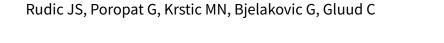


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# Ursodeoxycholic acid for primary biliary cirrhosis (Review)



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#### [Intervention Review]

# Ursodeoxycholic acid for primary biliary cirrhosis

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#### **ABSTRACT**

## **Background**

Ursodeoxycholic acid is administered to patients with primary biliary cirrhosis, a chronic progressive inflammatory autoimmune-mediated liver disease with unknown aetiology. Despite its controversial effects, the U.S. Food and Drug Administration has approved its usage for primary biliary cirrhosis.

#### **Objectives**

To assess the beneficial and harmful effects of ursodeoxycholic acid in patients with primary biliary cirrhosis.

# Search methods

We searched for eligible randomised trials in The Cochrane Hepato-Biliary Group Controlled Trials Register, The Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*, MEDLINE, EMBASE, Science Citation Index Expanded, LILACS, Clinicaltrials.gov, and the WHO International Clinical Trials Registry Platform. The literature search was performed until January 2012.

#### **Selection criteria**

Randomised clinical trials assessing the beneficial and harmful effects of ursodeoxycholic acid versus placebo or 'no intervention' in patients with primary biliary cirrhosis.

# Data collection and analysis

Two authors independently extracted data. Continuous data were analysed using mean difference (MD) and standardised mean difference (SMD). Dichotomous data were analysed using risk ratio (RR). Meta-analyses were conducted using both a random-effects model and a fixed-effect model, with 95% confidence intervals (CI). Random-effects model meta-regression was used to assess the effects of covariates across the trials. Trial sequential analysis was used to assess risk of random errors (play of chance). Risks of bias (systematic error) in the included trials were assessed according to Cochrane methodology bias domains.

# **Main results**

Sixteen randomised clinical trials with 1447 patients with primary biliary cirrhosis were included. One trial had low risk of bias, and the remaining fifteen had high risk of bias. Fourteen trials compared ursodeoxycholic acid with placebo and two trials compared ursodeoxycholic acid with 'no intervention'. The percentage of patients with advanced primary biliary cirrhosis at baseline varied from 15% to 83%, with a median of 51%. The duration of the trials varied from 3 to 92 months, with a median of 24 months. The results showed no



significant difference in effect between ursodeoxycholic acid and placebo or 'no intervention' on all-cause mortality (45/699 (6.4%) versus 46/692 (6.6%); RR 0.97, 95% CI 0.67 to 1.42, I<sup>2</sup> = 0%; 14 trials); on all-cause mortality or liver transplantation (86/713 (12.1%) versus 89/706 (12.6%); RR 0.96, 95% CI 0.74 to 1.25, I<sup>2</sup> = 15%; 15 trials); on serious adverse events (94/695 (13.5%) versus 107/687 (15.6%); RR 0.87, 95% CI 0.68 to 1.12, I<sup>2</sup> = 23%; 14 trials); or on non-serious adverse events (27/643 (4.2%) versus 18/634 (2.8%); RR 1.46, 95% CI 0.83 to 2.56, I<sup>2</sup> = 0%; 12 trials). The random-effects model meta-regression showed that the risk of bias of the trials, disease severity of patients at entry, ursodeoxycholic acid dosage, and trial duration were not significantly associated with the intervention effects on all-cause mortality, or on all-cause mortality or liver transplantation. Ursodeoxycholic acid did not influence the number of patients with pruritus (168/321 (52.3%) versus 166/309 (53.7%); RR 0.96, 95% CI 0.84 to 1.09, I<sup>2</sup> = 0%; 6 trials) or with fatigue (170/252 (64.9%) versus 174/244 (71.3%); RR 0.90, 95% CI 0.81 to 1.00,  $I^2 = 62\%$ ; 4 trials). Two trials reported the number of patients with jaundice and showed a significant effect of ursodeoxycholic acid versus placebo or no intervention in a fixed-effect meta-analysis (5/99 (5.1%) versus 15/99 (15.2%); RR 0.35, 95% CI 0.14 to 0.90,  $I^2 = 51\%$ ; 2 trials). The result was not supported by the random-effects meta-analysis (RR 0.56, 95% CI 0.06 to 4.95). Portal pressure, varices, bleeding varices, ascites, and hepatic encephalopathy were not significantly affected by ursodeoxycholic acid. Ursodeoxycholic acid significantly decreased serum bilirubin concentration (MD -8.69 µmol/l, 95% CI -13.90 to -3.48, I<sup>2</sup> = 0%; 881 patients; 9 trials) and activity of serum alkaline phosphatases (MD -257.09 U/L, 95% CI -306.25 to -207.92, I<sup>2</sup> = 0%; 754 patients, 9 trials) compared with placebo or no intervention. These results were supported by trial sequential analysis. Ursodeoxycholic acid also seemed to improve serum levels of gamma-glutamyltransferase, aminotransferases, total cholesterol, and plasma immunoglobulin M concentration. Ursodeoxycholic acid seemed to have a beneficial effect on worsening of histological stage (random; 66/281 (23.5%) versus 103/270 (38.2%); RR 0.62, 95% CI  $0.44 \text{ to } 0.88, I^2 = 35\%; 7 \text{ trials}.$ 

#### **Authors' conclusions**

This systematic review did not demonstrate any significant benefits of ursodeoxycholic acid on all-cause mortality, all-cause mortality or liver transplantation, pruritus, or fatigue in patients with primary biliary cirrhosis. Ursodeoxycholic acid seemed to have a beneficial effect on liver biochemistry measures and on histological progression compared with the control group. All but one of the included trials had high risk of bias, and there are risks of outcome reporting bias and risks of random errors as well. Randomised trials with low risk of bias and low risks of random errors examining the effects of ursodeoxycholic acid for primary biliary cirrhosis are needed.

## PLAIN LANGUAGE SUMMARY

# Ursodeoxycholic acid for primary biliary cirrhosis

Primary biliary cirrhosis is an uncommon and slowly progressive autoimmune disease of the liver that primarily affects middle-aged women. The cause of the disease is unknown. Over the last 30 years, the prevalence of primary biliary cirrhosis has increased substantially. 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 is the only drug approved by the U.S. Food and Drug Administration for primary biliary cirrhosis, but the effects of ursodeoxycholic acid remain controversial. This review contains updated evidence and re-evaluates beneficial and harmful effects of ursodeoxycholic acid on patients with primary biliary cirrhosis. The review includes 16 randomised clinical trials with a total of only 1447 patients. The primary outcomes were all-cause mortality, all-cause mortality or liver transplantation, adverse events, and quality of life. Although ursodeoxycholic acid indicated a reduction in liver biochemistry, jaundice, and histological progression, this review did not demonstrate any benefits of ursodeoxycholic acid on all-cause mortality, all-cause mortality or liver transplantation, or symptoms (pruritus and fatigue). The use of ursodeoxycholic acid is associated with costs and may cause adverse events. All but one of the trials had high risk of bias and the trials seem to have selective reporting of outcomes.