

Review: Ursodeoxycholic acid does not reduce risk for mortality or liver transplantation in primary biliary cirrhosis

Gong Y, Huang Z, Christensen E, Gluud C. 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. *Am J Gastroenterol.* 2007;102:1799-807.

Clinical impact ratings: Gastroenterology ★★★★★☆

QUESTION

In patients with primary biliary cirrhosis (PBC), does ursodeoxycholic acid (UDCA) reduce risk for mortality or liver transplantation?

METHODS

Data sources: Cochrane Hepato-Biliary Group Controlled Trials Register, Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE/Excerpta Medica, Science Citation Index-Expanded, Chinese Biomedical CD Database, and LILACS (all to January 2007); and reference lists.

Study selection and assessment: Randomized controlled trials that compared UDCA with placebo or no intervention (control) in patients with PBC. 15 RCTs ($n = 1419$) met the selection criteria and provided appropriate data. Quality assessment of individual trials was based on randomization method, allocation concealment, and blinding. 9 of the 15 trials were considered to have high risk for bias. UDCA dose ranged from 7.7 to 15.5 (median 10) mg/kg per day. Trial duration ranged from 3 to 92 (median 24) months.

Outcomes: Mortality, a composite endpoint of mortality or liver transplantation, liver transplantation, pruritus, fatigue, and adverse events.

MAIN RESULTS

UDCA did not reduce risks for mortality or liver transplantation, individually or combined (Table). Meta-regression showed that the estimate of treatment effect of UDCA was greater in more severely affected patients and smaller in trials of longer duration. UDCA did not improve pruritus or fatigue but did reduce the proportions of patients with jaundice (relative risk [RR] 0.35, 95% CI 0.14 to 0.90; 2 RCTs) and ascites (RR

0.42, CI 0.19 to 0.93; 4 RCTs). Patients in the UDCA group were more likely than those in the control group to report adverse events, mainly weight gain (mean weight gain 3.6 vs 0.06 kg).

CONCLUSION

In patients with primary biliary cirrhosis, ursodeoxycholic acid does not reduce risk for mortality or liver transplantation.

Sources of funding: Copenhagen Hospital Corporation and S.C. Van Foundation.

For correspondence: Dr. Y. Gong, Copenhagen University Hospital, Copenhagen, Denmark. E-mail ygong@ctu.rh.dk.

Ursodeoxycholic acid (UDCA) vs placebo or no intervention (control) in patients with primary biliary cirrhosis*

Outcomes at a median 24 mo	Number of trials (n)	Weighted event rates		RRR (95% CI)	NNT
		UDCA	Control		
Mortality	14 (1391)	6.4%	6.6%	3% (-42 to 33)	Not significant
Liver transplantation	14 (1391)	4.9%	5.9%	18% (-26 to 47)	Not significant
Mortality or liver transplantation	15 (1419)	12%	13%	8% (-21 to 29)	Not significant

*Abbreviations defined in Glossary. RRR, NNT, and CI calculated from data in article using a fixed-effects model.

COMMENTARY

The review by Gong and colleagues is the third and most up-to-date meta-analysis on the effects of UDCA in PBC. The authors concluded that UDCA has no effect on such hard endpoints as mortality and liver transplantation. Moreover, UDCA does not alleviate the main PBC symptoms of fatigue and pruritus.

I had commented in this journal on the first meta-analysis and was reserved in my acceptance of its findings because the trials were too short relative to the long duration of the disease (1). Goulis and colleagues (2) acknowledged this fact in their critique of the analyzed trials, stating that the overall number of patients (1272) was low and the median trial duration (2 y) too short, considering that the median survival of patients with PBC is 10 to 15 years. This restriction is tempered in the meta-analysis by Gong and colleagues because metaregression showed that effects on relevant outcomes were reduced in longer trials. Furthermore, no dose effect was observed, contrary to a claim based on a previous meta-analysis of selected trials (3).

Beneficial effects of UDCA were restricted to amelioration of liver enzymes and bilirubin levels. Fewer patients had ascites in some UDCA groups, but the most important determinants of ascites—serum albumin and wedged hepatic vein pressure—were not affected by UDCA.

Gong and colleagues showed that UDCA improves serum bilirubin and liver enzymes but has no effect on survival or need for liver transplantation. In the absence of sufficiently powered trials with adequate treatment duration, the use of UDCA in PBC is not supported by current evidence.

*Juerg Reichen, MD
University of Berne
Berne, Switzerland*

References

1. Reichen J. Review: Long-term ursodeoxycholic acid does not prevent mortality or morbidity in primary biliary cirrhosis. *ACP J Club.* 2000;132:68. Comment on: Goulis J, Leandro G, Burroughs AK. Randomised controlled trials of ursodeoxycholic-acid therapy for primary biliary cirrhosis: a meta-analysis. *Lancet.* 1999;354:1053-60.
2. Goulis J, Leandro G, Burroughs AK. Randomized controlled trials of ursodeoxycholic acid therapy for primary biliary cirrhosis: a meta-analysis. *Lancet.* 1999;354:1053-60.
3. Shi J, Wu C, Lin Y, et al. Long-term effects of mid-dose ursodeoxycholic acid in primary biliary cirrhosis: a meta-analysis of randomized controlled trials. *Am J Gastroenterol.* 2006;101:1529-38.