Ursodeoxycholic acid for primary biliary cirrhosis (Review)

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TABLE OF CONTENTS

[Intervention Review]

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ABSTRACT

Background

Primary biliary cirrhosis is a rare autoimmune liver disease and an effective treatment has been difficult to establish. Some randomised clinical trials have found an effect of ursodeoxycholic acid for primary biliary cirrhosis.

Objectives

Evaluate the beneficial effects and adverse effects of peroral ursodeoxycholic acid for primary biliary cirrhosis versus placebo or no intervention.

Search strategy

The Controlled Trials Register of The Cochrane Hepato-Biliary Group, The Cochrane Library, MEDLINE, EMBASE and the full text of the identified studies were searched until April 2001. The electronic searches were done by entering the search terms 'ursodeoxycholic acid', 'UDCA', 'primary biliary cirrhosis', and 'PBC'.

Selection criteria

Randomised clinical trials evaluating ursodeoxycholic acid administered perorally at any dose versus placebo or no intervention in patients with primary biliary cirrhosis diagnosed by any method. Only trials using an adequate method for randomisation were included, regardless of blinding and language.

Data collection and analysis

The methodologic quality of the randomised clinical trials was evaluated by components and the Jadad-score. The following outcomes were extracted: mortality, liver transplantation, pruritus, other clinical symptoms (jaundice, portal pressure, (bleeding) oesophageal varices, ascites, hepatic encephalopathy, hepato-renal syndrome, autoimmune conditions), liver biochemistry, liver function, liver biopsy findings, quality of life, and adverse events. All analyses were performed according to the intention-to-treat method.

Main results

A total of 16 randomised clinical trials evaluating ursodeoxycholic acid against placebo (n = 15) or no intervention (n = 1) in 1422 patients were identified. The median Jadad-score was 3 (range 1-5). A number of trials described as double blind had problems with the blinding. Neither mortality (odds ratio = 0.94; 95% confidence interval (CI) 0.60 to 1.48), liver transplantation (odds ratio = 0.83; 95% CI 0.52 to 1.32), mortality or liver transplantation (odds ratio = 0.90; 95% CI 0.65 to 1.26), pruritus, fatigue, autoimmune conditions, quality of life, liver histology, or portal pressure were significantly affected by ursodeoxycholic acid (given in doses of 8-

15 mg/kg/day for three months to five years). However, ursodeoxycholic acid significantly (P < 0.05) reduced ascites, jaundice, and biochemical variables such as serum bilirubin and liver enzymes. Ursodeoxycholic acid was not significantly associated with adverse events. Including data after patients had been switched onto open label ursodeoxycholic acid confirmed the findings regarding the lack of a significant effect of ursodeoxycholic acid on mortality and mortality or liver transplantation. A significant (P = 0.04) effect was, however, observed on the incidence of liver transplantation (odds ratio = 0.68; 95% CI 0.48 to 0.98).

Authors' conclusions

Ursodeoxycholic acid has a marginal therapeutic effect for primary biliary cirrhosis. On the positive side, ursodeoxycholic acid has few side effects. The general usage of ursodeoxycholic acid for primary biliary cirrhosis needs reevaluation.

PLAIN LANGUAGE SUMMARY

Ursodeoxycholic acid may not be as effective as widely held

Primary biliary cirrhosis is an uncommon cholestatic liver disease, occurring mainly in middle-aged women. Primary biliary cirrhosis demonstrates autoimmune features and treatments that have efficacy have been difficult to identify. Ursodeoxycholic acid is a bile acid, constituting in man only one to three per cent of biliary bile acids. Ursodeoxycholic acid is less hepatotoxic than other bile acids when retained in the liver as a result of cholestasis. Treating patients with primary biliary cirrhosis with ursodeoxycholic acid (8-5mg/kg/day) for three months to five years did not significantly effect mortality, liver transplantation, mortality or liver transplantation, pruritus, fatigue, autoimmune conditions, quality of life, liver histology, or portal pressure. Ursodeoxycholic acid significantly reduced ascites, jaundice, and liver biochemistry. Ursodeoxycholic acid was not associated with an increase in adverse events. A reevaluation of the role of ursodeoxycholic acid for primary biliary cirrhosis seems necessary.

BACKGROUND

Primary biliary cirrhosis (PBC) is a rather rare, chronic liver disease of unknown etiology. It was first comprehensively described around 1950 (MacMahon 1949; Ahrens 1950). A progressive granulomatous hepatitis destroys small septal and interlobular bile ducts eventually leading to cholestasis and biliary cirrhosis. Patients may be diagnosed during an asymptomatic phase of the disease, which has a relatively favourable prognosis (Beswick 1985; Balasubramaniam 1990), or may be diagnosed due to symptoms (the common ones being pruritus, fatigue, jaundice, liver enlargement, signs of portal hypertension, sicca complex, and scleroderma-like lesions), in which case survival is significantly decreased. Ninety percent of patients are females between the ages of 40 and 60 years.

Although the etiology remains unknown, PBC is in many respects analogous to the graft-versus-host syndrome where the immune system has become sensitised to foreign proteins. Most PBC patients show increased class II human leukocyte antigen (HLA) histocompatibility antigen expression on bile duct cells (Ballardini 1984; van den Oord 1986), and cytotoxic T-cells are infiltrating the bile duct epithelium (Yamada 1986). Other duct systems of the body with a high concentration of HLA class II antigens on their epithelium such as the lacrimal and pancreatic glands are involved in the disease process (Epstein 1982).

Earlier attempts to treat PBC using immune-modulating and other agents such as azathioprine (Heathcote 1976; Christensen 1985), prednisolone (Mitchison 1992), chlorambucil (Hoofnagle 1986), cyclosporine (Wiesner 1990), colchicine (Kaplan 1986; Warnes 1987; Vuoristo 1995), D-penicillamine (Epstein 1981; Matloff 1982; Dickson 1985; Neuberger 1985), or methotrexate (Kaplan 1991; Lindor 1995) have resulted in clinical effects that have not led to widespread acceptance of these drugs in PBC (Kaplan 1994).

Due to the bile duct lesions and the developing cirrhosis, cholestasis occurs in PBC leading to the accumulation of the hydrophobic bile acids chenodeoxycholic acid and cholic acid, which may be hepatotoxic (Hofmann 1987; Chretien 1989). Ursodeoxycholic acid (UDCA) is the 7 beta-epimer of chenodeoxycholic acid. UDCA is a more polar and hydrophilic tertiary bile acid, constituting in man only one to three per cent of biliary bile acids. The hydrophilic properties render UDCA less hepatotoxic when retained in the liver as a result of cholestasis. UDCA has been shown in animals to increase bile flow (Dumont 1980), and UDCA inhibits expression of cell surface HLA markers (Calmus 1990). It has been demonstrated that UDCA administration at a dose of 10-15 mg/

kg/day leads to UDCA becoming the predominant circulating bile acid, and the circulating concentrations of endogenous bile acids diminish with a reduction of cholic acid, chenodeoxycholic acid, and 3-beta-hydroxy-5-chenolenoic acid (Poupon 1993).

UDCA has been used since 1973 for oral dissolution of gallbladder stones (Nakamo 1973). In 1981, Leuschner et al. (Leuschner 1981) observed that patients with gallstones and chronic hepatitis subjected to UDCA gallstone therapy showed improvement in symptoms and laboratory tests. Later on, PBC patients were reported to respond favourably to UDCA (David 1985; Poupon 1987). These observations led to the launch of several randomised clinical trials (RCTs), and the therapeutic subject has been extensively reviewed (Guslandi 1990; Lirussi 1992; Cirillo 1994; Leuschner 1994; Lim 1995; Poupon 1995; Goulis 1999 a; Goulis 1999 b).

A meta-analysis published in 1994 (Simko 1994) concluded that UDCA treatment of PBC patients resulted in a beneficial effect on certain liver tests, histology, and reduction of the number of patients developing serious complications. However, this meta-analysis included non-randomised clinical trials, which may be biased. Further, research has demonstrated that even RCTs, which reported inadequate or unclear randomisation methods, yielded estimates of intervention effects that were exaggerated by 30 to 40 per cent (Schulz 1995; Moher 1998; Kjaergard 1999). Finally, several RCTs have been published since 1992, which represented the last year of publication of studies included in the meta-analysis of Simko et al. (Simko 1994), and the last meta-analysis based on 11 RCTs concluded that the therapeutic benefit of UDCA for PBC needs to be re-examined (Goulis 1999 b). The present systematic review intends to assess the efficacy and adverse effects of UDCA in PBC versus placebo treatment or no intervention on the basis of the results of RCTs.

OBJECTIVES

The objectives are on the basis of the RCTs to evaluate the effects of peroral UDCA treatment of PBC patients versus placebo or no intervention on:

1. Mortality (outcome measure).

2. Need for liver transplantation (outcome measure).

3. Pruritus.

4. Other clinical symptoms.

5. Liver biochemistry.

6. Liver biopsy findings.

7. Quality of life.

8. Adverse events.

RESULTS

Mortality

Combining the results of 14 RCTs demonstrated no significant effects regarding mortality (OR = 0.94; 95% CI 0.60 to 1.48). In the UDCA group 44/699 (6.3%) patients died versus 46/692 (6.6%) patients in the control group (Comparison 01-01).

Selecting RCTs that included patients with a median (or mean) s-bilirubin at entry above 25 micromol (µmol)/l in both arms of the trial (ATHENS;DALLAS; MAYO-I; MILAN; TAIPEI; TORONTO) demonstrated an OR = 0.85 (95% CI 0.49 to 1.49) compared to an OR = 1.14 (95% CI 0.53 to 2.43) in RCTs with entry s-bilirubin below 26 µmol/l.

Sensitivity analyses taking UDCA dose and duration into consideration did not reveal differing results (Comparison 03-03). RCTs administrating low UDCA dose (< 10 mg/kg/day) for short treatment duration (< 12 months) (i.e., MILAN) observed an OR = 1.0 (95% CI 0.06 to 16.24), which did not differ significantly from RCTs administrating low dose (< 10 mg/kg/day) for long treatment duration (=> 12 months) or administrating high dose (=> 10 mg/kg/day) for short treatment duration (< 12 months) (i.e., FRANKFURT; GÖTEBORG; NEWARK-II; TAIPEI; TOKYO) (OR = 0.97 (95%CI 0.06 to 15.66) and from RCTs administrating high dose (=> 10 mg/kg/day) for long treatment duration (=> 12 months) (OR = 0.94 (95% CI 0.60 to 1.49)).

Performing sensitivity analyses on this outcome variable stratifying RCTs according to their methodological quality (either the Jadad-score (Comparison 03-01) or the quality-score, taking concealment of allocation into consideration (data not shown)) did not change this estimate significantly. The same observation was done stratifying the RCTs according to the adequacy of generation of the allocation sequence (Comparison 03-04), allocation concealment (Comparison 03-05), and blinding (Comparison 04-06) as well as the use of intention-to-treat analysis (Comparison 03-07).

Including data from the extended follow-up during UDCA-UDCA versus placebo-UDCA into the analyses (now comprising 72 deaths in 699 patients (10.3%) originally randomised to UDCA versus 68 deaths in 692 patients (9.8%) originally randomised to placebo) demonstrated an OR = 1.06 (95% CI 0.74 to 1.53) (Comparison 04-01). This estimate was not significantly changed taking methodological quality (Comparison 04-01) or s-bilirubin at entry (Comparison 04-04) into consideration.

Liver transplantation

Combining the results of 14 RCTs demonstrated no significant effects regarding liver transplantation (OR = 0.83; 95% CI 0.52 to 1.32) (Comparison 01-02). In the UDCA group 35/699 (5.0%) patients were transplanted versus 41/692 (5.9%) patients in the control group.

Including data from the extended follow-up during UDCA-UDCA versus placebo-UDCA into the analyses (now comprising 57 liver transplantations in 699 patients (8.2%) originally randomised to UDCA versus 78 liver transplantations in 692 patients (11.3%) originally randomised to placebo/no intervention) demonstrated an OR = 0.68 (95% CI 0.48 to 0.98) (Comparison 04-02). This difference was significant (P = 0.04). This estimate was not significantly changed taking methodological quality or s-bilirubin at entry into consideration.

Mortality or liver transplantation

This combined outcome measure was available in 15 RCTs. No significant effect of UDCA was observed (OR = 0.90; 95% CI 0.65 to 1.26) (Comparison 01-03).

Selecting RCTs with a median (or mean) s-bilirubin at entry above 25 µmol/l in both arms of the trial (ATHENS; DALLAS; MAYO-I; MILAN; TAIPEI; TORONTO) demonstrated an OR = 0.84 (95% CI 0.55 to 1.29) opposed to an OR = 1.01 (95% CI 0.59 to 1.72) in RCTs with median (or mean) s-bilirubin at entry below 26 µmol/l (Comparison 03-09).

Sensitivity analyses taking UDCA dose and duration into consideration did not reveal different results. RCTs administrating low UDCA dose (<10 mg/kg/day) for short treatment duration (<12 months) (i.e., MILAN) observed an OR = 1.0 (95% CI 0.06 to 16.24)), which did not differ significantly from RCTs administrating low dose (<10 mg/kg/day) for long treatment duration (=>12 months) or administrating high dose (=>10 mg/kg/day) for short treatment duration (<12 months) (i.e., FRANKFURT; GÖTEBORG; NEWARK-II; TAIPEI; TOKYO) (OR = 0.72 (95%CI 0.16 to 3.26) and from RCTs administrating high dose (= >10 mg/kg/day) for long treatment duration (=>12 months) (OR = 0.92 (95% CI 0.65 to 1.29)) (Comparison 03-10).

Performing sensitivity analyses on this outcome stratifying RCTs according to their methodological quality according to the Jadad-score did not change this estimate significantly (Comparison 03-08). The same observations were done when stratifying the RCTs according to the quality scale (data not shown) or according to the adequacy of generation of the allocation sequence (Comparison 03-11), allocation concealment (Comparison 03-12), and blinding (Comparison 04-13) as well as the use of intention-to-treat analysis (Comparison 03-14).

Including data from the extended follow-up during UDCA-UDCA versus placebo/no intervention-UDCA (now comprising 135 deaths or liver transplantations in 713 patients (18.9%) originally randomised to UDCA versus 151 deaths or liver transplantations in 706 patients (21.4%) originally randomised to placebo/no intervention) demonstrated an OR = 0.84 (95% CI 0.64 to 1.11) (Comparison 04-03). This estimate was not significantly changed taking methodological quality (Comparison 04-03) or s-bilirubin at entry (Comparison 04-06) into consideration.

Pruritus, fatigue, and jaundice

UDCA did not significantly influence either the number of patients with pruritus (OR = 0.94; 95% CI 0.63 to 1.39) or the pruritus score. Fatigue was not significantly influenced by UDCA (OR = 0.76; 95% CI 0.49 to 1.17). The two RCTs (TOKYO; VILLEJUIF) reporting the number of patients with jaundice observed a significant (P = 0.02) effect of UDCA (OR = 0.32; 95% CI 0.13 to 0.82).

Autoimmune conditions

In most of the RCTs information on autoimmune conditions was sparse. However, the MAYO-I trial (Zukowski 1998) evaluated the autoimmune conditions during UDCA and placebo and did not find any significant effect of UDCA on associated sicca syndrome, Raynaud's phenomenon, arthritis, or Hashimoto's thyroiditis - neither on disappearance of conditions present at entry nor acquisition of new conditions.

Portal hypertension

Neither portal pressure (weighted mean difference (WMD) = 0.8 mmHg; 95% CI -2.2 to 3.8 mmHg), number of patients with development of varices (OR = 0.54; 95% CI 0.25 to 1.17), number of patients with bleeding varices (OR = 0.53; 95% CI 0.20 to 1.38) nor patients developing hepatic encephalopathy (OR = 0.33; 95% CI 0.05 to 2.38) were significantly affected by UDCA intervention. However, the number of patients developing ascites was significantly (P = 0.02) lower in the UDCA group compared to the control group (OR = 0.40; 95% CI 0.16 to 0.88).

Biochemical variables

UDCA intervention led to a significant improvement in:

s-bilirubin WMD (95%CI) = -10.8 µmol/l (-16.3 to -5.3); P < 0.001 - corresponding to a decrease compared to the control group of about 25%;

s-alkaline phosphatases WMD (95% CI Random) = 359.0 international units (IU)/l (-527.4 to -190.5); P < 0.001 - corresponding to a decrease of about 40%;

s-gamma-glutamyl transpeptidase WMD (95% CI) = -258.2 IU/l (-321.7 to -194.7); P < 0.001 - corresponding to a decrease of about 50%;

s-aspartate aminotransferase WMD (95% CI Random) = -35.4 IU/L (-53.3 to -17.5); P < 0.001 - corresponding to a decrease of about 33%;

s-alanine aminotransferase (WMD (95% CI Random) = -36.1 IU/l (-58.1 to -14.0); P < 0.001 - corresponding to a decrease of about 35%,

s-total cholesterol WMD (95% CI) = -0.5 mmol/l (-0.8 to -0.2); P < 0.001 - corresponding to a decrease of about 8%; and

plasma immunoglobulin M WMD (95% CI) = -1.2 g/l (-1.9 to -0.6); P < 0.001 - corresponding to a decrease of about 24%.

Only one RCT reported s-albumin concentrations (MILAN) and one the prothrombin index (VILLEJUIF). These variables were not significantly affected by UDCA intervention.

Liver histology

There were no significant effects of UDCA on either histological stage or worsening of fibrosis (OR = 0.70; 95% CI Random 0.37 to 1.31), histological stage (WMD = -0.96; 95% CI Random -2.82 to 0.91), or florid duct lesions (Comparison 01-25). About half of the patients entered into the BARCELONA trial observed significant improvements in the UDCA group versus the placebo group in histological stage, portal inflammation, piecemeal necroses, but no significant effects on ductular proliferation or cholestasis (Comparison 01-26). Further, the placebo group had significantly fewer bile ducts per portal tract (Comparison 01-27).

Quality of life

None of the RCTs examined specific quality-of-life scales. Two RCTs (NEWCASTLE; GÖTEBORG) evaluated symptoms using visual analogue scales. None of these showed any significant difference between the UDCA- and placebo-arms. However, significantly (P<0.01) more patients felt better or much better following UDCA intervention than after placebo in the GÖTEBORG-trial.

Adverse events

There were neither a significant increase in total adverse events (OR = 1.33; 95% CI 0.72 to 2.46) nor severe adverse events (OR = 7.39; 95% CI 0.15 to 372.41) in comparing UDCA-patients to control patients (Comparison 02).

Funnel plot asymmetry

There were no significant associations between numbers of included patients and the observed OR of mortality or liver transplantation (R = -0.18, degrees of freedom = 12, z = 0.64, NS).

DISCUSSION

This systematic review could not demonstrate any significant effect of UDCA on mortality, liver transplantation, and mortality or liver transplantation of patients with PBC when tested against placebo/no intervention. When we performed sensitivity analyses taking disease severity into account - expressed by the s-bilirubin level at entry - this did not change our observations. Further, UDCA was without a significant effect on variables generally considered important for the prognosis of PBC like s-albumin, prothrombin time, portal pressure, or liver histology. However, the number of RCTs reporting these outcomes was few. Further, this review confirms and extends previous observations demonstrating a significant reduction in liver biochemistry, including s-bilirubin and liver enzyme activities, jaundice, and ascites following UDCA intervention. We also observed a significantly lower incidence of liver transplantation in those patients originally randomised to UDCA when including data from the UDCA-UDCA versus the placebo/no intervention-UDCA period (see below). UDCA appeared to be safe and we did not observe any significant increase in the occurrence of serious and non-serious adverse events based on the results of the RCTs.

This review included all RCTs published before 2001 dealing with UDCA intervention for patients with PBC tested versus placebo or no intervention. Our present findings regarding mortality, liver transplantation, and mortality or liver transplantation during the treatment period in which UDCA was compared versus placebo/no intervention were not sensitive to either dose or duration of UDCA intervention. The systematic review confirms and extends the findings of Goulis et al. (Goulis 1999 b), who based their meta-analysis on 11 RCTs including 1114 randomised patients with PBC. In the present review, we assessed 16 RCTs randomising a total of 1422 patients. Despite expanding the evidence base of about 45 per cent for the number of trials and 28 per cent for the number of included PBC patients, we were unable to demonstrate significant effects of UDCA on major outcomes in PBC patients. In a recent cohort study of 592 PBC patients survival was not related to UDCA treatment (Prince 2001).

There was no significant funnel plot asymmetry, and accordingly, no statistical signs of publication bias or other biases. However, the RCTs included in this review varied regarding methodological quality. A number of the RCTs failed to report adequate methods to generate the allocation schedule, conceal the allocation, as well as preserve the double blinding during interventions. Thus, the majority of these trials has not been sufficiently blinded and are therefore liable to bias resulting in an overestimation of intervention efficacy (Schulz 1995; Kjaergard 1999; Kjaergard 2001). This unblinding may have led to a more optimistic attitude of the physician and patients towards the course of the disease, which may have led to an increased likelihood of bias in the reporting of symptoms. Dimensions of methodological quality of trials have been shown to have a significant influence on the effect of interventions, i.e., trials with inadequate methodological quality do significantly overestimate the efficacy of interventions (Schulz 1995; Moher 1998; Kjaergard 1999; Kjaergard 2001). Sensitivity analyses taking methodological quality into account, however, did not reveal any significant association between trial quality and the estimates of the effect of UDCA in this sample of 16 RCTs.

This systematic review was not able to demonstrate a significant efficacy of UDCA on the major outcome measures: mortality, liver transplantation, and mortality or liver transplantation during the period in which patients were treated with UDCA versus placebo/no intervention. This observation is in contrast to some previous attempts to aggregate data from UDCA-PBC studies (Simko

1994; Poupon 1997; Poupon 2000). However, Simko et al. (Simko 1994) included non-randomised studies in their meta-analysis, which are more liable to bias than RCTs. Poupon et al. (Poupon 1997) only included three RCTs in their analysis and Poupon (Poupon 2000) only included five RCTs in the most recent meta-analysis. Such meta-analyses run the risk of trial selection bias (Gluud 2001). Further the two Poupon meta-analyses (Poupon 1997; Poupon 2000) included data on patients from RCTs after these trials had been terminated - and placebo treated patients and UDCA treated patients had been switched onto open label UDCA. When we performed a meta-analysis on the total sample of RCTs including data on patients switched onto open label UDCA we were again not able to demonstrate any significant effect of UDCA on mortality or on the combined outcome measure of mortality or liver transplantation. This is also in agreement with the results of the meta-analyses of Goulis et al. (Goulis 1999 b). However, absence of evidence is not the same as evidence of absence of an effect of UDCA.

It cannot be excluded that the lack of effect observed in this review may be due to insufficient dose of UDCA or too short a treatment duration. However, we were unable to detect any consistent association between the dose and/or treatment duration and intervention efficacy in the sensitivity analyses. In fact, the group of trials treating for more than 12 months with a dose of UDCA above 10 mg/kg/day did not find any significant effect on mortality (OR = 0.94 (95% CI 0.60 to 1.49). Further, it is noteworthy that the two trials with the longest duration of treating patients with UDCA, i.e., the ATHENS and the BARCELONA trials, both observed a trend to a negative effect of UDCA on mortality and on mortality and liver transplantation. Angulo et al. (Angulo 1999 c) compared in a one year randomised trial three doses of UDCA for PBC. They observed significantly better effects on liver biochemistry of a 13-15 mg/kg/day UDCA dose than of a 5-7 mg/kg/day dose. However, they did not observe any significant differences between the 13-15 mg/kg/day and the 23-25 mg/kg/day UDCA dose. A short-term dose finding study also concluded that UDCA 13.5 mg/kg/day was the optimal dose (Verma 1999).

We observed a significant effect of UDCA on liver transplantation when including data from the UDCA-UDCA versus the placebo/no intervention-UDCA period. The decision of if and when to perform liver transplantation is influenced by many factors: the attitude of the patient, the attitude of the physician, the time of referral, the length of the waiting list, etc. Therefore, liver transplantation is an imprecise measure of the stage of progression of the disease and thus most likely a biased outcome measure. The fact that s-bilirubin and jaundice decreased in the UDCA treated group compared to the placebo treated could lead to the observation of fewer liver transplants in the UDCA group. S-bilirubin is part of all prognostic indices used for patients with PBC (Pasha 1997). Therefore, a lower s-bilirubin will provide the clinicians with less impetus to transplant. Accordingly, liver transplantation as an outcome measure in UDCA trials may make a comparator look worse. In accordance, when including data from the time where patients were switched onto open label UDCA we found a significantly lower incidence of liver transplantation in the UDCA group than in the group originally randomised to placebo/no intervention. However, UDCA had no significant effect on mortality or the combined outcome measure of mortality and liver transplantation even when including data from the period of open UDCA treatment in both arms of the trials. Second, the referrals for liver transplantation occurred mainly after the blinding of the RCTs had been removed. Unblinded comparisons may exaggerate intervention efficacy significantly (Schulz 1995; Kjaergard 2001). Third, the effect of UDCA on liver transplantation was only marginally significant. Taking the number of comparisons performed into consideration, a spurious significant P-value due to repetitive testing ('mass significance') cannot be excluded. However, the observation should stimulate further research on the effects of UDCA for PBC. Bonnand et al. (Bonnand 1999) recently demonstrated that UDCA treated patients, who normalised their s-bilirubin concentration, obtained a survival free of liver transplantation not significantly different from placebo treated patients with a normal baseline s-bilirubin concentration. This study did not provide data on survival and liver transplantation individually.

Based on the results of four RCTs, we noticed that the prevalence of patients with ascites was significantly less in the UDCA group than in the placebo group. This observation may be real, but could also be a chance finding due to the number of comparisons having been made without correction of the significance level. Second, the diagnosis of ascites was clinical and the assessment and the effect of UDCA on liver biochemistry and/or lack of efficient blinding could have biased the assessment. Third, UDCA was without significant effects on portal pressure and s-albumin, which are important in the pathogenesis of ascites. However, the latter observations rest on the results of only one RCT each.

PBC is a pathological process starting with portal inflammation which progresses towards three irreversible stages: a stage of compensated cirrhosis, a stage of decompensated cirrhosis (defined by high bilirubin levels (> 100 µmol/l), ascites, and variceal bleeding), and a terminal stage, in which death occurs unless liver transplantation is performed. The mean time to acquire cirrhosis is four to six years. About 20 per cent develop the decompensated stage over a four-year period (Christensen 1980) and the mean time to reach the terminal phase is about four years. The purpose of the RCTs assessing UDCA for PBC has not been to evaluate whether this bile acid could reverse the decompensated stage or the terminal stage of the disease, but rather if UDCA could slow the progression towards the cirrhotic stage and the more advanced stages. It is, therefore. interesting to study the effect of UDCA on liver histology. In this review, we were not able to identify any significant effect of UDCA on histology. Only one of the individual RCTs found significant effects on liver histology (BARCELONA). It observed

positive effects on a number of histological variables, including the histological stage. This finding, however, may be a spurious result. Only about half of the randomised patients had a follow-up liver biopsy. Further, as the trial showed a trend towards a higher death rate and liver transplantation rate in the UDCA group, this could have removed some of the more seriously affected livers from the UDCA group, making those having a biopsy look relatively less affected. Such subgroup results should be interpreted cautiously (Yusuf 1991; Oxman 1992; Assmann 2000). Another study (Angulo 1999) has reported a positive effect of UDCA on liver histology. However, this study was not randomised, but compared liver histology of a selected group of 16 patients from one study to that of 51 patients from another trial. Such non-randomised comparisons cannot be taken as evidence for efficacy of UDCA in PBC. On the other hand, the findings of the BARCELONA-trial are interesting and should stimulate more research into the effect of UDCA on progression of fibrosis in PBC and eventually cirrhosis development. In this respect, the Markov model analysis of data from the VILLEJUIF-trial by Corpechot et al. published in 2000 may support an effect of UDCA on liver histology. However, the Markov analysis includes data from the UDCA-UDCA and the placebo-UDCA period and not only from the period in which patients were strictly randomised to UDCA versus placebo. Further, some patients entered the analysis with two sets of data (from the UDCA versus placebo period and the UDCA-UDCA versus placebo-UDCA period) while other patients entered with only one set of data. This may raise serious statistical problems and may invalidate the results of the Markov analysis.

It has been claimed that UDCA is a cost-effective therapy for PBC (Pasha 1999). However, this cost-effectiveness rests on extrapolation from the results of two selected RCTs (MAYO-I; TORONTO). It is evident that cost-effectiveness analyses ought to be performed on the basis of all available evidence and not just on selected evidence. Considering the annual cost of UDCA of about $2500 (Pasha 1999) and the findings of the present review, we challenge the conclusion drawn by Pasha et al. (Pasha 1999) that UDCA is cost-effective for PBC.

So where are we now? This systematic review as well as the meta-analysis of Goulis et al. (Goulis 1999 a; Goulis 1999 b) have been unable to demonstrate a significant effect of UDCA on the incidence of death, liver related death, death or liver transplantation, and complications of liver disease based on an analysis of data before and after the patients had been switched onto open label UDCA. However, in contrast to the meta-analysis of Goulis et al. (Goulis 1999 a), the present systematic review observed that UDCA significantly reduced the incidence of liver transplantation if data after the switch to open label UDCA are considered. Further, we found a significant effect of UDCA on liver biochemistry and ascites and it is possible that UDCA can reduce the progression of liver histology (BARCELONA). Finally, UDCA appears safe. Accordingly, we face a difficult situation in which UDCA has first been perceived as a drug which could reduce mortality (Poupon 1997), but where later, more comprehensive analyses (Goulis 1999 b, the present review) cannot confirm this finding. This places both clinicians and researchers in a difficult position where one has to base therapeutic decisions on surrogate measures such as liver biochemistry, liver histology, or outcomes which are likely to be biased (liver transplantation). The choice is, therefore, not straightforward and more research is needed.

Both meta-analyses are based on incidence rates and do not have the advantage of performing survival analyses taking time to events into consideration. In spite of this shortcoming, we are surprised by the lack of firm clinical evidence speaking in favour of UDCA for PBC considering the many articles stating that UDCA improves survival in PBC (Heathcote 2000). If one could obtain individual patient data from all RCTs treating patients with UDCA versus placebo or no intervention, analyses adjusting for prognostic variables might reveal important information. In fact, we strongly support the performance of individual patient data meta-analysis which could identify subgroups of PBC patients having the best chance of benefiting from UDCA treatment. Such analyses ought, however, to include data from all or almost all of the trials performed to date. With information on updated prognosis, such analyses might give important information.

Evidence about how much medical interventions work may change over time. Ioannidis and Lau (Ioannidis 2000) recently applied 'recursive cumulative meta-analyses' of randomised clinical trials to evaluate the relative change in the pooled treatment effect over time for 60 medical interventions within pregnancy/perinatal medicine and cardiology. With 500 accumulated patients, the pooled relative risk may change by about 0.6 to 1.7 fold in the immediate future. When 2000 patients have been randomised, the pooled relative risk may change by 0.7 to 1.3 fold. Ioannidis and Lau concluded that early, wide oscillations in the evolution of the treatment effect for specific interventions may signal further major changes in the future (Ioannidis 2000). With 1422 PBC patients randomised we may all look forward to surprises in the future. Applying the interpolated 'change factors' derived from Ioannidis and Lau to UDCA for PBC could lead to a reduction of mortality in the future (odds ratio = 0.94 x 0.65 = 0.61), but could also demonstrate that UDCA increases the mortality (odds ratio = 0.94 x 1.4 = 1.32). Both estimates are close to the 95% CI of the estimates based on the RCTs reviewed. The only way to clarify this issue is by the production of new high quality evidence sufficiently powered, or possibly by performing a systematic review based on individual patient data from all or almost all of the RCTs thus far performed. In such an analysis, the data from trials which cannot provide individual patient data ought to be included in the analysis based on the published, aggregated data.

AUTHORS' CONCLUSIONS

Implications for practice

The review confirms and extends previous observations showing a beneficial effect of UDCA on a number of liver biochemical variables, including s-bilirubin concentration and s-enzyme activities, jaundice, and ascites in PBC patients. UDCA has few side effects and it is possible that UDCA may decrease the number of patients undergoing liver transplantation. However, the review could not demonstrate a significant effect of UDCA on mortality, the combined outcome measure of mortality and liver transplantation, pruritus, fatigue, portal pressure, s-albumin, prothrombin index, and quality of life of patients with PBC. The decision to use UDCA at present for PBC may, therefore, depends on the importance of these outcomes to the patient.

Implications for research

This review calls for a reevaluation of the role of UDCA in PBC even if there is effect on several surrogate outcomes. The absence of evidence for an effect of UDCA on clinically important outcome variables, however, does not mean that there is evidence of lack of effect. Therefore, meta-analyses based on individual patient data, including subgroup analyses, ought to be performed in order to identify subgroups that may benefit from UDCA. Such meta-analysis ought to include the data from the majority of PBC patients randomised and take into account data from trials from which individual patient data cannot be obtained. The possible effect on UDCA on liver histology needs more study. One important surrogate marker is the progression to cirrhosis. The evaluation of the effect of UDCA on progression to cirrhosis could potentially be evaluated from individual patient data from previous randomised trials.

A large randomised trial in non-cirrhotic PBC patients also seems necessary testing UDCA versus placebo on clinically meaningful outcome measures. It may also be relevant to carry out trials randomising PBC patients on UDCA to placebo or continued UDCA treatment. Future trials should use adequate placebo preparations, and follow recommendations for reporting of trials (www.consort-statement.org).

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* *Indicates the major publication for the study*

FEEDBACK

Ursodyeoxycholic acid for primary biliary cirrhosi

Summary

It would be helpful if the Comment had a sentence on what the substantive change is between the original article and the update so its significance, or lack thereof, is apparent.Thank you for your consideration.
I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.
Karyn Driessen, CA, USA
11.06.2003

Author's reply

Thank you very much for showing your interest in our review and for your comment.
The changes that occurred in our review between the version published in Issue I, 2003 (and previous issues) and in Issue II, 2003 were of no material importance to the data or conclusions of the review. The only encompassed minor stylistic changes as well as addition of an extra reference in the Background section.
Our original text in the Background was:

"Primary biliary cirrhosis (PBC) is a rather rare, chronic liver disease of unknown etiology. It was first comprehensively described by Ahrens and co-workers in 1950 (Ahrens 1950)."
This was changed into:
"Primary biliary cirrhosis (PBC) is a rather rare, chronic liver disease of unknown etiology. It was first comprehensively described around 1950 (MacMahon 1949; Ahrens 1950)."
Therefore, the review was not marked as 'Updated', we only changed the date of last amendment.
Your comment has made me realise the importance of keeping track of all changes, no matter how small. We shall remember that when we update our review in late 2003.
Christian Gluud
The Copenhagen Trial Unit
H:S Rigshospitalet
I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.
11.06.2003

Contributors

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- Copenhagen Hospital Corporation DENMARK

NOTES

In the first protocol (Christensen 1997) published for this systematic review we intended to perform meta-analyses adjusting for prognostic variables. However, we chose not to perform such analyses as most of the RCTs reported balanced randomisation results at entry.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Cholagogues and Choleretics [adverse effects; *therapeutic use]; Liver Cirrhosis, Biliary [*drug therapy]; Randomized Controlled Trials as Topic; Ursodeoxycholic Acid [adverse effects; *therapeutic use]

MeSH check words

Humans