G.17 Ursodeoxycholic acid

Review question: What is the effectiveness of ursodeoxycholic acid for preventing liver disease progression in people with cystic fibrosis?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation O'Brien, S., Fitzgerald, M. X., Hegarty, J. E., A controlled trial of ursodeoxycholic acid treatment in cystic fibrosis-related liver disease, European Journal of Gastroenterology and Hepatology, 4, 857-863, 1992 Ref Id 340385 Country/ies where the study was carried out Ireland Study type Randomised controlled trial Aim of the study To assess the effect of UDCA on liver function, biliary excretion and nutrition. Study dates	Sample size N = 12 Characteristics All participants had CF related liver disease. Evidence of advanced liver disease was present in 11/12 participants (91.7%) as determined by the presence of portal hypertension and or histological features of CFRLD. None of the participants had experienced any deterioration in liver function or complications of their liver disease during the 6 month trial. Median age in yrs (range): UDCA (n = 6): 17 (12 - 20) Control (n = 6): 17.5 (14 - 25) Gender (M/F): UDCA: 2/4 Control: 4/2	Interventions Intervention UDCA, 20 mg/kg per day Control No additional treatment	Details Patients were evaluated at 3 month intervals with clinical examination, pulmonary function tests, liver biochemistry, serum albumin and prothrombin tim and at 6 months with biliary scintigraphy. Setting Adult Cystic Fibrosis Centre Randomisation method 6 patients were randomised to receive UDCA and 6 were randomised to receive no additional treatment. Allocation concealment Sealed envelopes Statistics All data expressed as mean ± SEM. Values before and after treatment compared with Wilcoxon signed ranks tests.	Results Baseline enzyme values (IU/L) AST UDCA: 79.3 ± 11.3 Control: 75.2 ± 23.0 ALT UDCA: 81.2 ± 12.4 Control: 73.5 ± 23.6 GGT UDCA: 129.0 ± 36.2 Control: 133 ± 62.9 After 6 months: AST UDCA: 49.5 ± 7.8; n=6 Control: 50.8 ± 9.2; n=6 ALT UDCA: 49.0 ± 7.3; n=6 Control: 49.2 ± 8.9; n=6 GGT UDCA: 40.0 ± 10.4; n=6 Control: 136.0 ± 83.3; n=6 Mean change of enzymes from baseline (IU/L): AST UDCA: -29.8 Control: -24.4 ALT	The quality of this trial was assessed using the Cochrane risk of bias assessment tool. Random sequence generation: unclear (specific method of randomisation was not reported) Allocation concealment: low risk Blinding of participants and personnel: low risk (both participants and individuals administering the intervention were kept blind to treatment allocation) Blinding of outcome assessment: low risk (outcome assessors were blinded) Incomplete outcome data: low risk (All groups were followed up for an equal length of time, all participants completed the trial) Selective reporting: low risk (The groups were comparable with respect to the availability of outcome data). Other bias: low risk (The groups were comparable at baseline, including all major confounding and prognostic factors. The comparison

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June 1988 - December 1989 Source of funding None reported.	Splenomegaly/varices UDCA: 5/6 Control: 5/6 Inclusion criteria CF and presence of liver disease defined on the basis of hepatomegaly and/or splenomegaly, confirmed by abdominal ultrasound and/or liver biochemistry (GGT > 50 IU/L, 5'nucleotidase > 15 IU/L) for at least 6 months. No evidence of recent viral infection (confirmed by viral screen tests) No hepatotoxic drug within the previous 3 months No alcohol ingestion Exclusion criteria Questionable drug compliance Presence of normal liver function tests			UDCA: -32.2 Control: -24.3 GGT UDCA: -89 Control: 3 Baseline Bilirubin value (umol/l) UDCA: 14.2 ± 5.9 Control: 11.8 ± 1.8 Bilirubin, after 6 months: UDCA: 13.2 ± 3.6 Control: 9.2 ± 1.6 Mean change in bilirubin (umol/l): UDCA: -1 Control: -2.6	groups received the same care apart from the intervention(s) studied. The study had an appropriate length of follow-up. The study used a precise definition of outcome. A valid and reliable method was used to determine the outcome. OVERALL QUALITY: LOW RISK OF BIAS Other information None
Full citation Merli, M., Bertasi, S.,	Sample size N = 51 Characteristics	Interventions UDCA	Details The patients were randomised to receive	Results (Results from UDC-Tau group not presented).	Limitations

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Servi, R., Diamanti, S., Martino, F., De Santis, A., Goffredo, F., Quattrucci, S., Antonelli, M., Angelico, M., Effect of a medium dose of ursodeoxycholic acid with or without taurine supplementation on the nutritional status of patients with cystic fibrosis: a randomized, placebo-controlled, crossover trial, Journal of Pediatric Gastroenterology & Nutrition, 19, 198-203, 1994 Ref Id 340405 Country/ies where the study was carried out Italy Study type Randomised, cross-over Aim of the study	Sex: Male: n = 27; Female: n = 24 Age, median (range): 14 yrs (8 - 32) Liver disease: 10/51 participants had persistent abnormality in liver function tests (AST, ALT and cholestatic enzymes). Of these, 2 had liver cirrhosis. Inclusion criteria Diagnosis of CF, documented by raised sweat chloride vales and pulmonary and digestive symptoms Evidence of malnutrition, determined by body mass percentile (BMP) ≤ 90% age > 6 yrs good compliance with previous monitored treatments no previous UDCA treatment Exclusion criteria None reported.	12 mg/kg/day orally in 2 doses alone or with taurine (TAU, 18 - 22 mg/kg/day) for 6 months. Placebo Glucose tablets	either UDCA alone or with taurine for 6 months. For each group, the treatment period was compared with a 6 month placebo period. A 1 month washout period was instituted for patients who had received UDCA before they went on to placebo. Setting Patients were selected from a larger cohort followed at the Cystic Fibrosis Centre and the Department of Paediatrics at the University of Rome. Randomisation method The treatment-placebo or placebo-treatment sequence was randomised within each group. Allocation concealment Not reported. Statistics Data expressed as mean ± SD. Student t test for paired data was used to compare values before and after 6 months.	After 6 months (mU/ml): Placebo: AST: 34 ± 13; n=19 ALT: 27 ± 13; n=19 GGT: 25 ± 16; n=19 UDCA: AST: 38 ± 16 ALT: 25 ± 15 GGT: 20 ± 9.0 Mean change from baseline (mU/ml): Placebo: AST: 2 ALT: 0 GGT: 5 UDCA: AST: 5 ALT: -3 GGT: -2 In 8 participants who had biochemical evidence of liver disease, liver function tests improved. All participants who did not have CF related liver disease (11/19) did not develop liver disease.	The quality of this trial was assessed using the Cochrane risk of bias assessment tool. Random sequence generation: high risk (randomisation was done, however the groups were not comparable at baseline, as more participants (n = 8) had liver damage in UDCA-TAU group than UDCA (n = 2). Allocation concealment: unclear Blinding of participants and personnel: unclear (blinding for participants and personnel not reported) Blinding of outcome assessment: unclear (not reported) Incomplete outcome data: low risk (there were no important or systematic differences between groups in terms of those who did not complete treatment, however 5 participants in UDCA and 4 in UDCA-TAU group did not complete treatment). Selective reporting: low risk (the groups were comparable with respect to the availability of outcome data) Other bias: low risk (The comparison groups received the same care apart from the intervention(s) studied. All groups were followed up for an equal length of time. The

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To investigate whether the administration of a medium dose of UDCA ameliorates the nutritional status of malnourished young adult CF patients with chronic liver disease. Study dates April 1990 - February 1991 Source of funding None reported.					study had an appropriate length of follow-up. The study used a precise definition of outcome. A valid and reliable method was used to determine the outcome. Overall quality: Unclear/unknown risk Other information Only 8 had biochemical evidence of liver disease at baseline, 11/19 had no biochemical evidence of liver disease.
Full citation Cheng, Katharine, Ashby, Deborah, Smyth, Rosalind L., Ursodeoxycholic acid for cystic fibrosis-related liver disease, Cochrane Database of Systematic Reviews, 2014 Ref Id 340505	Sample size N = 118 participants 3 studies (Colombo 1996, Merli 1994, O'Brien 1992). Results from Merli 1994 and O'Brien 1992 are presented here as authors could not obtain individual participant data (raw data) from 1 study included (Colombo 1996). Characteristics Included studies: Colombo 1996,	Interventions UDCA 1 study (O'Brien 1992) UDCA + Taurine 2 studies (Merli 1994, Colombo 1996).	Details Merli 1994: cross-over trial of UDCA (12 mg/kg/day) alone or with taurine (18 - 22 mg/kg/day) for 6 months and then each treatment group was compared with placebo (glucose) for 6 months. O'Brien 1992: UDCA 20 mg/kg/day for 6 months, control: no additional therapy. Randomisation method	Results Data from 2 studies (Merli 1994 and O'Brien 1992) was presented in this Cochrane review. Data from Colombo 1996 was extracted separately. Lack of normalisation of AST Merli 1994 UDCA: 1/1 Control: 2/2 O'Brien 1992 UDCA: 5/5 Control: 3/6	Limitations In a well-conducted, relevant systematic review: The review addresses an appropriate and clearly focused question that is relevant to the guideline review question: Yes The review collects the type of studies you consider relevant to the guideline review question: Yes The literature search is sufficiently rigorous to identify all the relevant studies: Full paper (Bittner 1991) not identified in sys review, only abstract paper.

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Country/ies where the study was carried out UK Study type Cochrane systematic review Aim of the study To analyse evidence that UDCA improved indices of liver function, reduces the risk of developing chronic liver disease and improves outcomes in general cystic fibrosis. Study dates Evidence last searched on 29 May 2014. Source of funding NHS North West Region R&D Programme, UK.	Merli 1994, O'Brien 1992 In 2 trials, the comparison was placebo (Colombo 1996, Merli 1992). In the third, the comparison was existing conventional therapy (O'Brien 1992). Length of follow-up was generally short and ranged from 6 months (Merli 1994, O'Brien 1992) and 12 months (Colombo 1996). Important long term outcomes such as death was not reported. Participants O'Brien 1992: participants with CF (diagnosed by sweat test and clinically) with liver disease. N = 12, age: 12 - 42 yrs. Merli 1994: participants with CF (raised sweat chloride values and clinical symptoms). N = 51, only 10 had liver disease (8 with		Merli 1994 and O'Brien 1992: Randomisation stated, with no details on randomisation method provided. Blinding Merli 1994: no description of blinding method provided.	Lack of normalisation of ALT Merli 1994 UDCA: 0/2 Control: 1/1 O'Brien 1992 UDCA: 4/6 Control: 2/3 Lack of normalisation of GGT Merli 1994 UDCA: 0/1 Control: 0/1 O'Brien 1992 UDCA: 2/5 Control: 2/3 Need for liver transplant Merli 1994 UDCA: 0/6 Control: 0/12 O'Brien 1992 UDCA: 0/6 Control: 0/6	Study quality is assessed and reported: Yes An adequate description of the methodology used is included, and the methods used are appropriate to the question: Yes Indirectness: Not all participants from 1 study included (Merli 1994) have liver disease. Attrition bias: Merli 1994 - 9 participants (5 UDCA, 4 UDCA + taurine) withdrew, were not followed up and analysed. Other information None

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	enlarged liver and fibrosis and 2 with cirrhosis). Inclusion criteria Included in this Cochrane review are RCTs (published or unpublished). Trials where pseudo-randomisation methods are used such as alternation. Exclusion criteria Non RCTs.				
Full citation Colombo, C., Battezzati, P. M., Podda, M., Bettinardi, N., Giunta, A., Ursodeoxycholic acid for liver disease associated with cystic fibrosis: a double-blind multicenter trial. The Italian Group for the Study of Ursodeoxycholic Acid in Cystic Fibrosis, Hepatology, 23, 1484-90, 1996 Ref Id	Sample size N = 55 UDCA With Taurine: n=15 Without Taurine: n=15 Placebo With taurine: n=12 Without Taurine: n=13 Characteristics CF had been diagnosed at a median age of 1 year (range: 1 month - 13 years) Liver disease had been diagnosed at a median age of 9 years (range: 2 months - 18 years).	Interventions Participants to receive, on a weight basis: UDCA or placebo at the daily dose of 1 to 3 300 mg capsules for 1 year. Patients in the 2 groups who received UDCA assumed an average daily dose of 12 ± 3 mg/kg body weight (range: 10 - 20 mg). Taurine or a second placebo at the dose of 1 to 3 500 mg	Details Clinical and standard laboratory evaluations were performed at the time of enrolment and every 3 months thereafter. Blood samples were obtained for determination of serum liver enzyme levels (alanine and aspartate aminotransferase, GGT and alkaline phosphatase), total and conjucated bilirubin, cholinesterase, total and high density lipoprotein cholesterol, triglycerides, glucose, albumin, gamma globulins,	Results In patients receiving UCDA + taurine and Placebo + Taurine, there is a difference in participants at baseline in terms of number of oesophageal varices. Therefore, only results for UDCA without Taurine and Placebo without Taurine are presented. Change / normalisation of hepatocellular enzymes (baseline and follow-up after 12 months) GGT Baseline UDCA without Taurine: 2.4 ± 1.6; n=15 Placebo without Taurine: 2.8 ± 2.6; n=12	Limitations The quality of this trial was assessed using the Cochrane risk of bias assessment tool. Random sequence generation: unclear (randomization was conducted, but patients in UDCA group had more oesophageal varices than placebo) Allocation concealment: unclear (not reported) Blinding of participants and personnel: low risk (both were blinded) Blinding of outcome assessment: low risk (blinded) Incomplete outcome data: low risk (2 participant from UDCA with Placebo/without Taurine

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340507 Country/ies where the study was carried out Italy Study type Double-blind, multicenter trial Aim of the study To evaluate efficacy and safety of treatment with UDCA on an extended spectrum of outcome measures. In addition, the effects of taurine supplements, which was administered randomly to patients taking UDCA or placebo. Objective The primary objective was to compare treatment groups with respect to changes in clinically relevant and nutritional parameters	Gender (Male/Female): 33/22 Age, mean (SD) UDCA + Taurine: 14.2 ± 4.2 UDA without Taurine: 11.3 ± 3.6 Placebo + Taurine: 14.8 ± 3.7 Placebo without Taurine: 12.8 ± 3.8 With multilobular cirrhosis UDCA + Taurine: 8 UDCA without Taurine: 8 Placebo + Taurine: 6 Placebo without Taurine: 6 With oesophageal varices (at study entry) UDCA + Taurine: 4 UDA without Taurine: 1 Placebo + Taurine: 0 Placebo without Taurine: 0 Inclusion criteria Patients with a diagnosis of CF and chronic liver disease with persistent alterations of serum liver enzymes.	capsules daily were randomly added double-blind to patients in either group.	immunoglobulins, prothrombin time, complete blood counts, urea and creatine. Bloos samples for determination of fasting serum bile acid levels Setting 12 Italian centers. The tests were performed in the clinical laboratory of each participating center by routine automated techniques. Randomisation method A centrally computer-generated list Allocation concealment Does not state method of concealment, only states "double-blind". Statistical analysis Serum liver enzymes were standardised according to reference values for each laboratory and expressed as upper limit of reference values. ANOVA for factorial designs was used for estimation of the effects of UDCA, of taurine and of their interaction.	% Change UDCA without Taurine: -26 ± 35; n=15 Placebo without Taurine: -15 ± 33; n=12 AST Baseline UDCA without Taurine: 2.1 ± 1.3; n=15 Placebo without Taurine: 2.1 ± 1.8; n=12 % Change UDCA without Taurine: -24 ±25; n=15 Placebo without Taurine: -10 ± 40; n=12 ALT Baseline UDCA without Taurine: 2.2 ± 1.0; n=15 Placebo without Taurine: 3.6 ± 4.3; n=12 % Change UDCA without Taurine: -30 ± 32; n=15 Placebo without Taurine: -17 ± 41; n=12 Withdrawal Two patients, both in the UDCA + placebo (UDCA without taurine) group were withdrawn for deterioration of clinical conditions involving pulmonary disease in one	group did not complete treatment) Selective reporting: low risk (the groups were comparable in terms of availability of data reported) Other bias: low risk (The comparison groups received the same care apart from the intervention(s) studied. All groups were followed up for an equal length of time. The study had an appropriate length of follow-up. The study used a precise definition of outcome). Overall quality: low risk Other information None

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(Shwackman-Kulczycki score (SKS)), faecal fat excretion, seru m prealbumin and lipid levels, prothrombin time and urinary creatine besides improvement in serum liver enzymes (serum transaminases, GGTP, and 5'-nucleotidase). Study dates June - December 1990 Source of funding Not reported.	Diagnosis of Cf previously established on the basis of: increased sweat chloride concentrations, typical symptoms of pulmonary and pancreatic involvement Chronic liver disease was defined on the basis of: presence of hepatomegaly, confirmed by abnormal ultrasonographic findings (increased liver size, nonhomogeneous echogenic pattern and irrecgular surface), the presence of abnormal liver biochemistries (serum transaminases, GGT) of at least 1 year duration. Presence of serum transaminase and GGT levels exceeding 1.5 times the upper limit of normal reference values on at least 3 determinations over		Bartlett's test was used for testing of homogeneity of variances. When nonhomogeneity of variances or departure from normality were detected, data were analysed using a logarithmic transformation or the rank transformation approach. The associations between changes in serum liver enzyme levels and UDCA dosage, expressed on a weight basis, was studies by multiple regression analysis. In this analysis, the final values of serum liver enzymes were included as the independent variable, the logarithm of the dose and baseline serum liver enzyme values as independent variables. Intention to treat analysis Yes	case and liver disease in another. Liver transplantation The one patient who deteriorated due to liver disease had jaundice (liver failure) and became a candidate for liver transplantation, which was performed successfully.	

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	the year before entry into the study was required for admission into study. Exclusion criteria Less than 3 years old Serum bilirubin > 3 mg/dL Ascites Chronic viral hepatitis concominent severe pulmonary disease previous episodes of variceal bleeding or encephalopaty Portosystemic shunting Patients previously treated with corticosteroids or other immunosuppressant agents in previous 6 months patients previously included in other clinical studies on UDCA				
Full citation Lepage, G., Paradis, K., Lacaille, F., Senechal, L.,	Sample size N = 19 Characteristics All patients had CF and liver dysfunction.	Interventions UDCA administered at a dosage of 15 mg/kg per day.	Details 19 participants were randomly assigned to receive either placebo or UDCA. Participants	Results Normal range enzyme values (IU/L) - obtained from normal, aged matched controls AST: <43	Limitations The quality of this trial was assessed using the Cochrane risk of bias assessment tool.

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Ronco, N., Champagne, J., Lenaerts, C., Roy, C. C., Rasquin-Weber, A., Ursodeoxycholic acid improves the hepatic metabolism of essential fatty acids and retinol in children with cystic fibrosis, Journal of Pediatrics, 130, 52-8, 1997 Ref Id 340509 Country/ies where the study was carried out Canada Study type Double-blind, crossover study of 1 year duration. Aim of the study To examine changes in the lipid profile and in the status of fat-soluble vitamins in response to UDCA.	Cirrhosis was suspected in 12 patients because of the presence of a nodular or hard liver, splenomegaly, the presence of indicators of portal hypertension on Doppler ultrasonography or a combination of these. Sex (M/F): 13 male and 6 females Age: 7 - 17 years (11.9 ± 0.6 years) Inclusion criteria Entry criteria for liver dysfunction: abnormal findings in at least 2 liver function tests (AST, ALT, GGT) and an abnormal findings in an abdominal ultrasound examination or liver biopsy or both. Exclusion criteria None stated.	In absence of 50% decrease of alanine transaminase (ALT) or aspartate transaminase (AST) or both within 2 months, the dose was increased to 30 mg/kg. Placebo	completed 6 months of placebo and then treated with 6 months of UDCA - participants acted as their own controls. After crossover study completed, patients taking UDCA were allowed to continue to to take it for a mean period of 25 ± 2 months. 13 participants continued to take UDCA as: 1 patient died, 4 moved away and 1 discontinued medication. Only data for the 1 year trial will be presented here. Randomisation Method unclear, only "randomly assigned" stated. Allocation concealment Not reported Statistics All results were expressed as mean ± SEM. Differences between placebo and UDCA at 6 months were assessed by repeated measures analysis of variance (ANOVA) and by paired t test.	ALT: <25 GGT: <30 Baseline enzyme values in participants (IU/L), median (range) AST: 67 (46 - 348) ALT: 52 (27 - 186) GGT: 58 (35 - 194) Enzyme values, mean ± SEM AST After 6 mo Placebo: 95.6 ± 17.4; n=19 After 6 mo UDCA: 61.0 ± 8.8; n=19 ALT After 6 mo Placebo: 70.8 ± 10.7; n=19 After 6 mo UDCA: 40.3 ± 8.8*; n=19 *p < 0.05 when compared to placebo GGT After 6 mo Placebo After 6 mo Placebo: 70.7 ± 9.1; n=19 After 6 mo UDCA: 21.3 ± 2.6**; n=19 **p < 0.001 when compared to placebo	Random sequence generation: unclear Allocation concealment: unclear (not reported) Blinding of participants and personnel: unclear Blinding of outcome assessment: unclear Incomplete outcome data: low risk (all participants completed the trial) Selective reporting; low risk (The groups were comparable with respect to the availability of outcome data) Other bias: low risk (The comparison groups received the same care apart from the intervention(s) studied. All groups were followed up for an equal length of time. The study had an appropriate length of follow-up. The study used a precise definition of outcome) Overall quality: Unclear/unknown risk Other information Poor outcome reporting. Dose of UDCA increased by double within 2 months if a 50% decrease of ALT, AST or both was absent.

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Study dates Not reported. Source of funding Medical Research Council of Canada and Canadian Cystic Fibrosis Foundation.					