Ursodeoxycholic acid in primary sclerosing cholangitis: meta-analysis of randomized controlled trials

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CRD summary
This review concluded that ursodeoxycholic acid improved liver biochemistry and could improve liver histology and cholangiography, but it conveyed no survival benefits, among patients with primary sclerosing cholangitis. The review was well conducted, but in view of the small amount of evidence available and possible publication bias, caution may be advisable in interpreting the authors’ conclusions.

Authors’ objectives
To assess the effectiveness and safety of ursodeoxycholic acid for primary sclerosing cholangitis.

Searching
PubMed (including MEDLINE), EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), and the Web of Science were searched for articles from their inception to January 2009. The reference lists of eligible studies were checked. Search terms were reported and the search was not limited by language or publication status.

Study selection
Randomised controlled trials (RCTs) of ursodeoxycholic acid compared with placebo or no treatment for primary sclerosing cholangitis (diagnosed by established criteria) were eligible for inclusion.

The mean age of participants in the included trials ranged from 30 to 52 years, where reported. The daily dose of ursodeoxycholic acid ranged from 600 to 750mg, or 10 to 23mg per kg. Most of the RCTs were placebo-controlled. Outcomes reported in the review were death and liver transplantation either combined (primary outcome) or as separate outcomes; liver biochemistry (aspartate transaminase, alanine transaminase, alkaline phosphatase, gamma glutamyl transpeptidase, bilirubin, albumin, or Mayo score); symptoms (fatigue or pruritus); histology; cholangiography; cholangiocarcinoma; and adverse events. The mean follow-up interval ranged across trials from three to 60 months; in most cases it was between 12 and 24 months. Two trials were available only as abstracts.

Two reviewers independently selected trials for inclusion, with disagreements resolved by consensus.

Assessment of study quality
Trial quality was evaluated using the Jadad scale, which assesses the adequacy of reported randomisation, double-blinding, and withdrawals or dropouts. Each trial was awarded a score out of a maximum of five points, with trials scoring two points or less graded as low quality and those scoring three or more graded as high quality.

The assessment was conducted independently by two reviewers, with disagreements resolved by consensus.

Data extraction
Odds ratios and 95% confidence intervals were extracted or calculated from the event rates in the two groups of each trial. Data from trial arms that received interventions other than those of interest were excluded.

Data were extracted by two reviewers working independently, with disagreements resolved by consensus.

Methods of synthesis
Trials were combined using the Mantel-Haenszel fixed-effect model to calculate pooled odds ratios and 95% confidence intervals. The χ² test was used to assess for statistical heterogeneity, and funnel plots were used to check for publication bias. Sensitivity analyses were conducted to check the effects of control condition, trial quality, publication
status, duration of follow-up, use of intention-to-treat analysis, sample size, and ursodeoxycholic acid dose. It was planned to use a random-effects model in the event of significant statistical heterogeneity.

**Results of the review**

Eight RCTs were included (n=465, range 14 to 219). One RCT scored two points for quality, two scored three points, three scored four points, and two scored five points. Three RCTs described an appropriate method of sequence generation, four described an appropriate method of double blinding, and all described withdrawals and drop outs. Four used intention-to-treat analysis.

**Clinical events:** There was no statistically significant difference between ursodeoxycholic acid and placebo or no treatment in the rates of death and liver transplantation (either combined or separately; eight RCTs), cholangiocarcinoma (eight RCTs), adverse events (six RCTs), cholangiographic improvement (three RCTs), cholangiographic deterioration (five RCTs), histological improvement (three RCTs), nor histological deterioration (four RCTs). No significant statistical heterogeneity was detected, but funnel plots suggested possible publication bias.

There were trends, which were not statistically significant, for benefit from the intervention for cholangiographic and histological outcomes, one of which bordered on statistical significance (histological improvement: p=0.05, three RCTs). Sensitivity analyses did not change the statistical significance of any of the results.

**Symptoms and biochemical values:** No individual RCT reported a statistically significant symptom improvement in the intervention group, compared with controls. All relevant trials individually reported a significant improvement or a trend to improvement in the intervention group, compared with controls, in serum levels of aspartate transaminase (five RCTs), alanine transaminase (three RCTs), alkaline phosphatase (seven RCTs), gamma glutamyl transpeptidase (five RCTs), and bilirubin (seven RCTs). None reported a statistically significant difference between the groups in albumin levels (five RCTs).

**Authors’ conclusions**

Ursodeoxycholic acid improved liver biochemistry and could improve liver histology and cholangiography, but it conveyed no survival benefits.

**CRD commentary**

The objectives and inclusion criteria were clear and relevant sources were searched, without restrictions in language or publication status. An appropriate test was used to assess publication bias, and the results suggested that bias was present. Steps were taken to minimise the risk of reviewer bias and error, with more than one reviewer independently selecting trials, assessing their validity, and extracting the data. Appropriate statistical techniques were used to combine the trials, assess for statistical heterogeneity, and investigate differences between trials. The authors noted that most of the trials had a relatively short duration of follow-up, a small sample size, and a low ursodeoxycholic acid dose, and this may have made them underpowered for the clinical and histological outcomes.

The review was well conducted, but in view of the small amount of evidence available and possible publication bias, caution may be advisable in interpreting the authors’ conclusions.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that the effect of ursodeoxycholic acid on survival requires further investigation in a large scale RCT.

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Record Status
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.