UDCA), 78 (Control)

Heterogeneity: $Chi^2 = 9.10$, df = 8 (P = 0.33); $I^2 = 12\%$

Test for overall effect: Z = 0.19 (P = 0.85)

Analysis 4.2. Comparison 4 UDCA-UDCA versus placebo/no intervention-UDCA, Outcome 2 Mortality or liver transplantation.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

Comparison: 4 UDCA-UDCA versus placebo/no intervention-UDCA

Outcome: 2 Mortality or liver transplantation

Study or subgroup	UDCA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
ATHENS	23/43	17/43		10.0 %	1.35 [0.85, 2.15]
BARCELONA	17/99	11/93		6.7 %	1.45 [0.72, 2.93]
DALLAS	21/77	20/74		12.0 %	1.01 [0.60, 1.70]
FRANKFURT	0/10	0/10			Not estimable
GÖTEBORG	5/60	7/56		4.3 %	0.67 [0.22, 1.98]
HELSINKI	0/30	5/31		3.2 %	0.09 [0.01, 1.63]
MANCHESTER	4/14	2/14		1.2 %	2.00 [0.43, 9.21]
MAYO-I	28/89	42/91		24.5 %	0.68 [0.47, 1.00]
MILAN	0/44	0/44			Not estimable
NEWARK-II	0/9	0/10			Not estimable
NEWCASTLE	3/22	4/24		2.3 %	0.82 [0.21, 3.25]
TAIPEI	0/6	0/6			Not estimable
TOKYO	0/26	0/26			Not estimable
TORONTO	35/111	39/111		23.0 %	0.90 [0.62, 1.30]
VILLEJUIF	10/73	22/73		13.0 %	0.45 [0.23, 0.89]
Total (95% CI)	**713**	**706**		**100.0 %**	**0.86 [0.71, 1.03]**
Total events: 146 (UDCA), 169 (Control)					
Heterogeneity: Chi^2 = 14.82, df = 9 (P = 0.10); I^2 =39%					
Test for overall effect: Z = 1.60 (P = 0.11)					

Analysis 4.3. Comparison 4 UDCA-UDCA versus placebo/no intervention-UDCA, Outcome 3 Liver transplantation.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

Comparison: 4 UDCA-UDCA versus placebo/no intervention-UDCA

Outcome: 3 Liver transplantation

Study or subgroup	UDCA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
ATHENS	6/43	3/43		3.3 %	2.00 [0.53, 7.49]
BARCELONA	7/99	7/93		8.0 %	0.94 [0.34, 2.58]
DALLAS	14/77	16/74		18.1 %	0.84 [0.44, 1.60]
FRANKFURT	0/10	0/10			Not estimable
GÖTEBORG	4/60	6/56		6.9 %	0.62 [0.19, 2.09]
HELSINKI	0/30	3/31		3.8 %	0.15 [0.01, 2.74]
MAYO-I	14/89	19/91		20.9 %	0.75 [0.40, 1.41]
MILAN	0/44	0/44			Not estimable
NEWARK-II	0/9	0/10			Not estimable
NEWCASTLE	2/22	1/24		1.1 %	2.18 [0.21, 22.42]
TAIPEI	0/6	0/6			Not estimable
TOKYO	0/26	0/26			Not estimable
TORONTO	15/111	22/111		24.5 %	0.68 [0.37, 1.24]
VILLEJUIF	4/73	12/73		13.3 %	0.33 [0.11, 0.99]
Total (95% CI)	**699**	**692**		**100.0 %**	**0.74 [0.55, 0.99]**
Total events: 66 (UDCA), 89 (Control)					
Heterogeneity: Chi² = 6.79, df = 8 (P = 0.56); I² =0.0%					
Test for overall effect: Z = 2.05 (P = 0.040)					

ADDITIONAL TABLES

Table 1. Summary of characteristics of the included trials

Trial	Risk of bias	UDCA dose*	Trial duration (months)	Severity of PBC#¤
ATHENS	High	13.5	92.4	0.6400
BARCELONA	Low	15.5	63.6	0.2708
DALLAS	High	11.5	24.0	0.6689
FRANKFURT	Low	10.0	9.0	0.1500
GOTEBORG	Low	7.7	24.0	0.3350
HELSINKI	Low	13.5	24.0	0.3333
MANCHESTER	High	10.0	15.0	0.3200
MAYO-I	Low	14.0	48.0	0.6833
MILAN	High	8.7	12.0	0.4950
NEWARK-II	High	10.0	6.0	0.6666
NEWCASTLE	Low	10.0	24.0	0.8261
TAIPEI	High	9.2	3.0	0.5833
TOKYO	High	9.2	6.0	0.3795
TORONTO	High	14.0	24.0	0.5270
VILLEJUIF	High	14.0	24.0	0.4658

* UDCA dose in mg/kg/day.
# PBC: primary biliary cirrhosis.
¤ proportion of patients with stage III or IV at entry; or proportion of symptomatic patients at entry.

Table 2. UDCA effects on mortality adjusted for trial-level covariates

Covariates	Coefficient	95% CI	P-value
Risk of bias (low versus high)	0.07	-0.56 to 0.71	0.82
UDCA dose (mg/kg/day)	-0.14	-0.42 to 0.14	0.34
Trial duration (year)	0.01	0.01 to 0.02	0.003¤

Table 2. UDCA effects on mortality adjusted for trial-level covariates (*Continued*)

Severity of PBC*	-2.66	-5.11 to -0.20	0.03¤

*PBC: primary biliary cirrhosis.
¤The result reaches statistical significance at P < 0.05 level.

Table 3. UDCA effects on mortality or transplantation adjusted for trial-level covariates

Covariate	Coefficient	95% CI	P-value
Risk of bias (low vs. high)	0.37	-0.35 to 1.09	0.32
UDCA dose (mg/kg/day)	-0.10	-0.29 to 0.09	0.28
Trial duration (year)	0.01	-0.02 to 0.03	0.08
Severity of PBC*	-1.04	-3.19 to 1.11	0.34

*PBC: primary biliary cirrhosis.

Table 4. Bayesian estimate of UDCA effect on mortality

	Median OR (95%CrI)	Coefficient (95%CrI)
No covariate	0.89 (0.50 - 1.49)	Not applicable
Underlying risk of death at randomisation	0.82 (0.43 - 1.51)	0.10 (-0.62 to 0.65)
Trial duration (year)	0.71 (0.39 - 1.29)	0.03 (0.01 to 0.05)
Severity of PBC (%)	0.80 (0.43 - 1.46)	-0.67 (-4.26 to 2.75)

PBC: primary biliary cirrhosis.

APPENDICES

Appendix 1. Search strategies

Database	Searching period	Search term
The Cochrane Hepato-Biliary Group Controlled Trials Register	1948 to January 2007.	#1= 'primary biliary cirrhosis' and 'ursodeoxycholic acid'
The Cochrane Central Register of Controlled Trials in The Cochrane Library	Issue 4, 2006.	#1 = LIVER CIRRHOSIS BILIARY: MESH #2 = primary and biliary and cirrhosis #3 = primary biliary cirrhosis #4 = pbc #5 = #1 or #2 or #3 or #4 #6 = URSODEOXYCHOLIC ACID: MESH #7 = DEOXYCHOLIC ACID: MESH #8 = 'ursodeoxycholic acid' or 'UDCA' #9 = #6 or #7 or #8 #10 = #5 and #9
PubMed	Until January 2007.	#1 = LIVER-CIRRHOSIS-BILIARY: MESH #2 = primary and biliary and cirrhosis #3 = primary biliary cirrhosis #4 = PBC #5 = #1 or #2 or #3 or #4 #6 = URSODEOXYCHOLIC ACID: MESH #7 = DEOXYCHOLIC ACID: MESH #8 = 'ursodeoxycholic*' or 'UDCA' #9 = deoxycholic* #10 = #6 or #7 or #8 or #9 #11 = #5 and #10 #12 = random* or placebo* or blind* or meta-analysis #13 = #11 and #12
MEDLINE	January 1966 to January 2007.	#1 = LIVER-CIRRHOSIS-BILIARY: MESH #2 = primary and biliary and cirrhosis #3 = primary biliary cirrhosis #4 = PBC #5 = #1 or #2 or #3 or #4 #6 = URSODEOXYCHOLIC ACID: MESH #7 = DEOXYCHOLIC ACID: MESH #8 = 'ursodeoxycholic*' or 'UDCA' #9 = deoxycholic* #10 = #6 or #7 or #8 or #9 #11 = #5 and #10 #12 = random* or placebo* or blind* or meta-analysis #13 = #11 and #12

(*Continued*)

EMBASE	January 1980 to January 2007.	#1 = PRIMARY-BILIARY-CIRRHOSIS: MESH #2 = BILIARY-CIRRHOSIS: MESH #3 = primary and biliary and cirrhosis #4 = primary biliary cirrhosis #5 = PBC #6 = #1 or #2 or #3 or #4 or #5 #7 = URSODEOXYCHOLIC ACID: MESH #8 = DEOXYCHOLIC ACID: MESH #9 = 'ursodeoxycholic*' or 'UDCA* #10 = deoxycholic* #11 = #7 or #8 or #9 or #10 #12 = #6 and #11 #13 = random* or placebo* or blind* or meta-analysis #14 = #12 and #13
Chinese Biochemical CD Database	January 1979 to January 2007.	#1 = LIVER-CIRRHOSIS-BILIARY: MESH #2 = primary and biliary and cirrhosis #3 = primary biliary cirrhosis #4 = PBC #5 = #1 or #2 or #3 or #4 #6 = URSODEOXYCHOLIC ACID: MESH #7 = DEOXYCHOLIC ACID: MESH #8 = 'ursodeoxycholic*' or 'UDCA' #9 = deoxycholic* #10 = #6 or #7 or #8 or #9 #11 = #5 and #10 #12 = random* or placebo* or blind* or meta-analysis #13 = #11 and #12
LILACS	1982 to January 2007.	#1 = (primary and biliary and cirrhosis) or (primary biliary cirrhosis) #2 = primary biliary cirrhosis #3 = ursodeoxycholic acid
SCI-EXPANDED	1945 to January 2007.	#1 = PRIMARY-BILIARY-CIRRHOSIS: MESH #2 = BILIARY-CIRRHOSIS: MESH #3 = primary and biliary and cirrhosis #4 = primary biliary cirrhosis #5 = PBC #6 = #1 or #2 or #3 or #4 or #5 #7 = URSODEOXYCHOLIC ACID: MESH #8 = DEOXYCHOLIC ACID: MESH #9 = 'ursodeoxycholic*' or 'UDCA* #10 = deoxycholic* #11 = #7 or #8 or #9 or #10 #12 = #6 and #11 #13 = random* or placebo* or blind* or meta-analysis #14 = #12 and #13

FEEDBACK

Ursodeoxycholic acid for primary biliary cirrhosis

Summary

It would be helpful if the Comment had a sentence on what the substantive change is between the original article and the update so its significance, or lack thereof, is apparent.Thank you for your consideration.
I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.
Karyn Driessen, CA, USA
11.06.2003

Reply

Thank you very much for showing your interest in our review and for your comment.
The changes that occurred in our review between the version published in Issue I, 2003 (and previous issues) and in Issue II, 2003 were of no material importance to the data or conclusions of the review. The only encompassed minor stylistic changes as well as addition of an extra reference in the Background section.
Our original text in the Background was:
"Primary biliary cirrhosis (PBC) is a rather rare, chronic liver disease of unknown etiology. It was first comprehensively described by Ahrens and co-workers in 1950 (Ahrens 1950)."
This was changed into:
"Primary biliary cirrhosis (PBC) is a rather rare, chronic liver disease of unknown etiology. It was first comprehensively described around 1950 (MacMahon 1949; Ahrens 1950)."
Therefore, the review was not marked as 'Updated', we only changed the date of last amendment.
Your comment has made me realise the importance of keeping track of all changes, no matter how small. We shall remember that when we update our review in late 2003.
Christian Gluud
The Copenhagen Trial Unit
H:S Rigshospitalet
I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.
11.06.2003

Contributors

Christian Gluud; Erik Christensen, Denmark.

WHAT'S NEW

Last assessed as up-to-date: 10 January 2008.

Date	Event	Description
14 August 2008	Amended	A small typo error corrected.

HISTORY

Protocol first published: Issue 4, 1997

Review first published: Issue 1, 2002

Date	Event	Description
5 May 2008	New citation required but conclusions have not changed	Conclusions did not change.
27 March 2008	Amended	Converted to new review format.
10 January 2008	New search has been performed	Mortality and liver transplantation data from three trials and adverse events data from one trial are updated

CONTRIBUTIONS OF AUTHORS

YG made searches, identified trials with updated information, performed statistical analyses, drafted the review; ZBH performed a part of the statistical analyses; EC and CG validated a selection of trials as well as reviewed the article.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- The Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Denmark.
- Copenhagen Hospital Corporation, Denmark.

External sources

- S.C. Van Foundation, Denmark.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Peer reviewers requested that we included data from the trials after the period in which fair comparisons could be made.

NOTES

This is an updated systematic review to the Gluud et al (Gluud 2001 b).

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Cholagogues and Choleretics [adverse effects; *therapeutic use]; Liver Cirrhosis, Biliary [*drug therapy; mortality]; Randomized Controlled Trials as Topic; Treatment Outcome; Ursodeoxycholic Acid [adverse effects; *therapeutic use]

MeSH check words

Humans