Network Meta-Analysis of Randomized Controlled Trials: Efficacy and Safety of UDCA-Based Therapies in Primary Biliary Cirrhosis

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Abstract: Major ursodeoxycholic acid (UDCA)-based therapies for primary biliary cirrhosis (PBC) include UDCA only, or combined with either methotrexate (MTX), corticosteroids (COT), colchicine (COC), or bezafibrate (BEF). As the optimum treatment regimen is unclear and warrants exploration, we aimed to compare these therapies in terms of patient mortality or liver transplantation (MOLT) and adverse events (AE).

PubMed, the Cochrane Library, and Scopus were searched for randomized controlled trials up to August 31, 2014. We estimated the hazard ratios (HRs) for MOLT and odds ratios (ORs) for AE. A sensitivity analysis based on the dose of UDCA was also executed.

Thirty-one eligible articles were included. Compared with COT plus UDCA, UDCA (HR 0.38, 95% confidence interval [CI] 0.09–1.39), BEF plus UDCA (HR 0.29, 95% CI 0.02–4.83), COC plus UDCA (HR 0.39, 95% CI 0.07–2.25), MTX plus UDCA (HR 0.28, 95% CI 0.05–1.63), or OBS (HR 0.49, 95% CI 0.11–2.01) all provided an increased risk of MOLT. With respect to drug AE profile, although not differing appreciably, BEF plus UDCA was associated with more AEs compared with UDCA (OR 3.16, 95% CI 0.59–20.67), COT plus UDCA (OR 2.27, 95% CI 0.15–33.36), COC plus UDCA (OR 1.00, 95% CI 0.09–12.16), MTX plus UDCA (OR 2.03, 95% CI 0.23–17.82), or OBS (OR 3.00, 95% CI 0.53–20.75). The results of sensitivity analyses were highly consistent with previous analyses.

COT plus UDCA was the optimal UDCA-based regimen for both MOLT and AEs. BEF plus UDCA was most likely to cause AEs, whereas monotherapy with UDCA and coadministration of COT plus UDCA appeared to be associated with the fewest AEs for PBC treatment.

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Abbreviations: AE = adverse event, BEF = bezafibrate, CI = confidence interval, COC = colchicine, COT = corticosteroids, HR = hazard ratio, MOLT = mortality or liver transplantation, MTX = methotrexate, OBS = observation, OR = odds ratio, PBC = primary biliary cirrhosis, RCT = randomized controlled trial, UDCA = ursodeoxycholic acid.

INTRODUCTION

Primary biliary cirrhosis (PBC) is a chronic disease of the liver and is presumed to be autoimmune in nature. PBC usually leads to progressive cholestasis and often end-stage liver disease and principally affects middle-aged women with a female/male ratio of 9:1. The main feature of PBC is the destruction of liver architecture such as found in small septal and interlobular bile ducts that may result in tissue and organ disease such as progressive fibrosis and eventual cirrhosis or liver failure.[1]

UDCA is, to date, the only medical treatment that has received US Food and Drug Administration (FDA) approval for the treatment of patients with PBC.[2] Approximately 65% of patients with PBC respond fully to treatment with ursodeoxycholic acid (UDCA) and have a normal life expectancy.[3] UDCA treatment has been shown to be effective in randomized clinical trials (RCTs)[4,5] and is effective primarily because of its protective effects on cholangiocytes against cytotoxicity of hydrophobic bile acids, and via enhanced hepatobiliary secretion and concomitant protection of hepatocytes against bile acid-induced apoptosis.[1] UDCA has been shown to be disease modifying, as it improves both symptoms, manages liver enzyme elevation and liver histology, and confers an improvement on patient survival.[6] Despite these findings in patients with PBC, 2 comprehensive traditional meta-analyses concluded that the use of UDCA did not demonstrate benefit on mortality and mortality or liver transplantation (MOLT).[7,8]

For many years, patients have been offered adjuvant therapy with colchicine (COC), bezafibrate (BEF), corticosteroids (COT), and methotrexate (MTX). Treatment with UDCA plus COC in patients with PBC has been evaluated.[9,10] Results from the Japanese study indicate no benefits of COC plus UDCA, whereas the French RCT suggests that COC plus UDCA provides a marginal advantage over UDCA monotherapy. The role of combination therapy with MTX and UDCA were evaluated by Leung et al, which showed a clinical improvement compared with that predicted by the Mayo model.[2,11] However, another RCT evaluating MTX plus UDCA demonstrated that there appeared to be no improvement in symptoms and that this treatment regime was associated with substantial toxicity. Consistently, the clinical outcomes of other additional therapies (COT or BEF) to UDCA still remain unclear.[12,13]

Previous studies have suggested that a definition of optimum UDCA-based treatment for patients with PBC may be controversial, which can be resolved by performing a large-scale clinical trial with multiple comparator arms. However, it is impossible that any single trial will compare all available treatment options. On this basis, network meta-analysis, which allows us to integrate direct and/or indirect comparisons to simultaneously compare several treatments,[14,15] is a potential solution to the above problem.

In doing so, our aims were to summarize a much broader evidence base and indirectly compare the efficacy and safety of the 5 major UDCA-based therapies (UDCA, MTX plus UDCA, COT plus UDCA, COC plus UDCA, or BEF plus UDCA) for patients with PBC.

METHODS

Search Strategy

The protocol for the systematic review was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline (Supplementary 1, http://links.lww.com/MD/A229).[16] PubMed, the Cochrane Library, and Scopus were searched with an end date of August 2014 for randomized controlled trials investigating any UDCA-based therapies for patients with PBC. Key terms used were "treatments and/or therapies, primary biliary cirrhosis, randomized clinical trial." No language or other date restrictions were designated in the search criteria. Relevant meta-analyses and systematic reviews were included in the reference lists. An independent assessment was conducted by 2 reviewers (G.-Q.Z. and K.-Q.S.) who ensure quality control for eligibility of identified abstracts and titles.

Selection Criteria

For a study to be selected for inclusion in the analysis, it had to fulfill the following criteria: study population to comprise patients with PBC according to established criteria that were to include at least 3 of the following: no evidence of biliary obstruction (confirmed by ultrasonography or other related tests, gamma glutamyl transpeptidase and/or alkaline phosphatase higher than normal value, and antimitochondrial antibodies positive at a titer of 1:40); study design to be randomized, placebo, or an untreated controlled trial; patients receiving therapeutic intervention including monotherapy with UDCA or OBS and/or coadministration with UDCA; and assessment of ≥1 clinical that included MOLT and adverse events (AEs). Other exclusion criteria were trials that comprised a nonrandomized design or compared other therapeutic interventions.

Data Extraction

Two investigators (G.-Q.Z. and K.-Q.S.) independently abstracted data from each study. Discrepancies regarding the extraction of data were resolved by an additional investigator (M.-H.Z.). A predesigned electronic database facilitated data extraction from each study. Abstracted data included the publication date and author and study details (year of publication, country of population studied, and so on), the clinical protocols, patient demography and the number of patients randomised, and the number of events of interest in each group. Two clinically meaningful events were chosen to estimate efficacy and safety of UDCA-based treatments for the network meta-analysis. These were MOLT, which is commonly considered the most important parameter, and AEs, including serious or nonserious events. Serious events were defined as any untoward life-threatening medical occurrence that may have resulted in death, was persistent, or led to significant disability, and nonserious AEs, defined as any medical occurrence not necessarily having a causal relationship with the treatment administered. In cases where relevant information on design or outcomes was unclear, or when some data was unavailable directly from the study and needed for the analyses, the original authors were contacted for clarifications and assistance by e-mail.

Study Quality

The quality of the methodology was independently assessed by 2 reviewers using the Cochrane Risk of Bias Tool that is an established tool based on assessing sequence generation for subject randomization, allocation concealment of treatment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias.[17] Trials with high or unclear risk for bias for any 1 of the first 3 components were regarded as trials with high risk of bias.

Data Analysis

A traditional pairwise meta-analysis was first performed that enabled study synthesis and compared the same interventions using STATA 12.0 (Stata Corporation, College Station, TX). The DerSimonian and Laird random effects model was used to calculate pooled estimates of hazard ratios (HRs), odds ratios (ORs), and 95% confidence intervals (CIs) for direct comparisons between 2 strategies according to Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. Clinical judgment using experts from the field formed the first assessment of clinical heterogeneity. Egger test and Begg test was first used to determine statistical heterogeneity by comparison of P values from pairwise meta-analysis, which if >0.05 suggested heterogeneity. A formal and confirmatory assessment of heterogeneity was then determined by deriving the I^2 statistic and as is standard, I^2 values >50% were considered to be of significant heterogeneity, I^2 values between 25% and 50% to be of moderate, and I^2 values <25% were considered to be of no significant heterogeneity. Where heterogeneity was suspected, a sensitivity analysis was employed[18] to investigate the robustness of the main analyses and was conducted using the important covariate and the dose of UDCA. The sensitivity analysis for the dose of UDCA included trials with patients administered with a dose of 13 to 15 mg/kg/d, according to American Association for the Study of Liver Diseases practice guidelines.[19] A multiple-treatment meta-analysis was performed according to the methods that we had previously described.[20,21]
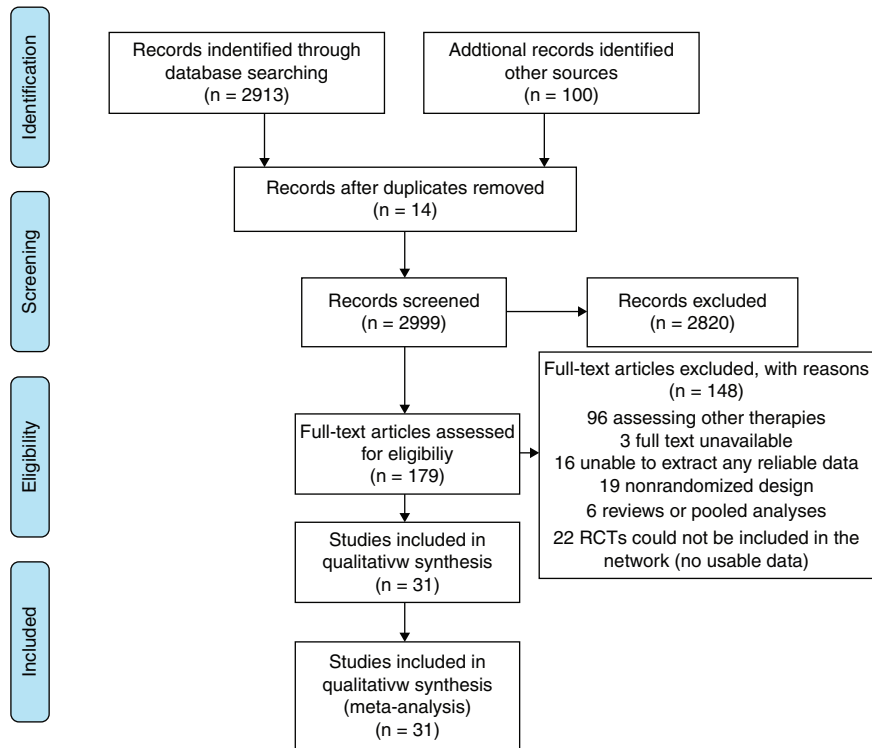
FIGURE 1. Study selection.

RESULTS

Study Characteristics

After reviewing the title and abstract, 3013 studies were identified (Figure 1). However, 2982 articles were excluded after the detailed assessment (Supplementaries 2 and 3, http://links.lww.com/MD/A229). In this meta-analysis, 31 studies were included, with a total of 2360 patients (Figure 2). Most trials (30 [94%] of 31) were 2-grouped studies and only one[22] was a 3-grouped study. The mean study sample was 36.9 patients per group (minimum−maximum, 4−133). The duration of treatment ranged from 3 months to 10 years and the mean age of trial participants was 54.6 years and ranged from 43 to 75 years. For the primary outcome, 7 unique comparisons were available for 24 different trials.[4,5,12,13,23−42] In terms of adverse effects, there were also 24 trials[4,5,9,10,13,23−36,38−40,43,44] providing data for 7 unique comparisons. Table 1 summarizes the characteristics of the 31 studies that met our inclusion criteria. There were few randomized trials at low risk of bias in every question-based entry (Supplementary 4, http://links.lww.com/MD/A229).

Results From Pairwise Comparisons

Pairwise meta-analysis was accomplished for 5 different comparisons. The weighted HRs and ORs for MOLT and AEs,
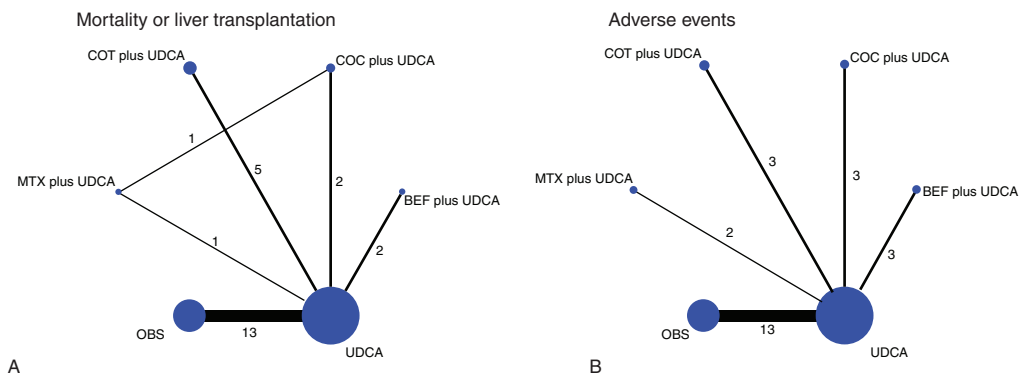
FIGURE 2. Network of the comparisons for the Bayesian network meta-analysis. (A) Mortality or liver transplantation. (B) Adverse events. The numbers along the link lines indicate the number of trials or pairs of trial arms. Lines connect the interventions that have been studied in head-to-head (direct) comparisons in the eligible controlled trials. The width of the lines represents the cumulative number of trials for each comparison and the size of every node is proportional to the number of enrolled participants (sample size). BEF = bezafibrate, COC = colchicine, COT = corticosteroids, MTX = methotrexate, OBS = observation, UDCA = ursodeoxycholic acid.

TABLE 1. Characteristics of Included Studies

Author (Year)	Country	Mean Age (Range)	Treatment/Control	Dose	Treatment Duration	Study Size	Mortality or Liver Transplantation (%) Treatment/Control	Adverse Events (%) Treatment/Control
Itakura (2004)[13]	Japan	57 (47–67)	BEF plus UDCA/UDCA	BEF: 400 mg/d; UDCA: 600 mg/d	6 months	16	8/6	11/14
Iwasaki (2008)[44]	Japan	56 (45–67)	BEF plus UDCA/UDCA	BEF: 400 mg/d; UDCA: 600 mg/d	52 weeks	22	0/0	42/10
Kanda (2003)[40]	Japan	57 (52–72)	BEF plus UDCA/UDCA	BEF: 400 mg/d; UDCA: 600 mg/d	6 months	22	11/11	18/9
Leuschner (1999)[34]	German	50 (40–60)	COT plus UDCA/UDCA	COT: 3 mg three times daily; UDCA: 10–15 mg/kg/d in 3 divided doses	2 years	40	5/5	10/5
Combes (2005)[43]	United States	53 (42–60)	MTX plus UDCA/UDCA	MTX: in 4 doses over 48 h (total dose 10 mg/wk); UDCA: 500 mg/d	117 months	265	NR/NR	10/9
Gonzalez-Koch (1997)[32]	Chile	53 (45–75)	MTX plus UDCA/UDCA	UDCA: 13–15 mg/kg/d; MTX: 0.25 mg/kg/wk	48 weeks	25	12/10	25/8
Lindor (1995)[22]	United States	59.5 (40–75)	MTX plus UDCA/UDCA/OBS	UDCA: 13–15 mg/kg/d; MTX: 0.25 mg/kg/wk	2 years	121	NR/NR/NR	22/NR/NR
Leung (2011)[42]	United States	54 (52–56)	MTX plus UDCA/COC plus UDCA	UDCA: 13–15mg/kg/d; MTX: 0.25 mg/kg/wk; COC: 1 mg/d	10 years	29	NR/NR	NR/NR
Battezzati (1993)[26]	Italy	57 (42–60)	UDCA/OBS	500 mg/d	1 year	88	43/43	9/2
Combes (1995)[29]	United States	49 (52–56)	UDCA/OBS	10–12 mg/kg/d	2 years	151	70/70	17/16
Eriksson (1997)[31]	Sweden	57 (46–70)	UDCA/OBS	500 mg/d	2 years	116	58/52	12/7
Heathcote (1994)[4]	Canada	56 (50–62)	UDCA/OBS	14 mg/kg/d	2 years	222	91/94	16/24
Hwang (1993)[27]	China	58 (50–66)	UDCA/OBS	600 mg/d	3 months	12	6/6	17/17
Leuschner (1989)[23]	German	53 (53–73)	UDCA/OBS	10 mg/kg/d	9 months	20	9/9	10/10
Lindor (1994)[5]	United States	53 (51–55)	UDCA/OBS	13–15 mg/kg/d	4 years	180	75/68	8/13
Oka (1990)[24]	Japan	59 (51–67)	UDCA/OBS	600 mg/d	24 weeks	52	25/25	15/4
Papatheodoridis (2002)[39]	Greece	54 (44–64)	UDCA/OBS	12–15 mg/kg/d	92 months	86	26/29	53/40
Pares (2000)[36]	Spain	54 (44–64)	UDCA/OBS	14–16 mg/kg/d	2 years	192	89/89	26/18
Poupon (1991)[25]	France	56 (47–65)	UDCA/OBS	13–15 mg/kg/d	2 years	146	67/63	15/26
Turner (1994)[28]	England	57 (54–60)	UDCA/OBS	10 mg/kg/d	2 years	46	21/21	27/29
Vuoristo (1995)[30]	Finland	55 (50–60)	UDCA/OBS	12–15 mg/kg/d	2 years	59	29/26	3/29
Chazouilleres (1998)[33]	France	50 (47–53)	UDCA/COT plus UDCA	UDCA: 13–15 mg/kg/d; COT: 0.5 mg/kg/d	23 months	11	3/5	20/33
Gunsar (2002)[38]	Turkey	44 (40–55)	UDCA/COT plus UDCA	UDCA: 13 mg/kg/d; COT: 0.5 mg/kg/d	28 months	20	12/5	15/14
Chazouilleres (2006)[48]	France	41 (39–57)	UDCA/COT plus UDCA	UDCA: 13–15 mg/kg/d; COT: 0.5 mg/kg/d	90 months	17	NR/NR	NR/NR
Heurgue (2007)[49]	France	44 (41–56)	UDCA/COT plus UDCA	UDCA: 13–15 mg/kg/d; COT: 0.5 mg/kg/d	60 months	13	NR/NR	NR/NR
Ozaslan (2010)[41]	Turkey	44 (40–51)	UDCA/COT plus UDCA	UDCA: 13–15 mg/kg/d; COT: 0.5 mg/kg/d	31 months	12	2/6	NR/NR
Tanaka (2011)[12]	Japan	54 (50–60)	UDCA/COT plus UDCA	UDCA: 10 mg/kg/d; COT: 0.5 mg/kg/d	73 months	25	14/8	NR/NR
Ikeda (1996)[9]	Japan	57 (55–60)	COC plus UDCA/UDCA	COC: 1 mg/kg/d; UDCA: 600 mg/d	30 months	22	NR/NR	30/8
Poupon (1996)[10]	France	53 (51–55)	COC plus UDCA/UDCA	COC: 1 mg/d, 5 d/wk; UDCA: 13–15 mg/d	2 years	74	NR/NR	5/3
Almasio (2000)[35]	Italy	55 (45–65)	COC plus UDCA/UDCA	COC: 1 mg/daily; UDCA: 500 mg/daily	3 years	90	35/41	4/2
Battezzati (2001)[37]	Italy	58 (48–68)	COC plus UDCA/UDCA	COC: 1 mg/daily; UDCA: 500 mg/daily	10 years	44	14/8	NR/NR

BEF = bezafibrate, COC = colchicine, COT = corticosteroids, MTX = methotrexate, NR = not reported, OBS = observation, UDCA = ursodeoxycholic acid.

respectively, were calculated for each comparison. The geometric distribution of controlled trials on MOLT (Figure 2A) and AEs (Figure 2B) were displayed. For primary outcome (Supplementary 5, http://links.lww.com/MD/A229), meta-analysis of the direct comparisons did not show any significant efficacy for all treatment comparisons (Table 2). In comparisons between UDCA-based therapies, monotherapy with UDCA was inferior to combination with COT and UDCA (HR 0.68, 95% CI 0.20–2.27) and OBS (HR 0.93, 95% CI 0.65–1.31), whereas addition of BEF (HR 0.75, 95% CI 0.04–14.58), COC (HR 0.42, 95% CI 0.03–5.30), and MTX (HR 1.17, 95% CI 0.09–14.55) to UDCA were superior to monotherapy with UDCA. These results arise from 23 independent analyses. For secondary outcomes of AEs (Supplementary 6, http://links.lww.com/MD/A229), there is a trend that UDCA appears to have a safer profile than BEF plus UDCA (OR 2.58, 95% CI 0.58–11.57), COC plus UDCA (OR 2.66, 95% CI 0.65–10.92), MTX plus UDCA (OR 1.30, 95% CI 0.58–2.94), or observation (OR 0.96, 95% CI 0.64–1.44), with the exception of COT plus UDCA (OR 1.08, 95% CI 0.24–4.89), which has a superior AE profile than monotherapy with UDCA.

Overall, statistical heterogeneity was moderate (Table 3). In the meta-analyses of direct comparisons for efficacy, I^2 values >75% were recorded for only 1 comparison: COC plus UDCA versus UDCA (86.9%), with 2 studies in the meta-analysis, whereas for AEs, I^2 values for the comparison of UDCA versus COT plus UDCA (0%), UDCA versus UDCA plus BEF (0%), UDCA versus UDCA plus COC (0%), UDCA versus UDCA plus MTX (3.3%), and UDCA versus OBS (35.8%) were <40%. In addition, no publication bias was found for Begg rank correlation test and Egger test among those pairwise comparisons of different treatment regimens.

Network Meta-Analysis Results

Figure 3A and B illustrates the HRs and ORs for MOLT and AEs, respectively. Although not differing significantly, the combination of COT plus UDCA showed a trend in reducing the risk of MOLT when compared with OBS (HR 2.05, 95% CI 0.50–8.93), monotherapy with UDCA (HR 2.63, 95% CI 0.72–10.75), COC plus UDCA (HR 2.55, 95% CI 0.44–15.03), MTX plus UDCA (HR 3.58, 95% CI 0.61–21.96), or BEF plus UDCA (HR 3.48, 95% CI 0.21–56.93). Consistently, for outcome of AEs (Figure 3B), all comparisons among treatments showed no statistical significance. Combined therapy of COT plus UDCA

and monotherapy with UDCA were associated with a superior AE profile than COC plus UDCA (OR 0.45, 95% CI 0.03–6.65; OR 0.32, 95% CI 0.05–1.58, respectively), MTX plus UDCA (OR 0.91, 95% CI 0.08–10.06; OR 0.65, 95% CI 0.17–2.01, respectively), BEF plus UDCA (OR 0.44, 95% CI 0.03–6.77; OR 0.32, 95% CI 0.05–1.68, respectively), as well as OBS (OR 1.34, 95% CI 0.16–11.84; OR 0.95, 95% CI 0.59–1.56, respectively).

Figure 4 shows all UDCA-based therapies ordered by their overall probability of best treatment in terms of both efficacy and safety. Combined therapy of COT plus UDCA had the highest probabilities in MOLT rates reduction (Figure 5), suggesting a regimen of COT plus UDCA was more efficacious than the other remaining interventions. COT plus UDCA, as shown by assessment of the cumulative probabilities, was ranked among the most efficacious intervention in improving survival rate. In addition, combination of BEF and UDCA was ranked the lowest in the primary outcome of efficacy, which may suggest that it was least effective in reducing mortality rate for patients with PBC. Consistently, for AEs, BEF plus UDCA appeared to be associated with more adverse effects than the other remaining regimens as this regime had more probability of causing AEs, whereas COT plus UDCA showed the best AE profile, the cumulative probabilities of being among the most efficacious in receiving safe-effects was COT plus UDCA. Figure 4 was the comparison-adjusted funnel plot for UDCA-based therapies network. It showed no evidence of asymmetry.

Traditional Pairwise Versus Network Meta-Analyses

The results from the traditional pairwise and network meta-analyses are shown in Table 2. The pooled outcomes show slight differences, however, the CIs in these 2 groups were general overlapped. The *P* values show no significant difference between direct and indirect effects (Table 4). In general, the results of the node-splitting method showed no significant inconsistency within the networks for any of the 3 outcomes.

Sensitivity Analysis

In the sensitivity analysis, there were 11 trials[9,13,24,26,27,31,32,35,37,40,44] that included patients reported to have been administered a high (>500 mg/kg/d) dose of UDCA (BEF plus UDCA excluded). Twenty independent studies were performed for the primary outcome, MOLT.

TABLE 2. Comparison of Outcomes Between Pairwise and Network Meta-Analysis

Treatment Comparisons	Results of Pairwise Meta-Analysis	Results of Network Meta-Analysis
Clinical improvement		
UDCA vs OBS	0.93 (0.65, 1.31)	0.78 (0.45, 1.27)
UDCA vs UDCA plus COT	0.68 (0.20, 2.27)	0.38 (0.09, 1.39)
UDCA vs UDCA plus BEF	0.75 (0.04, 14.58)	0.77 (0.06, 9.89)
MTX plus UDCA vs UDCA	0.42 (0.03, 5.30)	0.74 (0.24, 2.44)
COC plus UDCA vs UDCA	1.17 (0.09, 14.55)	1.05 (0.33, 3.26)
Adverse events		
UDCA vs OBS	0.96 (0.64, 1.44)	0.95 (0.59, 1.56)
UDCA vs COT plus UDCA	1.08 (0.24, 4.89)	1.42 (0.17, 11.86)
UDCA vs UDCA plus BEF	2.58 (0.58, 11.57)	3.16 (0.59, 20.67)
UDCA vs UDCA plus MTX	1.30 (0.58, 2.94)	1.54 (0.50, 5.96)
UDCA vs UDCA plus COC	2.66 (0.65, 10.92)	3.12 (0.63, 18.75)

BEF = bezafibrate, COC = colchicine, COT = corticosteroids, MTX = methotrexate, NA = not available, OBS = observation, UDCA = ursodeoxycholic acid.

TABLE 3. Assessment of Heterogeneity and Publication Bias for Trials Included in the Traditional Meta-Analysis

Treatment Comparisons	I^2 (%)	P Values of Begg Test	P Values of Egger Test
Mortality or liver transplantation			
UDCA vs OBS	1.0	0.89	0.53
UDCA vs UDCA plus COT	0.0	0.33	0.08
UDCA vs UDCA plus BEF	0.0	NA	NA
MTX plus UDCA vs UDCA	0.0	NA	NA
COC plus UDCA vs UDCA	86.9	0.32	NA
Adverse events			
UDCA vs OBS	35.8	0.90	0.77
UDCA vs COT plus UDCA	0.0	0.12	0.06
UDCA vs UDCA plus BEF	0.0	0.12	0.12
UDCA vs UDCA plus MTX	3.3	0.32	NA
UDCA vs UDCA plus COC	0.0	0.12	0.30

BEF = bezafibrate, COC = colchicine, COT = corticosteroids, MTX = methotrexate, NA = not available, OBS = observation, UDCA = ursodeoxycholic acid.

Overall, results closely resembled the results presented in the primary network meta-analysis with similar effect estimates and rankings. Supplementary 7A, http://links.lww.com/MD/A229, indicates that combination of COT and UDCA, and UDCA and OBS were the top-ranked treatment regimes, although they do not differ significantly. Same findings were also calculated for the AEs. BEF plus UDCA and COC plus UDCA was associated with more AEs than other UDCA-based treatments; similarly, COT plus UDCA was ranked the least possible regime to cause AEs (Supplementary 7B, http://links.lww.com/MD/A229).

DISCUSSION

We had performed a network meta-analysis that evaluates the efficacy and safety of UDCA-based treatments available for PBC, including 4 combination regimens and 1 monotherapy with UDCA. Our study found that combined therapy with COT and UDCA was the most effective in reducing the risk of MOLT with a weighted benefit-risk ratio for patients with PBC. BEF plus UDCA provided little further survival benefit and was associated with an increased adverse effect profile.

The present analysis has to be interpreted in view of several limitations. First, the study size assigned to different comparisons was relatively small in most included studies. However, our study has established the largest sample size

for trials on PBC performed to date in the world. Second, it may be argued that the inclusion of trial patients with optimum dose of UDCA and trials with a high dose of UDCA may introduce biased results. However, a sensitivity analysis excluding trials where patients were administered a high dose of UDCA yielded very similar results as the primary analysis. Third, factors such as trial bias, inconsistency and heterogeneity, may have affected the outcomes in the study.[45]

In this network meta-analysis, the indirect outcomes were often very similar to those obtained from the direct comparisons. This mainly was due to the less conventional geometry where our network of trials did not have any closed loops (Figure 2). Finally, this analysis revealed that not all AEs were reported consistently across included trials. In generally, because of greater uncertainty around the estimates, missing data can result in wider CIs. However, this network meta-analysis indeed provides the largest scale comparative information in current clinical practice.

Our study has several strengths. First, this analysis draws a complete picture for a number of UDCA-based treatment regimes associated with efficacy and safety outcomes among patients with PBC. Second, we had provided a rank order based on the capacity to reduce the MOLT risk. Furthermore, the effects of AEs were analyzed to acquire a benefit-risk ratio for patients with PBC based on major UDCA-based treatments.
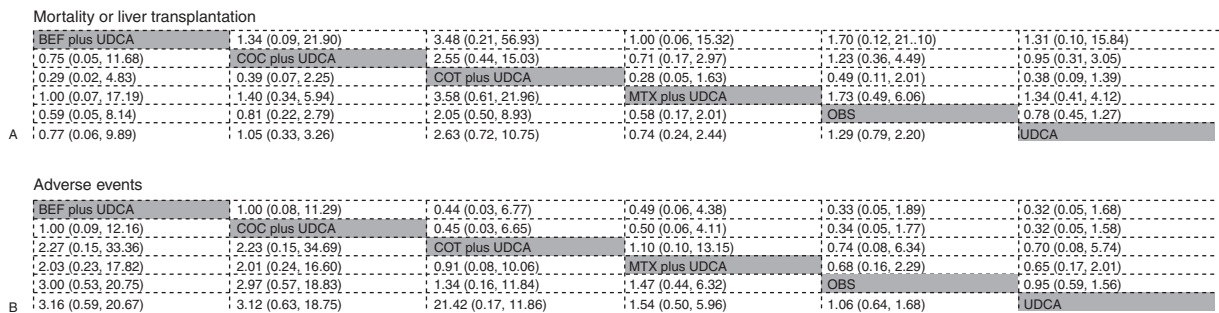

FIGURE 3. Clinical efficacy and safety of all treatments according to network meta-analysis. (A) Mortality or liver transplantation. (B) Adverse events. Treatments are reported in alphabetical order. The ORs were estimated in upper and lower triangle comparing column-defining with row-defining treatment. For mortality or liver transplantation, HRs >1 favor the column-defining treatment, whereas for adverse effects, ORs <1 favor the row-defining treatment. BEF = bezafibrate, COC = colchicine, COT = corticosteroids, HR = hazard ratio, MTX = methotrexate, OBS = observation, OR = odds ratio, UDCA = ursodeoxycholic acid.
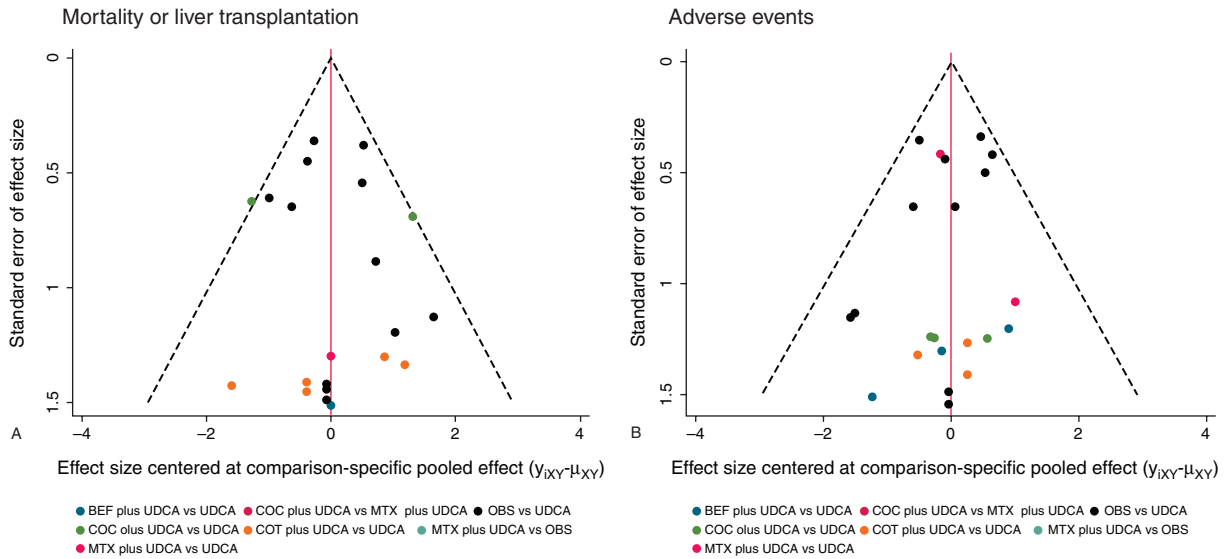
FIGURE 4. Comparison-adjusted funnel plot for the treatment network in terms of (A) mortality or liver transplantation and (B) adverse events. The red line represents the null hypothesis that the study-specific effect sizes do not differ from the respective comparison-specific pooled effect estimates. Different colors correspond to different comparisons. Estimates <1 indicate that the benefit of the experimental intervention is more pronounced in the trial than the pooled estimate. Observations from small studies missing on the right side of the line of null effect (ratio of rate ratios > 1) indicate that small studies tend to exaggerate the effectiveness of experimental treatments. BEF = bezafibrate, COC = colchicines, COT = corticosteroids, MTX = methotrexate, OBS = observation, UDCA = ursodeoxycholic acid.

UDCA is safe and may be useful for preventing the progression of PBC, which is the only therapy approved by the US FDA.[19] However, the effects of UDCA remain controversial. Although it has been demonstrated by several studies,[4,6,46] results from previously published systematic reviews yield some inconsistencies in the findings. One traditional meta-analysis in 2008[7] and a further report published in 2012[8] of 16

RCTs both reported that they did not demonstrate any benefit of UDCA on mortality and MOLT of patients with PBC, which are consistent with our results. In addition, some trials included also concluded that UDCA has no beneficial effects on patient survival, but may be a safe option for patients with PBC. One of the possible explanations for inconsistent results was that the small patient population in those trials that supported

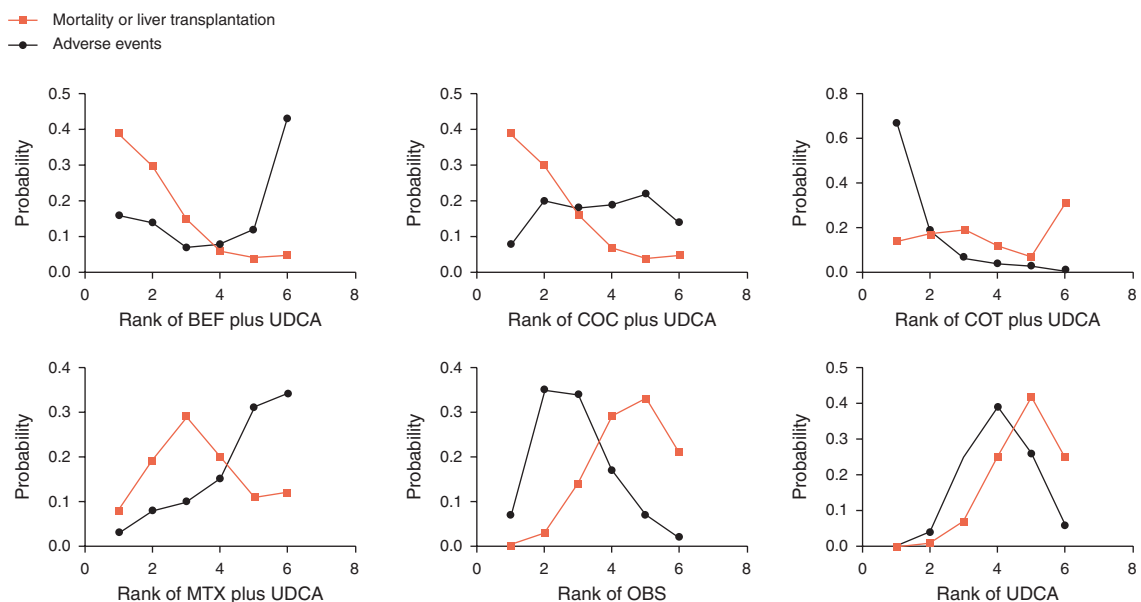**FIGURE 5.** Rankograms showing probability of each strategy having each specific rank (1–6) for mortality or liver transplantation and adverse events. Ranking indicates the probability to be the best treatment, the second best, the third best, and so on. Rank 1 is the worst and rank N is the best. BEF = bezafibrate, COC = colchicines, COT = corticosteroids, MTX = methotrexate, OBS = observation, UDCA = ursodeoxycholic acid.

TABLE 4. Assessment of Inconsistency Between Direct and Indirect Evidence

Treatment Comparisons	Direct Effect	Indirect Effect	Overall	*P* Value of Node-Splitting Method
Mortality or liver transplantation				
COC plus UDCA vs MTX plus UDCA	−0.0 (−2.49, 2.45)	−0.53 (−2.40, 1.18)	−0.34 (−1.78, 1.09)	0.69
COC plus UDCA vs UDCA	−0.16 (−1.40, 1.10)	0.46 (−2.32, 3.42)	−0.05 (−1.18, 1.11)	0.67
MTX plus UDCA vs UDCA	0.40 (−0.85, 1.81)	−0.18 (−2.92, 2.80)	0.30 (−0.89, 1.42)	0.69

COC = colchicine, MTX = methotrexate, UDCA = ursodeoxycholic acid.

UDCA or BEF plus UDCA was beneficial to patients. However, as presented in the network meta-analysis, we utilized the largest data on patients administrated by UDCA or combination of BEF, and furthermore, our results are robust as sensitivity analysis showed resemble results with our major outcomes.

Our findings are consistent with those of previous pairwise meta-analysis. A meta-analysis in 2013[47] was performed of RCTs concluded that the combination therapy of UDCA and COT was more effective in comparison to monotherapy with UDCA for patients with PBC, which we also found in both our direct and indirect comparisons. Similarly, 2 RCTs[48,49] of the analysis showed that COT plus UDCA appeared to be the best therapeutic option for patients with PBC. With regard to AEs, few AEs were reported, which included osteoporosis, bleeding, aggravated itching, and diarrhea in only 2 included RCTs[33,58] associated with COT plus UDCA.

Our study finds that monotherapy with UDCA ranked the second lowest with respect to AEs, following the combination therapy of COT and UDCA. Traditional meta-analysis in 2012[8] showed that UDCA was generally well tolerated. Administration of UDCA was consistently associated with nonserious AEs, including mild gastrointestinal disorders such as diarrhea, nausea, and vomiting.[8] The combination of BEF and UDCA was also evaluated in several studies. Some included RCTs reported that the combination of BEF plus UDCA was effective in the treatment of PBC. However, our results demonstrated that there appears to be no benefit of BEF plus UDCA in comparison to OBS for patients with PBC, which are consistent with a subsequent traditional meta-analysis in 2012.[50] With regard to AEs, BEF plus UDCA had the highest possibility of being associated with most AEs. However, there were few AEs reported for patients coadministered with BEF plus UDCA in some included trials. One of the possible explanations for this finding may be because of the small patient population (the mean study sample was 11 patients per group) that may have artefactually led to a bias. Hence, because of insufficient data, further trials on BEF plus UDCA should be conducted to investigate further clinical efficacy and safety.

In summary, our analysis shows the superiority of using COT plus UDCA treatment with weighted benefit-risk ratio in MOLT and AEs for patients with PBC, and also shows that BEF plus UDCA had the highest probability in causing AEs among 6 treatment regimens. In addition, monotherapy with UDCA and COT plus UDCA appear to be the 2 safest therapies for the treatment of PBC.

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