Systematic review and meta-analysis: bezafibrate in patients with primary biliary cirrhosis

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Background and aim: Ursodeoxycholic acid (UDCA) is the standard treatment for primary biliary cirrhosis (PBC), but not all cases respond well. Evidence has shown that combination therapy of UDCA with bezafibrate significantly improved liver function. A meta-analysis was performed to assess the efficacy and safety of UDCA and bezafibrate combination therapy in the treatment of PBC.

Results: Nine trials, with a total of 269 patients, were included in the analysis. The bias risk of these trials was high. Compared with UDCA alone, the combination with bezafibrate improved the Mayo risk score (mean difference [MD], 0.60; 95% confidence interval [CI], 0.25–0.95; P=0.0008) and liver biochemistry: alkaline phosphatase (MD, −238.21 IU/L; 95% CI, −280.83 to −195.60; P<0.00001); gamma-glutamyltransferase (MD, −38.23 IU/L; 95% CI, −50.16 to −25.85; P<0.00001); immunoglobulin M (MD, −128.63 IU/L; 95% CI, −151.55 to −105.71; P<0.00001); bilirubin (MD, −0.20 mg/dL; 95% CI, −0.33 to −0.07; P=0.002); triglycerides (MD, −26.84 mg/dL; 95% CI, −36.51 to −17.17; P<0.0001); total cholesterol (MD, −21.58 mg/dL; 95% CI, −30.81 to −12.34; P<0.0001), and serum alanine aminotransferase (MD, −10.24 IU/L; 95% CI, −12.65 to −7.85; P<0.00001). However, combination therapy showed no significant differences in the incidence of all-cause mortality or pruritus, and may have resulted in more adverse events (risk ratio [RR], 0.22; 95% CI, 0.07–0.67; P=0.008).

Conclusion: Combination therapy improved liver biochemistry and the prognosis of PBC, but did not improve clinical symptoms or incidence of death. Attention should be paid to adverse events when using bezafibrate.

Keywords: bezafibrate, meta-analysis, primary biliary cirrhosis, ursodeoxycholic acid

Introduction

Primary biliary cirrhosis (PBC) is a chronic progressive inflammatory autoimmune-mediated cholestatic disease. Ninety percent of patients with PBC are females and most are diagnosed after the age of 40 years. It is characterized by the destruction of bile ducts and nonsuppurative inflammation, and subsequent development of liver fibrosis and cirrhosis, eventually leading to liver failure.1,2 Patients with PBC have been treated with many drugs. Ursodeoxycholic acid (UDCA), a bile acid, is the most extensively used drug in these patients. However, some patients respond poorly, and we were unable to demonstrate any significant effect of UDCA on all-cause mortality or liver transplantation, pruritus, or fatigue in patients with PBC.2 Over the years, a number of other drugs have been tried for the treatment of PBC, including immunomodulatory drugs,3–7 corticosteroids,8 budesonide,9 and fibrates.10 Immunomodulatory drugs, such as azathioprine, prednisolone, cyclosporine, D-penicillamine, methotrexate, or colchicine, did not lead to widespread acceptance of these drugs for PBC patients and were associated with a number of adverse events. The use of corticosteroids to suppress the inflammation in PBC has always been considered as a very attractive approach,
but corticosteroids cannot improve the clinical symptoms as well as the mortality.

Bezafibrate was originally developed as a drug for treatment of hyperlipidemia and used for the prevention of cardiovascular diseases. Bezafibrate decreases serum hepatobiliary enzyme activity even in normal subjects, and this used to be considered as a side effect. Recently, this drug has come to be recognized as a potential anticholestatic medicine for the treatment of PBC that does not respond sufficiently to UDCA monotherapy. The mechanism by which bezafibrate improves cholestasis, cytology, and modifies the immune response in patients with PBC are not known. A recent study elucidated that bezafibrate inhibits hepatic synthesis and the uptake of bile acids, enhances bile-acid detoxification, and stimulates canicular MDR3, MDR1, and MRP2 activities as a dual peroxisome proliferator-activated receptors/PXR agonist. And most of the people agree that bezafibrate induces multidrug resistant-3 gene expression and upregulates P-glycoprotein expression, thus facilitating the production of biliary phospholipids. This results in a reduction in the cytotoxic effects of these phospholipids on the biliary epithelia. We therefore performed a meta-analysis to assess the effects of bezafibrate in PBC.

Materials and methods

Search strategy

All the studies were identified and selected by searching PubMed, the Cochrane Library, the Chinese Biomedical Database, EMBASE, and Medline (updated to April 2015) using the search terms “ursodeoxycholic acid”, “bezafibrate”, “PBC”, and “randomized controlled trial”. A manual search of all review articles, conference literature, retrieved original studies, and abstracts was conducted. Principal authors were contacted to obtain missing information and additional published or unpublished trials.

Inclusion criteria

Randomized clinical trials assessing bezafibrate in patients with PBC, irrespective of blinding, language, publication year, or publication status, were included. For crossover trials, only data from the first period were used. Self-control clinical trials were also included in this study. For assessment of adverse events, quasi-randomized and observational studies were also considered, but we did not perform specific searches for these studies. All the study protocol complies with good clinical practice according to the Declaration of Helsinki and was approved by the Institutional Ethics Committee.

Data extraction

Two of the authors (Qin Yin and Jingjing Li) independently scrutinized all articles, and any disagreement was resolved by consensus. The following data were extracted from each included study: name of the first author, year of publication, daily dose of oral therapy, number of patients, duration of treatment, Mayo risk score, liver biochemistry, symptoms, death, and adverse events.

Data analysis

The meta-analysis was performed using RevMan 5.2 software (The Nordic Cochrane Center, The Cochrane Collaboration, Oxford, UK). For dichotomous outcomes, we calculated the risk ratio (RR), and for continuous outcomes, the mean difference (MD), all with 95% confidence intervals (CIs). To calculate the MDs, we combined data reported as change from baseline values with final measurement values in the meta-analysis using the MD method in RevMan. We tested heterogeneity using the $\chi^2$ and $P$ tests, and a $P$-value <0.10 or an $F$-value >50% was considered to indicate substantial heterogeneity. Meta-analysis of the data was performed with both a random-effects model and a fixed-effects model to ensure robustness of the results. A fixed-effects model was used when the heterogeneity test showed $P>0.10$ and $F<50%$; if $F>50%$ in the subgroup, a random-effects model was used. We did not perform a funnel plot, as there were only nine trials in this meta-analysis.

We performed subgroup analyses, in which trials were grouped according to the duration of treatment and severity of adverse events.

Methodological quality of the included studies

We assessed the methodological quality of the randomized clinical trials using six components: allocation sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential sources of bias (Table 1). The nine included trials were evaluated according to the parameters mentioned in Table 1 and are summarized in Figure 1. Risk of bias was assessed according to seven components: allocation sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, handling of incomplete outcome data, selective outcome reporting, and other potential sources of bias. All the nine included trials were assessed as having high risk of bias; therefore, our statistical analyses are based only on trials with high risk of bias (Figure 2).
Descriptive results are shown in Table 3. From 147 trials, nine were selected for the analysis (Figure 3). These studies involved 269 patients: 144 were randomized to the UDCA monotherapy group and 125 to the combination therapy (UDCA and bezafibrate) group. The baseline characteristics of the nine trials are listed in Table 2. The mean age was 54–64 years and the mean follow-up interval was 3–96 months. The daily doses of UDCA were 600–1,500 mg/day, and the daily dose of bezafibrate was 400 mg/day. Eight trials were published as full text articles and one trial as an abstract and letter to the editor. The descriptive results are shown in Table 3.

### Meta-analysis
1. Mortality: nine trials, which included 269 patients, reported data regarding this end point. One of 144 patients in the monotherapy groups and three of 125 patients in the combination therapy groups died. There was medium heterogeneity (P=0.20, I²=38%) and there were no significant differences between the groups (RR, 0.41; 95% CI, 0.07–2.29; P=0.31; Figure 4).
2. Pruritus: four trials, which included 131 patients, reported data regarding this end point. Symptoms improved in 22 of 68 patients in the monotherapy groups and in 12 of 63 patients in the combination therapy groups. There was medium heterogeneity (P=0.09, I²=54%) and no significant differences between the groups (RR, 1.60; 95% CI, 0.90–2.85; P=0.11; Figure 5).
3. Adverse events: nine trials provided information on adverse events and could be included in the analyses.
The included trials reported 15 of 352 patients having adverse events. The incidence of adverse events was one of 186 patients in the monotherapy groups versus 14 of 166 patients in the combination therapy groups. Meta-analyses showed that combination therapy may cause more adverse events (RR, 0.22; 95% CI, 0.07–0.67; \( P=0.008 \); Figure 6).

The subgroup analyses, stratifying the trials according to the severity of the adverse events, did not reveal significant differences (Figure 6). Heterogeneity was absent (\( P=0.83, I^2=0\% \)).

4. Mayo risk score: two trials, which included 60 patients, reported data regarding this end point.\(^\text{11,13} \) Combination therapy significantly decreased the Mayo risk score compared with UDCA monotherapy (MD, 0.60; 95% CI, 0.25–0.95; \( P=0.0008 \); Figure 7). This suggests that addition of bezafibrate to UDCA may improve the prognosis of PBC. There was low heterogeneity (\( P=0.24, I^2=26\% \)).

5. Alkaline phosphatase (ALP): nine trials, which included 247 patients, reported data regarding this end point.\(^\text{11,13–20} \) Combination therapy with UDCA and bezafibrate was more effective than UDCA monotherapy in decreasing the serum ALP (MD, \(-238.21\) IU/L; 95% CI, \(-280.83\) to \(-195.60\); \( P<0.00001 \); Figure 8).

The subgroup analyses, stratifying the trials according to the duration of treatment, did not reveal significant differences (Figure 8). There was substantial heterogeneity (\( P=0.0003, I^2=65\% \)).

6. Gamma-glutamyltransferase: seven trials, which included 194 patients, reported data regarding this end point.\(^\text{11,13,14,16,18–20} \) Combination therapy with UDCA and bezafibrate was more effective than UDCA monotherapy in decreasing gamma-glutamyltransferase (MD, \(-38.23\) IU/L; 95% CI, \(-50.16\) to \(-25.85\); \( P<0.00001 \); Figure 9). In the subgroup counting change from the baseline, there were no significant differences between the groups (MD, \(-15.47\) IU/L; 95% CI, \(-32.11\) to \(1.18\); \( P=0.07; I^2=44\% \)). However, in the subgroup counting final measurement values, there were significant differences between the groups (MD, \(-25.85\) IU/L; 95% CI, \(-44.38\) to \(-7.32\); \( P=0.0087; I^2=50\% \)).

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**Figure 1** Risk of bias in included studies.

**Notes:** +, 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.
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Table 2 Baseline characteristics of the trials included in the meta-analysis

| First author, year | Mean age (years) | Monotherapy (n) | Combination therapy (n) | UDCA dose (mg/day) | Bezafibrate dose (mg/day) | Duration of treatment (months) | Publication type |
|--------------------|----------------|----------------|-------------------------|-------------------|--------------------------|-------------------------------|-----------------|
| Nakai et al, 2020  | 58             | 13             | 10                      | 600               | 400                      | 12                            | Letter          |
| Kanda et al, 2003  | 56             | 11             | 11                      | 600               | 400                      | 6                             | Full text       |
| Itakura et al, 2004| 57             | 7              | 9                       | 600               | 400                      | 6                             | Full text       |
| Iwasaki et al, 2008| 54             | 10             | 9                       | 600               | 400                      | 12                            | Full text       |
| Hazzan and Tur-Kaspa, 2010 | 64 | 8            | 8                       | 900–1,500         | 400                      | 24                            | Full text       |
| Takeuchi et al, 2011| 57             | 22             | 15                      | 600               | 400                      | 24                            | Full text       |
| Honda et al, 2013  | 58             | 31             | 19                      | 600               | 400                      | 3                             | Full text       |
| Lens et al, 2014   | 53             | 28             | 28                      | 900–1,500         | 400                      | 3                             | Full text       |
| Hosonuma et al, 2015| 64             | 14             | 13                      | 600–900           | 400                      | 96                            | Full text       |

Abbreviation: UDCA, ursodeoxycholic acid.
Table 3 Meta-analysis of clinical events and biochemical parameter changes in the included studies

| Outcome title                                      | No of studies | No of participants | Statistical method | Effect size          | P-value  |
|----------------------------------------------------|---------------|--------------------|--------------------|----------------------|----------|
| Mortality                                          | 9             | 269                | Risk ratio (M–H, fixed, 95% CI) | 0.41 (0.07, 2.29)    | 0.31     |
| Pruritus                                           | 4             | 131                | Risk ratio (M–H, fixed, 95% CI) | 1.60 (0.90, 2.85)    | 0.11     |
| Adverse events                                     |               |                    |                    |                      |          |
| 1. Permanent discontinuation of treatment          | 2             | 83                 | Risk ratio (M–H, fixed, 95% CI) | 0.14 (0.02, 1.08)    | 0.06     |
| 2. Not necessitating permanent discontinuation of treatment | 9             | 269                |                     | 0.29 (0.08, 1.08)    | 0.06     |
| Mayo risk score                                    | 2             | 60                 | Mean difference (IV, fixed, 95% CI) | 0.60 (0.25, 0.95)    | 0.0008   |
| Alkaline phosphatase                               |               |                    |                    |                      |          |
| 1. Trial duration ≤24 months                       | 6             | 171                | Mean difference (IV, random, 95% CI) | −255.57 (−301.38, −209.77) | <0.0001 |
| 2. Trial duration >24 months                       | 3             | 76                 |                     | −191.35 (−263.62, −119.08) | <0.0001 |
| Gamma-glutamyltransferase                          |               |                    |                    |                      |          |
| 1. Change from baseline                            | 3             | 57                 | Mean difference (IV, fixed, 95% CI) | −15.47 (−32.11, 1.18) | 0.07     |
| 2. Final measurement values                        | 4             | 137                |                     | −66.41 (−84.93, −47.88) | <0.0001 |
| Alanine aminotransfer                              |               |                    |                    |                      |          |
| 1. Trial duration ≤24 months                       | 3             | 75                 | Mean difference (IV, fixed, 95% CI) | −14.89 (−21.07, −8.71) | <0.0001 |
| 2. Trial duration >24 months                       | 1             | 37                 |                     | −9.40 (−12.02, −6.78) | <0.0001 |
| Immunoglobulin M                                   |               |                    |                    |                      |          |
| 1. Trial duration ≤24 months                       | 5             | 162                | Mean difference (IV, fixed, 95% CI) | −82.22 (−108.76, −55.68) | <0.0001 |
| 2. Trial duration >24 months                       | 1             | 37                 |                     | −264.70 (−310.15, −219.25) | <0.0001 |
| Triglycerides                                      | 4             | 115                | Mean difference (IV, fixed, 95% CI) | −26.84 (−36.51, −17.17) | <0.0001 |
| Total cholesterol                                  | 4             | 115                | Mean difference (IV, fixed, 95% CI) | −21.58 (−30.81, −12.34) | <0.0001 |
| Serum bilirubin                                    | 4             | 97                 | Mean difference (IV, fixed, 95% CI) | −0.20 (−0.33, −0.07) | 0.002    |
| Albumin                                            | 2             | 63                 | Mean difference (IV, fixed, 95% CI) | −0.09 (−0.27, 0.10)  | 0.35     |
| AST                                                | 2             | 39                 | Mean difference (IV, fixed, 95% CI) | 4.53 (−2.54, 11.60)  | 0.21     |

Abbreviations: AST, aspartate aminotransferase; M–H, Mantel–Haenszel; CI, confidence interval; IV, inverse-variance.

Figure 4 Mortality in primary biliary cirrhosis patients treated with monotherapy versus combination therapy.

Abbreviations: CI, confidence interval; COM, combination therapy; df, degrees of freedom; SD, standard deviation; M–H, Mantel–Haenszel; UDCA, ursodeoxycholic acid monotherapy.
### Table 1: Effects of monotherapy versus combination therapy on pruritus in patients with primary biliary cirrhosis.

| Study or subgroup | UDCA | COM | Weight | Risk ratio M–H, fixed, 95% CI |
|------------------|------|-----|--------|-----------------------------|
| Events Total     | Total Events Total | | |
| Itakura et al16  | 1    | 7   | 1      | 6.6%                        |
| Kanda et al19    | 5    | 11  | 6      | 45.0%                       |
| Lens et al14     | 9    | 28  | 1      | 3.8%                        |
| Takeuchi et al17 | 7    | 22  | 5      | 44.6%                       |
| **Total (95% CI)** | **68** | **63** | **100%** | **1.60 (0.90, 2.85)** |
| **Total events** | 22   | 12  |        |                             |
| Heterogeneity: $\chi^2=6.49$, $df=3$ ($P=0.09$); $I^2=54\%$ |
| Test for overall effect: $Z=1.59$ ($P=0.11$) |

**Figure 5** Effects of monotherapy versus combination therapy on pruritus in patients with primary biliary cirrhosis.

**Abbreviations:** CI, confidence interval; COM, combination therapy; df, degrees of freedom; M–H, Mantel–Haenszel; UDCA, ursodeoxycholic acid monotherapy.

### Table 2: Adverse events in primary biliary cirrhosis patients treated with monotherapy versus combination therapy.

| Study or subgroup | UDCA | COM | Weight | Risk ratio M–H, fixed, 95% CI |
|------------------|------|-----|--------|-----------------------------|
| Events Total     | Total Events Total | | |
| Permanent discontinuation of treatment |
| Hosonuma et al15 | 0    | 14  | 2      | 13 15.9% 0.19 (0.01, 3.56) |
| Lens et al14     | 0    | 28  | 4      | 28 27.6% 0.11 (0.01, 1.97) |
| Subtotal (95% CI) | 42   | 41  | 43.5% 0.14 (0.02, 1.08) |
| **Total events** | 0    | 6   |        |                             |
| Heterogeneity: $\chi^2=0.06$, $df=1$ ($P=0.80$); $I^2=0\%$ |
| Test for overall effect: $Z=1.88$ ($P=0.06$) |

**Not necessitating permanent discontinuation of treatment**

| Study or subgroup | UDCA | COM | Weight | Risk ratio M–H, fixed, 95% CI |
|------------------|------|-----|--------|-----------------------------|
| Events Total     | Total Events Total | | |
| Hazan and Tur-Kaspa14 | 0    | 8   | 0      | 8  Not estimable |
| Honda et al11     | 0    | 31  | 0      | 19  Not estimable |
| Hosonuma et al15  | 0    | 14  | 3      | 13 22.2% 0.13 (0.01, 2.36) |
| Itakura et al16   | 1    | 7   | 1      | 9 5.4% 1.29 (0.10, 17.14) |
| Kanda et al19     | 0    | 11  | 1      | 11 9.2% 0.33 (0.02, 7.39) |
| Nakai et al20     | 0    | 13  | 0      | 10  Not estimable |
| Lens et al14      | 0    | 28  | 0      | 28  Not estimable |
| Takeuchi et al17  | 0    | 22  | 0      | 15  Not estimable |
| Subtotal (95% CI) | 144  | 125 | 56.5% 0.29 (0.08, 1.08) |
| **Total events** | 1    | 8   |        |                             |
| Heterogeneity: $\chi^2=1.70$, $df=3$ ($P=0.64$); $I^2=0\%$ |
| Test for overall effect: $Z=1.85$ ($P=0.06$) |

**Figure 6** Adverse events in primary biliary cirrhosis patients treated with monotherapy versus combination therapy.

**Abbreviations:** CI, confidence interval; COM, combination therapy; df, degrees of freedom; SD, standard deviation; M–H, Mantel–Haenszel; UDCA, ursodeoxycholic acid monotherapy.

### Table 3: Mayo risk score in primary biliary cirrhosis patients treated with monotherapy versus combination therapy.

| Study or subgroup | UDCA Mean SD Total | COM Mean SD Total | Weight | Mean difference IV, fixed, 95% CI |
|------------------|---------------------|-------------------|--------|----------------------------------|
| Events Total     | Tus                  | Total             | Tus    |                                  |
| Hosonuma et al15 | 0.2                 | 0.56              | 14     | −0.62                            |
| Takeuchi et al17 | 0                   | 0.8               | 22     | −0.4                             |
| **Total (95% CI)** | **36**  | **24**           | **100%** | **0.60 (0.25, 0.95)** |
| Heterogeneity: $\chi^2=1.36$, $df=1$ ($P=0.24$); $I^2=26\%$ |
| Test for overall effect: $Z=3.34$ ($P=0.0008$) |

**Figure 7** Mayo risk score in primary biliary cirrhosis patients treated with monotherapy versus combination therapy.

**Abbreviations:** CI, confidence interval; COM, combination therapy; df, degrees of freedom; SD, standard deviation; UDCA, ursodeoxycholic acid monotherapy; IV, inverse-variance.
12. Albumin: two trials, which included 63 patients, reported data regarding this end point.13 Heterogeneity was absent (P=0.38, F=0%) and there were no significant differences between the two groups (MD, 4.53 mg/dL; 95% CI, −2.54 to 11.60; P=0.21; Figure 16).

Discussion

Evidence shows that the combination therapy of UDCA and bezafibrate significantly improved liver function early in 1 month.21 Combination therapy reduced the serum levels

| Study or subgroup | COM Mean (SD) | UDCA Mean (SD) | Weight (IV, random, 95% CI) | Mean difference (IV, random, 95% CI) |
|------------------|--------------|---------------|----------------------------|--------------------------------------|
| **Trial duration <24 months** | | | | |
| Honda et al16 | 324 27 19 | 597 51 31 | 24.2% | −273.00 (−294.67, −251.33) |
| Itakura et al18 | −362 489 9 | 25 108.5 7 | 1.6% | −387.00 (−716.43, −57.57) |
| Iwasaki et al15 | 310.7 103.8 10 | 561.2 173.6 9 | 7.6% | −250.50 (−380.89, −120.11) |
| Kanda et al15 | 400.26 124.41 11 | 524.16 86.24 11 | 12.1% | −123.90 (−213.36, −34.44) |
| Nakai et al15 | 179 65.3 10 | 401 224 12 | 7.3% | −222.00 (−355.04, −89.96) |
| Lens et al15 | 344 35 21 | 648 59 21 | 23.0% | −364.00 (−333.34, −274.66) |
| **Subtotal (95% CI)** | **80** | **91** | **75.7%** | −255.57 (−301.38, −209.77) |

Heterogeneity: χ²=1,512.61; I²=15.88, df=5 (P=0.007); F=69%
Test for overall effect: Z=10.94 (P<0.00001)

| Study or subgroup | COM Mean (SD) | UDCA Mean (SD) | Weight (IV, random, 95% CI) | Mean difference (IV, random, 95% CI) |
|------------------|--------------|---------------|----------------------------|--------------------------------------|
| **Trial duration ≥24 months** | | | | |
| Hazan and Tur-Kaspa16 | 300.8 107 8 | 428.1 166.5 8 | 7.0% | −127.30 (−264.45, 9.85) |
| Hosonuma et al15 | 290.3 125.8 9 | 464.5 164.5 14 | 8.6% | −174.20 (−293.28, −55.12) |
| Takeuchi et al15 | −242.5 187 15 | 12.5 165 22 | 8.7% | −255.00 (−372.09, −137.91) |
| **Subtotal (95% CI)** | **32** | **44** | **24.3%** | −191.35 (−263.62, −119.08) |

Heterogeneity: χ²=105.65; I²=2.05, df=2 (P=0.36), P=3%
Test for overall effect: Z=5.19 (P<0.000001)

| Study or subgroup | COM Mean (SD) | UDCA Mean (SD) | Weight (IV, fixed, 95% CI) | Mean difference (IV, fixed, 95% CI) |
|------------------|--------------|---------------|----------------------------|--------------------------------------|
| **Change from baseline** | | | | |
| Itakura et al18 | −125 141 9 | −34 60.8 7 | 1.5% | −91.00 (−193.54, 11.54) |
| Iwasaki et al15 | −109.3 116.4 10 | −35.7 102.6 9 | 1.6% | −73.60 (−172.08, 24.88) |
| Kanda et al15 | −14.6 26 11 | −3 12.8 11 | 52.3% | −11.60 (−28.73, 5.53) |
| **Subtotal (95% CI)** | **30** | **27** | **55.3%** | −15.47 (−32.11, 1.18) |

Heterogeneity: χ²=3.82, df=2 (P=0.16); F=45%
Test for overall effect: Z=1.82 (P=0.07)

| Study or subgroup | COM Mean (SD) | UDCA Mean (SD) | Weight (IV, fixed, 95% CI) | Mean difference (IV, fixed, 95% CI) |
|------------------|--------------|---------------|----------------------------|--------------------------------------|
| **Final measurement values** | | | | |
| Hazan and Tur-Kaspa15 | 155.4 99.5 8 | 201.2 76.3 8 | 2.0% | −45.80 (−132.69, 41.09) |
| Honda et al11 | 99 41 19 | 178 59 31 | 19.9% | −79.00 (−106.77, −51.23) |
| Nakai et al22 | 73 73 10 | 123 127 12 | 2.1% | −50.00 (−134.91, 34.91) |
| Lens et al21 | 261 39 28 | 319 54 21 | 20.7% | −58.00 (−85.24, −30.76) |
| **Subtotal (95% CI)** | **65** | **72** | **44.7%** | −66.41 (−84.93, −47.88) |

Heterogeneity: χ²=1.52, df=3 (P=0.068); F=0%
Test for overall effect: Z=7.03 (P<0.000001)

| Study or subgroup | COM Mean (SD) | UDCA Mean (SD) | Weight (IV, fixed, 95% CI) | Mean difference (IV, fixed, 95% CI) |
|------------------|--------------|---------------|----------------------------|--------------------------------------|
| **Total (95% CI)** | | | | |
| **95** | **99** | **100%** | **−38.23** (−50.61, −25.85) |

Heterogeneity: χ²=21.21, df=6 (P=0.002); F=72%
Test for overall effect: Z=6.05 (P<0.00001)
Test for subgroup differences: χ²=16.07, df=1 (P<0.0001); F=93.8%

Figure 8 Alkaline phosphatase levels in primary biliary cirrhosis patients treated with monotherapy versus combination therapy. Abbreviations: CI, confidence interval; COM, combination therapy; df, degrees of freedom; SD, standard deviation; UDCA, ursodeoxycholic acid monotherapy; IV, inverse-variance.

Figure 9 Gamma-glutamyltransferase levels in primary biliary cirrhosis patients treated with monotherapy versus combination therapy. Abbreviations: CI, confidence interval; COM, combination therapy; df, degrees of freedom; SD, standard deviation; UDCA, ursodeoxycholic acid monotherapy; IV, inverse-variance.
| Study or subgroup | COM Mean (SD) | Total | UDCA Mean (SD) | Total | Weight | Mean difference (IV, fixed, 95% CI) |
|------------------|--------------|-------|----------------|-------|--------|---------------------------------|
| **Trial duration <24 months** | | | | | | |
| Itakura et al<sup>16</sup> | -29 (33) | 9 | 14 (14.55) | 7 | 1.0% | -15.00 (-39.10, 9.10) |
| Iwasaki et al<sup>13</sup> | 50.4 (42.3) | 10 | 41.1 (23.5) | 9 | 0.6% | 9.30 (-21.08, 39.68) |
| Lens et al<sup>11</sup> | 55 (9) | 19 | 71 (12) | 21 | 13.6% | -16.00 (-22.54, -9.46) |
| **Subtotal (95% CI)** | | | | | | 38 | 37 | 15.3% | -14.89 (-21.07, -8.71) |

Heterogeneity: $\chi^2=2.55$, df=2 ($P=0.28$); $I^2=21$
Test for overall effect: $Z=4.72$ ($P<0.00001$)

| Study or subgroup | COM Mean (SD) | Total | UDCA Mean (SD) | Total | Weight | Mean difference (IV, fixed, 95% CI) |
|------------------|--------------|-------|----------------|-------|--------|---------------------------------|
| **Trial duration ≥24 months** | | | | | | |
| Takeuchi et al<sup>17</sup> | -10.9 (5.1) | 15 | -1.5 (1.1) | 22 | 84.7% | -9.40 (-12.02, -6.78) |
| **Subtotal (95% CI)** | | | | | | 53 | 59 | 100% | -10.24 (-12.65, -7.82) |

Heterogeneity: not applicable
Test for overall effect: $Z=7.03$ ($P<0.00001$)

Figure 10 Alanine aminotransferase levels in primary biliary cirrhosis patients treated with monotherapy versus combination therapy.

Abbreviations: CI, confidence interval; COM, combination therapy; df, degrees of freedom; SD, standard deviation; UDCA, ursodeoxycholic acid monotherapy; IV, inverse-variance.

| Study or subgroup | COM Mean (SD) | Total | UDCA Mean (SD) | Total | Weight | Mean difference (IV, fixed, 95% CI) |
|------------------|--------------|-------|----------------|-------|--------|---------------------------------|
| **Trial duration <24 months** | | | | | | |
| Honda et al<sup>11</sup> | 232 (41) | 19 | 306 (60) | 31 | 66.8% | -74.00 (-102.04, -45.96) |
| Itakura et al<sup>16</sup> | -163 (180) | 9 | -60 (113.8) | 7 | 2.5% | -103.00 (-247.69, 41.69) |
| Iwasaki et al<sup>13</sup> | 237.3 (86.8) | 8 | 329 (188.9) | 4 | 1.4% | -91.70 (-286.73, 103.33) |
| Kanda et al<sup>13</sup> | 135 (80) | 11 | 257 (265) | 11 | 2.0% | -122.00 (-285.56, 41.58) |
| Nakai et al<sup>10</sup> | 187 (82) | 10 | 486 (282) | 12 | 1.9% | -299.00 (-466.45, -131.55) |
| **Subtotal (95% CI)** | | | | | | 57 | 65 | 74.6% | -82.22 (-108.76, -55.68) |

Heterogeneity: $\chi^2=7.08$, df=4 ($P=0.13$); $I^2=44$
Test for overall effect: $Z=6.07$ ($P<0.00001$)

| Study or subgroup | COM Mean (SD) | Total | UDCA Mean (SD) | Total | Weight | Mean difference (IV, fixed, 95% CI) |
|------------------|--------------|-------|----------------|-------|--------|---------------------------------|
| **Trial duration ≥24 months** | | | | | | |
| Takeuchi et al<sup>17</sup> | -211.7 (82.7) | 15 | 53 (42.4) | 22 | 25.4% | -264.70 (-310.15, -219.25) |
| **Subtotal (95% CI)** | | | | | | 72 | 87 | 100% | -128.63 (-151.55, -105.71) |

Heterogeneity: not applicable
Test for overall effect: $Z=11.42$ ($P<0.00001$)

| Study or subgroup | COM Mean (SD) | Total | UDCA Mean (SD) | Total | Weight | Mean difference (IV, fixed, 95% CI) |
|------------------|--------------|-------|----------------|-------|--------|---------------------------------|
| **Total (95% CI)** | | | | | | 55 | 60 | 100% | -26.84 (-36.51, -17.17) |

Heterogeneity: $\chi^2=2.18$, df=3 ($P=0.54$); $I^2=0$
Test for overall effect: $Z=5.44$ ($P<0.00001$)

Figure 11 Immunoglobulin M levels in primary biliary cirrhosis patients treated with monotherapy versus combination therapy.

Abbreviations: CI, confidence interval; COM, combination therapy; df, degrees of freedom; SD, standard deviation; UDCA, ursodeoxycholic acid monotherapy; IV, inverse-variance.

| Study or subgroup | COM Mean (SD) | Total | UDCA Mean (SD) | Total | Weight | Mean difference (IV, fixed, 95% CI) |
|------------------|--------------|-------|----------------|-------|--------|---------------------------------|
| **Figure 12 Triglycerides levels in primary biliary cirrhosis patients treated with monotherapy versus combination therapy.** | | | | | | |
| Itakura et al<sup>16</sup> | 23 (93) | 9 | 14 (23.3) | 7 | 2.3% | 9.00 (-54.16, 72.16) |
| Iwasaki et al<sup>13</sup> | 78 (32) | 12 | 105 (40) | 10 | 9.9% | -37.00 (-67.70, 3.70) |
| Lens et al<sup>11</sup> | 114 (19) | 19 | 140 (16) | 21 | 78.0% | -26.00 (-36.95, -15.05) |
| Takeuchi et al<sup>17</sup> | 84 (40) | 15 | 126 (56) | 22 | 9.8% | -42.00 (-72.94, -11.06) |
| **Total (95% CI)** | | | | | | 55 | 60 | 100% | -26.84 (-36.51, -17.17) |

Heterogeneity: $\chi^2=4.18$, df=3 ($P=0.00001$); $I^2=97.8$
Test for overall effect: $Z=5.44$ ($P<0.00001$)

Figure 12 Triglycerides levels in primary biliary cirrhosis patients treated with monotherapy versus combination therapy.

Abbreviations: CI, confidence interval; COM, combination therapy; df, degrees of freedom; SD, standard deviation; UDCA, ursodeoxycholic acid monotherapy; IV, inverse-variance.
Figure 13  Total cholesterol levels in primary biliary cirrhosis patients treated with monotherapy versus combination therapy.

**Abbreviations:** CI, confidence interval; COM, combination therapy; df, degrees of freedom; SD, standard deviation; UDCA, ursodeoxycholic acid monotherapy; IV, inverse-variance.

| Study or subgroup | COM Mean ± SD | Total | UDCA Mean ± SD | Total | Weight | Mean difference ± 95% CI | Mean difference ± 95% CI |
|------------------|---------------|-------|----------------|-------|--------|-------------------------|-------------------------|
| Itakura et al18   | 26 ± 60 9    | –4    | 16 ± 14 7      | 5.1%  | 30.00 (–11.04, 71.04)    |                          |
| Iwasaki et al19   | 199 ± 27 12  | 225 ± 28 10 | 15.9%  | –26.00 (–49.12, –2.88)  |                          |
| Lens et al14      | 283 ± 19 19  | 289 ± 21 21 | 61.3%  | –26.00 (–37.79, –14.21) |                          |
| Takeuchi et al17  | 190 ± 30 15  | 207 ± 22 17.7%| –17.00 (–38.97, 4.97) |     |        |                          |                         |
| Total (95% CI)    | 55 ± 60 100%|       | –21.58 (–30.81, –12.34) | |        |                          |                         |

Heterogeneity: $\chi^2=6.92, df=3 (P=0.07); I^2=57%$

Test for overall effect: $Z=4.58 (P<0.00001)$

Figure 14  Serum bilirubin levels in primary biliary cirrhosis patients treated with monotherapy versus combination therapy.

**Abbreviations:** CI, confidence interval; COM, combination therapy; df, degrees of freedom; SD, standard deviation; UDCA, ursodeoxycholic acid monotherapy; IV, inverse-variance.

| Study or subgroup | COM Mean ± SD | Total | UDCA Mean ± SD | Total | Weight | Mean difference ± 95% CI | Mean difference ± 95% CI |
|------------------|---------------|-------|----------------|-------|--------|-------------------------|-------------------------|
| Hosonuma et al15 | 0.48 ± 0.11 9 | 0.69 ± 0.32 14 | 48.6% | –21.00 (–39.00, –0.03) |                          |
| Itakura et al18  | –0.19 ± 0.24 9 | –0.03 ± 0.48 7 | 10.7% | –16.00 (–55.23, 29.23) |                          |
| Iwasaki et al13  | 0.6 ± 0.1 10 | 0.8 ± 0.3 8 | 34.3% | –20.00 (–42.02, 0.02) |                          |
| Lens et al14     | 1.7 ± 0.9 19 | 1.9 ± 0.7 21 | 6.4% | –20.00 (–70.30, 31.50) |                          |
| Total (95% CI)   | 47 ± 50 100%|       | –20.00 (–33.00, –0.07) | |        |                          |                         |

Heterogeneity: $\chi^2=0.05, df=3 (P=1.00); I^2=0%$

Test for overall effect: $Z=3.09 (P=0.002)$

Figure 15  Albumin levels in primary biliary cirrhosis patients treated with monotherapy versus combination therapy.

**Abbreviations:** CI, confidence interval; COM, combination therapy; df, degrees of freedom; SD, standard deviation; UDCA, ursodeoxycholic acid monotherapy; IV, inverse-variance.

| Study or subgroup | COM Mean ± SD | Total | UDCA Mean ± SD | Total | Weight | Mean difference ± 95% CI | Mean difference ± 95% CI |
|------------------|---------------|-------|----------------|-------|--------|-------------------------|-------------------------|
| Hosonuma et al15 | 41.5 ± 0.6 19 | 41.8 ± 0.5 21 | 29.4% | –30.00 (–64.04, 0.04) |                          |
| Lens et al14     | 4 ± 0.3 9    | 4 ± 0.2 14 | 70.6% | 0.00 (–0.22, 0.22) |                          |
| Total (95% CI)   | 28 ± 35 100%|       | –0.09 (–0.27, 0.10) | |        |                          |                         |

Heterogeneity: $\chi^2=2.06, df=1 (P=0.15); I^2=51%$

Test for overall effect: $Z=0.93 (P=0.35)$

Figure 16  AST levels in primary biliary cirrhosis patients treated with monotherapy versus combination therapy.

**Abbreviations:** AST, aspartate aminotransferase; CI, confidence interval; COM, combination therapy; df, degrees of freedom; SD, standard deviation; UDCA, ursodeoxycholic acid monotherapy; IV, inverse-variance.

| Study or subgroup | COM Mean ± SD | Total | UDCA Mean ± SD | Total | Weight | Mean difference ± 95% CI | Mean difference ± 95% CI |
|------------------|---------------|-------|----------------|-------|--------|-------------------------|-------------------------|
| Hosonuma et al15 | 32.7 ± 10.9 9 | 27.1 ± 4.2 14 | 89.9% | 5.60 (–1.85, 13.05) |                          |
| Itakura et al18  | –17 ± 28.5 9  | –12 ± 16.4 7 | 10.1% | –5.00 (–27.23, 17.23) |                          |
| Total (95% CI)   | 18 ± 21 100%|       | 4.53 (–2.54, 11.60) | |        |                          |                         |

Heterogeneity: $\chi^2=0.78, df=1 (P=0.38); I^2=0%$

Test for overall effect: $Z=1.26 (P=0.21)$
of gamma-glutamyltransferase, ALP, and immunoglobulin M, but there were no significant differences in the incidence of all-cause mortality, adverse events, and pruritus.\textsuperscript{12,22} However, none of the studies elucidated the long-term prognosis, efficacy, and safety of combination therapy. Most recently, Hosonuma et al reported that long-term combination therapy showed significant improvements in the serum ALP levels and Mayo risk score, but may cause notable adverse events such as renal dysfunction and increased serum creatinine levels.\textsuperscript{15} We therefore undertook this meta-analysis and paid special attention to the adverse events.

We did not find statistically significant effects of bezafibrate on mortality or pruritus, but combination therapy with UDCA could improve liver biochemistry indicators such as ALP, gamma-glutamyltransferase, immunoglobulin M, total cholesterol, bilirubin, ALT, and triglycerides in PBC patients. The Mayo risk score, used as an indicator of the severity of PBC, in the combination therapy group was significantly lower than that in the UDCA monotherapy group. We did not have enough data to record changes in the histological parameters. Only one case report, including three patients, observed improvements in the histopathological condition after the use of bezafibrate.\textsuperscript{21} Further studies are required to evaluate whether this combination therapy improves the histological staging and prognosis. We performed subgroup analyses, in which trials were grouped according to duration of treatment, but there were no significant differences in liver biochemistry indicators.

PBC is an autoimmune disease characterized by chronic progressive destruction of small intrahepatic bile ducts with portal inflammation, which ultimately leads to fibrosis.\textsuperscript{24,25} It has been proposed that bezafibrate plays a therapeutic role by downregulation of nitrite production by dendritic cells.\textsuperscript{21} One study evaluated changes in the serum cytokine levels in response to treatment to identify the cytokines that reflect improved clinical results. Serum interleukin-18 (IL-18) levels in the groups at two time points were measured before (baseline) assignment of either treatment and after 12 months of the assigned treatment, but no significant difference was observed between the two groups.\textsuperscript{15} Adverse events in the combination therapy group were more frequent than in the monotherapy group. Most of the adverse events were myalgia, polydipsia, aggravated pruritus, arthritis, leg edema, and gastrointestinal discomfort such as nausea or heartburn. Two studies mentioned a self-limited serum creatine phosphokinase elevation in patients who received bezafibrate.\textsuperscript{13,15} During long-term administration of the combination therapy, bezafibrate treatment was discontinued in two cases due to a gradual elevation of the serum creatinine levels shortly after the initiation of bezafibrate treatment.\textsuperscript{15} Close attention should be paid to adverse events during long-term combination therapy.

To complete the results, we also covered some nonrandomized studies and conference reports. A retrospective study including 1,121 PBC patients suggested that normalization of ALT levels with additional bezafibrate treatment significantly decreased the rate of occurrence of liver-related symptoms in asymptomatic PBC patients with suboptimal responses to UDCA.\textsuperscript{24} We found one related conference report that stated that higher ALT and ALP levels at diagnosis and sustained high levels of ALT are predictors for poor prognosis in PBC.\textsuperscript{25} We infer that ALT may play an important role in the progression of PBC.\textsuperscript{26,27}

**Limitations**

There are some limitations of this study. Firstly, although we included nine studies in this analysis, the sample size was small and only one long-term combination therapy study was included. Subgroup analyses according to duration of treatment failed to identify significant differences. More long-term clinical studies on the combination therapy of bezafibrate and UDCA may be needed. Secondly, of the nine trials, all were assessed as having a high risk of bias.\textsuperscript{28} Finally, there were insufficient data to record changes in the histological parameters and quality of life; there were only two studies that reported the Mayo risk score, and the smaller trials were less statistically significant. We suggest that a pathogenesis of PBC should be established and improved in the near future, including inflammation of the liver,\textsuperscript{29,30} apoptosis and autophagy,\textsuperscript{31–33} the molecular mechanisms of injury and repair,\textsuperscript{34,35} inflammation and fibrosis,\textsuperscript{36} inflammation and cancer,\textsuperscript{37–39} and other important signaling pathways and related targets; therefore, early treatment can effectively achieve or delay the progression of liver disease. We also should pay attention to the evidence-based medical research of PBC.

**Conclusion**

Significant improvements in the Mayo risk score and liver biochemistry indicators, such as ALP, gamma-glutamyltransferase, immunoglobulin M, total cholesterol, bilirubin, ALT, and triglycerides, compared with UDCA monotherapy suggest that combination therapy is more favorable, although the survival rate was not significantly different between the groups. However, close attention should be paid to adverse events during long-term combination therapy. Larger,
controlled multicenter studies are required to evaluate whether this combination therapy improves the occurrence of adverse events, histological staging, quality of life, and prognosis. We also suggest that an animal model of autoimmune liver disease should be established to facilitate research into the pathogenesis of PBC and target therapies.40–42

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

Disclosure
The authors report no conflicts of interest in this work.

References
1. Prince MI, James OF. The epidemiology of primary biliary cirrhosis. Clin Liver Dis. 2003;7:795–819.
2. Rudic JS, Poropat G, Krstic MN, et al. Ursodeoxycholic acid for primary biliary cirrhosis (Review). Cochrane Database Syst Rev. 2012;12:CD000551.
3. Gong Y, Klingenberg SL, Gluud C. Systematic review and meta-analysis: D-Penicillamine vs placebo/no intervention in patients with primary biliary cirrhosis – Cochrane Hepato-Biliary Group. Aliment Pharmacol Ther. 2006;24(11–12):1535–1544.
4. Giljaac V, Poropat G, Stimac D, Gluud C. Methotrexate for primary biliary cirrhosis. Cochrane Database Syst Rev. 2010;(5):CD004385.
5. Gong Y, Gluud C. Colchicine for primary biliary cirrhosis: a Cochrane Hepato-Biliary Group systematic review of randomized clinical trials. Am J Gastroenterol. 2005;100(8):1876–1885.
6. Gong G, Christensen E, Gluud C. Azathioprine for primary biliary cirrhosis. Cochrane Database Syst Rev. 2007;(3):CD006000.
7. Gong Y, Christensen E, Gluud C. Cyclosporin A for primary biliary cirrhosis. Cochrane Database Syst Rev. 2007;(3):CD005526.
8. Zhang Y, Lu J, Dai W, et al. Combination therapy of ursodeoxycholic acid and corticosteroids for primary biliary cirrhosis with features of autoimmune hepatitis: a meta-analysis. Gastroenterol Res Pract. 2013;2013:490731. doi:10.1155/2013/490731.
9. Zhang H, Yang J, Zhu R, et al. Combination therapy of ursodeoxycholic acid and budesonide for PBC–AHI overlap syndrome: a meta-analysis. Drug Des Devel Ther. 2015;9:567–574.
10. Zhang Y, Li S, He L, et al. Combination therapy of fenofibrate and ursodeoxycholic acid in patients with primary biliary cirrhosis who respond incompletely to UDCA monotherapy: a meta-analysis. Drug Des Devel Ther. 2015;9:2757–2566.
30. Cheng P, Chen K, Xia Y, et al. Hydrogen sulfide, a potential novel drug, attenuates concanavalin A-induced hepatitis. *Drug Des Devel Ther*. 2014;8:1277–1286. doi:10.2147/DDDT.S66573.

31. Shen M, Lu J, Dai W, et al. Ethyl pyruvate ameliorates hepatic ischemia-reperfusion injury by inhibiting intrinsic pathway of apoptosis and autophagy. *Meditators Inflamm*. 2013;2013:461536. doi:10.1155/2013/461536. Epub 2013 Dec 25.

32. Cheng P, Wang F, Chen K, et al. Hydrogen sulfide ameliorates ischemia/reperfusion-induced hepatitis by inhibiting apoptosis and autophagy pathways. *Meditators Inflamm*. 2014;2014:935251. doi:10.1155/2014/935251. Epub 2014 May 21.

33. Wang C, Chen K, Xia Y, et al. N-Acetylcysteine attenuates ischemia-reperfusion-induced apoptosis and autophagy in mouse liver via regulation of the ROS/JNK/Bcl-2 pathway. *PLoS One*. 2014;9(9):e108855. doi:10.1371/journal.pone.0108855.

34. Wang C, Xia Y, Zheng Y, et al. Protective effects of N-acetylcysteine in concanavalin A induced hepatitis in mice, induced hepatitis in mice. *Meditators Inflamm*. 2015;2015:189785.

35. Li J, Wang F, Xia Y, et al. Astaxanthin pretreatment attenuates hepatic ischemia reperfusion-induced apoptosis and autophagy via the ROS/MAPK pathway in mice. *Marine Drugs*. 2015;13(6):3368–3387.

36. Shen M, Chen K, Lu J, et al. Protective effect of astaxanthin on liver fibrosis through modulation of TGF-β1 expression and autophagy. *Meditators Inflamm*. 2014;2014:954502. doi:10.1155/2014/954502. Epub 2014 Apr 17.

37. Dai W, Wang F, He L, et al. Genistein inhibits hepatocellular carcinoma cell migration by reversing the epithelial-mesenchymal transition: partial mediation by the transcription factor NFAT1. *Mol Carcinog*. 2015;54(4):301–311.

38. Dai W, Wang F, Lu J, et al. By reducing hexokinase 2, resveratrol induces apoptosis in HCC cells addicted to aerobic glycolysis and inhibits tumor growth in mice. *Oncotarget*. 2015;6(15):13703–13717.

39. Jie L, Fan W, Weiqi D, et al. The hippo-yes association protein pathway in liver cancer. *Gastroenterol Res Pract*. 2013;2013:187070. doi:10.1155/2013/187070. Epub 2013 Aug 6.

40. Zhou Y, Dai W, Lin C, et al. Protective effects of necrostatin-1 in concanavalin A induced acute hepatic injury in mice. *Meditators Inflamm*. 2013;2013:706156. doi:10.1155/2013/706156. Epub 2013 Oct 1.

41. Shen M, Lu J, Cheng P, et al. Ethyl pyruvate pretreatment attenuates concanavalin A-induced autoimmune hepatitis in mice. *PLoS One*. 2014;9(2):e87977. doi:10.1371/journal.pone.0087977.

42. Zhou Y, Chen K, He L, et al. The protective effect of resveratrol on concanavalin-A-induced acute hepatic injury in mice. *Gastroenterol Res Pract*. 2015;(2015):506390.