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Pharmacological interventions for primary biliary cholangitis: an attempted network meta-analysis (Review)

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[Intervention Review]

Pharmacological interventions for primary biliary cholangitis: an attempted network meta-analysis

Francesca Saffioti[1,2], Kurinchi Selvan Gurusamy[3], Leonardo Henry Eusebi[4,5], Emmanuel Tsochatzis[1], Brian R Davidson[3], Douglas Thorburn[1]

[1]Sheila Sherlock Liver Centre, Royal Free Hospital and the UCL Institute of Liver and Digestive Health, London, UK. [2]Department of Clinical and Experimental Medicine, Division of Clinical and Molecular Hepatology, University of Messina, Messina, Italy. [3]Department of Surgery, Royal Free Campus, UCL Medical School, London, UK. [4]The Royal Free Sheila Sherlock Liver Centre, Royal Free Hampstead NHS Foundation Trust and UCL Institute of Liver and Digestive Health, London, UK. [5]Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy

Contact address: Kurinchi Selvan Gurusamy, Department of Surgery, Royal Free Campus, UCL Medical School, Royal Free Hospital, Rowland Hill Street, London, NW3 2PF, UK. k.gurusamy@ucl.ac.uk.

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ABSTRACT

Background

Primary biliary cholangitis (previously primary biliary cirrhosis) is a chronic liver disease caused by the destruction of small intra-hepatic bile ducts resulting in stasis of bile (cholestasis), liver fibrosis, and liver cirrhosis. The optimal pharmacological treatment of primary biliary cholangitis remains uncertain.

Objectives

To assess the comparative benefits and harms of different pharmacological interventions in the treatment of primary biliary cholangitis through a network meta-analysis and to generate rankings of the available pharmacological interventions according to their safety and efficacy. However, it was not possible to assess whether the potential effect modifiers were similar across different comparisons. Therefore, we did not perform the network meta-analysis, and instead, assessed the comparative benefits and harms of different interventions using standard Cochrane methodology.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 2), MEDLINE, Embase, Science Citation Index Expanded, World Health Organization International Clinical Trials Registry Platform, and randomised controlled trials registers to February 2017 to identify randomised clinical trials on pharmacological interventions for primary biliary cholangitis.

Selection criteria

We included only randomised clinical trials (irrespective of language, blinding, or publication status) in participants with primary biliary cholangitis. We excluded trials which included participants who had previously undergone liver transplantation. We considered any of the various pharmacological interventions compared with each other or with placebo or no intervention.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. We calculated the odds ratio (OR) and rate ratio with 95% confidence intervals (CI) using both fixed-effect and random-effects models based on available-participant analysis with Review Manager 5. We assessed risk of bias according to Cochrane, controlled risk of random errors with Trial Sequential Analysis, and assessed the quality of the evidence using GRADE.

Main results

We identified 74 trials including 5902 participants that met the inclusion criteria of this review. A total of 46 trials (4274 participants) provided information for one or more outcomes. All the trials were at high risk of bias in one or more domains. Overall, all the evidence was low or very low quality. The proportion of participants with symptoms varied from 19.9% to 100% in the trials that reported this information. The proportion of participants who were antimitochondrial antibody (AMA) positive ranged from 80.8% to 100% in the trials that reported this information. It appeared that most trials included participants who had not received previous treatments or included participants regardless of the previous treatments received. The follow-up in the trials ranged from 1 to 96 months.

The proportion of people with mortality (maximal follow-up) was higher in the methotrexate group versus the no intervention group (OR 8.83, 95% CI 1.01 to 76.96; 60 participants; 1 trial; low quality evidence). The proportion of people with mortality (maximal follow-up) was lower in the azathioprine group versus the no intervention group (OR 0.56, 95% CI 0.32 to 0.98; 224 participants; 2 trials; I^2 = 0%; low quality evidence). However, it has to be noted that a large proportion of participants (25%) was excluded from the trial that contributed most participants to this analysis and the results were not reliable. There was no evidence of a difference in any of the remaining comparisons. The proportion of people with serious adverse events was higher in the D-penicillamine versus no intervention group (OR 28.77, 95% CI 1.57 to 526.67; 52 participants; 1 trial; low quality evidence). The proportion of people with serious adverse events was higher in the obeticholic acid plus ursodeoxycholic acid (UDCA) group versus the UDCA group (OR 3.58, 95% CI 1.02 to 12.51; 216 participants; 1 trial; low quality evidence). There was no evidence of a difference in any of the remaining comparisons for serious adverse events (proportion) or serious adverse events (number of events). None of the trials reported health-related quality of life at any time point.

Funding: nine trials had no special funding or were funded by hospital or charities; 31 trials were funded by pharmaceutical companies; and 34 trials provided no information on source of funding.

Authors' conclusions

Based on very low quality evidence, there is currently no evidence that any intervention is beneficial for primary biliary cholangitis. However, the follow-up periods in the trials were short and there is significant uncertainty in this issue. Further well-designed randomised clinical trials are necessary. Future randomised clinical trials ought to be adequately powered; performed in people who are generally seen in the clinic rather than in highly selected participants; employ blinding; avoid post-randomisation dropouts or planned cross-overs; should have sufficient follow-up period (e.g. five or 10 years or more); and use clinically important outcomes such as mortality, health-related quality of life, cirrhosis, decompensated cirrhosis, and liver transplantation. Alternatively, very large groups of participants should be randomised to facilitate shorter trial duration.

PLAIN LANGUAGE SUMMARY

Medical treatment of primary biliary cholangitis

Background

Primary biliary cholangitis (previously called primary biliary cirrhosis) is a chronic liver disease caused by the destruction of small bile ducts within the liver (tubes that carry the bile produced by the liver) resulting in stagnation of bile (cholestasis) and liver damage and replacement of liver cells with scar tissue (liver cirrhosis). The best way to treat people with primary biliary cholangitis is unclear. We sought to resolve this issue by searching for existing trials on the topic. We included all randomised clinical trials (clinical studies where people are randomly put into one of two or more intervention groups) reported to February 2017. We included only trials in which participants with primary biliary cholangitis had not undergone liver transplantation previously. Apart from using standard Cochrane methods which allow comparison of only two treatments at a time (direct comparison), we planned to use an advanced method which allows comparison of the many different treatments that are individually compared in the trials (network meta-analysis). However, because of the nature of the information available, we could not determine whether the network meta-analysis results were reliable. Therefore, we used standard Cochrane methodology.

Study characteristics

We identified 74 randomised clinical trials (5902 participants). Of these, 46 randomised clinical trials (4274 participants) provided information for one or more measures (outcomes). The trials included people with primary biliary cholangitis with and without symptoms; with and without antimitochondrial antibody (AMA) (an indicator of primary biliary cholangitis) regardless of whether they received previous treatments. The average follow-up period in the trials ranged from one month to eight years in the trials that reported this information.

Funding: nine trials receive no additional funding or were funded by parties with no vested interest in the results. Thirty-one trials were partially or fully funded by the pharmaceutical companies that would benefit based on the results of the trial. The source of funding was not available from the remaining trials.

Quality of evidence

The overall quality of evidence was very low and all the trials were at high risk of bias, which means that there is possibility of making wrong conclusions overestimating benefits or underestimating harms of one treatment or the other because of the way that the trials were conducted.

Key results

There was no reliable evidence of decrease in the deaths between any of the interventions versus no intervention. There was no evidence of decrease in serious complications or complications of any severity between any of the treatments and no treatment. None of the trials reported health-related quality of life (a measure of a person's satisfaction with their life and health) at any time point.

Overall, there is currently no evidence of benefit of any intervention in primary biliary cholangitis. There is significant uncertainty in this issue and further high-quality randomised clinical trials are required.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

UDCA versus no intervention for primary biliary cholangitis

Patient or population: people with primary biliary cholangitis
Settings: secondary or tertiary care
Intervention: UDCA
Comparison: no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	No intervention	UDCA			
Mortality at maximal follow-up Follow-up: 12 to 89 months	**208 per 1000**	**206 per 1000** (136 to 301)	**OR 0.99** (0.60 to 1.64)	**734** (6 trials)	⊕◯◯◯ **Very low**[1,2]
Serious adverse events (proportion) Follow-up: 12 to 41 months	There were no events in either group			**380** (3 trials)	⊕◯◯◯ **Very low**[1,2,3]
Serious adverse events (number of events)	None of the trials reported this outcome.				
Health-related quality of life	None of the trials reported this outcome.				

*The basis for the **assumed risk** is the mean control group proportion across all the trials. 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; **OR:** odds ratio; **UDCA:** ursodeoxycholic acid.

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] Risk of bias in the trial(s) was high (downgraded by two levels).
[2] Sample sizes were small and 95% confidence intervals overlapped clinically significant and clinically insignificant or no effect (downgraded by two levels).
[3] There was moderate heterogeneity (downgraded by one level).

BACKGROUND

Description of the condition

Primary biliary cholangitis (previously named primary biliary cirrhosis) is a chronic liver disease caused by the destruction of small intrahepatic bile ducts resulting in stasis of bile (cholestasis), liver fibrosis, and liver cirrhosis (NCBI 2014). There is global variation in the incidence and prevalence of primary biliary cholangitis with annual incidence varying from 1.6 to 3.2 per 100,000 people and prevalence varying from 5 to 38 per 100,000 people, with a trend of increasing incidence and prevalence in many countries (Metcalf 1997; Boberg 1998; Kim 2000; Sood 2004; Lazaridis 2007; Pla 2007; Rautiainen 2007; Myers 2009; Baldursdottir 2012; Boonstra 2014). It is more common in women, particularly aged 25 to 40 years (Metcalf 1997; Kim 2000; Gershwin 2005; Pla 2007; Myers 2009; Baldursdottir 2012). The mean age at diagnosis is 40 to 60 years (Kim 2000; Parikh-Patel 2001; Gershwin 2005; Myers 2009; Baldursdottir 2012).

The aetiology of primary biliary cholangitis is unclear. The associations with primary biliary cholangitis include family history of primary biliary cholangitis, Sjögren's syndrome (autoimmune disease characterised by dry mouth and dry eyes), systemic lupus erythematosus (autoimmune connective tissue disorder), autoimmune thyroid disease, multiple sclerosis (autoimmune disorder of the central nervous system), scleroderma (autoimmune disease affecting the skin and internal organs), polymyositis (chronic inflammation of the muscles, possibly an autoimmune disease), history of cigarette smoking, history of hair dye use, and urinary tract infections (Parikh-Patel 2001; Gershwin 2005; Lazaridis 2007; Prince 2010; Lammert 2013). People with primary biliary cholangitis have other coexisting autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus, autoimmune thyroid disease, multiple sclerosis, scleroderma, and polymyositis (Parikh-Patel 2001; Gershwin 2005; Prince 2010; Lammert 2013). Although the strong association between personal and family history of autoimmune diseases suggests that primary biliary cholangitis may have an autoimmune aetiology, the clustering of primary biliary cholangitis in certain areas and associations between primary biliary cholangitis and hair dye use, past smoking, and history of urinary tract infections have prompted people to consider environmental factors such as toxins and infections as possible aetiologies or triggering factors for primary biliary cholangitis (Leung 2005; Dronamraju 2010; Prince 2010; Selmi 2010). A significant proportion of people with primary biliary cholangitis are asymptomatic at the time of diagnosis (up to about 60% in some studies (Pla 2007)). Itching and fatigue are the most common symptoms (Pla 2007; Myers 2009). Other ways of clinical presentation include Raynaud's syndrome (bluish discolouration of the fingers and toes due to vasospasm in response to cold or emotional stress); features of portal hypertension; osteoporosis; high cholesterol (particularly high ratio of high-density lipoprotein cholesterol (which is considered protective for the heart) to low-density lipoprotein cholesterol); and rarely deficiencies of vitamin A, vitamin D, vitamin E, and vitamin K (Kim 2000; Gershwin 2005; Pla 2007; Myers 2009; Baldursdottir 2012). Approximately 3% to 8% of people require liver transplantation in about five to six years from diagnosis (Kim 2000; Lindor 2009; Myers 2009; Baldursdottir 2012). Approximately 3% to 4% of people with primary biliary cholangitis die every year, usually because of liver-related causes such as decompensated liver disease or hepatocellular carcinoma (Rautiainen 2007; Myers 2009). Overall, approximately 21% to 50% of people are dead in about 10 to 11 years from diagnosis (Kim 2000; Rautiainen 2007; Myers 2009; Floreani 2011; Baldursdottir 2012).

The diagnosis of primary biliary cholangitis is made in the presence of any two of the following three criteria (Lindor 2009).

- Elevation of alkaline phosphatases.
- Presence of antimitochondrial antibody (AMA).
- Liver biopsy demonstrating non-suppurative destructive cholangitis and destruction of interlobular bile ducts.

Some variations of primary biliary cholangitis are AMA-negative primary biliary cholangitis that requires liver biopsy for establishing the diagnosis and the primary biliary cholangitis - autoimmune hepatitis overlap syndrome (Lindor 2009). However, there is currently no strong evidence that the course of the disease is different between the classic primary biliary cholangitis and these variants (Lindor 2009).

Description of the intervention

Various pharmacological interventions have been tried to treat people with primary biliary cholangitis. These include bile acids such as ursodeoxycholic acid (UDCA) (Kaplan 2004; Combes 2005; Rautiainen 2005; Rudic 2012a); fibrates such as bezafibrate (Kurihara 2000; Rudic 2012b); immunosuppressants or immunomodulators such as glucocorticosteroids (Prince 2005; Rautiainen 2005), colchicine (Almasio 2000; Gong 2004a; Kaplan 2004), methotrexate (Kaplan 2004; Combes 2005; Giljaca 2010), azathioprine (Gong 2007a), ciclosporin (Gong 2007b), chlorambucil (Li Wei 2012), mycophenolate mofetil (Jones 1999; Talwalkar 2005), and thalidomide (McCormick 1994); and copper-chelating agents such as D-penicillamine (Gong 2004b) and tetrathiomolybdate (Askari 2010). Several other interventions such as bisphosphonates and hormonal replacement to prevent or treat osteoporosis (Ormarsdottir 2004; Rudic 2011a; Rudic 2011b; Guanabens 2013); antidepressants such as fluoxetine and fluvoxamine to overcome fatigue (Ter Borg 2004; Talwalkar 2006); cholesterol-lowering agents such as simvastatin to decrease the high cholesterol (Cash 2013); and cholestyramine, rifampicin, and S-adenosyl methionine for pruritus (Bergasa 2000) have been evaluated for control of various symptoms. Liver transplantation is performed in some people with decompensated liver disease due to

primary biliary cholangitis (Kim 2000; Lindor 2009; Myers 2009; Baldursdottir 2012).

How the intervention might work

Certain bile acids are protective while other bile acids are harmful to hepatocytes (liver cells), cholangiocytes (cells that line the bile duct), and gastrointestinal cells lining the oesophagus and stomach (Perez 2009). Bile acids such as UDCA may protect the cholangiocytes from the damage caused by hydrophobic bile acids by decreasing the oxidative stress (by direct antioxidant effect or an increase in antioxidant defences) (Paumgartner 2002; Perez 2009). Bile acids also stimulate the secretion of bile acids from hepatocytes, thereby decreasing their stasis and the resulting damage to the cells and inhibit apoptosis (programmed cell death) (Paumgartner 2002; Perez 2009). Fibrates inactivate hydrophobic bile acids and, therefore, decrease the damage to the cells (Kurihara 2000). Since primary biliary cholangitis is considered an autoimmune disorder, altering the immunity and inflammatory response using glucocorticoids and other immunosuppressants may decrease the damage resulting from the inflammatory response. D-Penicillamine and tetrathiomolybdate might remove the excess copper, thereby protecting the cells from the damage caused by copper accumulation. They also have antifibrotic properties (Song 2008). In this Cochrane Review, we included only pharmacological interventions aimed at controlling the liver disease (i.e. we excluded symptomatic treatments, lifestyle modifications, and liver transplantation).

Why it is important to do this review

The optimal pharmacological treatment of primary biliary cholangitis is unknown. Currently, both the European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) recommend UDCA for the management of primary biliary cholangitis (EASL 2009; Lindor 2009). However, one Cochrane Review that compared UDCA versus placebo or no intervention reported that there was no survival or symptomatic benefit for UDCA (Rudic 2012a). Therefore, there is clearly a discordance between the evidence and guideline recommendation. Network meta-analysis allows combination of the direct evidence and indirect evidence, and allows ranking of different interventions in terms of the different outcomes (Salanti 2011; Salanti 2012). There has been no Cochrane Review on the different pharmacological interventions for primary biliary cholangitis. This systematic review and attempted network meta-analysis provides the best level of evidence for the role of different interventions used in the treatment of people with primary biliary cholangitis.

OBJECTIVES

To assess the comparative benefits and harms of different pharmacological interventions in the treatment of primary biliary cholangitis through a network meta-analysis and to generate rankings of the available pharmacological interventions according to their safety and efficacy. However, it was not possible to assess whether the potential effect modifiers were similar across different comparisons. Therefore, we did not perform the network meta-analysis, and, instead, assessed the comparative benefits and harms of different interventions using standard Cochrane methodology.

When more trials become available with adequate description of potential effect modifiers, we will attempt to conduct network meta-analysis to generate rankings of the available interventions according to their safety and efficacy. This is why we retained the planned methodology for network meta-analysis in our Appendix 1. Once data appear allowing for the conduct of network meta-analysis, this Appendix 1 will be moved back into the Methods section.

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomised clinical trials only for this network meta-analysis, irrespective of the language, publication status, or date of publication. We excluded studies of other design because of the risk of bias in such studies. We are all aware that such exclusions make us focus much more on potential benefits and not fully assess the risks of serious adverse events as well as risks of adverse events.

Types of participants

We included randomised clinical trials with participants with primary biliary cholangitis irrespective of the method of diagnosis of the disease or the presence of symptoms. We excluded randomised clinical trials in which participants had undergone liver transplantation previously.

Types of interventions

Any of the following pharmacological interventions that are possible treatments used either alone or in combination for primary biliary cholangitis and can be compared with each other or with placebo or no intervention.

The interventions that we considered were:

- UDCA;

- obeticholic acid;
- bezafibrate;
- glucocorticosteroids;
- colchicine;
- methotrexate;
- azathioprine;
- ciclosporin;
- chlorambucil;
- mycophenolate mofetil;
- thalidomide;
- D-penicillamine;
- tetrathiomolybdate.

The above list was not exhaustive. If we identified pharmacological interventions that we were not aware of, we considered them as eligible and included them in the review if they were used primarily for the treatment of primary biliary cholangitis.

Types of outcome measures

We assessed the comparative benefits and harms of available pharmacological interventions aimed at treating people with primary biliary cholangitis for the following outcomes.

Primary outcomes

- Mortality at maximal follow-up.
- Mortality:
  - short-term mortality (up to one year);
  - medium-term mortality (one to five years).
- Adverse events (within three months after cessation of treatment). Depending on the availability of data, we attempted to classify adverse events as serious or non-serious. We defined a non-serious adverse event as any untoward medical occurrence not necessarily having a causal relationship with the treatment but resulting in a dose reduction or discontinuation of treatment (any time after commencement of treatment) (ICH-GCP 1997). We defined a serious adverse event as any event that would increase mortality; was life threatening; required hospitalisation; resulted in persistent or significant disability; was a congenital anomaly/birth defect; or any important medical event that might jeopardise the person or require intervention to prevent it. We used the definition used by study authors for non-serious and serious adverse events:
  - proportion of participants with serious adverse events;
  - number of serious adverse events;
  - proportion of participants with any type of adverse event;
  - number of any type of adverse event.
- Health-related quality of life as defined in the included trials using a validated scale such as EQ-5D or 36-item Short Form (SF-36) (EuroQol 2014; Ware 2014):
  - short-term (up to one year);
  - medium-term (one to five years);
  - long-term (beyond five years).

We considered long-term quality of life more important than short-term or medium-term quality of life, although short-term and medium-term quality of life are also important primary outcomes.

Secondary outcomes

- Liver transplantation (maximal follow-up):
  - proportion of participants with liver transplantation;
  - time to liver transplantation.
- Decompensated liver disease (maximal follow-up):
  - proportion of participants with decompensated liver disease;
  - time to liver decompensation.
- Cirrhosis (maximal follow-up):
  - proportion of participants with cirrhosis;
  - time to cirrhosis.
- Hepatocellular carcinoma (maximal follow-up).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, and Science Citation Index Expanded (Royle 2003) from inception to 27 February 2017 for randomised clinical trials comparing two or more of the above interventions without applying any language restrictions. We searched for all possible comparisons formed by the interventions of interest. To identify further ongoing or completed trials, we also searched the World Health Organization International Clinical Trials Registry Platform Search Portal (apps.who.int/trialsearch/), which searches various trial registers, including ISRCTN and ClinicalTrials.gov. Appendix 2 shows the search strategies we used.

Searching other resources

We searched the references of the identified trials and existing Cochrane Reviews on primary biliary cholangitis to identify additional trials for inclusion.

Data collection and analysis

Selection of studies

Two review authors (KG and FS) independently identified the trials for inclusion by screening the titles and abstracts. We sought

full-text articles for any references that at least one of the review authors identified for potential inclusion. We selected trials for inclusion based on the full-text articles. We listed the excluded full-text references with reasons for their exclusion in the Characteristics of excluded studies table. We have also listed any ongoing trials identified primarily through the search of the clinical trial registers for further follow-up. We resolved discrepancies through discussion.

Data extraction and management

Two review authors (KG and FS or LHE) independently extracted the following data.

- Outcome data (for each outcome and for each treatment arm whenever applicable):
  - number of participants randomised;
  - number of participants included for the analysis;
  - number of participants with events for binary outcomes, mean and standard deviation for continuous outcomes, number of events for count outcomes, and the number of participants with events and the mean follow-up period for time-to-event outcomes;
  - definition of outcomes or scale used if appropriate.
- Data on potential effect modifiers:
  - participant characteristics such as age, sex, comorbidities, proportion of symptomatic participants, proportion with AMA-positive status, proportion of participants with overlap syndrome, and responders;
  - details of the intervention and control (including dose, frequency, and duration);
  - risk of bias (assessment of risk of bias in included studies).
- Other data:
  - year and language of publication;
  - country in which the participants were recruited;
  - year(s) in which the trial was conducted;
  - inclusion and exclusion criteria;
  - follow-up time points of the outcome.

If available, we planned to obtain the data separately for symptomatic participants and asymptomatic participants from the report. If available, we also planned to obtain the data separately for people with AMA-positive status and people with AMA-negative status and for responders and non-responders separately. We sought unclear or missing information by contacting the trial authors. If there was any doubt whether trials shared the same participants, completely or partially (by identifying common authors and centres), we attempted to contact the trial authors to clarify whether the trial report was duplicated. We resolved any differences in opinion through discussion.

Assessment of risk of bias in included studies

We followed the guidance given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and described in the Cochrane Hepato-Biliary Module (Gluud 2017) to assess the risk of bias in included trials. Specifically, we assessed the risk of bias in included trials for the following domains using the methods below (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Savović 2012a; Savović 2012b; Lundh 2017).

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 were adequate if performed by an independent person not otherwise involved in the trial.
- Unclear risk of bias: the method of sequence generation was not specified.
- High risk of bias: the sequence generation method was not random.

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. Allocation was controlled by a central and independent randomisation unit. The allocation sequence was unknown to the investigators (e.g. if the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Unclear risk of bias: 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: the allocation sequence was likely to be known to the investigators who assigned the participants.

Blinding of participants and personnel

- Low risk of bias: any of the following: no blinding or incomplete blinding, but the review authors judged that the outcome was not likely to be influenced by lack of blinding; or blinding of participants and key study personnel ensured, and it was unlikely that the blinding could have been broken.
- Unclear risk of bias: any of the following: insufficient information to permit judgement of 'low risk' or 'high risk'; or the trial did not address this outcome.
- High risk of bias: any of the following: no blinding or incomplete blinding, and the outcome was likely to be influenced by lack of blinding; or blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome was likely to be influenced by lack of blinding.

Blinding of outcome assessors

- Low risk of bias: any of the following: no blinding of outcome assessment, but the review authors judged that the outcome measurement was not likely to be influenced by lack of

blinding; or blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.

- Unclear risk of bias: any of the following: insufficient information to permit judgement of 'low risk' or 'high risk'; or the trial did not address this outcome.
- High risk of bias: any of the following: no blinding of outcome assessment, and the outcome measurement was likely to be influenced by lack of blinding; or blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.

Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. Sufficient methods, such as multiple imputation, were employed to handle missing data.
- Unclear risk of bias: there was insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias on the results.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk of bias: the trial reported at least the following predefined outcomes: mortality, decompensated liver disease, requirement for transplantation, or treatment-related adverse events. If the original trial protocol was available, the outcomes should have been those called for in that protocol. If the trial protocol was obtained from a trial registry (e.g. www.clinicaltrials.gov), the outcomes sought should have been those enumerated in the original protocol if the trial protocol was registered before or at the time that the trial was begun. If the trial protocol was registered after the trial was begun, those outcomes were not considered to be reliable.
- Unclear risk: not all predefined, or clinically relevant and reasonably expected, outcomes were reported fully, or it was unclear whether data on these outcomes were recorded or not.
- High risk: one or more predefined or clinically relevant and reasonably expected outcomes were not reported, even though data on these outcomes were likely to have been available and even recorded.

For-profit bias

- Low risk of bias: the trial appeared to be free of industry sponsorship or other type of for-profit support that may manipulate the trial design, conductance, or results of the trial.
- Unclear risk of bias: the trial may or may not have been free of for-profit bias as no information on clinical trial support or sponsorship was provided.
- High risk of bias: the trial was sponsored by industry or received other type of for-profit support.

Other bias

- Low risk of bias: the trial appeared to be free of other components (e.g. inappropriate control or dose or administration of control) that could put it at risk of bias.
- Unclear risk of bias: the trial may or may not have been 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 (e.g. inappropriate control or dose or administration of control).

We considered a trial at low risk of bias if we assessed the trial to be at low risk of bias across all domains. Otherwise, we considered trials to be at unclear risk of bias or at high risk of bias regarding one or more domains as at high risk of bias.

Measures of treatment effect

For dichotomous variables (e.g. short-term and medium-term mortality, liver transplantation, proportion of participants with adverse events, decompensated liver disease, cirrhosis, or hepatocellular carcinoma), we calculated the odds ratio (OR) with 95% confidence intervals (CI). For continuous variables (e.g. quality of life reported on the same scale), we planned to calculate the mean difference with 95% CI. We planned to use standardised mean difference values with 95% CI for quality of life if included trials used different scales. For count outcomes (e.g. number of adverse events), we calculated the rate ratio with 95% CI. For time-to-event data (e.g. mortality at maximal follow-up or requirement for liver transplantation, time to liver decompensation, and time to cirrhosis), we planned to use the hazard ratio (HR) with 95% CIs. We also calculated Trial Sequential Analysis-adjusted CI to control random errors (Thorlund 2011).

Unit of analysis issues

The unit of analysis was people with primary biliary cholangitis according to the intervention group to which they were randomly assigned.

Cluster randomised clinical trials

We found no cluster randomised clinical trials. However, if we had found them, we would have included them provided that the effect estimate adjusted for cluster correlation was available.

Cross-over randomised clinical trials

If we found cross-over randomised clinical trials, we included the outcomes after the period of first intervention only since primary biliary cholangitis is a chronic disease and the interventions could potentially have a residual effect.

Trials with multiple treatment groups

We collected data for all trial intervention groups that met our inclusion criteria.

Dealing with missing data

We performed an intention-to-treat analysis whenever possible (Newell 1992). Otherwise, we used the data that were available to us (e.g. a trial may have reported only per-protocol analysis results). As such per-protocol analyses may be biased, we planned to conduct best-worst case scenario analysis (good outcome in intervention group and bad outcome in control group) and worst-best case scenario analysis (bad outcome in intervention group and good outcome in control group) as sensitivity analyses whenever possible.

For continuous outcomes, we planned to impute the standard deviation from P values according to guidance given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If the data were likely to be normally distributed, we planned to use the median for meta-analysis when the mean was not available. If it was not possible to calculate the standard deviation from the P value or the CIs, we planned to impute the standard deviation using the largest standard deviation in other trials for that outcome. This form of imputation may decrease the weight of the study for calculation of mean differences and may bias the effect estimate to no effect for calculation of standardised mean differences (Higgins 2011).

Assessment of heterogeneity

We assessed clinical and methodological heterogeneity by carefully examining the characteristics and design of included trials. We assessed the presence of clinical heterogeneity by comparing effect estimates in the presence or absence of symptoms, the presence or absence of AMA, responders versus non-responders, and the doses of the pharmacological interventions. Different study designs and risk of bias may contribute to methodological heterogeneity. We used the I^2 test and Chi^2 test for heterogeneity, and overlapping of CIs to assess heterogeneity.

Assessment of reporting biases

We planned to use visual asymmetry on a funnel plot to explore reporting bias in the presence of at least 10 trials that could be included for a direct comparison (Egger 1997; Macaskill 2001). In the presence of heterogeneity that could be explained by subgroup analysis, we planned to produce a funnel plot for each subgroup in the presence of an adequate number of trials (at least 10 trials). We planned to use the linear regression approach described by Egger 1997 to determine funnel plot asymmetry.

We also considered selective reporting as evidence of reporting bias.

Data synthesis

We performed the meta-analyses according to the recommendations of Cochrane (Higgins 2011), using the software package Review Manager 5 (RevMan 2014). We used a random-effects model (DerSimonian 1986) and a fixed-effect model (DeMets 1987). In the case of a discrepancy between the two models, we reported both results; otherwise, we reported only the results from the fixed-effect model.

Calculation of required information size and Trial Sequential Analysis

For calculation of the required information size, see Appendix 3. We performed Trial Sequential Analysis to control the risk of random errors when there were at least two trials included for mortality at maximal follow-up, serious adverse events (proportion) and health-related quality of life, the three outcomes that determine whether an intervention should be used (Wetterslev 2008; Thorlund 2011; TSA 2011; Wetterslev 2017). We used an alpha error as per guidance of Jakobsen 2014, power of 90% (beta error of 10%), a relative risk reduction of 20%, a control group proportion observed in the trials, and the diversity observed in the meta-analysis.

Subgroup analysis and investigation of heterogeneity

We planned to assess the differences in the effect estimates between the following subgroups.

- Trials at low risk of bias compared to trials at high risk of bias.
- Participants with symptomatic compared to participants with asymptomatic primary biliary cholangitis.
- AMA-positive participants compared to AMA-negative participants.
- Responders compared to non-responders to bile acids.
- Different doses of pharmacological interventions. For example, various doses of UDCA used in randomised clinical trials include 5 mg/kg to 7 mg/kg, 13 mg/kg to 15 mg/kg (moderate dose), and 23 mg/kg to 25 mg/kg (high dose) (Angulo 1999a; Lindor 1997).

We planned to use the Chi^2 test for subgroup differences to identify subgroup differences.

Sensitivity analysis

If a trial reported only per-protocol analysis results, we planned to re-analyse the results using the best-worst case scenario and worst-best case scenario analyses as sensitivity analyses whenever possible.

Presentation of results and GRADE assessments

We reported mortality, serious adverse events, and health-related quality of life, the three most important outcomes that determine the use of an intervention in a 'Summary of findings' table format, downgrading the quality of evidence for risk of bias, inconsistency, indirectness, imprecision, and publication bias using GRADE (Guyatt 2011). We have presented the 'Summary of findings' tables for all comparisons in which two trials were included for one of mortality at maximal follow-up, serious adverse events, or health-related quality of life.

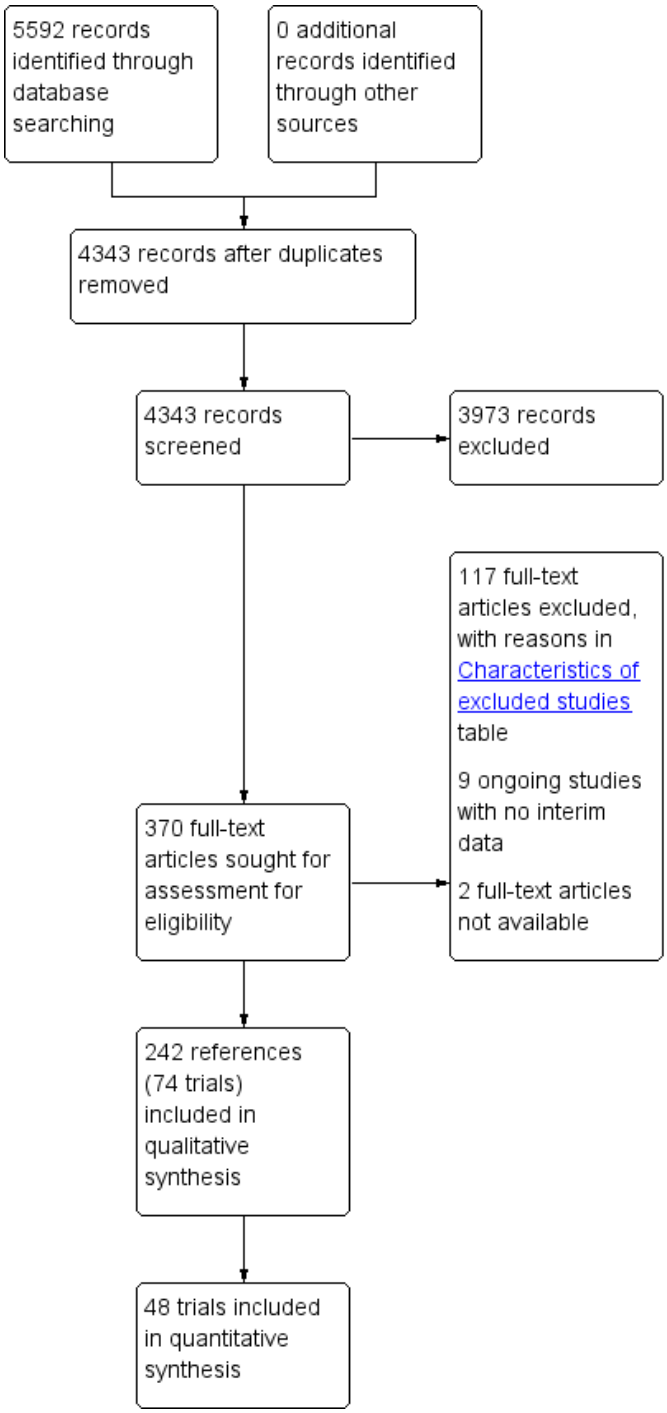
RESULTS

Description of studies

Results of the search

We identified 5592 references through electronic searches of CENTRAL (n = 1104), MEDLINE (n = 2383), Embase (n = 604), Science Citation Index Expanded (n = 1362), World Health Organization International Clinical Trials Registry Platform (n = 88), and ClinicalTrials.gov (n = 51). After the removal of 1249 duplicates we obtained 4343 references. We then excluded 3973 clearly irrelevant references through screening titles and reading abstracts. We retrieved 370 references for further assessment. No references were identified through scanning reference lists of the identified randomised trials. We excluded 117 references for the reasons stated in the Characteristics of excluded studies table. Nine references are an ongoing trial without any interim data (ChiCTR-IPR-16008935; EUCTR2015-002698-39-GB; NCT02308111; NCT02701166; NCT02823353; NCT02823366; NCT02937012; NCT02943447; NCT02965911). We were unable to obtain the full texts for two references (O'Brian 1990; Zaman 2006). In total, 242 references (74 trials) met the inclusion criteria. The reference flow is summarised in the study flow diagram (Figure 1).

Figure 1. Study flow diagram.



Included studies

The 74 trials that met the inclusion criteria for this review included 5902 participants. Some 28 trials did not contribute any information for this review leaving 4274 participants included in one or more outcomes in the review (Bodenheimer 1988; Arora 1990; Oka 1990; Smart 1990; Poupon 1991a; Senior 1991; Battezzati 1993; Manzillo 1993a; Manzillo 1993b; Bobadilla 1994; Goddard 1994; Lim 1994; McCormick 1994; Steenbergen 1994; Lindor 1997; Kaplan 1999; Leuschner 1999; Nakai 2000; Mazzarella 2002; Ueno 2005; Iwasaki 2008a; Iwasaki 2008b; Askari 2010; Liberopoulos 2010; Cash 2013; Bowlus 2014; Kowdley 2014a; Mayo 2015). In the main review unstratified by the dose of UDCA or obeticholic acid, 4060 participants were included in one or more outcomes in the review. The mean or median age of the participants ranged from 46 to 64 years in the trials that reported this information. The proportion of females ranged from 77.8% to 100% in the trials that reported this information. The proportion of participants with symptoms varied from 19.9% to 100% in the trials that reported this information. The proportion of participants who were AMA positive ranged from 80.8% to 100% in the trials that reported this information. Ten trials included non-responders to bile acids only (Van Hoogstraten 1998; Wolfhagen 1998; Kanda 2003; Ueno 2005; Iwasaki 2008b; Mason 2008; Liberopoulos 2010; Hirschfield 2015; Hosonuma 2015; Nevens 2016). The remaining trials did not state whether they included responders or non-responders, or both. However, it appeared that most trials included participants who had not received previous treatments or regardless of the previous treatments received. The interventions, controls, number of participants included in each trial, and the follow-up period reported in the different trials are listed in Table 1.

Source of funding: nine trials receive no additional funding or were funded by parties with no vested interest in the results (Heathcote 1976; Hoofnagle 1986; Almasio 2000; Nakai 2000; Iwasaki 2008a; Iwasaki 2008b; Askari 2010; Cash 2013; Hosonuma 2015). Thirty-one trials were partially or fully funded by the pharmaceutical companies that would benefit based on the results of the trial (Triger 1980; Matloff 1982; Christensen 1985; Dickson 1985; Bodenheimer 1988; Minuk 1988; Oka 1990; Wiesner 1990; Poupon 1991a; Senior 1991; Lombard 1993; Mitchison 1993; Heathcote 1994; Lindor 1994; McCormick 1994; Combes 1995a; Poupon 1996; Eriksson 1997; Van Hoogstraten 1998; Wolfhagen 1998; Leuschner 1999; Pares 2000; Papatheodoridis 2002; Combes 2005; Rautiainen 2005; Mason 2008; Bowlus 2014; Kowdley 2014a; Mayo 2015; Ma 2016; Nevens 2016). The source of funding was not available from the 34 remaining trials.

Excluded studies

The reasons for exclusion are summarised in the Characteristics of excluded studies table. While the reasons for exclusion for most references were self-explanatory, the reasons for exclusion of 15 references required some explanation (Poupon 1994; Lindor 1995a; Emond 1996; Lindor 1996; Angulo 1999b; Angulo 1999c; Degott 1999; Corpechot 2000; Jorgensen 2002; Kaplan 2004; Combes 2005b; Leung 2010; Leung 2011; Kowdley 2015; Carbone 2016). These 15 references were long-term follow-up reports of included trials, but the randomisation was not maintained and the 'no intervention' group received the intervention. While this is acceptable if some participants crossed over for specific reasons in an intention-to-treat analysis, it is not acceptable if the cross-over from one group to another was done in a systematic manner. Therefore, we excluded these references.

Risk of bias in included studies

The risk of bias is summarised in Figure 2, Figure 3, and Table 2.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

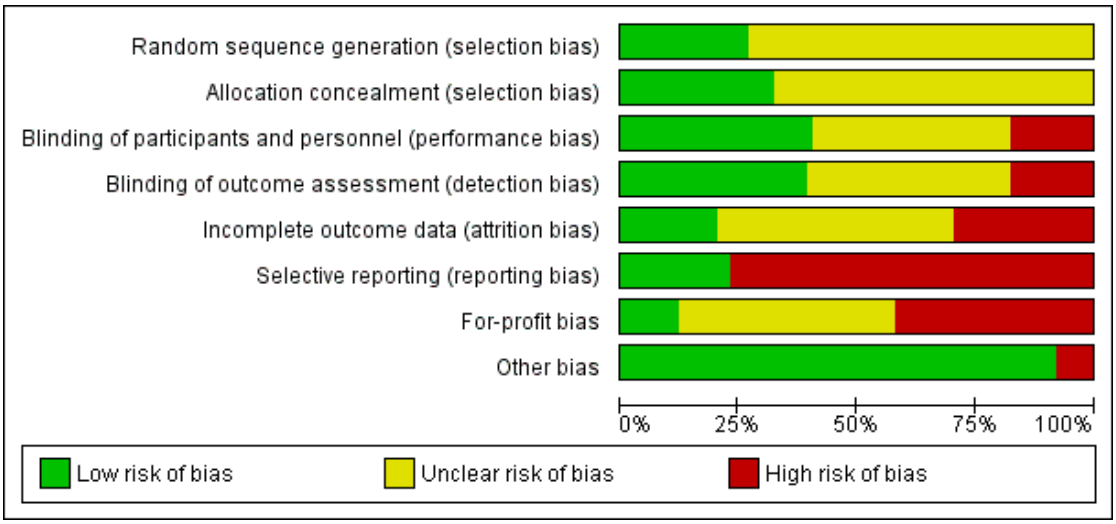
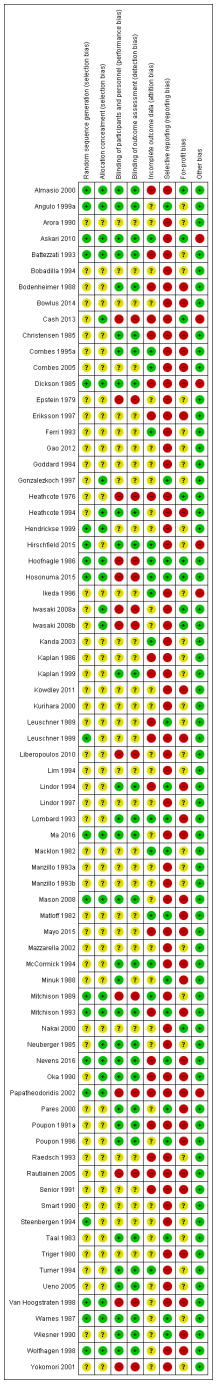


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Twenty trials were at low risk of bias due to random sequence generation (Dickson 1985; Hoofnagle 1986; Warnes 1987; Mitchison 1989; Battezzati 1993; Mitchison 1993; Steenbergen 1994; Van Hoogstraten 1998; Wolfhagen 1998; Angulo 1999a; Hendrickse 1999; Leuschner 1999; Almasio 2000; Papatheodoridis 2002; Mason 2008; Askari 2010; Hirschfield 2015; Hosonuma 2015; Ma 2016; Nevens 2016). The remaining trials were at unclear risk of bias.

Twenty-four trials were at low risk of bias due allocation concealment (Dickson 1985; Neuberger 1985; Hoofnagle 1986; Warnes 1987; Mitchison 1989; Oka 1990; Battezzati 1993; Mitchison 1993; Heathcote 1994; Gonzalezkoch 1997; Van Hoogstraten 1998; Wolfhagen 1998; Angulo 1999a; Hendrickse 1999; Almasio 2000; Papatheodoridis 2002; Iwasaki 2008a; Iwasaki 2008b; Mason 2008; Askari 2010; Cash 2013; Hosonuma 2015; Ma 2016; Nevens 2016). The remaining trials were at unclear risk of bias.

Sixteen trials were at low risk of both random sequence generation bias and allocation concealment bias (Dickson 1985; Warnes 1987; Mitchison 1989; Battezzati 1993; Mitchison 1993; Van Hoogstraten 1998; Wolfhagen 1998; Angulo 1999a; Hendrickse 1999; Almasio 2000; Papatheodoridis 2002; Mason 2008; Askari 2010; Hosonuma 2015; Ma 2016; Nevens 2016); these trials were considered to be at low risk of selection bias. The remaining trials were at unclear risk of selection bias.

Blinding

Thirty trials were at low risk of performance bias (Taal 1983; Christensen 1985; Dickson 1985; Neuberger 1985; Warnes 1987; Bodenheimer 1988; Minuk 1988; Oka 1990; Wiesner 1990; Poupon 1991a; Battezzati 1993; Lombard 1993; Mitchison 1993; Heathcote 1994; Lindor 1994; McCormick 1994; Turner 1994; Combes 1995a; Poupon 1996; Wolfhagen 1998; Angulo 1999a; Kaplan 1999; Almasio 2000; Pares 2000; Ueno 2005; Mason 2008; Askari 2010; Hirschfield 2015; Ma 2016; Nevens 2016). Thirteen trials were at high risk of performance bias (Heathcote 1976; Epstein 1979; Hoofnagle 1986; Mitchison 1989; Van Hoogstraten 1998; Yokomori 2001; Papatheodoridis 2002; Rautiainen 2005; Iwasaki 2008a; Iwasaki 2008b; Liberopoulos 2010; Cash 2013; Hosonuma 2015). The remaining trials were at unclear risk of performance bias.

Twenty-nine trials were at low risk of detection bias (Taal 1983; Christensen 1985; Dickson 1985; Neuberger 1985; Warnes 1987; Bodenheimer 1988; Oka 1990; Wiesner 1990; Poupon 1991a; Battezzati 1993; Lombard 1993; Mitchison 1993; Heathcote 1994; Lindor 1994; McCormick 1994; Turner 1994; Combes 1995a; Poupon 1996; Wolfhagen 1998; Angulo 1999a; Kaplan 1999; Almasio 2000; Pares 2000; Ueno 2005; Mason 2008; Askari 2010; Hirschfield 2015; Ma 2016; Nevens 2016). Thirteen trials were at high risk of detection bias (Heathcote 1976; Epstein 1979; Hoofnagle 1986; Mitchison 1989; Van Hoogstraten 1998; Yokomori 2001; Papatheodoridis 2002; Rautiainen 2005; Iwasaki 2008a; Iwasaki 2008b; Liberopoulos 2010; Cash 2013; Hosonuma 2015). The remaining trials were at unclear risk of detection bias.

Twenty-nine trials were at low risk of performance bias and detection bias (Taal 1983; Christensen 1985; Dickson 1985; Neuberger 1985; Warnes 1987; Bodenheimer 1988; Oka 1990; Wiesner 1990; Poupon 1991a; Battezzati 1993; Lombard 1993; Mitchison 1993; Heathcote 1994; Lindor 1994; McCormick 1994; Turner 1994; Combes 1995a; Poupon 1996; Wolfhagen 1998; Angulo 1999a; Kaplan 1999; Almasio 2000; Pares 2000; Ueno 2005; Mason 2008; Askari 2010; Hirschfield 2015; Ma 2016; Nevens 2016). Thirteen trials were at high risk of performance bias and detection bias (Heathcote 1976; Epstein 1979; Hoofnagle 1986; Mitchison 1989; Van Hoogstraten 1998; Yokomori 2001; Papatheodoridis 2002; Rautiainen 2005; Iwasaki 2008a; Iwasaki 2008b; Liberopoulos 2010; Cash 2013; Hosonuma 2015). The remaining trials were at unclear risk of performance and detection bias.

Incomplete outcome data

Fifteen trials were at low risk of attrition bias (Macklon 1982; Matloff 1982; Hoofnagle 1986; Mitchison 1989; Ferri 1993; Lombard 1993; McCormick 1994; Turner 1994; Combes 1995a; Ikeda 1996; Kanda 2003; Combes 2005; Askari 2010; Hirschfield 2015; Hosonuma 2015). Twenty-two trials were at high risk of attrition bias due to dropouts which may have been related to the intervention that the participant received (Heathcote 1976; Christensen 1985; Dickson 1985; Kaplan 1986; Bodenheimer 1988; Leuschner 1989; Oka 1990; Poupon 1991a; Senior 1991; Battezzati 1993; Mitchison 1993; Raedsch 1993; Lindor 1994; Eriksson 1997; Kaplan 1999; Leuschner 1999; Almasio 2000; Papatheodoridis 2002; Rautiainen 2005; Cash 2013; Mayo 2015; Nevens 2016). The remaining trials were at unclear risk of attrition bias.

Selective reporting

We were unable to find any protocols published prior to the full study reports. Seventeen trials were at low risk of due to selecting outcome reporting (Macklon 1982; Matloff 1982; Taal 1983; Hoofnagle 1986; Warnes 1987; Minuk 1988; Leuschner 1989; Wiesner 1990; Lombard 1993; Mitchison 1993; Lindor 1994; Poupon 1996; Gonzalezkoch 1997; Angulo 1999a; Pares 2000;

Hosonuma 2015; Nevens 2016). The remaining trials were at high risk of bias due to selective reporting (reporting bias).

Other potential sources of bias

For profit bias: nine trials receive no additional funding or were funded by parties with no vested interest in the results and were at low risk of for-profit bias (Heathcote 1976; Hoofnagle 1986; Almasio 2000; Nakai 2000; Iwasaki 2008a; Iwasaki 2008b; Askari 2010; Cash 2013; Hosonuma 2015). Thirty-one trials partially or fully funded by the pharmaceutical companies that would benefit based on the results of the trial were at high risk of for-profit bias (Triger 1980; Matloff 1982; Christensen 1985; Dickson 1985; Bodenheimer 1988; Minuk 1988; Oka 1990; Wiesner 1990; Poupon 1991a; Senior 1991; Lombard 1993; Mitchison 1993; Heathcote 1994; Lindor 1994; McCormick 1994; Combes 1995a; Poupon 1996; Eriksson 1997; Van Hoogstraten 1998; Wolfhagen 1998; Leuschner 1999; Pares 2000; Papatheodoridis 2002; Combes 2005; Rautiainen 2005; Mason 2008; Bowlus 2014; Kowdley 2014a; Mayo 2015; Ma 2016; Nevens 2016). The remaining trials were at unclear risk of for-profit bias.

Six trials were at high risk of other bias: authors presented the results of only a subgroup of participants without explaining the reason for this approach (Dickson 1985; Ikeda 1996); a significant proportion of participants crossed over from placebo to UDCA (Papatheodoridis 2002); it was unclear whether the participants continued to take UDCA in both groups (Askari 2010); participants continued to take varying doses of UDCA (Hirschfield 2015); and participants were allowed to continue previous prescriptions for primary biliary cholangitis (it was unclear whether this was balanced across groups) (Cash 2013). The remaining trials were at low risk of other bias.

Overall risk of bias

All trials were at high risk of bias in one or more domains.

Effects of interventions

See: **Summary of findings for the main comparison** Ursodeoxycholic acid (UDCA) versus no intervention for primary biliary cholangitis; **Summary of findings 2** Azathioprine versus no intervention for primary biliary cholangitis; **Summary of findings 3** Colchicine versus no intervention for primary biliary cholangitis; **Summary of findings 4** Ciclosporin versus no intervention for primary biliary cholangitis; **Summary of findings 5** D-Penicillamine versus no intervention for primary biliary cholangitis; **Summary of findings 6** Colchicine plus ursodeoxycholic acid (UDCA) versus UDCA for primary biliary cholangitis; **Summary of findings 7** Methotrexate plus ursodeoxycholic acid (UDCA) versus UDCA for primary biliary cholangitis

Mortality at maximal follow-up

Twenty-eight trials including 2823 participants reported mortality at maximal follow-up (Heathcote 1976; Epstein 1979; Macklon 1982; Matloff 1982; Taal 1983; Christensen 1985; Neuberger 1985; Hoofnagle 1986; Kaplan 1986; Warnes 1987; Minuk 1988; Leuschner 1989; Mitchison 1989; Wiesner 1990; Lombard 1993; Mitchison 1993; Heathcote 1994; Lindor 1994; Turner 1994; Poupon 1996; Gonzalezkoch 1997; Hendrickse 1999; Almasio 2000; Pares 2000; Papatheodoridis 2002; Combes 2005; Hosonuma 2015; Nevens 2016). The period of follow-up in these trials varied between 11 and 96 months. The proportion of people with mortality (maximal follow-up) was higher in the methotrexate group (adjusted proportion: 23.3%) than in the no intervention group (1/30 (3.3%)) (OR 8.83, 95% CI 1.01 to 76.96; 60 participants; 1 trial). The proportion of people with mortality (maximal follow-up) was lower in the azathioprine group (adjusted proportion: 53.5%) than in the no intervention group (72/107 (67.3%)) (OR 0.56, 95% CI 0.32 to 0.98; 224 participants; 2 trials; I^2 = 0%). There was no evidence of a difference in any of the remaining comparisons (Analysis 1.1).

Mortality (up to one year)

Eight trials including 655 participants reported mortality (up to year) (Heathcote 1976; Neuberger 1985; Warnes 1987; Minuk 1988; Leuschner 1989; Gonzalezkoch 1997; Almasio 2000; Nevens 2016). There was no evidence of a difference in any of the comparisons (Analysis 1.2).

Mortality (one to five years)

Twenty trials including 2168 participants reported mortality (one to five years) (Epstein 1979; Macklon 1982; Matloff 1982; Taal 1983; Christensen 1985; Hoofnagle 1986; Kaplan 1986; Mitchison 1989; Wiesner 1990; Lombard 1993; Mitchison 1993; Heathcote 1994; Lindor 1994; Turner 1994; Poupon 1996; Hendrickse 1999; Pares 2000; Papatheodoridis 2002; Combes 2005; Hosonuma 2015). The proportion of people with mortality (one to five years) was higher in the methotrexate group (adjusted proportion: 23.3%) than in the no intervention group (1/30 (3.3%)) (OR 8.83, 95% CI 1.01 to 76.96; 60 participants; 1 trial). There was no evidence of a difference in any of the remaining comparisons (Analysis 1.3).

Serious adverse events (proportion)

Eleven trials including 1076 participants reported serious adverse events (proportion) (Matloff 1982; Warnes 1987; Leuschner 1989; Lindor 1994; Poupon 1996; Kurihara 2000; Pares 2000; Kanda 2003; Mason 2008; Hirschfield 2015; Nevens 2016). The period of follow-up varied from three to 41 months. The proportion of people with serious adverse events (proportion) was higher

in the D-penicillamine group (adjusted proportion: 28.8%; based on a control group proportion of 1%) versus the no intervention group (0/26 (0.0%)) (OR 28.77, 95% CI 1.57 to 526.67; 52 participants; 1 trial). The proportion of people with serious adverse events (proportion) was higher in the obeticholic acid plus UDCA group (adjusted proportion: 4.1%) versus the UDCA group (19/143 (13.3%)) (OR 3.58, 95% CI 1.02 to 12.51; 216 participants; 1 trial). There was no evidence of a difference in any of the remaining comparisons (Analysis 1.4).

Serious adverse events (number of events)

One trial including 216 participants reported serious adverse events (number of events) (Nevens 2016). The period of follow-up was 12 months. There was no evidence of a difference between the UDCA plus obeticholic acid versus the UDCA groups (Analysis 1.5).

Adverse events (proportion)

Nineteen trials including 1652 participants reported adverse events (proportion) (Macklon 1982; Dickson 1985; Minuk 1988; Leuschner 1989; Wiesner 1990; Ferri 1993; Lombard 1993; Mitchison 1993; Raedsch 1993; Lindor 1994; Ikeda 1996; Gonzalezkoch 1997; Kurihara 2000; Pares 2000; Yokomori 2001; Kanda 2003; Rautiainen 2005; Gao 2012; Hirschfield 2015). The proportion of people with adverse events (proportion) was higher in the ciclosporin group (adjusted proportion: 76.2%) versus the no intervention group (97/189 (51.3%) (OR 3.04, 95% CI 1.98 to 4.68; 390; 3 trials; I^2 = 27%), D-penicillamine group (adjusted proportion: 50.6%) versus the no intervention group (25/135 (18.5%)) (OR 4.51, 95% CI 2.56 to 7.93; 287 participants; 2 trials; I^2 = 0%); malotilate group (adjusted proportion: 19.2%) versus the no intervention group (1/49 (2.0%)) (OR 11.43, 95% CI 1.40 to 93.04; 101 participants; 1 trial); and obeticholic acid group (adjusted proportion: 96.1%) versus the no intervention group (32/38 (84.2%)) (OR 4.58, 95% CI 1.31 to 15.95; 165 participants; 1 trial). The proportion of people with adverse events (proportion) was higher in the glucocorticosteroids plus UDCA (adjusted proportion: 15.8%) versus the UDCA group (2/61 (3.3%) (OR 5.54, 95% CI 1.35 to 22.84; 135 participants; 2 trials; I^2 = 0%) and methotrexate plus UDCA (adjusted proportion: 100.0%) versus the UDCA group (0/12 (0.0%)) (OR 115.00, 95% CI 4.98 to 2657.48; 25 participants; 1 trial). The proportion of people with adverse events (proportion) was higher in the taurodeoxycholic acid (TUDCA) group (adjusted proportion: 60.0%) versus the UDCA group (1/15 (6.7%)) (OR 21.00, 95% CI 2.16 to 204.61; 30 participants; 1 trial). There was no evidence of a difference in any of the remaining comparisons (Analysis 1.6).

Adverse events (number)

Fourteen trials including 1304 participants reported adverse events (number) (Matloff 1982; Taal 1983; Dickson 1985; Hoofnagle 1986; Minuk 1988; Wiesner 1990; Lombard 1993; Mitchison 1993; Ikeda 1996; Gonzalezkoch 1997; Wolfhagen 1998; Hirschfield 2015; Hosonuma 2015; Ma 2016). The number of adverse events was higher in the chlorambucil group (adjusted rate: 57.9 events per 100 participants) versus the no intervention group (3/11 (27.3 events per 100 participants)) (rate ratio 3.67, 95% CI 1.04 to 12.87; 24 participants; 1 trial); ciclosporin group (adjusted rate: 84.4 events per 100 participants) versus the no intervention group (128/189 (67.7 events per 100 participants)) (rate ratio 2.58, 95% CI 1.26 to 5.31; 390 participants; 3 trials; I^2= 69%); D-penicillamine group (adjusted rate: 48.4 events per 100 participants) versus the no intervention group (37/155 (23.9 events per 100 participants)) (rate ratio 2.99, 95% CI 1.04 to 8.63; 303 participants; 3 trials; I^2 = 75%), malotilate group (adjusted rate: 20.7 events per 100 participants) versus the no intervention group (2/49 (4.1 events per 100 participants)) (rate ratio 6.13, 95% CI 1.38 to 27.14; 101 participants; 1 trial); and obeticholic acid group (adjusted rate: 175.0 events per 100 participants) versus the no intervention group (96/38 (252.6 events per 100 participants)) (rate ratio 1.41, 95% CI 1.13 to 1.75; 76 participants; 1 trial); ; ; ; . The number of adverse events was higher in the methotrexate plus UDCA group (adjusted rate: 30.6 events per 100 participants) versus the UDCA group (0/12 (0.0 events per 100 participants)) (rate ratio 30.64, 95% CI 1.84 to 510.76; 27 participants; 1 trial). There was no evidence of a difference in any of the remaining comparisons (Analysis 1.7).

Health-related quality of life

None of the trials reported health-related quality of life at any time point.

Liver transplantation

Eleven trials including 1561 participants reported liver transplantation (Neuberger 1985; Wiesner 1990; Lombard 1993; Heathcote 1994; Lindor 1994; Turner 1994; Eriksson 1997; Hendrickse 1999; Papatheodoridis 2002; Combes 2005; Hosonuma 2015). There was no evidence of a difference in any of the comparisons (Analysis 1.8).

Decompensated liver disease

Seven trials including 909 participants reported decompensated liver disease (Taal 1983; Combes 1995a; Almasio 2000; Papatheodoridis 2002; Combes 2005; Gao 2012; Nevens 2016). There was no evidence of a difference in any of the comparisons (Analysis 1.9).

Cirrhosis

Three trials including 103 participants reported cirrhosis (Heathcote 1976; Turner 1994; Wolfhagen 1998). There was no evidence of a difference in any of the comparisons (Analysis 1.10).

Hepatocellular carcinoma

None of the trials reported hepatocellular carcinoma.

Subgroup analysis

All the trials were at high risk of bias for one or more domains. None of the trials reported separate data for symptomatic and asymptomatic participants, AMA-positive and AMA-negative participants, or for responders and non-responders to bile acids. A secondary analysis performed by stratifying for the doses of UDCA and obeticholic acid revealed no differences between the main analysis except for the following.

There was no evidence of differences in the proportion of people with adverse events when stratified by the dose of obeticholic acid (obeticholic acid (high) versus no intervention: OR 16.60, 95% CI 0.90 to 305.59; 79 participants; 1 trial; obeticholic acid (moderate) versus no intervention: OR 8.81, 95% CI 1.01 to 76.73; 86 participants; 1 trial; and obeticholic acid (low) versus no intervention: OR 1.59, 95% CI 0.41 to 6.17; 76 participants; 1 trial). In addition, when stratified by dose, only obeticholic acid (high) had higher number of adverse events than no intervention (rate ratio 1.91, 95% CI 1.50 to 2.44; 79 participants; 1 trial). It also had higher number of adverse events than obeticholic acid (moderate) and obeticholic acid (low) (obeticholic acid (moderate) versus obeticholic acid (high): rate ratio 0.66, 95% CI 0.53 to 0.81; 89 participants; 1 trial; obeticholic acid (low) versus obeticholic acid (high): rate ratio 0.55, 95% CI 0.43 to 0.70; 79 participants; 1 trial).

Sensitivity analysis

We did not perform a sensitivity analysis of imputing information based on different scenarios because of paucity of data to carry out these analyses. We did not impute standard deviation; therefore, we did not perform a sensitivity analysis to assess the impact of imputing the standard deviation.

Reporting bias

We did not assess reporting bias by creating a funnel plot because of the few trials included under each comparison.

Using fixed-effect model versus random-effects model

The interpretation of results was not altered based on the model used for analysis.

Quality of evidence

The overall quality of evidence was very low for all the outcomes (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6; Summary of findings 7). This was because of the high risk of bias in all the trials (downgraded by two levels); small sample sizes for all outcomes and wide CIs (downgraded by two levels for imprecision) and heterogeneity (downgraded by two levels) for some of the outcomes.

Sample size calculations and Trial Sequential Analysis

The required sample size for identifying a 20% relative risk reduction in the different outcomes based on an alpha error of 5%, a beta error of 20%, and the control group proportion observed across trials were as follows.

- Mortality (up to one year) (control group proportion: 25.2%): 2166 participants.
- Mortality (one to five years) (control group proportion: 20.0%): 2894 participants.
- Mortality at maximal follow-up (control group proportion: 20.8%): 2758 participants.
- Serious adverse events (proportion) (control group proportion: 0.4%): 175,996 participants.
- Adverse events (proportion) (control group proportion: 27%): 1978 participants.
- Liver transplantation (control group proportion: 7.4%): 8910 participants.
- Decompensated liver disease (control group proportion: 20.8%): 2758 participants.
- Cirrhosis (control group proportion: 55.6%): 632 participants.

The above mentioned are sample sizes uncorrected for heterogeneity. In the presence of heterogeneity, for example, in the presence of a heterogeneity of 27%, the required information size for adverse events (proportion) is 1978/(1 - 0.27) = 2710 participants. As shown in Figure 4, Figure 5, and Figure 6, the accrued sample sizes were only small fractions of the diversity-adjusted required information size (DARIS) and therefore, the boundaries could not be drawn. There was a high risk of random errors. The TSA-adjusted CI could not be calculated as there was too little information for the calculation (i.e. the CIs were wide).

Figure 4. Trial Sequential Analysis of mortality at maximal follow-up: azathioprine versus no intervention and colchicine versus no intervention.Based on an alpha error of 2.5%, power of 90% (beta error of 10%), a relative risk reduction (RRR) of 20%, a control group proportion observed in the trials (Pc = 20%), and diversity observed in the analyses (0%), the accrued sample size (224 for azathioprine versus intervention and 122 for colchicine versus no intervention) was only a small fraction of the diversity adjusted required information size (DARIS) (4580 for both comparisons); therefore, the trial sequential monitoring boundaries were not drawn. The Z-curve (blue line) crossed the conventional boundaries (dotted green line) favouring azathioprine for azathioprine versus no intervention, but did not cross the conventional boundaries for colchicine versus no intervention. This indicates that there is a high risk of random errors in both these comparisons.

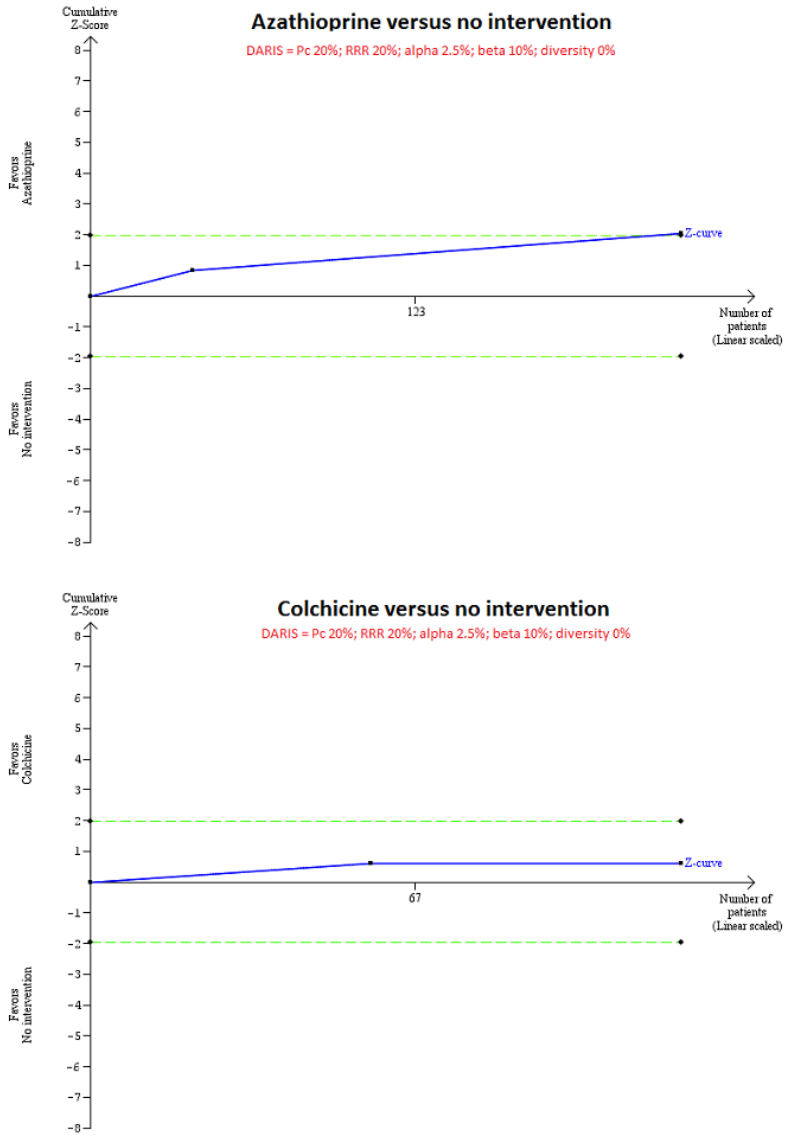


Figure 5. Trial Sequential Analysis of mortality at maximal follow-up: ciclosporin versus no intervention and D-penicillamine versus no intervention.Based on an alpha error of 2.5%, power of 90% (beta error of 10%), a relative risk reduction (RRR) of 20%, a control group proportion observed in the trials (Pc = 20%), and diversity observed in the analyses (82% for ciclosporin versus no intervention and 61% for D-penicillamine versus no intervention), the accrued sample size (394 for ciclosporin versus no intervention and 423 for D-penicillamine versus no intervention) was only a small fraction of the diversity adjusted required information size (DARIS) (25,098 for ciclosporin versus no intervention and 11,623 for D-penicillamine versus no intervention); therefore, the trial sequential monitoring boundaries were not drawn. The Z-curve (blue line) crossed the conventional boundaries (dotted green line) favouring ciclosporin for ciclosporin versus no intervention, but did not cross the conventional boundaries for D-penicillamine versus no intervention. This indicates that there is a high risk of random errors in both these comparisons.

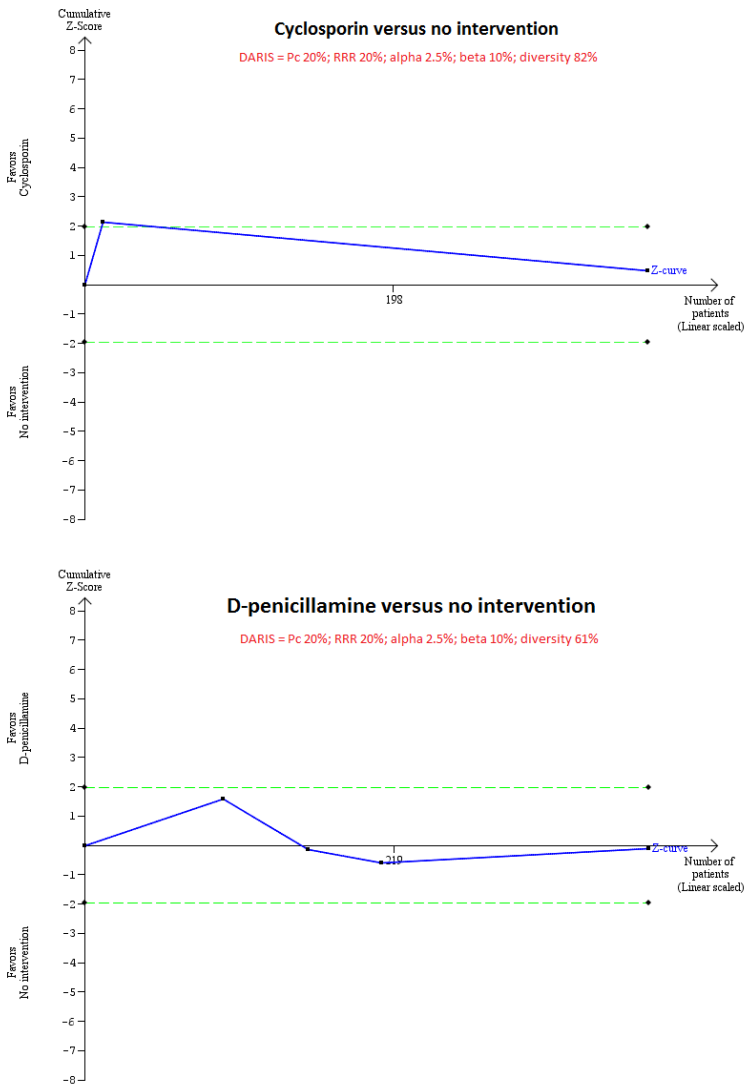
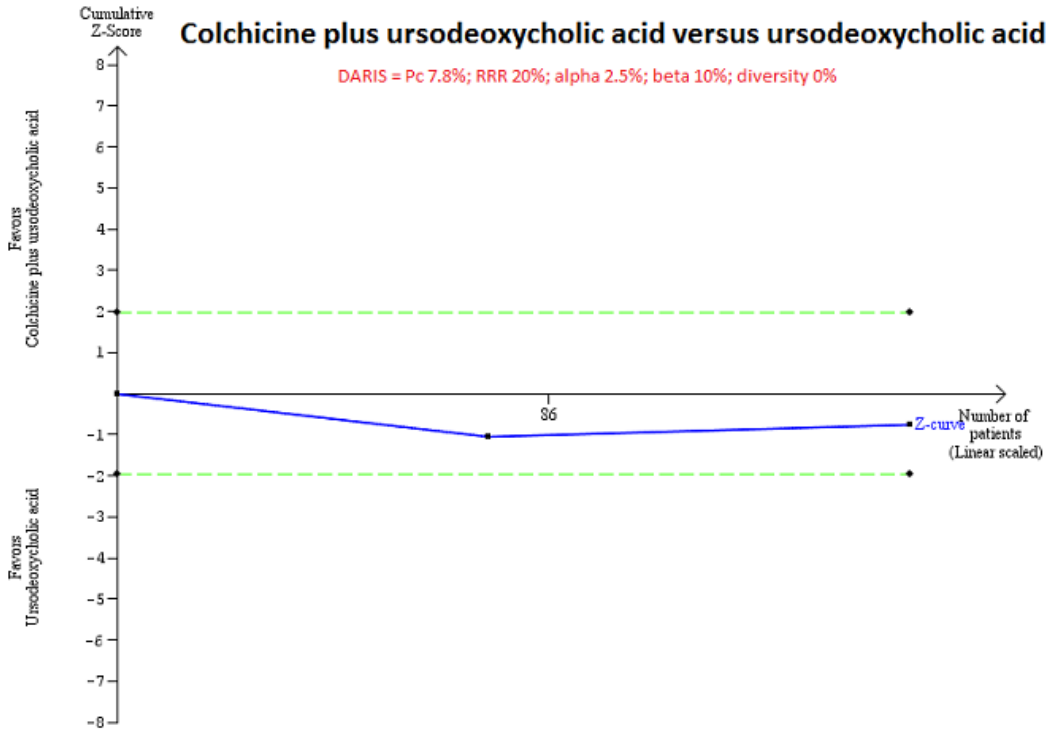


Figure 6. Trial Sequential Analysis of mortality at maximal follow-up: colchicine plus UDCA versus UDCA.Based on an alpha error of 2.5%, power of 90% (beta error of 10%), a relative risk reduction (RRR) of 20%, a control group proportion observed in the trials (Pc = 7.8%), and diversity observed in the analyses (0%), the accrued sample size (160 participants) was only a small fraction of the diversity adjusted required information size (DARIS) (13,316); therefore, the trial sequential monitoring boundaries were not drawn. The Z-curve (blue line) did not cross the conventional boundaries (green dotted line). This indicates that there is a high risk of random errors in both this comparison.



ADDITIONAL SUMMARY OF FINDINGS [*Explanation*]

Azathioprine versus no intervention for primary biliary cholangitis

Patient or population: people with primary biliary cholangitis
Settings: secondary or tertiary care
Intervention: azathioprine
Comparison: no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	No intervention	Azathioprine			
Mortality at maximal follow-up Follow-up: 63 months in 1 trial and not stated in 1 trial	**208 per 1000**	**128 per 1000** (78 to 205)	**OR 0.56** (0.32 to 0.98)	**224** (2 trials)	⊕◯◯◯ **Very low**[1,2]
Serious adverse events (proportion)	None of the trials reported this outcome.				
Serious adverse events (number of events)	None of the trials reported this outcome.				
Health-related quality of life	None of the trials reported this outcome.				

*The basis for the **assumed risk** is the mean control group proportion across all the trials. 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; **OR:** odds 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] Risk of bias in the trial(s) was high (downgraded by two levels).
[2] Sample sizes were small and 95% confidence intervals overlapped clinically significant and clinically insignificant or no effect (downgraded by two levels).

Colchicine versus no intervention for primary biliary cholangitis

Patient or population: people with primary biliary cholangitis
Settings: secondary or tertiary care
Intervention: colchicine
Comparison: no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	No intervention	Colchicine			
Mortality at maximal follow-up Follow-up: 12 to 24 months	**208 per 1000**	**168 per 1000** (78 to 327)	**OR 0.77** (0.32 to 1.85)	**122** (2 trials)	⊕◯◯◯ **Very low**[1,2]
Serious adverse events (proportion) Follow-up: 12 months	There were no events in either group			**64** (1 trial)	⊕◯◯◯ **Very low**[1,2,3]
Serious adverse events (number of events)	None of the trials reported this outcome.				
Health-related quality of life	None of the trials reported this outcome.				

*The basis for the **assumed risk** is the mean control group proportion across all the trials. 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; **OR:** odds 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] Risk of bias in the trial(s) was high (downgraded by two levels).

[2] Sample sizes were small and 95% confidence intervals overlapped clinically significant and clinically insignificant or no effect (downgraded by two levels).

[3] There was moderate heterogeneity (downgraded by one level).

Ciclosporin versus no intervention for primary biliary cholangitis

Patient or population: people with primary biliary cholangitis
Settings: secondary or tertiary care
Intervention: ciclosporin
Comparison: no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	No intervention	Ciclosporin			
Mortality at maximal follow-up Follow-up: 31 to 35 months	**208 per 1000**	**188 per 1000** (118 to 283)	**OR 0.88** (0.51 to 1.50)	**390** (3 trials)	⊕◯◯◯ **Very low**[1,2]
Serious adverse events (proportion)	None of the trials reported this outcome.				
Serious adverse events (number of events)	None of the trials reported this outcome.				
Health-related quality of life	None of the trials reported this outcome.				

*The basis for the **assumed risk** is the mean control group proportion across all the trials. 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; **OR:** odds 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] Risk of bias in the trial(s) was high (downgraded by two levels).

[2] Sample sizes were small and 95% confidence intervals overlapped clinically significant and clinically insignificant or no effect (downgraded by two levels).

D-Penicillamine versus no intervention for primary biliary cholangitis

Patient or population: people with primary biliary cholangitis
Settings: secondary or tertiary care
Intervention: D-penicillamine
Comparison: no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	No intervention	D-Penicillamine			
Mortality at maximal follow-up (Follow-up 24 to 66 months)	**208 per 1000**	**191 per 1000** (130 to 274)	**OR 0.90** (0.57 to 1.44)	**423** (5 trials)	⊕◯◯◯ **Very low**[1,2,3]
Serious adverse events (proportion) (Follow-up 24 months)	**4 per 1000**	**104 per 1000** (6 to 679)	**OR 28.77** (1.57 to 526.67)	**52** (1 trial)	⊕◯◯◯ **Very low**[1,2,3]
Serious adverse events (number of events)	None of the trials reported this outcome.				
Health-related quality of life	None of the trials reported this outcome.				

*The basis for the **assumed risk** is the mean control group proportion across all the trials. 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; **OR:** odds 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] Risk of bias in the trial(s) was high (downgraded by two levels).

[2] Sample sizes were small and 95% confidence intervals overlapped clinically significant and clinically insignificant or no effect (downgraded by two levels).

[3] There was moderate heterogeneity (downgraded by one level).

Colchicine plus UDCA versus UDCA for primary biliary cholangitis

Patient or population: people with primary biliary cholangitis
Settings: secondary or tertiary care
Intervention: colchicine + UDCA
Comparison: UDCA

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	UDCA	Colchicine + UDCA			
Mortality at maximal follow-up Follow-up: 24 months in 1 trial; not reported in 1 trial	**110 per 1000**	**185 per 1000** (45 to 524)	**OR 1.84** (0.38 to 8.91)	**158** (2 trials)	⊕◯◯◯ **Very low**[1,2]
Serious adverse events (proportion) Follow-up: not stated	**14 per 1000**	**42 per 1000** (2 to 526)	**OR 3.08** (0.12 to 78.14)	**74** (1 trial)	⊕◯◯◯ **Very low**[1,2,3]
Serious adverse events (number of events)	None of the trials reported this outcome.				
Health-related quality of life	None of the trials reported this outcome.				

*The basis for the **assumed risk** is the mean control group proportion across all the trials. 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; **OR:** odds ratio; **UDCA:** ursodeoxycholic acid.

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] Risk of bias in the trial(s) was high (downgraded by two levels).
[2] Sample sizes were small and 95% confidence intervals overlapped clinically significant and clinically insignificant or no effect (downgraded by two levels).
[3] There was moderate heterogeneity (downgraded by one level).

Methotrexate plus UDCA versus UDCA for primary biliary cholangitis

Patient or population: people with primary biliary cholangitis
Settings: secondary or tertiary care
Intervention: methotrexate + UDCA
Comparison: UDCA

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	UDCA	Methotrexate + UDCA			
Mortality at maximal follow-up Follow-up: 11 to 91 months	**110 per 1000**	**126 per 1000** (64 to 237)	**OR 1.17** (0.55 to 2.51)	**290** (2 trials)	⊕◯◯◯ **Very low**[1,2]
Serious adverse events (proportion)	None of the trials reported this outcome.				
Serious adverse events (number of events)	None of the trials reported this outcome.				
Health-related quality of life	None of the trials reported this outcome.				

*The basis for the **assumed risk** is the mean control group proportion across all the trials. 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; **OR:** odds ratio; **UDCA:** ursodeoxycholic acid.

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] Risk of bias in the trial(s) was high (downgraded by two levels).

[2] Sample sizes were small and 95% confidence intervals overlapped clinically significant and clinically insignificant or no effect (downgraded by two levels).

[3] There was moderate heterogeneity (downgraded by one level).

DISCUSSION

Summary of main results

We included 74 trials (5902 participants) in this review, and included 4274 participants from 46 trials in one or more outcomes in this review. We did not perform the planned network meta-analysis because there was no closed loop (i.e. outcomes for which direct and indirect estimates were available to allow us estimation of inconsistency). Therefore, we reported only the direct comparisons. We reported the results from frequentist meta-analysis only as it is more familiar to people.

Although mortality at maximal follow-up was lower in people who received azathioprine versus no intervention, there was no evidence of any reduction in mortality by any intervention, either at less than one year or between one and five years. However, this evidence is unreliable because the Christensen 1985 trial excluded a large proportion of participants (25%) (i.e. only 185/224 participants were included in the meta-analysis). The Trial Sequential Analysis showed that only a small proportion of the required information size was reached and the risk of random errors was high. In addition to the risk of systematic errors and random errors, the proportion of people who died was high (71.3%) in the no intervention group of the Christensen 1985 trial compared to the other trials (the overall mortality at maximal follow-up was 20.8%). Although this difference could be due to the shorter follow-up periods in some of the other trials, the mortality observed in this trial was much higher than that observed in the other trials with similar or longer follow-up such as Epstein 1979; Hendrickse 1999; and Papatheodoridis 2002. The general care of people with cirrhosis is likely to have improved since the 1980s and it is unlikely to be as high as that mortality observed in Christensen 1985. This is another reason why there is no need to recommend azathioprine routinely in people with primary biliary cholangitis.

There was no evidence of a decrease in liver transplantation, decompensated liver disease, or cirrhosis in any of the interventions compared with no intervention. However, several interventions increased the number of people with, and total number of, adverse events. Although the Trial Sequential Analysis revealed that only a small proportion of the required information size was reached, the risk of random errors was high. Thus, concluding that there were more adverse events in some of these comparisons is only of academic interest because none of the interventions appeared to result in clinical benefit.

However, it has to be pointed out that the periods of follow-up in the trials were sufficiently long to identify any differences in clinical outcomes because primary biliary cholangitis is a slowly progressive disease. Trials with sufficient follow-up (e.g. five or 10 years) are required to detect any differences in clinically important outcomes.

Overall completeness and applicability of evidence

The trials included symptomatic and asymptomatic primary biliary cholangitis, AMA-positive and AMA-negative primary biliary cholangitis, treatment-naive people, and people regardless of the treatments that they had received previously. However, majority of the trials excluded people with advanced liver cirrhosis and primary biliary cholangitis in people with other liver diseases. Therefore, this review is applicable to people with primary biliary cholangitis without advanced liver cirrhosis or with coexisting other liver diseases.

Quality of the evidence

The overall quality of evidence was very low for all the outcomes. The major reasons for this were the high risk of bias in the trials, in particular, exclusion of participants from the analysis after randomisation, small sample size, and imprecision. Overall, there were serious concerns about whether the effect estimates observed were the true effect estimates.

Potential biases in the review process

We followed the guidance of the *Cochrane Handbook for Systematic Reviews of Interventions* with two review authors independently selecting trials and extracting data (Higgins 2011). We performed a thorough search of the literature. However, the search period includes the premandatory trial registration era and it is possible that some trials on treatments that were not effective or were harmful were not reported at all.

We excluded studies which compared variations in the different treatments. Hence, this review does not provide information on whether one variation is better than another.

We only included randomised clinical trials which are known to focus mostly on benefits and do not collect and report harms in a detailed manner. Therefore, we might have missed a large number of studies that addressed the reporting of harms. Accordingly, this review is biased towards benefits ignoring harms. We did not search for interventions and trials registered at regulatory authorities (e.g. US Food and Drug Administration; European Medicines Agency, etc.). This may have overlooked trials and as such trials usually are unpublished, the lack of inclusion of such trials may make our comparisons look more advantageous than they really are. However, this is of academic interest only because there is no evidence of benefit of any treatment in people with primary biliary cholangitis (i.e. there is no reason to suggest that any of the treatments should be used in routine clinical practice regardless of the adverse event profile of the intervention).

We planned to perform a network meta-analysis. However, it was not possible to assess whether the potential effect modifiers were similar across different comparisons. Performing a network meta-analysis in this scenario can be misleading. Therefore, we did not perform the network meta-analysis, and assessed the compara-

tive benefits and harms of different interventions using standard Cochrane methodology.

Agreements and disagreements with other studies or reviews

We identified three network meta-analyses on this topic (Zhu 2015a; Zhu 2015b; Zhu 2015c). We disagreed with the authors of these reviews that UDCA in combination with corticosteroids or methotrexate are effective interventions in the treatment of primary biliary cholangitis. The disagreements were probably due to considering mortality and liver transplantation separately in this review compared to Zhu 2015a and Zhu 2015b and only including evidence prior to cross-over in our review. In particular, the cross-over was not true cross-over where the interventions were swapped but all the participants belonging to the 'no intervention' were switched over to the intervention. Therefore, it was not possible to obtain the effect estimate adjusted for intra-participant correlation either. It should be also noted that the decision to switch the no intervention to intervention was based on improvement of some laboratory parameters which are invalidated surrogate outcomes. This can only be considered as observational evidence. We disagree with current EASL and AASLD guideline recommendations that UDCA should be used for the management of primary biliary cholangitis (EASL 2009; Lindor 2009). Again, these recommendations were based on observational evidence and invalidated surrogate outcomes (Gluud 2007).

We agreed with several systematic reviews that showed that none of the interventions are effective in improving survival or other major clinical outcomes such as cirrhosis or liver transplantation (Giljaca 2010; Rudic 2012a; Rudic 2012b; Yin 2015; Zhang 2015).

AUTHORS' CONCLUSIONS

Implications for practice

Based on very low quality evidence, there is currently no evidence that any intervention is beneficial for primary biliary cholangitis.

Implications for research

Randomised clinical trials need to be conducted and reported according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement (Chan 2013) and the CONSORT statement (Schulz 2010). Future randomised clinical trials ought to be adequately powered, performed in people who are generally seen in the clinic rather than in highly selected participants, employ blinding, avoid post-randomisation dropouts or planned cross-overs, should have sufficient follow-up period (e.g. five to 10 years or more), and use clinically important outcomes such as mortality, health-related quality of life, cirrhosis, decompensated cirrhosis, and liver transplantation.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Almasio 2000

Methods	Randomised clinical trial.
Participants	Country: Italy. Number randomised: 90. Post-randomisation dropouts: 6 (6.7%). Revised sample size: 84. Mean age: 54 years. Females: 81 (96.4%). Symptomatic participants: 84 (100%). AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: symptomatic participants only. • AMA status: not stated. • Response status: not stated. Exclusion criteria • People with biliary obstruction. • Anticipated requirement for liver transplantation in 1 year. • Pregnancy. • Aged < 18 years or > 70 years. • Coexisting liver disease. • Anticipated life expectancy < 3 years.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (low) + colchicine (n = 42). Further details: UDCA: 250 mg BD for 3 years + colchicine: 1 mg/day for 3 years Group 2: UDCA (low) (n = 42). Further details: UDCA: 250 mg BD for 3 years.
Outcomes	Mortality, decompensated liver disease.
Notes	Reasons for post-randomisation dropouts: adverse effects and low compliance

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Colchicine, 1 mg daily, or an indistinguishable placebo were randomly assigned to patients according to a computer-generated list developed separately for each centre"
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed by a central study unit…"

Almasio 2000 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used and authors stated double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used and authors stated double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: adverse events not reported.
For-profit bias	Low risk	Comment: no money received for the trial; the drug was provided by Abc Farmaceutici S.p.a (author's reply)
Other bias	Low risk	Comment: no other bias noted.

Angulo 1999a

Methods	Randomised clinical trial.
Participants	Country: USA. Number randomised: 155. Post-randomisation dropouts: not stated. Revised sample size: 155. Mean age: 53 years. Females: 130 (83.9%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 12 months Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: not stated. • Response status: not stated. Exclusion criteria • People with decompensated cirrhosis. • Hepatocellular carcinoma. • Concomitant immunosuppressive regimen. • Other major diseases unrelated to primary biliary cholangitis. • Alcohol abuse. • Low compliance.
Interventions	Participants were randomly assigned to 3 groups. Group 1: UDCA (low) (n = 52). Further details: UDCA: 5 mg/kg/day to 7 mg/kg/day; duration: 1 to 2 years Group 2: UDCA (moderate) (n = 49).

Angulo 1999a (*Continued*)

	Further details: UDCA: 13 mg/kg/day to 15 mg/kg/day; duration: 1 to 2 years Group 3: UDCA (high) (n = 54). Further details: UDCA: 23 mg/kg/day to 25 mg/kg/day; duration: 1 to 2 years
Outcomes	Mortality, adverse events, liver transplantation.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was carried out separately for each of the eight strata with a computer-generated, blocked, randomized drug assignment schedule"
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomized by a statistician (D.W. M.), and the drug was provided by a pharmacist who was not involved in the patient's clinical evaluation or follow-up"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The patients, physicians, nurses, and study coordinator were unaware throughout the study which dose was being administered. To assure blindness patients received the same number of tablets by mixing UDCA-tablets with placebo-tablets in a ratio defined by their assigned dose; therefore, the number of tablets taken per day according to the body weight was exactly the same regardless of the dose assigned". Comment: identical placebo used and authors stated double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used and authors stated double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: unclear whether all participants randomised were included in the analysis
Selective reporting (reporting bias)	Low risk	Comment: mortality and morbidity reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other risk of bias.

Arora 1990

Methods	Randomised clinical trial.
Participants	Country: USA. Number randomised: 9. Post-randomisation dropouts: not stated. Revised sample size: 9. Mean age: not stated. Females: not stated. Symptomatic participants: 9 (100%). AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 5 months Inclusion criteria • Symptom status: symptomatic participants only. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (low) (n = 5). Further details: UDCA: 10 mg/kg/day for 5 months. Group 2: placebo (n = 4).
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: placebo used and authors stated double blind; however, unclear whether identical placebo used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: placebo used and authors stated double blind; however, unclear whether identical placebo used
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Unclear risk	Comment: information not available.

Arora 1990 (*Continued*)

Other bias	Low risk	Comment: no other risk of bias.

Askari 2010

Methods	Randomised clinical trial.
Participants	Country: USA. Number randomised: 28. Post-randomisation dropouts: 0 (0%). Revised sample size: 28. Mean age: 54 years. Females: 26 (92.9%). Symptomatic participants: not stated. AMA positive: 27 (96.4%). Responders: not stated. Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: AMA-positive and AMA-negative participants. • Response status: not stated. Exclusion criteria • Did not take UDCA in the previous 3 months. • Decompensated cirrhosis. • Required renal dialysis. • Pregnant or nursing. • Had a serious illness of other types such as uncontrolled congestive heart failure, severe diabetic neuropathy, severe pulmonary disease, advanced cancer, etc.
Interventions	Participants were randomly assigned to 2 groups. Group 1: tetrathiomolybdate (n = 13). Further details: tetrathiomolybdate: 10 mg/day to 120 mg/day based on serum ceruloplasmin levels; duration: not stated Group 2: placebo (n = 15).
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The patients were assigned to the placebo arm or the tetrathiomolybdate arm using a table of random numbers"
Allocation concealment (selection bias)	Low risk	Quote: "Central allocation by pharmacy" (author's reply).

Askari 2010 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used and authors stated double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used and authors stated double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "There were not post-randomisation drop-outs" (author's reply)
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Low risk	Quote: "Supported by Grant FD-02590-02 from the U. S. Food and Drug Administration's Orphan Products Office, the General Clinical Research Center of the University of Michigan Hospitals, Grant MO1- RR000042 from the National Institutes of Health, and Grant Ul1- RR024986 Clinical and Translational Science Awards"
Other bias	High risk	Comment: unclear whether the participants continued to take UDCA in both groups

Battezzati 1993

Methods	Randomised clinical trial.
Participants	Country: Italy. Number randomised: 88. Post-randomisation dropouts: 2 (2.3%). Revised sample size: 86. Mean age: 55 years. Females: 78 (90.7%). Symptomatic participants: 86 (100%). AMA positive: 77 (89.5%). Responders: not stated. Mean follow-up period (for all groups): minimum 6 months. Inclusion criteria • Symptom status: symptomatic participants only. • AMA status: AMA-positive and AMA-negative participants. • Response status: not stated. Exclusion criteria • Serum bilirubin levels > 10 mg/dL. • Decompensated liver disease. • Evidence of malignancy. • Alcohol abuse.

Battezzati 1993 (*Continued*)

Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (low) (n = 42). Further details: UDCA: 250 mg BD for 6 months. Group 2: placebo (n = 44).
Outcomes	None of the outcomes of interest reported.
Notes	Reasons for post-randomisation dropouts: lost to follow-up.

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization of treatment assignments was performed separately for each centre: patients were consecutively given indistinguishable medications, which had been assigned by the central pharmacy according to a computer-generated list. UDCA and an identical-appearing placebo were obtained through the courtesy of ABC Farmaceutici, Torino, Italy"
Allocation concealment (selection bias)	Low risk	Quote: "Randomization of treatment assignments was performed separately for each centre: patients were consecutively given indistinguishable medications, which had been assigned by the central pharmacy according to a computer-generated list. UDCA and an identical-appearing placebo were obtained through the courtesy of ABC Farmaceutici, Torino, Italy"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Randomization of treatment assignments was performed separately for each centre: patients were consecutively given indistinguishable medications, which had been assigned by the central pharmacy according to a computer-generated list. UDCA and an identical-appearing placebo were obtained through the courtesy of ABC Farmaceutici, Torino, Italy"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Randomization of treatment assignments was performed separately for each centre: patients were consecutively given indistinguishable medications, which had been assigned by the central pharmacy according to a computer-generated list. UDCA and an identical-appearing placebo were obtained through the courtesy of ABC Farmaceutici, Torino, Italy"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.

Battezzati 1993 (*Continued*)

Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other risk of bias.

Bobadilla 1994

Methods	Randomised clinical trial.
Participants	Country: Mexico. Number randomised: 40. Post-randomisation dropouts: not stated. Revised sample size: 40. Mean age: not stated. Females: not stated. Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 12 months Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) + colchicine (n = 21). Further details: UDCA: 13 mg/kg/day to 15 mg/kg/day for 1 year + colchicine: 1 mg/day for 5 days in a week for 1 year Group 2: placebo (n = 19).
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although placebo used in double-blind trial, unclear whether the placebo was identical

Bobadilla 1994 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although placebo used in double-blind trial, unclear whether the placebo was identical
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

Bodenheimer 1988

Methods	Randomised clinical trial.
Participants	Country: USA. Number randomised: 57. Post-randomisation dropouts: 10 (17.5%). Revised sample size: 47. Mean age: 52 years. Females: not stated. Symptomatic participants: 45 (95.7%). AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): 33 months. Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: AMA-positive and AMA-negative participants. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: colchicine (n = 28). Further details: colchicine: 0.6 mg BD orally for 5 years. Group 2: placebo (n = 29).
Outcomes	None of the outcomes of interest reported.
Notes	Reasons for post-randomisation dropouts: non-compliance.

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.

Bodenheimer 1988 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The design of our trial was that of a double-blind, randomized evaluation of colchicine (0.6 mg) twice daily compared with an identically appearing placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The design of our trial was that of a double-blind, randomized evaluation of colchicine (0.6 mg) twice daily compared with an identically appearing placebo"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	High risk	Quote: "The colchicine and placebo tablets were prepared and generously supplied by Eli Lilly and Company, Indianapolis, Ind"
Other bias	Low risk	Comment: no other source of bias.

Bowlus 2014

Methods	Randomised clinical trial.
Participants	Country: multicentric; international. Number randomised: 216. Post-randomisation dropouts: not stated. Revised sample size: 216. Mean age: 56 years. Females: 197 (91.2%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 12 months Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 3 groups. Group 1: obeticholic acid (low) (n = 73). Further details: obeticholic acid (low): 5 mg orally for 12 months; frequency not stated Group 2: obeticholic acid (low) (n = 73). Further details: obeticholic acid (low): 10 mg orally for 12 months; frequency not stated Group 3: placebo (n = 70).
Outcomes	None of the outcomes of interest reported.

Bowlus 2014 (*Continued*)

Notes	

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although placebo was used in double-blind trial, unclear whether the placebo was identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although placebo was used in double-blind trial, unclear whether the placebo was identical
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	High risk	Comment: Several authors had advised pharmaceutical companies or were employees of pharmaceutical company
Other bias	Low risk	Comment: no other source of bias.

Cash 2013

Methods	Randomised clinical trial.
Participants	Country: UK. Number randomised: 21. Post-randomisation dropouts: 8 (38.1%). Revised sample size: 13. Mean age: 55 years. Females: not stated. Symptomatic participants: not stated. AMA positive: 13 (100%). Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 12 months Inclusion criteria • Symptom status: not stated. • AMA status: AMA-positive participants only. • Response status: not stated. Exclusion criteria

Cash 2013 (*Continued*)

	• Aged < 19 years or > 76 years. • Cholesterol < 5 mmol/L. • Known hypertension. • Diabetes mellitus. • History of cardiovascular disease. • Already prescribed lipid-lowering agents or hormonal preparations. • Pregnancy.
Interventions	Participants were randomly assigned to 2 groups. Group 1: simvastatin (n = 7). Further details: simvastatin: 20 mg/day orally for 12 months Group 2: placebo (n = 6).
Outcomes	None of the outcomes of interest reported.
Notes	Reasons for post-randomisation dropouts: adverse effects.

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Low risk	Quote: "Patient treatment randomization and allocation was performed independently by the Department of Research Pharmacology in the Royal Victoria Hospital at the initial baseline visit"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The patients were blinded but the healthcare providers were not" (author's reply)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Outcome assessors were not blinded" (author's reply)
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Low risk	Quote: "Financial support: The Royal Victoria Hospital Liver Support Group"
Other bias	High risk	Quote: "Patients were allowed to continue previous prescriptions for primary biliary cholangitis. It was not clear whether this was balanced across groups"

Christensen 1985

Methods	Randomised clinical trial.
Participants	Country: multicentric; international. Number randomised: 248. Post-randomisation dropouts: 63 (25.4%). Revised sample size: 185. Mean age: 55 years. Females: not stated. Symptomatic participants: not stated. AMA positive: not stated. Mean follow-up period (for all groups): minimum 63 months. Inclusion criteria • Symptom status: not stated. • AMA status: AMA-positive and AMA-negative participants. • Response status: not stated. Exclusion criteria • No antimetabolites in the previous 6 months.
Interventions	Participants were randomly assigned to 2 groups. Group 1: azathioprine (n = 98). Further details: azathioprine: escalating doses up to a maximum of 100 mg/day; duration: not stated Group 2: placebo (n = 87).
Outcomes	Mortality.
Notes	Reasons for post-randomisation dropouts: lost to follow-up.

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were randomized to azathioprine or placebo separately for each centre and for each sex by the sealed envelope technique" Comment: further details of sealed envelope technique were not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used and authors stated double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used and authors stated double-blind

Christensen 1985 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: adverse events not reported.
For-profit bias	High risk	Quote: "This work was also supported by the Wellcome Foundation. J.N. was supported by Ciba-Geigy Ltd"
Other bias	Low risk	Comment: no other source of bias.

Combes 1995a

Methods	Randomised clinical trial.
Participants	Country: USA. Number randomised: 151. Post-randomisation dropouts: 0 (0%). Revised sample size: 151. Mean age: 49 years. Females: 134 (88.7%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 24 months Inclusion criteria • Symptom status: not stated. • AMA status: AMA-positive and AMA-negative participants. • Response status: not stated. Other exclusion criteria • Recurrent bleeds from oesophagogastric varices, spontaneous encephalopathy, or diuretic-resistant ascites. • Serum bilirubin ≥ 20 mg/dL. • Pregnancy. • Aged < 19 years. • Findings of other causes of liver disease.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) (n = 77). Further details: UDCA: 10 mg/kg/day to 12 mg/kg/day for 2 years Group 2: placebo (n = 74).
Outcomes	Decompensated liver disease.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**

Combes 1995a (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used in double-blind trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	High risk	Quote: "Supported in part by a research grant from Ciba-Geigy"
Other bias	Low risk	Comment: no other risk of bias.

Combes 2005

Methods	Randomised clinical trial.
Participants	Country: USA. Number randomised: 265. Post-randomisation dropouts: 0 (0%). Revised sample size: 265. Mean age: 51 years. Females: 245 (92.5%). Symptomatic participants: not stated. AMA positive: 265 (100%). Responders: not stated. Median follow-up period (for all groups): 91 months. Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: AMA-positive participants only. • Response status: not stated. Exclusion criteria • People with advanced biliary cirrhosis. • People with decompensated cirrhosis. • Aged < 19 years or > 69 years. • History of alcohol abuse. • Pregnant or unwilling to use contraception. • Use of immunosuppressive agents.

Combes 2005 (*Continued*)

	• Renal or pulmonary dysfunction.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) + methotrexate (n = 132). Further details: UDCA: 15 mg/kg/day for 2 years + methotrexate: 2.5 mg orally once a week Group 2: UDCA (moderate) (n = 133). Further details: UDCA: 15 mg/kg/day for 2 years.
Outcomes	Mortality, liver transplantation, decompensated liver disease
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: placebo used in this double-blind trial; however, the authors did not state whether the placebo was identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: placebo used in this double-blind trial; however, the authors did not state whether the placebo was identical
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: adverse events not reported.
For-profit bias	High risk	Quote: "By provision of UDCA by Ciba-Geigy Corporation, and subsequently Novartis; by provision of methotrexate and its placebo by Lederle Laboratories, and subsequently Wyeth-Ayerst Laboratories"
Other bias	Low risk	Comment: no other source of bias.

Dickson 1985

Methods	Randomised clinical trial.
Participants	Country: USA. Number randomised: 309. Post-randomisation dropouts: 82 (26.5%). Revised sample size: 227. Mean age: not stated. Females: 200 (88.1%). Symptomatic participants: 182 (80.2%). AMA positive: not stated. Responders: not stated. Median follow-up period (for all groups): 60 months. Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: not stated. • Response status: not stated. Exclusion criteria • People with severe hepatitis. • Evidence of inflammatory bowel disease. • Malignant condition other than skin cancer. • Evidence of prior or present extrahepatic obstruction. • Use of cholestatic or hepatotoxic drugs. • Excessive alcohol intake. • Presence of hepatitis B antigen.
Interventions	Participants were randomly assigned to 2 groups. Group 1: D-penicillamine (n = 111). Further details: D-penicillamine: 1000 mg/day; duration: not stated Group 2: placebo (n = 116).
Outcomes	Adverse events.
Notes	Reasons for post-randomisation dropouts: histological stages < 3; alcoholism

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to drug or placebo groups according to a table of random numbers"
Allocation concealment (selection bias)	Low risk	Quote: "Penicillamine and placebo (furnished to us through the courtesy of Merck Sharp and Dohme, West Point, Pa.) were dispensed in identical yellow capsules by a central pharmacist"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in double-blind trial.

Dickson 1985 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used in double-blind trial.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: mortality not reported.
For-profit bias	High risk	Quote: "Penicillamine and placebo (furnished to us through the courtesy of Merck Sharp and Dohme, West Point, Pa.) were dispensed in identical yellow capsules by a central pharmacist"
Other bias	High risk	Comment: authors presented the results of only a subgroup of participants without explaining the reason for this

Epstein 1979

Methods	Randomised clinical trial.
Participants	Country: UK. Number randomised: 98. Post-randomisation dropouts: not stated. Revised sample size: 98. Mean age: not stated. Females: not stated. Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): mean: 66 months. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: D-penicillamine (n = 61). Further details: D-penicillamine: 600 mg/day to 900 mg/day for 12 months Group 2: placebo (n = 37).
Outcomes	Mortality.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**

Epstein 1979 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The original double-blind design of the trial was discontinued after a year because both major and minor side effects identified treated patients"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "The original double-blind design of the trial was discontinued after a year because both major and minor side effects identified treated patients"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: adverse events not reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

Eriksson 1997

Methods	Randomised clinical trial.
Participants	Country: Sweden. Number randomised: 116. Post-randomisation dropouts: 15 (12.9%). Revised sample size: 101. Mean age: 57 years. Females: 99 (98%). Symptomatic participants: 39 (38.6%). AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 24 months Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: not stated. • Response status: not stated. Exclusion criteria • People with severe end-stage liver disease. • Pregnancy. • Alcohol or drug abuse.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (low) (n = 60). Further details: UDCA: 500 mg/day for 24 months.

Eriksson 1997 (*Continued*)

	Group 2: placebo (n = 56).
Outcomes	Liver transplantation.
Notes	Reasons for post-randomisation dropouts: adverse effects, alcoholic hepatitis, liver transplantation, death

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: placebo used in this double-blind trial; however, the authors did not state whether the placebo was identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: placebo used in this double-blind trial; however, the authors did not state whether the placebo was identical
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	High risk	Quote: "We acknowledge the financial support from Meda AB, Searle AB, and the Swedish Medical Research Council (03x-4793)"
Other bias	Low risk	Comment: no other source of bias.

Ferri 1993

Methods	Randomised clinical trial.
Participants	Country: Italy. Number randomised: 30. Post-randomisation dropouts: 0 (0%). Revised sample size: 30. Mean age: 53 years. Females: 27 (90%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 6 months

Ferri 1993 (*Continued*)

	Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated. Exclusion criteria • People with decompensated cirrhosis. • Extrahepatic biliary obstruction. • Severe kidney or heart disease. • Neoplasms. • Pregnancy or breastfeeding. • Excessive alcohol consumption.
Interventions	Participants were randomly assigned to 2 groups. Group 1: TUDCA (moderate) (n = 15). Further details: TUDCA: 13 mg/day to 15 mg/day for 6 months. Group 2: UDCA (moderate) (n = 15). Further details: UDCA: 13 mg/day to 15 mg/day for 6 months.
Outcomes	Adverse events.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: adverse events, the only outcome of interest reported in this study were available from all randomised participants
Selective reporting (reporting bias)	High risk	Comment: mortality not reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

Gao 2012

Methods	Randomised clinical trial.
Participants	Country: China. Number randomised: 79. Post-randomisation dropouts: not stated. Revised sample size: 79. Mean age: 53 years. Females: 77 (97.5%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated. Other inclusion criteria • Only people with Sjogren's syndrome were included. Exclusion criteria • People with decompensated cirrhosis. • Aged > 70 years. • Other autoimmune diseases.
Interventions	Participants were randomly assigned to 3 groups. Group 1: UDCA (moderate) (n = 29). Further details: UDCA: 13 mg/kg/day to 15 mg/kg/day; duration: not stated Group 2: UDCA (moderate) + glucocorticosteroids (n = 37). Further details: UDCA: 13 mg/kg/day to 15 mg/kg/day; duration: not stated + prednisolone: 7.5 mg/day; duration: not stated Group 3: UDCA (moderate) + azathioprine (n = 13). Further details: UDCA: 13 mg/kg/day to 15 mg/kg/day; duration: not stated + azathioprine: 1 mg/kg/day; duration: not stated
Outcomes	Adverse events, decompensated liver disease.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available.

Gao 2012 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: mortality not reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

Goddard 1994

Methods	Randomised clinical trial.
Participants	Country: UK. Number randomised: 57. Post-randomisation dropouts: not stated. Revised sample size: 57. Mean age: not stated. Females: not stated. Symptomatic participants: 30 (52.6%). AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): 15 months. Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 4 groups. Group 1: UDCA (low) (n = not stated). Further details: UDCA: 10 mg/kg/day; duration: not stated. Group 2: colchicine (n = not stated). Further details: colchicine: 1 mg/day; duration: not stated. Group 3: UDCA (low) + colchicine (n = not stated). Further details: UDCA: 10 mg/kg/day; duration: not stated + colchicine: 1 mg/day; duration: not stated Group 4: placebo (n = not stated).
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias ***Risk of bias***

Goddard 1994 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: placebo used; however, the authors did not mention blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: placebo used; however, the authors did not mention blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

Gonzalezkoch 1997

Methods	Randomised clinical trial.
Participants	Country: Chile. Number randomised: 25. Post-randomisation dropouts: not stated. Revised sample size: 25. Mean age: 50 years. Females: 25 (100%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 11 months Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated. Exclusion criteria • Other concomitant liver or biliary diseases. • Decompensated cirrhosis. • Presence of other serious diseases (e.g. diabetes mellitus, chronic renal insufficiency). • Need to use additional medications.

Gonzalezkoch 1997 (*Continued*)

	• Pregnancy. • Any pharmacological therapy during the previous 6 months.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (low) + methotrexate (n = 13). Further details: UDCA: 250 mg BD for 48 weeks + methotrexate: 10 mg/week given over 48 hours each week for 48 months Group 2: UDCA (low) (n = 12). Further details: UDCA: 250 mg BD for 48 weeks.
Outcomes	Mortality, adverse events.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Low risk	Quote: "A physician who was blinded to the treatment, followed them up clinically, evaluated clinical symptoms, adverse side effects, complications and compliance"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: placebo used in this double-blind trial; however, the authors did not state whether the placebo was identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: placebo used in this double-blind trial; however, the authors did not state whether the placebo was identical
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	Low risk	Comment: mortality and morbidity reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

Heathcote 1976

Methods	Randomised clinical trial.
Participants	Country: UK. Number randomised: 45. Post-randomisation dropouts: 6 (13.3%). Revised sample size: 39. Mean age: 51 years. Females: not stated. Symptomatic participants: 39 (100%). AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: symptomatic participants only. • AMA status: not stated. • Response status: not stated. Exclusion criteria • Established cirrhosis or liver failure. • Presence of oesophageal varices. • Recurrent suppurative infections. • Treatment with other immunosuppressants.
Interventions	Participants were randomly assigned to 2 groups. Group 1: azathioprine (n = 19). Further details: azathioprine: 2 mg/kg; frequency and duration: not stated Group 2: control (n = 20).
Outcomes	Mortality, cirrhosis.
Notes	Reasons for post-randomisation dropouts: adverse events, wrong diagnosis

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were randomly allocated to the treatment or control group, using the sealed envelope technique" Comment: further details of sealed envelope technique not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "No placebo was given to the control patients".
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "No placebo was given to the control patients".

Heathcote 1976 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: adverse events not reported.
For-profit bias	Low risk	Quote: "This work was supported by the Medical Research Council and the Ingram Fund"
Other bias	Low risk	Comment: no other source of bias.

Heathcote 1994

Methods	Randomised clinical trial.
Participants	Country: Canada. Number randomised: 222. Post-randomisation dropouts: not stated. Revised sample size: 222. Mean age: 56 years. Females: 206 (92.8%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 24 months Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: not stated. • Response status: not stated. Exclusion criteria • Aged < 18 years. • On transplant list. • Needed to take enzyme-inducing drugs. • Pregnant. • Other medical illnesses with anticipated life expectancy < 5 years.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) (n = 111). Further details: UDCA: 14 mg/kg/day for 2 years. Group 2: placebo (n = 111).
Outcomes	Mortality, liver transplantation.
Notes	

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement

Heathcote 1994 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was done separately at each centre by the study pharmacist using consecutive identification numbers, and patients were stratified according to whether they were symptomatic or asymptomatic"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Once informed consent was obtained from the patients, double-blind randomization to UDCA or an identical placebo (1 : 1) was conducted"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Once informed consent was obtained from the patients, double-blind randomization to UDCA or an identical placebo (1 : 1) was conducted"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: unclear whether the authors have reported the outcomes on all randomised participants
Selective reporting (reporting bias)	High risk	Comment: adverse events not reported.
For-profit bias	High risk	Quote: "Study medications kindly provided by Interfalk Canada and Jouveinal Inc., Quebec, Canada"
Other bias	Low risk	Comment: no other source of bias.

Hendrickse 1999

Methods	Randomised clinical trial.
Participants	Country: UK. Number randomised: 60. Post-randomisation dropouts: not stated. Revised sample size: 60. Mean age: 57 years. Females: 55 (91.7%). Symptomatic participants: 57 (95%). AMA positive: 51 (85%). Responders: not stated. Mean follow-up period (for all groups): minimum 68 months. Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: AMA-positive and AMA-negative participants. • Response status: not stated. Exclusion criteria • Advanced liver disease. • Continuing or recent alcohol abuse. • Immunosuppressive drugs in the previous 6 months.

Hendrickse 1999 (*Continued*)

	• Contemplation of pregnancy. • Haematological abnormalities. • Other serious medical illness that might cause liver dysfunction or limit life expectancy.
Interventions	Participants were randomly assigned to 2 groups. Group 1: methotrexate (n = 30). Further details: methotrexate: 2.5 mg 3 times weekly for 6 years Group 2: placebo (n = 30). Further details: placebo: 3 times weekly for 6 years.
Outcomes	Mortality, liver transplantation.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized in groups of 10 by a random-number technique, operated by the hospital pharmacy, to receive 2.5 mg MTX [methotrexate] or identical placebo tablets, both supplied by Lederle Laboratories, on Friday, Saturday, and Sunday of each week for up to 6 years"
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomized in groups of 10 by a random-number technique, operated by the hospital pharmacy, to receive 2.5 mg MTX or identical placebo tablets, both supplied by Lederle Laboratories, on Friday, Saturday, and Sunday of each week for up to 6 years"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: placebo used in this double-blind trial; however, the authors did not state whether the placebo was identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: placebo used in this double-blind trial; however, the authors did not state whether the placebo was identical
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor morbidity reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

Hirschfield 2015

Methods	Randomised clinical trial.
Participants	Country: multicentric; international. Number randomised: 165. Post-randomisation dropouts: 0 (0%). Revised sample size: 165. Mean age: 55 years. Females: 157 (95.2%). Symptomatic participants: not stated. AMA positive: 134 (81.2%). Responders: 0 (0%). Mean follow-up period (for all groups): all participants followed up for 3 months Inclusion criteria • Symptom status: not stated. • AMA status: AMA-positive and AMA-negative participants. • Response status: non-responders only. Exclusion criteria • Advanced liver disease or decompensated liver disease. • Immunosuppressive drugs in the previous 3 months. • Other concomitant liver diseases.
Interventions	Participants were randomly assigned to 3 groups. Group 1: obeticholic acid (low) (n = 38). Further details: obeticholic acid (low): 10 mg for 85 days; frequency not stated Group 2: obeticholic acid (moderate) (n = 48). Further details: obeticholic acid (moderate): 25 mg for 85 days; frequency not stated Group 3: obeticholic acid (high) (n = 41). Further details: obeticholic acid (high): 50 mg for 85 days; frequency not stated Group 4: placebo (n = 38).
Outcomes	Adverse events.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The computerized randomization schedule used a block size of 4 at each center"
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.

Hirschfield 2015 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: mortality not reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	High risk	Quote: "Patients received varying doses of UDCA".

Hoofnagle 1986

Methods	Randomised clinical trial.
Participants	Country: multicentric; international. Number randomised: 24. Post-randomisation dropouts: 0 (0%). Revised sample size: 24. Mean age: 47 years. Females: 23 (95.8%). Symptomatic participants: 24 (100%). AMA positive: 22 (91.7%). Responders: not stated. Mean follow-up period (for all groups): 52 months. Inclusion criteria • Symptom status: symptomatic participants only. • AMA status: AMA-positive and AMA-negative participants. • Response status: not stated. Exclusion criteria • Advanced liver disease or decompensated liver disease.
Interventions	Participants were randomly assigned to 2 groups. Group 1: chlorambucil (n = 13). Further details: chlorambucil: 2 mg OD; duration: not stated Group 2: control (n = 11).
Outcomes	Mortality, adverse events.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized by random numbers (generated by pharmacy) to either chlorambucil or no therapy. Pre-computer age. They were kept in envelopes" (author's reply)

Hoofnagle 1986 (*Continued*)

Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomized by random numbers (generated by pharmacy) to either chlorambucil or no therapy. Pre-computer age. They were kept in envelopes" (author's reply)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Not a blinded study" (author's reply).
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "The outcomes were not blinded" (author's reply).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no post-randomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and morbidity reported.
For-profit bias	Low risk	Quote: "The study was funded by the NIH intramural program" (author's reply)
Other bias	Low risk	Comment: no other source of bias.

Hosonuma 2015

Methods	Randomised clinical trial.
Participants	Country: Japan. Number randomised: 27. Post-randomisation dropouts: 0 (0%). Revised sample size: 27. Mean age: 64 years. Females: 22 (81.5%). Symptomatic participants: not stated. AMA positive: not stated. Responders: 0 (0%). Mean follow-up period (for all groups): minimum: 96 months. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: non-responders only. Other inclusion criteria • People with dyslipidaemia. Exclusion criteria • Other liver diseases, e.g. alcoholic liver disease. • Obstructive biliary disease.

Hosonuma 2015 (*Continued*)

Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) + bezafibrate (n = 13). Further details: UDCA: 12 mg/kg/day to 15 mg/kg/day; duration: not stated + bezafibrate: 400 mg/day; duration: not stated Group 2: UDCA (moderate) (n = 14). Further details: UDCA: 12 mg/kg/day to 15 mg/kg/day; duration: not stated
Outcomes	Mortality, adverse events, liver transplantation.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Sealed opaque envelopes" (author's reply).
Allocation concealment (selection bias)	Low risk	Quote: "These patients were randomly allocated to treatment with either UDCA alone (the UDCA group) or with the combination therapy (the UDCA+BF [bezafibrate] group), according to sequential sealed envelopes in blocks of four to ensure equal randomization for the duration of the study"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "However, our study was an unblinded, open trial and was therefore not free from bias"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "However, our study was an unblinded, open trial and was therefore not free from bias"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no post-randomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events reported.
For-profit bias	Low risk	Quote: "This study was supported by the authors' own research funds"
Other bias	Low risk	Comment: no other source of bias.

Ikeda 1996

Methods	Randomised clinical trial.
Participants	Country: Japan. Number randomised: 22. Post-randomisation dropouts: 0 (0%). Revised sample size: 22. Mean age: 61 years. Females: 19 (86.4%). Symptomatic participants: 7 (31.8%). AMA positive: 22 (100%). Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 24 months Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: AMA-positive participants only. • Response status: not stated. Exclusion criteria • Other liver diseases. • No immunosuppressants or hepatotoxic drugs in the previous 6 months. • Alcohol or drug abuse.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) + colchicine (n = 10). Further details: UDCA: 9 mg/kg/day to 15 mg/kg/day for 2 years + colchicine: 1 mg/day for 2 years Group 2: UDCA (moderate) (n = 12). Further details: UDCA: 9 mg/kg/day to 15 mg/kg/day for 2 years
Outcomes	Adverse events.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available.

Ikeda 1996 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: mortality not reported.
For-profit bias	Unclear risk	Quote: "Part of the present study was supported by a grant from the Intractable Liver Diseases Research Committee, the Ministry of Health and Welfare, Japan" Comment: unclear how the remaining part of the funds were obtained
Other bias	High risk	Comment: dose range for UDCA was very wide.

Iwasaki 2008a

Methods	Randomised clinical trial.
Participants	Country: Japan. Number randomised: 45. Post-randomisation dropouts: not stated. Revised sample size: 45. Mean age: 56 years. Females: 37 (82.2%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 12 months Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated. Exclusion criteria • Cirrhosis. • Advanced liver disease or decompensated cirrhosis. • Renal insufficiency. • Malignancy. • Pregnancy. • Aged < 19 years.
Interventions	Participants were randomly assigned to 2 groups. Group 1: bezafibrate (n = 20). Further details: bezafibrate: 400 mg/day for 52 weeks. Group 2: UDCA (low) (n = 25). Further details: UDCA: 600 mg/day for 52 weeks.
Outcomes	None of the outcomes of interest reported.
Notes	

Iwasaki 2008a (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Low risk	Quote: "Consecutive patients from these hospitals were randomized centrally at the Kanagawa Dental University and were enrolled into the study if they met the following criteria"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "A randomized, open study design was used because there was no suitable placebo for bezafibrate available"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "A randomized, open study design was used because there was no suitable placebo for bezafibrate available"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Low risk	Quote: "The Ministry of Health, Labour and Welfare of Japan supported this study from 2002 to 2004 with a Health Science Research Grant on a Specific Disease (Study of Intractable Liver Diseases) to chief scientist Gotaro Toda"
Other bias	Low risk	Comment: no other bias.

Iwasaki 2008b

Methods	Randomised clinical trial.
Participants	Country: Japan. Number randomised: 22. Post-randomisation dropouts: not stated. Revised sample size: 22. Mean age: 54 years. Females: 19 (86.4%). Symptomatic participants: not stated. AMA positive: not stated. Responders: 0 (0%). Mean follow-up period (for all groups): all participants followed up for 12 months Inclusion criteria • Symptom status: not stated.

	• AMA status: not stated. • Response status: non-responders only. Exclusion criteria • Cirrhosis. • Advanced liver disease or decompensated cirrhosis. • Renal insufficiency. • Malignancy. • Pregnancy. • Aged < 19 years.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (low) + bezafibrate (n = 10). Further details: UDCA: 600 mg/day for 52 weeks + bezafibrate: 400 mg/day for 52 weeks Group 2: UDCA (low) (n = 12). Further details: UDCA: 600 mg/day for 52 weeks.
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Low risk	Quote: "Consecutive patients from these hospitals were randomized centrally at the Kanagawa Dental University and were enrolled into the study if they met the following criteria"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "A randomized, open study design was used because there was no suitable placebo for bezafibrate available"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "A randomized, open study design was used because there was no suitable placebo for bezafibrate available"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Low risk	Quote: "The Ministry of Health, Labour and Welfare of Japan supported this study from 2002 to 2004 with a Health Science Research Grant on a Specific Disease (Study of In-

Iwasaki 2008b (*Continued*)

		tractable Liver Diseases) to chief scientist Gotaro Toda"
Other bias	Low risk	Comment: no other bias.

Kanda 2003

Methods	Randomised clinical trial.
Participants	Country: Japan. Number randomised: 22. Post-randomisation dropouts: 0 (0%). Revised sample size: 22. Mean age: 56 years. Females: 19 (86.4%). Symptomatic participants: not stated. AMA positive: not stated. Responders: 0 (0%). Mean follow-up period (for all groups): minimum 7 months. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: non-responders only. Other inclusion criteria • Treatment with UDCA for ≥ 6 months prior the study. • Prior compliance with UDCA therapy. Exclusion criteria • Other chronic liver diseases or decompensated liver disease. • Previous colchicine, corticosteroid, or immunosuppressive treatment. • Thyroid or renal dysfunction.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (low) + bezafibrate (n = 11). Further details: UDCA: 600 mg/day for 6 months + bezafibrate: 400 mg/day for 52 weeks Group 2: UDCA (low) (n = 11). Further details: UDCA: 600 mg/day for 6 months.
Outcomes	Adverse events.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.

Kanda 2003 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: mortality was not reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other bias.

Kaplan 1986

Methods	Randomised clinical trial.
Participants	Country: USA. Number randomised: 60. Post-randomisation dropouts: 3 (5%). Revised sample size: 57. Mean age: not stated. Females: 57 (100%). Symptomatic participants: 45 (78.9%). AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 24 months Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: AMA-positive and AMA-negative participants. • Response status: not stated. Exclusion criteria • Concomitant debilitating cardiovascular illness. • End-stage cirrhosis.
Interventions	Participants were randomly assigned to 2 groups. Group 1: colchicine (n = 28). Further details: colchicine: 0.6 mg BD for ≥ 2 years. Group 2: placebo (n = 29).
Outcomes	Mortality.
Notes	Reasons for post-randomisation dropouts: adverse effects, despondent about treatment

Kaplan 1986 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: authors stated that this was a double-blind trial and used a placebo; however, they did not state whether the placebo was identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: authors stated that this was a double-blind trial and used a placebo; however, they did not state whether the placebo was identical
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: adverse events not reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other bias.

Kaplan 1999

Methods	Randomised clinical trial.
Participants	Country: USA. Number randomised: 87. Post-randomisation dropouts: 2 (2.3%). Revised sample size: 85. Mean age: 51 years. Females: 82 (96.5%). Symptomatic participants: 71 (83.5%). AMA positive: 77 (90.6%). Responders: not stated. Mean follow-up period (for all groups): minimum 24 months. Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: AMA-positive and AMA-negative participants. • Response status: not stated. Exclusion criteria • End-stage liver failure. • History of alcohol abuse.

Kaplan 1999 (*Continued*)

	• Administration of drugs associated with chronic liver disease. • Contemplation of pregnancy. • Other serious medical illnesses such as renal or heart disease that may cause liver dysfunction or shorten life expectancy. • Hypersplenism.
Interventions	Participants were randomly assigned to 2 groups. Group 1: colchicine (n = 43). Further details: colchicine: 0.6 mg BD for 2 years. Group 2: methotrexate (n = 42). Further details: methotrexate: 15 mg/week orally.
Outcomes	None of the outcomes of interest reported.
Notes	Reasons for post-randomisation dropouts: withdrawal from study

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both the patients and investigators were blinded to the treatment assignments"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Both the patients and investigators were blinded to the treatment assignments" Comment: authors stated that this was a double-blind trial and used a placebo; however, they did not state whether the placebo was identical
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other bias.

Kowdley 2011

Methods	Randomised clinical trial.
Participants	Country: multicentric; international. Number randomised: 59. Post-randomisation dropouts: not stated. Revised sample size: 59. Mean age: 55 years. Females: 50 (84.7%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 3 groups. Group 1: obeticholic acid (low) (n = 20). Further details: obeticholic acid (low): 10 mg OD for 12 weeks Group 2: obeticholic acid (high) (n = 16). Further details: obeticholic acid (high): 50 mg OD for 12 weeks Group 3: placebo (n = 23).
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although this was a double-blind trial and placebo was used, unclear whether the placebo was identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although this was a double-blind trial and placebo was used, unclear whether the placebo was identical
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.

Kowdley 2011 (*Continued*)

For-profit bias	High risk	Comment: some of the coauthors were from the pharmaceutical industry
Other bias	Low risk	Comment: no other source of bias.

Kurihara 2000

Methods	Randomised clinical trial.
Participants	Country: Japan. Number randomised: 24. Post-randomisation dropouts: not stated. Revised sample size: 24. Mean age: 60 years. Females: 23 (95.8%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated. Exclusion criteria • Cirrhosis. • Advanced liver disease or decompensated cirrhosis. • Renal insufficiency. • Malignancy. • Pregnancy. • Aged < 19 years of age.
Interventions	Participants were randomly assigned to 2 groups. Group 1: bezafibrate (n = 12). Further details: bezafibrate: 400 mg/day for 1 year. Group 2: UDCA (low) (n = 12). Further details: UDCA: 600 mg/day for 1 year.
Outcomes	Adverse events.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.

Kurihara 2000 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: mortality not reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other bias.

Leuschner 1989

Methods	Randomised clinical trial.
Participants	Country: Germany. Number randomised: 20. Post-randomisation dropouts: 2 (10%). Revised sample size: 18. Mean age: not stated. Females: 18 (100%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 12 months Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated. Exclusion criteria • Decompensated liver cirrhosis. • Chronic pancreatitis. • Taking immunosuppressive drugs, glucocorticosteroids, or sex hormones. • Taking other drugs for treatment of liver diseases or known to cause hepatotoxicity.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (low) (n = 10). Further details: UDCA: 10 mg/kg/day for 9 months. Group 2: placebo (n = 8).

Leuschner 1989 (*Continued*)

Outcomes	Mortality, adverse events.
Notes	Reasons for post-randomisation dropouts: not stated.

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although placebo was used in this double-blind trial, unclear whether identical placebo used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although placebo was used in this double-blind trial, unclear whether identical placebo used
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and morbidity reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

Leuschner 1999

Methods	Randomised clinical trial.
Participants	Country: Germany. Number randomised: 40. Post-randomisation dropouts: 1 (2.5%). Revised sample size: 39. Mean age: 58 years. Females: 37 (94.9%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 24 months Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.

Leuschner 1999 (*Continued*)

	Exclusion criteria • Decompensated liver cirrhosis. • Diabetes mellitus. • Glaucoma. • Previous history of duodenal or gastric ulcer. • Pregnancy. • Hypertension.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) + corticosteroids (n = 20). Further details: UDCA: 10 mg/kg/day to 15 mg/kg/day for 2 years + budesonide: 3 mg 3 times daily for 2 years Group 2: UDCA (moderate) (n = 19).
Outcomes	None of the outcomes of interest reported.
Notes	Reasons for post-randomisation dropouts: personal reasons.

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Complete randomization was done according to Rancode + (version 3.1; IDV-Co., Marsaglia and Bray, Gauting, Germany)"
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although placebo was used in this double-blind trial, unclear whether identical placebo used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although placebo was used in this double-blind trial, unclear whether identical placebo used
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	High risk	Quote: "UDCA, budesonide, and placebo were provided by Dr. Falk Pharma GmbH (Freiburg, Germany)"
Other bias	Low risk	Comment: no other source of bias.

Liberopoulos 2010

Methods	Randomised clinical trial.
Participants	Country: Greece. Number randomised: 10. Post-randomisation dropouts: not stated. Revised sample size: 10. Mean age: 57 years. Females: 8 (80%). Symptomatic participants: not stated. AMA positive: not stated. Responders: 0 (0%). Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: non-responders only. Exclusion criteria • Cardiovascular disease. • Diabetes mellitus. • Cancer. • Renal disease. • Hypothyroidism. • Recent lipid-lowering agent use. • Agents that affect lipid metabolism.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (low) + fenofibrate (n = 6). Further details: UDCA: 600 mg/day for 8 weeks + fenofibrate: 200 mg/day for 8 weeks Group 2: UDCA (low) (n = 4). Further details: UDCA: 600 mg/day for 8 weeks.
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Continue open-label UDCA".

Liberopoulos 2010 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Continue open-label UDCA".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Unclear risk	Quote: "This study was conducted independently; no company or institution supported it financially. Some of the authors have given talks, attended conferences and participated in trials and advisory boards sponsored by various pharmaceutical companies". Comment: unclear whether the authors were in the advisory board of related pharmaceutical companies
Other bias	Low risk	Comment: no other source of bias.

Lim 1994

Methods	Randomised clinical trial.
Participants	Country: UK. Number randomised: 32. Post-randomisation dropouts: not stated. Revised sample size: 32. Mean age: not stated. Females: not stated. Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) (n = not stated). Further details: UDCA: 10 mg/kg/day to 12 mg/kg/day; duration: not stated Group 2: placebo (n = not stated).
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias	***Risk of bias***

Lim 1994 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although a placebo was used in this double-blind trial, unclear whether the placebo was identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although a placebo was used in this double-blind trial, unclear whether the placebo was identical
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

Lindor 1994

Methods	Randomised clinical trial.
Participants	Country: USA. Number randomised: 180. Post-randomisation dropouts: 10 (5.6%). Revised sample size: 170. Mean age: 53 years. Females: 160 (94.1%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 24 months Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: not stated. • Response status: not stated. Exclusion criteria • People with decompensated cirrhosis. • Hepatocellular carcinoma. • Concomitant immunosuppressive regimen. • Other major diseases unrelated to primary biliary cholangitis. • Alcohol abuse.

Lindor 1994 (*Continued*)

	• Low compliance. • Recurrent variceal haemorrhage, intractable ascites, spontaneous encephalopathy.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) (n = 86). Further details: UDCA: 13 mg/kg/day to 15 mg/kg/day; duration: not stated Group 2: placebo (n = 84).
Outcomes	Mortality, adverse events, liver transplantation.
Notes	Reasons for post-randomisation dropouts: not stated.

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The patients, physicians, nurses, and study coordinators were blinded as to whether active drug or placebo was being administered"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The patients, physicians, nurses, and study coordinators were blinded as to whether active drug or placebo was being administered"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and morbidity reported.
For-profit bias	High risk	Quote: "Supported by Falk Pharma and Interfalk".
Other bias	Low risk	Comment: no other risk of bias.

Lindor 1997

Methods	Randomised clinical trial.
Participants	Country: USA. Number randomised: 150. Post-randomisation dropouts: not stated. Revised sample size: 150. Mean age: not stated. Females: not stated.

	Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 12 months Inclusion criteria • Symptom status: not stated. • AMA status: AMA positive participants only. • Response status: not stated.
Interventions	Participants were randomly assigned to 3 groups. Group 1: UDCA (low) (n = not stated). Further details: UDCA: 5 mg/kg/day to 7 mg/kg/day; duration: not stated Group 2: UDCA (moderate) (n = not stated). Further details: UDCA: 13 mg/kg/day to 15 mg/kg/day; duration: not stated Group 3: UDCA (high) (n = not stated). Further details: UDCA: 22 mg/kg/day to 25 mg/kg/day; duration: not stated
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other risk of bias.

Lombard 1993

Methods	Randomised clinical trial.
Participants	Country: multicentric; international. Number randomised: 349. Post-randomisation dropouts: 0 (0%). Revised sample size: 349. Mean age: 54 years. Females: 298 (85.4%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Median follow-up period (for all groups): 31 months. Inclusion criteria • Symptom status: not stated. • AMA status: AMA-positive and AMA-negative participants. • Response status: not stated. Exclusion criteria • Significant renal impairment. • Serious non-hepatic or malignant disease limiting life expectancy. • Inability to attend for regular follow-up. • Consideration for a liver transplant.
Interventions	Participants were randomly assigned to 2 groups. Group 1: ciclosporin (n = 176). Further details: ciclosporin: 3 mg/kg/day to maintain levels at 150 ng/mL by polyclonal radioimmunoassay or 75 ng/mL by monoclonal radioimmunoassay Group 2: placebo (n = 173).
Outcomes	Mortality, adverse events, liver transplantation.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Quote: "Sealed envelopes" (author's reply).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.

Lombard 1993 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no post-randomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and morbidity reported.
For-profit bias	High risk	Quote: "The authors are grateful to Sandoz Pharmaceuticals, Basle, Switzerland and their international sub-offices for supplying Sandimmune and placebo for this study and for their support throughout. The authors are grateful to Sandoz Pharmaceuticals, Basle, Zerland and their international sub-offices for supplying Sandimmune and placebo for this study and for their support throughout"
Other bias	Low risk	Comment: no other source of bias.

Ma 2016

Methods	Randomised clinical trial.
Participants	Country: China. Number randomised: 199. Post-randomisation dropouts: 8 (4.0%). Revised sample size: 191. Mean age: 51 years. Females: 167 (83.9%). Symptomatic participants: 38 (19.9%). AMA positive: 187 (97.9%). Responders: not stated. Mean follow-up period (for all groups): all participants: 6 months Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: AMA-positive and AMA-negative participants. • Response status: not stated. Exclusion criteria • Advanced or decompensated liver disease. • Pregnancy or breastfeeding. • Other causes of liver diseases. • Serious comorbidities.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) (n = 66). Further details: UDCA: 250 mg 3 times daily for 24 weeks. Group 2: TUDCA (moderate) (n = 125). Further details: TUDCA: 250 mg 3 times daily for 24 weeks.
Outcomes	Adverse events.
Notes	Reason for drop-outs: not reported.

Ma 2016 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "A centralized telecommunication-based interactive voice response system was used for patient randomization after patient eligibility was determined through clinical and laboratory screening assessments"
Allocation concealment (selection bias)	Low risk	Quote: "A centralized telecommunication-based interactive voice response system was used for patient randomization after patient eligibility was determined through clinical and laboratory screening assessments"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: unclear whether all participants were included in the analysis
Selective reporting (reporting bias)	High risk	Comment: mortality not reported.
For-profit bias	High risk	Quote: "This study was sponsored by the Beijing Trendful Kangjian Medical Information Consulting Co., Ltd. and the Major Science and Technology Special Project of China Twelfth Five-year Plan (2012ZX10002003). Registration Number: NCT01829698"
Other bias	Low risk	Comment: no other source of bias.

Macklon 1982

Methods	Randomised clinical trial.
Participants	Country: UK. Number randomised: 60. Post-randomisation dropouts: 0 (0%). Revised sample size: 60. Mean age: not stated. Females: not stated. Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated.

Macklon 1982 (*Continued*)

	Mean follow-up period (for all groups): 37 months. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: D-penicillamine (n = 41). Further details: D-penicillamine: 250 mg/day or 1 g/day; duration: not stated Group 2: placebo (n = 19).
Outcomes	Mortality, adverse events.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although placebo was used, there is no mention of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although placebo was used, there is no mention of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no post-randomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and morbidity reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other bias.

Manzillo 1993a

Methods	Randomised clinical trial.
Participants	Country: Italy. Number randomised: 32. Post-randomisation dropouts: not stated. Revised sample size: 32.

Manzillo 1993a (*Continued*)

	Mean age: not stated. Females: not stated. Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 1 month Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: SAMe (n = 16). Further details: SAMe: 800 mg/day IV for 2 weeks. Group 2: placebo (n = 16).
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although placebo was used, there was no mention of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although placebo was used, there was no mention of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other bias.

Manzillo 1993b

Methods	Randomised clinical trial.
Participants	Country: Italy. Number randomised: 6. Post-randomisation dropouts: not stated. Revised sample size: 6. Mean age: not stated. Females: not stated. Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 2 months Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: SAMe (n = 3). Further details: SAMe: 1600 mg/day orally for 8 weeks. Group 2: placebo (n = 3).
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although placebo was used, there was no mention of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although placebo was used, there was no mention of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Unclear risk	Comment: information not available.

Manzillo 1993b (*Continued*)

Other bias	Low risk	Comment: no other bias.

Mason 2008

Methods	Randomised clinical trial.
Participants	Country: multicentric; international. Number randomised: 59. Post-randomisation dropouts: 0 (0%). Revised sample size: 59. Mean age: 56 years. Females: 58 (98.3%). Symptomatic participants: not stated. AMA positive: 59 (100%). Responders: 0 (0%). Mean follow-up period (for all groups): all participants followed up for 6 months Inclusion criteria • Symptom status: not stated. • AMA status: AMA-positive participants only. • Response status: non-responders only. Other exclusion criteria • Advanced or decompensated liver disease. • Use of immunosuppressants or anti-inflammatory drugs in previous 3 months. • Significant renal impairment. • Excessive alcohol consumption. • Pregnant, breastfeeding, or not using contraceptives in sexually active women of child-bearing age.
Interventions	Participants were randomly assigned to 2 groups. Group 1: lamivudine + zidovudine + UDCA (moderate) (n = 30). Further details: lamivudine: 150 mg BD for 6 months + zidovudine: 300 mg BD for 6 months + UDCA: 13 mg/kg/day to 15 mg/kg/day for 6 months Group 2: UDCA (moderate) (n = 29). Further details: UDCA: 13 mg/kg/day to 15 mg/kg/day for 6 months
Outcomes	Adverse events.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed centrally at the University of Alberta by a dynamic randomization" (author's reply)
Allocation concealment (selection bias)	Low risk	Quote: "Sealed opaque envelopes" (author's reply).

Mason 2008 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Dilan Clinical Packaging Ltd (Mississauga, ON, Canada) coded samples ensuring that the investigators and patients were blinded to the treatment"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Dilan Clinical Packaging Ltd (Mississauga, ON, Canada) coded samples ensuring that the investigators and patients were blinded to the treatment"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: mortality not reported.
For-profit bias	High risk	Quote: "This study was funded in full by GlaxoSmithKline and Axcan Pharma"
Other bias	Low risk	Comment: no other bias.

Matloff 1982

Methods	Randomised clinical trial.
Participants	Country: USA. Number randomised: 52. Post-randomisation dropouts: 0 (0%). Revised sample size: 52. Mean age: 52 years. Females: 48 (92.3%). Symptomatic participants: not stated. AMA positive: 42 (80.8%). Responders: not stated. Mean follow-up period (for all groups): minimum 24 months. Inclusion criteria • Symptom status: not stated. • AMA status: AMA-positive and AMA-negative participants. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: D-penicillamine (n = 26). Further details: D-penicillamine: 1 g/day; duration: not stated Group 2: placebo (n = 26).
Outcomes	Mortality, adverse events.
Notes	

Risk of bias	***Risk of bias***

Matloff 1982 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although placebo was used in this double-blind trial, there was no mention about identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although placebo was used in this double-blind trial, there was no mention about identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no post-randomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and morbidity reported.
For-profit bias	High risk	Quote: "We are indebted to Merck, Sharp and Dohme Research Laboratories for providing the D-penicillamine and placebo tablets"
Other bias	Low risk	Comment: no other bias.

Mayo 2015

Methods	Randomised clinical trial.
Participants	Country: multicentric; international. Number randomised: 45. Post-randomisation dropouts: 3 (6.7%). Revised sample size: 42. Mean age: 56 years. Females: 38 (90.5%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: NGM282 (n = 27). Further details: NGM282: 0.3 mg/day or 3 mg/day SC for 28 days

Mayo 2015 (*Continued*)

	Group 2: placebo (n = 15).
Outcomes	None of the outcomes of interest reported.
Notes	Reasons for post-randomisation dropouts: not stated.

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although placebo was used in this double-blind trial, unclear whether the placebo was identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although placebo was used in this double-blind trial, unclear whether the placebo was identical
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	High risk	Quote: "Grant/Research Support: Intercept, Salix, NGM, Lumena, Gilead"
Other bias	Low risk	Comment: no other bias.

Mazzarella 2002

Methods	Randomised clinical trial.
Participants	Country: Italy. Number randomised: 42. Post-randomisation dropouts: not stated. Revised sample size: 42. Mean age: not stated. Females: 37 (88.1%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 72 months Inclusion criteria • Symptom status: not stated.

Mazzarella 2002 (*Continued*)

	• AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (high) (n = 21). Further details: UDCA (high): 30 mg/kg/day for 6 years. Group 2: UDCA (moderate) (n = 21). Further details: UDCA (moderate): 10.5 mg/kg/day for 6 years
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other bias.

McCormick 1994

Methods	Randomised clinical trial.
Participants	Country: UK. Number randomised: 18. Post-randomisation dropouts: 0 (0%). Revised sample size: 18. Mean age: 60 years. Females: 14 (77.8%).

	Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated. Exclusion criteria • Premenopausal or unsterilised women.
Interventions	Participants were randomly assigned to 2 groups. Group 1: thalidomide (n = 10). Further details: thalidomide: 100 mg/day for 6 months. Group 2: placebo (n = 8).
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used in double-blind trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	High risk	Quote: "Thalidomide and identical placebo tablets were supplied by Penn Pharmaceuticals Ltd"
Other bias	Low risk	Comment: no other bias.

Minuk 1988

Methods	Randomised clinical trial.
Participants	Country: Canada. Number randomised: 12. Post-randomisation dropouts: 0 (0%). Revised sample size: 12. Mean age: 55 years. Females: 11 (91.7%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: ciclosporin (n = 6). Further details: ciclosporin: maintain serum radioimmunoassay dosage between 100 ng/mL and 200 ng/mL for 12 months Group 2: placebo (n = 6).
Outcomes	Mortality, adverse events.
Notes	

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Quote: "…patients were randomized by sealed envelope to receive either cyclosporin A or placebo". Comment: further details of the sealed envelope method not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although a placebo was used, there was no mention about blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: although a placebo was used, there was no mention about blinding

Minuk 1988 (*Continued*)

Selective reporting (reporting bias)	Low risk	Comment: mortality and morbidity reported.
For-profit bias	High risk	Comment: the drugs were provided by the pharmaceutical company
Other bias	Low risk	Comment: no other bias.

Mitchison 1989

Methods	Randomised clinical trial.
Participants	Country: UK. Number randomised: 36. Post-randomisation dropouts: 0 (0%). Revised sample size: 36. Mean age: 55 years. Females: 33 (91.7%). Symptomatic participants: 35 (97.2%). AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 36 months Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: not stated. • Response status: not stated. Exclusion criteria • Aged > 70 years. • Treatment for primary biliary cirrhosis in the preceding 4 months. • Early liver disease.
Interventions	Participants were randomly assigned to 2 groups. Group 1: glucocorticosteroids (n = 19). Further details: prednisolone: 10 mg/day for 36 months (loading dose was used) Group 2: placebo (n = 17).
Outcomes	Mortality.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were paired according to the presence or absence of cirrhosis, their age by decade, menopausal status (for women) and their serum bilirubin (greater or less than 30 µmoles per litre)" Comment: minimisation used.

Mitchison 1989 (*Continued*)

Allocation concealment (selection bias)	Low risk	Quote: "Patients were paired according to the presence or absence of cirrhosis, their age by decade, menopausal status (for women) and their serum bilirubin (greater or less than 30 µmoles per litre)" Comment: minimisation used.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Study was double-blind for the first year, single blind thereafter (patients were blinded)"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Study was double-blind for the first year, single blind thereafter (patients were blinded)"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: adverse events not reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other bias.

Mitchison 1993

Methods	Randomised clinical trial.
Participants	Country: multicentric; international. Number randomised: 104. Post-randomisation dropouts: 3 (2.9%). Revised sample size: 101. Mean age: 54 years. Females: 93 (92.1%). Symptomatic participants: 101 (100%). AMA positive: not stated. Responders: not stated. Median follow-up period (for all groups): 25 months. Inclusion criteria • Symptom status: symptomatic participants only. • AMA status: not stated. • Response status: not stated. Exclusion criteria • Aged > 65 years. • Immunosuppressive drugs in the preceding 6 months. • Advanced liver disease or decompensated liver disease.
Interventions	Participants were randomly assigned to 2 groups. Group 1: malotilate (n = 52). Further details: malotilate: 500 mg 3 times daily; mean duration: 23 months

Mitchison 1993 (*Continued*)

	Group 2: placebo (n = 49).
Outcomes	Mortality, adverse events.
Notes	Reasons for post-randomisation dropouts: elementary data not available

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Random sequence was generated by the trial statistician with tables with random numbers" (author's reply)
Allocation concealment (selection bias)	Low risk	Quote: "Sequentially numbered identical containers" (author's reply)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both patients and doctors were unaware of the nature of the tablets". Comment: placebo used to achieve blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Both patients and doctors were unaware of the nature of the tablets". Comment: placebo used to achieve blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and morbidity reported.
For-profit bias	High risk	Quote: "The study was supported in part by Zyma S.A., Nyon, Switzerland, and by Nihon Nohyaku, Tokyo, Japan"
Other bias	Low risk	Comment: no other source of bias.

Nakai 2000

Methods	Randomised clinical trial.
Participants	Country: Japan. Number randomised: 23. Post-randomisation dropouts: not stated. Revised sample size: 23. Mean age: 57 years. Females: not stated. Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 12 months

Nakai 2000 (*Continued*)

	Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (low) + bezafibrate (n = 13). Further details: UDCA: 600 mg/day; duration: not stated + bezafibrate: 400 mg/day; duration: not stated Group 2: UDCA (low) (n = 10). Further details: UDCA: 600 mg/day; duration: not stated.
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Low risk	Quote: "This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan"
Other bias	Low risk	Comment: no other source of bias.

Neuberger 1985

Methods	Randomised clinical trial.
Participants	Country: multicentric; international. Number randomised: 189. Post-randomisation dropouts: not stated. Revised sample size: 189. Mean age: not stated. Females: 174 (92.1%). Symptomatic participants: 172 (91%). AMA positive: 163 (86.2%). Responders: not stated. Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: AMA-positive and AMA-negative participants. • Response status: not stated. Exclusion criteria • Taking azathioprine in the previous 6 months.
Interventions	Participants were randomly assigned to 2 groups. Group 1: D-penicillamine (n = 98). Further details: D-penicillamine: 1200 mg/day; duration: not stated Group 2: placebo (n = 91).
Outcomes	Mortality, liver transplantation.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Low risk	Quote: "Opaque sealed envelopes" (author's reply).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind trial, identical appearing placebo" (author's reply)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Assessors were blinded, identical placebo" (author's reply)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: adverse events not reported.

Neuberger 1985 (*Continued*)

For-profit bias	Unclear risk	Quote: "Not pharmaceutical funding" (author's reply).
Other bias	Low risk	Comment: no other source of bias.

Nevens 2016

Methods	Randomised clinical trial.
Participants	Country: multicentric; international. Number randomised: 217. Post-randomisation dropouts: 1. Revised sample size: 216. Mean age: 56 years. Females: 196 (90.7%). Symptomatic participants: not stated. AMA positive: not stated. Responders: 0 (0%). Mean follow-up period (for all groups): all participants followed up for 12 months Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: non-responders only. • Aged > 18 years. • Alkaline phosphatase level ≥ 1.67 times the upper limit of the normal range or an abnormal total bilirubin level < 2 times the upper limit of the normal range.
Interventions	Participants were randomly assigned to 2 groups. Group 1: obeticholic acid (low) + UDCA (moderate) (n = 143). Further details: obeticholic acid: 5 mg to 10 mg for 1 year + UDCA: 13 mg/kg/day to 15 mg/kg/day for 1 year Group 2: UDCA (moderate) (n = 73). Further details: UDCA: 13 mg/kg/day to 15 mg/kg/day for 1 year
Outcomes	Mortality, adverse events.
Notes	Reasons for post-randomisation dropouts: withdrawal from study

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "On a predefined randomization code (generated by the Sponsor or designee) using an IWRS"
Allocation concealment (selection bias)	Low risk	Quote: "The randomization number will be recorded in the CRF and will serve for patient identification and for assignment of appropriate study medication and bottle number (s) by the IWRS"

Nevens 2016 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used and authors stated double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used and authors stated double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and morbidity reported.
For-profit bias	High risk	Quote: "Supported by Intercept Pharmaceuticals". Comment: trial funded by industrial sources which might benefit by the nature of the results
Other bias	Low risk	Comment: no other source of bias.

Oka 1990

Methods	Randomised clinical trial.
Participants	Country: Japan. Number randomised: 52. Post-randomisation dropouts: 7 (13.5%). Revised sample size: 45. Mean age: 59 years. Females: 41 (91.1%). Symptomatic participants: 17 (37.8%). AMA positive: 41 (91.1%). Responders: not stated. Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: symptomatic and asymptomatic participants. • AMA status: AMA-positive and AMA-negative participants. • Response status: not stated. Exclusion criteria • Advanced liver disease or decompensated liver disease. • Pregnancy. • Complications from illnesses other than primary biliary cholangitis. • Use of treatment for primary biliary cholangitis within the past 3 months.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (low) (n = 22). Further details: UDCA: 600 mg/day for 24 weeks. Group 2: placebo (n = 23).

Oka 1990 (*Continued*)

Outcomes	None of the outcomes of interest reported.
Notes	Reasons for post-randomisation dropouts: worsening liver disease, lack of compliance

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Low risk	Quote: "The patients were allocated to two groups, a UDCA group and a placebo group, by a single monitor according to a randomization scheme in which the number of patients allocated to two groups tended to be equal"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	High risk	Quote: "UDCA and placebo tablets were generously furnished by Tokyo Tanabe Pharmaceutical Company"
Other bias	Low risk	Comment: no other source of bias.

Papatheodoridis 2002

Methods	Randomised clinical trial.
Participants	Country: Greece. Number randomised: 92. Post-randomisation dropouts: 6 (6.5%). Revised sample size: 86. Mean age: 54 years. Females: 77 (89.5%). Symptomatic participants: 86 (100%). AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): 89 months.

Papatheodoridis 2002 (*Continued*)

	Inclusion criteria • Symptom status: symptomatic participants only. • AMA status: not stated. • Response status: not stated. Exclusion criteria • Extrahepatic biliary obstruction. • Other liver diseases. • Aged > 70 years. • Immunosuppression within previous 12 months. • Advanced or decompensated liver disease.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) (n = 43). Further details: UDCA: 12 mg/kg//day to 15 mg/kg//day for ≥ 2 years Group 2: control (n = 43).
Outcomes	Mortality, liver transplantation, decompensated liver disease
Notes	Reasons for post-randomisation dropouts: not stated.

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was carried out by serially numbered sealed envelopes containing random table numbers 14 patients crossed over from placebo to UDCA"
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was carried out by serially numbered sealed envelopes containing random table numbers 14 patients crossed over from placebo to UDCA"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Patients and healthcare providers were not blinded" (author's reply)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "The outcome assessors were not blinded" (author's reply)
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts in the initial report
Selective reporting (reporting bias)	High risk	Comment: adverse events not reported.
For-profit bias	High risk	Quote: "Support for this work was provided during the first 2 years of the study by a research grant the pharmaceutical company Galenica Hellas and by the Greek Ministry of Health and Welfare"

Papatheodoridis 2002 (*Continued*)

Other bias	High risk	Comment: 14 participants crossed over from placebo to UDCA.

Pares 2000

Methods	Randomised clinical trial.
Participants	Country: Spain. Number randomised: 192. Post-randomisation dropouts: 0 (0%). Revised sample size: 192. Mean age: 54 years. Females: 179 (93.2%). Symptomatic participants: not stated. AMA positive: 172 (89.6%). Responders: not stated. Median follow-up period (for all groups): 41 months. Inclusion criteria • Symptom status: not stated. • AMA status: AMA-positive and AMA-negative participants. • Response status: not stated. Exclusion criteria • Aged > 72 years. • Immunosuppression within previous 6 months. • Life expectancy < 6 months. • Pregnancy. • Drug addiction. • Other liver diseases.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) (n = 99). Further details: UDCA 14 mg/kg/day to 16 mg/kg/day; duration: 25 to 73 months Group 2: placebo (n = 93).
Outcomes	Mortality, adverse events.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.

Pares 2000 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: unclear whether all participants were included in the analysis
Selective reporting (reporting bias)	Low risk	Comment: mortality and morbidity reported.
For-profit bias	High risk	Quote: "We are indebted to Zambon S. A., Laboratorio Farmaceutico for supplying the UDCA and placebo capsules, and for the invaluable administrative support"
Other bias	Low risk	Comment: no other risk of bias.

Poupon 1991a

Methods	Randomised clinical trial.
Participants	Country: France. Number randomised: 149. Post-randomisation dropouts: 3 (2%). Revised sample size: 146. Mean age: 56 years. Females: 134 (91.8%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated. Exclusion criteria • Received any of the following drugs during the previous 6 months: ursodiol, azathioprine, chlorambucil, colchicine, corticosteroids, D-penicillamine, and ciclosporin. • Serum bilirubin concentration > 150 μmol/L. • Serum albumin concentration < 25 g/L. • Past or active gastrointestinal bleeding from oesophageal varices. • Evidence of past or present extrahepatic obstruction of the bile ducts. • Excessive alcohol consumption (> 50 g/day). • Positive test for hepatitis B surface antigen.

Poupon 1991a (*Continued*)

Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) (n = 73). Further details: UDCA: 13 mg/kg/day to 15 mg/kg/day for 2 years Group 2: placebo (n = 73).
Outcomes	None of the outcomes of interest reported.
Notes	Reasons for post-randomisation dropouts: bilirubin > 300 μmol/L, ascites, other coexisting disease

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	High risk	Quote: "This work was supported in part by Synthélabo-Recherche and in Canada by Jouveinal and Interfalk"
Other bias	Low risk	Comment: no other source of bias.

Poupon 1996

Methods	Randomised clinical trial.
Participants	Country: France. Number randomised: 74. Post-randomisation dropouts: not stated. Revised sample size: 74. Mean age: 54 years. Females: 63 (85.1%). Symptomatic participants: not stated.

Poupon 1996 (*Continued*)

	AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 24 months Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated. Exclusion criteria • Received any of the following drugs during the previous 6 months: ursodiol, azathioprine, chlorambucil, colchicine, corticosteroids, D-penicillamine, and ciclosporin. • Serum bilirubin concentration > 150 μmol/L. • Serum albumin concentration < 25 g/L. • Past or active gastrointestinal bleeding from oesophageal varices. • Evidence of past or present extrahepatic obstruction of the bile ducts. • Excessive alcohol consumption (> 50 g/day). • Other identified causes of liver or biliary diseases. • Aged ≥ 75 years.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) + colchicine (n = 37). Further details: UDCA: 13 mg/kg/day to 15 mg/kg/day for 2 years + colchicine: 1 mg/day for 5 days in a week for 2 years Group 2: UDCA (moderate) (n = 37). Further details: UDCA: 13 mg/kg/day to 15 mg/kg/day for 2 years
Outcomes	Mortality, adverse events.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: unclear whether all randomised participants were included for analysis

Poupon 1996 (*Continued*)

Selective reporting (reporting bias)	Low risk	Comment: mortality and morbidity reported.
For-profit bias	High risk	Quote: "Supported in part by Laboratoires Houde (France) and Jouveinal (Canada)"
Other bias	Low risk	Comment: no other source of bias.

Raedsch 1993

Methods	Randomised clinical trial.
Participants	Country: Germany. Number randomised: 28. Post-randomisation dropouts: 8 (28.6%). Revised sample size: 20. Mean age: 54 years. Females: 20 (100%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 24 months Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) + colchicine (n = 8). Further details: UDCA: 10 mg/kg/day to 12 mg/kg/day for 24 months + colchicine: 1 mg/day for 24 months Group 2: UDCA (moderate) (n = 12). Further details: UDCA: 10 mg/kg/day to 12 mg/kg/day for 24 months
Outcomes	Adverse events.
Notes	Reasons for post-randomisation dropouts: adverse events, lost to follow-up

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.

Raedsch 1993 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although a placebo used in this double-blind trial, unclear whether the placebo was identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although a placebo used in this double-blind trial, unclear whether the placebo was identical
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: mortality not reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

Rautiainen 2005

Methods	Randomised clinical trial.
Participants	Country: Finland. Number randomised: 77. Post-randomisation dropouts: 8 (10.4%). Revised sample size: 69. Mean age: 53 years. Females: 60 (87%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 36 months Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated. Exclusion criteria • Aged < 18 years or > 70 years. • Pregnancy or inadequate contraceptive use. • Systemic immunosuppressive use. • Other liver diseases. • Cirrhosis.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) + glucocorticosteroids (n = 37). Further details: UDCA: 15 mg/kg/day for 3 years + budesonide: 6 mg/day for 3 years Group 2: UDCA (moderate) (n = 32). Further details: UDCA: 15 mg/kg/day for 3 years.
Outcomes	Adverse events.

Rautiainen 2005 (*Continued*)

Notes	Reasons for post-randomisation dropouts: adverse effects, death, refused follow-up biopsy

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomization was done centrally at Helsinki University Hospital with sealed envelopes in a block of 10" Comment: further details of sealed envelope technique not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Study design was randomized but open because placebo for budesonide was not available for us"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Study design was randomized but open because placebo for budesonide was not available for us"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: mortality not reported.
For-profit bias	High risk	Quote: "Medication was supplied free of charge by AstraZeneca Finland (budesonide, Entocort) and Leiras Finland (UDCA, Adursal)"
Other bias	Low risk	Comment: no other source of bias.

Senior 1991

Methods	Randomised clinical trial.
Participants	Country: USA. Number randomised: 20. Post-randomisation dropouts: 1 (5%). Revised sample size: 19. Mean age: not stated. Females: not stated. Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 18 months

Senior 1991 (*Continued*)

	Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (low) (n = 9). Further details: UDCA (low): 8 mg/kg/day to 12 mg/kg/day for 6 months Group 2: placebo (n = 10).
Outcomes	None of the outcomes of interest reported.
Notes	Reasons for post-randomisation dropouts: had coexisting gallstones

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although a placebo used in this double-blind trial, unclear whether the placebo was identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although a placebo used in this double-blind trial, unclear whether the placebo was identical
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	High risk	Quote: "and ursodiol supplies provided by Ciba-Geigy Corporation"
Other bias	Low risk	Comment: no other source of bias.

Smart 1990

Methods	Randomised clinical trial.
Participants	Country: UK. Number randomised: 20. Post-randomisation dropouts: not stated.

Smart 1990 (*Continued*)

	Revised sample size: 20. Mean age: not stated. Females: not stated. Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: antioxidants (n = not stated). Further details: antioxidant: cocktail of vitamin E 100 mg, zinc 135 mg, and selenium 100 μg daily; duration: not stated Group 2: placebo (n = not stated).
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although a placebo was used, no mention of blinding made
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although a placebo was used, no mention of blinding made
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

Steenbergen 1994

Methods	Randomised clinical trial.
Participants	Country: Belgium. Number randomised: 14. Post-randomisation dropouts: not stated. Revised sample size: 14. Mean age: 51 years. Females: 12 (85.7%). Symptomatic participants: not stated. AMA positive: 13 (92.9%). Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 24 months Inclusion criteria • Symptom status: not stated. • AMA status: AMA-positive and AMA-negative participants. • Response status: not stated. Exclusion criteria • Presence of cirrhosis. • Excessive alcohol consumption. • Other viral diseases. • Mental disorders. • Pregnancy. • Chronic infection.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (low) + methotrexate (n = 8). Further details: UDCA: 500 mg/day; duration: not stated + methotrexate: 15 mg/week; duration: not stated Group 2: control (n = 6).
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Using a random number table…".
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not available.

Steenbergen 1994 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

Taal 1983

Methods	Randomised clinical trial.
Participants	Country: Netherlands. Number randomised: 24. Post-randomisation dropouts: not stated. Revised sample size: 24. Mean age: 49 years. Females: 23 (95.8%). Symptomatic participants: 24 (100%). AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 18 months Inclusion criteria • Symptom status: symptomatic participants only. • AMA status: not stated. • Response status: not stated. Exclusion criteria • Advanced or decompensated liver disease. • Use of cholestatic drug in the previous 6 months. • Associated inflammatory bowel disease. • Neoplasm within last 5 years. • Pregnancy.
Interventions	Participants were randomly assigned to 2 groups. Group 1: D-penicillamine (n = 11). Further details: D-penicillamine: 250 mg/day to 1000 mg/day (escalating dose) and then 500 mg/day: total duration: 1 year Group 2: placebo (n = 13).
Outcomes	Mortality, adverse events, decompensated liver disease.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**

Taal 1983 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

Triger 1980

Methods	Randomised clinical trial.
Participants	Country: UK. Number randomised: 35. Post-randomisation dropouts: not stated. Revised sample size: 35. Mean age: not stated. Females: not stated. Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: D-penicillamine (n = not stated). Further details: D-penicillamine: 250 mg to 875 mg (escalating dose) Group 2: placebo (n = not stated).
Outcomes	Mortality.

Triger 1980 (*Continued*)

Notes	

Risk of bias		***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: in this double-blind trial, unclear whether the placebo was identical to active treatment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: in this double-blind trial, unclear whether the placebo was identical to active treatment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: adverse events not reported.
For-profit bias	High risk	Quote: "The UDCA and placebo tablets were generously donated by Thames Laboratories, Wrexham, Wales"
Other bias	Low risk	Comment: no other source of bias.

Turner 1994

Methods	Randomised clinical trial.
Participants	Country: UK. Number randomised: 46. Post-randomisation dropouts: 0 (0%). Revised sample size: 46. Mean age: 58 years. Females: 44 (95.7%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): all participants followed up for 24 months Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: not stated.

Turner 1994 (*Continued*)

Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (low) (n = 22). Further details: UDCA: 10 mg/kg/day for 2 years. Group 2: placebo (n = 24).
Outcomes	Mortality, liver transplantation, cirrhosis.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no post-randomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: adverse events not reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

Ueno 2005

Methods	Randomised clinical trial.
Participants	Country: Japan. Number randomised: 20. Post-randomisation dropouts: not stated. Revised sample size: 20. Mean age: not stated. Females: 16 (80%). Symptomatic participants: not stated. AMA positive: not stated. Responders: 0 (0%).

Ueno 2005 (*Continued*)

	Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: non-responders only Exclusion criteria • Aged < 20 years or > 70 years. • History of antiretroviral or steroid treatment. • Renal dysfunction. • Other causes of liver damage.
Interventions	Participants were randomly assigned to 2 groups. Group 1: lamivudine (n = not stated). Further details: lamivudine: 100 mg/day for 3 months. Group 2: placebo (n = not stated).
Outcomes	None of the outcomes of interest reported.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: neither mortality nor adverse events reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

Van Hoogstraten 1998

Methods	Randomised clinical trial.
Participants	Country: Netherlands. Number randomised: 61. Post-randomisation dropouts: 2 (3.3%). Revised sample size: 59. Mean age: 57 years. Females: 55 (93.2%). Symptomatic participants: not stated. AMA positive: not stated. Responders: 0 (0%). Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: non-responders only. Exclusion criteria • Decompensated liver disease.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (low) (n = 32). Further details: UDCA (low): 10 mg/kg/day for 6 months. Group 2: UDCA (moderate) (n = 27). Further details: UDCA (moderate): 20 mg/kg/day for 6 months.
Outcomes	Adverse events.
Notes	Reasons for post-randomisation dropouts: developed liver failure, lost to follow-up

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Tables with random numbers" (author's reply).
Allocation concealment (selection bias)	Low risk	Quote: "Opaque closed envelopes" (author's reply).
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "randomised open controlled trial".
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "randomised open controlled trial".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.

Van Hoogstraten 1998 (*Continued*)

Selective reporting (reporting bias)	High risk	Comment: mortality not reported.
For-profit bias	High risk	Quote: "This study was supported in part by Zambon Nederland BV, Amersfoort, the Netherlands"
Other bias	Low risk	Comment: no other source of bias.

Warnes 1987

Methods	Randomised clinical trial.
Participants	Country: UK. Number randomised: 64. Post-randomisation dropouts: not stated. Revised sample size: 64. Mean age: not stated. Females: not stated. Symptomatic participants: not stated. AMA positive: 64 (100%). Responders: not stated. Median follow-up period (for all groups): 19 months. Inclusion criteria • Symptom status: not stated. • AMA status: AMA-positive participants only. • Response status: not stated.
Interventions	Participants were randomly assigned to 2 groups. Group 1: colchicine (n = 34). Further details: colchicine: 0.5 mg BD; duration: not stated Group 2: placebo (n = 30).
Outcomes	Mortality, adverse events.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "To ensure that treatment groups were comparable, patients were stratified according to serum bilirubin level at entry (A, < 19/µmol/1; B, 20-34/ µmol/L; C, 35-102/ µmol/L; D, >102/µmol/1). The first patient in any pair was allocated by the staff pharmacist to the treatment or placebo group by reference to random tables. The pair was completed when another patient, in the same bilirubin group and with an age within 5 years of the first patient, was entered into the study. The second member of the pair was

Warnes 1987 (*Continued*)

		allocated to the alternative treatment group. The study was double-blind". Comment: minimisation method used.
Allocation concealment (selection bias)	Low risk	Quote: "To ensure that treatment groups were comparable, patients were stratified according to serum bilirubin level at entry (A, < 19/μmol/1; B, 20-34/ μmol/L; C, 35-102/ μmol/L; D, >102/μmol/1). The first patient in any pair was allocated by the staff pharmacist to the treatment or placebo group by reference to random tables. The pair was completed when another patient, in the same bilirubin group and with an age within 5 years of the first patient, was entered into the study. The second member of the pair was allocated to the alternative treatment group. The study was double-blind". Comment: minimisation method used.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	Low risk	Comment: mortality and morbidity reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

Wiesner 1990

Methods	Randomised clinical trial.
Participants	Country: USA. Number randomised: 40. Post-randomisation dropouts: 11 (27.5%). Revised sample size: 29. Mean age: 46 years. Females: 28 (96.6%). Symptomatic participants: not stated. AMA positive: not stated. Responders: not stated. Median follow-up period (for all groups): 35 months. Inclusion criteria

	• Symptom status: not stated. • AMA status: not stated. • Response status: not stated. Exclusion criteria • Cirrhosis or advanced liver disease. • Renal dysfunction. • Uncontrolled hypertension. • Neoplastic disease. • Skin cancer. • Previous immunosuppressive therapy. • Other liver diseases.
Interventions	Participants were randomly assigned to 2 groups. Group 1: ciclosporin (n = 19). Further details: ciclosporin: 4 mg/kg/day. Group 2: placebo (n = 10).
Outcomes	Mortality, adverse events, liver transplantation.
Notes	Reasons for post-randomisation dropouts: follow-up < 1 year.

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	Low risk	Comment: mortality and morbidity reported.
For-profit bias	High risk	Quote: "Supported by a grant from Sandoz and by the Mayo foundation"
Other bias	Low risk	Comment: no other source of bias.

Wolfhagen 1998

Methods	Randomised clinical trial.
Participants	Country: Netherlands. Number randomised: 50. Post-randomisation dropouts: not stated. Revised sample size: 50. Mean age: 52 years. Females: 45 (90%). Symptomatic participants: not stated. AMA positive: not stated. Responders: 0 (0%). Mean follow-up period (for all groups): all participants followed up for 12 months Inclusion criteria • Symptom status: not stated. • AMA status: not stated. • Response status: non-responders only. Exclusion criteria • Advanced or decompensated liver disease. • Alcohol abuse. • Other causes of liver disease.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (moderate) + azathioprine + glucocorticosteroids (n = 26) Further details: UDCA: 10 mg/kg/day for 6 months + azathioprine: 50 mg/day for 6 months + prednisolone: 10 mg/day for 6 months Group 2: UDCA (moderate) (n = 24). Further details: UDCA: 10 mg/kg/day for 6 months.
Outcomes	Adverse events, cirrhosis.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Tables with random numbers" (author's reply).
Allocation concealment (selection bias)	Low risk	Quote: "Opaque closed envelopes" (author's reply).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: identical placebo used in this double-blind trial.

Wolfhagen 1998 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: mortality not reported.
For-profit bias	High risk	Quote: "Supported by…Zambon Nederland B.v. and Glaxo Wellcome Research and Development Ltd"
Other bias	Low risk	Comment: no other source of bias.

Yokomori 2001

Methods	Randomised clinical trial.
Participants	Country: Japan. Number randomised: 11. Post-randomisation dropouts: not stated. Revised sample size: 11. Mean age: 54 years. Females: 9 (81.8%). Symptomatic participants: 11 (100%). AMA positive: not stated. Responders: not stated. Mean follow-up period (for all groups): not stated. Inclusion criteria • Symptom status: symptomatic participants only. • AMA status: not stated. • Response status: not stated. Exclusion criteria • Advanced or decompensated liver disease. • Pregnancy. • Treatment with immunosuppressants or other drugs that interfere with bile secretion. • Severe complications other than primary biliary cholangitis.
Interventions	Participants were randomly assigned to 2 groups. Group 1: UDCA (low) + colestilan (n = 5). Further details: UDCA: 600 mg/day for 8 weeks + colestilan: 6.42 mg/day for 4 weeks Group 2: UDCA (low) (n = 6). Further details: UDCA: 600 mg/day for 8 weeks.
Outcomes	Adverse events.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**

Yokomori 2001 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Comment: information not available.
Allocation concealment (selection bias)	Unclear risk	Comment: information not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label".
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open-label".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not available.
Selective reporting (reporting bias)	High risk	Comment: mortality not reported.
For-profit bias	Unclear risk	Comment: information not available.
Other bias	Low risk	Comment: no other source of bias.

AMA: antimitochondrial antibody; BD: twice daily; IV: intravenous; OD: once daily; SAMe: S-adenosyl methionine; SC: subcutaneous; TUDCA: taurodeoxycholic acid; UDCA: ursodeoxycholic acid.

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

Study	Reason for exclusion
Angulo 1999b	Long-term follow-up of participants included in an included trial (Lindor 1994), but the randomisation was not maintained.
Angulo 1999c	Long-term follow-up of participants included in an included trial (Lindor 1994), but the randomisation was not maintained.
Angulo 2002	Comparison of different administration schedules of the same dose of UDCA
Attili 1994	Not in people with primary biliary cholangitis.
Avezov 2004a	Not a randomised clinical trial.
Avezov 2004b	Not a randomised clinical trial.
Bach 2003	Not a randomised clinical trial.

(*Continued*)

Batta 1989	Not a randomised clinical trial.
Beukers 1988	Not a randomised clinical trial.
Blanche 1994	Not a randomised clinical trial.
Bonis 2006	Not a randomised clinical trial.
Borum 1990	Not a primary study (editorial).
Bray 1991	Cross-over RCT; no results presented before cross-over.
Carbone 2016	Long-term follow-up of Nevens 2016, but excluded because randomisation not maintained.
Chazouilleres 1995	Not a randomised clinical trial.
Christensen 1986	Not a primary study (letter to editor).
Combes 1989	Not a primary study (editorial).
Combes 2004	Not a primary study (editorial).
Combes 2005b	Long-term follow-up of participants in an included RCT (Combes 1995a); however, all participants received the intervention after the end of the initial study
Copaci 2001	Not a randomised clinical trial.
Corpechot 2000	Long-term follow-up of an included trial (Poupon 1991a); however, all participants received the active intervention at the end of the trial period
Corpechot 2001	Not a primary study (editorial).
Crosignani 1996a	Cross-over RCT; no outcomes of interest reported before cross-over
Crosignani 1996b	In this RCT of different doses of TUDCA, participants who were intolerant to the drug were replaced. This affected the randomisation
De la Mora 1994	No separate data on people who were randomised (included non-randomised participants in the results)
Degott 1999	Long-term follow-up of an included trial (Poupon 1991a); however, all participants received the active intervention at the end of the trial period
Dickson 1991	No separate data on people who were randomised (included non-randomised participants in the results)
Emond 1996	Long-term follow-up of an included trial (Combes 1995a); however, all participants received the active intervention at the end of the trial period
Fischer 1967	Not a randomised clinical trial.

(*Continued*)

Golovanova 2010	Not a randomised clinical trial.
Heathcote 1993	Not a randomised clinical trial.
Heathcote 1995	Not a primary study.
Hirschfield 2011	Not a randomised clinical trial.
Hishon 1982	Not a randomised clinical trial.
Howat 1966	Not a randomised clinical trial.
Hwang 1993	Cross-over RCT; none of the outcomes of interest reported prior to cross-over
Invernizzi 1996	Cross-over RCT, no results presented before cross-over.
Invernizzi 2015	Not a primary study.
Itakura 2004	Not a primary study.
Jazrawi 1999	Not a randomised clinical trial.
Jones 2006	Not a primary study (letter to editor).
Jorgensen 2002	Long-term follow-up of an included trial (Lindor 1994); however, all participants received the active intervention at the end of the trial period
Joshi 2002	Not a primary study.
Kaplan 1993	Not a primary study (editorial).
Kaplan 1998	Not a primary study (letter to editor).
Kaplan 2004	Long-term follow-up of an included trial (Kaplan 1999), but the treatment was changed at the completion of the RCT
Kaplan 2009	Not a primary study (letter to editor).
Kisand 1996	Quasi-randomised study (allocation by case numbers).
Kisand 1998	Quasi-randomised study (allocation by case numbers).
Kowdley 2014a	Not a randomised clinical trial.
Kowdley 2014b	Not a randomised clinical trial.
Kowdley 2015	Long-term follow-up of Kowdley 2011, but excluded because randomisation was not maintained.

(*Continued*)

Kugler 1991	Not a primary study (commentary).
Kurihara 2002	Not a randomised clinical trial.
Lampe 1972	Not a randomised clinical trial.
Larghi 1997	Cross-over RCT; no results presented before cross-over.
Lee 2003	Not a randomised clinical trial.
Leung 2010	Long-term follow-up of a subgroup of participants in an included trial (Kaplan 1999), where additional interventions were added after completion of the trial period
Leung 2011	Long-term follow-up of a subgroup of participants in an included trial (Kaplan 1999), where additional interventions were added after completion of the trial period
Leuschner 1990	Not a primary study (review).
Leuschner 1993a	Not a primary study (review).
Leuschner 1993b	Quasi-randomised study (allocation by alternation).
Leuschner 1996a	Quasi-randomised study (allocation by alternation).
Leuschner 1996b	Quasi-randomised study (allocation by alternation).
Leuschner 1997	Not a primary study (review).
Leuschner 1998	Not a primary study (review).
Levy 2004	Not a primary study (editorial).
Licinio 2015	Not a primary study (letter to editor).
Lim 2000	Not a randomised clinical trial.
Lindor 1994a	Not a randomised clinical trial
Lindor 1995a	Long-term follow-up an included RCT (Lindor 1994); however, all participants received the intervention after the completion of the RCT
Lindor 1995b	Not a randomised clinical trial.
Lindor 1995c	Not a primary study (review).
Lindor 1996	Long-term follow-up an included RCT (Lindor 1994); however, all participants received the intervention after the completion of the RCT

(*Continued*)

Lindor 2000	Not a primary study (letter to editor).
Lindor 2005	Not a primary study (review).
Lindor 2007	Not a primary study (review).
Lytvyak 2015	Cross-over RCT; no outcomes reported prior to cross-over.
Lytvyak 2016	Not a randomised clinical trial
Miettinen 1993	Quasi-randomised study (allocation by case numbers).
Miettinen 1995	Quasi-randomised study (allocation by case numbers).
Muntoni 2010	Only 4 participants in this trial had primary biliary cholangitis and separate data not available for these 4 participants
Nikolaidis 2006	Only 5 participants had primary biliary cholangitis and only 1 of them received placebo. Separate data not available on these participants
Ohmoto 2001	Not a randomised clinical trial.
Ohmoto 2006	Not a randomised clinical trial.
Pan 2013	Only 5 participants had primary biliary cholangitis. Separate data not available for these participants
Pares 2009	Not a randomised clinical trial.
Podda 1989	Cross-over study of different doses of UDCA; outcomes not reported at the end of first treatment
Poupon 1989	Not a primary study (review).
Poupon 1990	Not a primary study (review).
Poupon 1991b	Not a primary study (commentary).
Poupon 1994	Long-term follow-up of an included trial (Poupon 1991a); however, all participants received the active intervention at the end of the trial period
Poupon 1997	Not a primary study.
Poupon 1999	Not a randomised clinical trial.
Poupon 2003	Not a primary study.
Raedsch 1989	Not a randomised clinical trial.

(*Continued*)

Reed 1982	Not a primary study (editorial).
Robson 1994	Not a randomised clinical trial.
Roda 2002	Not a randomised clinical trial.
Savolainen 1983	Unclear whether this was a randomised clinical trial.
Schaffner 1982	Comparison of 2 doses of D-penicillamine with no other treatment as comparator
Setchell 1994	In this RCT of different doses of TUDCA, participants who were intolerant to the drug were replaced. This affected the randomisation
Setchell 1996	In this RCT of different doses of TUDCA, participants who were intolerant to the drug were replaced. This affected the randomisation
Stellaard 1979	Not a randomised clinical trial.
Taal 1985	Not a randomised clinical trial.
Tang 2008	Not a pharmacological agent.
Tong 2012	Not a pharmacological agent.
Verma 1999	Cross-over RCT; no results presented before cross-over.
Verma 2000	Not a primary study (review).
Vogel 1988	Not a randomised clinical trial.
Vuoristo 1995	Quasi-randomised study (allocation by case numbers).
Vuoristo 1997	Quasi-randomised study (allocation by case numbers).
Wiesner 1994	Not a randomised clinical trial.
Wolfhagen 1995	Not a randomised clinical trial.
Yan 2007	Not a primary study (letter to editor).
Yano 2002	Not a randomised clinical trial.
Zuin 1991	Symptomatic treatment of dyslipidaemia associated with primary biliary cholangitis

TUDCA: taurodeoxycholic acid; UDCA: ursodeoxycholic acid.

Characteristics of studies awaiting assessment *[ordered by study ID]*

O'Brian 1990

Methods	Full text not available.
Participants	
Interventions	
Outcomes	
Notes	

Zaman 2006

Methods	Full text not available.
Participants	
Interventions	
Outcomes	
Notes	

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

ChiCTR-IPR-16008935

Trial name or title	Biochemical Response of PBC-AIH Overlap Syndrome Induced by Ursodeoxycholic Acid Only or Combination Therapy of Immunosuppressive Agents
Methods	Randomised parallel clinical trial
Participants	People with primary biliary cholangitis and autoimmune hepatitis overlap syndrome
Interventions	Group 1: UDCA + immunosuppression Further details: not provided. Group 2: UDCA. Further details: not provided.
Outcomes	Adverse events
Starting date	Not stated.
Contact information	yangli_hx@scu.edu.cn
Notes	Status: recruiting.

EUCTR2015-002698-39-GB

Trial name or title	A 12-Week, Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Evaluate the Effects of Two Doses of MBX-8025 in Subjects with Primary Biliary Cirrhosis (PBC) and an Inadequate Response to Ursodeoxycholic Acid (UDCA)
Methods	Randomised, placebo-controlled, double-blind clinical trial.
Participants	People with primary biliary cholangitis (non-responders).
Interventions	Group 1: MBX-8025. Further details: not provided. Group 2: placebo.
Outcomes	None of the outcomes of interest for this review measured in this trial
Starting date	Not stated.
Contact information	KRosemark@cymabay.com
Notes	Status: recruiting.

NCT02308111

Trial name or title	A Phase 3b, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Patients With Primary Biliary Cirrhosis
Methods	Phase 3, double-blind, randomised, placebo-controlled, multicentre study
Participants	People with primary biliary cholangitis.
Interventions	Group 1: obeticholic acid. Further details: obeticholic acid 5 mg to 10 mg tablets once daily for the duration of the study based on tolerability at 3 months Group 2: placebo. Further details: 1 tablet daily for the remainder of the study
Outcomes	Mortality, liver transplantation, liver decompensation, hepatocellular carcinoma
Starting date	December 2014.
Contact information	dshapiro@interceptpharma.com
Notes	Status: recruiting.

NCT02701166

Trial name or title	The Effect of Bezafibrate on Cholestatic Itch
Methods	Double-blind, randomised, placebo-controlled clinical trial.
Participants	People with primary biliary cholangitis.
Interventions	Group 1: bezafibrate. Further details: bezafibrate 400 mg/day. Group 2: placebo.
Outcomes	None of the outcomes of interest for this review are measured in this trial
Starting date	February 2016.
Contact information	u.h.beuers@amc.uva.nl
Notes	Status: recruiting.

NCT02823353

Trial name or title	Fenofibrate in Combination with Ursodeoxycholic Acid in Primary Biliary Cirrhosis: a Randomized Control Study
Methods	Phase 3, open-label, randomised clinical trial.
Participants	People with primary biliary cholangitis.
Interventions	Group 1: UDCA + fenofibrate. Further details: not provided. Group 2: UDCA. Further details: not provided.
Outcomes	None of the outcomes of interest for this review are measured in this trial
Starting date	January 2016.
Contact information	hanying@fmmu.edu.cn
Notes	Status: recruiting.

NCT02823366

Trial name or title	Fenofibrate for Patients with Primary Biliary Cirrhosis who had an Inadequate Response to Ursodeoxycholic Acid
Methods	Phase 3, open-label, randomised clinical trial.

NCT02823366 (*Continued*)

Participants	People with primary biliary cholangitis.
Interventions	Group 1: UDCA + fenofibrate Further details: not provided. Group 2: UDCA. Further details: not provided.
Outcomes	None of the outcomes of interest for this review measured in this trial
Starting date	January 2016.
Contact information	hanying@fmmu.edu.cn
Notes	Status: recruiting. May be the same as NCT02823353.

NCT02937012

Trial name or title	Efficacy and Security of Bezafibrate in Patients with Primary Biliary Cirrhosis without Biochemical Response to Ursodeoxycholic Acid: a Randomized, Double-blind, Placebo-controlled Trial
Methods	Randomised, double-blind, placebo-controlled clinical trial.
Participants	People with primary biliary cholangitis (non-responders).
Interventions	Group 1: UDCA + bezafibrate. Further details: bezafibrate 200 mg capsule every 12 hours + UDCA 13 mg/kg/day to 15 mg/kg/day for 12 months Group 2: UDCA + placebo. Further details: placebo capsule (for bezafibrate 200 mg capsule) every 12 hours + UDCA 13 mg/kg/day to 15 mg/kg/day for 12 months
Outcomes	Quality of life.
Starting date	October 2016.
Contact information	ericlopezmendez@yahoo.com.mx sergio_sg@hotmail.com
Notes	Status: recruiting.

NCT02943447

Trial name or title	A Phase 2, Randomized, Double-Blind, Placebo Controlled Study Evaluating the Safety, Tolerability, and Efficacy of GS-9674 in Subjects with Primary Biliary Cholangitis without Cirrhosis
Methods	Randomised, double-blind, placebo-controlled clinical trial.
Participants	People with primary biliary cholangitis.
Interventions	Group 1: GS-9674. Further details: GS-9674 30 mg for 12 weeks. Group 2: placebo.
Outcomes	Adverse events.
Starting date	December 2016.
Contact information	GS-US-427-4024@Gilead.com
Notes	Status: recruiting.

NCT02965911

Trial name or title	A Randomized Controlled Clinical Trial on the Efficacy and Safety of Fenofibrate Combined with Ursodeoxycholic Acid in PBC Patients with an Incomplete Biochemical Response to UDCA
Methods	Open-label, randomised clinical trial.
Participants	People with primary biliary cholangitis.
Interventions	Group 1: fenofibrate + UDCA. Further details: UDCA 13 mg/kg/day to 15 mg/kg/day + fenofibrate 200 mg once daily for 12 months Group 2: UDCA. Further details: UDCA 13 mg/kg/day to 15 mg/kg/day.
Outcomes	None of the outcomes of interest for this review measured in this trial
Starting date	January 2016.
Contact information	zszou302@163.com
Notes	Status: recruiting.

UDCA: ursodeoxycholic acid.

DATA AND ANALYSES

Comparison 1. Main analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality at maximal follow-up	28		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Azathioprine versus no intervention	2	224	Odds Ratio (M-H, Fixed, 95% CI)	0.56 [0.32, 0.98]
1.2 Chlorambucil versus no intervention	1	24	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 3.28]
1.3 Colchicine versus no intervention	2	122	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.32, 1.85]
1.4 Cyclosporin versus no intervention	3	390	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.51, 1.50]
1.5 D-Penicillamine versus no intervention	5	423	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.57, 1.44]
1.6 Glucocorticosteroids versus no intervention	1	36	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.14, 2.92]
1.7 Malotilate versus no intervention	1	101	Odds Ratio (M-H, Fixed, 95% CI)	2.0 [0.47, 8.48]
1.8 Methotrexate versus no intervention	1	60	Odds Ratio (M-H, Fixed, 95% CI)	8.83 [1.01, 76.96]
1.9 UDCA versus no intervention	6	734	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.60, 1.64]
1.10 Bezafibrate plus UDCA versus UDCA	1	27	Odds Ratio (M-H, Fixed, 95% CI)	9.67 [0.45, 207.78]
1.11 Colchicine plus UDCA versus UDCA	2	158	Odds Ratio (M-H, Fixed, 95% CI)	1.84 [0.38, 8.91]
1.12 Methotrexate plus UDCA versus UDCA	2	290	Odds Ratio (M-H, Fixed, 95% CI)	1.17 [0.55, 2.51]
1.13 Obeticholic acid plus UDCA versus UDCA	1	216	Odds Ratio (M-H, Fixed, 95% CI)	1.55 [0.06, 38.46]
2 Mortality (< 1 year)	8		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Azathioprine versus no intervention	1	39	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.16, 2.10]
2.2 Colchicine versus no intervention	1	64	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.22, 3.33]
2.3 Cyclosporin versus no intervention	1	12	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 3.63]
2.4 D-Penicillamine versus no intervention	1	189	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.35, 1.42]
2.5 Ursodeoxycholic acid (UDCA) versus no intervention	1	18	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.6 Colchicine plus UDCA versus UDCA	1	84	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.13, 7.45]
2.7 Methotrexate plus UDCA versus UDCA	1	25	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

2.8 Obeticholic acid plus UDCA versus UDCA	1	216	Odds Ratio (M-H, Fixed, 95% CI)	1.55 [0.06, 38.46]
3 Mortality (1 to 5 years)	20		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Azathioprine versus no intervention	1	185	Odds Ratio (M-H, Fixed, 95% CI)	0.56 [0.30, 1.04]
3.2 Chlorambucil versus no intervention	1	24	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 3.28]
3.3 Colchicine versus no intervention	1	58	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.22, 2.25]
3.4 Cyclosporin versus no intervention	2	378	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.54, 1.64]
3.5 D-Penicillamine versus no intervention	4	234	Odds Ratio (M-H, Fixed, 95% CI)	1.10 [0.59, 2.08]
3.6 Glucocorticosteroids versus no intervention	1	36	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.14, 2.92]
3.7 Malotilate versus no intervention	1	101	Odds Ratio (M-H, Fixed, 95% CI)	2.0 [0.47, 8.48]
3.8 Methotrexate versus no intervention	1	60	Odds Ratio (M-H, Fixed, 95% CI)	8.83 [1.01, 76.96]
3.9 UDCA versus no intervention	5	716	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.60, 1.64]
3.10 Bezafibrate plus UDCA versus UDCA	1	27	Odds Ratio (M-H, Fixed, 95% CI)	9.67 [0.45, 207.78]
3.11 Colchicine plus UDCA versus UDCA	1	74	Odds Ratio (M-H, Fixed, 95% CI)	5.28 [0.24, 113.87]
3.12 Methotrexate plus UDCA versus UDCA	1	265	Odds Ratio (M-H, Fixed, 95% CI)	1.17 [0.55, 2.51]
4 Serious adverse events (proportion)	11		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Colchicine versus no intervention	1	64	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 D-Penicillamine versus no intervention	1	52	Odds Ratio (M-H, Fixed, 95% CI)	28.77 [1.57, 526.67]
4.3 Obeticholic acid versus no intervention	1	165	Odds Ratio (M-H, Fixed, 95% CI)	1.83 [0.21, 15.73]
4.4 UDCA versus no intervention	3	380	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.5 UDCA versus bezafibrate	1	24	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.6 Bezafibrate plus UDCA versus UDCA	1	22	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.7 Colchicine plus UDCA versus UDCA	1	74	Odds Ratio (M-H, Fixed, 95% CI)	3.08 [0.12, 78.14]
4.8 Lamivudine plus zidovudine plus UDCA versus UDCA	1	59	Odds Ratio (M-H, Fixed, 95% CI)	0.47 [0.04, 5.43]
4.9 Obeticholic acid plus UDCA versus UDCA	1	216	Odds Ratio (M-H, Fixed, 95% CI)	3.58 [1.02, 12.51]
5 Serious adverse events (number of events)	1		Rate Ratio (Fixed, 95% CI)	Subtotals only
5.1 Obeticholic acid plus UDCA versus UDCA	1	216	Rate Ratio (Fixed, 95% CI)	1.66 [0.75, 3.66]

6 Adverse events (proportion)	19		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Cyclosporin versus no intervention	3	390	Odds Ratio (M-H, Fixed, 95% CI)	3.04 [1.98, 4.68]
6.2 D-Penicillamine versus no intervention	2	287	Odds Ratio (M-H, Fixed, 95% CI)	4.51 [2.56, 7.93]
6.3 Malotilate versus no intervention	1	101	Odds Ratio (M-H, Fixed, 95% CI)	11.43 [1.40, 93.04]
6.4 Obeticholic acid versus no intervention	1	165	Odds Ratio (M-H, Fixed, 95% CI)	4.58 [1.31, 15.95]
6.5 UDCA versus no intervention	3	380	Odds Ratio (M-H, Fixed, 95% CI)	1.45 [0.50, 4.25]
6.6 Azathioprine plus UDCA versus UDCA	1	42	Odds Ratio (M-H, Fixed, 95% CI)	19.67 [0.94, 413.50]
6.7 Bezafibrate versus UDCA	1	24	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.8 Bezafibrate plus UDCA versus UDCA	1	22	Odds Ratio (M-H, Fixed, 95% CI)	3.29 [0.12, 89.81]
6.9 Colchicine plus UDCA versus UDCA	2	42	Odds Ratio (M-H, Fixed, 95% CI)	6.20 [0.63, 60.80]
6.10 Colestilan plus UDCA versus UDCA	1	11	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.11 Glucocorticosteroids plus UDCA versus UDCA	2	135	Odds Ratio (M-H, Fixed, 95% CI)	5.54 [1.35, 22.84]
6.12 Methotrexate plus UDCA versus UDCA	1	25	Odds Ratio (M-H, Fixed, 95% CI)	115.0 [4.98, 2657. 48]
6.13 TauroUDCA versus UDCA	1	30	Odds Ratio (M-H, Fixed, 95% CI)	21.0 [2.16, 204.61]
6.14 Glucocorticosteroids plus UDCA versus azathioprine plus UDCA	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.40 [0.08, 2.12]
7 Adverse events (number)	14		Rate Ratio (Random, 95% CI)	Subtotals only
7.1 Chlorambucil versus no intervention	1	24	Rate Ratio (Random, 95% CI)	3.67 [1.04, 12.87]
7.2 Cyclosporin versus no intervention	3	390	Rate Ratio (Random, 95% CI)	2.58 [1.26, 5.31]
7.3 D-Penicillamine versus no intervention	3	303	Rate Ratio (Random, 95% CI)	2.99 [1.04, 8.63]
7.4 Malotilate versus no intervention	1	101	Rate Ratio (Random, 95% CI)	6.13 [1.38, 27.14]
7.5 Obeticholic acid versus no intervention	1	76	Rate Ratio (Random, 95% CI)	1.41 [1.13, 1.75]
7.6 Azathioprine plus glucocorticosteroids plus UDCA versus UDCA	1	50	Rate Ratio (Random, 95% CI)	1.32 [0.88, 1.97]
7.7 Bezafibrate plus UDCA versus UDCA	1	29	Rate Ratio (Random, 95% CI)	11.79 [0.65, 213.14]
7.8 Colchicine plus UDCA versus UDCA	1	24	Rate Ratio (Random, 95% CI)	5.91 [0.28, 123.08]
7.9 Methotrexate plus UDCA versus UDCA	1	27	Rate Ratio (Random, 95% CI)	30.64 [1.84, 510.76]
7.10 TauroUDCA versus UDCA	1	191	Rate Ratio (Random, 95% CI)	1.17 [0.81, 1.71]

8 Liver transplantation	11		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Cyclosporin versus no intervention	2	378	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.43, 1.72]
8.2 D-Penicillamine versus no intervention	1	189	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.06, 15.05]
8.3 Methotrexate versus no intervention	1	60	Odds Ratio (M-H, Fixed, 95% CI)	0.17 [0.02, 1.58]
8.4 UDCA versus no intervention	5	640	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.48, 1.68]
8.5 Bezafibrate plus UDCA versus UDCA	1	27	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.6 Methotrexate plus UDCA versus UDCA	1	265	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.35, 1.39]
9 Decompensated liver disease	7		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 D-Penicillamine versus no active treatment	1	24	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 UDCA versus no intervention	2	237	Odds Ratio (M-H, Fixed, 95% CI)	1.60 [0.86, 2.98]
9.3 Azathioprine plus UDCA versus UDCA	1	42	Odds Ratio (M-H, Fixed, 95% CI)	0.52 [0.05, 5.18]
9.4 Colchicine plus UDCA versus UDCA	1	84	Odds Ratio (M-H, Fixed, 95% CI)	0.21 [0.04, 1.07]
9.5 Glucocorticosteroids plus UDCA versus UDCA	1	66	Odds Ratio (M-H, Fixed, 95% CI)	0.55 [0.11, 2.69]
9.6 Methotrexate plus UDCA versus UDCA	1	265	Odds Ratio (M-H, Fixed, 95% CI)	1.34 [0.77, 2.33]
9.7 Obeticholic acid plus UDCA versus UDCA	1	216	Odds Ratio (M-H, Fixed, 95% CI)	1.55 [0.06, 38.46]
9.8 Glucocorticosteroids plus UDCA versus azathioprine plus UDCA	1	50	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.10, 11.18]
10 Cirrhosis	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Azathioprine versus no intervention	1	31	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.18, 3.41]
10.2 UDCA versus no intervention	1	22	Odds Ratio (M-H, Fixed, 95% CI)	0.15 [0.01, 1.53]
10.3 Azathioprine plus glucocorticosteroids plus UDCA versus UDCA	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.28 [0.03, 2.90]

Comparison 2. Stratified by dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality at maximal follow-up	29		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Azathioprine versus no intervention	2	224	Odds Ratio (M-H, Fixed, 95% CI)	0.56 [0.32, 0.98]

1.2 Chlorambucil versus no intervention	1	24	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 3.28]
1.3 Colchicine versus no intervention	2	122	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.32, 1.85]
1.4 Cyclosporin versus no intervention	3	390	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.51, 1.50]
1.5 D-Penicillamine versus no intervention	5	423	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.57, 1.44]
1.6 Glucocorticosteroids versus no intervention	1	36	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.14, 2.92]
1.7 Malotilate versus no intervention	1	101	Odds Ratio (M-H, Fixed, 95% CI)	2.0 [0.47, 8.48]
1.8 Methotrexate versus no intervention	1	60	Odds Ratio (M-H, Fixed, 95% CI)	8.83 [1.01, 76.96]
1.9 UDCA (low) versus no intervention	2	64	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.03, 3.47]
1.10 UDCA (moderate) versus no intervention	4	670	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.62, 1.77]
1.11 UDCA (low) versus UDCA (high)	1	106	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.06, 17.06]
1.12 UDCA (moderate) versus UDCA (high)	1	103	Odds Ratio (M-H, Fixed, 95% CI)	0.36 [0.01, 9.05]
1.13 UDCA (low) plus colchicine versus UDCA (low)	1	84	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.13, 7.45]
1.14 UDCA (low) plus methotrexate versus UDCA (low)	1	25	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.15 UDCA (moderate) versus UDCA (low)	1	101	Odds Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.72]
1.16 Bezafibrate plus UDCA (moderate) versus UDCA (moderate)	1	27	Odds Ratio (M-H, Fixed, 95% CI)	9.67 [0.45, 207.78]
1.17 Colchicine plus UDCA (moderate) versus UDCA (moderate)	1	74	Odds Ratio (M-H, Fixed, 95% CI)	5.28 [0.24, 113.87]
1.18 Methotrexate plus UDCA (moderate) versus UDCA (moderate)	1	265	Odds Ratio (M-H, Fixed, 95% CI)	1.17 [0.55, 2.51]
1.19 Obeticholic acid (low) plus UDCA (moderate) versus UDCA (moderate)	1	216	Odds Ratio (M-H, Fixed, 95% CI)	1.55 [0.06, 38.46]
2 Mortality (< 1 year)	9		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Azathioprine versus no intervention	1	39	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.16, 2.10]
2.2 Colchicine versus no intervention	1	64	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.22, 3.33]
2.3 Cyclosporin versus no intervention	1	12	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 3.63]
2.4 D-Penicillamine versus no intervention	1	189	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.35, 1.42]

2.5 UDCA (low) versus no intervention	1	18	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.6 UDCA (low) versus UDCA (high)	1	106	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.06, 17.06]
2.7 UDCA (moderate) versus UDCA (high)	1	103	Odds Ratio (M-H, Fixed, 95% CI)	0.36 [0.01, 9.05]
2.8 Obeticholic acid (low) plus UDCA (moderate) versus UDCA (moderate)	1	216	Odds Ratio (M-H, Fixed, 95% CI)	1.55 [0.06, 38.46]
2.9 UDCA (low) plus colchicine versus UDCA (low)	1	84	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.13, 7.45]
2.10 UDCA (low) plus methotrexate versus UDCA (low)	1	25	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.11 UDCA (moderate) versus UDCA (low)	1	101	Odds Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.72]
3 Mortality (1 to 5 years)	20		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Azathioprine versus no intervention	1	185	Odds Ratio (M-H, Fixed, 95% CI)	0.56 [0.30, 1.04]
3.2 Chlorambucil versus no intervention	1	24	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 3.28]
3.3 Colchicine versus no intervention	1	58	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.22, 2.25]
3.4 Cyclosporin versus no intervention	2	378	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.54, 1.64]
3.5 D-Penicillamine versus no intervention	4	234	Odds Ratio (M-H, Fixed, 95% CI)	1.10 [0.59, 2.08]
3.6 Glucocorticosteroids versus no intervention	1	36	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.14, 2.92]
3.7 Malotilate versus no intervention	1	101	Odds Ratio (M-H, Fixed, 95% CI)	2.0 [0.47, 8.48]
3.8 Methotrexate versus no intervention	1	60	Odds Ratio (M-H, Fixed, 95% CI)	8.83 [1.01, 76.96]
3.9 UDCA (low) versus no intervention	1	46	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.03, 3.47]
3.10 UDCA (moderate) versus no intervention	4	670	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.62, 1.77]
3.11 Bezafibrate plus UDCA (moderate) versus UDCA (moderate)	1	27	Odds Ratio (M-H, Fixed, 95% CI)	9.67 [0.45, 207.78]
3.12 Colchicine plus UDCA (moderate) versus UDCA (moderate)	1	74	Odds Ratio (M-H, Fixed, 95% CI)	5.28 [0.24, 113.87]
3.13 Methotrexate plus UDCA (moderate) versus UDCA (moderate)	1	265	Odds Ratio (M-H, Fixed, 95% CI)	1.17 [0.55, 2.51]
4 Serious adverse events (proportion)	12		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Colchicine versus no intervention	1	64	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

4.2 D-Penicillamine versus no intervention	1	52	Odds Ratio (M-H, Fixed, 95% CI)	28.77 [1.57, 526.67]
4.3 Obeticholic acid (high) versus no intervention	1	79	Odds Ratio (M-H, Fixed, 95% CI)	5.14 [0.57, 46.17]
4.4 Obeticholic acid (low) versus no intervention	1	76	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 8.22]
4.5 Obeticholic acid (moderate) versus no intervention	1	86	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.05, 13.01]
4.6 UDCA (low) versus no intervention	1	18	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.7 UDCA (moderate) versus no intervention	2	362	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.8 UDCA (low) versus bezafibrate	1	24	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.9 Obeticholic acid (low) versus obeticholic acid (high)	1	79	Odds Ratio (M-H, Fixed, 95% CI)	0.09 [0.00, 1.61]
4.10 Obeticholic acid (moderate) versus obeticholic acid (high)	1	89	Odds Ratio (M-H, Fixed, 95% CI)	0.15 [0.02, 1.37]
4.11 Obeticholic acid (moderate) versus obeticholic acid (low)	1	86	Odds Ratio (M-H, Fixed, 95% CI)	2.43 [0.10, 61.39]
4.12 Lamivudine plus zidovudine plus UDCA (moderate) versus UDCA (moderate)	1	59	Odds Ratio (M-H, Fixed, 95% CI)	0.47 [0.04, 5.43]
4.13 UDCA (moderate) versus obeticholic acid (low) plus UDCA (moderate)	1	216	Odds Ratio (M-H, Fixed, 95% CI)	0.28 [0.08, 0.98]
4.14 Bezafibrate plus UDCA (low) versus UDCA (low)	1	22	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.15 UDCA (moderate) versus UDCA (low)	1	59	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.16 Colchicine plus UDCA (moderate) versus UDCA (moderate)	1	74	Odds Ratio (M-H, Fixed, 95% CI)	3.08 [0.12, 78.14]
5 Serious adverse events (number of events)	1		Rate Ratio (Fixed, 95% CI)	Subtotals only
5.1 Obeticholic acid (low) plus UDCA (moderate) versus UDCA (moderate)	1		Rate Ratio (Fixed, 95% CI)	1.66 [0.75, 3.66]
6 Adverse events (proportion)	20		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Cyclosporin versus no intervention	3	390	Odds Ratio (M-H, Fixed, 95% CI)	3.04 [1.98, 4.68]
6.2 D-Penicillamine versus no intervention	2	287	Odds Ratio (M-H, Fixed, 95% CI)	4.51 [2.56, 7.93]
6.3 Malotilate versus no intervention	1	101	Odds Ratio (M-H, Fixed, 95% CI)	11.43 [1.40, 93.04]
6.4 Obeticholic acid (high) versus no intervention	1	79	Odds Ratio (M-H, Fixed, 95% CI)	16.6 [0.90, 305.59]

6.5 Obeticholic acid (low) versus no intervention	1	76	Odds Ratio (M-H, Fixed, 95% CI)	1.59 [0.41, 6.17]
6.6 Obeticholic acid (moderate) versus no intervention	1	86	Odds Ratio (M-H, Fixed, 95% CI)	8.81 [1.01, 76.73]
6.7 UDCA (low) versus no intervention	1	18	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.8 UDCA (moderate) versus no intervention	2	362	Odds Ratio (M-H, Fixed, 95% CI)	1.45 [0.50, 4.25]
6.9 Glucocorticosteroids plus UDCA (moderate) versus azathioprine plus UDCA (moderate)	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.40 [0.08, 2.12]
6.10 UDCA (low) versus bezafibrate	1	24	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.11 Obeticholic acid (low) versus obeticholic acid (high)	1	79	Odds Ratio (M-H, Fixed, 95% CI)	0.09 [0.00, 1.78]
6.12 Obeticholic acid (moderate) versus obeticholic acid (high)	1	89	Odds Ratio (M-H, Fixed, 95% CI)	0.38 [0.02, 9.62]
6.13 Obeticholic acid (moderate) versus obeticholic acid (low)	1	86	Odds Ratio (M-H, Fixed, 95% CI)	5.53 [0.59, 51.70]
6.14 Bezafibrate plus UDCA (low) versus UDCA (low)	1	22	Odds Ratio (M-H, Fixed, 95% CI)	3.29 [0.12, 89.81]
6.15 Colestilan plus UDCA (low) versus UDCA (low)	1	11	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.16 Methotrexate plus UDCA (low) versus UDCA (low)	1	25	Odds Ratio (M-H, Fixed, 95% CI)	115.0 [4.98, 2657. 48]
6.17 UDCA (moderate) versus UDCA (low)	1	59	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.18 Azathioprine plus UDCA (moderate) versus UDCA (moderate)	1	42	Odds Ratio (M-H, Fixed, 95% CI)	19.67 [0.94, 413.50]
6.19 Colchicine plus UDCA (moderate) versus UDCA (moderate)	2	42	Odds Ratio (M-H, Fixed, 95% CI)	6.20 [0.63, 60.80]
6.20 Glucocorticosteroids plus UDCA (moderate) versus UDCA (moderate)	2	135	Odds Ratio (M-H, Fixed, 95% CI)	5.54 [1.35, 22.84]
6.21 TauroUDCA (moderate) versus UDCA (moderate)	1	30	Odds Ratio (M-H, Fixed, 95% CI)	21.0 [2.16, 204.61]
7 Adverse events (number)	15		Rate Ratio (Fixed, 95% CI)	Subtotals only
7.1 Chlorambucil versus no intervention	1		Rate Ratio (Fixed, 95% CI)	3.67 [1.04, 12.87]
7.2 Cyclosporin versus no intervention	3		Rate Ratio (Fixed, 95% CI)	1.87 [1.51, 2.32]
7.3 D-Penicillamine versus no intervention	3		Rate Ratio (Fixed, 95% CI)	2.64 [1.78, 3.91]

7.4 Malotilate versus no intervention	1		Rate Ratio (Fixed, 95% CI)	6.13 [1.38, 27.14]
7.5 Obeticholic acid (high) versus no intervention	1		Rate Ratio (Fixed, 95% CI)	1.91 [1.50, 2.44]
7.6 Obeticholic acid (low) versus no intervention	1		Rate Ratio (Fixed, 95% CI)	1.05 [0.80, 1.39]
7.7 Obeticholic acid (moderate) versus no intervention	1		Rate Ratio (Fixed, 95% CI)	1.25 [0.97, 1.62]
7.8 Obeticholic acid (low) versus obeticholic acid (high)	1		Rate Ratio (Fixed, 95% CI)	0.55 [0.43, 0.70]
7.9 Obeticholic acid (moderate) versus obeticholic acid (high)	1		Rate Ratio (Fixed, 95% CI)	0.66 [0.53, 0.81]
7.10 Obeticholic acid (moderate) versus obeticholic acid (low)	1		Rate Ratio (Fixed, 95% CI)	1.19 [0.93, 1.53]
7.11 UDCA (low) versus UDCA (high)	1		Rate Ratio (Fixed, 95% CI)	2.08 [0.78, 5.53]
7.12 UDCA (moderate) versus UDCA (high)	1		Rate Ratio (Fixed, 95% CI)	0.73 [0.21, 2.60]
7.13 UDCA (low) plus methotrexate versus UDCA (low)	1		Rate Ratio (Fixed, 95% CI)	30.64 [1.84, 510.76]
7.14 UDCA (moderate) versus UDCA (low)	1		Rate Ratio (Fixed, 95% CI)	0.35 [0.11, 1.10]
7.15 Azathioprine plus glucocorticosteroids plus UDCA (moderate) versus UDCA (moderate)	1		Rate Ratio (Fixed, 95% CI)	1.32 [0.88, 1.97]
7.16 Bezafibrate plus UDCA (moderate) versus UDCA (moderate)	1		Rate Ratio (Fixed, 95% CI)	11.79 [0.65, 213.14]
7.17 Colchicine plus UDCA (moderate) versus UDCA (moderate)	1		Rate Ratio (Fixed, 95% CI)	5.91 [0.28, 123.08]
7.18 TauroUDCA (moderate) versus UDCA (moderate)	1		Rate Ratio (Fixed, 95% CI)	1.17 [0.81, 1.71]
8 Liver transplantation	12		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Cyclosporin versus no intervention	2	378	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.43, 1.72]
8.2 D-Penicillamine versus no intervention	1	189	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.06, 15.05]
8.3 Methotrexate versus no intervention	1	60	Odds Ratio (M-H, Fixed, 95% CI)	0.17 [0.02, 1.58]
8.4 UDCA (low) versus no intervention	2	162	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.24, 4.06]
8.5 UDCA (moderate) versus no intervention	3	478	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.44, 1.76]
8.6 UDCA (low) versus UDCA (high)	1	106	Odds Ratio (M-H, Fixed, 95% CI)	3.17 [0.13, 79.71]

8.7 UDCA (moderate) versus UDCA (high)	1	103	Odds Ratio (M-H, Fixed, 95% CI)	3.37 [0.13, 84.70]
8.8 UDCA (moderate) versus UDCA (low)	1	101	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.06, 17.47]
8.9 Bezafibrate plus UDCA (moderate) versus UDCA (moderate)	1	27	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.10 Methotrexate plus UDCA (moderate) versus UDCA (moderate)	1	265	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.35, 1.39]
9 Decompensated liver disease	7		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 D-Penicillamine versus no intervention	1	24	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 UDCA (moderate) versus no intervention	2	351	Odds Ratio (M-H, Fixed, 95% CI)	1.33 [0.84, 2.12]
9.3 Obeticholic acid (low) plus UDCA (moderate) versus UDCA (moderate)	1	216	Odds Ratio (M-H, Fixed, 95% CI)	1.55 [0.06, 38.46]
9.4 UDCA (low) plus colchicine versus UDCA (low)	1	84	Odds Ratio (M-H, Fixed, 95% CI)	0.21 [0.04, 1.07]
9.5 Azathioprine plus UDCA (moderate) versus UDCA (moderate)	1	42	Odds Ratio (M-H, Fixed, 95% CI)	0.52 [0.05, 5.18]
9.6 Glucocorticosteroids plus UDCA (moderate) versus UDCA (moderate)	1	66	Odds Ratio (M-H, Fixed, 95% CI)	0.55 [0.11, 2.69]
9.7 Methotrexate plus UDCA (moderate) versus UDCA (moderate)	1	151	Odds Ratio (M-H, Fixed, 95% CI)	2.00 [0.79, 5.04]
9.8 Glucocorticosteroids plus UDCA (moderate) versus azathioprine plus UDCA (moderate)	1	50	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.10, 11.18]
10 Cirrhosis	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Azathioprine versus no intervention	1	31	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.18, 3.41]
10.2 UDCA (low) versus no intervention	1	22	Odds Ratio (M-H, Fixed, 95% CI)	0.15 [0.01, 1.53]
10.3 Azathioprine plus glucocorticosteroids plus UDCA (moderate) versus UDCA (moderate)	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.28 [0.03, 2.90]

ADDITIONAL TABLES

Table 1. Characteristics of included studies arranged by comparison

Study name	No participants randomised	Post-randomisation dropouts	No participants for whom outcome was reported	Intervention(s)	Control	Mean follow-up period (months)
Smart 1990	20	Not stated	20	Antioxidants	No intervention	Not stated
Christensen 1985	248	63	185	Azathioprine	No intervention	63
Heathcote 1976	45	6	39	Azathioprine	No intervention	Not stated
Hoofnagle 1986	24	0	24	Chlorambucil	No intervention	52
Bodenheimer 1988	57	10	47	Colchicine	No intervention	33
Kaplan 1986	60	3	57	Colchicine	No intervention	24
Warnes 1987	64	Not stated	64*	Colchicine	No intervention	19 (median)
Bobadilla 1994	40	Not stated	40	Colchicine + UDCA	No intervention	12
Lombard 1993	349	0	349	Ciclosporin	No intervention	31 (median)
Minuk 1988	12	0	12	Ciclosporin	No intervention	Not stated
Wiesner 1990	40	11	29	Ciclosporin	No intervention	35 (median)
Dickson 1985	309	82	227	D-Penicillamine	No intervention	60 (median)
Epstein 1979	98	Not stated	98	D-Penicillamine	No intervention	66
Macklon 1982	60	0	60	D-Penicillamine	No intervention	37
Matloff 1982	52	0	52	D-Penicillamine	No intervention	24
Neuberger 1985	189	Not stated	189	D-Penicillamine	No intervention	Not stated
Taal 1983	24	Not stated	24	D-Penicillamine	No intervention	18
Triger 1980	35	Not stated	35	D-Penicillamine	No intervention	Not stated
Mitchison 1989	36	0	36	Glucocorticosteroids	No intervention	36

Table 1. Characteristics of included studies arranged by comparison *(Continued)*

Ueno 2005	20	Not stated	20	Lamivudine	No intervention	Not stated
Mitchison 1993	104	3	101	Malotilate	No intervention	25 (median)
Hendrickse 1999	60	Not stated	60	Methotrexate	No intervention	68
Steenbergen 1994	14	Not stated	14	Methotrexate + UDCA	No intervention	24
Mayo 2015	45	3	42	NGM282	No intervention	Not stated
Bowlus 2014	216	Not stated	216	Obeticholic acid	No intervention	12
Hirschfield 2015	165	0	165	Obeticholic acid	No intervention	3
Kowdley 2014a	59	Not stated	59	Obeticholic acid	No intervention	Not stated
Manzillo 1993a	32	Not stated	32	S-Adenosyl methionine	No intervention	1
Manzillo 1993b	6	Not stated	6	S-Adenosyl methionine	No intervention	2
Cash 2013	21	8	13	Simvastatin	No intervention	12
Askari 2010	28	0	28	Tetrathiomolybdate	No intervention	Not stated
McCormick 1994	18	0	18	Thalidomide	No intervention	Not stated
Arora 1990	9	Not stated	9	UDCA	No intervention	5
Battezzati 1993	88	2	86	UDCA	No intervention	6
Combes 1995a	151	0	151	UDCA	No intervention	24
Eriksson 1997	116	15	101	UDCA	No intervention	24
Heathcote 1994	222	Not stated	222	UDCA	No intervention	24
Leuschner 1989	20	0	18	UDCA	No intervention	12
Lim 1994	32	Not stated	32	UDCA	No intervention	Not stated
Lindor 1994	180	10	170	UDCA	No intervention	24
Oka 1990	52	7	45	UDCA	No intervention	Not stated

Table 1. Characteristics of included studies arranged by comparison *(Continued)*

Papatheodoridis 2002	92	6	86	UDCA	No intervention	89
Pares 2000	192	0	192	UDCA	No intervention	41 (median)
Poupon 1991a	149	3	146	UDCA	No intervention	Not stated
Senior 1991	20	1	19	UDCA	No intervention	18
Turner 1994	46	0	46	UDCA	No intervention	24
Goddard 1994	57	Not stated	57	Intervention 1: UDCA Intervention 2: colchicine Intervention 3: colchicine + UDCA	No intervention	15
Wolfhagen 1998	50	Not stated	50	Azathioprine + glucocorticos-teroids + UDCA	UDCA	12
Iwasaki 2008a	45	Not stated	45	Bezafibrate	UDCA	12
Kurihara 2000	24	Not stated	24	Bezafibrate	UDCA	Not stated
Hosonuma 2015	27	0	27	Bezafibrate + UDCA	UDCA	96
Iwasaki 2008b	22	Not stated	22	Bezafibrate + UDCA	UDCA	12
Kanda 2003	22	0	22	Bezafibrate + UDCA	UDCA	7
Nakai 2000	23	Not stated	23	Bezafibrate + UDCA	UDCA	12
Almasio 2000	90	6	84	Colchicine + UDCA	UDCA	Not stated
Ikeda 1996	22	0	22	Colchicine + UDCA	UDCA	24
Poupon 1996	74	Not stated	74	Colchicine + UDCA	UDCA	24
Raedsch 1993	28	8	20	Colchicine + UDCA	UDCA	24

Table 1. Characteristics of included studies arranged by comparison *(Continued)*

Yokomori 2001	11	Not stated	11	Colestilan + UDCA	UDCA	Not stated
Liberopoulos 2010	10	Not stated	10	Fenofibrate + UDCA	UDCA	Not stated
Leuschner 1999	40	0	39	Glucocorticos-teroids + UDCA	UDCA	24
Rautiainen 2005	77	8	69	Glucocorticos-teroids + UDCA	UDCA	36
Gao 2012	79	Not stated	79	Intervention 1: glucocorticos-teroids + UDCA Intervention 2: azathioprine + UDCA	UDCA	Not stated
Mason 2008	59	0	59	Lamivudine + zi-dovudine + UDCA	UDCA	6
Combes 2005	265	0	265	Methotrexate + UDCA	UDCA	91 (median)
Gonzalezkoch 1997	25	Not stated	25	Methotrexate + UDCA	UDCA	11
Nevens 2016	217	Not stated	216	Obeticholic acid + UDCA	UDCA	12
Ferri 1993	30	0	30	TUDCA	UDCA	6
Ma 2016	199	8	191	TUDCA	UDCA	6
Kaplan 1999	87	2	85	Colchicine	Methotrexate	24
Comparison of doses						**Comparison of**
Lindor 1997	150	Not stated	150	Intervention 1: UDCA (high) Intervention 2: UDCA (moder-ate)	UDCA (low)	12
Angulo 1999a	155	Not stated	155	Intervention 1: UDCA (high) Intervention 2:	UDCA (low)	12

Table 1. Characteristics of included studies arranged by comparison *(Continued)*

				UDCA (moderate)		
Van Hoogstraten 1998	61	2	59	UDCA (moderate)	UDCA (low)	Not stated
Mazzarella 2002	42	Not stated	42	UDCA (high)	UDCA (moderate)	72

TUDCA: taurodeoxycholic acid; UDCA: ursodeoxycholic acid.

Table 2. Risk of bias arranged according to comparisons

Name of studies	Intervention(s)	Control	Random sequence generation	Allocation concealment	Blinding of participants and health professionals	Blinding of outcome assessors	Missing outcome bias	Selective outcome reporting	For-profit bias	Other bias
Smart 1990	Antioxidants	No intervention	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low
Christensen 1985	Azathioprine	No intervention	Unclear	Unclear	Low	Low	High	High	High	Low
Heathcote 1976	Azathioprine	No intervention	Unclear	Unclear	High	High	High	High	Low	Low
Hoofnagle 1986	Chlorambucil	No intervention	Low	Low	High	High	Low	Low	Low	Low
Bodenheimer 1988	Colchicine	No intervention	Unclear	Unclear	Low	Low	High	High	High	Low
Kaplan 1986	Colchicine	No intervention	Unclear	Unclear	Unclear	Unclear	High	High	Unclear	Low
Warnes 1987	Colchicine	No intervention	Low	Low	Low	Low	Unclear	Low	Unclear	Low

Table 2. Risk of bias arranged according to comparisons (*Continued*)

Bobadilla 1994	Colchicine + UDCA	No intervention	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low
Lombard 1993	Ciclosporin	No intervention	Unclear	Unclear	Low	Low	Low	Low	High	Low
Minuk 1988	Ciclosporin	No intervention	Unclear	Unclear	Low	Unclear	Unclear	Low	High	Low
Wiesner 1990	Ciclosporin	No intervention	Unclear	Unclear	Low	Low	Unclear	Low	High	Low
Dickson 1985	D-Penicillamine	No intervention	Low	Low	Low	Low	High	High	High	High
Epstein 1979	D-Penicillamine	No intervention	Unclear	Unclear	High	High	Unclear	High	Unclear	Low
Macklon 1982	D-Penicillamine	No intervention	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear	Low
Matloff 1982	D-Penicillamine	No intervention	Unclear	Unclear	Unclear	Unclear	Low	Low	High	Low
Neuberger 1985	D-Penicillamine	No intervention	Unclear	Low	Low	Low	Unclear	High	Unclear	Low
Taal 1983	D-Penicillamine	No intervention	Unclear	Unclear	Low	Low	Unclear	Low	Unclear	Low
Triger 1980	D-Penicillamine	No intervention	Unclear	Unclear	Unclear	Unclear	Unclear	High	High	Low
Mitchison 1989	Glucocorticosteroids	No intervention	Low	Low	High	High	Low	High	Unclear	Low
Ueno 2005	Lamivudine	No intervention	Unclear	Unclear	Low	Low	Unclear	High	Unclear	Low
Mitchison 1993	Malotilate	No intervention	Low	Low	Low	Low	High	Low	High	Low
Hendrickse 1999	Methotrexate	No intervention	Low	Low	Unclear	Unclear	Unclear	High	Unclear	Low

Table 2. Risk of bias arranged according to comparisons (*Continued*)

Steenbergen 1994	Methotrexate + UDCA	No intervention	Low	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low
Mayo 2015	NGM282	No intervention	Unclear	Unclear	Unclear	Unclear	High	High	High	Low
Bowlus 2014	Obeticholic acid	No intervention	Unclear	Unclear	Unclear	Unclear	Unclear	High	High	Low
Hirschfield 2015	Obeticholic acid	No intervention	Low	Unclear	Low	Low	Low	High	Unclear	High
Kowdley 2011	Obeticholic acid	No intervention	Unclear	Unclear	Unclear	Unclear	Unclear	High	High	Low
Manzillo 1993a	S-Adenosyl methionine	No intervention	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low
Manzillo 1993b	S-Adenosyl methionine	No intervention	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low
Cash 2013	Simvastatin	No intervention	Unclear	Low	High	High	High	High	Low	High
Askari 2010	Tetrathiomolybdate	No intervention	Low	Low	Low	Low	Low	High	Low	High
McCormick 1994	Thalidomide	No intervention	Unclear	Unclear	Low	Low	Low	High	High	Low
Arora 1990	UDCA	No intervention	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low
Battezzati 1993	UDCA	No intervention	Low	Low	Low	Low	High	High	Unclear	Low
Combes 1995a	UDCA	No intervention	Unclear	Unclear	Low	Low	Low	High	High	Low
Eriksson 1997	UDCA	No intervention	Unclear	Unclear	Unclear	Unclear	High	High	High	Low

Table 2. Risk of bias arranged according to comparisons (*Continued*)

Heathcote 1994	UDCA	No intervention	Unclear	Low	Low	Low	Unclear	High	High	Low
Leuschner 1989	UDCA	No intervention	Unclear	Unclear	Unclear	Unclear	High	Low	Unclear	Low
Lim 1994	UDCA	No intervention	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low
Lindor 1994	UDCA	No intervention	Unclear	Unclear	Low	Low	High	Low	High	Low
Oka 1990	UDCA	No intervention	Unclear	Low	Low	Low	High	High	High	Low
Papatheodoridis 2002	UDCA	No intervention	Low	Low	High	High	High	High	High	High
Pares 2000	UDCA	No intervention	Unclear	Unclear	Low	Low	Unclear	Low	High	Low
Poupon 1991a	UDCA	No intervention	Unclear	Unclear	Low	Low	High	High	High	Low
Senior 1991	UDCA	No intervention	Unclear	Unclear	Unclear	Unclear	High	High	High	Low
Turner 1994	UDCA	No intervention	Unclear	Unclear	Low	Low	Low	High	Unclear	Low
Goddard 1994	Intervention 1: UDCA Intervention 2: colchicine Intervention 3: colchicine + UDCA	No intervention	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low
Wolfhagen 1998	Azathioprine + glucocorticosteroids +	UDCA	Low	Low	Low	Low	Unclear	High	High	Low

Table 2. Risk of bias arranged according to comparisons (*Continued*)

	UDCA									
Iwasaki 2008a	Bezafibrate	UDCA	Unclear	Low	High	High	Unclear	High	Low	Low
Kurihara 2000	Bezafibrate	UDCA	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low
Hosonuma 2015	Bezafibrate + UDCA	UDCA	Low	Low	High	High	Low	Low	Low	Low
Iwasaki 2008b	Bezafibrate + UDCA	UDCA	Unclear	Low	High	High	Unclear	High	Low	Low
Kanda 2003	Bezafibrate + UDCA	UDCA	Unclear	Unclear	Unclear	Unclear	Low	High	Unclear	Low
Nakai 2000	Bezafibrate + UDCA	UDCA	Unclear	Unclear	Unclear	Unclear	Unclear	High	Low	Low
Almasio 2000	Colchicine + UDCA	UDCA	Low	Low	Low	Low	High	High	Low	Low
Ikeda 1996	Colchicine + UDCA	UDCA	Unclear	Unclear	Unclear	Unclear	Low	High	Unclear	High
Poupon 1996	Colchicine + UDCA	UDCA	Unclear	Unclear	Low	Low	Unclear	Low	High	Low
Raedsch 1993	Colchicine + UDCA	UDCA	Unclear	Unclear	Unclear	Unclear	High	High	Unclear	Low
Yokomori 2001	Colestilan + UDCA	UDCA	Unclear	Unclear	High	High	Unclear	High	Unclear	Low
Liberopoulos 2010	Fenofibrate + UDCA	UDCA	Unclear	Unclear	High	High	Unclear	High	Unclear	Low

Table 2. Risk of bias arranged according to comparisons (*Continued*)

Leuschner 1999	Glucocorticosteroids + UDCA	UDCA	Low	Unclear	Unclear	Unclear	High	High	High	Low
Rautiainen 2005	Glucocorticosteroids + UDCA	UDCA	Unclear	Unclear	High	High	High	High	High	Low
Gao 2012	Glucocorticosteroids + UDCA Azathioprine + UDCA	UDCA	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low
Mason 2008	Lamivudine + zidovudine + UDCA	UDCA	Low	Low	Low	Low	Unclear	High	High	Low
Combes 2005	Methotrexate + UDCA	UDCA	Unclear	Unclear	Unclear	Unclear	Low	High	High	Low
Gonzalezkoch 1997	Methotrexate + UDCA	UDCA	Unclear	Low	Unclear	Unclear	Unclear	Low	Unclear	Low
Nevens 2016	Obeticholic acid + UDCA	UDCA	Low	Low	Low	Low	High	Low	High	Low
Ferri 1993	TUDCA	UDCA	Unclear	Unclear	Unclear	Unclear	Low	High	Unclear	Low
Ma 2016	TUDCA	UDCA	Low	Low	Low	Low	Unclear	High	High	Low
Kaplan 1999	Colchicine	Methotrexate	Unclear	Unclear	Low	Low	High	High	Unclear	Low
Comparison of doses										**Comparison of**

Table 2. Risk of bias arranged according to comparisons (*Continued*)

Lindor 1997	Intervention 1: UDCA (high) Intervention 2: UDCA (moderate)	UDCA (low)	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low
Angulo 1999a	Intervention 1: UDCA (high) Intervention 2: UDCA (moderate)	UDCA (low)	Low	Low	Low	Low	Unclear	Low	Unclear	Low
Van Hoogstrate 1998	UDCA (moderate)	UDCA (low)	Low	Low	High	High	Unclear	High	High	Low
Mazzarella 2002	UDCA (high)	UDCA (moderate)	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low

TUDCA: taurodeoxycholic acid; UDCA: ursodeoxycholic acid.

CONTRIBUTIONS OF AUTHORS

FS identified the trials, extracted the data for half the trials, and completed the characteristics tables.

KG identified the trials, extracted the data, performed the analysis, and wrote the review.

LHE extracted the data for half the trials.

ET, BD, and DT critically commented on the review.

DECLARATIONS OF INTEREST

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ET has participated in advisory boards for Astra Zeneca and ViiV healthcare.

BD has no financial disclosures.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- It was not possible to assess whether the potential effect modifiers were similar across different comparisons. Therefore, we did not perform the network meta-analysis and assessed the comparative benefits and harms of different interventions using standard Cochrane methodology. The methodology that we plan to use if we conduct a network meta-analysis in the future is available in Appendix 1.
- We performed Trial Sequential Analysis in addition to conventional method of assessing the risk of random errors using P values.

NOTES

There is considerable overlap between the 'Methods' of this review and those of several other reviews written by the same group of authors.