# Review: Long-term ursodeoxycholic acid does not prevent mortality or morbidity in primary biliary cirrhosis

Goulis J, Leandro G, Burroughs AK. **Randomised controlled trials of ursodeoxycholic-acid therapy for primary biliary cirrhosis: a meta-analysis.** Lancet. 1999 Sep 25;354:1053-60.

### Question

In patients with primary biliary cirrhosis, does long-term ursodeoxycholic acid (UDCA) decrease mortality and disease progression?

### Data sources

English-language studies were identified by searching MEDLINE and EMBASE/Excerpta Medica (1987 to July 1998) using the terms primary biliary cirrhosis, ursodeoxycholic acid, and treatment. Lists of conference abstracts and bibliographies of relevant review articles and studies were also scanned.

### Study selection

Randomized controlled trials were selected if UDCA was compared with placebo, patients had confirmed primary biliary cirrhosis with no biliary obstruction, and follow-up was > 6 months.

### Data extraction

Data were extracted on patient numbers and characteristics, laboratory values, study quality, and outcomes (death, death related to liver disease, transplantation, death or transplantation, complications of liver disease, side effects, and study-specific predefined end points). Missing data were also sought from trial investigators.

### Main results

164 articles were assessed; 11 met the inclusion criteria. 1272 patients were studied: Mean age range was 49 to 57 years, mean follow-up was 9 to 64 months, and mean daily dose of UDCA was 7.7 to 15.0 mg/kg of body weight. No differences were found in any of the outcomes for any trial or meta-analysis of the trials (Table), except for 1 study of 190 patients that found a decreased rate of treatment failure with UDCA. No effect or very little effect was shown for fatigue, pruritus, hepatic fibrosis, progression of histologic stage, or most other histologic features. UDCA treatment decreased laboratory levels of alkaline phosphatase, γ-glutamyl transpeptidase, alanine transaminase, and aspartate transaminase. Bilirubin levels were reduced in some studies, but serum albumin levels and prothrombin times did not change in most studies.

### Conclusion

Long-term ursodeoxycholic acid does not improve outcomes (death, death related to liver disease, liver transplantation, liver transplantation or death, ascites or bleeding, side effects, or rate of treatment failure).

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**Ursodeoxycholic acid vs placebo for primary biliary cirrhosis (mean follow-up 9 to 64 mo)**

| Outcomes | Number of studies | Combined odds ratio (95% CI)* |
|---|---|---|
| Death | 8 | 1.18 (0.70 to 1.99) |
| Liver-related death | 4 | 0.74 (0.24 to 2.40) |
| Liver transplantation | 8 | 1.21 (0.75 to 1.95) |
| Death or liver transplantation | 8 | 1.20 (0.83 to 1.74) |
| Ascites or hemorrhage | 5 | 1.19 (0.56 to 2.53 |
| Author-defined primary end point | 11 | 1.53 (0.97 to 2.42) |

*Der Simonian and Laird methods.

## Commentary

The meta-analysis by Goulis and colleagues unequivocally shows that the purported gold standard for the treatment of primary biliary cirrhosis, UDCA, has no effect on the hard end points of survival, time to transplantation, or occurrence of such substantial events as variceal bleeding or ascites. Moreover, no effect on the main symptoms of primary biliary cirrhosis—fatigue and pruritus—could be shown.

How can it be that a treatment with reported beneficial effects on hard and surrogate end points in different studies does not withstand the scrutiny of meta-analysis? Although the reasons are carefully analyzed by Goulis and colleagues, I feel some additional reasons need to be noted. First, in most studies reporting positive effects, different end points had to be combined to achieve statistical significance. Second, the longest reported treatment was 64 months, but most studies reported on treatment of up to 24 months. This period is clearly insufficient for a disease with a very slow evolution.

Thus, is UDCA nothing but a glorified and expensive placebo? The verdict is not in yet. The ultimate study—a placebo-controlled trial with sufficient numbers of events—has yet to be done. There is a hint that UDCA could be active: 1 of the most relevant prognostic indicators, serum bilirubin levels, was decreased in 7 of 11 studies. Goulis and colleagues assume that this is simply a washout effect; however, serum bilirubin level has recently been shown to be a valid prognostic factor even in UDCA-treated patients (1) and may be the sole predictor of death or need for liver transplantation. Thus, further placebo-controlled trials of adequate duration are needed.

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***Reference***

1. **Bonnand AM, Heathcote EJ, Lindor KD, Poupon RE.** Clinical significance of serum bilirubin levels under ursodeoxycholic acid therapy in patients with primary biliary cirrhosis. Hepatology. 1999;29:39-43.