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[Intervention Review]

Bezafibrate for primary biliary cirrhosis

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ABSTRACT

Background

Treatment of primary biliary cirrhosis is complicated. There are studies suggesting that bezafibrate, alone or in combination with ursodeoxycholic acid (UDCA), is effective in the treatment of primary biliary cirrhosis, but no systematic review has summarised the evidence yet.

Objectives

To assess the beneficial and harmful effects of bezafibrate in patients with primary biliary cirrhosis.

Search methods

The Cochrane Hepato-Biliary Group Controlled Trials Register, The Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*, MEDLINE, EMBASE, Science Citation Index Expanded, LILACS, Clinicaltrials.gov, the WHO International Clinical Trials Registry Platform, and full text searches were conducted until November 2011. The searches in Chinese Bio-medical Literature Database, China Network Knowledge Information, Chinese Science Journal Database, Chinese Medical Citation Index, Wanfang Database, and full text searches were conducted until January 2011. Manufacturers and authors were contacted.

Selection criteria

All randomised clinical trials comparing bezafibrate at any dose or regimen in patients with primary biliary cirrhosis with placebo or no intervention, or with another drug. Any concomitant interventions were allowed if received equally by all treatment groups in a trial.

Data collection and analysis

Two authors extracted data. RevMan Analysis was used for statistical analysis of dichotomous data with risk ratio (RR) or risk difference (RD), and of continuous data with mean difference (MD), both with 95% confidence intervals (CI). Methodological domains were used to assess risk of systematic errors (bias). Trial sequential analysis was used to control for random errors (play of chance).

Main results

Six trials with 151 Japanese patients were included. All trials had high risk of bias. Four trials compared bezafibrate plus UDCA with no intervention plus UDCA (referenced as bezafibrate versus no intervention in the remaining text), and two trials compared bezafibrate with UDCA. No patient died and no patient developed liver-related complications in any of the included trials. Bezafibrate was without significant effects on the occurrence of adverse events compared with no intervention (5/32 (16%) versus 0/28 (0%)) (RR 5.40, 95% CI 0.69

to 42.32; 3 trials with 60 patients; I^2 = 0%) or with UDCA (2/32 (6%) versus 0/37 (0%)) (RR 6.19, 95% CI 0.31 to 122.05; 2 trials with 69 patients; I^2 = 0%). Bezafibrate significantly decreased the activity of serum alkaline phosphatases compared with no intervention (MD -186.04 U/L, 95% CI -249.03 to -123.04; 4 trials with 79 patients; I^2 = 34%) and when compared with UDCA (MD -162.90 U/L, 95% CI -199.68 to -126.12; 2 trials with 48 patients; I^2 = 0%). These results were supported by trial sequential analyses. Bezafibrate compared with no intervention significantly decreased plasma immunoglobulin M (MD -164.00 mg/dl, 95% CI -259.47 to -68.53; 3 trials with 50 patients; I^2 = 46%) and serum bilirubin concentration (MD -0.19 mg/dl, 95% CI -0.38 to -0.00; 2 trials with 34 patients; I^2 = 0%). However, the latter two results were not supported by trial sequential analyses. Bezafibrate compared with no intervention had no significant effect on the activity of serum gamma-glutamyltransferase (MD -1.22 U/L, 95% CI -11.97 to 9.52; 4 trials with 79 patients; I^2 = 42%) and serum alanine aminotransferase (MD -5.61 U/L, 95% CI -24.50 to 13.27; 2 trials with 35 patients; I^2 = 34%). Bezafibrate compared with UDCA had no significant effect on the activity of serum gamma-glutamyltransferase (MD 38.44 U/L, 95% CI -180.67 to 257.55; 2 trials with 49 patients; I^2 = 89%), serum alanine aminotransferase (MD -2.34 U/L, 95% CI -34.73 to 30.06; 2 trials with 49 patients; I^2 = 95%), and plasma immunoglobulin M concentration (MD -20.23 mg/dl, 95% CI -218.71 to 178.25; 2 trials with 41 patients; I^2 = 90%) in random-effects model meta-analyses, but bezafibrate significantly decreased the activity of serum gamma-glutamyltransferase (MD -58.18, 95% CI -76.49 to -39.88; 2 trials with 49 patients; I^2 = 89%), serum alanine aminotransferase (MD -13.94, 95% CI -18.78 to -9.09; 2 trials with 49 patients; I^2 = 95%), and plasma immunoglobulin M concentration (MD -99.90, 95% CI -130.72 to -69.07; 2 trials with 41 patients; I^2 = 90%) in fixed-effect model meta-analyses. One patient had bezafibrate withdrawn due to an adverse event compared to no intervention (RD 0.03, 95% CI -0.09 to 0.16; 2 trials with 60 patients; I^2 = 0%).

Authors' conclusions

This systematic review did not demonstrate any effect of bezafibrate versus no intervention on mortality, liver-related morbidity, adverse events, and pruritus in patients with primary biliary cirrhosis. Furthermore, we found no significant effects of bezafibrate on mortality, liver-related morbidity, or adverse events when compared with ursodeoxycholic acid, None of the trials assessed quality of life or fatigue. The data seem to indicate a possible positive intervention effect of bezafibrate on some liver biochemistry measures compared with the control group, but the observed effects could be due to systematic errors or random errors. We need more randomised clinical trials on the effects of bezafibrate on primary biliary cirrhosis with low risks of systematic errors and random errors.

PLAIN LANGUAGE SUMMARY

Bezafibrate for primary biliary cirrhosis

Primary biliary cirrhosis is a chronic disease of the liver that is characterised by progressive inflammation and destruction of the liver tissue, eventually progressing to liver cirrhosis and the need for liver transplantation. Primary biliary cirrhosis primarily affects middle-aged women. Bezafibrate is a hypolipidaemic agent used in treatment of hypertriglyceridaemia. There are studies suggesting that bezafibrate, alone or in combination with ursodeoxycholic acid, is effective in treatment of primary biliary cirrhosis. Mechanisms through which bezafibrate improves lipid serum concentration balance and prevents biliary cell damage still need to be fully understood. This review evaluates all data on the benefits and harms of bezafibrate for patients with primary biliary cirrhosis in randomised clinical trials. The findings of this review are based on six randomised clinical trials with 151 Japanese patients. Bezafibrate was compared with no intervention in four trials (with co-intervention of ursodeoxycholic acid in both the bezafibrate and control groups) and with ursodeoxycholic acid in two trials. The primary findings of the review are that bezafibrate has no statistically significant effects on mortality, liver-related morbidity, adverse events, and quality of life of patients with primary biliary cirrhosis. A possible positive intervention effect of bezafibrate versus no intervention on liver biochemistry measures can be real but could also be due to systematic errors or random errors. The benefits and harms of bezafibrate for patients with primary biliary cirrhosis need further assessment in randomised clinical trials comparing bezafibrate with placebo. Such trials ought to be conducted with impeccable methodology to reduce the risks of random errors and sufficiently large patient groups to reduce the risks of random errors.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Bezafibrate compared with no intervention for primary biliary cirrhosis

Bezafibrate compared with no intervention for primary biliary cirrhosis

Patient or population: patients with primary biliary cirrhosis.
Settings: out-patients.
Intervention: bezafibrate.
Comparison: no intervention.

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No intervention	Bezafibrate				
All-cause mortality	**Study population**		**RD 0.00** (-0.11 to 0.11)	60 (3 trials)	⊕⊖⊖⊖ **very low** [2,3]	
	0 per 1000	**0 per 1000** (0 to 0)[1]				
Liver morbidity	**Study population**		**RD 0.00** (-0.11 to 0.11)	60 (3 trials)	⊕⊖⊖⊖ **very low** [2,3]	
	0 per 1000	**0 per 1000** (0 to 0)[1]				
Adverse events	**Study population**		**RR 5.4** (0.69 to 42.32)	60 (3 trials)	⊕⊖⊖⊖ **very low** [2,3]	
	0 per 1000	**0 per 1000** (0 to 0)				
Serum alkaline phosphatases (U/L)		The mean serum alkaline phosphatases activity in the intervention groups was **186.04 lower** (249.03 to 123.04 lower)		79 (4 trials)	⊕⊕⊖⊖ **low** [4,5,6]	
Serum alkaline phosphatases (U/L) - duration of		The mean serum alkaline phosphatases activity (duration of administration 6 months) in the intervention groups was **141.97 lower** (228.3 to 55.64 lower)		38 (2 trials)	⊕⊖⊖⊖ **very low** [4,6,7]	

administration 6 months				
Serum alkaline phosphatases (U/L) - duration of administration 12 to 13 months		The mean serum alkaline phosphatases activity (duration of administration 12 to 13 months) in the intervention groups was **236.23 lower** (328.35 to 144.1 lower)	41 (2 trials)	⊕⊕⊖⊖ **low** [6,8]
Serum bilirubin (mg/dl)		The mean serum bilirubin concentration in the intervention groups was **0.19 lower** (0.38 lower to 0 higher)	34 (2 trials)	⊕⊖⊖⊖ **very low** [3,8]

*The basis for the **assumed risk** (eg, the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Dichotomous outcome was expressed as risk difference (RD) with 95% confidence intervals (CI).
[2] The main limitations in design was the lack of clarity of reporting on adverse events, the lack of clarity of the generation of allocation sequence, concealment of allocation, blinding, and the length of follow-up.
[3] Included trials in our meta-analysis include few patients and few events indicating that we have little knowledge about the intervention effect, and that further information is needed.
[4] The main limitations in design was the lack of clarity of the generation of allocation sequence, concealment of allocation, blinding, and the length of follow-up.
[5] Statistical heterogeneity I^2 = 34%.
[6] According to the results of trial sequential analysis there is a evidence for a beneficial effect of bezafibrate versus no intervention on the activity of serum alkaline phosphatases when the cumulative meta-analysis is adjusted for sparse data and multiple testing on accumulating data. Therefore there is no risk for random error.
[7] Statistical heterogeneity I^2 = 56%.
[8] The main limitations in design was the lack of clarity of the generation of allocation sequence and concealment of allocation in one trial. One trial was unblinded and another was likely unblinded.

Summary of findings 2. Bezafibrate compared with ursodeoxycholic acid for primary biliary cirrhosis

Bezafibrate compared with ursodeoxycholic acid for primary biliary cirrhosis
Patient or population: patients with primary biliary cirrhosis.

Settings: out-patients.
Intervention: bezafibrate.
Comparison: ursodeoxycholic acid.

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Ursodeoxycholic acid	Bezafibrate				
All-cause mortality	**Study population**		**RD 0.00** (-0.08 to 0.08)	69 (2 trials)	⊕⊖⊖⊖ **very low** [2,3]	
	0 per 1000	**0 per 1000** (0 to 0)[1]				
Liver morbidity	**Study population**		**RD 0.00** (-0.08 to 0.08)	69 (2 trials)	⊕⊖⊖⊖ **very low** [2,3]	
	0 per 1000	**0 per 1000** (0 to 0)[1]				
Adverse events	**Study population**		**RR 6.19** (0.31 to 122.05)	69 (2 trials)	⊕⊖⊖⊖ **very low** [2,3]	
	0 per 1000	**0 per 1000** (0 to 0)				
Serum alkaline phosphatases (U/L)		The mean serum alkaline phosphatases activity in the intervention groups was **162.9 lower** (199.68 to 126.12 lower)		48 (2 trials)	⊕⊕⊕⊖ **moderate** [2,4]	

*The basis for the **assumed risk** (eg, the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Dichotomous outcome was expressed as risk difference (RD) with 95% confidence intervals (CI).
[2] The main limitations in design was the lack of clarity of the generation of allocation sequence and concealment of allocation in one trial. One trial was not blinded, and another trial was likely unblinded.

[3] Included trials in our meta-analysis include few patients and few events indicating that we have little knowledge about the intervention effect, and that further information is needed.

[4] According to the results of trial sequential analysis, there is no risk for random error for a beneficial effect of bezafibrate versus ursodeoxycholic acid on the activity of serum alkaline phosphatases when the cumulative meta-analysis is adjusted for sparse data and multiple testing on accumulating data.

BACKGROUND

Description of the condition

Primary biliary cirrhosis is a chronic progressive inflammatory autoimmune-mediated liver disease that primarily affects middle-aged women with sex ratio 1:10. It is characterised by destruction of the intrahepatic bile ducts in the liver that mainly targets the cholangiocytes. The annual incidence of primary biliary cirrhosis ranges from 1 to 49 persons per million, and the prevalence was estimated between 7 to 402 persons per million (Prince 2003; Poupon 2010). The disease seems to cluster within specific geographical areas, being most prevalent in northern Europe (Prince 2003).

The aetiology of primary biliary cirrhosis is still enigmatic, but it is thought to involve multiple genetic factors and environmental triggers leading to an intense autoimmune response, which is directed against the biliary epithelial cells. Most asymptomatic people with primary biliary cirrhosis will develop symptoms and progress to cirrhosis and end stage liver disease which may necessitate liver transplantation as the only treatment option. The most common symptoms and findings are fatigue and pruritus, hyperlipidaemia, hypothyroidism, osteoporosis, and coexisting autoimmune diseases (Kaplan 2005). Diagnosis is made upon the elevated biochemical markers of cholestasis (particularly alkaline phosphatases) for more than six months in the presence of detectable serum antimitochondrial antibodies, and on exclusion of other possible aetiologies of liver damage (Heathcote 2000; EASL 2009). Characteristic liver histological changes confirm the diagnosis and are used for staging and assessing disease activity before therapeutic intervention. However, according to the latest clinical guidelines (EASL 2009), a liver biopsy shall not necessarily be used for diagnosis of primary biliary cirrhosis. During routine laboratory analyses, paying attention to findings of elevated serum alkaline phosphatases or total serum cholesterol or both in each person may lead to an early diagnosis of primary biliary cirrhosis. Asymptomatic patients have about equivalent survival compared with an age-matched and sex-matched healthy population (Lee 2005). On the other hand, the overall median survival for symptomatic patients is between 10 and 15 years. Serum bilirubin level is an independent predictor of survival and is used for prognosis in patients with primary biliary cirrhosis (Shapiro 1979).

Description of the intervention

Bezafibrate was first introduced in 1977 by Boehringer Mannheim Ltd. (Williams 1984). Bezafibrate is a hypolipidaemic agent, which reduces cholesterol and triglyceride synthesis in the liver by inhibiting acetyl coenzyme A carboxylase activity. Fibrates are known to reduce the flow of fatty acids to the liver, decrease very low-density lipoprotein hepatic synthesis, stimulate lipoprotein-lipase activity, and increase the biliary excretion of hepatic cholesterol. Bezafibrate is used in treatment of hypertriglyceridaemia and combined hyperlipidaemia (Vessby 1980). Bezafibrate effectively reduces low-density lipoprotein and triglycerides, and elevates high-density lipoproteins levels thus improving hyperlipidaemia (The BIP Study Group 2000). Fibrates are associated with a number of adverse effects, including liver enzyme elevations, gastrointestinal adverse effects, and rhabdomyolysis (Muscari 2002). In patients with metabolic syndrome, bezafibrate decreases the incidence of myocardial infarction and reduces the risk of cardiac mortality (Tenenbaum 2005). Bezafibrate decreases the incidence of type 2 diabetes and may delay the onset of type 2 diabetes in patients with impaired glucose tolerance (Tenenbaum 2004).

How the intervention might work

Bezafibrate decreases the activity of the cholestatic liver enzymes (alkaline phosphatases and gamma-glutamyl transferase) in asymptomatic patients (Fukuo 1996). In some small studies, biochemical improvement was reported by using bezafibrate alone or in combination with ursodeoxycholic acid (Kurihara 2000; Nakai 2000; Kurihara 2002; Yano 2002). There are two possible mechanisms of the bezafibrate effects on primary biliary cirrhosis involving multiple drug-resistant gene (MDR-2) and peroxisome proliferative-activated receptor alpha (PPAR-α) system pathway. Bezafibrate is a ligand of PPAR-α, which is involved in immune function and inflammation control by regulation of leukotriene B4 and through this mechanism it improves lipid serum concentration balance (Devchand 1996; Delerive 2001). Secondly, bezafibrate induces the expression of MDR-2 and thus controls the balance of biliary phospholipids and bile acids which prevents biliary cell damage through activation of the MDR-2 gene of a knockout mice (mimicking the human MDR-3 gene) (Smit 1993; Chianale 1996). In human studies, defects of the MDR-3 gene may produce progressive familial intrahepatic cholestasis, and in advanced primary biliary cirrhosis the expression of MDR-3 messenger RNA and proteins is increased (Jacquemin 2001; Ros 2003). Bezafibrate lowers the proportion of Fas antigen (surface transmembrane protein that mediates apoptosis)-positive T cells in the peripheral blood and suppresses the inflammatory response in patients with primary biliary cirrhosis (Ishimaru 2002). Fibrates might inhibit migration of inflammatory cells by RANTES (hepatic regulated upon activation, normal T-cell expressed and secreted) to the liver in patients with primary biliary cirrhosis (Hirano 2002). The exact mechanisms yielding the therapeutic benefits of bezafibrate in primary biliary cirrhosis are still to be understood.

Why it is important to do this review

There are studies concluding that bezafibrate, alone or in combination with ursodeoxycholic acid, is effective in treatment of primary biliary cirrhosis (Iwasaki 1999; Miyaguchi 2000; Kanda 2003). However, we could not identify any meta-analyses or systematic reviews that have summarised the evidence.

OBJECTIVES

To assess the beneficial and harmful effects of bezafibrate in patients with primary biliary cirrhosis.

METHODS

Criteria for considering studies for this review

Types of studies

We considered for inclusion randomised clinical trials assessing bezafibrate in patients with primary biliary cirrhosis, irrespective of blinding, language, publication year, or publication status. For cross-over trials, we only used data from the first period. For assessment of harm we also considered quasi-randomised studies and observational studies, but we did not perform specific electronic searches for these studies.

Types of participants

Patients with primary biliary cirrhosis, ie, patients having at least two of the following: elevated serum activity of alkaline phosphatases, a positive antimitochondrial antibody, and liver biopsy compatible with primary biliary cirrhosis were included (EASL 2009; AASLD 2010).

Types of interventions

Bezafibrate administered at any dose or regimen versus placebo or no intervention, or any other drug that is being used for treatment of primary biliary cirrhosis, eg, ursodeoxycholic acid, colchicine, glucocorticoids, azathioprine, d-penicillamine, cyclosporine A, methotrexate, or any other drug that is being compared.

Any concomitant interventions were allowed if received equally by all treatment groups in a trial.

Types of outcome measures

Primary outcomes

1. All-cause mortality.
2. Liver-related morbidity (number of patients who developed jaundice, upper gastrointestinal haemorrhage, ascites, hepatic encephalopathy, hepato-renal syndrome).
3. Adverse events. Serious adverse events are defined as any untoward medical occurrence that was life threatening, resulted in death, or was persistent or led to significant disability; or any medical event, which had jeopardised the patient or required intervention to prevent it (ICH-GCP 1997). All other adverse events (that is, any medical occurrence not necessarily having a causal relationship with the treatment) will be considered as non-serious.
4. Quality of life.

Secondary outcomes

1. Pruritus: number of patients with pruritus or pruritus score.
2. Fatigue: number of patients with fatigue.
3. Serum alkaline phosphatases, serum gamma-glutamyltransferase, serum aspartate aminotransferase, serum alanine aminotransferase, plasma immunoglobulin M, total cholesterol, triglyceride, platelet count, and serum bilirubin.
4. Liver biopsy findings (histological stage).
5. Number of patients having bezafibrate withdrawn due to adverse events.

Search methods for identification of studies

Electronic searches

Relevant randomised clinical trials were identified by electronic searches of The Cochrane Hepato-Biliary Group Controlled Trials Register (Gluud 2011), The Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*, MEDLINE, EMBASE, Science Citation Index Expanded, and LILACS until November 2011, and The Chinese Bio-medical Literature Database (CBM), China Network Knowledge Information (CNKI), Chinese Science Journal Database (VIP), Chinese Medical Citation Index (CMCI), and Wanfang Database until January 2011 (Royle 2003). The search strategies and the time span of the searches are given in Appendix 1.

Searching other resources

The reference lists of relevant articles were scanned for additional trials. In order to obtain unpublished trials, the principal authors of the identified clinical trials and pharmaceutical companies involved in the production of bezafibrate were inquired about additional trials they might know of. We searched Clinicaltrials.gov (http://clinicaltrials.gov/) and the WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/) for ongoing trials.

Data collection and analysis

Selection of studies

We listed the identified studies, and two of the authors (JR and GP) independently assessed their fulfilment of the inclusion criteria. Disagreements were resolved by discussion and arbitrated by CG.

Data extraction and management

JR and GP extracted data independently using data extraction forms that were developed for the purpose. If more then one publication of a trial existed, we listed the publications under the publication with the most complete data and marked it as primary. If information was not available in the published trial, in order to obtain missing data and assess the trials correctly, we contacted authors of the trial publications. We added information obtained through correspondence with these authors to the data extraction form. In the 'Notes' section of the respective trial ('Table of included studies'), we provided the date when the information was requested and received. Disagreements were resolved by discussion among the review authors.

From each trial the following information was extracted: first author; country of origin; trial design (parallel or cross-over); inclusion and exclusion criteria; number of patients randomised; characteristics of patients: age range (mean or median) and sex ratio; dose of bezafibrate, duration, frequency and mode of administration; type and dose of additional interventions; and outcomes at the end of treatment.

Assessment of risk of bias in included studies

The confidence that the design and the report of the randomised clinical trial would restrict bias in the comparison of the intervention defines methodological quality, and hence risk of bias, which we assessed using the following domains (Schulz 1995; Moher 1998; Kjaergard 2001; Gluud 2006; Wood 2008).

Allocation sequence generation

- Low risk of bias: sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice are adequate if performed by an independent adjudicator.
- Uncertain risk of bias: the trial is described as randomised, but the method of sequence generation was not specified.
- High risk of bias: the sequence generation method is not, or may not be, random. Quasi-randomised studies, those using dates, names, or admittance numbers in order to allocate patients are inadequate and will be excluded for the assessment of benefits but not for harms.

Allocation concealment

- Low risk of bias: allocation was controlled by a central and independent randomisation unit, sequentially numbered, opaque

and sealed envelopes or similar, so that intervention allocations could not have been foreseen in advance of, or during, enrolment.
- Uncertain risk of bias: the trial was described as randomised but the method used to conceal the allocation was not described, so that intervention allocations may have been foreseen in advance of, or during, enrolment.
- High risk of bias: if the allocation sequence was known to the investigators who assigned patients or if the study was quasi-randomised. Quasi-randomised studies will be excluded for the assessment of benefits but not for harms.

Blinding
- Low risk of bias: the trial was described as blinded, the parties that were blinded, and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial.
- Uncertain risk of bias: the trial was described as blind, but the method of blinding was not described, so that knowledge of allocation was possible during the trial.
- High risk of bias, the trial was not blinded, so that the allocation was known during the trial.

Incomplete outcome data
- Low risk of bias: the numbers and reasons for dropouts and withdrawals in all intervention groups were described or if it was specified that there were no dropouts or withdrawals.
- Uncertain risk of bias: the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated.
- High risk of bias: the number or reasons for dropouts and withdrawals were not described.

Selective outcome reporting
- Low risk of bias: pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
- Uncertain risk of bias: not all pre-defined, or clinically relevant and reasonably expected outcomes are reported on or are not reported fully, or it is unclear whether data on these outcomes were recorded or not.
- High risk of bias: one or more clinically relevant and reasonably expected outcomes were not reported on; data on these outcomes were likely to have been recorded.

Other bias
- Low risk of bias: the trial appears to be free of other components that could put it at risk of bias.
- Uncertain risk of bias: the trial may or may not be free of other components that could put it at risk of bias.
- High risk of bias: there are other factors in the trial that could put it at risk of bias, eg, for-profit involvement, authors have conducted trials on the same topic etc.

Trials assessed as having 'low risk of bias' in all of the specified individual domains were considered 'trials with low risk of bias'. Trials assessed as having 'uncertain risk of bias' or 'high risk of bias' in one or more of the specified individual domains were considered 'trials with high risk of bias' (Gluud 2011).

Measures of treatment effect

For dichotomous outcomes, we calculated the relative risk (RR) and/or risk difference (RD), and for continuous outcomes the mean difference (MD), all with 95% confidence intervals (CI). Mean differences based on changes from baseline can usually be assumed to be addressing exactly the same underlying intervention effects as analyses based on final measurements (Higgins 2011). Therefore, we combined data reported as change from baseline values with final measurement values in meta-analysis when using the mean difference method in RevMan.

Dealing with missing data

We planned to perform all analyses according to the intention-to-treat method including all participants irrespective of compliance or follow-up. However, we performed analyses according to the intention-to-treat method only for dichotomous outcomes. For continuous outcomes we performed available case analysis and included data only on those whose results were known.

Regarding the primary outcome measures we planned to include patients with incomplete or missing data in the sensitivity analyses by imputing them according to the below two scenarios (Hollis 1999; Gluud 2011).

- 'Best-worst' case scenario analyses: participants with missing outcome are considered successes in the experimental group and failures in the control group. The denominator will include all the participants in the trial.

- 'Worst-best' case scenario analyses: participants with missing outcome data are considered failures in the experimental group and successes in the control group. The denominator will include all the participants in the trial.

When such data would be available in the future, we will conduct such analyses.

Assessment of heterogeneity

We explored the presence of statistical heterogeneity by the chi-squared test with significance less than or equal to P 0.10 and measured the quantity of heterogeneity by I^2 (Higgins 2003).

Assessment of reporting biases

We intended to use funnel plot graphs in order to inform us of the likelihood of bias in the meta-analysis (Egger 1997; Macaskill 2001). We did not perform a funnel plot as we did not have the recommended minimal number of ten or more trials in any meta-analysis.

Data synthesis

We performed this review according to the recommendations of *The Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and the Cochrane Hepato-Biliary Group Module (Gluud 2011). For the statistical analyses, we used Review Manager 5.1 (RevMan 2011). We meta-analysed the data with both a random-effects model (DerSimonian 1986) and a fixed-effect model (DeMets 1987) to ensure robustness of the results. In case of significant differences of the results that the two models produced, we presented the result with both methods. We presented the results with the fixed-effect model if the results of the two models did not differ (Higgins 2002).

Complimentary analyses

Trial sequential analysis
In order to control for the risks of random errors due to sparse data and multiplicity, we performed trial sequential analysis (Brok

2008; Wetterslev 2008; Thorlund 2009). We calculated the required information size (ie, the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) (Wetterslev 2008). In our analysis, the required information size was based on the minimal relevant difference of a half standard deviation of the meta-analysis, the variance of the meta-analysis, a type I error of 5%, and a type II error of 20% (Wetterslev 2008). As default, diversity-adjusted required information size was used unless otherwise stated (Wetterslev 2008; Wetterslev 2009).

The underlying assumption of trial sequential analysis is that testing for significance may be performed each time a new trial is added to the meta-analysis. We added the trials according to the year of publication, and if more than one trial was published in a year, trials were added alphabetically according to the last name of the first author (Wetterslev 2008).

On the basis of the required information size, trial sequential monitoring boundaries were constructed (Wetterslev 2008). These boundaries determine the statistical inference one may draw regarding the cumulative meta-analysis that has not reached the required information size. If the trial sequential monitoring boundary is crossed before the required information size is reached, firm evidence may be established and further trials may turn out to be superfluous. On the other hand, if the boundary is not surpassed, it is most probably necessary to continue doing trials in order to detect or reject a certain intervention effect.

Subgroup analysis and investigation of heterogeneity

The following subgroup analyses were planned to compare:
- trials with low risk of bias compared to trials with high risk of bias;
- different doses of bezafibrate;
- different duration of administration of bezafibrate;
- patients treated for primary biliary cirrhosis with a drug different than bezafibrate before bezafibrate administration compared to patients with no pretreatment;
- patients with advanced compared to patients with non-advanced primary biliary cirrhosis.

RESULTS

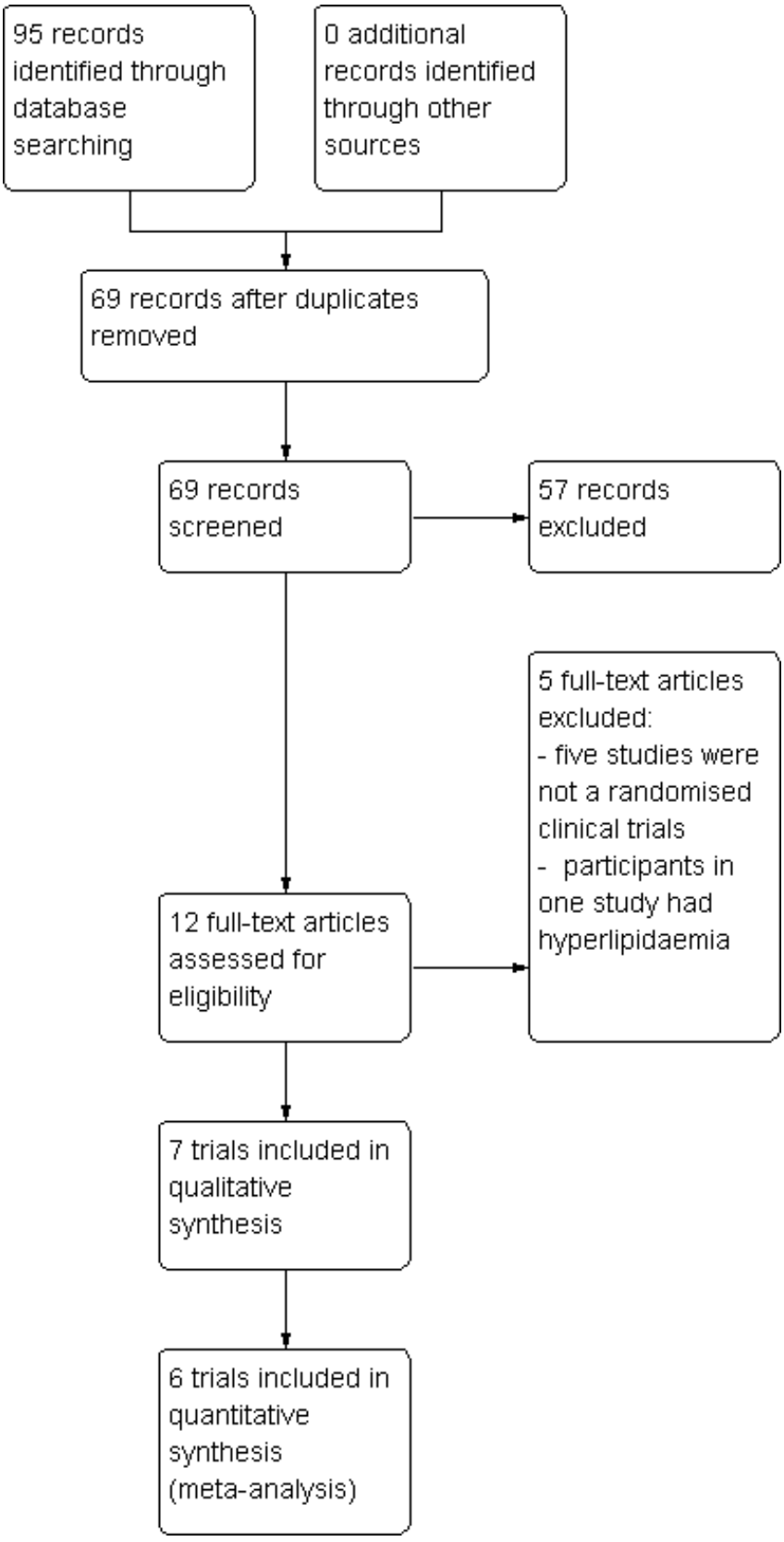
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

Our search strategy identified 95 publications, out of which 26 were duplicates. Of the remaining 69 publications, 57 were excluded, either because they were reviews or because they did not relate to primary biliary cirrhosis or because they did not describe a randomised clinical trial investigating the effect of bezafibrate in patients with primary biliary cirrhosis. Twelve full text articles were assessed for eligibility, out of which five were excluded with listed reasons (Figure 1).

Figure 1. Study flow diagram.



We identified a total of seven publications referring to six randomised clinical trials (Characteristics of included studies). Four trials were published as full text articles (Kanda 2003; Itakura 2004; Iwasaki 2008a; Iwasaki 2008b). One trial was published as an abstract and as a letter to the editor (Nakai 1999). Another trial was published only as a letter to the editor (Kurihara 2000). The primary authors were contacted for further information and data relating to the trials. Dr. Shinji Iwasaki kindly provided data on the method of sequence generation, the number of patients in each intervention group at the end of treatment, adverse events, and outcome measures (Iwasaki 2008a; Iwasaki 2008b). No other responses have so far been received.

We contacted manufacturers of bezafibrate and asked for any information about unpublished or on-going trials using bezafibrate involving patients with primary biliary cirrhosis. No responses have so far been received.

Through a search for ongoing trials in Clinicaltrials.gov (http://clinicaltrials.gov/) we have not identified any registered ongoing or planned trials. However, through a search for ongoing trials in the WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/), we identified one ongoing trial. This trial has been classified as an ongoing trial (Characteristics of ongoing studies).

Included studies

A total of 151 patients with primary biliary cirrhosis were randomised in the six randomised clinical trials. All trials were conducted in Japan. From the publications which reported sex of the patients, more than 86% were females. In four trials, all patients had non-advanced primary biliary cirrhosis according to inclusion and exclusion criteria (Kanda 2003; Itakura 2004; Iwasaki 2008a; Iwasaki 2008b). In two trials, no data about severity of primary biliary cirrhosis among the patients and the exclusion criteria were provided (Nakai 1999; Kurihara 2000). Five trials had the parallel group design (Nakai 1999; Kurihara 2000; Kanda 2003; Iwasaki 2008a; Iwasaki 2008b), and one trial had the cross-over group design (Itakura 2004). Four trials assessed bezafibrate plus ursodeoxycholic acid versus no intervention plus ursodeoxycholic acid (referenced as bezafibrate versus no intervention in the following) (Nakai 1999; Kanda 2003; Itakura 2004; Iwasaki 2008b), and two trials assessed bezafibrate versus ursodeoxycholic acid (Kurihara 2000; Iwasaki 2008a). Bezafibrate was given in a dose of 400 mg daily and ursodeoxycholic acid in a dose of 600 mg daily in all trials. In two trials duration of administration of bezafibrate was six months (Kanda 2003; Itakura 2004), and in four trials duration of administration of bezafibrate was 12 to 13 months (Nakai 1999; Kurihara 2000; Iwasaki 2008a Iwasaki 2008b). All the trials reported similar outcome measures: clinical events, changes in biochemical and immunological variables, and adverse events. None of the trials reported on quality of life or fatigue.

Excluded studies

Five studies were excluded; four studies were not randomised clinical trials (Iwasaki 1999; Miyaguchi 2000; Ohmoto 2001; Hazzan 2010), and in one study patients had hyperlipidaemia, not primary biliary cirrhosis (Fukuo 1996) (Characteristics of excluded studies).

Risk of bias in included studies

Risk of bias was assessed according to six components: allocation sequence generation; allocation concealment; blinding; handling of incomplete outcome data; selective outcome reporting; and other potential sources of bias. Of the six included trials, all trials were assessed as having high risk of bias (Nakai 1999; Kurihara 2000; Kanda 2003 ; Itakura 2004; Iwasaki 2008a; Iwasaki 2008b) (Figure 2). Our statistical analyses are, therefore, based only on trials with high risk of bias (Figure 3).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

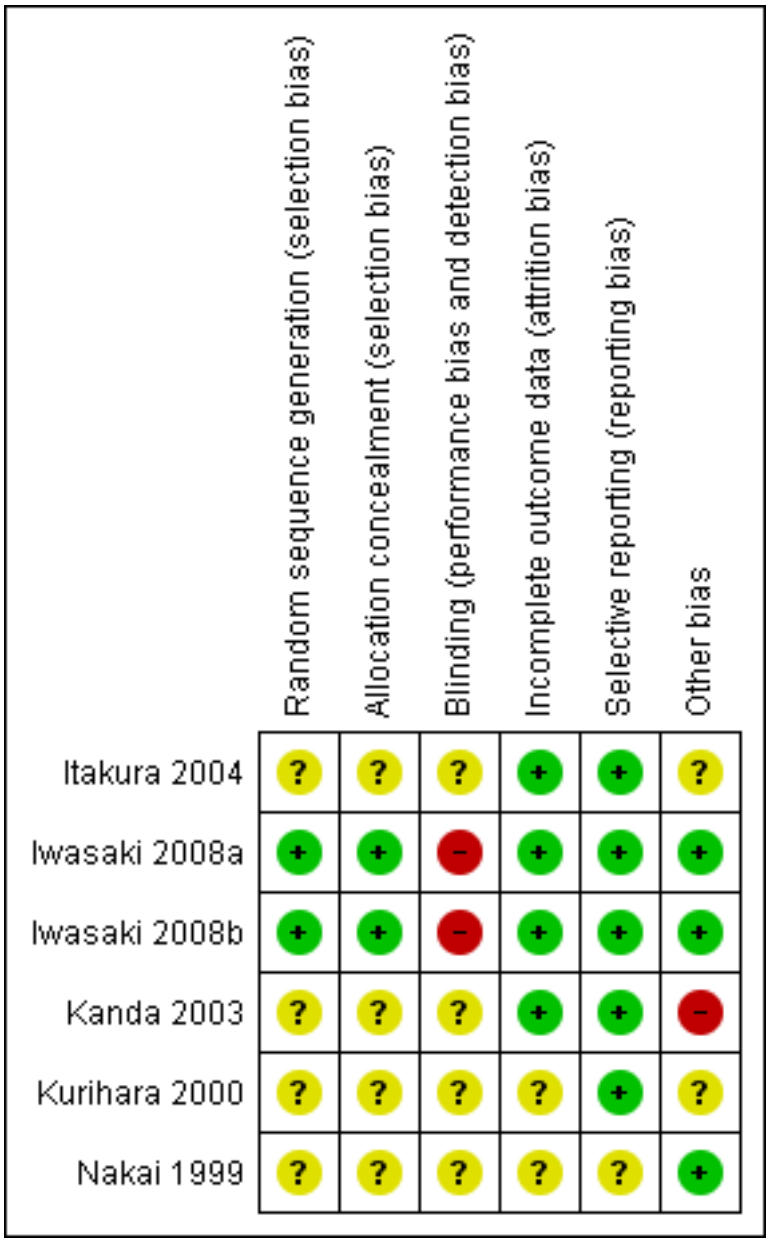
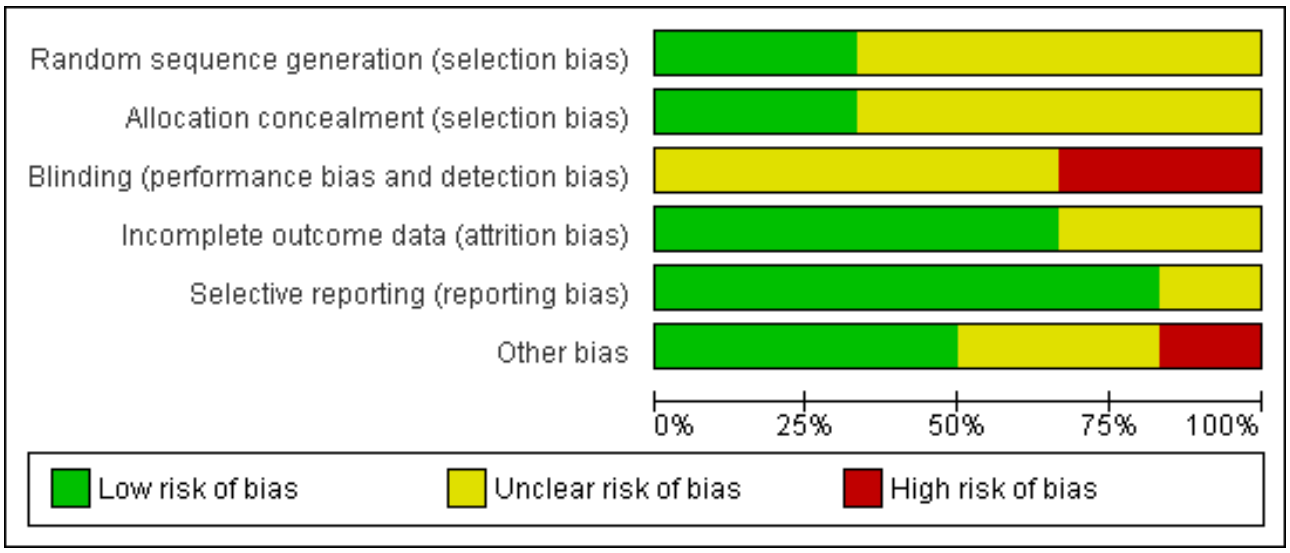


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Two trials described a "computer-generated random digits" block method for the generation of the randomisation allocation sequence (Iwasaki 2008a; Iwasaki 2008b). We judged the risk of bias due to the generation of the randomisation sequence as unclear in the remaining four trials (Nakai 1999; Kurihara 2000; Kanda 2003; Itakura 2004).

In two trials allocation concealment was controlled by a central and independent randomisation unit (Iwasaki 2008a; Iwasaki 2008b). Concealment of allocation and hence risk of bias was unclear in the other four trials (Nakai 1999; Kurihara 2000; Kanda 2003; Itakura 2004).

Blinding

Four trials did not address this component and likely have not been blinded (Nakai 1999; Kurihara 2000; Kanda 2003; Itakura 2004). Two trials reported that there was no suitable placebo for bezafibrate available, so the allocation was known during the trial (Iwasaki 2008a; Iwasaki 2008b). Accordingly, all six trials were considered of high risk of bias regarding this domain.

Incomplete outcome data

Four trials described withdrawals or dropouts from treatment (Kanda 2003; Itakura 2004; Iwasaki 2008a; Iwasaki 2008b). In two trials it was not specifically stated if there had been no dropouts or withdrawals (Nakai 1999; Kurihara 2000).

Selective reporting

The trial protocols were not available for any of the trials. However, five trials included expected outcomes (Kurihara 2000; Kanda 2003; Itakura 2004; Iwasaki 2008a; Iwasaki 2008b). In one trial we considered positively their reporting equalizing the term ‘’no adverse reaction’’ with ‘’no adverse event’’ (Kurihara 2000). Also, in three trials (Kurihara 2000; Kanda 2003; Itakura 2004), in their reporting about adverse events, we considered positively that no one died or developed liver-related complications when they reported ''no other adverse event was noted''. Only in one trial, it was reported that no side effects of bezafibrate had been noted, so we could not consider positively their reporting equalizing the term ‘’side effects’’ with ‘’adverse events’’ (Nakai 1999).

Other potential sources of bias

Three trials reported the following support: Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan (Nakai 1999), The Ministry of Health, Labour and Welfare of Japan with a Health Science Research Grant on a Specific Disease (Study of Intractable Liver Diseases) to chief scientist Gotaro Toda (Iwasaki 2008a; Iwasaki 2008b). In one trial it was reported that Kissei Pharmaceutical, Matsumoto, Japan provided bezafibrate, and Mitsubishi-Tokyo Pharmaceuticals, Tokyo, Japan supplied with ursodeoxycholic acid (Kanda 2003). Industrial sponsorship was not addressed in two trials (Kurihara 2000; Itakura 2004).

Effects of interventions

See: **Summary of findings for the main comparison** Bezafibrate compared with no intervention for primary biliary cirrhosis; **Summary of findings 2** Bezafibrate compared with ursodeoxycholic acid for primary biliary cirrhosis

See: Summary of findings for the main comparison; Summary of findings 2.

Bezafibrate versus no intervention

Three trials provided data on all-cause mortality, liver morbidity, adverse events, and number of patients having bezafibrate withdrawn due to adverse events (Kanda 2003; Itakura 2004; Iwasaki 2008b). Two trials provided data on the number of patients with pruritus (Kanda 2003; Itakura 2004). Four trials reported on the activity of serum alkaline phosphatases and serum gamma-glutamyltransferase (Nakai 1999; Kanda 2003; Itakura 2004; Iwasaki 2008b). Three trials reported on plasma immunoglobulin M concentration (Nakai 1999; Itakura 2004; Iwasaki 2008b). Two trials provided data on the activity of serum alanine aminotransferase,

total cholesterol, triglycerides, and serum bilirubin concentration (Itakura 2004; Iwasaki 2008b).

Primary outcomes

All-cause mortality
Bezafibrate did not demonstrate any significant effect on all-cause mortality (RD 0.00, 95% CI -0.11 to 0.11, I^2 = 0%) (Analysis 1.1). No deaths were reported in any of the two groups (0/32 versus 0/28 patients).

Liver-related morbidity
Bezafibrate had no significant effect on liver-related morbidity (RD 0.00, 95% CI -0.11 to 0.11, I^2 = 0%) (Analysis 1.2). Jaundice, upper gastrointestinal haemorrhage, ascites, hepatic encephalopathy, or hepato-renal syndrome occurred in 0/32 versus 0/28 patients in the bezafibrate and control groups.

Adverse events
Several adverse events were reported in the bezafibrate group of the included trials (polydipsia (Kanda 2003), serum creatine phosphokinase elevation, and myalgia (Iwasaki 2008b)). However, there was no statistically significant difference in the occurrence of adverse events in patients in the bezafibrate group versus the control group (5/32 versus 0/28 patients) (RR 5.40, 95% CI 0.69 to 42.32, I^2 = 0%) (Analysis 1.3).

For assessment of harm, besides the data provided by the three randomised trials (Kanda 2003; Itakura 2004; Iwasaki 2008b), we also considered the data from four non-randomised studies which reported on harm (Iwasaki 1999; Miyaguchi 2000; Ohmoto 2001; Hazzan 2010). In each of four studies it was reported that there were no adverse effects or side effects attributable to treatment (Characteristics of excluded studies).

Quality of life
No quality of life measurements were reported.

Secondary outcomes

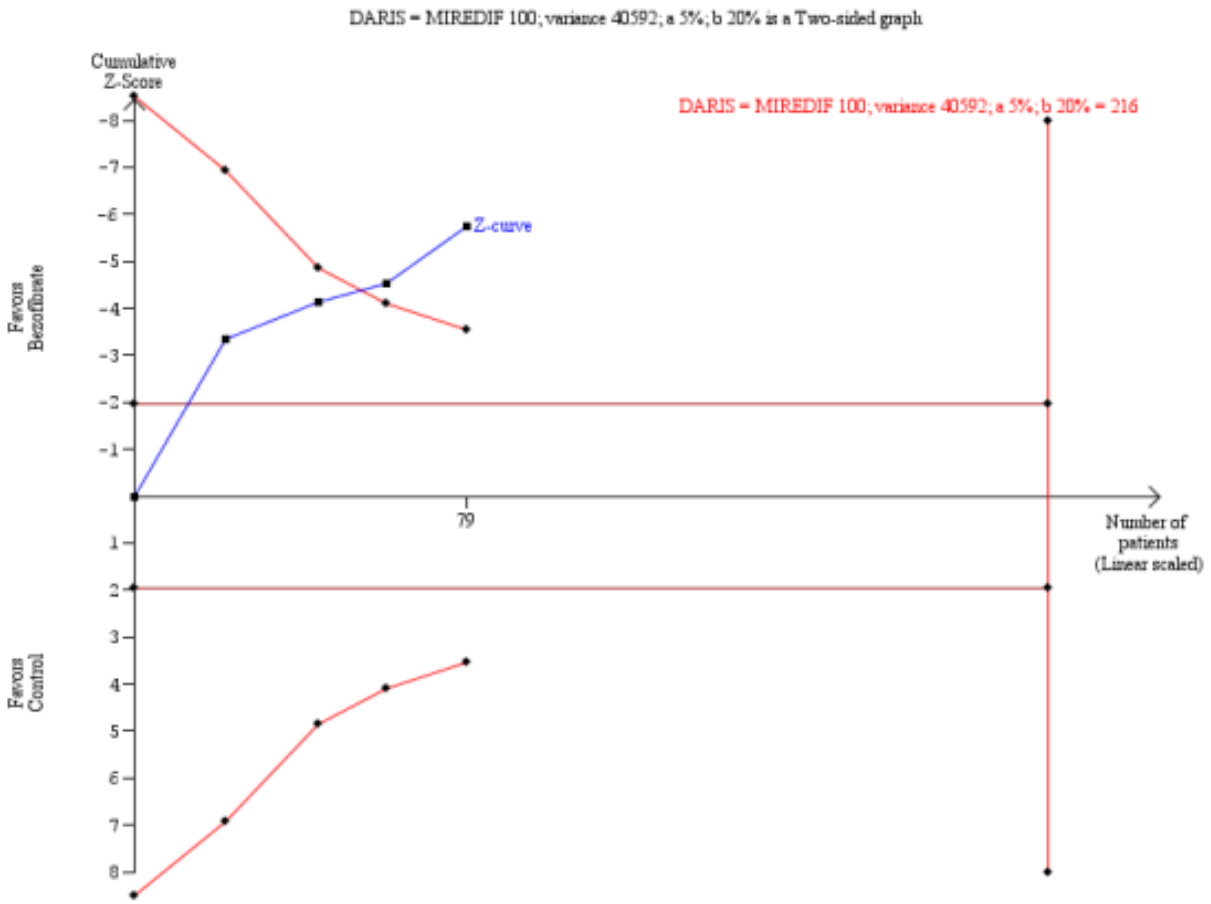
Pruritus
Bezafibrate did not significantly influence the number of patients with pruritus (RR 1.12, 95% CI 0.50 to 2.53, I^2 = 0%) (Analysis 1.4).

Fatigue
None of the trials reported on fatigue.

Biochemical indices
These data were reported either as change from baseline (Itakura 2004) or final values (Nakai 1999; Kanda 2003; Iwasaki 2008b). The data were reported either as means with standard deviations (Kanda 2003; Iwasaki 2008b) or as standard error of the mean; therefore, we converted them to standard deviation (Itakura 2004). In one trial we have judged whether standard error of the mean or standard deviation is reported in a data table in the trial report, based on the standard deviations for laboratory values at randomisation given in a data table from the other trial reports we included (Nakai 1999). The results reported in one trial were depicted graphically, and we extracted data from the graphs (Kanda 2003).

In fixed-effect meta-analysis, bezafibrate significantly decreased the activity of serum alkaline phosphatases (MD -186.04 U/L, 95% CI -249.03 to -123.04, I^2 = 34%) (Analysis 1.5). Trial sequential analysis of these data supports the finding in the meta-analysis (Figure 4). The result of the trial sequential analysis is shown by the cumulated Z-curve (blue curve) which crosses the trial sequential monitoring boundary (red curve) implying that there is firm evidence for a beneficial effect of 100 U/L decrease in the activity of serum alkaline phosphatases in the bezafibrate group (Figure 4).

Figure 4. Figure 4 . Trial sequential analysis of the cumulative meta-analysis of the effect of bezafibrate versus no intervention on the activity of serum alkaline phosphatases in patients with primary biliary cirrhosis. The diversity-adjusted required information size (DARIS) of 216 patients is calculated based on a minimal relevant intervention effect (MIREDIF) of 100 U/L, a standard deviation of 200 U/L, a risk of type I error of 5%, a power of 80%, and a diversity of 41%. The cumulated Z-curve (blue curve) crosses the trial sequential monitoring boundary (red curve) implying that there is firm evidence for a beneficial effect of 100 U/L decrease in the activity of serum alkaline phosphatases when the cumulative meta-analysis is adjusted for sparse data and multiple testing on accumulating data.



In fixed-effect meta-analyses, bezafibrate significantly decreased plasma immunoglobulin M (MD -164.00 mg/dl, 95% CI -259.47 to -68.53, I^2 = 46%) (Analysis 1.8) and serum bilirubin concentration (MD -0.19 mg/dl, 95% CI -0.38 to -0.00, I^2 = 0%) (Analysis 1.11). Trial sequential analyses on these data do not support the findings in Analysis 1.8 and Analysis 1.11. Even though the Z-curve (blue curve) lies in the direction of a decrease in plasma immunoglobulin M and serum bilirubin concentration in the bezafibrate group, it does not cross the trial sequential monitoring boundary, implying that there is no firm evidence for a beneficial effect of 121.5 mg/dl decrease in plasma immunoglobulin M concentration (Figure 5) and of 0.20 mg/dl decrease in serum bilirubin concentration (Figure 6).

Figure 5. Figure 5 . Trial sequential analysis of the cumulative meta-analysis of the effect of bezafibrate versus no intervention on concentration of plasma immunoglobulin M in patients with primary biliary cirrhosis. The diversity-adjusted required information size (DARIS) of 239 patients is calculated based on a minimal relevant intervention effect (MIREDIF) of 121.5 mg/dl, a standard deviation of 243 mg/dl, a risk of type I error of 5%, a power of 80%, and a diversity of 47%. The cumulated Z-curve (blue curve) does not cross the trial sequential monitoring boundary implying that there is no firm evidence for a beneficial effect of 121.5 mg/dl decrease in plasma immunoglobulin M concentration when the cumulative meta-analysis is adjusted for sparse data and multiple testing on accumulating data.

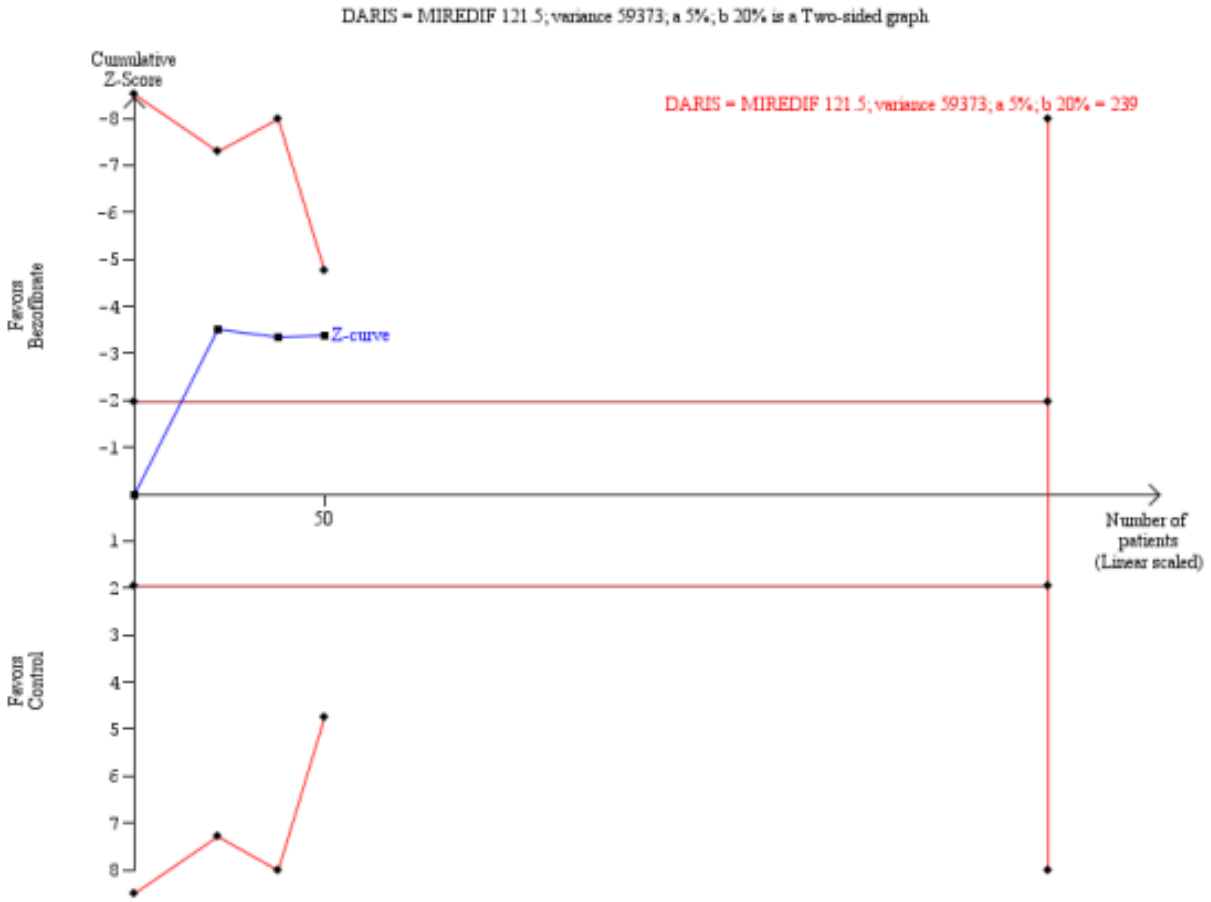
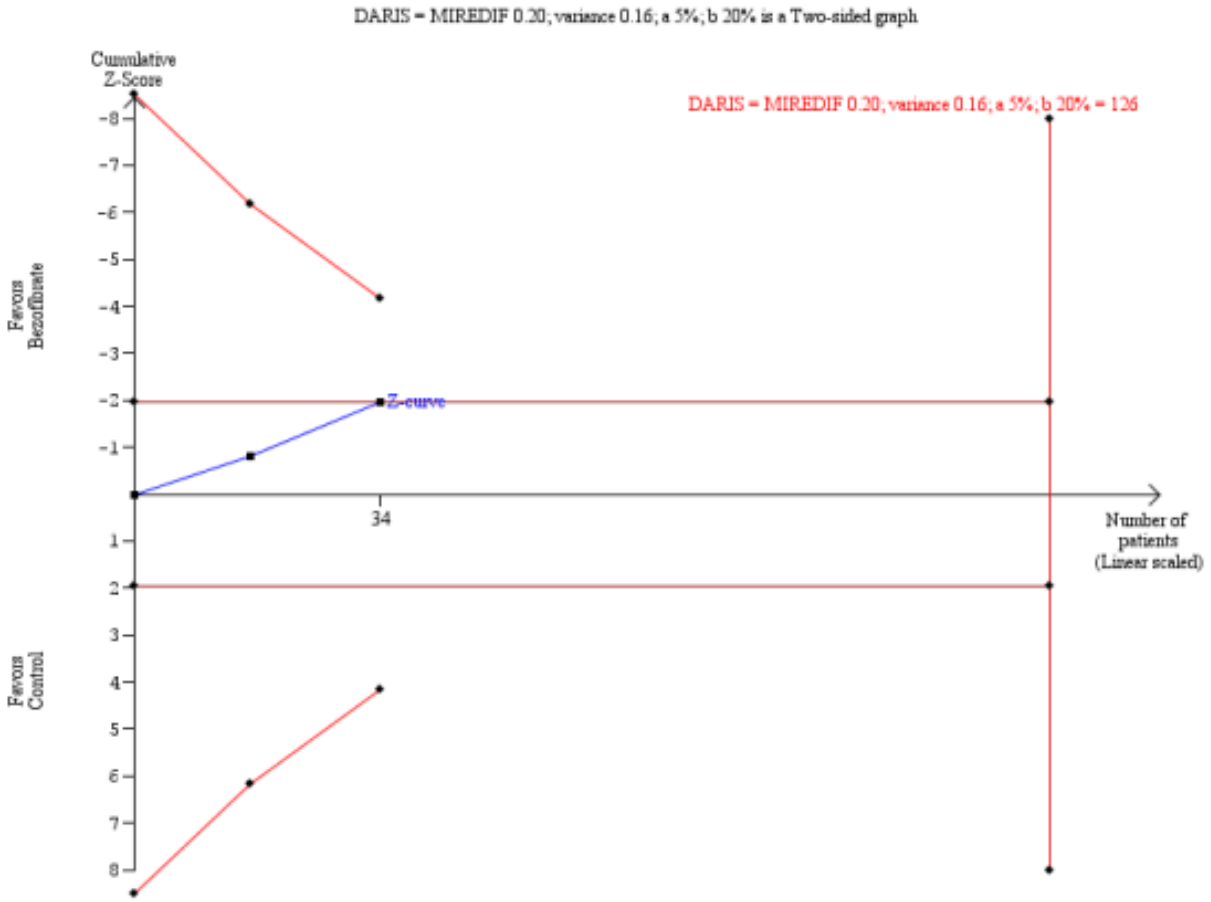


Figure 6. Figure 6 . Trial sequential analysis of the cumulative meta-analysis of the effect of bezafibrate versus no intervention on concentration of serum bilirubin concentration in patients with primary biliary cirrhosis. The diversity-adjusted required information size (DARIS) of 126 patients is calculated based on a minimal relevant intervention effect (MIREDIF) of 0.20 mg/dl, a standard deviation of 0.40 mg/dl, a risk of type I error of 5%, a power of 80%, and a diversity of 0%. The cumulated Z-curve (blue curve) does not cross the trial sequential monitoring boundary implying that there is no firm evidence for a potentially beneficial effect of 0.20 mg/dl decrease in serum bilirubin concentration when the cumulative meta-analysis is adjusted for sparse data and multiple testing on accumulating data.



In fixed-effect meta-analyses, bezafibrate had no significant effect on the activity of serum gamma-glutamyltransferase (MD -1.22 U/L, 95% CI -11.97 to 9.52, I^2 = 42%) (Analysis 1.6), serum alanine aminotransferase (MD -5.61 U/L, 95% CI -24.50 to 13.27, I^2 = 34%) (Analysis 1.7), total cholesterol (MD -12.51 mg/dl, 95% CI -32.65 to 7.64, I^2 = 82%) (Analysis 1.9), and triglyceride concentration (MD -20.12 mg/dl, 95% CI -47.73 to 7.49, I^2 = 1%) (Analysis 1.10).

Liver biopsy findings (histological stage of primary biliary cirrhosis)

No data about liver biopsy findings after bezafibrate administration were reported.

Number of patients having bezafibrate withdrawn due to adverse events

One patient had bezafibrate withdrawn due to an adverse event (RD 0.03, 95% CI -0.09 to 0.16, I^2 = 0%) (Analysis 1.12).

Bezafibrate versus ursodeoxycholic acid

Two trials provided data on all-cause mortality, liver-related morbidity, adverse events, number of patients having bezafibrate withdrawn due to adverse events, the activity of serum alkaline phosphatases, serum gamma-glutamyltransferase, serum alanine aminotransferase, and plasma immunoglobulin M concentration (Kurihara 2000; Iwasaki 2008a).

Primary outcomes

All-cause mortality

Bezafibrate did not demonstrate any significant effect on all-cause mortality (RD 0.00, 95% CI -0.08 to 0.08, I^2 = 0%) (Analysis 2.1). No deaths were reported in the bezafibrate or ursodeoxycholic acid groups (0/32 versus 0/37 patients).

Liver-related morbidity

Bezafibrate had no significant effect on liver morbidity (RD 0.00, 95% CI -0.08 to 0.08, I^2 = 0%) (Analysis 2.2). Jaundice, upper

gastrointestinal haemorrhage, ascites, hepatic encephalopathy, or hepato-renal syndrome occurred in 0/32 (0%) versus 0/37 (0%) patients in the bezafibrate and ursodeoxycholic acid groups.

Adverse events

A mild upper gastrointestinal pain was reported in the bezafibrate group (Iwasaki 2008a), but no discontinuation of bezafibrate administration occurred. However, there was no statistically significant difference in the occurrence of adverse events in patients in the bezafibrate group versus the ursodeoxycholic acid group (2/32 versus 0/37 patients) (RR 6.19, 95% CI 0.31 to 122.05) (Analysis 2.3).

Quality of life

No quality of life measurements were reported.

Secondary outcomes

Pruritus

None of the trials reported on pruritus.

Fatigue

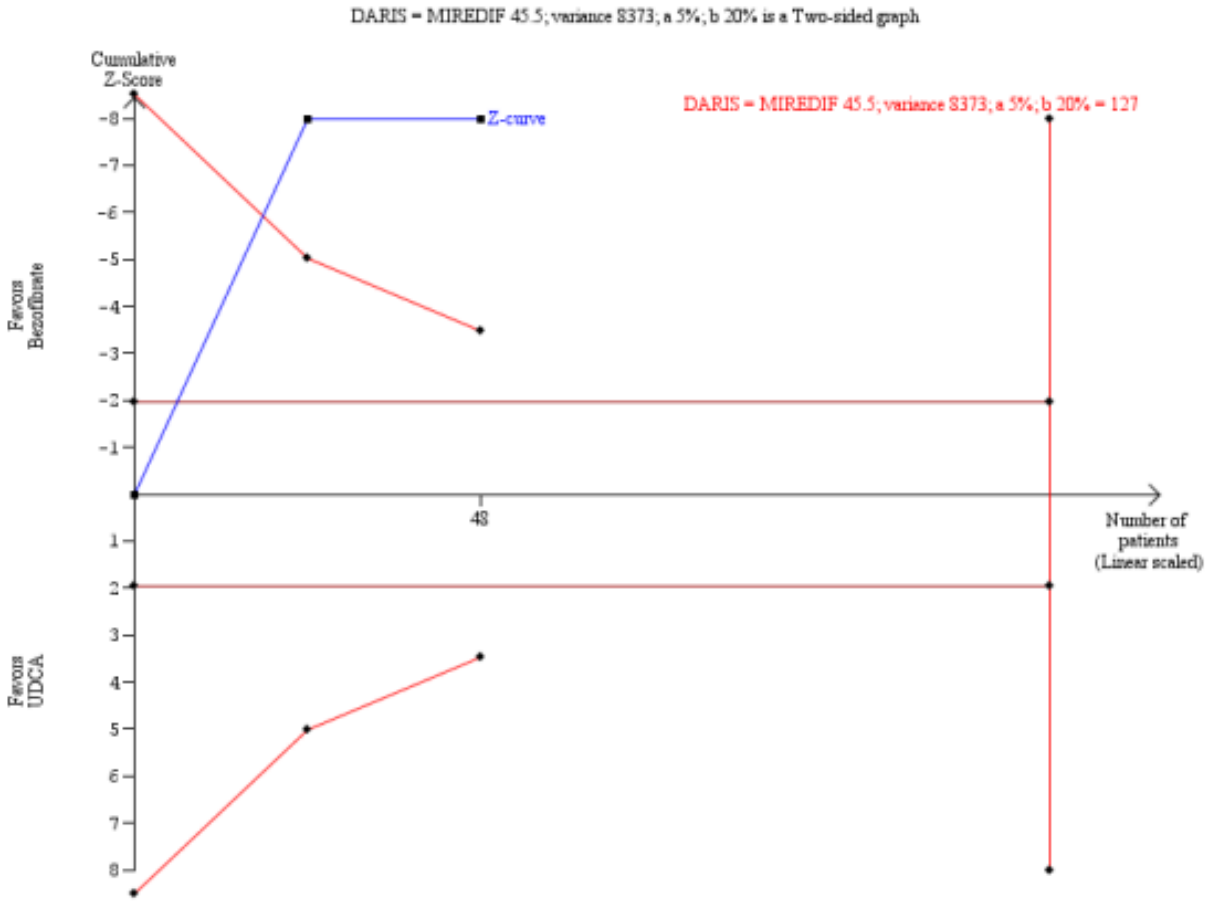
None of the trials reported on fatigue.

Biochemical indices

These data were reported either as change from baseline (Kurihara 2000) or final values (Iwasaki 2008a). The data were reported as means with standard deviations (Iwasaki 2008a) or as standard error of the mean; therefore, we converted them to standard deviation (Kurihara 2000). The results reported in one trial were depicted graphically, and we extracted data from the graphs (Kurihara 2000). The data were reported as the degree of change from baseline (%) (Kurihara 2000), and we extracted data as final values from the graphs.

In fixed-effect meta-analyses, bezafibrate significantly decreased the activity of serum alkaline phosphatases (MD -162.90 U/L, 95% CI -199.68 to -126.12, I^2 = 0%) (Analysis 2.4), serum gamma-glutamyltransferase (MD -58.18 U/L, 95% CI -76.49 to -39.88, I^2 = 89%) (Analysis 2.5), serum alanine aminotransferase (MD -58.18 U/L, 95% CI -76.49 to -39.88, I^2 = 95%) (Analysis 2.6), and plasma immunoglobulin M concentration (MD -99.90 mg/dl, 95% CI -130.72 to -69.07, I^2 = 90%) (Analysis 2.7). Trial sequential analysis of these data supports the finding in the meta-analysis of activity of serum alkaline phosphatases Analysis 2.4. The result of the trial sequential analysis is shown by the cumulated Z-curve (blue curve) which crosses the trial sequential monitoring boundary (red curve) implying that there is firm evidence for a beneficial effect of 45.5 U/L decrease in the activity of serum alkaline phosphatases in the bezafibrate group (Figure 7).

Figure 7. Figure 7 . Trial sequential analysis of the cumulative meta-analysis of the effect of bezafibrate versus ursodeoxycholic acid on the activity of serum alkaline phosphatases in patients with primary biliary cirrhosis. The diversity-adjusted required information size (DARIS) of 127 patients is calculated based on a minimal relevant intervention effect (MIREDIF) of 45.5 U/L, a standard deviation of 91 U/L, a risk of type I error of 5%, a power of 80%, and a diversity of 0%. The cumulated Z-curve (blue curve) crosses the trial sequential monitoring boundary (red curve) implying that there is firm evidence for a beneficial effect of 45.5 U/L decrease in the activity of serum alkaline phosphatases when the cumulative meta-analysis is adjusted for sparse data and multiple testing on accumulating data.



In random-effect meta-analyses, bezafibrate had no significant effect on the activity of serum gamma-glutamyltransferase (MD 38.44 U/L, 95% CI -180.67 to 257.55, I^2 = 89%), serum alanine aminotransferase (MD -2.34 U/L, 95% CI -34.73 to 30.06, I^2 = 95%), and plasma immunoglobulin M concentration (MD -20.23 mg/dl, 95% CI -218.71 to 178.25, I^2 = 90%).

Liver biopsy findings (histological stage of primary biliary cirrhosis)

No data about liver biopsy findings after bezafibrate administration were reported.

Number of patients having bezafibrate withdrawn due to adverse effects

No patient had bezafibrate withdrawn due to adverse effects (RD 0.00, 95% CI -0.08 to 0.08, I^2 = 0%) (Analysis 2.8).

Subgroup analyses

Only a subgroup analysis on different durations of administration of bezafibrate was performed. Due to the paucity of trials none of the other planned analyses could be conducted.

Subgroup analysis on trials with low risk of bias compared to trials with high risk of bias

All included trials were judged to be at high risk of bias (Figure 2). As such, a subgroup analysis comparing trials with low risk of bias to trials with high risk of bias was not possible.

Subgroup analysis on different doses of bezafibrate

Bezafibrate was given as one single dose of 400 mg in four trials; three trials assessing bezafibrate versus no intervention (Nakai 1999; Itakura 2004; Iwasaki 2008b) and in one trial assessing bezafibrate with ursodeoxycholic acid (Iwasaki 2008a). Bezafibrate was divided into two orally administered doses, a post-breakfast and a post-dinner dose of 200 mg, in one trial assessing bezafibrate

versus no intervention (Kanda 2003) and in another trial assessing bezafibrate with ursodeoxycholic acid (Kurihara 2000). As such, a subgroup analysis comparing different doses of bezafibrate was not possible.

Subgroup analysis on duration of administration of bezafibrate
Subgroup analysis was performed in order to compare the duration of bezafibrate administration. Bezafibrate was administered for six months in two trials (Kanda 2003; Itakura 2004) and for 12 to 13 months in another two trials (Nakai 1999; Iwasaki 2008b).

According to our subgroup analyses, the duration of bezafibrate administration did not influence the serum alkaline phosphatases activity (MD -141.97 U/L, 95% CI -228.30 to -55.64, I^2 = 56% compared to MD -236.23 U/L, 95% CI -328.35 to -144.10, I^2 = 0%; test of interaction Chi^2 = 2.14; P = 0.14) (Analysis 1.5), nor did it influence the serum gamma-glutamyltransferase activity (MD -1.23 U/L, 95% CI -12.17 to 9.72, I^2 = 66% compared to MD -1.20 U/L, 95% CI -56.79 to 54.39, I^2 = 55%; test of interaction Chi^2 = 0.00; P = 1.00) (Analysis 1.6).

Subgroup analysis on patients treated for primary biliary cirrhosis with a different drug before bezafibrate administration compared to patients with no pretreatment
In five trials patients were treated with ursodeoxycholic acid before bezafibrate was administrated (Nakai 1999; Kanda 2003; Itakura 2004; Iwasaki 2008a; Iwasaki 2008b). In one trial there are no data about pretreatment of patients (Kurihara 2000). As such, a subgroup analysis on patients treated for primary biliary cirrhosis with a drug different than bezafibrate before bezafibrate administration compared to patients with no pretreatment was not possible. Duration of ursodeoxycholic acid administration was different in each trial: one year or more (Nakai 1999); at least six months (Kanda 2003); and more than 26 weeks (Iwasaki 2008b). In one trial three patients received treatment with ursodeoxycholic acid for 2 to 11 years, but before entry into this trial, patients discontinued the use of ursodeoxycholic acid for at least three months (Itakura 2004). In one trial it was only reported that not all patients had been treated with ursodeoxycholic acid or bezafibrate within the previous four weeks (Iwasaki 2008a).

Subgroup analysis on patients with advanced compared to patients with non-advanced primary biliary cirrhosis
A subgroup analysis on patients with advanced primary biliary cirrhosis compared to patients with non-advanced primary biliary cirrhosis was not possible.

DISCUSSION

Summary of main results

We identified six trials assessing the effects of bezafibrate in patients with primary biliary cirrhosis. All trials had high risk of bias. Bezafibrate did not demonstrate any significant effect on mortality, liver-related morbidity, or adverse events when compared with no intervention, or when compared with ursodeoxycholic acid. Bezafibrate did not demonstrate any significant effect on pruritus compared with no intervention. It was not possible to evaluate changes in quality of life and fatigue since none of the trials reported these outcome measures.

Bezafibrate significantly decreased the activity of serum alkaline phosphatases compared with no intervention. The results of trial sequential analysis imply that there is firm evidence for a beneficial effect of 100 U/L decrease in the activity of serum alkaline phosphatases in the bezafibrate group. Bezafibrate significantly decreased plasma immunoglobulin M and serum bilirubin concentration compared with no intervention. However, the results of trial sequential analysis imply that there is no firm evidence for a beneficial effect of 121.5 mg/dl decrease in plasma immunoglobulin M concentration and of 0.20 mg/dl decrease in serum bilirubin concentration in the bezafibrate group. Bezafibrate did not seem to have significant effect on the activity of serum gamma-glutamyltransferase, serum alanine aminotransferase, total cholesterol, and triglyceride concentration compared with no intervention.

Bezafibrate significantly decreased the activity of serum alkaline phosphatases compared with ursodeoxycholic acid. The results of trial sequential analysis imply that there is firm evidence for a beneficial effect of 45.5 U/L decrease in the activity of serum alkaline phosphatases in the bezafibrate group. Bezafibrate significantly decreased the activity of serum gamma-glutamyltransferase, serum alanine aminotransferase, and plasma immunoglobulin M concentration compared with ursodeoxycholic acid in fixed-effect model meta-analyses. However, these latter findings were not confirmed when using random-effect model meta-analyses.

One patient discontinued bezafibrate administration due to an adverse event.

Overall completeness and applicability of evidence

This systematic review examined the evidence from six included randomised clinical trials for the use of bezafibrate in patients with primary biliary cirrhosis. We could not obtain all relevant data regarding all reasonably expected outcomes, as the trials identified insufficiently addressed all of the objectives of our review.

Five trials reported on mortality, liver morbidity, and adverse events, and the results were inconclusive. The lack of significant differences in mortality, liver morbidity, and adverse events may be related to the small number of patients involved and the short duration of the trials.

Most of the included trials reported on biochemical and immunological indices. These data were reported either as change from baseline or final values, so we combined them in our meta-analysis using mean difference method in RevMan. Mean differences based on changes from baseline can usually be assumed to be addressing exactly the same underlying intervention effects as analyses based on final measurements (Higgins 2011).

Quality of the evidence

We conducted this review according to *The Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and the Cochrane Hepato-Biliary Group Module (Gluud 2011). The results of our meta-analysis, however, are only as strong as the primary trials included.

The main limitations in the design and implementation was the lack of clarity of reporting on mortality, liver morbidity, and adverse events as well as the lack of clarity of the generation of allocation sequence, concealment of allocation, blinding, length of follow-up, and the small number of patients enrolled in the trials.

We explored the presence of statistical heterogeneity by the chi-squared test and measured the quantity of heterogeneity by I^2 (Higgins 2003). The chi-squared test has low power in the situation of a meta-analysis when trials have small sample size or are few in number as in our included trials. This means that while a statistically significant result may indicate a problem with heterogeneity, a non-significant result must not be taken as evidence of no heterogeneity. This is also why we used a P value of 0.10 to determine statistical significance regarding heterogeneity. To reflect our concern with heterogeneity, we looked at both fixed-effect and random-effects models in order to provide more conservative estimates of effect. Although the statistical heterogeneity of the analysis showing that bezafibrate significantly decreased the activity of serum alkaline phosphatases compared with no intervention was high, I^2 = 34%, there was no discrepancy in the results using either the fixed-effect or random-effects model. Also, the results of trial sequential analysis confirmed a beneficial effect of bezafibrate on decreasing the activity of serum alkaline phosphatases in the bezafibrate group, so there should be no risk of random error. However, we performed available case analysis for all continuous outcomes including data only on those patients whose results were known. Variation in the degree of missing data may also be considered as a potential source of bias and heterogeneity in our analyses.

Regarding precision of our results, included trials in our meta-analysis include few patients and few events and thus have wide confidence intervals around the estimate of effect.

Potential biases in the review process

In this systematic review a comprehensive literature search was performed, inclusion and exclusion criteria were specified, and data analysis was conducted. A potential limitation of our approach may be that we have not specifically searched for trials in the grey literature which may have introduced a slight risk of bias into our meta-analysis (Egger 2003). This bias, however, is unlikely to influence our results in a beneficial way as trials found in grey literature rarely report beneficial effects.

Risk of bias is known to impact the estimated intervention effect, with trials of a high risk of bias tending to overestimate the beneficial intervention effects (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008). Of the six included trials, two (33%) reported adequate allocation sequence generation and adequate allocation concealment, none (0%) was blinded, four (67%) adequately addressed incomplete data, five (83%) reported on clinically relevant and reasonably expected outcomes, and three (50%) appeared to be free of other components that could put them at risk of bias. Accordingly, all trials were at high risk of bias. Therefore, the estimated intervention effect for all significant beneficial effects may possibly be due to systematic errors.

Another limitation of this review is that all six included trials had a small sample size, with an average of 25 patients with primary biliary cirrhosis. Small trials have less power, meaning that there is less chance of detecting a small but true effect as statistically significant (Kjaergard 2001). The risk of random error is higher when data come from small information sizes (or 'sample sizes' for individual trials), so information sizes need to be sufficiently large in order to reduce the risk of random error and increase the chance of observing a true intervention effect (Brok 2008; Wetterslev 2008). This is one reason that we also analysed the data using trial sequential analysis. Trial sequential analysis is a statistical method which controls for random error caused by sparse data and formal, or informal repetitive testing of accumulating data.

According to the results of trial sequential analysis, there seem to be firm evidence for a beneficial effect of bezafibrate on decreasing the activity of serum alkaline phosphatases in patients with primary biliary cirrhosis compared with no intervention or with ursodeoxycholic acid when the cumulative meta-analysis is adjusted for sparse data and multiple testing on accumulating data. However, this beneficial effect may still be due to systematic errors, as estimated intervention effect for the activity of serum alkaline phosphatases was calculated using data from trials which were all assessed as having 'high risk of bias'. Additionally, trial sequential analysis provides us with important information regarding the need for additional trials and the required information size.

At present, we do not yet know if alkaline phosphatases is a valid surrogate outcome measure in patients with primary biliary cirrhosis. The assumption is that alkaline phosphatases may act as a surrogate outcome measure for efficacy of therapy on clinical and patient-relevant outcome measures. This assumption, however, needs to be confirmed in trials and systematic reviews of trials assessing both the activity of alkaline phosphatases and clinical and patient-relevant outcome measures (Gluud 2007). Therefore, nobody knows whether the decreasing effect of bezafibrate on serum alkaline phosphatases can be turned into any beneficial clinical effect.

All trials dealt with patients of Japanese decent. We have no knowledge if ethnicity or race plays a role when treating patients with primary biliary cirrhosis.

Agreements and disagreements with other studies or reviews

We could not compare our results with the results from other systematic reviews or meta-analysis, as we could not identify any meta-analyses or systematic reviews assessing bezafibrate in primary biliary cirrhosis.

AUTHORS' CONCLUSIONS

Implications for practice

We found no evidence to support or refute an effect of bezafibrate on mortality, liver morbidity, adverse events, pruritus, and fatigue in patients with primary biliary cirrhosis. Our results suffer from both risks of systematic errors (bias) and random errors (play of chance).

Bezafibrate seems to have an effect on decreasing the activity of serum alkaline phosphatases compared with no intervention or with ursodeoxycholic acid in patients with primary biliary cirrhosis with no risk of random error, but we lack data from trials with low risk of bias.

Accordingly, treatment of primary biliary cirrhosis with bezafibrate can neither be supported nor refuted based on the best current evidence available ensuing from trials in Japanese patients.

Implications for research

Randomised clinical trials which assess bezafibrate versus placebo in primary biliary cirrhosis with larger sample sizes and minimised risk of bias are needed. Multi-centre trials would be appropriate for patient recruitment as primary biliary cirrhosis is a relatively rare disease. Such trials ought to be reported according to the CONSORT guidelines (http://www.consort-statement.org/).

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Protocol
Peer Reviewers: Sombat Treeprasertsuk, Thailand; Jane R. Campos, Philippines; A. Galbois, France; Luit Penninga, Denmark.
Contact Editor: Rosa Simonetti, Italy.

Review
Peer Reviewers: Jun Itakura, Japan; Luit Penninga, Denmark.
Contact Editor: Rosa Simonetti, Italy.

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* Nakai S, Masaki T, Morita T, Deguchi A, Nishioka M. The effect of bezafibrate in patients with primary biliary cirrhosis [abstract]. Hepatology 1999; Vol. 30, issue 4:566A.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Itakura 2004

Methods	Randomised clinical trial with cross-over group design (two interventions groups). Trial duration: six months.
Participants	Country: Japan. Number of patients randomised: 16, median age 54/61 years (89%/57% females). Inclusion criteria: - at least a 1.3-fold elevated alkaline phosphatase level; - at least a 40-fold positive excess of anti-mitochondrial antibodies; - liver-biopsy proven primary biliary cirrhosis. Exclusion criteria: - histological overlapping with autoimmune hepatitis; - positive serum antigen or antibody associated with the hepatitis B virus; - positive serum antibody of hepatitis C virus; - positive serum antibody of human immunodeficiency virus; - history of drinking excessive amounts of alcohol or drug use; - ascites or oesophageal varices; - renal insufficiency; - cardiac failure; - hepatocellular carcinoma.
Interventions	Patients were randomly assigned to receive: Intervention group 1: bezafibrate (400 mg per day) and ursodeoxycholic acid (600 mg per day), n = 9; Intervention group 2: ursodeoxycholic acid alone (600 mg per day), n = 7. Three patients received treatment with ursodeoxycholic acid for 2 to 11 years, but before entry into the trial, they had discontinued the use of ursodeoxycholic acid for at least three months.
Outcomes	Outcome measure(s): - clinical events; - laboratory data (serum alkaline phosphatases, serum gamma-glutamyltransferase, serum alanine aminotransferase, IgM, total serum bilirubin, and total cholesterol and triglyceride levels); - adverse events.
Notes	Additional information requested on 17th February 2011, but no response has been received so far. We have used the data from the first period of the cross-over trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial is described as randomised, but the method of sequence generation was not specified.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation was not described, so that intervention allocations may have been foreseen in advance of or during enrolment.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The trial did not provide information for assessment of this domain, but it is not likely to have been blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	All expected outcomes are reported.
Other bias	Unclear risk	Industrial sponsorship was not addressed.

Iwasaki 2008a

Methods	Multicenter randomised clinical trial with parallel group design (two interventions groups). Trial duration: 52 weeks.
Participants	Country: Japan. Number of patients randomised: 45, mean age 55 years (82% females). Inclusion criteria: - a medical history and laboratory tests consistent with chronic cholestatic liver disease; - positive antimitochondrial antibody or antipyruvate dehydrogenase complex (PDC); - serum alkaline phosphatases elevation of at least 1.5 times the upper limit of normal; - the absence of biliary tract obstruction on imaging results; - hyperlipoproteinaemia. Exclusion criteria: - treatment with D-penicillamine, corticosteroids, colchicine or immunosuppressive agents within 4 weeks; - diagnosis of cirrhosis; - diuretic-resistant ascites, hepatic encephalopathy, haemorrhage from oesophageal or gastric varices; - hyperbilirubinaemia (greater than 5.0 mg/dL); - serum albumin level less than 3.0 g/dL; - renal insufficiency; - malignancy; - pregnancy; - below 19 years of age.
Interventions	Patients were randomly assigned to receive: Intervention group 1: bezafibrate (400 mg daily orally), n = 20; Intervention group 2: ursodeoxycholic acid (orally at a dose of 600 mg daily), n = 25. All patients had not been treated with ursodeoxycholic acid or bezafibrate within the previous four weeks.
Outcomes	Outcome measure(s): - clinical events; - laboratory data (serum alkaline phosphatases, serum gamma-glutamyltransferase, serum alanine aminotransferase, IgM, total serum bilirubin, and total cholesterol and triglyceride levels); - adverse events.
Notes	Additional information requested on 14th February 2011 and reply received on 16th February 2011 through personal communication with the principal author Dr. Shinji Iwasaki. Dr. Shinji Iwasaki provided data on the following: - the method of sequence generation; - the number of patients in each intervention group at the end of treatment; - tables with numeric values for biochemical indices; - adverse events; - all-cause mortality and liver-related morbidity.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	It was generated by block method using computer-generated random digits.
Allocation concealment (selection bias)	Low risk	Allocation was controlled by a central and independent randomisation unit, so that intervention allocations could not have been foreseen in advance of, or during enrolment.

Iwasaki 2008a *(Continued)*

Blinding (performance bias and detection bias) All outcomes	High risk	The trial was not blinded, so that the allocation was known during the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	All expected outcomes are reported.
Other bias	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Iwasaki 2008b

Methods	Multicenter randomised clinical trial with parallel group design (two interventions groups). Trial duration: 52 weeks.
Participants	Country: Japan. Number of patients randomised: 22, mean age 54 years (86.4% females). Inclusion criteria: - a medical history and laboratory tests consistent with chronic cholestatic liver disease; - positive antimitochondrial antibody or antipyruvate dehydrogenase complex (PDC); - serum alkaline phosphatases elevation of at least 1.5 times the upper limit of normal after treatment with ursodeoxycholic acid for more than 26 weeks before the study started; - the absence of biliary tract obstruction on imaging results; - hyperlipoproteinaemia. Exclusion criteria: - treatment with D-penicillamine, corticosteroids, colchicine or immunosuppressive agents within 4 weeks; - diagnosis of cirrhosis; - diuretic-resistant ascites, hepatic encephalopathy, haemorrhage from oesophageal or gastric varices; - hyperbilirubinaemia (greater than 5.0 mg/dL); - serum albumin level less than 3.0 g/dL; - renal insufficiency; - malignancy; - pregnancy; - below 19 years of age.
Interventions	Patients were randomly assigned to receive: Intervention group 1: bezafibrate plus ursodeoxycholic acid, n = 12; Intervention group 2: ursodeoxycholic acid, n = 10. Ursodeoxycholic acid was given orally at a dose of 600 mg daily, and bezafibrate was given at a dose of 400 mg daily for 52 weeks. All patients were treated with ursodeoxycholic acid for more than 26 weeks before the trial start.
Outcomes	Outcome measure(s): - clinical events; - laboratory data (serum alkaline phosphatases, serum gamma-glutamyltransferase, serum alanine aminotransferase, IgM, total serum bilirubin, and total cholesterol and triglyceride levels); - adverse events.
Notes	Additional information requested on 14th February 2011 and reply received on 16th February 2011 through personal communication with the principal author Dr. Shinji Iwasaki.

Iwasaki 2008b *(Continued)*

Dr. Shinji Iwasaki provided data on the following:

- the method of sequence generation;
- the number of patients in each intervention group at the end of treatment;
- tables with numeric values for biochemical indices;
- adverse events;
- all-cause mortality and liver-related morbidity.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	It was generated by block method using computer-generated random digits.
Allocation concealment (selection bias)	Low risk	Allocation was controlled by a central and independent randomisation unit, so that intervention allocations could not have been foreseen in advance of, or during enrolment.
Blinding (performance bias and detection bias) All outcomes	High risk	The trial was not blinded, so that the allocation was known during the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for dropouts and withdrawals in all intervention groups were described.
Selective reporting (reporting bias)	Low risk	All clinically relevant and reasonably expected outcomes are reported on.
Other bias	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Kanda 2003

Methods	Randomised clinical trial with parallel group design (two interventions groups). Trial duration: six months.
Participants	Country: Japan. Number of patients randomised: 22, mean age 56 years (86% females). Inclusion criteria: elevated serum alkaline phosphatases level despite receiving 600 mg/day of ursodeoxycholic acid, liver-biopsy proven primary biliary cirrhosis, no positive serum antigen or antibody associated with the hepatitis B virus, no positive serum antibody of hepatitis C virus, human immunodeficiency virus negativity, no other cause of liver disease (such as excessive amount of alcohol use, metabolic disorders or drug-induced liver injury), no ascites, hepatic encephalopathy, oesophageal varices, or hyperbilirubinaemia (total bilirubin ≥ 2.0 mg/dl), no previous treatment with colchicine, corticosteroids, or immunosuppressive drugs, no thyroid dysfunction or renal insufficiency (serum creatine level ≥ 2.0 mg/dl), and prior compliance with ursodeoxycholic acid therapy. Exclusion criteria: none listed.
Interventions	Patients were randomly assigned to receive: Intervention group 1: bezafibrate (400 mg per day of bezafibrate divided into two orally administered doses, post-breakfast and post-dinner), plus 600 mg per day of ursodeoxycholic acid divided into three orally administered post-meal doses), n = 11. Bezafibrate was administrated for a period of six months. Intervention group 2: 600 mg per day of ursodeoxycholic acid divided into three orally administered post-meal doses, n = 11. All patients had been treated with 600 mg per day of ursodeoxycholic acid for at least six months.

Kanda 2003 *(Continued)*

	All patients were given 600 mg per day of ursodeoxycholic acid in the same manner before, during, and after the 6-month period of administration of bezafibrate.
Outcomes	Outcome measure(s): - clinical variables (pruritus, ascites, upper gastrointestinal bleeding, and hepatic encephalopathy); - biochemical variables (serum alkaline phosphatases and serum gamma-glutamyltransferase levels); - adverse events.
Notes	Additional information requested on 16th February 2011, but no response has been received so far.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial is described as randomised, but the method of sequence generation was not specified.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation was not described, even though the trial was described as randomised and intervention allocations may have been foreseen in advance of, or during, enrolment.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The trial did not provide information for assessment of this domain, but it is not likely to have been blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	It was specified that all patients participated until the end of the trial.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
Other bias	High risk	It was reported that Kissei Pharmaceutical, Matsumoto, Japan provided bezafibrate, and Mitsubishi-Tokyo Pharmaceuticals, Tokyo, Japan supplied with ursodeoxycholic acid.

Kurihara 2000

Methods	Randomised clinical trial with parallel group design (two interventions groups). Trial duration: 12 months.
Participants	Country: Japan. Number of patients randomised: 24, mean age 60 years (95.8% females). Inclusion criteria: patients with liver biopsy proven primary biliary cirrhosis. Exclusion criteria: none listed.
Interventions	Patients were randomly assigned to receive: Intervention group 1: bezafibrate (400 mg per day of bezafibrate divided into two orally administered doses, 200 mg was taken in the morning and 200 mg in the evening), n = 12; Intervention group 2: 600 mg per day of ursodeoxycholic acid divided into three orally administered doses (200 mg was taken in the morning, afternoon, and evening), n = 12. Both drugs were taken for 12 months.
Outcomes	Outcome measure(s): - biochemical variables (serum alkaline phosphatases, serum gamma-glutamyltransferase levels, serum alanine aminotransferase, and IgM levels);

Kurihara 2000 *(Continued)*

	- adverse events.
Notes	Additional information requested on 18th February 2011, and no response has been received so far.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial is described as randomised, but the method of sequence generation was not specified.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation was not described, so that intervention allocations may have been foreseen in advance of, or during enrolment.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The trial did not provide information for assessment of this domain, but it is not likely to have been blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was not specifically stated if there had been no dropouts or withdrawals.
Selective reporting (reporting bias)	Low risk	Pre-defined, or clinically relevant and reasonably expected outcomes are reported on. We considered positively their reporting equalising the term ''no adverse reaction'' with ''no adverse event''.
Other bias	Unclear risk	Industrial sponsorship was not addressed.

Nakai 1999

Methods	Randomised clinical trial with parallel group design (two interventions groups). Trial duration: 12 months.
Participants	Country: Japan. Number of patients randomised: 22, mean age 58 years (90.9% females). Inclusion criteria: patients with primary biliary cirrhosis who had positive mitochondrial antibody test and liver biopsy-proven diagnosis. Exclusion criteria: none listed.
Interventions	Patients were randomly assigned to receive: Intervention group 1: 400 mg per day of bezafibrate and 600 mg per day of ursodeoxycholic acid, n = 10; Intervention group 2: 600 mg per day of ursodeoxycholic acid, n = 12. All patients had been treated with ursodeoxycholic acid for one year or more.
Outcomes	Outcome measure(s): changes in biochemical and immunological variables (serum alkaline phosphatases, serum gamma-glutamyltransferase levels, and IgM levels after 3, 6, 9, and 12 months of treatment).
Notes	Additional information requested on 18th February 2011, but no response has been received so far.

Risk of bias

Bias	Authors' judgement	Support for judgement

Nakai 1999 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	The trial is described as randomised, but the method of sequence generation was not specified.
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation was not described, so that intervention allocations may have been foreseen in advance of, or during enrolment.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The trial did not provide information for assessment of this domain, but it is not likely to have been blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was not specifically stated if there had been dropouts or withdrawals.
Selective reporting (reporting bias)	Unclear risk	Not all pre-defined expected outcomes are reported fully, or it is unclear whether data on these outcomes were recorded or not.
Other bias	Low risk	The trial appears to be free of other components that could put it at risk of bias.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Fukuo 1996	Patients had hyperlipidaemia, not primary biliary cirrhosis.
Hazzan 2010	Not a randomised clinical trial. The study group included 8 patients with primary biliary cirrhosis, 52 to 76 years old, who had been treated with ursodeoxycholic acid (900 to 1500 mg per day) for 2 to 11 years with only a partial response (19% to 56% reduction in alkaline phosphatase level). Bezafibrate (400 mg per day) was added to ursodeoxycholic acid, and the patients were followed for 4 to 12 months. There were no adverse effects attributable to the treatment.
Iwasaki 1999	Not a randomised clinical trial. The aim of this study was to evaluate the efficacy of bezafibrate in primary biliary cirrhosis (11 precirrhotic patients with primary biliary cirrhosis were treated with 400 mg per day of bezafibrate for 12 to 21 months). Bezafibrate was co-administered in seven patients who had been treated with ursodeoxycholic acid but shown incomplete responses. There were no side effects attributable to the treatment.
Miyaguchi 2000	Not a randomised clinical trial. Bezafibrate was administered additionally to 13 out of 21 patients with primary biliary cirrhosis who were treated by monotherapy of ursodeoxycholic acid for 18 months and whose liver enzymes did not remain within normal range. There were no adverse effects attributable to the treatment.
Ohmoto 2001	Not a randomised clinical trial. The aim of this study was to evaluate the efficacy of bezafibrate in ten patients with primary biliary cirrhosis (two men and eight women aged 43 to 66 years at the start of treatment: five in stage I of

Study	Reason for exclusion
	Scheuer's classification, two in stage II, two in stage III, and one in stage IV), who had shown an inadequate response to ursodeoxycholic acid monotherapy. There were no adverse effects attributable to the treatment.

Characteristics of ongoing studies *[ordered by study ID]*

JPRN-C000000225

Trial name or title	Randomised clinical trial of ursodeoxycholic acid with or without bezafibrate in primary biliary cirrhosis.
Methods	Randomised trial with parallel design.
Participants	Primary biliary cirrhosis.
Interventions	Intervention: ursodeoxycholic acid plus bezafibrate. Control: ursodeoxycholic acid only.
Outcomes	Primary outcome(s): serum alkaline phosphatases and serum gamma-glutamyltransferases. Secondary outcome(s): cytokines.
Starting date	December 2003.
Contact information	http://apps.who.int/trialsearch/Trial.aspx?TrialID=JPRN-C000000225.
Notes	Sponsor is Gunma Liver Study Group. Open public recruiting.

DATA AND ANALYSES

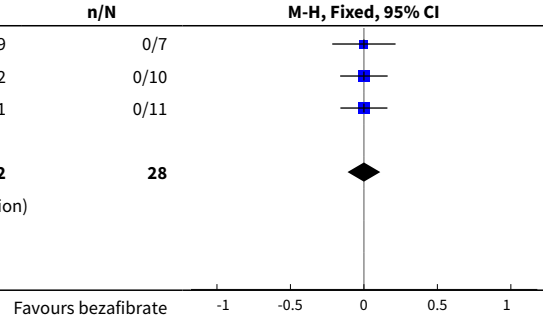
Comparison 1. Bezafibrate vs no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	3	60	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.11, 0.11]
2 Liver morbidity	3	60	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.11, 0.11]
3 Adverse events	3	60	Risk Ratio (M-H, Fixed, 95% CI)	5.4 [0.69, 42.32]
4 Pruritus	2	38	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.50, 2.53]
5 Serum alkaline phosphatases (U/L)	4	79	Mean Difference (IV, Fixed, 95% CI)	-186.04 [-249.03, -123.04]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Duration of administration 6 months	2	38	Mean Difference (IV, Fixed, 95% CI)	-141.97 [-228.30, -55.64]
5.2 Duration of administration 12-13 months	2	41	Mean Difference (IV, Fixed, 95% CI)	-236.23 [-328.35, -144.10]
6 Serum gamma-glutamyltransferase (U/L)	4	79	Mean Difference (IV, Fixed, 95% CI)	-1.22 [-11.97, 9.52]
6.1 Duration of administration 6 months	2	38	Mean Difference (IV, Fixed, 95% CI)	-1.23 [-12.17, 9.72]
6.2 Duration of administration 12-13 months	2	41	Mean Difference (IV, Fixed, 95% CI)	-1.20 [-56.79, 54.39]
7 Serum alanine aminotransferase (U/L)	2	35	Mean Difference (IV, Fixed, 95% CI)	-5.61 [-24.50, 13.27]
8 Plasma immunoglobulin M (mg/dl)	3	50	Mean Difference (IV, Fixed, 95% CI)	-164.00 [-259.47, -68.53]
9 Total cholesterol (mg/dl)	2	38	Mean Difference (IV, Fixed, 95% CI)	-12.51 [-32.65, 7.64]
10 Triglycerides (mg/dl)	2	38	Mean Difference (IV, Fixed, 95% CI)	-20.12 [-47.73, 7.49]
11 Serum bilirubin (mg/dl)	2	34	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.38, -0.00]
12 Number of patients having bezafibrate withdrawn due to adverse events	3	60	Risk Difference (M-H, Fixed, 95% CI)	0.03 [-0.09, 0.16]

Analysis 1.1. Comparison 1 Bezafibrate vs no intervention, Outcome 1 All-cause mortality.

Study or subgroup	Bezafibrate n/N	Placebo/no intervention n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
Itakura 2004	0/9	0/7		26.44%	0[-0.22,0.22]
Iwasaki 2008b	0/12	0/10		36.63%	0[-0.16,0.16]
Kanda 2003	0/11	0/11		36.93%	0[-0.16,0.16]
Total (95% CI)	**32**	**28**		**100%**	**0[-0.11,0.11]**
Total events: 0 (Bezafibrate), 0 (Placebo/no intervention)					
Heterogeneity: $Tau^2=0$; $Chi^2=0$, df=2(P=1); $I^2=0\%$					
Test for overall effect: Not applicable					



Analysis 1.2. Comparison 1 Bezafibrate vs no intervention, Outcome 2 Liver morbidity.

Study or subgroup	Bezafibrate n/N	Placebo/no intervention n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
Itakura 2004	0/9	0/7		26.44%	0[-0.22,0.22]
Iwasaki 2008b	0/12	0/10		36.63%	0[-0.16,0.16]
Kanda 2003	0/11	0/11		36.93%	0[-0.16,0.16]
Total (95% CI)	**32**	**28**		**100%**	**0[-0.11,0.11]**
Total events: 0 (Bezafibrate), 0 (Placebo/no intervention)					
Heterogeneity: $Tau^2=0$; $Chi^2=0$, df=2(P=1); $I^2=0\%$					
Test for overall effect: Not applicable					

Favours bezafibrate — Favours control

Analysis 1.3. Comparison 1 Bezafibrate vs no intervention, Outcome 3 Adverse events.

Study or subgroup	Bezafibrate n/N	Placebo/no intervention n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Itakura 2004	0/9	0/7			Not estimable
Iwasaki 2008b	4/12	0/10		52%	7.62[0.46,126.4]
Kanda 2003	1/11	0/11		48%	3[0.14,66.53]
Total (95% CI)	**32**	**28**		**100%**	**5.4[0.69,42.32]**
Total events: 5 (Bezafibrate), 0 (Placebo/no intervention)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.2$, df=1(P=0.66); $I^2=0\%$					
Test for overall effect: Z=1.61(P=0.11)					

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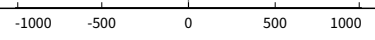
Analysis 1.4. Comparison 1 Bezafibrate vs no intervention, Outcome 4 Pruritus.

Study or subgroup	Bezafibrate n/N	Placebo/no intervention n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Itakura 2004	1/9	1/7		18.37%	0.78[0.06,10.37]
Kanda 2003	6/11	5/11		81.63%	1.2[0.52,2.79]
Total (95% CI)	**20**	**18**		**100%**	**1.12[0.5,2.53]**
Total events: 7 (Bezafibrate), 6 (Placebo/no intervention)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.1$, df=1(P=0.75); $I^2=0\%$					
Test for overall effect: Z=0.28(P=0.78)					

Favours bezafibrate — Favours control

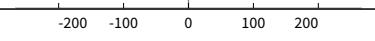
Analysis 1.5. Comparison 1 Bezafibrate vs no intervention, Outcome 5 Serum alkaline phosphatases (U/L).

Study or subgroup	Bezafibrate N	Bezafibrate Mean(SD)	Placebo/no intervention N	Placebo/no intervention Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.5.1 Duration of administration 6 months							
Itakura 2004	9	-362 (489)	7	25 (108.5)		3.66%	-387[-716.43,-57.57]
Kanda 2003	11	400.3 (124.4)	11	524.2 (86.2)		49.59%	-123.9[-213.36,-34.44]
Subtotal ***	**20**		**18**			**53.24%**	**-141.97[-228.3,-55.64]**
Heterogeneity: Tau^2=0; Chi^2=2.28, df=1(P=0.13); I^2=56.18%							
Test for overall effect: Z=3.22(P=0)							
1.5.2 Duration of administration 12-13 months							
Iwasaki 2008b	10	310.7 (103.8)	9	561.2 (173.6)		23.34%	-250.5[-380.89,-120.11]
Nakai 1999	10	179 (48)	12	401 (224)		23.42%	-222[-352.18,-91.82]
Subtotal ***	**20**		**21**			**46.76%**	**-236.23[-328.35,-144.1]**
Heterogeneity: Tau^2=0; Chi^2=0.09, df=1(P=0.76); I^2=0%							
Test for overall effect: Z=5.03(P<0.0001)							
Total ***	**40**		**39**			**100%**	**-186.04[-249.03,-123.04]**
Heterogeneity: Tau^2=0; Chi^2=4.52, df=3(P=0.21); I^2=33.55%							
Test for overall effect: Z=5.79(P<0.0001)							
Test for subgroup differences: Chi^2=2.14, df=1 (P=0.14), I^2=53.3%							



Analysis 1.6. Comparison 1 Bezafibrate vs no intervention, Outcome 6 Serum gamma-glutamyltransferase (U/L).

Study or subgroup	Bezafibrate N	Bezafibrate Mean(SD)	Placebo/no intervention N	Placebo/no intervention Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.6.1 Duration of administration 6 months							
Itakura 2004	9	-125 (141)	7	-34 (60.8)		1.1%	-91[-193.54,11.54]
Kanda 2003	11	30.8 (15)	11	31 (11)		95.17%	-0.19[-11.2,10.82]
Subtotal ***	**20**		**18**			**96.27%**	**-1.23[-12.17,9.72]**
Heterogeneity: Tau^2=0; Chi^2=2.98, df=1(P=0.08); I^2=66.43%							
Test for overall effect: Z=0.22(P=0.83)							
1.6.2 Duration of administration 12-13 months							
Iwasaki 2008b	10	144.7 (88.1)	9	109.3 (75.4)		2.13%	35.4[-38.14,108.94]
Nakai 1999	10	73 (73)	12	123 (127)		1.6%	-50[-134.91,34.91]
Subtotal ***	**20**		**21**			**3.73%**	**-1.2[-56.79,54.39]**
Heterogeneity: Tau^2=0; Chi^2=2.22, df=1(P=0.14); I^2=54.96%							
Test for overall effect: Z=0.04(P=0.97)							
Total ***	**40**		**39**			**100%**	**-1.22[-11.97,9.52]**
Heterogeneity: Tau^2=0; Chi^2=5.2, df=3(P=0.16); I^2=42.29%							
Test for overall effect: Z=0.22(P=0.82)							
Test for subgroup differences: Chi^2=0, df=1 (P=1), I^2=0%							



Analysis 1.7. Comparison 1 Bezafibrate vs no intervention, Outcome 7 Serum alanine aminotransferase (U/L).

Study or subgroup	Bezafibrate N	Bezafibrate Mean(SD)	Placebo/no intervention N	Placebo/no intervention Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Itakura 2004	9	-29 (33)	7	-14 (14.6)		61.37%	-15[-39.1,9.1]
Iwasaki 2008b	10	50.4 (42.3)	9	41.1 (23.5)		38.63%	9.3[-21.08,39.68]
Total ***	**19**		**16**			**100%**	**-5.61[-24.5,13.27]**

Heterogeneity: Tau²=0; Chi²=1.51, df=1(P=0.22); I²=33.69%

Test for overall effect: Z=0.58(P=0.56)

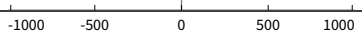
Favours bezafibrate — Favours control

Analysis 1.8. Comparison 1 Bezafibrate vs no intervention, Outcome 8 Plasma immunoglobulin M (mg/dl).

Study or subgroup	Bezafibrate N	Bezafibrate Mean(SD)	Placebo/no intervention N	Placebo/no intervention Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Itakura 2004	9	-163 (180)	7	-60 (113.8)		43.53%	-103[-247.69,41.69]
Iwasaki 2008b	8	237.3 (88.6)	4	329 (188.9)		23.96%	-91.7[-286.73,103.33]
Nakai 1999	10	187 (82)	12	486 (282)		32.5%	-299[-466.45,-131.55]
Total ***	**27**		**23**			**100%**	**-164[-259.47,-68.53]**

Heterogeneity: Tau²=0; Chi²=3.71, df=2(P=0.16); I²=46.05%

Test for overall effect: Z=3.37(P=0)



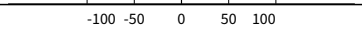
Favours bezafibrate — Favours control

Analysis 1.9. Comparison 1 Bezafibrate vs no intervention, Outcome 9 Total cholesterol (mg/dl).

Study or subgroup	Bezafibrate N	Bezafibrate Mean(SD)	Placebo/no intervention N	Placebo/no intervention Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Itakura 2004	9	26 (60)	7	-4 (16.4)		24.09%	30[-11.04,71.04]
Iwasaki 2008b	12	199 (27)	10	225 (28)		75.91%	-26[-49.12,-2.88]
Total ***	**21**		**17**			**100%**	**-12.51[-32.65,7.64]**

Heterogeneity: Tau²=0; Chi²=5.43, df=1(P=0.02); I²=81.58%

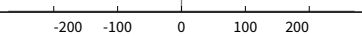
Test for overall effect: Z=1.22(P=0.22)



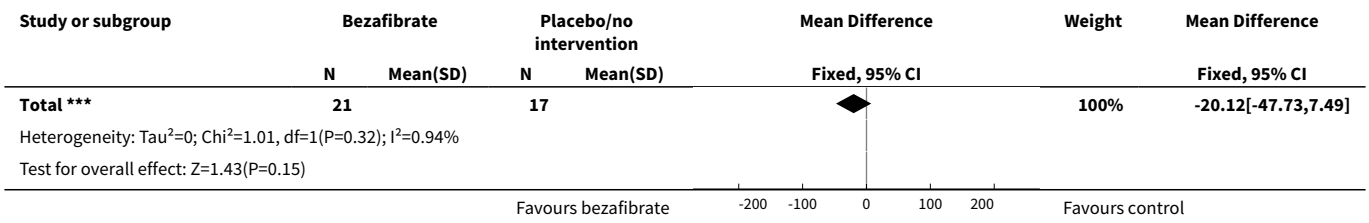
Favours bezafibrate — Favours control

Analysis 1.10. Comparison 1 Bezafibrate vs no intervention, Outcome 10 Triglycerides (mg/dl).

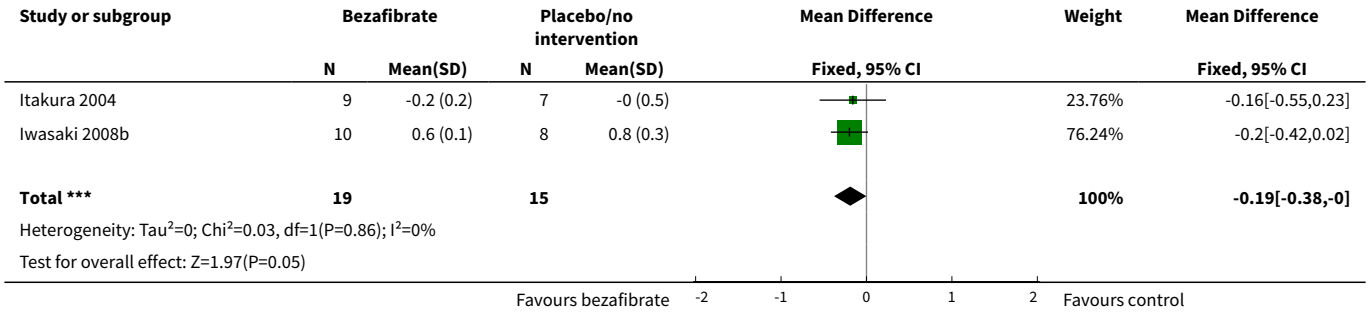
Study or subgroup	Bezafibrate N	Bezafibrate Mean(SD)	Placebo/no intervention N	Placebo/no intervention Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Itakura 2004	9	23 (93)	7	14 (23.3)		19.11%	9[-54.16,72.16]
Iwasaki 2008b	12	78 (32)	10	105 (40)		80.89%	-27[-57.7,3.7]



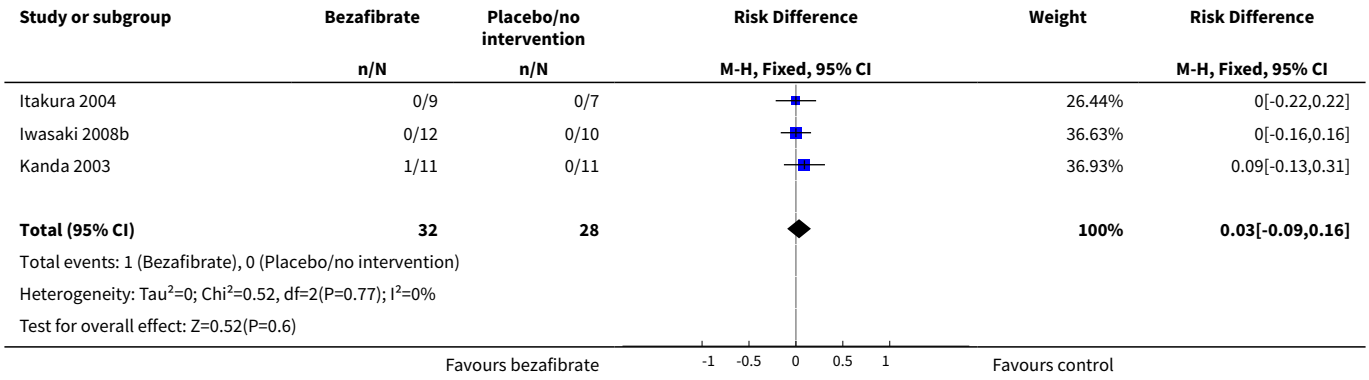
Favours bezafibrate — Favours control



Analysis 1.11. Comparison 1 Bezafibrate vs no intervention, Outcome 11 Serum bilirubin (mg/dl).



Analysis 1.12. Comparison 1 Bezafibrate vs no intervention, Outcome 12 Number of patients having bezafibrate withdrawn due to adverse events.



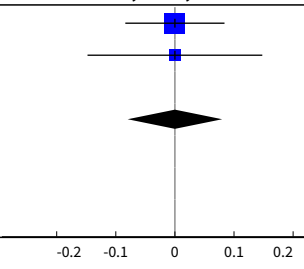
Comparison 2. Bezafibrate vs ursodeoxycholic acid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	2	69	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.08, 0.08]
2 Liver morbidity	2	69	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.08, 0.08]
3 Adverse events	2	69	Risk Ratio (M-H, Fixed, 95% CI)	6.19 [0.31, 122.05]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Serum alkaline phosphatases (U/L)	2	48	Mean Difference (IV, Fixed, 95% CI)	-162.90 [-199.68, -126.12]
5 Serum gamma-glutamyltransferase (U/L)	2	49	Mean Difference (IV, Fixed, 95% CI)	-58.18 [-76.49, -39.88]
6 Serum alanine aminotransferase (U/L)	2	49	Mean Difference (IV, Fixed, 95% CI)	-13.94 [-18.78, -9.09]
7 Plasma immunoglobulin M (mg/dl)	2	41	Mean Difference (IV, Fixed, 95% CI)	-99.90 [-130.72, -69.07]
8 Number of patients having bezafibrate withdrawn due to adverse effects	2	69	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.08, 0.08]

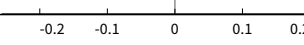
Analysis 2.1. Comparison 2 Bezafibrate vs ursodeoxycholic acid, Outcome 1 All-cause mortality.

Study or subgroup	Bezafibrate n/N	UDCA n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
Iwasaki 2008a	0/20	0/25		64.94%	0[-0.08,0.08]
Kurihara 2000	0/12	0/12		35.06%	0[-0.15,0.15]
Total (95% CI)	**32**	**37**		**100%**	**0[-0.08,0.08]**
Total events: 0 (Bezafibrate), 0 (UDCA)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=1); I^2=0%					
Test for overall effect: Not applicable					



Analysis 2.2. Comparison 2 Bezafibrate vs ursodeoxycholic acid, Outcome 2 Liver morbidity.

Study or subgroup	Bezafibrate n/N	UDCA n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
Iwasaki 2008a	0/20	0/25		64.94%	0[-0.08,0.08]
Kurihara 2000	0/12	0/12		35.06%	0[-0.15,0.15]
Total (95% CI)	**32**	**37**		**100%**	**0[-0.08,0.08]**
Total events: 0 (Bezafibrate), 0 (UDCA)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=1); I^2=0%					
Test for overall effect: Not applicable					

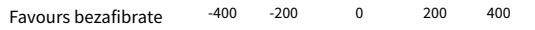


Analysis 2.3. Comparison 2 Bezafibrate vs ursodeoxycholic acid, Outcome 3 Adverse events.

Study or subgroup	Bezafibrate n/N	UDCA n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Iwasaki 2008a	2/20	0/25		100%	6.19[0.31,122.05]
Kurihara 2000	0/12	0/12			Not estimable
Total (95% CI)	**32**	**37**		**100%**	**6.19[0.31,122.05]**
Total events: 2 (Bezafibrate), 0 (UDCA)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.2(P=0.23)					

Analysis 2.4. Comparison 2 Bezafibrate vs ursodeoxycholic acid, Outcome 4 Serum alkaline phosphatases (U/L).

Study or subgroup	Bezafibrate N	Bezafibrate Mean(SD)	UDCA N	UDCA Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Iwasaki 2008a	12	340.4 (162.4)	12	439.2 (255.3)		4.62%	-98.8[-269.99,72.39]
Kurihara 2000	12	188.9 (32.3)	12	354.9 (58.2)		95.38%	-166[-203.66,-128.34]
Total ***	**24**		**24**			**100%**	**-162.9[-199.68,-126.12]**
Heterogeneity: Tau^2=0; Chi^2=0.56, df=1(P=0.45); I^2=0%							
Test for overall effect: Z=8.68(P<0.0001)							

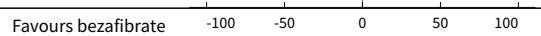


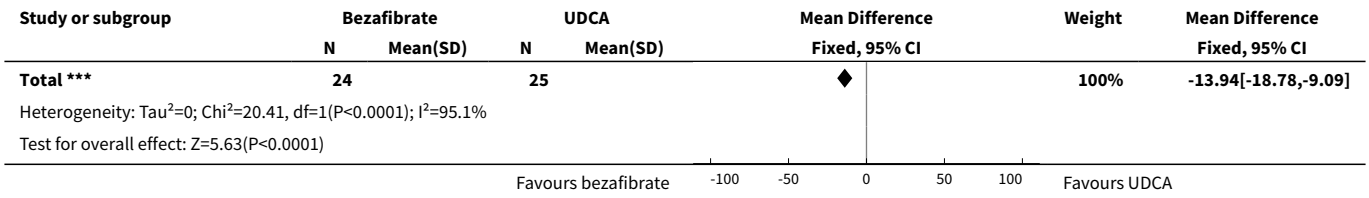
Analysis 2.5. Comparison 2 Bezafibrate vs ursodeoxycholic acid, Outcome 5 Serum gamma-glutamyltransferase (U/L).

Study or subgroup	Bezafibrate N	Bezafibrate Mean(SD)	UDCA N	UDCA Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Iwasaki 2008a	12	254.3 (249.4)	13	91 (78.8)		1.54%	163.3[15.83,310.77]
Kurihara 2000	12	55.8 (16.7)	12	117.5 (28)		98.46%	-61.65[-80.1,-43.2]
Total ***	**24**		**25**			**100%**	**-58.18[-76.49,-39.88]**
Heterogeneity: Tau^2=0; Chi^2=8.8, df=1(P=0); I^2=88.64%							
Test for overall effect: Z=6.23(P<0.0001)							

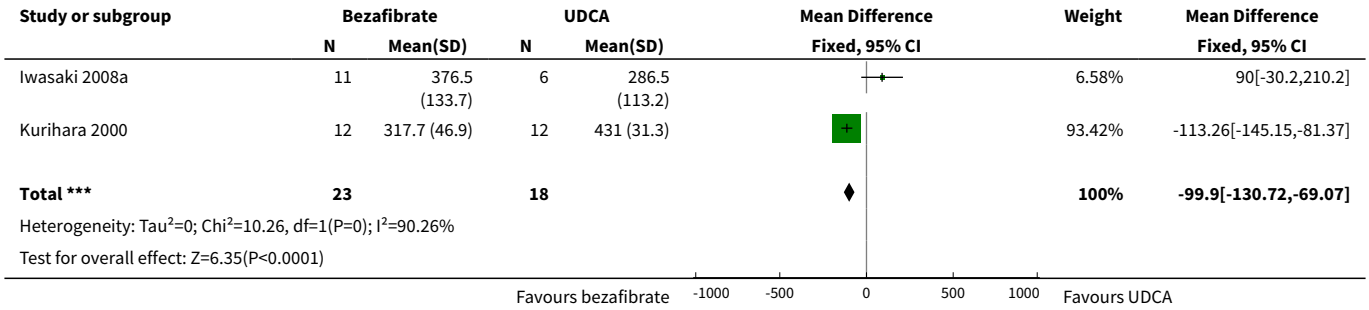
Analysis 2.6. Comparison 2 Bezafibrate vs ursodeoxycholic acid, Outcome 6 Serum alanine aminotransferase (U/L).

Study or subgroup	Bezafibrate N	Bezafibrate Mean(SD)	UDCA N	UDCA Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Iwasaki 2008a	12	46.3 (21)	13	31.5 (11.3)		13.13%	14.8[1.42,28.18]
Kurihara 2000	12	20.3 (6.5)	12	38.6 (6.5)		86.87%	-18.28[-23.48,-13.08]

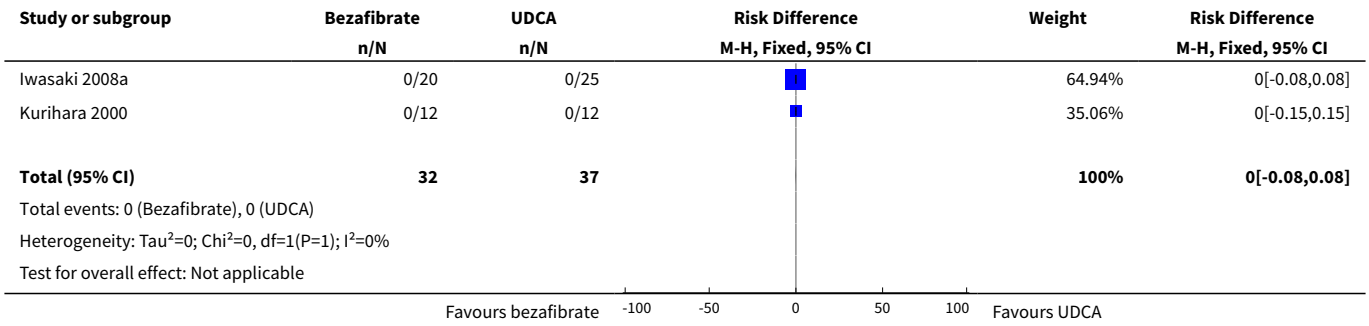




Analysis 2.7. Comparison 2 Bezafibrate vs ursodeoxycholic acid, Outcome 7 Plasma immunoglobulin M (mg/dl).



Analysis 2.8. Comparison 2 Bezafibrate vs ursodeoxycholic acid, Outcome 8 Number of patients having bezafibrate withdrawn due to adverse effects.



APPENDICES

Appendix 1. Search Strategies

Database	Time span	Search strategy
The Cochrane Hepato-Biliary Group Controlled Trials Register	November 2011.	(bezafibrat* OR bezalip OR betafizal OR bezatol OR bezatard OR benzofibrate OR fibrazate OR zimbacol OR cedur OR difaterol) AND ('primary biliary cirrhosis' OR PBC)
Cochrane Central Register of Controlled Tri-	Issue 4, 2011.	#1 MeSH descriptor Bezafibrateexplode all trees

(Continued)

als (CENTRAL) in *The Cochrane Library*		#2 bezafibrat* OR bezalip OR betafizal OR bezatol OR bezatard OR benzofibrate OR fibrazate OR zimbacol OR cedur OR difaterol #3 (#1 OR #2) #4 MeSH descriptor Liver Cirrhosis, Biliary explode all trees #5 primary biliary cirrhosis OR PBC #6 (#4 OR #5) #7 (#3 AND #6)
MEDLINE (Ovid SP)	1977 to November 2011.	1. exp Bezafibrate/ 2. (bezafibrat* or bezalip or betafizal or bezatol or bezatard or benzofibrate or fibrazate or zimbacol or cedur or difaterol).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] 3. 1 or 2 4. exp Liver Cirrhosis, Biliary/ 5. (primary biliary cirrhosis or PBC).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] 6. 4 or 5 7. 3 and 6
EMBASE (Ovid SP)	1980 to November 2011.	1. exp BEZAFIBRATE/ 2. (bezafibrat* or bezalip or betafizal or bezatol or bezatard or benzofibrate or fibrazate or zimbacol or cedur or difaterol).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer] 3. 1 or 2 4. exp primary biliary cirrhosis/ 5. (primary biliary cirrhosis or PBC).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer] 6. 4 or 5 7. 3 and 6 8. (random* or blind* or placebo* or meta-analysis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer] 9. 7 and 8
Science Citation Index Expanded (http://apps.isiknowledge.com)	1977 to November 2011.	#3 #2 AND #1 #2 TS=(primary biliary cirrhosis or PBC) #1 TS=(bezafibrat* or bezalip or betafizal or bezatol or bezatard or benzofibrate or fibrazate or zimbacol or cedur or difaterol) (42 hits)
LILACS	1980 to November 2011.	bezafibrat* OR bezalip OR betafizal OR bezatol OR bezatard OR benzofibrate OR fibrazate OR zimbacol OR cedur OR difaterol [Words] AND primary biliary cirrhosis OR PBC [Words]
The Chinese Biomedical Database (CBM), China Network Knowledge Information (CNKI), Chinese Science Journal Database (VIP), Chinese Medical Citation Index (CMCI) and Wanfang Database	From date of inception to January 2011.	#1 key words = Bezafibrate; #2 key words = primary biliary cirrhosis; #3 #1 AND #2

CONTRIBUTIONS OF AUTHORS

JR, GP, MK, GB, and CG were involved in the study concept and design.
JR and GP screened the literature, selected publications for inclusion and exclusion according to the eligibility criteria, extracted data, and made the risk of bias judgements.
JR, GB, and CG analysed and interpreted the data and results.
JR drafted the manuscript and performed the meta-analyses.
MK, GB, and CG were involved in critical revision of the manuscript for important intellectual content.

DECLARATIONS OF INTEREST

None known.

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Internal sources

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External sources

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- Clinic of Gastroenterology, Clinical Centre of Serbia, Belgrade, Serbia.

INDEX TERMS

Medical Subject Headings (MeSH)

Alanine Transaminase [blood]; Alkaline Phosphatase [blood]; Bezafibrate [adverse effects] [*therapeutic use]; Bilirubin [blood]; Drug Therapy, Combination [methods]; Hypolipidemic Agents [adverse effects] [*therapeutic use]; Immunoglobulin M [blood]; Liver Cirrhosis, Biliary [blood] [*drug therapy]; Randomized Controlled Trials as Topic; Ursodeoxycholic Acid [therapeutic use]; gamma-Glutamyltransferase [blood]

MeSH check words

Humans