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Ursodeoxycholic Acid for Patients With Primary Biliary Cirrhosis: An Updated Systematic Review and Meta-Analysis of Randomized Clinical Trials Using Bayesian Approach as Sensitivity Analyses

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OBJECTIVES: Ursodeoxycholic acid (UDCA) is used for primary biliary cirrhosis (PBC), but the beneficial effects remain controversial.

METHODS: We performed an updated systematic review to evaluate the benefits and harms of UDCA in patients with PBC. We included randomized clinical trials evaluating UDCA *versus* placebo or no intervention in patients with PBC. The primary outcomes, mortality and mortality or liver transplantation, were reported as relative risk (RR) with 95% confidence interval (CI). Meta-regression was used to investigate the associations between UDCA effects and the trial's risk of bias, UDCA dose, duration, and PBC severity at trial entry. We used Bayesian meta-analytic approaches as sensitivity analyses.

RESULTS: Sixteen randomized clinical trials (1,447 patients) evaluating UDCA *versus* placebo or no intervention were identified. Over half of the trials had high risk of bias. Comparing with placebo or no intervention, UDCA did not significantly affect mortality (RR 0.97, 95% CI 0.67–1.42) and mortality or liver transplantation (RR 0.92, 95% CI 0.71–1.21). The findings were supported by the Bayesian meta-analyses. Meta-regression analyses suggested that UDCA effects seem to be associated with patient's disease severity and trial duration. UDCA did not improve pruritus, fatigue, autoimmune conditions, liver histology, or portal pressure. UDCA seemed to improve biochemical variables, such as serum bilirubin, and ascites and jaundice, but the findings were based on few trials with sparse data. The use of UDCA was significantly associated with adverse events, mainly weight gain.

CONCLUSIONS: This updated systematic review did not demonstrate any benefit of UDCA on mortality and mortality or liver transplantation in patients with PBC.

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INTRODUCTION

Primary biliary cirrhosis (PBC) is an uncommon and slowly progressive autoimmune disease of the liver that primarily affects middle-aged women. It was first comprehensively described around 1950 (1, 2). Over the last 30 yr, substantial increases in the prevalence of PBC have been observed (3). PBC is now a frequent cause of liver morbidity, and the patients are significant users of health resources, including liver transplantation (4). Fatigue and pruritus are the most common presenting symptoms (5). The diagnosis of PBC is currently based on the following triad: the presence of detectable antimitochondrial antibodies in serum, elevation of liver enzymes (most commonly alkaline phosphatases) for more than 6 months, and characteristic liver histological changes in the absence of extrahepatic biliary obstruction (6).

Bile duct destruction leads to the retention of hydrophobic bile acids within the liver cell. This likely contributes to the gradual deterioration in liver function observed in patients with PBC. 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 PBC (7). UDCA is the only drug approved for PBC by the Food and Drug Administration. Doses of 13–15 mg/kg/day cause significant improvements in liver biochemistry and immunoglobulin levels and reduce titers

of antimitochondrial antibodies (8, 9). However, the effect of UDCA on mortality and histological progression remains controversial (10, 11). Since 2001, several randomized clinical trials have been published with the results of longer-term follow-up on patients' survival (12–14). We, therefore, re-evaluated the effects of UDCA in patients with PBC by updating our systematic review on the topic (11).

METHODS

We conducted the meta-analysis following our protocol (15) and the recommendations from the Cochrane Collaboration (16). We included and reviewed all randomized clinical trials assessing the effects of UDCA *versus* placebo or no intervention in patients with PBC, irrespective of blinding, language, year of publication, and publication status (15).

We searched for randomized trials in The Cochrane Hepato-Biliary Group Controlled Trials Register (17), The Cochrane Central Register of Controlled Trials in The Cochrane Library, MEDLINE, EMBASE, Science Citation Index-Expanded, The Chinese Biomedical CD Database, LILACS, and references of identified studies. The last search was performed in January 2007.

The primary outcome measures were mortality and mortality or liver transplantation. Secondary outcome measures were liver transplantation, pruritus, fatigue, clinical symptoms, liver biochemistry, liver biopsy, quality of life, adverse events (excluding mortality and liver transplantation), and cost-effectiveness.

In accordance with empirical evidence (18–20), we assessed the methodological quality of the trials. Trials with low risk of bias were the ones meeting the adequacy of three components: generation of the allocation sequence, allocation concealment, and blinding (18–20). Trials with high risk of bias were ones having one or more of these components regarded as inadequate or unclear.

We performed meta-analyses with Review Manager 4.2 (http://www.cochrane.dk). We analyzed data by random-effects (21) and fixed-effect (22) models. We presented binary outcome measures as relative risk (RR) with 95% confidence interval (CI) and continuous outcome measures as weighted mean difference (WMD) with 95% CI. Heterogeneity was explored by χ^2 test with significance set at $P < 0.10$. The degree of heterogeneity was measured by I^2 (23) and between-trial variance was estimated by the method of moments (21). The larger the I^2 and the moment-based between-trial variance, the larger degree of heterogeneity is present. We performed a meta-regression analysis with STATA (Intercooled STATA 8.0, Stata Corp., College Station, TX), which examined the effect size of UDCA in relation to the risk of bias, UDCA dosage, trial duration (treatment and follow-up), and severity of PBC at entry. We explored publication bias and other bias according to Begg's and Egger's methods (24, 25) with STATA.

We conducted the following sensitivity analyses to investigate the robustness of our main analyses on primary outcomes: (a) 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 (26). (b) Bayesian meta-analytic approach with WinBUGS (version 1.4.1, Medical Research Council, Biostatistics Unit, Cambridge, UK), 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 analog of a classical estimate is the marginal posterior median and the analog of a classical confidence interval is the credibility interval (CrI) (27). We used odds ratio (OR) as the summary statistic. For the ease of comparison, we reported the Bayesian results together with results from the classical meta-analysis presented as OR. (c) 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 (28). We also use this approach to investigate the relationship between one specific covariate (*e.g.*, UDCA dosage, trial duration, or disease severity of patients at entry) and the effects of UDCA adjusted for underlying risk.

RESULTS

We identified 863 references through electronic and hand searches. We excluded 762 duplicates or clearly irrelevant references and the remaining 101 references referred to 16 randomized clinical trials with 1,447 patients. Two of the 16 trials were published as abstracts only (29, 30), of which the De la Mora *et al*. trial (30) contained no extractable data with

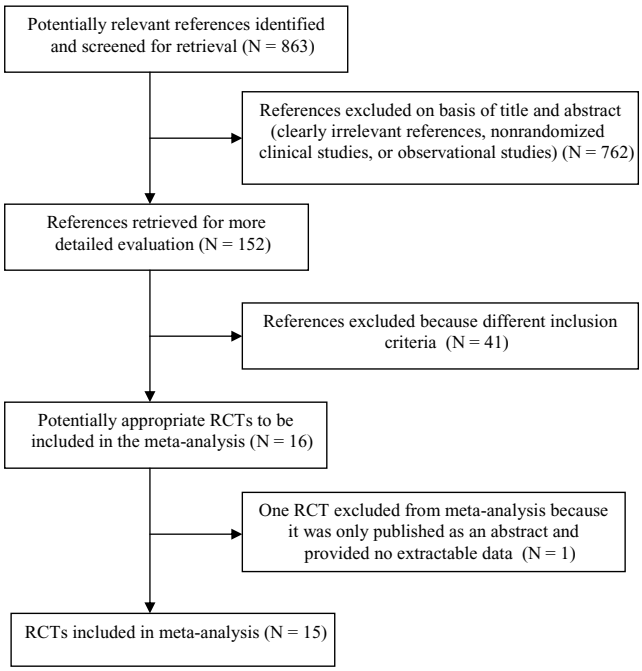

Figure 1. Flow diagram of trial selection.

Table 1. Characteristics of Included Trials of UDCA for Patients With PBC

Study ID	Risk of Bias	UDCA* Dose (mg/kg/day)†	Trial Duration‡ (months)	PBC§ Severity (%)¶	Notes
Athens 2002	High	13.5	92	64	14/43 control patients were crossed over to UDCA at their own request at a median of 3.5 yr (range 2–8 yr) after entry. The authors did both intention-to-treat analysis and treatment-as-received analysis.
Barcelona 2000	Low	15.5	64	27	None
Dallas 2004	High	11.5	24	67	Three patients randomized to receive placebo had high bile UDCA concentrations, suggesting UDCA intake. All patients were offered open-label UDCA following completion of the first 2 yr of the trial.
Frankfurt 1989	Low	10.0	9	15	None
Göteborg 1997	Low	7.7	24	34	At 24 months, 32 of 49 patients allocated to placebo and still remaining in the trial were switched to UDCA and 42 of 52 patients allocated to UDCA and still remaining in the trial continued with UDCA. Antihepatitis C virus tests not performed.
Helsinki 1995	Low	13.5	24	33	None
Manchester 1994	High	10.0	15	32	No exact data on number of patients randomized to each arm. No data given separately on mortality and liver transplantation.
Mayo-I 1994	Low	14.0	48	68	Patients originally receiving placebo switched to UDCA after 4 yr and followed for an additional 8 yr.
Milan 1993	High	8.7	12	50	Patients switched onto UDCA at the end of the trial.
Newark-II 1991	High	10.0	6	67	None
Newcastle 1994	Low	10.0	24	83	None
Taipei 1993	High	9.2	3	58	All patients switched to UDCA on completion of the 6 months crossover trial.
Tokyo 1990	High	9.2	6	38	None
Toronto 1994	High	14.0	24	53	Patients offered UDCA at the end of the trial.
Villejuif 1991	High	14.0	24	47	All patients treated for 2 yr with placebo were offered UDCA and further followed up for another 2 yr 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, violating the entry criteria.

*UDCA = ursodeoxycholic acid; †UDCA dose = average of the reported range; ‡Trial duration = includes treatment and follow-up; §PBC = primary biliary cirrhosis; ¶PBC severity = proportion of patients with stage III or IV at entry or with symptoms at entry.

28 patients (Fig. 1). Consequently, a summary of the 15 trials, *i.e.*, risk of bias, UDCA dose, trial duration, the percentage of patients with advanced PBC or presenting symptoms at entry, is given in Table 1. In the follow-up period, seven trials continued UDCA-treated patients on open-label UDCA (UDCA→UDCA) and offered open-label UDCA to all or some patients originally given placebo (placebo→UDCA) (8, 12–14, 31–33). Compared to the first version of this systematic review published in 2001 (11), the present review contains updated data on mortality and liver transplantation from three trials (12, 14, 34) and on adverse events from one trial (14) due to the new publications.

Mortality

Mortality data from 14 trials were combined. UDCA had no significant effects on mortality (RR 0.97, 95% CI 0.67–1.42, $I^2 = 0\%$, Fig. 2). 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-trial variance is 0.042.

To take the missing data into account, we used the uncertainty method to estimate the UDCA effect on mortality (26). The result was consistent with the main finding above (RR 1.08, 95% CI 0.68–1.70). The Bayesian meta-analysis results (median OR 0.89, 95% CrI 0.50–1.49) also supported the main analysis presented as OR with 95% CI (OR 0.97, 95% CI 0.62–1.51). When adjusted for underlying risks the median OR was 0.82 and 95% CrI was 0.43–1.51 (Table 2).

In a meta-regression model we included risk of bias of the trials, UDCA dose, trial duration, and severity of PBC at entry as covariates and the effects of UDCA on mortality as a dependent variable. The model identified trial duration and severity of PBC as two covariates that might have associations with the effects of UDCA (Table 3). 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 (Table 2).

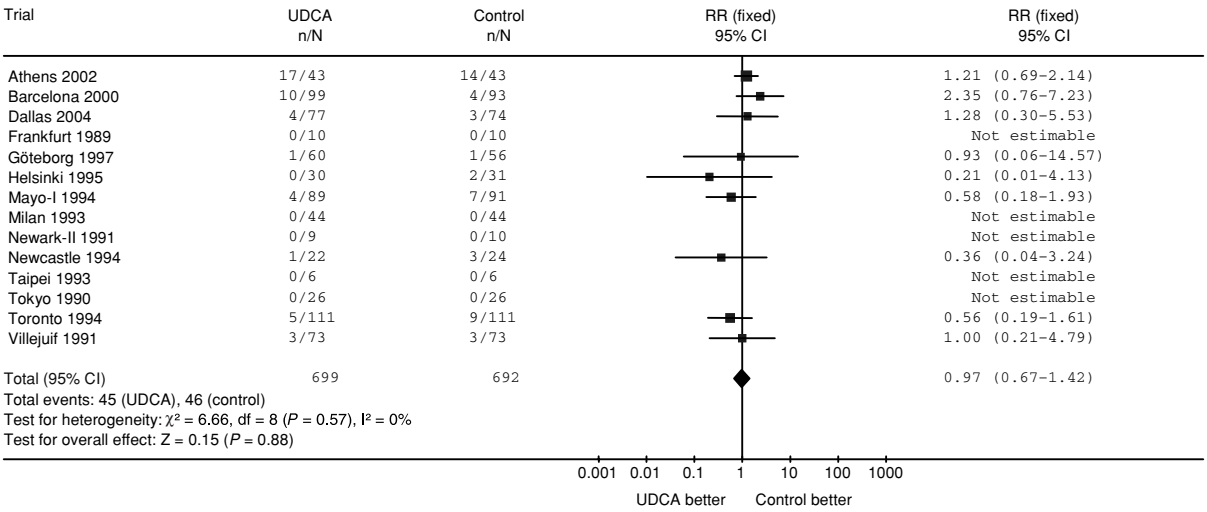

Figure 2. Forest plot of effect of UDCA on mortality. Abbreviations: CI = confidence interval; n = number of patients with outcome; N = number of participants at risk; df = degrees of freedom; I^2 = the percentage of total variation across studies that is due to heterogeneity rather than chance.The result and its 95% CI are represented by a diamond, with the relative risk (95% CI) and its statistical significance given alongside. Squares or diamonds to the left of the solid vertical line indicate benefit with UDCA, but this is conventionally significant ($P < 0{\cdot}05$) only if the horizontal line or diamond does not overlap the solid vertical line.

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 0.73–1.30. It compared 76 deaths in 699 patients (10.9%) originally randomized to UDCA with 78 deaths in 692 patients (11.3%) originally randomized to placebo or no intervention.

Mortality or Liver Transplantation

Combining the results of 15 trials demonstrated no significant effects on mortality or liver transplantation; neither UDCA nor placebo was favored (RR 0.92, 95% CI 0.71–1.21, Fig. 3). 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 RR 1.05 with 95% CI 0.75–1.48. The Bayesian analysis (median OR 0.84, 95% CrI 0.53–1.30) supported the main analysis presented as OR with 95% CI (OR 0.90, 95% CI 0.65–1.26). When adjusted for baseline risk, the median OR is 0.77 with 95% CrI 0.43–1.37.

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 (data not shown).

Including data from the extended follow-up for UDCA→UDCA *versus* placebo/no intervention→UDCA demonstrated a RR of 0.86 with 95% CI 0.71–1.03. It compared 146 deaths or liver transplantations in 713 patients (20.5%) originally randomized to UDCA with 169 deaths or liver transplantations in 706 patients (23.9%) originally randomized to placebo or no intervention.

Liver Transplantation

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

Table 2. Bayesian Estimate of UDCA Effect on Mortality Presented as Posterior Median OR When Including One of Three Trial-Level Covariates, in Comparison to No Covariate, and the Influence of Covariates Presented as Posterior Median Coefficient, Both Applied to Mortality Data from 14 Trials on UDCA *versus* Placebo or No Intervention in Patients with PBC

	Posterior Median OR (95% Credibility Interval)	Posterior Median Coefficient (95% Credibility Interval)
No covariate	0.89 (0.50–1.49)	Not applicable
Underlying risk	0.82 (0.43–1.51)	0.10 (−0.62–0.65)
Trial duration (yr)	0.71 (0.39–1.29)	0.03 (0.01–0.05)
*PBC severity (%)	0.80 (0.43–1.46)	−0.67 (−4.26–2.75)

*PBC = primary biliary cirrhosis.

Table 3. Meta-Regression Analysis: UDCA Effects on Mortality for Predefined Trial-Level Covariates, *i.e.*, Risk of Bias, UDCA Dose, Trial Duration, and PBC Severity at Entry

	Coefficient	95% Confidence Interval	*P* Value
Risk of bias (low compared to high)	0.07	−0.56–0.71	0.82
UDCA* dose (mg/kg/day)	−0.14	−0.42–0.14	0.34
Trial duration (yr)	0.01	0.01–0.02	0.003
PBC† severity (%)	−2.66	−5.11 to −0.20	0.03

* UDCA = ursodeoxycholic acid; †PBC = primary biliary cirrhosis.

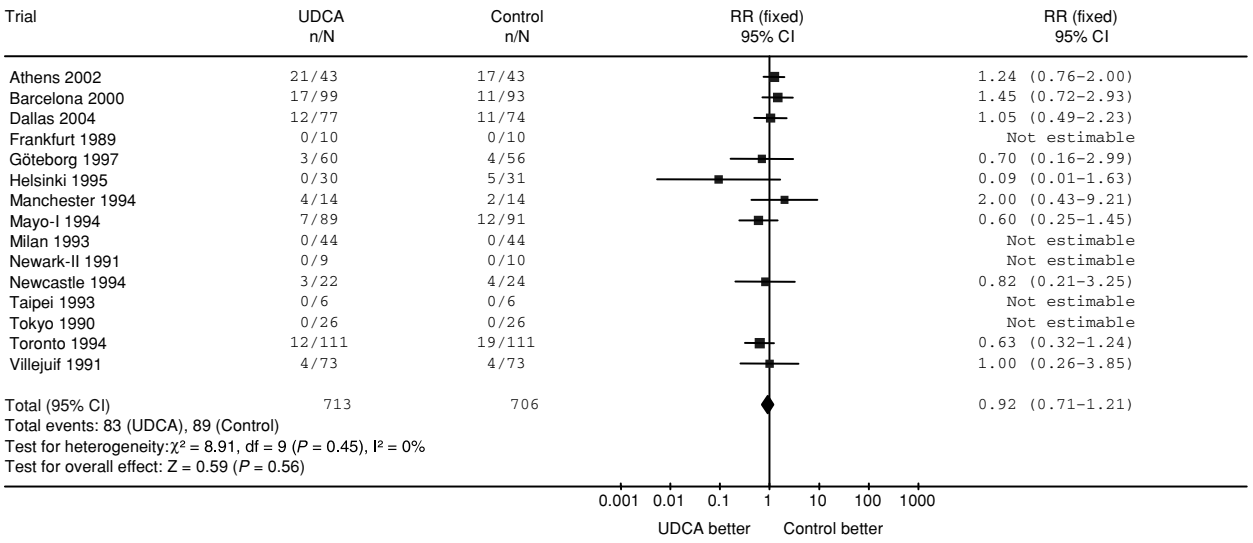

Figure 3. Forest plot of effect of UDCA on mortality or liver transplantation. Abbreviations: CI = confidence interval; n = number of patients with outcome; N = number of participants at risk; df = degrees of freedom; I^2 = the percentage of total variation across studies that is due to heterogeneity rather than chance. The result and its 95% CI are represented by a diamond, with the relative risk (95% CI) and its statistical significance given alongside. Squares or diamonds to the left of the solid vertical line indicate benefit with UDCA, but this is conventionally significant ($P < 0{\cdot}05$) only if the horizontal line or diamond does not overlap the solid vertical line.

Pruritus, Fatigue, Jaundice, and Other Clinical Symptoms

UDCA did not significantly influence either the number of patients with pruritus (RR 0.97, 95% CI 0.78–1.19, 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 0.76–1.06, 3 trials). Two trials reporting the number of patients with jaundice led to a significant effect favoring UDCA (RR 0.35, 95% CI 0.14–0.90) (33, 35). In most trials information on autoimmune conditions was sparse. However, the Mayo-I trial (36) evaluated the autoimmune conditions during the UDCA and placebo periods 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 0.29–1.17, 3 trials), bleeding varices (RR 0.55, 95% CI 0.21–1.41, 4 trials), nor hepatic encephalopathy (RR 0.39, 95% CI 0.06–2.56, 2 trials) were significantly improved by UDCA. The number of patients developing ascites was significantly lower in the UDCA group compared with the control group (RR 0.42, 95% CI 0.19–0.93, 4 trials).

Liver Biochemistry

UDCA intervention led to some improvements on liver biochemistry (Table 4). Only one trial reported s-albumin concentrations (32) and one prothrombin index (33). The two variables were not significantly affected by UDCA.

Liver Histology

There were no significant effects of UDCA on histological stage (RR 0.78, 95% CI 0.57–1.06, random, 5 trials), fibrosis (RR 0.88, 95% CI 0.57–1.38, 1 trial), or florid duct lesions (RR 0.84, 95% CI 0.40–1.76, 1 trial). About half of the patients in the Barcelona trial observed statistically significant improvements in histological stage, portal inflammation, and piecemeal necroses in the UDCA group, but not regarding ductular proliferation or cholestasis. The placebo group had significantly fewer bile ducts per portal tract (9).

Quality of Life

None of the trials examined specific quality-of-life scales. Two trials evaluated symptoms using visual analog scales, (31, 37) and neither showed any significant difference between the UDCA and placebo group.

Adverse Events

Only Battezzati *et al*. reported one serious adverse event in the UDCA group, while the other trials only reported nonserious adverse events (32). UDCA led to a significantly higher incidence of adverse events (OR 1.74, 95% CI 1.10–2.75, 11 trials), mainly weight gain (38). Patients in the UDCA group gained an average of 3.6 kg ± 6.5%, which was significantly greater than the average of 0.6 kg ± 6.9% gained in the placebo group ($P = 0.04$) (38).

Publication Bias and Other Biases

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

Table 4. Effects of UDCA on Liver Biochemistry

	WMD*	95% Confidence Interval	*P* Value	Number of Trials Analyzed
Bilirubin (μmoL/L)	−10	−16 to −5	<0.001	6
Alkaline phosphatases (IU/L)	−359	−525 to −193	<0.001	6
Gamma-glutamyl transpeptidase (IU/L)	−258	−318 to −197	<0.001	4
Aspartate aminotransferase (IU/L)	−36	−53 to −18	<0.001	5
Alanine aminotransferase (IU/L)	−48	−77 to −18	<0.001	5
Total cholesterol (mmoL/L)	−0.5	−0.8 to −0.2	<0.001	5
Plasma immunoglobulin M (g/L)	−1.3	−1.9 to −0.6	<0.001	4

*Weighted mean difference.

DISCUSSION

Our updated systematic review analyzed data from 15 randomized clinical trials assessing the effects of UDCA against placebo or no intervention for patients with PBC. 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 the Goulis *et al*. meta-analysis (10) and our previous Cochrane systematic review (11). Moreover, the potential effects of UDCA on mortality seem to be associated with trial duration and disease severity: the longer the trial, the less effects of UDCA (if any); the more severe 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" (5, 39). 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. Trial selection bias and outcome reporting bias should, therefore, be considered. UDCA is generally well tolerated in patients with PBC.

There were no statistical signs of publication bias or other bias. This review analyzed 15 trials involving 1,447 patients. This is a low number of patients (40). The median length of trial duration was 2 yr. This is not sufficiently long considering that the estimated median survival of a patient with PBC is 10–15 yr (41). It is, therefore, difficult to detect a significant difference on mortality based on the trials, most of which have low statistical power. Furthermore, nine of the 15 trials had high risk of bias in terms of methodological quality. In general, trials with high risk of bias overestimate intervention effects (18–20). If the same overestimation is valid for the included trials, the prospects for UDCA in PBC may look even worse.

This systematic review did not demonstrate any benefit favoring UDCA on our predefined primary outcomes: mortality and mortality or liver transplantation. This observation is in contrast to some previous attempts to aggregate data from studies assessing UDCA interventions for PBC (42–44). However, Simko *et al*. (42) included nonrandomized studies in their meta-analysis. Such studies are more liable to bias. Poupon *et al*. included only three and five out of the 15 randomized clinical trials in their meta-analyses, respectively (43, 44). Such meta-analyses run the risk of trial selection bias—"cherry picking" (45).

Our main findings using a 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.

A common criticism about meta-analyses is that they combine information from trials with very different patient characteristics and designs, regarded as sources of heterogeneity. 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," *i.e.*, the average risk of an event (*e.g.*, mortality) for a patient at randomization. The "true" UDCA effect on mortality after adjusting the different underlying risks, by using a Bayesian approach, is estimated as median OR 0.82 with 95% CrI 0.43–1.51, and the "true" UDCA effect on mortality or liver transplantation is estimated as median OR 0.77 with 95% CrI 0.43–1.37. These results, taking underlying risk into consideration, support our unadjusted main meta-analyses.

We also considered other important and predefined trial-level covariates, including trial risk of bias, UDCA dose, trial duration, and severity of PBC. 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 PBC, 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 a covariate.

The previous Lancet meta-analysis (10) and our Cochrane systematic review (11) were mainly criticized for including many trials of only 2-yr duration and with very heterogeneous lengths of follow-up (5, 46). Given the updated evidence from

randomized clinical trials and analyses on longer follow-up data, our present review does not seem to support long-term UDCA intervention, which was suggested in observational studies (47, 48). 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 0.39–1.29), has been consistent with the estimation from unadjusted pooled results (OR 0.89, 95% CrI 0.50–1.49). The adjusted result did not suggest any benefit of UDCA on mortality, even assuming that the trials have the same duration and underlying risk.

The relationship between UDCA effect and patients' severity of PBC 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 PBC. This indication is supported by an analysis combining the raw data of three large clinical trials, in which a survival benefit of UDCA was observed in patients with moderate-to-severe disease, but not in those with mild disease (43). However, this relationship was not supported by our Bayesian meta-regression, which included "severity" as a covariate. Therefore, whether the UDCA intervention effect (if any) is related to the severity of PBC or not should be further investigated. Despite the uncertainty, the UDCA effect adjusting for the PBC severity and the above-mentioned underlying risk (OR 0.80, 95% CrI 0.43–1.46) has been consistent with the unadjusted pooled results (OR 0.89, 95% CrI 0.50–1.49). The adjusted result did not suggest any benefit of UDCA on mortality, even assuming that the trials have the same percentage of advanced patients and same level of underlying risk.

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. Accordingly, our observation needs confirmation.

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 (9). It observed positive effects on a number of histological variables, *e.g.*, the histological stage. This finding may also be a spurious one. Only about half of the randomized 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 (49–51). 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 PBC and eventually cirrhosis development (9).

UDCA was generally well tolerated. We observed that UDCA was associated with nonserious adverse events, mostly weight gain. This finding ensued from new data from the Mayo-I trial (38). 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 nonserious adverse events included mild gastrointestinal disorders like diarrhea, nausea, vomiting, etc.

It has been claimed that UDCA is a cost-effective therapy for PBC (52). However, this claim rests on extrapolation from the results of two selected randomized clinical trials (8, 14). 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 $2,500 (52) and the findings of the present review, we challenge the conclusion drawn by Pasha *et al*. that UDCA is cost-effective for PBC.

Consistent with previous meta-analyses and reviews (10, 11), this updated systematic review did not demonstrate any benefit of UDCA on mortality and mortality or liver transplantation in patients with PBC. 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 (*e.g.*, mortality), there is insufficient evidence to support the use of UDCA in PBC, but if based on nonvalidated "surrogate" outcomes (*e.g.*, s-bilirubin level), there is evidence favoring the UDCA interventions for the disease (53). This dilemma was reflected in a survey regarding the use of UDCA for PBC among Danish doctors (54), who had very different answers to the question of why they prescribed UDCA for PBC patients. Sixteen percent of the doctors thought UDCA reduced mortality, 27% thought UDCA reduced morbidity, and 23% thought it benefited "surrogate" outcomes (54, 55).

The Mayo Risk Score Model has identified several prognostic biomarkers for PBC, *e.g.*, 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" (56). In the absence of validated surrogate outcomes in UDCA for PBC, confirmatory trials assessing the UDCA effect should only be based on clinical outcomes, *e.g.*, survival. We believe that such clinical outcomes-based evaluation will benefit patients in the long run (53).

We also realize that the challenge of performing a new trial on intervention for PBC is high. The estimated median survival of PBC is 10–15 yr. To spend 15 yr planning and

carrying out a trial for each new potential treatment for PBC would consume many patients' lifetimes, not to mention the expense and difficulty of retaining patients in such a long study (57). Nevertheless, there are at least an estimated one million patients with PBC worldwide. Therefore, it is possible to conduct large trials with appropriate statistical power, if international groups of PBC investigators collaborate. Such large trials do not need to be conducted for more than 2–4 yr.

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CONFLICT OF INTEREST

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