Randomised controlled trials of ursodeoxycholic-acid therapy for primary biliary cirrhosis: a meta-analysis

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Authors' objectives
To clarify the efficacy of ursodeoxycholic acid (UDCA) in primary biliary cirrhosis.

Searching
The authors searched the electronic databases MEDLINE and EMBASE (January 1987 to July 1998) using the search textwords: 'primary biliary cirrhosis', 'ursodeoxycholic acid', and 'treatment'. The authors also performed a manual search of all review articles, of the retrieved original studies, and all abstracts from meetings (January 1995 and October 1998) of: American Digestive Disease Week, American Association for the Study of Liver Diseases, European Association for the Study of Liver Diseases, and United European Gastroenterology Week. Only English language trials were included.

Study selection
Study designs of evaluations included in the review
Prospective, randomised placebo controlled trials. Trials with patients in the switch-over phases to UDCA were also included. Included trials had to have a mean follow-up of more than 6 months. Controlled trials without randomisation or those which compared a combination of treatments were excluded.

Specific interventions included in the review
Ursodeoxycholic acid (UDCA) and placebo. The daily dose of UDCA ranged from 7.7 mg/kg to 15 mg/kg, and duration of trials ranged from 9 to 63.6 months.

Participants included in the review
Patients with primary biliary cirrhosis (PBC) diagnosed according to established diagnostic criteria. The mean age of participants ranged from 49 to 57 years.

Outcomes assessed in the review
The authors assessed six outcomes: death, death related to liver disease, transplantation, death or transplantation, the development of complications of liver disease (ascites or gastrointestinal bleeding), and incidence of side effects. The authors also assessed the studies using the main end point stated by each included study, including those studies that used the term 'treatment failure' as their main endpoint.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The authors assessed the validity of studies using the following criteria: methods and efficacy of randomisation; blinding in evaluation of results; follow-up schedules; estimation of sample size; handling of withdrawals; evaluation of response; information about patient characteristics; evaluation of patient enrolment; and assessment of therapeutic intervention. The authors do not state how many of the authors performed the validity assessment although they do state that differences in assessment were resolved through discussion.

Data extraction
The authors state that data were extracted independently from each study using a predefined review form and
disagreement was resolved by consensus.

Data were extracted for the categories of study identification, patient numbers, mean patient years, duration of trial (months), UDCA dose (mg/kg daily), mean baseline billirubin (micromol/L), histological stage, and methodological quality (possible score 0-79).

Methods of synthesis
How were the studies combined?
Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using the fixed-effect model of Mantel-Haenszel as modified by Robbins (see Other Publications of Related Interest no.1) and the random-effects model of DerSimonian and Laird.

How were differences between studies investigated?
The authors used the chi-square statistic to test for heterogeneity within studies.

The authors also performed five sensitivity analyses: dose of the drug; duration of treatment; mean serum bilirubin level at entry; methodological quality; and type of publication.

Results of the review
Eleven RCTs were included in the review with 1272 participants. There were 611 participants randomised to the intervention groups and 601 participants randomised to the placebo group. There were six reports with switch-over phase data.

Methodological quality scores ranged from 18-69 on a scale of 0-79.

UCDA had a favourable effect on liver biochemistry in most of the studies but not on symptoms or the progression of histological stage; two studies did not assess survival, liver transplantation, or complications of liver disease.

Meta-analyses showed no difference between UDCA and placebo in the incidence of death (OR 1.21, 95% CI: 0.71, 2.04), liver-related death (OR 0.72, 95% CI: 0.22, 2.32), liver transplantation (OR 1.27, 95% CI: 0.78, 2.07), death or liver transplantation (OR 1.26, 95% CI: 0.87, 1.82), and in the development of complications of liver disease (OR 1.10, 95% CI: 0.64, 1.90).

With the primary end point defined by the authors (a combined end point in three studies, and death or liver transplantation in the others) an OR 1.53, (95% CI: 0.97, 2.42) was obtained.

Assessment of the switch-over phases, during which there was a longer follow-up, did not change the results of the meta-analysis.

Authors’ conclusions
The authors state that published randomised controlled trials of UCDA do not show evidence of therapeutic benefit in PBC and its use as a standard therapy needs to be re-examined.

CRD commentary
This is a good review. The authors have clearly stated their research question and the inclusion and exclusion criteria. The literature search appears to be thorough although only English-language trials were included. The quality of the included studies was formally assessed. While the authors have not reported on how the articles were selected, they have reported how many of the reviewers were involved in data extraction and how the data extraction was performed.

The data extraction is reported in tables and text and the meta-analysis was appropriate. There were tests for heterogeneity and the authors have gone further and also performed sensitivity analyses and discussed several methodological and data limitations of the review. The authors conclusions appear to follow from the results.
Implications of the review for practice and research

Practice: The authors state that if UDCA is still to be used as standard therapy, a decrease in bilirubin concentration should not be used as a marker of effectiveness until it has been validated as a surrogate marker of effectiveness and until it has been validated as a surrogate marker for improvement in prognosis in PBC.

Research: The authors state that a sufficiently large multicentre or multinational, randomised, placebo-controlled study is needed to assess the effect of UDCA on clinically meaningful end points in PBC. These end points should be death, liver transplantation (the indications for the operation and the clinical characteristics of the patients must be stated) and development of complications of liver disease (i.e. ascites, variceal bleeding and encephalopathy), and symptom severity.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.