Ursodeoxycholic Acid in Treatment of Non-cholestatic Liver Diseases: A Systematic Review

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Abstract

Aims: To systematically evaluate the literature for evidence to support the use of bile acids in non-cholestatic liver conditions. Methods: Searches were conducted on the databases of Medline (1948-March 31, 2015), Embase (1980-March 31, 2015) and the Cochrane Central Register of Controlled Trials, and on Google and Google Scholar to identify articles describing ursodeoxycholic acid (UDCA) and its derivatives for non-cholestatic hepatic indications. Combinations of the following search terms were used: ursodeoxycholic acid, ursodiol, bile acids and/or salts, non alcoholic fatty liver disease, non alcoholic steatohepatitis, fatty liver, alcoholic hepatitis, alcohol, liver disease, autoimmune, autoimmune hepatitis, liver transplant, liver graft, transplant rejection, graft rejection, ischemic reperfusion injury, reperfusion injury, hepatitis B, hepatitis C, viral hepatitis, chronic hepatitis, acute hepatitis, transaminases, alanine transaminase, liver enzymes, aspartate aminotransferase, gamma-glutamyl transferase, gamma-glutamyl transpeptidase, bilirubin, alkaline phosphatase. No search limits were applied. Additionally, references of the included studies were reviewed to identify additional articles. Results: The literature search yielded articles meeting inclusion criteria for the following indications: non-alcoholic fatty liver disease (n = 5); alcoholic liver disease (n = 2); autoimmune hepatitis (n = 6), liver transplant (n = 2) and viral hepatitis (n = 9). Bile acid use was associated with improved normalization of liver biochemistry in non-alcoholic fatty liver disease, autoimmune hepatitis and hepatitis B and C infections. In contrast, liver biochemistry normalization was inconsistent in alcoholic liver disease and liver transplantation. The majority of studies reviewed showed that normalization of liver biochemistry did not correlate to improvement in histologic disease. In the prospective trials reviewed, adverse effects associated with the bile acids were limited to minor gastrointestinal complaints (most often, diarrhea) and did not occur at increased frequency as compared to controls. As administration of bile acids was often limited to durations of 12 months or less, long-term side effects for non-cholestatic indications cannot be excluded. Conclusions: Based on the available literature, bile acids cannot be widely recommended for non-cholestatic liver diseases at present.

Keywords: Non-alcoholic fatty liver disease; Alcoholic liver disease; Autoimmune hepatitis; Liver transplantation; Viral hepatitis.

Abbreviations: UDCA, ursodeoxycholic acid; HCC, hepatocellular carcinoma; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; NAFLD, non-alcoholic fatty liver disease; ALD, alcoholic liver disease; AIH, autoimmune hepatitis; HBV, hepatitis B virus; HCV, hepatitis C virus; SR, systematic review; MA, meta-analysis; RCT, randomized controlled trial; ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; NAS, non-alcoholic fatty liver disease activity score; NASH, non-alcoholic steatohepatitis; ALP, alkaline phosphatase; Ig, immunoglobulin; ANA, antinuclear antibody; HLA, human leukocyte antigen; TUDCA, tauro-ursodeoxycholic acid; ACR, acute cellular rejection; MHC, major histocompatibility complex; IRI, ischemic reperfusion injury; ASMA, anti-smooth muscle antibodies.

Introduction

Ursodeoxycholic acid (UDCA) is a non-toxic, hydrophilic bile acid indicated for treatment of gallstones and primary biliary cirrhosis (PBC).1 Endogenous bile acids are hepatically synthesized and regulate cholesterol homeostasis and solubilization of dietary lipids. Chenodeoxycholic and deoxycholic acid—the two major human bile acids—are hydrophobic, and when in excess contribute to direct biliary toxicity through their detergent effects on lipid membranes.2 UDCA is naturally occurring in humans, comprising only 1–3% of the total bile acid pool. When used in treatment of PBC, doses of 13–15 mg/kg/day increase the concentration to 40–60%, making UDCA the predominant bile acid. Increasing bile pool hydrophilicity via UDCA serves to improve cholestasis and minimize toxicity.3 Additionally, UDCA is postulated to possess other pharmacologic mechanisms, including stimulation of hepatocellular and biliary ductular secretions, and to exert anti-inflammatory effects, making it attractive as treatment for a multitude of liver diseases. Moreover, studies have demonstrated that UDCA has efficacy in reducing histologic progression of PBC, as well as the need for liver transplantation and survival.4 While UDCA may be prescribed for other cholestatic conditions (i.e. primary sclerosing cholangitis (PSC), cholestasis of pregnancy and cystic fibrosis, and graft versus host disease), the supporting data reported to date is minimal and limited predominantly to surrogate biochemical markers.5,6 Furthermore, although UDCA is anecdotally used for non-cholestatic liver diseases, wherein liver biochemistry is frequently abnormal, the practice guidelines do not endorse its use.
Reardon J. et al: UDCA for the treatment of NAFLD

The objective of this review was to systemically evaluate the literature to ascertain evidence for UDCA in the following non-cholestatic liver diseases: non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD), autoimmune hepatitis (AIH), liver transplantation, and acute and chronic infections with hepatitis B (HBV) and/or C (HCV).

Methods

Literature search

Searches of the Medline (1948-March 31, 2015) and Embase (1980-March 31, 2015) databases, the Cochrane Central Register of Controlled Trials, Google and Google Scholar were conducted to identify articles describing UDCA and derivatives for non-cholestatic hepatic indications. Separate searches were conducted for each condition using the following combinations of both free-text and MeSH terms: ursodeoxycholic acid and/or ursodiol and/or bile acids and/or salts and/and: 1. non alcoholic fatty liver and/or non alcoholic steatohepatitis and/or fatty liver; 2. alcoholic hepatitis and/or alcohol and liver disease; 3. autoimmune and/or autoimmun hepatitis; 4. liver transplant and/or liver graft and/or transplant rejection and/or graft rejection; 5. ischimic reperfusion injury and/or reperfusion injury; 6. hepatitis B and/or hepatitis C and/or viral hepatitis and/or chronic hepatitis and/or acute hepatitis; 7. ursodeoxycholic acid and/or ursodiol and/or bile acids and/or salts and/and transaminases and/or alanine transaminase and/or liver enzymes and/or aspartate aminotransferase and/or gamma-glutamyl transferase and/or gamma-glutamyl transeptidase and/or bilirubin and/or alkaline phosphatase. No search limits were applied. The references lists of the retrieved studies were also reviewed to identify any additional articles that might meet our inclusion criteria.

Study selection

Randomized controlled trials (RCTs) and observational studies (i.e. cohort, case-control and case series) evaluating UDCA and derivatives in adults to treat the following non-cholestatic liver conditions were selected for inclusion in the study: NAFLD, ALD, AIH, liver transplant complication prophylaxis or treatment and acute or chronic HBV and HCV. Studies with the following characteristics were excluded: non-human, non-English language, publication only in abstract form, pediatric patients exclusively and bile acid use in purely cholestatic liver conditions such as PBC or PSC. No limitations were placed on trial quality.

Data extraction and evaluation

The following data were extracted from each included study: design, participant number, inclusion and exclusion criteria, baseline characteristics, drug dosing regimens, study outcomes and conclusions.

Results/Discussion

The search yielded 24 articles meeting inclusion criteria for the following indications: NAFLD (n = 5); ALD (n = 2); AIH (n = 6), liver transplant (n = 2) and viral hepatitis (n = 9). Tables 1–5 summarize the details of the individual trials.

NAFLD

Five publications comprising 1447 patients to examine the use of UDCA for patients with NAFLD were included, represented by 1 systematic review (SR) and meta-analysis (MA) of 12 RCTs, 2 RCTs not included in this MA, 1 observational trial and 1 non-RCT.7–11 UDCA doses ranged from 13–28 mg/kg/day for durations of 3 months to over 5 years.

Biochemistry

All studies evaluated UDCA impact on liver biochemistry. In the SR and 2 RCTs, compared to placebo or no therapy, UDCA was associated with greater improvement in one or more of: alanine transaminase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT).7–9,11 Combination therapy of UDCA with vitamin E ± vitamin C, polye polyphosphatidylcholine, silymarin, glycyrrhizin or tiopronin was associated with greater biochemistry normalization than the monotherapy.7 Most data for combination therapy employed vitamin E.6,10 Results were conflicting if high- versus low-dose UDCA conferred a greater benefit, with one study reporting a significant reduction in serum glucose, glycosylated hemoglobin and serum insulin concentrations at doses of 28–35 mg/kg/day.7 Improved glycemic control with UDCA at lower doses was reported by two additional trials.5,11

Histology

Four of the studies included in the SR and an additional RCT reported improvement in liver steatosis and fibrosis with UDCA therapy.7,11 Additionally, Pietu et al8 described 7 patients from their initial cohort with 5-year biopsies demonstrating an average improvement of –1 point on the 8-point NAFLD activity score (NAS) scale.

Summary

NAFLD is the most common liver disease in Western countries and encompasses a spectrum of liver pathology, ranging from steatosis to non-alcoholic steatohepatitis (NASH). A small percentage of NASH patients progress to liver cirrhosis and subsequent hepatocellular carcinoma (HCC). Risk factors for NAFLD include visceral obesity, insulin resistance, hypertension and hyperlipidemia (i.e. metabolic syndrome). There are currently no liver-specific pharmacological therapies for NAFLD and management focuses on diet and lifestyle modification and pharmacologic management of the diseases comprising the metabolic syndrome.12 Underlying pathological mechanisms causing NAFLD are not fully understood. Abnormal lipid metabolism and dysregulation of pro-inflammatory species likely contribute to disease progression. As a result, it is plausible that exogenous administration of a non-toxic bile acid, such as UDCA, may be cytoprotective. Animal models of UDCA in NAFLD have demonstrated anti-apoptotic and mitochondrial protective effects as well as reductions in pro-inflammatory cytokines, such as TNF-alpha.13–15 A less obvious role for UDCA in NAFLD is insulin sensitization; although the mechanism is unknown, improved glycemic control has been demonstrated in animal models and trials that are included in this review.14

While ALT and AST are typically elevated 3–5 times the upper normal limit in NAFLD, clinically significant histologic injury can occur with normal transaminases.16 Most patients
Table 1. Studies of bile acids in NAFLD

| AU/y | Study type | n | Patients | UDCA dose | Comparator | F/U | Biochemistry | Other |
|------|------------|---|----------|-----------|------------|-----|--------------|-------|
| Xiang\(^7\) 2013 | SR/MA of RCT | 12 RCTs\(^*\) 1160 pts | n = 6 Chinese n = 6 EUR or NA Age range: 31–50 y | UDCA: 13–28 mg/kg/d OR Fixed dose: 350–900 mg/d monotherapy OR Combination +/- Vit E, PPC, silymarin, glycyrrhizin, tiopronin | P or clofibrate or atorvastatin or PPC, or silymarin or no therapy | 3–24 m | UDCA vs. comparator\(8\) 12 SS improvement in biochemistry: Monotherapy (n = 8): ALT -26 to -41% GGT-45 to 51% Combination therapy (n = 5): ALT -42 to 79% | 4/12 RCTS SS improvement in steatosis/inflammation/fibrosis (2/8 mono; 2/5 combination therapy) |
| Troisi\(^11\) 2013 | RCT | 87 | Mean age: 73 y Metabolic syndrome Hepatic steatosis on U/S: severe (n = 23), moderate (n = 38), mild (n = 26) Exclusion: Age < 65 y, on medications associated with steatohepatitis | 300–450 mg/d + diet x 6 m | Diet only x 6 m | 6 m | UDCA pre/post: ALT (U/L): 48.1 vs. 79.8 (p < 0.001) AST (U/L): 34.5 vs. 41.2 (p < 0.001) GGT (U/L): 61.5 vs. 100.7 (p < 0.001) SS improvement in TC, TG, GLU | UDCA: Mean 75% decrease in steatosis on U/S; Authors state greater reduction vs. diet alone (statistical comparisons/values not reported) |
| Ersoz\(^9\) 2005 | RCT | 57 | NASH or steatosis on bx ALT > 1.2 ULN after 3m lifestyle intervention UDCA vs. Vit E/C NASH: 52 vs. 56% Mean age: 47 y | UDCA 10 mg/kg/d x 6 m | Vit E 600 IU/d + Vit C 500 mg/d x 6 m | 6 m | ALT WNL 55 vs. 63% (NS) −44.6 vs. −52.8 U/L UDCA vs. Vit E/C GGT: −40.3 vs. −21.5 U/L | No change on liver U/S |
| Pietu\(^8\) 2012 | Cohort | 101 | NASH on bx and ALT/AST/GGT elevationBMI 30 kg/m\(^2\) Median: 51 y 50% male 37% normal LFTs Median NAS: 6 (3–12) | UDCA 1000 mg/d (12.4 mg/kg/d) + Vit E 500 IU/d x 1–12 y | – | Median: 4 y (range 1–12) | ALT reduced 47%, GGT reduced 60% After treatment ALT normal in 70% (vs. 26% at entry) GGT normal in 65 (vs. 18% at entry) | Pt with repeat 5 y bx, (n = 10): NAS improved: 7/10 NAS Unchanged: 2/10 NAS worsened: 1/10 |
| Madan\(^10\) 2005 | NRCT | 42 | Mean age: 33 y Mean BMI: 27 kg/m\(^2\) | Group 2 (n = 12): UDCA 600 mg/d + diet/lifestyle Group 3 (n = 12): UDCA + Vit E 400 mg/d + diet, x 6–18 m | Group 1 (n = 18): Diet/lifestyle | 6–18 m | ALT normalization ALT SS group 3 vs. 1 and 2: 100 vs. 44 vs. 50% (p = 0.003) | Not assessed |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AU, Author; EUR, Europe; F/U, follow-up; GGT, gamma-glutamyl transferase; GLU, serum glucose; LFT, liver function test; M, month; MA, meta-analysis; NA, North America; NAS, NAFLD score; NASH, non-alcoholic steatohepatitis; NRCT, non-randomized controlled trial; P, placebo; PPC, polyene phosphatidylcholine; Pts, patients; RCT, randomized controlled trial; SR, systematic review; SS, statistically significant; TC, total cholesterol; TG, triglycerides; U/S, ultrasound; Wt, weight; WNL, within normal limits.

\(^*\)One included study included UDCA monotherapy and combination therapy arms, which were analyzed separately.
in the trials included herein were reported to have baseline transaminase elevations. In addition, the majority of studies demonstrated a significant reduction in liver transaminases with UDCA compared to controls; however, this was not consistently associated with histologic improvement. Based on the available data, histologic impact of aggressive normalization of transaminases with UDCA is unknown.

The included studies were limited by heterogeneity, as evidenced by the inability of Xiang et al.7 authors of the large systematic review, to meta-analyze their data. In that SR, the average study quality was 2.69, with many obvious methodological flaws, including lack of randomization, as well as small sample size (2.69 with many obvious methodological flaws, including lack of randomization).

Currently, there is insufficient evidence to recommend widespread use of UDCA in patients with NAFLD. UDCA administration was not associated with harm over prolonged periods. Given the minimal risk, a trial of UDCA in patients with NAFLD and persistently elevated transaminases and poor glycemic control may be justified. UDCA doses should be 13–15 mg/kg/day and discontinued if biochemical normalization is not achieved within 3.5 months.

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| AU/y     | Study type      | n  | Patients | Tx                                                                 | Comparator                  | F/U  | Biochemistry                                                                 | Other outcomes                                                                 |
|----------|-----------------|----|----------|---------------------------------------------------------------------|-----------------------------|------|-----------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Czaja27  | RCT             | 37 | AIH      | Treatment failure on steroids +/− AZA AIH 78% Female Mean age: 45 y (19–73) 73% on AZA + prednisone Mean duration AIH: 102 m (12–281) | UDCA 13–15 mg/kg/d + steroids x 6m After 1 m steroid withdrawal attempted | 6m   | UDCA vs. P: Improvement AST: 70 vs. 31% (p = 0.04) ALP: 47 vs. 7% (p = 0.02) | UDCA vs. P: Withdrawal/steroid dose reduction: 29 vs. 31% (p > 0.9) Clinical Improvement 48 vs. 44% (p > 0.9) Deterioration during treatment: 33 vs. 44% (p = 0.7) Repeat bx (n = 30): Modified histological activity score change: 0 vs. 0.5 (NS) Fibrosis score: 0 vs. 0 (NS) |
| Miyake25  | Non-randomized control trial | 147 | AIH on bx Japanese Median age: 55 y (16–79) Mean IDCD-AIH score: 17.3 | Group 1 (n = 25): UDCA 300–600 mg/d (PSL added in n = 8 in f/u) Group 2 (n = 40): UDCA 300–600 mg/d + PSL ≥ 20 + mg/d PSL tapered after biochemical remission Group 3 (n = 68): PSL Group 4 (n = 14): Other treatment, not defined PSL tapered after biochemical remission achieved | Group 1 vs. 2 vs. 3 ALT normal: 64 vs. 95 vs. 94% | Mean 6 y | Group A: Biochemical remission 15/18 (83%) at 3m and 17/18 (84%) at 6m | Relapse: Group 2 vs. 3: 58 vs. 57% (p = 0.97) Relapse on PSL 7.5 mg/d + UDCA vs. PSL 7.5 mg/d: 7 vs. 14% (p = 0.04) Other PSL doses NS for relapse In Group 1 pts achieving sustained biochemical remission on UDCA monotherapy: No liver failure or HCC over 49.7 m (13–137 m) f/u |
| Husa30    | Cohort          | 33 | AIH on bx Mean age: 45 y Chronic, active hepatitis Group A: 9/18; Group B: 14/15 | Group A (n = 18): UDCA monotherapy (doses not reported) x 12m | Group B (n = 15): biochemical remission with pred alone or pred + AZA, then UDCA added x 12m | 12m  | Group B: Biochemical remission 15/18 (83%) at 3m and 17/18 (84%) at 6m | Group B: P discontinuation or P/AZA dose reduction: 11/15 in P or AZA or both Average immunosuppressant daily dose reductions without relapse: AZA: 87 to 44 mg Pred: 8 to 4 mg |
| Vardar26  | Cohort          | 7  | AIH on bx No response to steroids + AZA or steroids alone Mean age: 42 y | UDCA 750 mg/d x 3m + PSL ≤ 10 mg/d | – | Mean ALT pre/post UDCA: 124/37 U/L | Mean PSL dose pre/post UDCA: 20 vs. 5 mg |

(continued)
The mechanisms of ALD are incompletely understood and pathology-dependent (steatosis vs. hepatitis). Evidence suggests that in patients with steatosis, alcohol stimulates lipogenesis and inhibits fatty acid oxidation, resulting in abnormal cellular signaling and maladaptive changes. Alcoholic hepatitis results from hepatocyte apoptosis incited by oxidative damage and stimulation of cytokine production. The mainstay of ALD treatment is abstinence from alcohol and nutritional support. Severe cases of hepatitis, however, may be managed with steroids or pentoxifylline; although, evidence for benefit has been debated. Postulated benefits of UDCA in ALD are derived from limited human data demonstrating attenuation of lipid peroxidation, reduced cytokine activity and stabilization of cell membranes with improvement in fibrosis. In the majority of patients, UDCA did not affect clinical outcomes with only a marginal improvement in liver biochemistry (mainly GGT) shown in one pilot study. Lack of significant improvement in liver biochemistry in ALD patients, as compared to other patient populations reviewed, may be attributable to the severity of illness (most patients had significant cirrhosis with an average Child-Pugh score of B-C) as well as persistent alcohol consumption. Given the limited data and lack of convincing benefits, UDCA does not appear to have a role in the management of ALD.

### AIH

One RCT, 1 non-randomized controlled trial, 2 cohort trials and 2 case series examined the effect of UDCA in 236 patients with AIH. The majority of patients were females, aged 40–50 years. UDCA doses ranged from 13–16 mg/kg/day or were fixed at 600 mg/day, with treatment durations of 3 months to > 6 years. Three trials enrolled patients with disease refractory to oral steroids ± azathioprine.

#### Biochemistry

Czaja et al. randomized patients with AIH and suboptimal responses to steroids ± azathioprine to receive add-on therapy with UDCA or placebo. Patients receiving UDCA had significant reductions in AST, ALT and alkaline phosphatase (ALP). Bilirubin, GGT, immunoglobulin (Ig) G and albumin levels were not affected. A non-RCT concluded that UDCA monotherapy was not as effective as the combination with prednisolone for normalization of transaminases. Patients receiving UDCA monotherapy required longer treatment durations to achieve normalization. Similarly, observational studies concluded that addition of UDCA alone or in combination with steroids was associated with transaminase normalization.

Two studies collected data on immunologic markers of AIH. Nakamura et al. reported decreased circulating IgG and gamma-globulin as well as achievement of negative antinuclear antibody (ANA) titers in 5/8 patients treated with UDCA over 2 years. Of note, patients were minimally symptomatic and considered to have mild disease not requiring steroids. Additionally, Husa et al. reported significantly decreased concentrations of IgG, IgA and IgM at 6 months in patients receiving UDCA monotherapy. Bilirubin and circulating immune complexes remained unchanged.
| Study type | n | Patients | Tx | Comparator | F/U | Biochemistry | Other outcomes |
|------------|---|----------|----|-----------|-----|--------------|----------------|
| Wang36     | RCT | 112     | OLT DCD UDCA vs. PD x leading to OLT: HCC: 41 vs. 43%; ALD: 19.6 vs. 12.5%; HBV cirrhosis: 25 vs. 34%; Graft failure: 5.4 vs. 1.8% HCV cirrhosis: 3.6 vs. 3.6%; Other: 5.4 vs. 5.4% Excluded: PBC, PSC, AIH Mean age: 48 y | UDCA 13–15 mg/kg/d initiated early post OLT x 4w | Placebo | Median 41.6 m (1–60) | UDCA vs. P: Day 7 post-randomization: ALT (U/L): 68 vs. 92 (p = 0.005) AST (U/L): 34 vs. 48 (p = 0.004) TB (μmol/L): 54 vs. 46.5 (p = 0.924) ALP (U/L): 51 vs. 52 (p = 0.779) GGT: 89 vs. 92 (p = 0.011) Day 28 post-randomization: ALT 25 vs. 30 (p = 0.017) AST 26 vs. 32 (p = 0.045) TB: 20 vs. 19 (p = 0.483) ALP: 102 vs. 110 (0.155) GGT: 64 vs. 90 (0.002) Biliary sludge/casts 3.6 vs. 14.3% (p = 0.047) Biliary complications: NS Acute rejection: NS Vascular complications: NS 1, 3, 5 y survival: 89.3, 83.8, 76.8% vs. 92.9, 86.9, 79.2% (NS) |
| Poropat37  | SR, MA | 335 | Mean age 44–51 1 study in children age 0–13 y Dx leading to TP: ETOH cirrhosis (19.4%) HCV cirrhosis 15.2% PBC 13.7% Cryptogenic cirrhosis 84% Metabolic disease 7.2% PSC 6.5% Non-specified cirrhosis 6.5% HBV: 4.9%, AIH cirrhosis 3.4% HCC 2.3% Biliary atresia 1.9% Other: 10.6% | UDCA 10–15 mg/kg/d OR TUDCA 500 mg/d Initiated 1–7 d post-OLP x 2–6m All patients on steroids, AZA and CYA OR TAC | P | 2–18m | UDCA vs. P: 1 study (n = 30): TB: MD 2.60 mg/dL (95% CI: –0.96, 6.16) Bile acid vs. P: All-cause mortality RR 0.85 (95%CI: 0.53–1.36); Allograft rejection-related mortality RR: 0.30 (95%CI: 0.01, 7.12); Re-transplantation RR: 0.76 (95%CI: 0.20, 2.86); Acute cellular rejection RR: 0.89 (95%CI: 0.74, 1.06); Chronic rejection fixed effects: RR 0.28 (95%CI: 0.08, 0.95) Random effects: RR 0.3 (0.08, 1.13) LOS: 1 study (n = 52) MD: –8.5 d (–16.7, 0.33) |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AU, author; CI, confidence interval; CYA, cyclosporine; DCD, donation after cardiac death; Dx, diagnosis; GGT, gamma-glutamyl transferase; HBV, hepatitis B; HCC, hepatocellular carcinoma; HCV, hepatitis C; LOS, length of hospital stay; M, month; MA, meta-analysis; MD, mean difference; NS, not statistically significant; OLT, orthotopic liver transplantation; P, placebo; Pts, patients; RCT, randomized controlled trial; RR, risk ratio; SR, systematic review; SS, statistically significant; TAC, tacrolimus; TB, total bilirubin; Tx, treatment; U/S, ultrasound.
Table 5. Studies of bile acids in viral hepatitis

| Study type | Study type | n  | Patients | Tx | Comparator | F/U | Biochemistry | Other outcomes |
|------------|------------|----|----------|----|------------|-----|--------------|----------------|
| RCT 596    | Chronic HCV ALT > 60 IU/L Mean age: 58.5 y | Group 1 (n = 199): UDCA 150 mg/d | P | Up to 2 y | Group 1 vs. 2 and 3: Median change ALT: -15.3, -29.2, -36.2% (p < 0.001) | Group 1 vs. 3: | Median change ALT: -15.3, -29.2, -36.2% (p < 0.001) | Group 1 vs. 2 and 3: Median change ALT: -15.3, -29.2, -36.2% (p < 0.001) | Group 1 vs. 3: | Median change ALT: -15.3, -29.2, -36.2% (p < 0.001) |
| 2007       | Group 2 (n = 200): UDCA 600 mg/d | Group 3 (n = 197): 900 mg/d x 24w with option to continue treatment (n = 247) | | | | | | |
|            | Previous IFN tx: 61 vs. 50.5 vs. 49.7% | Excluded: IFN x RBV in past 20 w, corticosteroids, immunosuppressants, decompensated cirrhosis | | | | | | |
|            | Group 1 vs. 2 vs. 3: Group 1 (n = 199): UDCA 150 mg/d | Group 2 (n = 200): UDCA 600 mg/d | Group 3 (n = 197): 900 mg/d x 24w with option to continue treatment (n = 247) | | | | | |
|            | | | | | | | | |
| SR, MA 29  | RCTs bile acids for viral hepatitis | UDCA 10–15 mg/kg/d or 400–800 mg/d | P or no intervention ± IFN (n = 17) ± Glycyrrhizin (n = 1) | Median: 9 m (6–18 m) | | Bile acid vs. P/comparator: Chronic HCV: Elevated ALT: RR 0.83 (95% CI: 0.77, 0.90) GGT reduction: WMD-14 IU/L (95% CI: -17, -11) Serum HCV RNA+ at end of tx: RR: 0.99 (95% CI: 0.91, 1.07) Serum HCV RNA+ at end of f/u: RR: 0.93 (95% CI: 0.87, 1.0) Acute HBV: Elevated GGT: RR: 0.32 (95% CI: 0.11, 0.90) Elevated ALT: RR: 0.35 (95% CI: 0.12, 1.02) +HBsAG tx end: RR: 0.40 (95% CI: 0.17, 0.92) Serum HBV RNA tx end: NS Chronic HBV: Elevated ALT: RR: 0.65 (95% CI: 0.45, 0.94) Chronic HCV + HBV: Elevated ALT: RR: 0.96 (0.76, 1.22) | Bile acid vs. P/comparator: Chronic HCV: Glrrosis: NS Knodell score change: WMD: 0.20 (95% CI: 0.08, 0.31) Acute HBV: Not assessed Chronic HBV: Not assessed Chronic HCV + HBV: All-cause mortality: NS Knodell score improvement: RR: 0.46 (0.20, 1.05) Graft rejection: RR: 2.67 (95% CI: 0.78, 9.09) |
| 2007       | Chronic HCV (n = 25, n = 1692) | Chronic HCV + HBV (n = 1, 60 pts) | Chronic HBV (n = 1, 112 pts) | Acute HBV (n = 1, 78 pts) | | | | |
|            | | | | | | | | |
|            | | | | | | | | |
| (continued)
| AU/y | Study type | n | Patients                                                                 | Tx | Comparator | F/U | Biochemistry                                                                 | Other outcomes                                                                 |
|------|------------|---|--------------------------------------------------------------------------|----|------------|-----|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
|      |            |   | -Histologic evidence of non-cholestatic chronic, active hepatitis-ALT or AST ≈ 2x ULN-82% HCV-Asymptomatic UDCA vs. P: ALT (IU/L): 200 vs. 203 TLHS = 9.9 ± 0.6 vs. 9.9 ± 0.7 | UDCA 600 mg/d x 1 year (≈8–10 mg/kg/d) | P  | 1 y | UDCA vs. P: 12 m ALT (IU/L): 163 vs. 187 (NS) | UDCA vs. P: -Portal/periportal necrosis, inflammation, intralobular degeneration, cholestasis, fibrosis: NS -Symptoms: NS TLHS After 12 m 10.8 (± 1.0) vs. 10.2 ± 0.8 [Statistical comparison not made] |
| Bellentani51 | RCT | 60 | Chronic, active HCV ALT ≈ 1.5 ULN x 6 m Interferon a-2a + UDCA 10 mg/kg/d x 9 m, biochemical responders randomized Mean age: 42 y Mean HCV RNA: 54 Mean viral load: 2 x times; 10⁶ copies/mL Mean Knodell score: 6.5 | UDCA 10 mg/kg/day x 12 m | P  | 21 m | UDCA vs. P 12m SVR: 46 vs. 32% (NS) | Knodell score score pre/post: UDCA 6.6 ± 3.1/5.6 ± 3.5 (NS) Logistic regression: baseline viral load < 10⁶ copies/mL associated with SVR (p < 0.002) |
| Boucher52 | RCT | 107 | Acute viral hepatitis Mean age 33 y (range 17–65) 56% HBV 14% HCV 19% HAV Other 12.7% | UDCA 600 mg/d x 3 w | No treatment | 12 w | UDCA vs. no tx: GGT reduction at 3x: 60.8% vs. 29.1% (p < 0.01) TB reduction at 3w: SS (values not reported) | No differences in seroconversion noted |
| Fabris50 | RCT | 79 | Chronic HCV -Hepatitis (n = 16) -Cirrhosis (n = 29) -Genotype 1b: (n = 29) IFN non-responders: (n = 12) IFN not indicated: (n = 33) | UDCA 600 mg/d (n = 23) x 12 m | No tx (n = 22) | 12 m | AST, ALT reduction: NS ALT/AST/GGT were 60–67% less and 45–53% less of those not treated at 6, 12 m (specific numbers not provided) Bilirubin and ALP remained WNL | No change in HCV RNA values |
| Lirussi59 | RCT | 45 |                             |                             |                             |     |                             | (continued)                                                             |

(continued)
| AU/y       | Study type | n | Patients | Tx                      | Comparator | F/U | Biochemistry | Other outcomes                                                                 |
|-----------|------------|---|----------|-------------------------|------------|-----|--------------|--------------------------------------------------------------------------------|
| Qureshi53 2006 | Cohort    | 30 | Chronic liver disease (abnormal ALT > 6m + portal hypertension or decompensation or low albumin or raised PT) Chronic HCV (n = 23) or HBV(n = 7) Mean age: 39 y Mean ALT: 101 IU/L (range: 57–268) | UDCA 500 mg/d x 4m | –  | 7 m | ALT reduction: 24/30 > 25% ALT reduction: 17/24 Mean ALT with cessation of UDCA: 90 IU/L No change in albumin, PT | No change in HBV, HCV infection, No change in portal hypertension Patient reported improvement in hepatic pain and appetite pre/post UDCA |
| Nakamura28 1999 | Cohort    | 39 | CHC (n = 30); C-AIH(n = 9) ALT > 1.5xULN Mean age: 58 y Past IFN tx: C-AIH 44% HCV cirrhosis: 63% No plan for future IFN tx | – | –  | 12 m | C-AIH vs. CHC 12m > ALT reduction (p < 0.05) ALT (U/L) pre/post: C-AIH 106/44 CHC: 138/97 TB (mg/dL) pre/post: C-AIH: 0.9/0.7 CHC: 0.8/0.8 C-AIH:-lgG or gamma-g lb unchanged -Reduced ANA: 7/9 -Reduced ASMA: 5/7 | Not assessed |

Abbreviations: ALT, alanine aminotransferase; ANA, anti-nuclear antibodies; ASMA, anti-smooth muscle antibodies; AST, aspartate aminotransferase; AU, author; C-AIH, autoimmune-associated chronic hepatitis C; CHC, chronic hepatitis C; CI, confidence interval; CYA, cyclosporine; GGT, gamma-glutamyl transferase; HAV, hepatitis A virus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IFN, interferon; IgG, immunoglobulin G; gamma-g, gamma-globulin; ITT, intention to treat; LOS, length of hospital stay; M, month; MA, meta-analysis; MD, mean difference; NS, not statistically significant; P, placebo; PT, prothrombin time; Pts, patients; RBV, ribavirin; RCT, randomized controlled trial; RR, risk ratio; SR, systematic review; SS, statistically significant; TAC, tacrolimus TB, total bilirubin; TLHS, total liver histological score; Tx, treatment; ULN, upper limit of normal; U/S, ultrasound; W, weeks.
Histology
In studies performing repeat liver biopsies or ultrasound at post-UDCA initiation, no difference in disease progression was observed.\textsuperscript{25,27,28}

Other clinical outcomes
Meta-analysis data from the largest number of patients in this review found no benefit for UDCA in facilitating steroid withdrawal.\textsuperscript{27} However, 4 individual studies not included in the meta-analysis reported ability to achieve lower steroid doses and greater successes in discontinuation when UDCA was used as adjunctive therapy.\textsuperscript{25,26,29,30}

Summary
AIH is a chronic inflammatory condition of the liver, likely resulting from interplay of immune and environmental factors in genetically-vulnerable individuals. Presentation varies from asymptomatic to acute fulminant hepatic failure to end-stage cirrhosis. Diagnosis is guided by consideration of elevated transaminases, elevated gamma-globulin and/or IgG, presence of autoantibodies (ANA, smooth muscle antibody or anti-liver kidney microsome-1) and exclusion of other liver etiologies. Treatment is recommended when biochemical or histologic abnormalities exist and/or symptoms are present.\textsuperscript{23} Corticosteroids and azathioprine alone or in combination are mainstays of treatment. Although highly effective at inducing remission in 80–90% of patients, relapse after discontinuation of drug therapy is common. Considering the potential for significant long-term adverse effects with chronic use of these agents, an ideal adjunctive pharmacotherapy would allow for immunosuppressant minimization and prevention of relapse. Proposed UDCA mechanisms that may theoretically fulfill this role include immunomodulation through reduced hepatic expression of human leukocyte antigen (HLA) class 1 and attenuation of cytokine production leading to blunted immune system reactivity.\textsuperscript{32,33}

Small sample sizes and heterogeneous patient populations limited generalizability of included studies of UDCA for AIH. Results were mixed in terms of liver biochemistry normalization, immunologic markers, steroid requirements and histologic improvement.

The magnitude of AST and gamma-globulin elevation has been associated with mortality in AIH patients. With this in mind, adjunctive UDCA in patients refractory to steroids and/ or azathioprine in an attempt to normalize these variables could be justified before attempting treatment with more toxic second-line options. Patients deriving the greatest benefits from UDCA were those who had less clinically severe disease. In practice, pharmacologic treatment of such patients may not be warranted, thus limiting the applicability of this data. Biochemical and histologic remission of AIH have been reported in case reports of patients on UDCA monotherapy.\textsuperscript{24,35} Considering the relatively benign side effect profile of UDCA, its use may be considered in patients with lower disease activity in an attempt to induce remission. In patients with more active AIH, UDCA may permit dosage reduction of immunosuppressants, particularly corticosteroids. Given the predilection of AIH for young females, this strategy could prove valuable in minimizing long-term side effects in this patient population. If used, a UDCA 13–15 mg/kg/day in divided doses should be employed for a minimum of 3 months to assess benefit. Larger, randomized trials are required to fully elucidate the role of UDCA in AIH management.

Liver transplantation
One RCT and SR of 7 additional RCTs reported on UDCA or tauro-ursodeoxycholic acid (TUDCA) use post-transplantation for prevention of complications in the acute transplant period in 447 patients. UDCA/TUDCA doses ranged from 10–15 mg/kg/day for 1–6 months. In all trials, bile acids were initiated within the first week post-transplant.\textsuperscript{36,37} The majority of trials excluded patients with chronic cholestatic liver diseases, such as PBC or PSC.

Biochemistry
Only 1 trial included in the SR reported on liver biochemistry, citing no difference in bilirubin between patients treated with bile acids versus placebo.\textsuperscript{27} The additional RCT by Wang et al,\textsuperscript{36} not included in the meta-analysis, found that administration of bile acids for the first 4 weeks post-liver transplant resulted in improvement in ALT, AST and GGT within 7 days, with no changes in bilirubin or ALP.

Histology
Poropat et al\textsuperscript{37} found a significant reduction in chronic rejection confirmed on biopsy for those receiving bile acids in a fixed effect model; however, this was not replicated in a random-effects model. Rates of acute rejection were not different for bile acids- versus placebo-treated patients.\textsuperscript{36,37}

Other clinical outcomes
Poropat et al\textsuperscript{37} found no benefit for allograft rejection-related mortality or need for re-transplantation on meta-analysis. Neither trial found a difference in all-cause mortality up to 5 years post-transplant between recipients of UDCA versus placebo.\textsuperscript{36,37} Wang et al\textsuperscript{36} reported a 10.7% reduction in biliary sludge and casts in the year post-transplant with UDCA compared to placebo (p = 0.047).

Summary
Liver transplantation has become an increasingly common treatment of end-stage liver disease. Early post-operative complications may be surgical, medical or immunological in nature. Surgical complications commonly involve the biliary tract and may result in accumulation of toxic bile acids secondary to a biliary leaks or strictures.\textsuperscript{22} Administration of UDCA to alter the proportion of hydrophobic to hydrophilic bile acids may exert cytoprotective effects in these patients. Immunologic complications are related to rejection, with concern of acute cellular rejection (ACR) in the early post-operative period. Early ACR typically occurs within the first few weeks after transplantation and is characterized by abnormal liver biochemistry and inflammatory histologic changes. Episodes usually result in no long-term impact on graft survival and are managed with pulse steroids and/or increased immunosuppression. An exception is HCV patients, in whom ACR treatment has been associated with increased risk of cirrhosis and mortality.\textsuperscript{10,19}
In liver transplant patients, UDCA may theoretically prevent allograft rejection by alteration of major histocompatibility complex (MHC) class I antigen expression in bile duct epithelium and central vein endothelium.\textsuperscript{40,41} Despite this, no differences in acute graft rejection were observed in the reviewed studies. Additionally, recognition of MHC class II antigens by CD4 T cells has been identified as an inciting mechanism in acute cellular rejection.\textsuperscript{42} As UDCA is thought only to impact MCH class I antigens, there may be no role for mitigation of rejection episodes by this pathway. Theoretically, as rejection risk is highest early in the post-transplant period, initiation of UDCA pre-operatively may be required to realize any benefit. The ability of bile acids to act as immuno-suppressant-sparing agents was observed in some studies, but further evaluation of this outcome is needed. Although some trials found benefit for reduced chronic rejection and transplant-related hospitalizations with UDCA compared to control, these results were confounded by differences in sample sizes and were considered high-risk for bias. Bile acid administration immediately post-transplant may improve liver biochemistry, but the differences observed were minimal and of questionable clinical relevance. There is currently no strong evidence to support or refute bile acids for management of liver-transplanted patients with non-cholestatic liver disease.

Another complication that may occur during transplantation is ischemic-reperfusion injury (IRI). Although underlying molecular mechanisms have yet to be elucidated, IRI induces graft dysfunction via direct cellular toxicity occurring during restoration of allograft blood flow intraoperatively.\textsuperscript{43} Although anecdotal UDCA may be used peri-transplant in an attempt to attenuate ischemic damage, no human data was found to support this practice. One animal model found no change in biochemical, hemodynamic or histologic parameters with UDCA administration post-transplant.\textsuperscript{44} Conversely, a rat study showed that intravenous infusion of UDCA at the time of graft reperfusion led to reduced release of liver enzymes and mitigated toxic effects of endogenous bile salts by improving graft bile flow.\textsuperscript{45} An additional animal study showed that administration of enteral UDCA to the liver donor at 3 hours pre-transplant led to lower ALT and less hepatocyte apoptosis post-transplant.\textsuperscript{46}

There is currently no strong evidence to support or refute bile acids for management of liver-transplanted patients with non-cholestatic liver disease pre- or post-transplant.

**Viral hepatitis**

An SR of 29 RCTs, 5 RCTs not included in the SR, 2 cohort studies and 1 case report evaluated UDCA or TUDCA for patients with viral hepatitis. The majority of included patients had HCV disease and had previously failed or were not candidates for interferon. UDCA/TUDCA doses ranged from 150–900 mg/day with treatment durations from 3 weeks to 2 years.\textsuperscript{47–55}

**Biochemistry**

A Cochrane systematic review by Chen et al\textsuperscript{48} of 29 RCTs comparing any dose or duration of bile acids with placebo or no intervention for treatment of patients with HBV or HCV found significant decreases in serum transaminases with acute HBV and chronic HBV and HCV. One included trial found UDCA reduced risk of hepatitis B surface antigen positivity and HBV DNA levels, as compared to placebo in patients with acute HBV. Viral loads were not affected by bile acid use in the other included studies. RCTs not included in the Cochrane review and observational studies were congruent with these findings, demonstrating persistence of viral loads in the setting of improving liver biochemistry with bile acid use.\textsuperscript{47,49–54} One dose-finding study reported superiority of UDCA at 600 mg/day over the dose of 150 mg/day for ALT, AST and GGT improvement. Doses of 900 mg/day provided no additional benefit.\textsuperscript{47}

**History**

In their meta-analysis, Chen et al\textsuperscript{48} report a significant, albeit small, increase in Knodell scores in patients on bile acids compared to controls. Other trials reviewed did not find any significant changes in liver fibrosis scores.\textsuperscript{48,51–53}

**Other clinical outcomes**

A case report by Anzi et al\textsuperscript{55} describes a 42-year-old woman with chronic HCV with lack of response to interferon. Implementation of combined low-dose interferon and UDCA led to successful progression disease-free survival in up to 4 years of follow-up. An observational trial reported subjective improvement in abdominal pain and appetite after initiation of UDCA.\textsuperscript{53}

**Summary**

The primary mechanism of purported benefit of exogenous bile acids in management of hepatitis involves anti-apoptotic mechanisms. All patients included in the studies had transaminase elevation. There is some data to suggest that improvement of elevated transaminases, as was seen in most studies, may mitigate disease progression in HCV.\textsuperscript{56} Despite enzyme improvement, viral loads were not significantly impacted by bile acid use. Interestingly, Nakamura et al\textsuperscript{57} noted a greater benefit of UDCA in patients with HCV and autoimmune features (elevated IgG, positive ANA or anti-smooth muscle antibodies (ASMA)) lending support to the hypothesis that an immunomodulatory effect of UDCA may be responsible for any observed benefits. The bulk of data evaluating UDCA for viral hepatitis was in chronic HCV patients with past or concurrent interferon use. Recent availability of direct acting antiviral agents has revolutionized HCV treatment, producing sustained virologic responses of > 90% for certain HCV genotypes. Superior efficacy to interferon and excellent tolerability have positioned these agents as first line HCV treatment options, arguably rendering pursuit of adjunctive therapies for HCV unnecessary. Finally, as the natural progression of viral hepatitis-induced cirrhosis is slow, the duration of these studies precludes meaningful interpretation of histologic outcomes and assessment of risk for HCC and liver-related mortality. The currently available evidence does not support use of bile acids in treatment of acute or chronic HBV or HCV.

**Safety**

In the prospective trials reviewed, adverse effects with bile acids were limited to minor gastrointestinal complaints (most commonly diarrhea) and did not occur at increased frequency compared to controls. If used, UDCA should be administered.
in divided doses to minimize gastrointestinal distress. Although not reported in the reviewed studies, PBC literature has exhibited risk of weight gain with UDCA at the doses of 13–15 mg/kg/day, plateauing at 5 pounds during the first year of use.\(^2\) Lastly, as administration of bile acids was often limited to 12 months durations or less, long-term side effects for non-cholestatic indications cannot be excluded. In clinical practice, UDCA is typically dosed empirically at 450–600 mg/day, administered in divided doses. For an average 70 kg male, this would be lower than the 13–15 mg/kg employed in many of the included studies.

**Limitations**

This review has several limitations. It included only articles published in English; however, all abstracts from identified articles (English and non-English) were screened and no abstracts of non-English articles appeared to contain relevant content. Studies assessed were of varying methodological quality and of small sample size. The majority of studies evaluated surrogate markers of liver disease and were not adequately powered to assess clinically relevant long-term outcomes. Although we intended to review evidence for UDCA, a minority of studies assessed patients treated with its taurine conjugate, TUDCA. TUDCA has demonstrated comparable efficacy and safety to UDCA, and therefore this should not have affected outcomes.\(^5\) Most included studies were published ≥ 10 years ago; however, with the exception of viral hepatitis treatments, the management of non-cholestatic liver disease has not changed so dramatically as to impact the relevance and applicability of these results.

A systematic literature review on use of exogenous, hydrophilic bile acids for treatment of non-cholestatic liver disease revealed heterogeneous data comprised of variable patient populations and methodologies, thus limiting generalizability. Bile acid use may be associated with improved normalization of liver biochemistry in NAFLD, AIH, HBV and HCV patients, but these findings have limited clinical relevance. Normalization of liver biochemistry did not correlate to improvement in histologic disease in the majority of studies. Larger studies would be required for proper evaluation of the impact of bile acid administration on clinically meaningful outcomes, such as disease burden and including progression to cirrhosis and HCC.

**Conflict of interest**

None

**Author contributions**

Formulated the research question and participated in development of the search strategy (JR, TH, NP, EMY), performed the literature search and drafted the initial manuscript (JR), revised the manuscript for important intellectual content (TH, MA, VMW, SRE, NP, EMY).

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