# Combination therapy of obeticholic acid and ursodeoxycholic acid in patients with primary biliary cholangitis who respond incompletely to ursodeoxycholic acid: a systematic review

Xuan Li, Min Liao, Qiong Pan, Qiaoling Xie, Hong Yang, Ying Peng, Qiao Li, Jiaquan Qu\* and Jin Chai\*

**Background:** Although the efficacy of ursodeoxycholic acid (UDCA) and obeticholic acid (OCA) for primary biliary cholangitis (PBC) has been suggested by small trials, a meta-analysis to summarize the evidence has not yet been carried out. The aim of this study was to evaluate the clinical outcomes of the combination therapy of UDCA and OCA compared with UDCA monotherapy in patients with PBC.

**Methods and materials:** We searched the PubMed, EMBASE, the web of science, and the Cochrane Library databases for English-language studies published before September 2018. Studies were included if they were randomized controlled trials (RCTs) and reported relative risk (RR) estimates with 95% confidence intervals (CIs) or related data for the clinical outcomes of different therapies in patients with PBC.

**Results:** Of the 1169 titles identified, two studies meeting the inclusion criteria were included in the meta-analysis. Approximately 222 patients with PBC were included in this analysis. The results of this study indicated that combination therapy was significantly superior to monotherapy in reducing serum alanine transaminase (mean difference: -15.63 IU/L; 95% CI, -21.59 to -9.68), aspartate transaminase (mean difference: -6.63 IU/L; 95% CI, -11.03 to -2.24), gamma-glutamyl transpeptidase (mean difference: -131.30 IU/L; 95% CI, -177.52 to -85.08), and C-reactive protein (mean difference=-1.17 mg/L; 95% CI, -2.19 to -0.14), but NS in improving primary endpoints of alkaline phosphatase level with 15.0% reduction from baseline, and equal or higher than the upper limit of normal serum total bilirubin (RR=2.75; 95% CI, 0.43-17.68), conjugated bilirubin (mean difference=-0.06 mg/dL; 95% CI, -0.28 to 0.15), IgM (mean difference=-41.18 mg/dL; 95% CI, -244.45 to 162.09), and adverse events (P > 0.05).

**Conclusion:** This meta-analysis demonstrated that combination therapy with UDCA and OCA provided satisfactory clinical outcomes, which may be a promising alternative for patients with PBC who had an inadequate response to UDCA therapy. Therefore, high-quality RCTs on the safety and efficacy of the combination therapy of UDCA and OCA compared with UDCA monotherapy in patients with PBC should be performed in the future. Eur J Gastroenterol Hepatol 32: 1116–1122 Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc.

## Introduction

Primary biliary cholangitis (PBC) is a chronic, autoimmune cholestatic liver disease that predominantly occurs in middle-aged women [1]. One crucial and unique feature of PBC is the progressive destruction of small intrahepatic

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monotherapy, primary biliary cholangitis, obeticholic acid, ursodeoxycholic acid

Department of Gastroenterology, Cholestatic Liver Diseases Center, Southwest Hospital, Third Military Medical University, Chongqing, China

Correspondence to Jin Chai, MD, PhD, Cholestatic Liver Diseases Center and Department of Gastroenterology, Southwest Hospital, Third Military Medical University, Chongqing 400038, China

Tel: +86 23 68765191; fax: +86 23 65410853; e-mail: jin.chai@cldcsw.org

\*Jiaquan Qu and Jin Chai contributed equally to the writing of this article.

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bile ducts, resulting in the development of fibrosis and potential cirrhosis [2]. The prevalence ranges from 1.91 to 40.20 per 100000 population according to different countries and has increased over time [1]. The etiology of PBC is unknown but presumed to be correlated with a combination of environmental triggers and genetically susceptible hosts [3].

Current evidence-based guidelines recommended that all patients with PBC should receive lifetime treatment. Because serum alkaline phosphatase and bilirubin are strongly associated with clinical outcomes (death or liver transplantation) in patients with PBC [4]. The only approved drug for PBC is ursodeoxycholic acid (UDCA), which slackens liver biochemical parameters and prolongs the time to liver transplantation [5,6]. However, nearly 40% of UDCA-treated patients do not have the adequate response in liver biochemistry parameters reduction and higher mortality compared to the favorable respondent, indicating a pressing unmet medical need for additional therapies [7,8].

Obeticholic acid (OCA), a selective farnesoid X receptor (FXR) agonist, has received accelerated approval in the USA in May 2016 for the treatment of patients with

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PBC who do not have an adequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA [9,10]. Recent studies of refractory PBC to UDCA monotherapy demonstrated that patients receiving OCA for salwage treatment may improve certain biochemical indexes, immunological indicators, and clinical symptoms, but the results from different institutions appeared to be inconsistent [8–11]. The differences mentioned between the studies may be explained partially by the sample size, methodology, eligibility criteria, outcome measures, etc. The aim of this meta-analysis was to evaluate the clinical outcomes of the combination of UDCA and OCA compared with UDCA monotherapy in patients with PBC.

## Methods and materials

#### Search strategy and selection criteria

A literature search of PubMed, EMBASE, the web of science, and the Cochrane Library, with no language restrictions, was conducted for studies published before September 2018 using the combination of the terms: PBC; randomized controlled trial (RCT); OCA. Titles and abstracts were screened for relative and duplicate references and the full texts of remained studies were retrieved for further assessment. We considered researches as eligible studies only if they met the following criteria: (1) population included in the studies were patients with PBC who incompletely responded to UDCA therapy; (2) patients in the intervention group were treated with combination therapy of OCA and UDCA; (3) patients in the control group were treated with placebo and UDCA or just UDCA; (4) RCT design; and (5) Effect size such as mean difference, relative risk (RR) with 95% confidence intervals (CIs) (or with data to calculate them) available. Reasons for exclusion were discussed by two reviewers (Li and Liao) and discrepancies were solved by other authors. The searching strategy is shown in Fig. 1.

## **Quality assessment**

Quality assessment was performed, using the 'Risk of bias table' recommended by the Cochrane Collaboration. The table consisted of six components: subject randomization,



Fig. 1. Literature search results.

allocation concealment of treatment, blinding, incomplete outcome data, selective reporting, and other sources of bias. Trials with high or unclear risk for bias for one of the first three components were considered as trials with high risks of bias [12]. This process was conducted independently by the reviewers (Xue and Cheng) who extracted data included authors, sample size, publication type, characteristics of the study population (including sex, age, treatment duration, and dose), and outcomes reported in all included studies. Any disagreement was resolved by consensus.

#### Statistical analyses

We selected the mean difference for continuous outcomes and the RR for dichotomous outcomes as the effect sizes, all were displayed with 95% CI. Data reported as final measurement values of trials were combined in the meta-analysis to calculate mean difference. Any outcome published as median (interquartile range) was converted as mean±SD by the method recommended by Luo and Wan [13,14]. Using the  $\chi^2$  and  $I^2$  tests, we detected the heterogeneity of all outcomes among included trials, and *P*-value <0.10 or an  $I^2$  value >50% was considered as statistically significant heterogeneity [12]. A fixed-effect model was applied to calculate the effect size when there was no heterogeneity of the results. Otherwise, the random-effect model was used.

All statistical analyses were performed with RevMan 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

## Results

A total of 1169 studies were recognized in our primary search, 1100 of which were excluded based on the screening of titles and abstracts (Fig. 1). The remained 69 publications were retrieved for full-text assessment. After excluding summary, case report, commentary, and abstract, we finally identified two RCTs that met the inclusion criteria.

The two studies were published in the year of 2015 and 2016, respectively, and the total sample size was n=381patients with PBC. A total of 222 patients were included in the analysis according to the inclusion criteria. The baseline demographic and clinical, laboratory characteristics of the included studies are shown in Table 1. The population in these two studies was patients with PBC who incompletely responded to the regular therapy of UDCA (13–15 mg/kg/day) initially. Then, these patients were randomly assigned to receive OCA therapy at different doses (5–25 mg/day). The mean age was 54.9 years and the ratio of male/female was 28/373. The duration of treatment of these two trials was 85 days and 12 months, respectively. The two trials included in the meta-analysis were considered with low quality as there are high or unclear risks for bias for at least one of the first three components in the risk bias table (Fig. 2).

#### **Primary endpoints**

Two randomised controlled trials comprising 222 patients had reported data for the primary endpoints (<1.67 times the upper limit of normal serum alkaline

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Table 1. Baseline cha	aracteristics	of the included s	studies				
Reference	Sample size	Mean age (year)	Sex (male/female)	UDCA dose (mg/kg/day) <sup>a</sup>	OCA dose (mg/day) <sup>a</sup>	Treatment duration	Publication type
Nevens et al. (2016)	216	56	20/216	13–15	5–10 <sup>b</sup> ;10	12 months	Original article
Hirschfield et al. (2015)	165	53.8	8/157	13–15	10;25;50	85 days	Original article

<sup>a</sup>mg/kg/day: once-daily oral dose of mg per kilogram of body weight. mg/day: once-daily oral dose of milligram.

<sup>b</sup>5–10: obeticholic acid at an initial dose of 5 mg with adjustment to 10 mg if applicable.

OCA, obeticholic acid; UDCA, ursodeoxycholic acid.



Fig. 2. Quality assessment. (a) Risk of bias in the included studies. +: low risks;?: unclear risks; -: high risks. (b) Risk of bias graph: review of the authors' judgments regarding each risk of bias item presented as percentages across all included studies. Low risk of bias is labeled as green, high risk of bias is labeled as red and unclear risk of bias is labeled as yellow.

phosphatase with 15% reduction from baseline, and equal or higher than the upper limit of normal serum total bilirubin at the end of trials). Fifty-eight of 111 patients in the combination therapy groups and 24 of 111 patients in the monotherapy groups had the primary endpoints, There were no significant differences between the groups (RR: 2.75; 95% CI, 0.43–17.68, P=0.29; Fig. 3). There was significant heterogeneity between studies ( $I^2=93\%$ , P<0.001).

#### Secondary endpoints

#### Liver biochemistry

The two included studies both reported the level of alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase (GGT), and conjugated bilirubin. We combined the data of the final measurement of trials and found that levels of alanine aminotransferase (mean difference: -15.63 IU/L; 95% CI, -21.59 to -9.68; P < 0.001), aspartate aminotransferase (mean difference: -6.63 IU/L; 95% CI, -11.03 to -2.24; P = 0.003), and GGT (mean difference: -131.30 IU/L; 95% CI, -177.52to -85.08; P < 0.001) in patients with combination therapy were significantly lower than those in UDCA monotherapy (Fig. 4). Due to the high heterogeneity ( $I^2 = 92\%$ , P < 0.001), we used the random-effect model to evaluate the mean difference for conjugated bilirubin. There was no significant difference between combination therapy groups and monotherapy groups (mean difference = -0.06 mg/dL; 95% CI, -0.28 to 0.15; P = 0.56).

	Combination th	herapy	UDC	A		<b>Risk Ratio</b>		Ris	sk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI		IV, Ran	dom, 95% Cl	
F. Nevens 2016	37	73	5	73	47.9%	7.40 [3.08, 17.76]				
Gideon M. Hirschfield 2014	21	38	19	38	52.1%	1.11 [0.72, 1.70]			+	
Total (95% CI)		111		111	100.0%	2.75 [0.43, 17.68]			-	
Total events	58		24							
Heterogeneity: Tau <sup>2</sup> = 1.68; C	Chi <sup>2</sup> = 14.62, df = 1	(P = 0.0)	001);  2=	93%				01		1000
Test for overall effect: Z = 1.0	6 (P = 0.29)						Combi	nation therap	by UDCA	1000

Fig. 3. Primary endpoints (alkaline phosphatase ≤1.67\*ULN and tBili ≤ULN) in patients with PBC treated with combination therapy vs. monotherapy. UDCA, ursodeoxycholic acid; M-H, Mante–Haenszel; CI, confidence interval; df, degrees of freedom; ULN, upper limit of the normal range; tBili, total bilirubin; PBC, primary biliary cholangitis.



Fig. 4. Liver chemistry (a) alanine aminotransferase (IU/L); (b) aspartate aminotransferase (IU/L); (c) GGT (IU/L); (d) conjugated bilirubin (mg/dL) levels in patients with PBC treated with combination therapy versus monotherapy. UDCA, ursodeoxycholic acid; IV, inverse-variance; CI, confidence interval; df, degrees of freedom; B: GGT, gamma-glutamyl transpeptidase; PBC, primary biliary cholangitis.



Fig. 5. Inflammatory markers (a) CRP (mg/L); (b) IgM (mg/dL) in patients with PBC treated with combination therapy vs. monotherapy. UDCA, ursodeoxycholic acid; IV, inverse-variance; CI, confidence interval; df, degrees of freedom; CRP, C-reactive protein; IgM, immunoglobulin M; PBC, primary biliary cholangitis.

## Immunological parameters

As shown in Fig. 5, the levels of C-reactive protein (CRP) and immunoglobulin M (IgM) reported in these two trials. As for the level CRP, there was no significant

heterogeneity between the included studies ( $I^2 = 9\%$ , P = 0.30). We pooled the data using a fix-effect model and found that the level of serum CRP exposed to combination therapy was significantly lower than that in controls

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Study or Subgroup	Events	Total F	Vents	Total	Weight	M-H Random 95% CI	M-H Random 95% Cl	
F. Nevens 2016	50	73	28	73	53.4%	1.79 [1.28, 2.48]		
Hirschfield 2014	18	38	19	38	46.6%	0.95 [0.60, 1.50]		
Total (05% CI)		111		111	100.0%	1 33 [0 72 2 47]	-	
Total events	68		47		100.070	1.00 [0.12, 2.47]		
Heterogeneity: Tau <sup>2</sup> =	0.16; Chi <sup>2</sup> = 4.79	, df = 1 (P =	= 0.03);	= 799	16			1000
Test for overall effect:	Z = 0.90 (P = 0.37	0					combination therapy UDCA	01000
	combination th	erany	UDC	A		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl	
F. Nevens 2016	13	73	13	73	92.9%	1.00 [0.50, 2.01]		
Hirschfield 2014	2	38	1	38	7.1%	2.00 [0.19, 21.14]		
Total (05% CI)		444		444	100.0%	1 07 10 55 2 001	-	
Total events	15		14		100.0%	1.07 [0.55, 2.09]		
Heterogeneity: Chi <sup>2</sup> =	0.31, df = 1 (P =	0.58); I <sup>=</sup> =	0%					1000
Test for overall effect:	Z = 0.20 (P = 0.8	(4)					combination therapy UDCA	1000
	5408 NO 18	100.	000072	15				
Study or Subgroup	combination th	Tetal	UDC.	A	Mainht	Risk Ratio	Risk Ratio	
E Nevens 2016	Events	73	13	73	76.5%	0.46 (0.19.1.15)	M-H, Fixed, 95% Cl	
Hirschfield 2014	3	38	4	38	23.5%	0.75 [0.18, 3.13]		
A Manufacture of the second second second second second						<ul> <li>Ri Ri Ri</li> <li>Ri Ri Ri Ri Ri Ri Ri Ri Ri Ri Ri</li> </ul>		
Total (95% CI)	12	111	1962	111	100.0%	0.53 [0.25, 1.14]		
Total events	9	0.67118-	17					18
Test for overall effect	Z = 1.63 P = 0.1	0)	0.10				0.001 0.1 1 10	1000
		- 66					combination therapy UDCA	
below with a second strategy	combination th	nerapy	UDC	A	CARD COMPANY	Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Fixed, 95% CI	M-H. Fixed, 95% Cl	
F. Nevens 2016	17	73	10	73	66.7%	1.70 [0.84, 3.46]		
Hirschtield 2014	7	38	5	38	33.3%	1.40 [0.49, 4.02]		
Total (95% CI)		111		111	100.0%	1.60 [0.89, 2.88]	•	
Total events	24	(a bill pilos finder	15			1970) (A. 1981)		200
Heterogeneity: Chi <sup>2</sup> =	0.09, df = 1 (P =	0.76); I <sup>2</sup> =	0%				0.001 0.1 1 10	1000
Test for overall effect.	Z = 1.56 (P = 0.1)	2)					combination therapy UDCA	
	combination th	nerapy	UDC	A		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
F. Nevens 2016	8	73	9	73	90.0%	0.89 [0.36, 2.18]		
Hirschfield 2014	4	38	38 <b>1</b> 23	38	10.0%	4.00 [0.47, 34.16]	20-20-02-02-02	
Total (95% CI)		111		111	100.0%	1.20 [0.54, 2.66]	-	
Total events	12		10			3040 84 88		
Heterogeneity: Chi <sup>2</sup> =	1.64, df = 1 (P =	0.20); I <sup>z</sup> =	39%					1000
Test for overall effect:	Z = 0.45 (P = 0.6	i5)					combination therapy UDCA	
	combination th	erany	UDC	Δ.		Risk Ratio	Risk Batio	
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Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl	
F. Nevens 2016	Events 8	Total 73	Events 8	Total 73	Weight 72.7%	M-H, Fixed, 95% Cl 1.00 [0.40, 2.52]	M-H, Fixed, 95% Cl	
F. Nevens 2016 Hirschfield 2014	Events 8 3	Total 73 38	Events 8 3	Total 73 38	Weight 72.7% 27.3%	M-H, Fixed, 95% CI 1.00 [0.40, 2.52] 1.00 [0.22, 4.65]	M-H, Fixed, 95% Cl	
F. Nevens 2016 Hirschfield 2014	Events 8 3	Total 73 38	Events 8 3	Total 73 38	Weight 72.7% 27.3%	M-H. Fixed, 95% CI 1.00 [0.40, 2.52] 1.00 [0.22, 4.65]	M-H, Fixed, 95% Cl	
F. Nevens 2016 Hirschfield 2014 Total (95% CI)	Events 8 3	Total 73 38 111	Events 8 3	Total 73 38 111	Weight 72.7% 27.3% 100.0%	<u>M-H, Fixed, 95% Cl</u> 1.00 [0.40, 2.52] 1.00 [0.22, 4.65] 1.00 [0.45, 2.21]	M-H, Fixed, 95% Cl	
Study or Subaroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> =	Events 8 3 11 0.00, df = 1 (P =	Total 73 38 111 1.00); I <sup>2</sup> =	Events 8 3 11 0%	Total 73 38 111	Weight 72.7% 27.3% 100.0%	M-H, Fixed, 95% CI 1.00 [0.40, 2.52] 1.00 [0.22, 4.65] 1.00 [0.45, 2.21]	M-H. Fixed, 95% Cl	
Study or Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect:	Events 8 3 11 0.00, df = 1 (P = Z = 0.00 (P = 1.0	Total 73 38 111 1.00); I <sup>2</sup> = 0)	Events 8 3 11 0%	Total 73 38 111	Weight 72.7% 27.3% 100.0%	M-H. Fixed, 95% CI 1.00 [0.40, 2.52] 1.00 [0.22, 4.65] 1.00 [0.45, 2.21]	M-H, Fixed, 95% Cl	1000
F. Nevens 2016 F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect:	Events 8 3 0.00, df = 1 (P = Z = 0.00 (P = 1.0	Total 73 38 111 1.00); I <sup>2</sup> = 0)	Events 8 3 11 0%	Total 73 38 111	Weight 72.7% 27.3% 100.0%	<u>M-H, Fixed, 95% CI</u> 1.00 [0.40, 2.52] 1.00 [0.22, 4.65] 1.00 [0.45, 2.21]	M-H, Fixed, 95% Cl	1000
Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect	Events 8 3 11 0.00, df = 1 (P = Z = 0.00 (P = 1.0 combination th	Total 73 38 111 1.00); I <sup>2</sup> = 0)	Events 8 3 11 0%	Total 73 38 111 A	Weight 72.7% 27.3% 100.0%	<u>M.H. Fixed, 95% C1</u> 1.00 [0.40, 2.52] 1.00 [0.42, 4.86] 1.00 [0.45, 2.21] Risk Ratio	M-H. Fixed, 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio	1000
Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Study of Subgroup E. Nevene 2016	Events 8 3 0.00, df = 1 (P = Z = 0.00 (P = 1.0 combination th <u>Events</u>	Total 73 38 111 1.00);   <sup>2</sup> = 0) terapy Total 73	Events 8 3 11 0% UDC. Events	Total 73 38 111 A Total 73	Weight 72.7% 27.3% 100.0% Weight	<u>M.H. Fixed, 95% C1</u> 1.00 [0.40, 2.52] 1.00 [0.22, 4.65] 1.00 [0.45, 2.21] Risk Ratio <u>M.H. Fixed, 95% C1</u> 0.50 m.16, 1.591	M-H. Fixed. 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H. Fixed. 95% Cl	1000
Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect Study of Subgroup F. Nevens 2016 Hirschfield 2014	Events 8 3 0.00, df = 1 (P = Z = 0.00 (P = 1.0 combination th Events 4 0	Total 73 38 111 1.00); I <sup>2</sup> = 0) herapy <u>Total</u> 73 38	Events 8 3 11 0% UDC. Events 8 2	Total 73 38 111 A Total 73 38	Weight 72.7% 27.3% 100.0% Weight 76.2% 23.8%	M.H., Fixed, 95% C1 1.00 [0.40, 2.52] 1.00 [0.22, 4.65] 1.00 [0.45, 2.21] Risk Ratio M.H., Fixed, 95% C1 0.50 [0.16, 1.59] 0.20 [0.01, 4.03]	M-H, Fixed, 95% Cl	1000
Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect Study of Subgroup F. Nevens 2016 Hirschfield 2014	Events         8           8         3           0.00, df=1 (P =         Z           Z = 0.00 (P = 1.0         Combination th           Events         4           0         0	Total 73 38 111 1.00); I <sup>2</sup> = 0) herapy <u>Total</u> 73 38	Events 8 3 11 0% UDC Events 8 2	Total 73 38 111 A Total 73 38	Weight 72.7% 27.3% 100.0% Weight 76.2% 23.8%	M-H, Fixed, 95% CI           1.00 [0.40, 2.52]           1.00 [0.22, 4.65]           1.00 [0.45, 2.21]           Risk Ratio           M-H, Fixed, 95% CI           0.50 [0.16, 1.59]           0.20 [0.01, 4.03]	M-H. Fixed. 95% CI	1000
Study or Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect Study or Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl)	Events         8           3         3           0.00, df = 1 (P =         Z           Z = 0.00 (P = 1.0         Combination the Events           4         0	Total 73 38 111 1.00); I² = 0) Total 73 38 111	Events 8 3 11 0% UDC. Events 8 2	Total 73 38 111 A Total 73 38 111	Weight 72.7% 27.3% 100.0% Weight 76.2% 23.8% 100.0%	M.H. Fixed, 95% C1 1.00 [0.40, 2.52] 1.00 [0.22, 4.65] 1.00 [0.45, 2.21] Risk Ratio M.H. Fixed, 95% C1 0.50 [0.16, 1.59] 0.20 [0.01, 4.03] 0.43 [0.15, 1.25]	M-H. Fixed, 95% Cl 0.001 0.1 10 combination therapy UDCA Risk Ratio M-H. Fixed, 95% Cl	1000
Study of Subgroup           F. Nevens 2016           Hirschfield 2014           Total (95% Cl)           Total events           Heterogeneity: Chi²=           Test for overall effect:           Study of Subgroup           F. Nevens 2016           Hirschfield 2014           Total (95% Cl)           Total events           Lincomercial (95% Cl)           Total events	Events 8 3 11 0.00, df = 1 (P = Z = 0.00 (P = 1.0 combination th Events 4 0	Total 73 38 111 1.00); F = 0) herapy Total 73 38 111	Events 8 3 11 0% UDC. Events 8 2 10	<u>Total</u> 73 38 111 A <u>Total</u> 73 38 111	Weight           72.7%           27.3%           100.0%           Weight           76.2%           23.8%           100.0%	M.H., Fixed, 95% C1           1.00 [0.40, 2.52]           1.00 [0.22, 4.65]           1.00 [0.45, 2.21]           Risk Ratio           M.H., Fixed, 95% C1           0.50 [0.16, 1.59]           0.20 [0.01, 4.03]           0.43 [0.15, 1.25]	M-H. Fixed. 95% Cl	1000
Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect	Events 8 3 0.00, df = 1 (P = Z = 0.00 (P = 1.0 combination th Events 4 0 0.32, df = 1 (P = 2 = 1.56 (P = 0.1	Total 73 38 111 1.00); P= 0) herapy Total 73 38 111 0.57); P= 2)	Events 8 3 11 0% UDC. Events 8 2 2 10 0%	Total 73 38 111 A <u>Total</u> 73 38 111	Weight 72.7% 27.3% 100.0% Weight 76.2% 23.8% 100.0%	<u>M.H. Fixed, 95% C1</u> 1.00 [0.40, 2.52] 1.00 [0.22, 4.65] <b>1.00 [0.45, 2.21]</b> Risk Ratio <u>M.H. Fixed, 95% C1</u> 0.50 [0.16, 1.59] 0.20 [0.01, 4.03] 0.43 [0.15, 1.25]	M-H, Fixed, 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H, Fixed, 95% Cl 0.001 0.1 1 10	1000
Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect:	Events           8           3           0.00, df = 1 (P =           Z = 0.00 (P = 1.0           combination the Events           4           0           0.32, df = 1 (P =           Z = 1.55 (P = 0.1	Total 73 38 111 1.00);  * = 0) Total 73 38 111 0.57);  * = 2)	Events 8 3 11 0% 10 <u>UDC.</u> Events 8 2 10 0%	Total 73 38 111 A Total 73 38 111	Weight 72.7% 27.3% 100.0% <u>Weight</u> 76.2% 23.8% 100.0%	M.H. Fixed, 95% C1 1.00 [0.40, 2.52] 1.00 [0.22, 4.65] 1.00 [0.45, 2.21] Risk Ratio M.H. Fixed, 95% C1 0.60 [0.16, 1.69] 0.20 [0.01, 4.03] 0.43 [0.15, 1.25]	M-H. Fixed, 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H. Fixed, 95% Cl 0.001 0.1 1 10 combination therapy UDCA	1000
Study or Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Study or Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect:	Events         8           11         3           0.00, df = 1 (P =         2           Z = 0.00 (P = 1.0         0           combination th           Events         4           0         4           0.32, df = 1 (P =         Z = 1.55 (P = 0.1           combination th           combination th	Total           73           38           111           1.00); F =           0)           terapy           Total           73           38           111           0.57); F =           2)           terapy	Events 8 3 11 0% UDCC Events 8 2 2 10 0% UDCC	Total 73 38 111 A Total 73 38 111	Weight 72.7% 27.3% 100.0% Weight 76.2% 23.8% 100.0%	M.H. Fixed, 95% C1 1.00 [0.40, 2.52] 1.00 [0.22, 4.65] 1.00 [0.45, 2.21] Risk Ratio M.H. Fixed, 95% C1 0.50 [0.16, 1.59] 0.20 [0.01, 4.03] 0.43 [0.15, 1.25] Risk Ratio	M-H. Fixed. 95% Cl 0.001 0.1 10 combination therapy UDCA Risk Ratio M-H. Fixed. 95% Cl 0.001 0.1 10 combination therapy UDCA Risk Ratio Risk Ratio	1000
Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect Study of Subgroup	Events         8           8         3           0.00, df = 1 (P =         2           Z = 0.00 (P = 1.0         0            4           0         0           0.32, df = 1 (P =         2           Z = 1.55 (P = 0.1         0            Events            Events	Total           73           38           111           1.00); P=           00           rotal           73           38           111           0.57); P=           2)           rotal           nerapy           rotal           111           0.57); P=           2)           rotal	Events 8 3 11 0% Events 8 2 2 10 0% 10 0%	Total 73 38 111 A Total 73 38 111 A A Total	Weight 72.7% 27.3% 100.0% Weight 100.0% 23.8% 100.0%	M.H. Fixed, 95% C1 1.00 [0.40, 2.52] 1.00 [0.22, 4.65] 1.00 [0.45, 2.21] Risk Ratio M.H. Fixed, 95% C1 0.50 [0.16, 1.59] 0.20 [0.01, 4.03] 0.43 [0.15, 1.25] Risk Ratio M.H. Fixed, 95% C1	M-H. Fixed, 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H. Fixed, 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H. Fixed, 95% Cl	1000
Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect Study of Subgroup F. Nevens 2016	Events           8           3           0.00, df = 1 (P =           Z = 0.00 (P = 1.0           combination the Events           4           0           0.32, df = 1 (P =           Z = 1.65 (P = 0.1           combination the Events           4           0           4           0           4           0           4           0           4           0	Total           733           111           1.00); F =           0)           Total           73           73           73           38           111           0.07); F =           2)           Total           73           73           73           73	Events 8 3 11 0% UDC. Events 2 10 0%	Total 73 38 111 A Total 73 38 111 A Total 73 73 73	Weight 72.7% 27.3% 100.0% Weight 76.2% 23.8% 100.0%	M-H, Fixed, 95% CI           1.00 [0.40, 2.52]           1.00 [0.22, 4.65]           1.00 [0.45, 2.21]           Risk Ratio           M-H, Fixed, 95% CI           0.60 [0.16, 1.59]           0.20 [0.01, 4.03]           0.43 [0.15, 1.25]           Risk Ratio           M-H, Fixed, 95% CI           0.50 [0.16, 1.59]	M-H. Fixed, 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H. Fixed, 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H. Fixed, 95% Cl	1000
Study or Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect Study or Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect Study or Subgroup F. Nevens 2016 Hirschfield 2014	$\begin{tabular}{ c c c c c } \hline Events & 8 & & & & & & & & & & & & & & & & & $	Total           73           38           111           1.00); P =           0)           terapy           Total           73           38           111           0.07); P =           2)           terapy           Total           73           38           111           0.57); P =           2)           terapy           Total           73           38           311           0.57); P =           2)	Events 8 3 11 0% UDC. Events 2 10 0% 10 0%	Total 73 38 111 A Total 73 38 111 A Total 73 38 38	Weight 72.7% 27.3% 100.0% Weight 76.2% 23.8% 100.0% Weight 69.6% 30.4%	M.H., Fixed, 95% CI           1.00 [0.40, 2.52]           1.00 [0.22, 4.65]           1.00 [0.45, 2.21]           Risk Ratio           M.H., Fixed, 95% CI           0.50 [0.16, 1.59]           0.43 [0.15, 1.25]           Risk Ratio           M.H., Fixed, 95% CI           0.43 [0.15, 1.25]           Risk Ratio           M.H., Fixed, 95% CI           0.61 [0.16, 1.59]           0.43 [0.15, 1.25]	M-H. Fixed, 95% CI	1000
Study or Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Study or Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Study or Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl)	$\begin{tabular}{ c c c c c c c } \hline Events & 8 & & & & & & \\ \hline & & & & & & & & \\ \hline & & & &$	Total           73           38           111           1.00); P=           0)           terapy           Total           38           111           0.57); P=           2)           terapy           Total           0.57); P=           2)           terapy           Total           38           111	Events 8 3 11 0% UDC. Events 8 2 10 0% 10 0%	Total 73 38 111 A Total 73 38 111 A Total 73 38 111	Weight 72.7% 27.3% 100.0% Weight 76.2% 23.8% 100.0% Weight 69.6% 30.4% 100.0%	M.H., Fixed, 95% C1           1.00 [0.40, 2.52]           1.00 [0.22, 4.65]           1.00 [0.45, 2.21]           Risk Ratio           M.H., Fixed, 95% C1           0.60 [0.16, 1.69]           0.20 [0.01, 4.03]           0.43 [0.15, 1.25]           Risk Ratio           M.H., Fixed, 95% C1           0.50 [0.16, 1.59]           0.50 [0.18, 1.59]           0.50 [0.18, 1.59]           0.39 [0.14, 1.13]	M-H. Fixed. 95% Cl 0.001 0.1 10 combination therapy UDCA Risk Ratio M-H. Fixed. 95% Cl 0.001 0.1 10 combination therapy UDCA Risk Ratio M-H. Fixed. 95% Cl M-H. Fixed. 95% Cl	1000
Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total (95% CI)	Events         8           8         3           0.00, df = 1 (P =         2           Z = 0.00 (P = 1.0         0           combination th Events           4         0           0.32, df = 1 (P =         2           Z = 1.55 (P = 0.1         0           combination th Events           4         0           4         0	Total           733           111           1.000; F =           00           Total           733           73           733           111           0.57); F =           2)           Total           73           38           111           0.57); F =           2)           Total           73           38           111	Events 8 3 0% 11 0% 10 5 5 7 7 8 2 0% 10 0% 10 0% 10 0% 10 3 3 11	Total 73 38 111 A Total 73 38 111 A Total 73 38 111	Weight 72.7% 27.3% 100.0% Weight 76.2% 23.8% 100.0% Weight 69.6% 30.4%	M-H, Fixed, 95% CI           1.00 [0.40, 2.52]           1.00 [0.22, 4.65]           1.00 [0.45, 2.21]           Risk Ratio           M-H, Fixed, 95% CI           0.50 [0.16, 1.59]           0.20 [0.01, 4.03]           0.43 [0.15, 1.25]           Risk Ratio           M-H, Fixed, 95% CI           0.60 [0.16, 1.59]           0.20 [0.01, 4.03]           0.43 [0.15, 1.25]           Risk Ratio           M-H, Fixed, 95% CI           0.50 [0.16, 1.59]           0.50 [0.16, 1.59]           0.39 [0.14, 1.13]	M-H. Fixed. 95% Cl	1000
Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl) Total events Heterogeneity: Chi <sup>a</sup> =	$\begin{tabular}{ c c c c c } \hline Events & 8 & $$\\ $& $\\ $$	Total           773           38           111           1.00); F =           0)           rerapy           Total           73           38           111           0.057); F =           2)           rerapy           Total           73           38           111           0.57); F =           73           38           111           0.43); F =	Events 8 3 0% 11 0% Events 8 2 10 0% 10 0%	Total 73 38 111 A Total 73 38 111 A Total 73 38 111	Weight 72.7% 27.3% 100.0% Weight 76.2% 23.8% 100.0% Weight 69.6% 30.4%	M.H., Fixed, 95% CI           1.00 [0.40, 2.52]           1.00 [0.22, 4.65]           1.00 [0.45, 2.21]           Risk Ratio           M.H., Fixed, 95% CI           0.60 [0.16, 1.59]           0.20 [0.01, 4.03]           0.43 [0.15, 1.25]           Risk Ratio           M.H., Fixed, 95% CI           0.50 [0.16, 1.59]           0.50 [0.16, 1.51]           0.50 [0.16, 1.52]           0.50 [0.16, 1.52]           0.50 [0.16, 1.52]           0.50 [0.16, 1.52]           0.50 [0.16, 1.52]           0.50 [0.16, 1.52]           0.51 [0.50]           0.52 [0.14, 1.53]	M-H. Fixed, 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H. Fixed, 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H. Fixed, 95% Cl 0.001 0.1 1 10 Combination therapy UDCA	1000
Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect	$\begin{tabular}{ c c c c c } \hline Events & 8 & & & & & & & & & & & & & & & & & $	Total           73           38           111           1.00); P =           0)           terapy           73           73           38           111           0.57); P =           2)           terapy           Total           38           111           0.57); P =           2)           terapy           Total           38           111           0.43); P =           8)	Events 8 3 0% 11 0% 2 0% 10 0% 10 0% 10 0%	Total 73 8 111 A Total 73 38 111 73 38 111	Weight 72.7% 27.3% 100.0% Weight 76.2% 23.8% 100.0% Weight 69.6% 30.4%	M.H., Fixed, 95% CI           1.00 [0.40, 2.52]           1.00 [0.22, 4.65]           1.00 [0.45, 2.21]           Risk Ratio           M.H., Fixed, 95% CI           0.60 [0.16, 1.59]           0.20 [0.01, 4.03]           0.43 [0.15, 1.25]           Risk Ratio           M.H., Fixed, 95% CI           0.50 [0.16, 1.59]           0.43 [0.15, 1.25]           0.43 [0.16, 1.59]           0.43 [0.16, 1.59]           0.43 [0.16, 1.59]           0.39 [0.14, 1.13]	M-H. Fixed, 95% Cl 0.001 0.1 1 0 combination therapy UDCA Risk Ratio M-H. Fixed, 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H. Fixed, 95% Cl 0.001 0.1 1 10 combination therapy UDCA	1000
Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect:	Events           8           3           0.00, df = 1 (P =           Z = 0.00 (P = 1.0           combination the Events           4           0           0.32, df = 1 (P =           Z = 1.55 (P = 0.1           combination the Events           4           0           0.83, df = 1 (P =           2           0.83, df = 1 (P = 0.0           combination the	Total           733           111           1.00); F =           0)           normalization           00           Total           733           111           1.00); F =           00           111           0.57); F =           2)           Total           73           38           111           0.43); F =           18)	Events 8 3 11 0% UDC. Events 8 3 10 UDC. Events 8 3 11 UDC. Events 10 10 10 10 10 10 10 10 10 10	Total 73 38 111 73 73 73 38 111 73 73 38 111	Weight 72.7% 27.3% 100.0% Weight 76.2% 23.8% 100.0% Weight 69.6% 30.4%	M-H, Fixed, 95% CI           1.00 [0.40, 2.52]           1.00 [0.22, 4.65]           1.00 [0.45, 2.21]           Risk Ratio           M-H, Fixed, 95% CI           0.50 [0.16, 1.59]           0.20 [0.01, 4.03]           0.43 [0.15, 1.25]           Risk Ratio           N-H, Fixed, 95% CI           0.50 [0.16, 1.59]           0.20 [0.01, 4.13]           0.50 [0.16, 1.59]           0.39 [0.14, 1.13]           Risk Ratio           Risk Ratio	M-H. Fixed. 95% CI	1000
Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl) Total (95% Cl)	Events           8           3           0.00, df = 1 (P =           Z = 0.00 (P = 1.0           combination the Events           4           0           0.32, df = 1 (P =           Z = 1.55 (P = 0.1           combination the Events           4           0           0.33, df = 1 (P =           4           0           0.83, df = 1 (P =           Z = 1.74 (P = 0.0           combination the Events	Total           733           111           1.00); F =           0)           Total           733           111           1.00); F =           0)           Total           733           38           111           0.57); F =           2)           Total           733           38           111           0.57); F =           733           38           111           0.43); F =           8)           Total           Ferapy           Total E	Events 8 3 11 0% Events 2 10 0% 10 Events 8 3 3 0%	Total 73 38 111 A Total 73 38 111 73 38 111	Weight 72.7% 27.3% 100.0% Weight 76.2% 23.8% 100.0% Weight 100.0%	M-H, Fixed, 95% CI           1.00 [0.40, 2.52]           1.00 [0.22, 4.65]           1.00 [0.45, 2.21]           Risk Ratio           M-H, Fixed, 95% CI           0.60 [0.16, 1.69]           0.20 [0.01, 4.03]           0.43 [0.15, 1.25]           Risk Ratio           M-H, Fixed, 95% CI           0.50 [0.16, 1.59]           0.50 [0.16, 1.59]           0.50 [0.16, 1.59]           0.50 [0.16, 1.59]           0.43 [0.14, 1.13]           Risk Ratio           M-H, Fixed, 95% CI	M-H. Fixed. 95% Cl 0.001 0.1 10 combination therapy UDCA Risk Ratio M-H. Fixed. 95% Cl 0.001 0.1 10 combination therapy UDCA Risk Ratio M-H. Fixed. 95% Cl 0.001 0.1 100 combination therapy UDCA Risk Ratio M-H. Rixed. 95% Cl 0.001 0.1 100 Combination therapy UDCA Risk Ratio M-H. Random. 95% Cl	1000
Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016	Events           8           3           0.00, df = 1 (P =           Z = 0.00 (P = 1.0           combination th           Events           4           0           0.32, df = 1 (P =           Z = 1.55 (P = 0.1           combination th           Events           4           0           0.83, df = 1 (P =           Z = 1.74 (P = 0.0              Events           0	Total           773           38           111           1.00); F =           (0)           terapy           Total           73           38           111           0.07); F =           111           0.57); F =           73           111           0.57); F =           73           111           0.57); F =           60           111           0.43); F =           80           111           0.43); F =           73           81           73           111	Events 8 3 11 0% 10 Events 2 10 0% 10% 1	Total 73 38 111 73 38 111 73 38 111 73 38 111 73 38 111 73 73 73	Weight 72.7% 27.3% 100.0% Weight 100.0% Weight 100.0% 09.6%	M.H., Fixed, 95% CI           1.00 [0.40, 2.52]           1.00 [0.40, 2.52]           1.00 [0.45, 2.21]           Risk Ratio           M.H., Fixed, 95% CI           0.60 [0.16, 1.59]           0.20 [0.01, 4.03]           0.43 [0.15, 1.25]           Risk Ratio           M.H., Fixed, 95% CI           0.50 [0.16, 1.59]           0.43 [0.15, 1.25]           Risk Ratio           M.H., Fixed, 95% CI           0.39 [0.14, 1.13]           Risk Ratio           M.H., Random, 95% CI           0.06 [0.00, 1.00]	M-H. Fixed, 95% CI	1000
Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Study of Subgroup F. Nevens 2016 Hirschfield 2014	$\begin{tabular}{ c c c c c } \hline Events & 8 & 8 & 3 & \\ \hline & & & & & & & \\ \hline & & & & & & & \\ \hline & & & &$	Total           733           111           1.00); F =           0)           rapy           Total           733           111           1.00); F =           0)           rapy           Total           733           38           111           0.57); F =           2)           rotal           7338           111           0.43); F =           (6)           rotal E           7338	Events 8 3 0% 11 0% 2 2 2 2 0% 10 0 0 0	Total 73 38 111 73 8 38 111 73 38 111 73 38 111	Weight 72.7% 27.3% 100.0% Weight 76.2% 23.8% 100.0% Weight 100.0% Weight 100.0%	M-H, Fixed, 95% CI           1.00 [0.40, 2.52]           1.00 [0.22, 4.65]           1.00 [0.45, 2.21]           Risk Ratio           M-H, Fixed, 95% CI           0.50 [0.16, 1.59]           0.20 [0.01, 4.03]           0.43 [0.15, 1.25]           Risk Ratio           M-H, Fixed, 95% CI           0.50 [0.16, 1.59]           0.43 [0.15, 1.25]           Risk Ratio           M-H, Fixed, 95% CI           0.50 [0.14, 1.13]           Risk Ratio           M-H, Fixed, 95% CI           0.39 [0.14, 1.13]           Risk Ratio           M-H, Random, 95% CI           0.06 [0.00, 1.00]           5.00 [0.25, 100.80]	M-H. Fixed. 95% Cl 0.001 0.1 1 0 combination therapy UDCA Risk Ratio M-H. Fixed. 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H. Fixed. 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H. Random, 95% Cl	1000
Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI)	Events           8           3           0.00, df = 1 (P =           Z = 0.00 (P = 1.0           combination the Events           4           0           0.32, df = 1 (P =           Z = 1.55 (P = 0.1           combination the Events           4           0           0.83, df = 1 (P =           Z = 1.74 (P = 0.0           combination the Events           0           2	Total           733           111           1.000; F =           00           Total           733           111           1.000; F =           00           Total           733           38           111           0.57); F =           2)           Total           733           38           111           0.43); F =           8)           Total           733           8           111           0.43); F =           73           73           111           0.43); F =           73           73           73           73           73           73           73           73           73           73           73           73           73           73           73           73           73           73      73           73	Events 8 3 11 0% UDC. Events 2 0% 10 UDC. Events 8 3 11 0% 10 UDC. Events 8 3 0 0 0 0 0 0 0 0 0 0 0 0 0	Total 73 38 111 A Total 73 38 111 73 38 111 73 38 111	Weight 72.7% 27.3% 100.0% Weight 100.0% 100.0% Weight 100.0% Weight 100.0%	M-H, Fixed, 95% CI           1.00 [0.40, 2.52]           1.00 [0.22, 4.65]           1.00 [0.45, 2.21]           Risk Ratio           M-H, Fixed, 95% CI           0.60 [0.16, 1.59]           0.20 [0.01, 4.03]           0.43 [0.15, 1.25]           Risk Ratio           M-H, Fixed, 95% CI           0.50 [0.16, 1.59]           0.51 [0.16, 1.59]           0.52 [0.14, 1.13]           Risk Ratio           M-H, Random, 95% CI           0.06 [0.00, 1.00]           5.00 [0.25, 100.80]	M-H. Fixed. 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H. Fixed. 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H. Fixed. 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H. Fixed. 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H. Risk Ratio M-H. Random. 95% Cl	1000
Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl) F. Nevens 2016 Hirschfield 2014 Hirschfield 2014 Hirschfield 2014 Hirschfield 2014 Total (95% Cl) Total (95% Cl) Total (95% Cl)	Events           8           3           0.00, df = 1 (P =           Z = 0.00 (P = 1.0           combination th           Events           4           0           0.32, df = 1 (P =           Z = 1.55 (P = 0.1           combination th           Events           4           0           0.83, df = 1 (P =           Z = 1.74 (P = 0.0           combination th           Events           0           2           2	Total           773           38           111           1.00); $P =$ (0)           Total           733           111           0.57); $P =$ 111           0.57); $P =$ 111           0.57); $P =$ 733           38           111           0.43); $P =$ (8)           Total           733           38           111	Events 8 3 11 0% 10 Events 2 10 0% 10 0% 10 Events 3 11 0% 11 0% 11 0%	Total           73           38           111           A           Total           73           38           111           A           Total           73           38           111           Total           73           38           111	Weight 72.7% 27.3% 100.0% Weight 76.2% 23.8% 100.0% Weight 50.6% 49.4% 100.0%	M-H, Fixed, 95% CI           1.00 [0.40, 2.52]           1.00 [0.40, 2.52]           1.00 [0.45, 2.21]           Risk Ratio           M-H, Fixed, 95% CI           0.60 [0.16, 1.69]           0.20 [0.01, 4.03]           0.43 [0.15, 1.25]           Risk Ratio           M-H, Fixed, 95% CI           0.60 [0.16, 1.59]           0.43 [0.15, 1.25]           Risk Ratio           M-H, Fixed, 95% CI           0.50 [0.16, 1.59]           0.14 [0.01, 2.67]           0.39 [0.14, 1.13]           Risk Ratio           M-H, Random, 95% CI           0.06 [0.00, 1.00]           5.00 [0.25, 100.80]           0.53 [0.01, 43.35]	M-H. Fixed. 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H. Fixed. 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H. Fixed. 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H. Random. 95% Cl	1000
Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> =	Events           8           3           0.00, df = 1 (P =           Z = 0.00 (P = 1.0           combination th           Fvents           4           0           0.32, df = 1 (P =           Z = 1.56 (P = 0.1           combination th           Fvents           4           0           0.83, df = 1 (P =           2           1.74 (P = 0.0           combination th           Events           0           2           7.91; Chi <sup>p</sup> = 4.56	Total           733           111           1.00); F =           0)           rapy           Total           733           111           1.00); F =           0)           rapy           Total           733           111           0.57); F =           2)           rotal           7338           1111           0.43); F =           (8)           rotal E           38           111           0.43); F =           (8)           111           0.43; H = 1 (P =	Events 8 3 0% 11 0% 2 2 2 0% 10% 1	Total           73         38           111	Weight 72.7% 27.3% 100.0% Weight 76.2% 23.8% 100.0% 30.4% 100.0% Weight 100.0% 49.4%	M-H, Fixed, 95% CI           1.00 [0.40, 2.52]           1.00 [0.22, 4.65]           1.00 [0.45, 2.21]           Risk Ratio           M-H, Fixed, 95% CI           0.50 [0.16, 1.59]           0.20 [0.01, 4.03]           0.43 [0.15, 1.25]           Risk Ratio           M-H, Fixed, 95% CI           0.50 [0.16, 1.59]           0.20 [0.01, 4.13]           0.50 [0.14, 1.13]           Risk Ratio           M-H, Fixed, 95% CI           0.39 [0.14, 1.13]           Risk Ratio           0.39 [0.14, 1.13]           0.50 [0.25, 100.80]           0.53 [0.01, 43.35]	M-H. Fixed. 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H. Fixed. 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H. Fixed. 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H. Random. 95% Cl 0.001 0.1 1 00 Combination therapy UDCA	1000
Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Tau <sup>a</sup> = Test for overall effect:	Events           8           3           11           0.00, df = 1 (P =           Z = 0.00 (P = 1.0           combination the Events           4           0           4           0           0.32, df = 1 (P =           Z = 1.55 (P = 0.1           combination the Events           4           0           4           0           4           0           2           2           7.91; Chi <sup>p</sup> = 4.56           Z = 0.28 (P = 0.76	Total           733           111           1.000); F =           00           Total           733           38           111           0.57); F =           2)           Total           733           38           111           0.57); F =           2)           Total           733           38           111           0.43); F =           8)           111           , df = 1 (P = 3)	Events 8 3 0% UDC. Events 2 0% 10 UDC. Events 8 3 0% 11 UDC. Events 8 3 0% 12 0% 10 0%	Total           73           38           111           A           Total           73           38           111           A           Total           73           38           111           Fotal           73           38           111           73           111           *= 785	Weight 72.7% 27.3% 100.0% Weight 100.0% 23.8% 100.0% 89.6% 30.4% 100.0% Weight 50.6% 49.4% 100.0% 6	M-H, Fixed, 95% CI           1.00 [0.40, 2.52]           1.00 [0.22, 4.65]           1.00 [0.45, 2.21]           Risk Ratio           M-H, Fixed, 95% CI           0.60 [0.16, 1.59]           0.20 [0.01, 4.03]           0.43 [0.15, 1.25]           Risk Ratio           M-H, Fixed, 95% CI           0.50 [0.16, 1.59]           0.50 [0.16, 1.59]           0.51 [0.14, 1.13]           Risk Ratio           M-H, Random, 95% CI           0.06 [0.00, 1.00]           5.00 [0.25, 100.80]           0.53 [0.01, 43.35]	M-H. Fixed. 95% Cl 0.001 0.1 10 combination therapy UDCA Risk Ratio M-H. Fixed. 95% Cl 0.001 0.1 10 combination therapy UDCA Risk Ratio M-H. Fixed. 95% Cl 0.001 0.1 100 combination therapy UDCA Risk Ratio M-H. Risk Ratio	1000 <sup>1</sup>
Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% Cl) Total events Heterogeneity: Tau <sup>a</sup> = Test for overall effect:	Events           8           3           0.00, df = 1 (P =           Z = 0.00 (P = 1.0           combination th           Events           4           0           combination th           Events           0           2           0           2           7.91; chi# = 4.56           2           2	Total           73           38           111           1.00); F =           0)           rerapy           Total           73           38           111           0.057); F =           2)           rotal           73           38           111           0.43); F =           8)           rotal           73           38           111           0.43); F =           73           38           111           0.43); F =           73           38           111           , df = 1 (P :           3)	Events 8 3 11 0% 10 Events 2 10 0% 0% 10 0 0% 10 0 0% 10 0 0 0	Total           73           38           111           A           Total           73           38           111           A           Total           73           38           111           73           38           111           73           38           111           73           38           111	Weight 72.7% 27.3% 100.0% Weight 100.0% 23.8% 100.0% 09.6% 30.4% 100.0% Weight 50.6% 49.4% 100.0%	M-H, Fixed, 95% CI           1.00 [0.40, 2.52]           1.00 [0.40, 2.52]           1.00 [0.45, 2.21]           Risk Ratio           M-H, Fixed, 95% CI           0.60 [0.16, 1.69]           0.20 [0.01, 4.03]           0.43 [0.15, 1.25]           Risk Ratio           M-H, Fixed, 95% CI           0.50 [0.16, 1.59]           0.43 [0.15, 1.25]           Risk Ratio           M-H, Fixed, 95% CI           0.50 [0.16, 1.59]           0.14 [0.01, 2.67]           0.39 [0.14, 1.13]           Risk Ratio           M-H, Random, 95% CI           0.06 [0.00, 1.00]           5.00 [0.25, 100.80]           0.53 [0.01, 43.35]	M-H. Fixed. 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H. Fixed. 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H. Fixed. 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H. Random. 95% Cl 0.001 0.1 1 10 combination therapy UDCA	1000 <sup>1</sup>
Study of Subaroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Study of Subaroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	Events           8           3           0.00, df = 1 (P =           Z = 0.00 (P = 1.0           combination th           Events           4           0           0.32, df = 1 (P =           Z = 1.56 (P = 0.1           combination th           Events           4           0           0.83, df = 1 (P =           2           1.74 (P = 0.0           combination th           Events           0           2           7.91; Chi <sup>p</sup> = 4.56           Z = 0.28 (P = 0.76           combination th	Total           733           111           1.00); F =           0)           rapy           Total           733           111           1.00); F =           0)           rapy           Total           733           111           0.57); F =           2)           rotal           7338           1111           0.43); F =           (8)           111           0.43); F =           38           111           0.43); F =           (8)           111           0.43); F =           (8)           111           (4f = 1 (P =           3)	Events 8 3 0% 11 0% 10 0 0 0	Total           73           38           111           A           Total           73           38           111           A           Total           73           38           111           A           Total           73           38           111           Total           73           38           111           *= 78%           A	Weight 72.7% 27.3% 100.0% Weight 76.2% 23.8% 100.0% 89.6% 30.4% 100.0% Weight 100.0% %	M-H, Fixed, 95% CI           1.00 [0.40, 2.52]           1.00 [0.40, 2.52]           1.00 [0.45, 2.21]           Risk Ratio           M-H, Fixed, 95% CI           0.50 [0.16, 1.59]           0.20 [0.01, 4.03]           0.43 [0.15, 1.25]           Risk Ratio           M-H, Fixed, 95% CI           0.50 [0.16, 1.59]           0.20 [0.01, 4.13]           0.50 [0.14, 1.13]           Risk Ratio           M-H, Fixed, 95% CI           0.39 [0.14, 1.13]           Risk Ratio           0.14 [0.01, 2.67]           0.39 [0.14, 1.13]           Risk Ratio           M-H, Random, 95% CI           0.06 [0.00, 1.00]           0.50 [0.25, 100.80]           0.53 [0.01, 43.35]	M-H. Fixed. 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H. Fixed. 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H. Fixed. 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H. Random. 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H. Random. 95% Cl 0.001 0.1 1 10 combination therapy UDCA	1000 <sup>1</sup>
Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect: Study of Subgroup F. Nevens 2016 Hirschfield 2014 Total (95% CI) Total events Heterogeneity: Tau <sup>a</sup> = Test for overall effect:	Events           8           3           0.00, df = 1 (P =           Z = 0.00 (P = 1.0           combination the Events           4           0           0.32, df = 1 (P =           Z = 1.55 (P = 0.1           combination the Events           4           0           0.83, df = 1 (P =           Z = 1.74 (P = 0.0           combination the Events           0           2           7.91; Chi <sup>p</sup> = 4.56           Z = 0.28 (P = 0.75           combination the Events	Total           733           111           1.000); F =           00           Total           733           38           111           1.000); F =           00           Total           733           38           111           0.57); F =           2)           Total           733           38           111           0.433; F =           83           111           , df = 1 (P = 3)           38           111           , df = 1 (P = 3)           39	Events 8 3 0% UDC. Events 2 0% 10 UDC. Events 8 3 11 0% 11 UDC. 8 3 11 0% 10 Events 8 3 0 11 UDC. Events 8 3 0 10 UDC. Events 8 2 0 10 UDC. Events 8 2 0 10 UDC. Events 8 3 0 UDC. Events 8 3 0 UDC. Events 8 3 0 UDC. Events 8 3 0 UDC. Events 8 3 0 UDC. Events 8 3 0 UDC. Events 8 3 0 UDC. Events 8 0 0 0 0 0 0 0 0 0 0 0 0 0	Total           73           38           111           A           Total           73           38           111             A           Total           73           38           111             Total           73           38           111             Total           73           38           111             **= 789           A           Total           A	Weight 72.7% 27.3% 100.0% Weight 100.0% 23.8% 100.0% 89.6% 30.4% 100.0% Weight 100.0% 6	M-H, Fixed, 95% CI           1.00 [0.40, 2.52]           1.00 [0.40, 2.52]           1.00 [0.45, 2.21]           Risk Ratio           M-H, Fixed, 95% CI           0.60 [0.16, 1.59]           0.20 [0.01, 4.03]           0.43 [0.15, 1.25]           Risk Ratio           M-H, Fixed, 95% CI           0.50 [0.16, 1.59]           0.50 [0.16, 1.59]           0.51 [0.14, 1.13]           Risk Ratio           M-H, Random, 95% CI           0.06 [0.00, 1.00]           5.00 [0.25, 100.80]           0.53 [0.01, 43.35]           Risk Ratio           M-H, Random, 95% CI           0.06 [0.00, 1.00]           5.00 [0.25, 100.80]           0.53 [0.01, 43.35]	M-H. Fixed. 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H. Fixed. 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H. Fixed. 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H. Random. 95% Cl 0.001 0.1 1 10 combination therapy UDCA Risk Ratio M-H. Random. 95% Cl 0.001 0.1 1 10 Combination therapy UDCA Risk Ratio M-H. Random. 95% Cl 0.001 0.1 1 10 Combination therapy UDCA Risk Ratio M-H. Random. 95% Cl	1000
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Fig. 6. Adverse events (a) pruritus; (b) nasopharyngitis; (c) headache; (d) fatigue; (e) nausea; (f) diarrhea; (g) upper respiratory tract infection; (h) urinary tract infection; (i) dyspepsia; (j) arthralgia in patients with PBC treated with combination therapy vs. monotherapy. UDCA, ursodeoxycholic acid; M-H, Mante-Haenszel; Cl, confidence interval; df, degrees of freedom; PBC, primary biliary cholangitis.

(mean difference = -1.17 mg/L; 95% CI, -2.19 to -0.14; P = 0.03). In the random-effect model, the pooled mean difference of IgM was -41.18 mg/dL (P = 0.69) in the combined therapy when compared to controls.

## Adverse events

Adverse events for therapy, including pruritus, nasopharyngitis, headache, fatigue, nausea, diarrhea, upper respiratory tract infection, urinary tract infection, dyspepsia, and arthralgia, were also recorded in the two trials. Due to no significant heterogeneity (all  $I^2$  values were <50% and all *P* values were >0.1), fix-effect models were performed to evaluate associations between different therapies and adverse events, except for pruritus, and dyspepsia. The results showed that no significant association with increased risks of adverse events was found between patients with different therapies (Fig. 6).

#### Discussion

In cholestasis, the primary mode of action of UDCA [9], an epimer of chenodeoxycholic acid (CDCA) but no FXR agonist properties, is thought to be choleretic by facilitating bile flow rather than suppressing its synthesis and buffering the bile. In contrast, OCA is a modified bile acid and is a potent agonist of the FXR [8], has marked suppressing bile salt synthesis and modulating the immune response in cholestatic liver diseases. Clinical trials testing OCA in PBC indicates good toleration and substantial improvements in liver biochemical indexes associated with cholestasis. Therefore, based on the different action mode between UDCA and OCA, rational combination therapy for refractory PBC would serve as a promising strategy. To our knowledge, this meta-analysis first evaluated the clinical outcomes of the combination therapy of UDCA and OCA compared with UDCA monotherapy in patients with PBC. The results of this study indicated that combination therapy did not differ significantly from monotherapy in improving primary endpoints, conjugated bilirubin, IgM, or adverse events, but was significantly superior to monotherapy in reducing liver biochemical indexes including alanine aminotransferase, aspartate aminotransferase, GGT, and immunological parameter CRP.

PBC is a chronic cholestatic disease that can lead to end-stage liver disease and impairs the quality of life, and risk stratification and disease management are crucial for long-term prognosis. Alkaline phosphatase [15] and bilirubin [4], along with aminotransferases, have been used in previous response criteria and primary endpoints for clinical trials [7]. Several studies have demonstrated that the rate of the primary endpoints was higher in the combination therapy group (61.3%) than in the monotherapy group (42.3%) and importantly treatment with OCA was associated with decreases in the levels of serum IgM [2,11,16]. Interestingly, serum CRP levels in patients with PBC who receive UDCA or OCA treatment have yielded diverse results. Some trial data have revealed that CRP was not different between OCA and the placebo [17]; however, in other studies, OCA has been associated with significant improvements in CRP [8,11]. The present study, via a meta-analysis of published studies, confirmed that the level of serum CRP in combination therapy was significantly lower than that in UDCA monotherapy.

Pruritus was the most common adverse event in patients with PBC, but neither its incidence nor its severity correlates with disease stage [18,19]. However, pruritus was OCA dose-related [20], with a higher incidence reported in the combination therapy group (61.3%) than in the monotherapy group (42.3%). The mechanism of OCArelated pruritus remains unclear, two putative mechanisms have been proposed: the activation of TGR5 [21–23] and activation of the autotoxin pathway [24,25]. Moreover, this meta-analysis did not show any significant association with increased risks of adverse events between different therapies. However, the conclusion should be addressed with caution, because subgroup meta-analysis could not be performed in this study due to the limitation of patient size and eligibility criteria biases.

Some weaknesses in the present work should be mentioned. First, only two eligible RCT studies were included in the meta-analysis and of low quality through the 'Risk of bias table'. Second, given the limited numbers of studies, sensitivity analysis was not performed to explore heterogeneous sources. Furthermore, for the publication bias, the funnel plot could not be performed because we did not have the recommended minimum number of five trials in the meta-analysis [26].

In summary, the present meta-analysis demonstrated that combination therapy with UDCA and OCA provided satisfactory clinical outcomes, which may be a promising alternative for patients with PBC who have an inadequate response to UDCA therapy. Therefore, high-quality RCTs on the safety and efficacy of the combination therapy of UDCA and OCA compared with UDCA or OCA monotherapy in patients with PBC should be performed in the future.

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#### **Conflicts of interest**

There are no conflicts of interest.

All of the authors conceived the study, performed the literature search, quality assessment, and performed the statistical analysis. All of the authors were involved in manuscript writing and preparation. All of the authors have read and approved of the final manuscript.

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