

Effectiveness of bezafibrate and ursodeoxycholic acid in patients with primary biliary cholangitis: a meta-analysis of randomized controlled trials

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Abstract

Background Ursodeoxycholic acid (UDCA) and obeticholic acid are currently approved treatments for primary biliary cholangitis (PBC). Since some patients do not respond adequately to UDCA, other therapies, such as bezafibrate, have been developed. In this meta-analysis we evaluated the efficacy and safety of using both UDCA and bezafibrate in patients with an inadequate response to UDCA.

Methods We evaluated all randomized controlled trials comparing the combination of UDCA and bezafibrate with UDCA monotherapy. Standardized mean difference (SMD) was used to assess the treatment effect of combination therapy compared with UDCA alone.

Results Ten trials with a total of 369 patients were analyzed. UDCA and bezafibrate combination therapy was more effective than UDCA monotherapy in improving alanine aminotransferase (SMD -2.04, 95% confidence interval [CI] -3.30 to -0.79), alkaline phosphatase at both less than 12 months (SMD -3.63, 95%CI -6.43 to -0.84) and more than 12 months (SMD -2.33, 95%CI -4.03 to -0.63), gamma-glutamyltransferase (SMD -1.29, 95%CI -2.67 to 0.08), triglyceride (SMD -0.80, 95%CI -1.41 to -0.19), immunoglobulin M (SMD -1.48, 95%CI -2.39 to -0.56), and cholesterol (SMD -4.61, 95%CI -7.34 to -1.89). There was no difference between the 2 groups in bilirubin, aspartate aminotransferase or albumin. None of the adverse effects differed statistically between the 2 groups.

Conclusion UDCA and bezafibrate combined treatment is superior to UDCA alone in UDCA non-responders with regard to decreasing liver biochemistry markers, without any significant increase in side effects in patients with PBC.

Keywords Primary biliary cholangitis, ursodeoxycholic acid, bezafibrate, combination therapy

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Introduction

Primary biliary cholangitis (PBC) is an autoimmune-mediated liver disease characterized by a triad of chronic cholestasis, anti-mitochondrial antibody (AMA) positivity, and liver biopsy findings of non-suppurative destructive cholangitis and interlobular bile duct destruction. It can eventually progress to cirrhosis [1,2]. Ursodeoxycholic acid (UDCA), the first and most widely used medication for PBC has shown to improve biochemical markers and improve transplant-free survival. However, 15% of such patients who biochemically respond to UDCA eventually develop hepatic complications [3-7]. A recent study estimated that around 20% of patients treated with UDCA show an inadequate response [6]. Compared to responders to

UDCA, these patients are at a greater risk of hepatic complications such as ascites, variceal bleeding and hepatic encephalopathy, as well as a 25% greater risk of liver transplantation [6,7]. In 2016, the Food and Drug Administration approved obeticholic acid for use in combination with UDCA in PBC patients who showed an inadequate response to UDCA. Obeticholic acid is also approved as monotherapy in patients unable to tolerate UDCA because of side effects; however, it is associated with pruritus, which can be a significant nuisance for the patient. There is limited research on the long-term effects of obeticholic acid [8,9].

Bezafibrate, a hypolipidemic fibrate currently approved for PBC treatment in France, has been shown to be beneficial when used in combination with UDCA in patients who have an inadequate response to UDCA alone [10]. It has known anti-inflammatory, anti-fibrotic and anti-cholestatic effects, yet its mechanism remains unclear in PBC. It is believed that the benefits are driven by its activation of the dual peroxisome proliferator activator receptor (PPAR) and pregnane X receptor agonist [11].

Several trials have addressed the effects of combination therapy in such patients; however, a major limitation of all these trials was their sample size. The most recent trial by Corpechot *et al*, the largest study on bezafibrate, included 100 patients [12]. We therefore performed a meta-analysis to assess the efficacy of combination therapy with bezafibrate and UDCA compared to UDCA alone in PBC patients who had shown an inadequate response to UDCA monotherapy.

Patients and methods

Search methodology

We performed this meta-analysis in accordance with the Preferred Reporting Items of Systematic Review and Meta-Analysis (PRISMA) guidelines [13]. We searched MEDLINE, EMBASE, Ovid, Scopus and the Cochrane Library (Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews) from inception to June 2019 to identify published articles analyzing the use of ursodeoxycholic acid and bezafibrate in PBC. No language or date limitations were imposed. The keywords used in combination were “randomized controlled trial”, “bezafibrate”, “ursodeoxycholic acid”, “primary biliary cholangitis”, “primary biliary cirrhosis”, and “fenofibrate”. In order to identify additional studies, the reference list of all eligible studies was reviewed. Proceedings of major scientific conferences were also searched to identify grey literature.

Inclusion criteria

We included only randomized controlled trials (RCT) that compared combination therapy with UDCA and bezafibrate to UDCA monotherapy. The study population comprised patients with PBC, diagnosed according to the presence of any 2 of the following criteria: 1) biopsy of the liver consistent with PBC; 2) biochemical evidence of cholestasis in absence of obstruction; and 3) presence of AMA.

Articles were excluded if they did not refer to RCT or if no outcomes were reported. Two reviewers independently performed study selection according to the eligibility criteria. Disagreements were resolved by discussion with a third reviewer (SS).

Data extraction and assessment of study quality

The following data were independently abstracted into a standardized form: study characteristics (study design, primary author, year of publication, and country of the population studied), characteristics of the study population (total number of patients in monotherapy and combination therapy group, age of patients, dose of UDCA and bezafibrate used), change in biochemical markers (triglycerides [TG], immunoglobulin M [IgM], alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyltransferase [GGT], alkaline phosphatase [ALP], albumin, total bilirubin [TB], total cholesterol, creatinine kinase [CK]) and side effects of therapy (reactive pruritus, myalgia, arthralgia, CK elevation). The revised Cochrane risk of bias tool (RoB 2) for RCTs was used to assess the quality of published trials [14].

Outcome definition

The primary outcome of this meta-analysis was defined as a change in biochemical markers such as ALT, AST, GGT, IgM, TB, and albumin. The secondary outcomes included mortality and the rate of adverse effects, including myalgias, reactive pruritus, and elevation of CK.

Statistical analysis

STATA (Version 14.0, College station, TX) was used for analysis. Continuous data were pooled to calculate standardized mean differences (SMD), while dichotomous outcomes were expressed as odds ratio (OR) with 95% confidence interval (CI) for both, using a random-effects model with inverse variance weighting. Heterogeneity across studies was evaluated using the Higgins I^2 statistic, where values of 25-50%, 50-75% and >75% represent mild, moderate and severe heterogeneity, respectively. Egger's regression test was used to test for publication bias. A P-value <0.05 was considered significant in all cases.

Results

Literature search results, study characteristics, and quality assessment

Our search strategy retrieved a total of 211 published articles. Among these, 10 RCTs comprising 369 patients

were included in our analysis. The baseline characteristics of the trials are listed in Table 1. The PRISMA flow chart (Fig. 1) summarizes the results of our literature review. Only 1 of the 10 trials was a double-blinded study. Nine of the 10 trials included in our meta-analysis were considered to have a high risk of bias (Fig. 2,3). Patient with inadequate biochemical response to UDCA therapy defined variably in different studies as per Barcelona criteria, Paris-2 criteria or study specific criteria were included in the study. The patients mean age ranged from 53-64 years and the mean follow-up interval from 3-24 months. The daily dose of bezafibrate used was 400 mg/day, while the UDCA daily dose ranged from 600-1500 mg daily.

Results of meta-analysis

The summarized results of our meta-analysis are presented in Table 2 and Fig. 4,5.

Bilirubin

A change in serum bilirubin was mentioned in 5 trials that included 164 patients. There was no statistically significant difference between the two groups (SMD -0.77, 95%CI -2.20 to 0.65; P=0.287) and there was severe heterogeneity (P<0.001, I²=92.6 %) (Fig. 4A).

ALT

Three trials that included 142 patients reported a change in ALT level from baseline. Combination therapy was associated with an extra decline in ALT level compared to monotherapy in patients with PBC (SMD -2.04, 95%CI -3.30 to -0.79; P=0.001). There was severe heterogeneity (P=0.001, I²=85.6%) (Fig. 4B).

AST

Three trials with 128 patients compared changes in AST between monotherapy and combination therapy groups. There was no statistical difference between these groups (SMD -0.34, 95%CI -1.76 to 1.08; P=0.639) and there was severe heterogeneity (P<0.001, I²=90.5%) (Fig. 4C).

ALP

Ten trials that included 335 patients reported data regarding this endpoint. Combination therapy with bezafibrate and UDCA was more effective than UDCA alone in reducing ALP level over a trial duration >12 months (SMD -2.33, 95%CI -4.03 to -0.63; P=0.007) and there was severe heterogeneity (P<0.001, I²=94.7%). The results for a trial duration <12 months were similar (SMD -3.63, 95%CI -6.43 to -0.84; P=0.01), showing significant heterogeneity (P<0.001, I²=95.6%) (Fig. 4D1,4D2).

GGT

This outcome was reported in 4 trials that included 146 patients. There was no significant difference between the monotherapy and combination therapy groups (SMD -1.29, 95%CI -2.67 to 0.08; P=0.065). There was significant heterogeneity (P<0.001, I²=90.7%) (Fig. 4E).

Albumin

A total of 144 patients from 3 trials were analyzed for changes in albumin levels. There was no statistically significant difference between the 2 groups (SMD 0.35, 95%CI -0.40 to 1.10; P=0.358). There was severe heterogeneity (P=0.013, I²=76.9%) (Fig. 4F).

Table 1 Baseline characteristics of the trials included in the meta-analysis

Study	Year of publication	Type	Treatment duration (months)	Bezafibrate dose (mg/day)	UDCA dose (mg/day)	Combination therapy (n)	Monotherapy (n)	Mean age (year)
Corpechot <i>et al</i> [12]	2018	RCT	24	400	900-1500	50	50	53
Hosonuma <i>et al</i> [15]	2015	RCT	96	400	600-900	13	14	64
Lens <i>et al</i> [16]	2014	RCT	3	400	900-1500	28	28	53
Honda <i>et al</i> [11]	2013	RCT	3	400	600	19	31	58
Takeuchi <i>et al</i> [20]	2011	RCT	24	400	600	15	22	57
Hazzan <i>et al</i> [16]	2010	RCT	24	400	900-1500	8	8	64
Iwasaki <i>et al</i> [18]	2008	RCT	12	400	600	12	10	54
Itakura <i>et al</i> [19]	2004	RCT	6	400	600	9	7	57
Kanda <i>et al</i> [21]	2003	RCT	6	400	600	11	11	56
Nakai <i>et al</i> [22]	2000	RCT	12	400	600	10	13	58

RCT, randomized controlled trial; UDCA, ursodeoxycholic acid

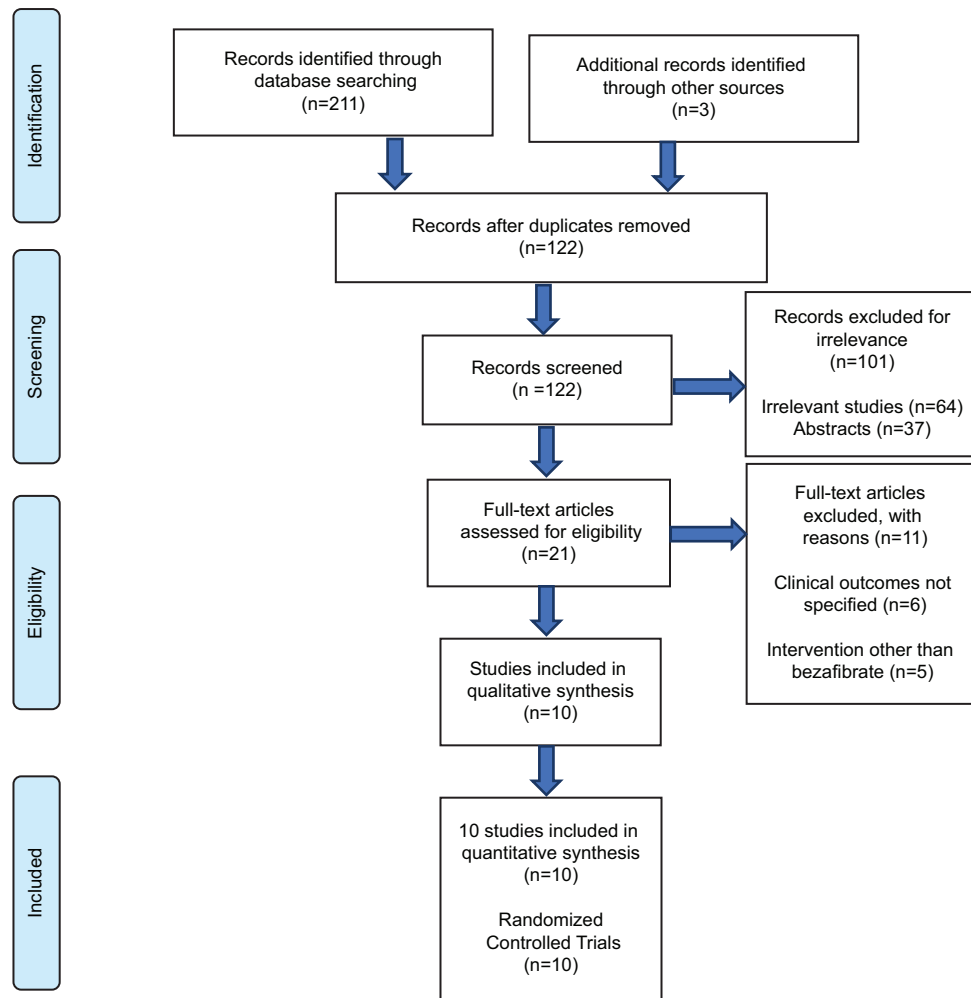


Figure 1 PRISMA diagram for selection of trials

TG level

Four trials that included 115 patients reported data regarding this endpoint. Combination therapy with bezafibrate and UDCA was more effective than monotherapy with UDCA in improving TG level (SMD -0.80, 95%CI -1.41 to -0.19; $P=0.01$). There was moderate heterogeneity ($P=0.075$, $I^2=56.6\%$) (Fig. 4G).

IgM

This endpoint was reported in 6 trials that included 199 patients. Combination therapy was more effective in lowering IgM as compared to monotherapy (SMD -1.48, 95%CI -2.39 to -0.56; $P=0.002$) and there was severe heterogeneity ($P<0.001$, $I^2=82.5\%$) (Fig. 4H).

Cholesterol

Five trials that included 196 patients reported a change in cholesterol levels. Combination therapy was more effective in lowering cholesterol compared to monotherapy (SMD -4.61,

95%CI -7.34 to -1.89; $P=0.001$). There was severe heterogeneity ($P<0.001$, $I^2=97.5\%$) (Fig. 4I).

Any adverse events

Any adverse event was reported in 5 trials that included 160 patients. No statistically significant difference was found between the 2 groups (OR 2.05, 95%CI 0.52-8.13; $P=0.308$) and there was mild heterogeneity ($P=0.196$, $I^2=33.8\%$) (Fig. 5A).

CK levels

Elevation of CK after initiation of therapy was analyzed in 3 trials that included 149 patients. In our meta-analysis no difference was found between UDCA monotherapy and combination therapy (SMD 4.44, 95%CI 0.70-28.12; $P=0.114$). There was no heterogeneity ($P=0.906$, $I^2=0\%$) (Fig. 5B).

Myalgias

The incidence of myalgias after the initiation of therapy was reported in 3 trials that included 149 patients and there was

no statistical difference between the 2 groups (OR 2.39, 95%CI 0.85-6.74; P=0.098). There was no heterogeneity (P=0.967, I²=0%) (Fig. 5C).

Pruritus

Five trials that included 205 patients evaluated differences in pruritus incidence between monotherapy and combination therapy groups. There was no statistically significant difference between the two groups (OR 0.58, 95%CI 0.16-2.08; P=0.406). There was moderate heterogeneity (P=0.056, I²=56.7%) (Fig. 5D).

Fatigue

No statistically significant difference was found between monotherapy and combination therapy groups in terms of fatigue, as reported in only one study that included 100 patients (OR 1.95, 95%CI 0.76-5.01; P=0.164). There was no heterogeneity (P=0.0, I²=0%) (Fig. 5E).

Mortality

Two trials that included 65 patients reported a change in mortality, but no statistical difference was found between the 2 groups (OR 2.28, 95%CI 0.12-43.25; P=0.582). There was mild heterogeneity (P=0.189, I²=42.1%) (Fig. 5F).

Discussion

Among the laboratory parameters studied, our analysis showed that there was a statistically significant reduction in ALT, ALP, TG, cholesterol, and IgM levels. The mechanisms via which bezafibrate influences these parameters are not completely understood. It has been suggested that the effects are driven by its action on PPAR- α , β/δ and γ , with resulting upregulation of *multidrug resistant gene 3 (MDR3)*. Decreased accumulation of cytotoxic bile acids within hepatocytes, via the downregulation of several proteins, including but not limited to cholesterol 7 α -hydroxylase/sterol 27-hydroxylase, and its effects on the cytochrome P450 system might also contribute to its anti-cholestatic effects. The reductions in cholesterol and TG levels are probably caused by a combination of β -hydroxy β -methylglutaryl-CoA reductase inhibition and PPAR-induced cholesterol efflux from hepatocytes [11]. Through the same mechanism of action, we would have expected a decrease in bilirubin, AST, GGT, and albumin levels, but the changes were not a statistically significant in our analysis. These findings are similar to the analysis presented by Hosonuma *et al*, who failed to show a significant reduction in bilirubin, AST and albumin levels [15]. However, several studies have documented a statistically significant decrease in GTT levels [16-19]. It is documented that PPAR- α is present on T and B lymphocytes, which could explain the anti-inflammatory effects of bezafibrate, as suggested by the reduced levels of IgM [18].

There was no statistically significant association between bezafibrate use and an increase in side-effects such as pruritus, myalgia, fatigue or elevations of CK levels. In fact, there was a trend, although statistically not significant, towards an improvement in pruritus that has been reported individually in several trials. The mechanism for this relief is not entirely clear, but it could partly involve its anti-cholestatic effect. This is an important difference to note, as obeticholic acid, an alternative therapy to PBC, is associated with significant pruritus [8]. The CK fluctuations are likely to be a consequence of bezafibrate-induced muscle injury. Corpechot *et al* reported elevated serum creatinine levels with bezafibrate use, which may be secondary to rhabdomyolysis causing elevation of both creatine kinase and myoglobin, inducing nephrotoxicity [13,23]. Other reported side effects are gastrointestinal discomfort (nausea, heartburn, diarrhea), arthralgia, myalgia, upper respiratory symptoms (nasopharyngitis, bronchitis), leg edema, polydipsia, and leg edema. These parameters were not reported in adequate numbers and therefore could not be analyzed.

Mortality was reported in only 2 trials and it was not a statistically significant outcome in our analysis. Our meta-analysis included trials with small sample sizes, only a few trials reported mortality, and moreover the trials we examined were constrained by short follow-up periods. The wide confidence intervals indicate the non-reliability of this finding; hence, larger trials will be needed to adequately assess the direct effect of bezafibrate on survival.

Variables of disease progression as assessed by histology, noninvasive measures of liver fibrosis (liver elastography) and prognostic scores were reported in only a few trials, limiting

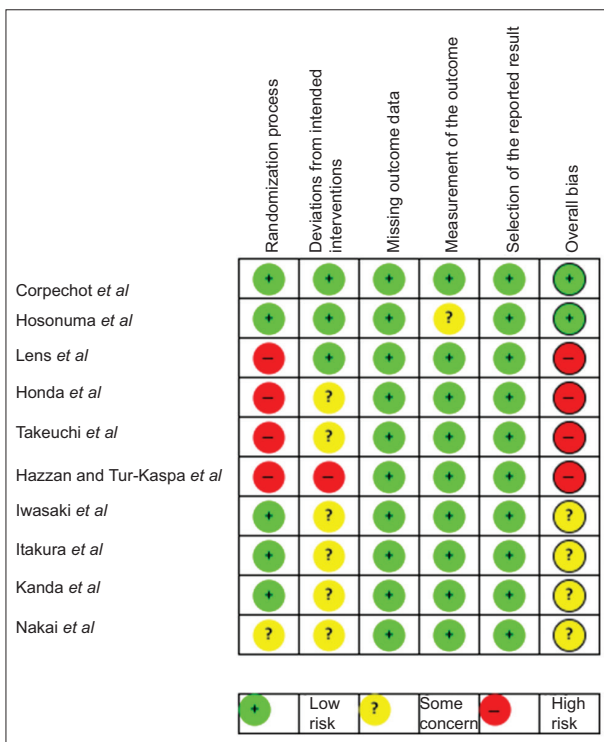


Figure 2 Risk of bias in included studies + indicates an increase, - indicates a decrease, and ? indicates this is unclear

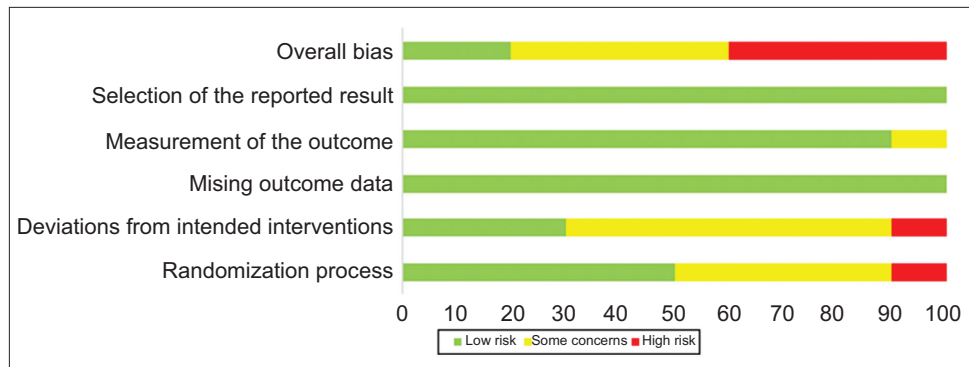


Figure 3 Risk of bias graph: review of authors' judgments regarding each risk of bias item presented as percentages across all included studies

Table 2 Meta-analysis of clinical events and changes in biochemical parameters in the included studies

Outcome	Number of studies	Number of participants	Statistical method	Effect size	P-value
Bilirubin	5	164	SMD (IV, random, 95%CI)	-0.77 (-2.20 to 0.65)	0.287
ALT	3	142	SMD (IV, random, 95%CI)	-2.04 (-3.30 to -0.79)	0.001
AST	3	128	SMD (IV, random, 95%CI)	-0.34 (-1.76 to 1.08)	0.639
ALP (duration >12 months)	6	205	SMD (IV, random, 95%CI)	-2.33 (-4.03 to -0.63)	0.007
ALP (duration <12 months)	4	130	SMD (IV, random, 95%CI)	-3.63 (-6.43 to -0.84)	0.01
GGT	4	146	SMD (IV, random, 95%CI)	-1.29 (-2.67 to 0.08)	0.065
Albumin	3	144	SMD (IV, random, 95%CI)	0.35 (-0.40 to 1.10)	0.358
TG	4	115	SMD (IV, random, 95%CI)	-0.80 (-1.41 to -0.19)	0.01
IgM	6	199	SMD (IV, random, 95%CI)	-1.48 (-2.39 to -0.56)	0.002
Cholesterol	5	196	SMD (IV, random, 95%CI)	-4.61 (-7.34 to -1.89)	0.001
Any adverse events	5	160	OR (M-H, random, 95%CI)	2.05 (0.52 to 8.13)	0.308
CK	3	149	SMD (IV, random, 95%CI)	4.44 (0.70 to 28.12)	0.114
Myalgia	3	149	OR (M-H, random, 95%CI)	2.39 (0.85 to 6.74)	0.098
Pruritus	5	205	OR (M-H, random, 95%CI)	0.58 (0.16 to 2.08)	0.406
Fatigue	1	100	OR (M-H, random, 95%CI)	1.95 (0.76 to 5.01)	0.164
Mortality	2	65	OR (M-H, random, 95%CI)	2.28 (0.12 to 43.25)	0.582

M-H, Mantel-Haenszel; CI, confidence interval; IV, inverse-variance; MD, mean difference; OR, odds ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; TG, triglyceride; CK, creatinine kinase

our analysis of the available data. An improvement in liver elastography in the patients receiving combination therapy was reported by 2 trials. Histological and fibrosis stage, along with activity grade on histology, did not vary significantly in a study by Corpechot *et al*, whereas significant differences were reported by Lens *et al* among patients receiving combination therapy [12,16]. Prognostic models, such as the Mayo risk score, have been used to estimate survival, but only 2 studies reported such findings. An improvement in the score was seen in both studies: the change was insignificant in a study by Takeuchi *et al* but significant according to Hosonuma *et al* [20,15]. The trials included in our analysis were completed prior to the validation of the GLOBE score, a prognostic model proposed by the Global PSC Study Group, which adequately predicts the transplant-free survival of patients being treated with UDCA [24].

Understanding the effect of bezafibrate on endpoints such as mortality, liver transplantation rates and histological improvements in liver biopsy are, of course, the most significant markers for this PBC therapy. However, the slow progression of the disease, the paucity of patients and the limited duration of studies make these hard endpoints difficult to obtain. We have evidence that the bilirubin and ALP reductions can predict outcomes such as liver transplantation and death [25,26]. Patients with ALP levels less than 2 times the upper limits of normal have an 84% survival rate at 10 years [25]. With these supporting studies, we can infer that the reductions in ALP achieved with combination therapy in patients who do not respond to UDCA alone can improve transplant-free survival and reduce death.

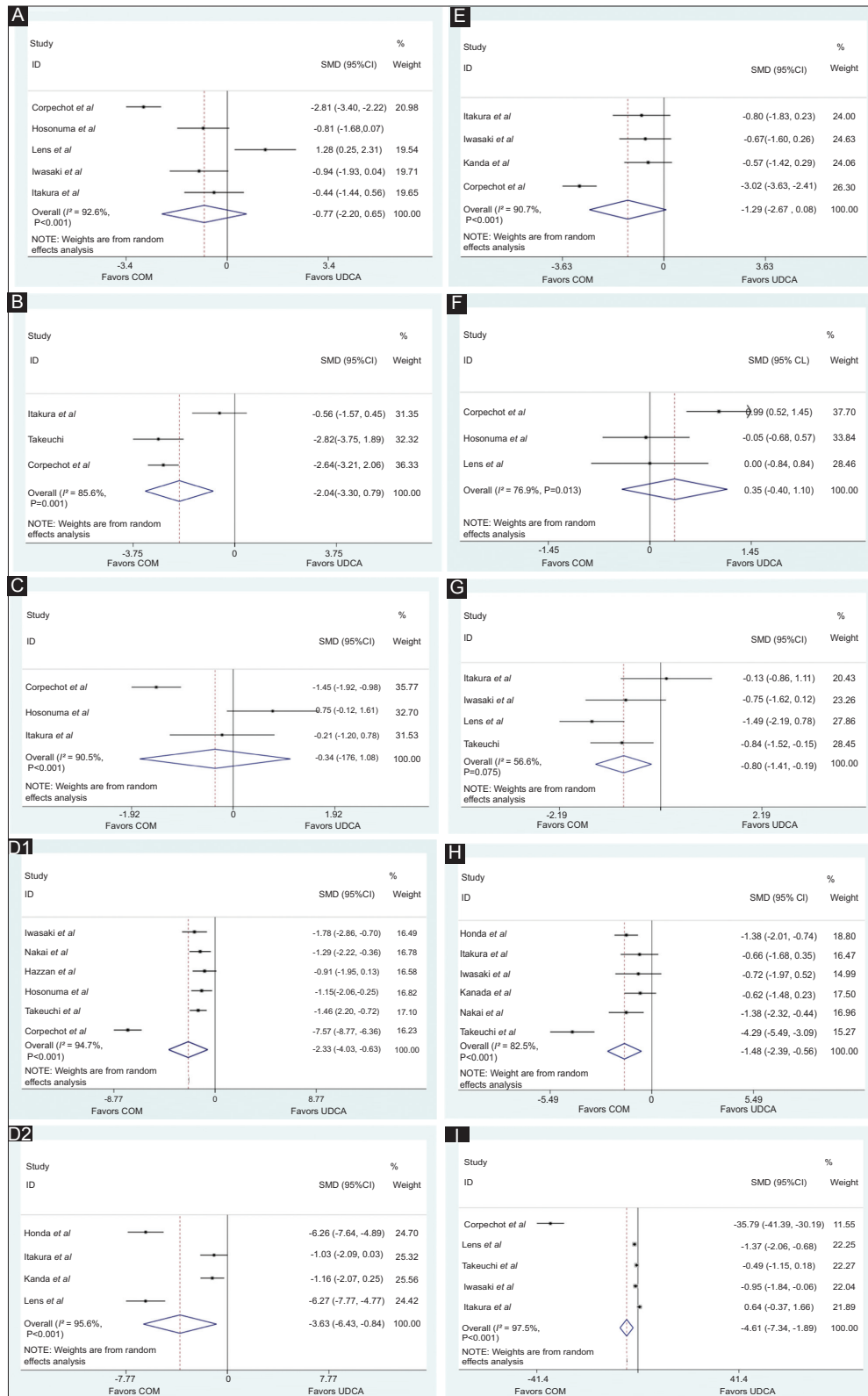


Figure 4 Biochemical parameters in PBC patients treated with UDCA versus combination therapy. (A) Bilirubin; (B) ALT; (C) AST; (D1): ALP (>12 months); (D2) (<12 months); (E) GGT; (F) Albumin; (G) TG; (H) IgM; (I) Cholesterol
PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; TG, triglyceride; COM, combination therapy; SMD, standard mean deviation; CI, confidence interval

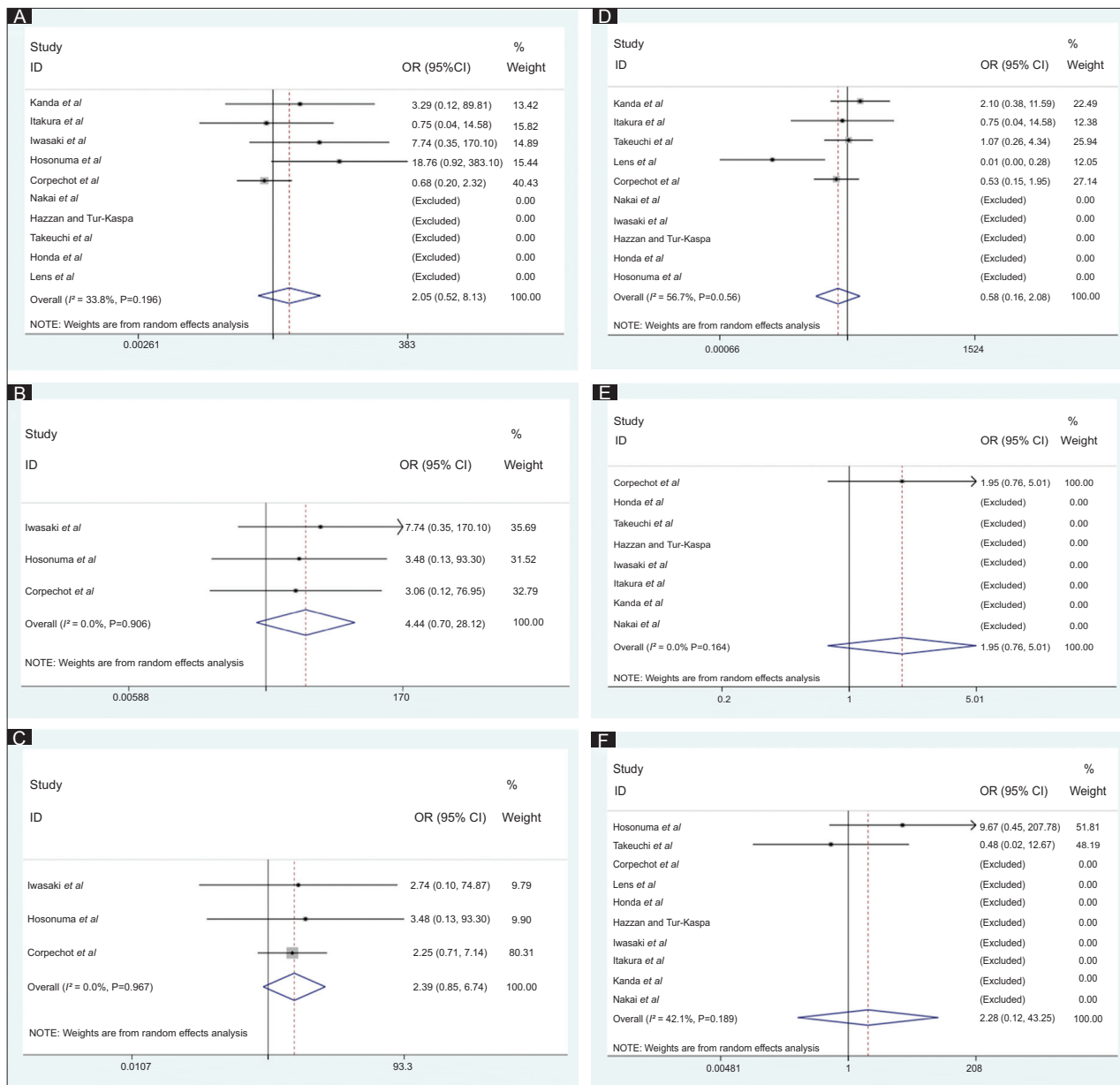


Figure 5 Adverse effects and mortality in PBC patients treated with UDCA versus combination therapy. (A) any adverse event; (B) CK; (C) myalgia; (D): pruritus; (E) fatigue; (F) mortality
 PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; COM, combination therapy; CK, creatinine kinase; OR, odds ratio; CI, confidence interval

This study had several limitations. First, we had a limited sample size of 369 patients, which reduced the power to detect a significant difference in some data points. We also did not have sufficient data to analyze important parameters such as histology, liver elastography, need for liver transplantation, mortality, quality of life and burden of side-effects, as most studies did not report this data. Lastly, these studies were also carried out over a short period of time; any long-term findings of bezafibrate would not be described in this meta-analysis.

In conclusion, a combination therapy of UDCA and bezafibrate is beneficial in improving biochemical parameters in patients with PBC who respond inadequately to UDCA alone. Using these biochemical parameters as a surrogate of survival, histological improvement and liver transplant-free periods, this meta-analysis suggests that bezafibrate may have a role in the management of such patients. However, larger trials with a more extensive follow up are needed to better characterize the long-term outcomes.

Summary Box

What is already known:

- Ursodeoxycholic acid (UDCA) is the primary treatment for primary biliary cholangitis; however, 20% of patients respond inadequately
- Obeticholic acid has been approved as monotherapy in patients unable to tolerate UDCA because of side-effects; however, the significant nuisance associated with it is pruritus
- A combination therapy of bezafibrate and UDCA has been proposed for patients who respond inadequately to UDCA

What the new findings are:

- Combination therapy is associated with a statistically significant reduction in alanine aminotransferase, alkaline phosphatase, triglyceride, cholesterol, and IgM levels
- There was no statistically significant association between bezafibrate use and side-effects such as pruritus, myalgia, fatigue or elevation of creatinine kinase levels
- We propose that combination therapy with bezafibrate and UDCA may be a safe and effective therapy in patients who respond inadequately to UDCA alone

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