Cochrane
Library

Cochrane Database of Systematic Reviews

Colchicine for alcoholic and non-alcoholic liver fibrosis and cirrhosis (Review)

Rambaldi A, Gluud C

Rambaldi A, Gluud C.
Colchicine for alcoholic and non-alcoholic liver fibrosis and cirrhosis.
Cochrane Database of Systematic Reviews 2005, Issue 2. Art. No.: CD002148.
DOI: [10.1002/14651858.CD002148.pub2](https://doi.org/10.1002/14651858.CD002148.pub2).

www.cochranelibrary.com

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	3
METHODS	3
Figure 1.	4
RESULTS	5
Figure 2.	7
Figure 3.	8
DISCUSSION	9
AUTHORS' CONCLUSIONS	9
ACKNOWLEDGEMENTS	10
REFERENCES	11
CHARACTERISTICS OF STUDIES	15
DATA AND ANALYSES	30
Analysis 1.1. Comparison 1 Colchicine versus placebo or no intervention, Outcome 1 Mortality.	34
Analysis 1.2. Comparison 1 Colchicine versus placebo or no intervention, Outcome 2 Liver-related mortality.	35
Analysis 1.3. Comparison 1 Colchicine versus placebo or no intervention, Outcome 3 Ascites.	36
Analysis 1.4. Comparison 1 Colchicine versus placebo or no intervention, Outcome 4 Variceal bleeding.	37
Analysis 1.5. Comparison 1 Colchicine versus placebo or no intervention, Outcome 5 Hepatic encephalopathy.	38
Analysis 1.6. Comparison 1 Colchicine versus placebo or no intervention, Outcome 6 Hepato-renal syndrome.	38
Analysis 1.7. Comparison 1 Colchicine versus placebo or no intervention, Outcome 7 Total number of complications (variceal bleeding, hepatic encephalopathy, ascites, hepatorenal-syndrome).	39
Analysis 1.8. Comparison 1 Colchicine versus placebo or no intervention, Outcome 8 Bilirubin (mg/dl).	40
Analysis 1.9. Comparison 1 Colchicine versus placebo or no intervention, Outcome 9 AST (U/l).	40
Analysis 1.10. Comparison 1 Colchicine versus placebo or no intervention, Outcome 10 ALT (U/l).	41
Analysis 1.11. Comparison 1 Colchicine versus placebo or no intervention, Outcome 11 ALP (U/l).	42
Analysis 1.12. Comparison 1 Colchicine versus placebo or no intervention, Outcome 12 GGT (U/l).	42
Analysis 1.13. Comparison 1 Colchicine versus placebo or no intervention, Outcome 13 Serum albumin (g/dl).	43
Analysis 1.14. Comparison 1 Colchicine versus placebo or no intervention, Outcome 14 Prothrombin (%).	43
Analysis 1.15. Comparison 1 Colchicine versus placebo or no intervention, Outcome 15 Prothrombin (seconds).	44
Analysis 1.16. Comparison 1 Colchicine versus placebo or no intervention, Outcome 16 White blood count (1.000 cells/ cubic mm).	44
Analysis 1.17. Comparison 1 Colchicine versus placebo or no intervention, Outcome 17 Collagen-peptidase.	44
Analysis 1.18. Comparison 1 Colchicine versus placebo or no intervention, Outcome 18 7S collagen (ng/ml).	45
Analysis 1.19. Comparison 1 Colchicine versus placebo or no intervention, Outcome 19 Prolidase (U/l).	45
Analysis 1.20. Comparison 1 Colchicine versus placebo or no intervention, Outcome 20 PIIP (ng/ml).	45
Analysis 1.21. Comparison 1 Colchicine versus placebo or no intervention, Outcome 21 Liver biopsy improvement.	46
Analysis 1.22. Comparison 1 Colchicine versus placebo or no intervention, Outcome 22 Liver biopsy findings (hepatitis).	47
Analysis 1.23. Comparison 1 Colchicine versus placebo or no intervention, Outcome 23 Liver biopsy findings (fibrosis).	47
Analysis 1.24. Comparison 1 Colchicine versus placebo or no intervention, Outcome 24 Alcohol consumption.	47
Analysis 1.25. Comparison 1 Colchicine versus placebo or no intervention, Outcome 25 Sustained biochemical response.	48
Analysis 1.26. Comparison 1 Colchicine versus placebo or no intervention, Outcome 26 Sustained virological response.	49
Analysis 2.1. Comparison 2 Adverse events, Outcome 1 Serious adverse events.	50
Analysis 2.2. Comparison 2 Adverse events, Outcome 2 Non-serious adverse events.	50
Analysis 3.1. Comparison 3 Sensitivity analyses, Outcome 1 Mortality and duration of treatment.	52
Analysis 3.2. Comparison 3 Sensitivity analyses, Outcome 2 Mortality - worst case scenario.	53
Analysis 3.3. Comparison 3 Sensitivity analyses, Outcome 3 Colchicine versus placebo or no intervention.	54
Analysis 3.4. Comparison 3 Sensitivity analyses, Outcome 4 Mortality and methodological quality.	54
APPENDICES	55

WHAT'S NEW	56
CONTRIBUTIONS OF AUTHORS	56
DECLARATIONS OF INTEREST	56
SOURCES OF SUPPORT	57
NOTES	57
INDEX TERMS	57

[Intervention Review]

Colchicine for alcoholic and non-alcoholic liver fibrosis and cirrhosis

Andrea Rambaldi¹, Christian Gluud¹¹Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Department 3344, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

Contact address: Andrea Rambaldi, Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Department 3344, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, Copenhagen, DK-2100, Denmark.
arambaldi@hotmail.com, rambaldi.andrea@libero.it.

Editorial group: Cochrane Hepato-Biliary Group.

Publication status and date: Edited (no change to conclusions), published in Issue 1, 2009.

Citation: Rambaldi A, Gluud C. Colchicine for alcoholic and non-alcoholic liver fibrosis and cirrhosis. *Cochrane Database of Systematic Reviews* 2005, Issue 2. Art. No.: CD002148. DOI: [10.1002/14651858.CD002148.pub2](https://doi.org/10.1002/14651858.CD002148.pub2).

Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Alcohol and hepatotropic viruses cause the majority of liver cirrhosis in the Western World. Colchicine is an anti-inflammatory and anti-fibrotic medication. Several randomised clinical trials have addressed the question whether colchicine has any efficacy in patients with alcoholic or non-alcoholic fibrosis and cirrhosis.

Objectives

To assess the beneficial and harmful effects of colchicine in patients with alcoholic or non-alcoholic fibrosis or cirrhosis, excluding patients with primary biliary cirrhosis.

Search methods

The Cochrane Hepato-Biliary Group Controlled Trials Register, The Cochrane Controlled Trials Register on The Cochrane Library, MEDLINE, EMBASE, Science Citation Index Expanded, and full text searches were combined (September 2004). Manufacturers and researchers in the field were also contacted.

Selection criteria

We included randomised trials irrespective of blinding, language, or publication status comparing per oral colchicine with placebo or no intervention for patients with fibrosis or cirrhosis induced by either alcohol, virus, or unknown factors (cryptogenic).

Data collection and analysis

The statistical package (RevMan Analyses) provided by The Cochrane Collaboration was used. The methodological quality of the randomised clinical trials was evaluated.

Main results

We could include 15 randomised clinical trials with 1714 patients. We found no significant effects of colchicine versus placebo/no intervention on mortality (relative risks (RR) 1.00, 95% confidence interval (CI) 0.87 to 1.16), liver-related mortality (RR 1.08, 95% CI 0.88 to 1.33), complications (RR 1.01, 95% CI 0.74 to 1.38), liver biochemistry, liver histology, or alcohol consumption (RR 1.03, 95% CI 0.77 to 1.39). Colchicine was associated with a significantly increased risk of serious adverse events (RR 8.38, 95% CI 1.08 to 65.2) and non-serious adverse events (RR 4.35, 95% CI 2.16 to 8.77).

Authors' conclusions

Colchicine should not be used for alcoholic, viral, or cryptogenic liver fibrosis or liver cirrhosis outside randomised clinical trials.

PLAIN LANGUAGE SUMMARY**Evidence supporting colchicine for alcoholic, viral, and cryptogenic liver fibrosis/cirrhosis is still lacking**

Alcohol and hepatotropic viruses are major causes of liver fibrosis and liver cirrhosis. Colchicine is an anti-inflammatory and anti-fibrotic drug. This systematic review could not demonstrate any significant beneficial effects of colchicine on mortality, liver-related mortality, liver complications, liver biochemistry, or liver histology of patients with liver fibrosis or liver cirrhosis due to alcohol, hepatitis B, hepatitis C, or unknown etiology. Colchicine was associated with a significant increase in adverse events. Accordingly, there seems to be no evidence for using colchicine for alcoholic, viral, or cryptogenic liver fibrosis/cirrhosis outside randomised clinical trials.

BACKGROUND

Liver fibrosis and liver cirrhosis are common reactions to hepatotoxic substances, hepatotropic viruses, autoimmune liver diseases, metabolic liver diseases, etc. Alcohol and hepatotropic viruses cause the majority of liver fibrosis and cirrhosis in the Western World. The attributable risk for symptomatic liver cirrhosis in Italy explained by alcohol consumption, hepatitis B virus, and hepatitis C virus was 98.1% in men and 67.0% in women (Corrao 1998a). These figures resemble those found in many other western countries.

Alcohol leads to fatty liver (Rubin 1968) and alcoholic hepatitis, fibrosis, and cirrhosis (Morgan 1999). Alcoholic hepatitis is associated with peripheral leukocytosis and marked hepatic portal and parenchymal inflammatory infiltration predominantly by neutrophils (Hill 1993; Sheron 1993). Alcoholic hepatitis is a predictor of liver fibrosis and cirrhosis (Sørensen 1984; Marbet 1987). About 70% of patients with clinical alcoholic hepatitis also have alcoholic cirrhosis at the time of diagnosis (Mendenhall 1984). Five year survival rates in patients with alcoholic cirrhosis who stop drinking are of order of 50% to 75%; whereas survival rates in patients continuing to drink rarely exceed 40% (Powell 1968). The progression of liver fibrosis and cirrhosis in alcoholics is enhanced by the presence of hepatitis C and hepatitis B virus markers (Chang 1994; Corrao 1998b).

Hepatitis B and hepatitis C viruses lead to viral hepatitis. In patients with chronic hepatitis the number of patients with cirrhosis is increasing over the years (Imperial 1999). Several studies have demonstrated that the risk of fibrotic progression of chronic hepatitis C is significantly enhanced by alcohol consumption (Poynard 1997; Wiley 1998). Liver histology of chronic hepatitis C in patients with chronic alcoholism may be indistinguishable from hepatitis C in non-alcoholic patients (Schiff 1997). Alcohol consumption may also speed the development of hepatitis B cirrhosis (Chevilotte 1983).

Colchicine is a plant alkaloid. It is effective against gouty arthritis and other forms of rheumatic diseases (rheumatoid arthritis, familial Mediterranean fever, Bechet's disease, etc) (Ben-Chetrit 1998). Colchicine inhibits the migration of granulocytes into the inflamed area and inhibits the metabolic and phagocytic activity of granulocytes. Further, colchicine is anti-mitotic (Shi 1998) and anti-fibrotic. Colchicine retards the microtubule-mediated transport of procollagen (Ehrlich 1972) and enhances collagenase activity (Harris 1971). Colchicine decreased liver fibrosis in rats with carbon tetrachloride induced cirrhosis (Rojkind 1975).

Several randomised clinical trials have addressed the question whether colchicine has any efficacy in patients with alcoholic or non-alcoholic fibrosis and cirrhosis. The results have largely been negative (Trinchet 1989a; Akriviadis 1990a; Colman 1998), although some studies found efficacy of colchicine on mortality (Kershenobich 1988). Based on a questionnaire survey among European hospital-based specialists in gastroenterology/hepatology, 8% to 35% of the specialists considered using colchicine for alcoholic hepatitis, fibrosis, or cirrhosis (Gluud 1993).

The present systematic review examines the beneficial and harmful effects of colchicine for alcoholic or non-alcoholic (viral or cryptogenic) fibrosis and cirrhosis. Although alcoholic and viral induced liver fibrosis/cirrhosis have differing pathogenic

mechanisms, these conditions often coexist and potentiate the development of fibrosis/cirrhosis. Primary biliary cirrhosis (PBC) (Warnes 1991) was not included as this disease has another pathogenic mechanisms and seldom coexist with alcoholic or non-alcoholic fibrosis or cirrhosis. Furthermore, the effects of colchicine in patients with PBC have been assessed in another Cochrane review (Gong 2004). We have been unable to identify other meta-analyses or systematic reviews on the topic.

OBJECTIVES

To assess the beneficial and harmful effects of colchicine for patients with alcoholic or non-alcoholic (viral or cryptogenic) fibrosis or cirrhosis, excluding PBC.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised trials regardless of publication status or language. The trials could be double blind, single blind, or unblinded. We excluded trials in which patients were allocated by a quasi-random method, that is, day of birth or date of admission.

Types of participants

Patients with alcoholic fibrosis, alcoholic hepatitis, or alcoholic cirrhosis as well as patients with viral induced or cryptogenic fibrosis or cirrhosis according to the diagnostic work-up used in the randomised clinical trial.

Types of interventions

Per oral administration of colchicine at any dose versus placebo or no intervention. Additional interventions were allowed as long as both intervention groups received the same co-interventions.

Types of outcome measures

- (1) Number of deaths (total and liver-related deaths) (primary outcome measure).
- (2) Development of clinical symptoms and complications (that is, variceal bleeding, hepatic encephalopathy, ascites, hepato-renal syndrome).
- (3) Liver biochemistry.
- (4) Liver fibrosis markers.
- (5) Liver histology.
- (6) Alcohol consumption.
- (7) Quality-of-life.
- (8) Health economics.
- (9) Adverse events. Number and type of adverse events (non-serious and serious). Adverse event was defined as any untoward medical occurrence that did not have a causal relationship with the treatment. Serious adverse event was defined according to the International Committee on Harmonization - Good Clinical Practice (ICH-GCP) guidelines (ICH-GCP 1997) as any event that would lead to death; was life-threatening; required inpatient hospitalisation; resulted in a persistent or significant disability; or any important medical event, which might have jeopardized the patient or required intervention to prevent it.

Search methods for identification of studies

Searches in *The Cochrane Hepato-Biliary Group Controlled Trials Register* (September 2004), *The Cochrane Controlled Trials*

Register (Issue 3 2004), *MEDLINE* (1966 to September 2004), *EMBASE* (1974 to September 2004), and *Web of Science* (<http://isi3.isiknowledge.com/portal.cgi> from 1945 to September 2004) were done using the search strategies specified in [Appendix 1](#) and [Figure 1](#).

Figure 1. Search results

Further trials were sought by reading the reference lists of the identified studies.

We sent letters to the principal authors of the identified randomised clinical trials and the pharmaceutical companies producing colchicine asking for information on additional trials.

Data collection and analysis

The review was conducted according to this protocol following the recommendations given by The Cochrane Collaboration ([Alderson 2004](#)).

Selection of trials for inclusion and data extraction

The two authors independently selected the trials to be included in the review following the selection criteria. The authors planned to confer with an 'ombudsman' in case disagreements could not be solved. Such cases did not occur.

Patient characteristics, diagnosis, and treatments

The following was recorded from the randomised clinical trials: mean (or median) age, sex ratio, alcohol consumption, form of liver disease, etiology (acute viral hepatitis B or C; chronic viral hepatitis B or C; alcoholic liver disease (alcoholic steatosis; alcoholic hepatitis; alcoholic fibrosis; alcoholic cirrhosis; mixed), duration of liver disease, severity of liver disease at entry, type and dose of colchicine intervention (route of administration, formulation,

frequency, and duration of dosing), and type of intervention in the control group. The diagnostic work-up before entry was registered, specifically if hepatitis markers were evaluated and which type of fibrosis/cirrhosis patients were excluded from the randomised clinical trials. Development of clinical symptoms and complications, liver biochemistry, liver fibrosis markers, liver biopsy findings, alcohol consumption, quality-of-life, health economics (that is, length of hospital stay, cost of medication, and cost of additional follow-up weighted against any gains in health) and adverse events during follow-up were registered.

Assessment of methodological quality

The methodological quality of the randomised clinical trials was assessed using generation of allocation sequence, allocation concealment, blinding, and withdrawals and dropouts ([Moher 1998](#); [Kjaergard 2001](#)).

Generation of the allocation sequence

The procedure used to create a random sequence ensuring that each participant has a known, unpredictable, and usually equal chance of being assigned to intervention groups. The allocation sequence generation can be classified as

(1) Adequate, if the allocation sequence was generated by a computer or random number table. Drawing of lots, tossing of a coin, shuffling of cards, or throwing dice may also be considered

as adequate if a person who was not otherwise involved in the recruitment of participants performed the procedure.

(2) Unclear, if the trial was described as randomised, but the method used for the allocation sequence generation was not described.

(3) Inadequate, if a system involving dates, names, or admittance numbers were used for the allocation of patients. Such studies are known as quasi-randomised studies and should usually be excluded from systematic reviews because they are associated with a considerable risk of bias.

Allocation concealment

The procedure used to conceal the allocation sequence from the investigators who assign participants to the intervention groups. The allocation concealment can be classified as

(1) Adequate, if the allocation of patients involved a central independent unit, on-site locked computer, identically appearing numbered drug bottles or containers prepared by an independent pharmacist or investigator, or sealed envelopes. Envelopes should be serially numbered, sealed, and opaque. However, this information is rarely provided, indicating an increased risk of bias. In that case, sealed envelopes may constitute an intermediate category between adequate and unclear.

(2) Unclear, if the trial was described as randomised, but the method used to conceal the allocation was not described.

(3) Inadequate, if the allocation sequence was known to the investigators who assigned participants.

Blinding

Blinding was classified as

(1) Adequate, if the trial was described as double blind and the method of blinding involved identical placebo and active drugs.

(2) Unclear, if the trial was described as double blind, but the method of blinding was not described.

(3) Not performed, if the trial was not double blind. We also included single blind trials in this category.

Follow-up

The reported follow-up was classified as

(1) Adequate, if the numbers and reasons for dropouts and withdrawals in all intervention groups were described or if it was specified that there were no dropouts or withdrawals.

(2) Unclear, if the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated.

(3) Inadequate, if the number or reasons for dropouts and withdrawals were not described.

Intention-to-treat analysis

We registered whether the randomised clinical trial reported or not on the use of intention-to-treat analysis.

Data on the number of patients with each outcome event by allocated treatment group, irrespective of compliance of follow-up, were sought to allow an intention-to-treat analysis. If the above data were not available in the trial reports, further information was sought by correspondence with the investigators.

Statistical methods

All analyses were performed according to the intention-to-treat method; that is, all randomised patients were included. We conducted analyses counting outcomes as reported in the individual trials. Further, for patients without clear description of the outcome on mortality, we conducted a 'worst-case scenario'

analysis considering patients dropped out or withdrawn because of death.

The statistical package (RevMan Analyses) provided by The Cochrane Collaboration was used. We analysed our data with both the fixed effect model and the random effects model. In case the models differed regarding significance ($P < 0.05$), we reported both. If the random effects model was used, it is stated in the text. Otherwise, the fixed effect model was reported.

Dichotomous data were analysed by calculating the relative risk (RR) and continuous outcomes as weighed mean difference (WMD), both with 95% confidence intervals (CI).

Heterogeneity and funnel plot asymmetry

Heterogeneity in the results of the trials was initially assessed by inspection of graphical presentations and by calculating a test of heterogeneity (Chi-square and I^2). Potential causes for heterogeneity (such as etiology of fibrosis/cirrhosis, stage of liver disease, dose and duration of treatment) were explored by performing sensitivity analyses. We performed subgroup analyses according to the adequacy of methodological components (Moher 1998; Kjaergard 2001).

Due to the risk of chance findings, statistical findings among the secondary outcome measures were interpreted conservatively.

Funnel plots to identify publication bias and other biases were analysed by measure of regression analyses (Egger 1997; Vickers 1998).

RESULTS

Description of studies

Search results

We identified a total of 852 references through electronic searches of *The Cochrane Library* ($n = 288$), *MEDLINE* ($n = 50$), *EMBASE* ($n = 100$), and *Science Citation Index expanded* ($n = 414$) (see Appendix 1 and Figure 1). After removing duplicates and studies not dealing with patients we got 52 publications. Of these we excluded 23 not fulfilling our inclusion criteria (see Characteristics of excluded studies and Characteristics of ongoing studies).

Included trials

The remaining 29 publications described 15 randomised clinical trials. Information about each trial is in the table "Characteristics of included studies"

Four of the 15 trials were published as abstracts only (Buligescu 1990; Sáinz 1992; Trande 1996; Morgan 2002).

A total of 1714 patients were randomised in the 15 trials. The dosage was 1 mg colchicine five days a week in the majority of the trials. Some used the same dosage but for six (Angelico 2000) or seven (Trinchet 1989; Akriviadis 1990; Buligescu 1990; Wang 1994; Colman 1998) days a week. Only one trial (Morgan 2002) used colchicine 1.2 mg per day.

The treatment duration varied from one month (Akriviadis 1990) to 55 months (Kershenovich 1988) with a median of 18 months in the 15 trials.

The entry criteria in the randomised clinical trials varied, but the inclusion criteria made it highly likely that all patients did in fact

have fibrosis or cirrhosis of the liver. We could divide the trials into four groups according to etiology:

- (1) alcohol (Trinchet 1989; Akriviadis 1990; Sáinz 1992; Colman 1998; Cortez-Pinto 2002; Morgan 2002),
- (2) chronic hepatitis B (Wang 1994),
- (3) chronic hepatitis C (Trande 1996; Angelico 2000),
- (4) mixed aetiologies (Reinhardt 1986; Kershenovich 1988; Buligescu 1990; Gültepe 1994; Parise 1995; Lin 1996). The mixed etiology group included patients with alcoholic liver disease, HBV-related liver disease, and cryptogenic causes of fibrosis or cirrhosis of the liver. In some of these trials it had not been possible to test for hepatitis C virus.

Thirteen trials reported random allocation of patients to colchicine versus control (placebo or no intervention) and two trials reported random allocation of patients to colchicine plus interferon versus control (no intervention) plus interferon (Trande 1996; Angelico 2000). Of the 15 trials, ten used placebo and five no intervention in the control group (Buligescu 1990; Sáinz 1992; Lin 1996; Trande 1996; Angelico 2000).

Excluded studies

Twenty publications described 18 clinical excluded studies. The reasons for exclusion are given under 'Characteristics of excluded studies'.

Ongoing studies

Three ongoing trials were identified, listed under 'Characteristics of ongoing studies'. One of these (Collins 2000) has randomised 551 patients with alcoholic cirrhosis to colchicine versus placebo. The second trial (Bui 1999) also studies alcoholic patients. The third trial (Floreni 2001) evaluates patients with chronic hepatitis B.

Risk of bias in included studies

Three trials provided sample size estimation based on histological findings (Trinchet 1989) or on mortality (Wang 1994; Morgan 2002).

All trials were described as randomised, but only eight (53.3%) had adequate generation of allocation sequence (Kershenovich 1988; Gültepe 1994; Wang 1994; Parise 1995; Lin 1996; Angelico 2000; Cortez-Pinto 2002; Morgan 2002), and only even (46.7%) reported adequate allocation concealment (Kershenovich 1988; Trinchet 1989; Akriviadis 1990; Wang 1994; Parise 1995; Angelico 2000; Morgan 2002).

Nine trials (60%) were double blind (Reinhardt 1986; Kershenovich 1988; Trinchet 1989; Akriviadis 1990; Wang 1994; Parise 1995; Colman 1998; Cortez-Pinto 2002; Morgan 2002). One trial (Gültepe 1994) was single blind.

There was generally a fair description of follow-up and withdrawals/drop-outs in all trials but two (Buligescu 1990; Trande 1996). However, only four (26.7%) randomised trials (Kershenovich 1988; Akriviadis 1990; Colman 1998; Angelico 2000) stated that they used the intention-to-treat method to evaluate data.

Effects of interventions

In summary, we did not find any significant effect of colchicine on mortality, liver-related mortality, liver complications, liver biochemistry, and liver histology when tested against placebo or no intervention in patients with alcoholic, viral, and cryptogenic liver fibrosis or cirrhosis. However, colchicine led to significantly more adverse events, the majority of which were non-serious.

Mortality

Combining the results of all trials demonstrated no significant effect of colchicine on mortality (relative risks (RR) 1.00, 95% confidence interval (CI) 0.87 to 1.16). In the colchicine group 222/867 (25.6%) patients died versus 217/847 (25.6%) patients in the control group (Comparison 01-01).

Sensitivity analyses stratifying the trials according to duration of treatment, worst case scenario analysis, placebo or no intervention treatment, and methodological quality did not change this estimate significantly (Comparison 03-01; 03-02; 03-03; 03-04). The same observation was made for patients with alcoholic cirrhosis (Trinchet 1989; Akriviadis 1990; Sáinz 1992; Colman 1998; Cortez-Pinto 2002; Morgan 2002), patients with HBsAg positive liver fibrosis or cirrhosis (Wang 1994), patients with fibrotic HCV antibody positive liver disease (Trande 1996; Angelico 2000), and patients with fibrosis or cirrhosis of the liver of mixed aetiologies (Reinhardt 1986; Kershenovich 1988; Buligescu 1990; Gültepe 1994; Parise 1995; Lin 1996) (Comparison 01-01).

Combining the results of all the 15 trials plus the seven trials included in the Cochrane review by Gong and Gluud (Gong 2004) demonstrated no significant effect of colchicine on mortality (RR 1.02, 95% confidence interval (CI) 0.89 to 1.18). In the colchicine group 247/1067 (23.1%) patients died versus 237/1045 (22.7%) patients in the control group (see additional Figure 2).

Figure 2.

Review: Colchicine for alcoholic and non-alcoholic liver fibrosis and cirrhosis

Comparison: 03 Sensitivity analyses

Outcome: 04 Mortality - patients alcohol non-alcoholic liver fibrosis and cirrhosis and primary biliary cirrhosis

Liver-related mortality

Combining the results of 11 trials reporting liver-related mortality (Kershenovich 1988; Trinchet 1989; Sáinz 1992; Gültepe 1994; Wang 1994; Parise 1995; Lin 1996; Trande 1996; Angelico 2000; Cortez-Pinto 2002; Morgan 2002) demonstrated no significant effect of colchicine on liver-related mortality (RR 1.08, 95% CI 0.88 to 1.33). In the colchicine group 133/630 (21.1%) patients died versus 119/607 (19.6%) patients in the control group (Comparison 01-02).

Colchicine had no significant effects on liver-related mortality in patients with alcoholic cirrhosis, chronic hepatitis B, chronic hepatitis C, or with mixed aetiologies (Comparison 01-02).

Clinical symptoms and complications

Combining the results of seven trials (Trinchet 1989; Akriviadis 1990; Sáinz 1992; Gültepe 1994; Wang 1994; Parise 1995; Angelico 2000) demonstrated no significant effect of colchicine on ascites, variceal bleeding, hepatic encephalopathy, or hepato-renal syndrome and combined complications (RR 1.01, 95% CI 0.74 to 1.38). In the colchicine group 53/222 (23.9%) versus 51/219 (23.3%) patients in the control group developed one of these complications (Comparison 01-03; 01-04; 01-05; 01-06; 01-07).

Only one trial determined the changes in hepatic vein pressure gradient in 30 patients (Wang 1994). No significant effect of colchicine on portal pressure was observed.

Biochemical variables

Colchicine intervention showed a significant beneficial effect on some of the biochemical measures when analysed with the fixed effect model, but not with the random effects model:

- serum(s)-bilirubin (mg/dl) weighed mean difference (WMD) -0.11 (95% CI -0.20 to -0.02) (fixed-effect model);
- serum(s)-bilirubin (mg/dl) weighed mean difference (WMD) 0.051 (95% CI -0.48 to 0.58) (random-effects model);
- s-aspartate aminotransferase (AST) (U/l) WMD -8.93 (95% CI -18.29 to 0.43);
- s-alanine aminotransferase (ALT) (U/l) WMD -27.37 (95% CI -35.62 to -19.12) (fixed-effect model);
- s-alanine aminotransferase (ALT) (U/l) WMD -21.38 (95% CI -51.23 to 8.47) (random-effects model);
- s-alkaline phosphatases (ALP) (U/l) WMD 13.34 (95% CI 8.31 to 18.37) (fixed-effect model);
- s-alkaline phosphatases (ALP) (U/l) WMD 7.54 (95% CI -11.07 to 26.16) (random-effects model);
- s-gamma-glutamyl-transpeptidase (GGT) (U/l) WMD 14.96 (95% CI -52.68 to 82.60);
- serum-albumin (g/dl) WMD 0.13 (95% CI 0.07 to 0.20) (fixed-effect model);
- serum-albumin (g/dl) WMD 0.03 (95% CI -0.22 to 0.27) (random-effects model);
- prothrombin (%) WMD 0.21 (95% CI -7.04 to 7.46);
- prothrombin (seconds) WMD -0.12 (95% CI -0.33 to 0.09);

- white blood cell count (1.000 cells/ cubic mm) WMD 1.0 (95% CI -3.67 to 5.67).

Liver fibrosis markers

Liver fibrosis markers were studied in seven trials, but only four reported data (Reinhardt 1986; Trinchet 1989; Gültepe 1994; Wang 1994). There was no significant effect of colchicine on collagen peptidase and serum N-terminal peptide of type III procollagen (P-III-P). There was a significant decreasing effect of colchicine on 7S collagen and prolidase (Comparison 01-17; 01-18; 01-19; 01-20).

Sustained biochemical and virological response

Sustained biochemical response was defined as normal alanine transaminase values and sustained virological response was defined as absence of HCV-RNA six months after completion of one-year treatment. The combination of colchicine plus interferon-alfa had no significant effects compared to interferon monotherapy (Angelico 2000) (Comparison 01-25; 01-26).

Liver histology

There were no significant effects of colchicine on histological improvement of liver biopsy findings or histological stage of hepatitis or fibrosis (Comparison 01-21; 01-22; 01-23).

Alcohol consumption

Combining the results of eight randomised clinical trials (Kershenovich 1988; Trinchet 1989; Sáinz 1992; Gültepe 1994; Wang 1994; Parise 1995; Angelico 2000; Cortez-Pinto 2002) demonstrated

no significant effect of colchicine versus control on alcohol consumption (RR 1.03, 95% CI 0.77 to 1.39) (Comparison 01-24).

Quality of life and health economics

None of the randomised clinical trials examined quality of life or health economics.

Adverse events

Combining the results of 11 trials (Kershenovich 1988; Trinchet 1989; Akriviadis 1990; Buligescu 1990; Sáinz 1992; Gültepe 1994; Wang 1994; Parise 1995; Lin 1996; Angelico 2000; Cortez-Pinto 2002) demonstrated a significant effect of colchicine on serious adverse events (RR 8.38, 95% CI 1.08 to 65.22). In the colchicine group 8/443 (1.8%) patient had a serious adverse event (serious leukopenia) versus 0/420 (0%) patient in the control group (Comparison 02-01). Colchicine was also associated with a significantly higher incidence of non-serious adverse events (RR 4.35, 95% CI 2.16 to 8.77). In the colchicine group 39/443 (8.8%) patients had non-serious adverse events (mostly transient diarrhoea) versus 5/420 (1.2%) patients in the control group (Comparison 02-02). Colchicine was also associated with a significantly higher incidence of adverse events irrespective of severity (data not shown).

Publication bias

A regression analysis in which the standard minimal deviate, defined as the RR divided by its standard error, was regressed against the estimate's precision, defined as the inverse of the standard error, showed no significant funnel plot asymmetry (see additional Figure 3).

Figure 3.

DISCUSSION

We did not find any significant effect of colchicine on any clinically meaningful outcomes (mortality, liver-related mortality, liver complications, liver biochemistry, and liver histology) of patients with alcoholic, viral, and cryptogenic liver fibrosis or cirrhosis. Further, colchicine was associated with a significant increase of both severe and non-severe adverse events.

In the group of randomised trials including patients with mixed aetiologies the trial of [Kershenobich 1988](#) et al showed a tendency of colchicine to decrease mortality. However, there are a number of things that may contest this observation. First, sensitivity analysis comparing intervention efficacy of colchicine on mortality by contrasting trials of less than 18 months of treatment with those of at least 18 months, did not reveal any significant effect of treatment duration. Accordingly, treatment duration may not be the explanation of the favourable effect observed by [Kershenobich 1988](#) et al. Second, the data of [Kershenobich 1988](#) et al are also contrasted by the absence of any significant therapeutic efficacy of colchicine in the groups of randomised clinical trials including single aetiologies - alcohol, hepatitis B, and hepatitis C. These are the likely aetiologies of the patients entered into the [Kershenobich 1988](#) et al trial. Third, we were unable to detect any significant influence of colchicine on a number of clinical outcomes, liver histology, or liver biochemistry. Fourth, both the size and the methodological quality of the [Kershenobich 1988](#) et al trial opens for both random and systematic errors. Fifth, and most importantly, colchicine was without significant effect on mortality in the pooled analysis of all trials. Further supporting the lack of significant effect of colchicine on mortality are the findings in liver patients with primary biliary cirrhosis ([Gong 2004](#)). Colchicine for patients with primary biliary cirrhosis was associated with a RR = 1.2 (95% CI 0.71 to 2.06) when compared with placebo/no intervention ([Gong 2004](#)). Sixth, the positive effect of colchicine on the mortality of cirrhotic patients of mixed aetiologies observed by [Kershenobich 1988](#) et al may be due to an uneven distribution of the aetiologies in the colchicine and placebo groups. The different aetiologies were not evenly distributed between the colchicine and the placebo arm (alcoholic 44% versus 46%; posthepatic 46% versus 35%; other etiologies 9% versus 20%). On the other hand, the [Kershenobich 1988](#) et al trial was the trial treating patients for the longest duration, that is, for almost five years. Their positive findings are weakly supported by the observations of a trend toward reduced mortality in the worst-case scenario analyses and a significantly reduced mortality in the colchicine group of a quasi-randomised trial ([Adhami 1998](#)). This study was excluded from this systematic review due to the quasi-randomisation, which may introduce bias.

Colchicine had a significant positive effect on two out of four serum markers of fibrotic activity (7S collagen and prolydase), but was without a significant effect on collagen-peptidase. The fibrotic markers were evaluated in four randomised trials including few patients. The contrasting results do not provide any evidence for concluding that colchicine may have a beneficial effect on liver fibrosis or cirrhosis, especially considering that colchicine was without any significant effect on liver histology and portal pressure. Furthermore, due to the large number of statistical comparisons having been performed it is not surprising that some of the comparisons may have come out with a significant difference

simply due to 'mass significance' (that is, spurious significant findings due to repetitive testing).

The lack of a significant effect of colchicine on a number of outcome variables does not appear to be confounded by an uneven distribution of alcohol consumption as the proportion of patients continuing to misuse alcohol did not differ significantly between the colchicine and the control arms of the randomised trials reporting on alcohol consumption during follow-up.

We found that colchicine intervention is associated with a significant increase in non-serious adverse events and serious adverse events. We were not able to identify data on the effects of colchicine on quality of life and health economics.

It is impossible to demonstrate that any intervention is without an effect. From inspection of the confidence intervals found in this review, colchicine may still favourably affect mortality of patients with chronic hepatitis B, chronic hepatitis C, and liver fibrosis/cirrhosis of mixed etiologies with about 40% to 50%. In patients with alcoholic liver disease the likelihood of a positive effect seems more remote, but could in fact amount to a reduction of mortality. On the other hand, colchicine could also increase the mortality. As demonstrated in this review colchicine does increase the risk of serious and non-serious adverse events. Therefore, colchicine ought not to be used outside randomised clinical trials and if such trials are planned, they need to involve a close monitoring of benefits as well as harms. Due to the trend towards a negative effect of colchicine for alcoholic fibrosis/cirrhosis, new randomised clinical trials in this patient group should await the reporting of the three ongoing randomised clinical trials ([Bui 1999](#); [Collins 2000](#); [Floareani 2001](#)).

AUTHORS' CONCLUSIONS

Implications for practice

We did not find any significant effect of colchicine on any clinically meaningful outcomes (mortality, liver-related mortality, liver complications, liver biochemistry, and liver histology) of patients with alcoholic, viral, and cryptogenic liver fibrosis or cirrhosis. Further, colchicine was associated with a significant increase of both severe and non-severe adverse events. Accordingly, there is no evidence for using colchicine for liver fibrosis/cirrhosis at present.

Implications for research

The absence of evidence for an effect of colchicine on clinically relevant outcomes, however, does not mean that there is evidence of absence of effect. If researchers wish to conduct new randomised trials they ought to be large and the treatment period ought to be several years and the benefits as well as harms need to be closely monitored. Further, patients with alcoholic liver disease should not be included in such trials before the results of ongoing randomised trials have been analysed and published. All trials ought to be conducted and reported in accordance with the CONSORT statement (www.consort-statement.org). Colchicine should not be used as a control intervention in randomised trials before it has been established that it has beneficial effect and before detrimental effects can be excluded.

ACKNOWLEDGEMENTS

The chief acknowledgement is to the patients with fibrosis and cirrhosis of the liver who took part in the trials reviewed here and to the researchers who conducted the trials. Special thanks to Mario Angelico, Edison Roberto Parise, Jean-Claud Trinchet, and Mustafa

Gültepe for providing us with more information on the trials they were involved in. Thanks to Erica Villa, Manfred Reinhardt, and Timothy R Morgan for responding to our questions.

We are indebted to Nader Salas for the expert technical computer assistance and to Dimitrinka Nikolova and Sarah Klingenberg for expert assistance with the retrieval of publications, and to Bodil Als-Nielsen for expert comments on commenting the updated review.

REFERENCES

References to studies included in this review

Akriviadis 1990 {published data only}

Akriviadis EA, Steindel H, Pinto PC, Fong T-L, Kanel G, Reynolds TB, et al. Failure of colchicine to improve short term survival in patients with severe alcoholic hepatitis. *Hepatology* 1988;**8**(5):83.

* Akriviadis EA, Steindel H, Pinto PC, Fong TL, Kanel G, Reynolds TB, et al. Failure of colchicine to improve short-term survival in patients with alcoholic hepatitis. *Gastroenterology* 1990;**99**:811-8.

Angelico 2000 {published data only}

Angelico M, Barlattani A, Cepparulo M, Guarascio P, Sarrecchia C, Liuti A, et al. Colchicine worsens the efficacy of interferon-alpha in patients with chronic hepatitis. Interim report of a randomized pilot study. *Hepatology* 1998;**28**(4):478A.

* Angelico M, Cepparulo M, Barlattani A, Liuti A, Gentile S, Hurtova M, et al. Unfavourable effects of colchicine in combination with interferon-alfa in the treatment of chronic hepatitis C. *Alimentary Pharmacology & Therapeutics* 2000;**14**:1459-67.

Buligescu 1990 {published data only}

Buligescu L, Voiculescu M. Randomized controlled clinical trial of colchicine in the long term treatment of liver cirrhosis. *Journal of Hepatology* 1989;**9**(Suppl 1):S12.

* Buligescu L, Voiculescu M. Randomized controlled clinical trial of colchicine in the long term treatment of liver cirrhosis. *Journal of Hepatology* 1990;**11**(Suppl 2):S12.

Colman 1998 {published data only}

Colman JC, Cromie SL, Cox JM, Roberts SK, Dudley E, Dudley FJ. The natural history of alcoholic cirrhosis: effect of colchicine. *Hepatology* 1998;**28**(Suppl 4):510A.

Cortez-Pinto 2002 {published data only}

* Cortez-Pinto H, Alexandrino P, Camilo ME, Gouveia-Oliveira A, Santos PM, Alves MM, et al. Lack of effect of colchicine in alcoholic cirrhosis: final results of a double-blind randomized trial. *European Journal of Gastroenterology and Hepatology* 2002;**14**(4):377-81.

Cortez-Pinto H, Alexandrino P, Camilo ME, Gouveia-Oliveira A, Santos PM, Alves MM, et al. Lack of effect of colchicine in alcoholic cirrhosis: final results of a double-blind randomized trial [abstract 1053]. *Hepatology* 2000;**32**(4, Pt2):423 A.

Cortez-Pinto H, Alexandrino P, Santos PM, Alves MM, Camilo ME, Moura MC. Colchicine in alcoholic cirrhosis - preliminary results of a double-blind randomized trial. *Hepatology* 1992;**16**(2):739.

Cortez-Pinto H, Serejo F, Camilo ME, Alexandrino P, Santos PM, Alves MM, et al. Colchicine in alcoholic cirrhosis - preliminary results of a double-blind randomized trial. *Gut* 1994;**35**(Suppl 4):A20.

Gültepe 1994 {published and unpublished data}

* Gültepe M, Ozcan A, Altin M, Ozturk G, Demirci M. Evaluation of the response of hepatic fibrosis to colchicine treatment by estimating serum prolidase activity on procollagen III aminoterminal propeptide levels. *Turk J Med Sci* 1994;**20**(2):99-04.

Ozturk G, Altin M, Demirci M, Ozcan A, Gültepe M, Holagu S, et al. The value of antifibrotic therapy in posthepatic chronic liver disease. II United European Gastroenterology Week. Barcelona, 1993:A-336.

Kershenobich 1988 {published data only}

Kershenobich D, Garcia-Tsao G, Pérez-Tamayo R, Rojkind M. Treatment of liver cirrhosis with colchicine: a double blind randomized trial from 1973 to 1983. *Hepatology* 1984;**4**(5):219.

Kershenobich D, García-Tsao G, Saldana SA, Rojkind M. Relationship between blood lactic acid and serum proline in alcoholic liver cirrhosis. *Gastroenterology* 1981;**80**:1012-5.

Kershenobich D, Uribe M, Suarez GI, Rojkind M. Treatment of cirrhosis with colchicine: a randomized trial. *Gastroenterology* 1976;**70**:986.

Kershenobich D, Uribe M, Suarez GI, Tamayo RP, Rojkind M. Colchicine, serum albumin, and alkaline phosphatase. *Annals of Internal Medicine* 1978;**89**(1):144.

Kershenobich D, Uribe M, Suárez GI, Mata JM, Pérez-Tamayo R, Rojkind M. Treatment of cirrhosis with colchicine. A double-blind randomized trial. *Gastroenterology* 1979;**77**:532-36.

* Kershenobich D, Vargas F, Garcia-Tsao G, Tamayo RP, Gent M, Rojkind M. Colchicine in the treatment of cirrhosis of the liver. *New England Journal of Medicine* 1988;**318**(26):1709-13.

Lin 1996 {published data only}

* Lin D-Y, Sheen L-S, Chu C-M, Liaw Y-F. A prospective randomized trial of colchicine in prevention of liver cirrhosis in chronic hepatitis B patients. *Alimentary Pharmacology & Therapeutics* 1996;**10**:961-6.

Morgan 2002 {published data only}

* Morgan TR, Nemchausky B, Schiff E, Anand BS, Bloor J, Kidao J, et al. Colchicine does not prolong life in patients with advanced alcoholic cirrhosis: results of a prospective, pandomized, placebo-controlled multi-center VA trial (CSP 352). *Gastroenterology* 2002;**122**:A641.

Parise 1995 {published data only}

* Parise ER, Chehter L, Nogueira MD, Leite-Mor MMB, Neves JRL, Ciuffardi G, et al. Colchicine in alcoholic chronic hepatopathy. Double-blind, randomized study of its effects on seric levels of plasma proteins and clinical evolution of the patients [Colchicina na doença hepática crônica de etiologia alcoólica. Estudo duplo-cego, randomizado, de seus efeitos sobre os níveis séricos das proteínas plasmáticas e evolucao clinica dos pacientes]. *Revista da Associacao Medica Brasileira* 1995;**41**(3):207-12.

Reinhardt 1986 {published data only}

- * Reinhardt M, Jorke D, Jahn G, Krombholz B, Muller A, Machnik G, et al. Colchicine therapy of fibrosing liver diseases - report of a randomized double-blind study [Die Colchizintherapie fibrosierender Lebererkrankungen - Bericht über eine randomisierte Doppelblindstudie]. *Deutsche Zeitschrift für Verdauungs- und Stoffwechselkrankheiten* 1986;**46**(5):257-75.

Sáinz 1992 {published data only}

- * Sáinz S, Guarner C, Villanueva C, Ordonez J, Sancho FJ, Enríquez J. Colchicine treatment in alcoholic liver disease. A controlled and randomized study. *Journal of Hepatology* 1992;**16**(Suppl 1):64.

Trande 1996 {published data only}

- * Trande P, Esposito P, Marchi S, Grottola A, Buttafuoco P, Ciccorossi P, et al. Hepatitis C virus-positive (HCV) chronic active hepatitis (CAH): a randomized, controlled trial of IFN with or without colchicine. *Journal of Hepatology* 1996;**25**(Suppl 1):590A.

Trinchet 1989 {published data only}

- * Trinchet JC, Beaugrand M, Callard P, Hartmann DJ, Gotheil C, Nusgens BV, et al. Treatment of alcoholic hepatitis with colchicine. Results of a randomized double blind trial. *Gastroenterologie clinique et biologique* 1989;**13**:551-5.

Trinchet JC, Beaugrand M, Ferrier JP, Galet B, Callard P, Hartmann D, et al. Treatment of active alcoholic liver disease (AALD) by colchicine: results of a 6 months double blind trial. *Journal of Hepatology* 1985;**Suppl 1**:S142.

Wang 1994 {published data only}

- * Wang Y-J, Lee S-D, Hsieh M-C, Lin H-C, Lee F-Y, Tsay S-H, et al. A double-blind randomized controlled trial of colchicine in patients with hepatitis B virus-related postnecrotic cirrhosis. *Journal of Hepatology* 1994;**21**(5):872-7.

Wang Y-J, Lee S-D, Tsai Y-T, Lo K-J. A controlled trial of colchicine in patients with hepatitis B virus (HBV)-related postnecrotic cirrhosis. *Hepatology* 1992;**16**(2):68A.

References to studies excluded from this review
A-Kader 2000 {published data only}

- * A-Kader HH, El-Karakasy H, El-Ghadban H, Mohsen NA, Karjoo M, Abdel-Khalik MK. The effect of colchicine therapy on fibrogenesis in children with hepatic fibrosis. *Gastroenterology* 2000;**118**:A989.

Adhami 1998 {published data only}

- * Adhami JE, Basho J. Treatment with colchicine and survival of patients with ascitic cirrhosis: a double-blind randomized trial. *Panminerva Medica* 1998;**40**(1):75-81.

Adhami JE, Resuli B, Bodinaku K, Basho J. Survival of cirrhotic patients treated by colchicine [Survie de cirrhotiques traités par colchicine]. *Medecine & Chirurgie Digestives* 1991;**20**(4):211-3.

Afdhal 2002 {published data only}

- * Afdhal NH, Freilich B, Black M, Levine R, Brass C. Comparison of therapy with peg-intron 0.5 mcg/kg versus colchicine 0.6 bid in 250 patients with cirrhosis and HCV; interim data from copilot. *Hepatology* 2002;**36**:312A.

Albornoza-Plata 1991 {published data only}

- * Albornoza-Plata A. Treatment of cirrhosis of the liver with colchicine. Study of 14 years. *Gastroenterology* 1991;**100**(5):A2.

Bahgat 1985 {published data only}

- * Bahgat MH, Sabbour MS, Osman LM, Ghali AF, Gadallah MA. Comparative study of different types of treatments in chronic active hepatitis. *Chemioterapia* 1985;**4**(3):227-35.

Campollo 2001 {published data only}

- Campollo O, Cervantes G, Cerda-Camacho FD, Segura EJ, Sanchez H, Lopez R. Soybean lecithin versus colchicine for the treatment of alcoholic liver fibrosis and cirrhosis. Interim report. *Hepatology* 2001;**34**:698A.

Floreani 1998 {published data only}

- * Floreani A, Lobello S, Brunetto M, Aneloni V, Chiaramonte M. Colchicine in chronic hepatitis B: a pilot study. *Alimentary Pharmacology & Therapeutics* 1998;**12**(7):653-6.

Floreani A, Lobello S, Brunetto MR, Aneloni V, Ferraretto L, Chiaramonte M. Colchicine in the treatment of HBV-related chronic hepatitis: a pilot study. Italian Journal of Gastroenterology and Hepatology. Annual Meeting of the Italian Association for the Study of Liver (AISF) Roma, February 12-14, 1997, 1997; Vol. 29:91.

Frysak 1996 {published data only}

- Frysak Z, Hrcakova Y. Colchicine in the treatment of liver cirrhosis. 12 years' experience [Soucasné postavení kolchicinu v léčbě jaterní cirhozy. 12leté zkušenosti]. *Vnitřní Lekarství* 1996;**42**(1):17-9.

Goral 1992 {published data only}

- Goral V, Degertekin H, Aksoy N. Colchicine in the treatment of cirrhosis of the liver. *Doga - Turk J Med Sci* 1992;**16**(8):583-4.

Kocak 1996 {published data only}

- Kocak N, Yuce A, Gurakan F, Ozen H, Gogus S, Kale G, et al. Colchicine in the treatment of hepatic fibrosis in children. *The American Journal of Gastroenterology* 1996;**91**(1):179-80.

Li 2003 {published data only}

- Li W, Wang C, Zhang J. Effects of da ding feng zhu decoction in 30 cases of liver fibrosis. *Journal of Traditional Chinese Medicine* 2003;**23**:251-4. [MEDLINE: 14719288]

Mancinella 1995 {published data only}

- Mancinella A. The use of colchicine in the treatment of alcoholic liver fibrosis in the elderly. Report of 80 cases. *La Clinica Terapeutica* 1995;**146**(3):191-201.

Mingxing 1983 {published data only}

Mingxing Z, Fangcen, L, Baolong C. A preliminary report on the treatment of refractory hepatitis with colchicine. *Chinese Journal of Infectious Diseases* 1983;**1**(Suppl 1):5-8.

Nak 1997 {published data only}

Nak SG, Gulten M, Gurel S, Dolar E, Karaaslan Y, Memik F. The effect of colchicine treatment on liver cirrhosis. *Gut* 1997;**41**:A230.

Nicolaescu 1986 {published data only}

Nicolaescu T, Bittman E, Bordeianu A, Gheorghe N, Stoiculescu P, Udrescu E, et al. Colchicine in the treatment of hepatic cirrhosis [Colchicina in tratamentul cirozelor hepatice]. *Revista de Medicina Interna, Neurologie, Psihiatrie, Neurochirurgie, Dermato-venerologie. Medicina Interna* 1986;**38**(1):61-9.

Simon 1991 {published data only}

Simon K, Gladysz A, Zalewska M, Machaj A. Evaluation of clinical effectiveness of colchicine in the treatment of chronic active hepatitis with transformation to liver cirrhosis. *Przegląd Epidemiologiczny* 1991;**45**(4):331-4.

Stancikova 1987 {published data only}

Stancikova M, Frysak Z, Trnavsky K. Effect of colchicine on the activity of cathepsine B and D in human liver cirrhosis. *Acta Medica Hungarica* 1987;**44**:181-8.

Tanriöger 1992 {published data only}

Tanriöger N, Kocak N, Özsoylu S, Gögüs S, Kale G, Caglar M, et al. Colchicine treatment in childhood cirrhosis and liver fibrosis [Cocukluk çağı siroz ve karaciger fibrozisinde kolsisin tedavisi: yirmi hastanın klinik, laboratuvar ve histopatolojik Bulgulan]. *Cocuk Sagligi ve Hastaliklan Dergisi* 1992;**35**:93-9.

References to ongoing studies
Bui 1999 {published data only}

* Bui H, Mendenhall C, Patton D, Hakim S, Morgan T. Reversal of fibrotic lesions of alcoholic liver disease. *Modern Pathology* 1999;**12**:161A.

Collins 2000 {published data only (unpublished sought but not used)}

* Collins JF, et al. Colchicine in the treatment of alcoholic cirrhosis of the liver. The metaRegister of Controlled Trials (mRCT) <http://www.controlled-trials.com/mrct/> accessed 20 May 2002.

Floreani 2001 {published data only}

Floreani A, Colloredo G, Lobello S, Di Marco M, Popovic A, Naccarato R. Preliminary results of a two-center trial with colchicine for the treatment of chronic hepatitis B. *The American Journal of Gastroenterology* 2001;**96**:3451-2. [PMID: 11774977]

Additional references
Adhami 1998

Adhami JE, Basho J. Treatment with colchicine and survival of patients with ascitic cirrhosis: a double-blind randomized trial. *Panminerva Medica* 1998;**40**(1):75-81.

Akriviadis 1990a

Akriviadis EA, Steindel H, Pinto PC, Fong T-L, Kanel G, Reynolds TB. Failure of colchicine to improve short-term survival in patients with alcoholic hepatitis. *Gastroenterology* 1990;**99**(3):811-18. [MEDLINE: 90337160]

Alderson 2004

Alderson P, Green S, Higgins JPT, editors. Cochrane Reviewers' Handbook 4.2.2 In: The Cochrane Library, Issue 1, 2004. [updated March 2004]. Chichester, UK: John Wiley & Sons, Ltd., 2004.

Ben-Chetrit 1998

Ben-Chetrit E, Levy M. Colchicine: 1998 update. *Seminars in Arthritis and Rheumatism* 1998;**28**(1):48-59.

Chang 1994

Chang TT, Lin CY, Chow NH, Hsu PI, Yang CC, Lin XZ, et al. Hepatitis B and hepatitis C virus infection among chronic alcoholic patients with liver disease in Taiwan. *Journal of Formosan Medical Association* 1994;**93**(2):128-33.

Chevilotte 1983

Chevilotte G, Durbec JP, Gerolami A, Berthezene P, Bidart JM, Camatte R. Interaction between hepatitis B virus and alcohol consumption in liver cirrhosis. An epidemiological study. *Gastroenterology* 1983;**85**(1):141-5.

Colman 1998

Colman JC, Cromie SL, Cox JM, Roberts SK, Dudley E, Dudley FJ. The natural history of alcoholic cirrhosis: effect of colchicine. *Hepatology* 1998;**28**(Suppl 4):510A.

Corrao 1998a

Corrao G, Zambon A, Torchio P, Arico S, La Vecchia C, Di Iorio F. Attributable risk for symptomatic liver cirrhosis in Italy. Collaborative Groups for the Study of Liver Diseases in Italy. *Journal of Hepatology* 1998;**28**(4):608-14.

Corrao 1998b

Corrao G, Arico S. Independent and combined action of hepatitis C virus infection and alcohol consumption on the risk of symptomatic liver cirrhosis. *Hepatology* 1998;**27**(4):914-9.

Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple graphical test. *British Medical Journal* 1997;**315**:629-34.

Ehrlich 1972

Ehrlich HP, Bornstein P. Microtubules in transcellular movement of procollagen. *Nature New Biology* 1972;**238**:257-60.

Gluud 1993

Gluud C, Afroudakis A, Caballeria J, Laskus T, Morgan MY, Rueff B, et al. Diagnosis and treatment of alcoholic liver disease in Europe. *Gastroenterology International* 1993;**6**(4):221-30.

Gong 2004

Gong Y, Gluud C. Colchicine for primary biliary cirrhosis. *The Cochrane Library* 2004, Issue 2.

Harris 1971

Harris ED, Krane SM. Effects of colchicine on collagenase in cultures of rheumatoid synovium. *Arthritis and Rheumatism* 1971;**14**:669-84.

Hill 1993

Hill DB, Marsano LS, McClain CJ. Increased plasma interleukin-8 concentrations in alcoholic hepatitis. *Hepatology* 1993;**18**(3):576-80.

ICH-GCP 1997

International Conference on Harmonisation. Code of Federal Regulations & ICH Guidelines. Philadelphia, US: Barnett International/PAREXEL, 1997.

Imperial 1999

Imperial JC. Natural history of chronic hepatitis B and C. *Journal of Gastroenterology and Hepatology* 1999;**14** Suppl:S1-5.

Kershenobich 1988

Kershenobich D, Vargas F, Garcia-Tsao G, Tamayo RP, Gent M, Rojkind M. Colchicine in the treatment of cirrhosis of the liver. *New England Journal of Medicine* 1988;**318**(26):1709-13.

Kjaergard 2001

Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. *Annals of Internal Medicine* 2001;**135**:982-9.

Marbet 1987

Marbet UA, Bianchi L, Meury U, Stalder GA. Long-term histological evaluation of the natural history and prognostic factors of alcoholic liver disease. *Journal of Hepatology* 1987;**4**(3):364-72.

Mendenhall 1984

Mendenhall CL, Anderson S, Garcia-Pont P, Goldenberg S, Kiernan T, Seeff LB, et al. Short-term and long-term survival in patients with alcoholic hepatitis treated with oxandrolone and prednisolone. *New England Journal of Medicine* 1984;**311**(23):1464-70.

Moher 1998

Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses. *The Lancet* 1998;**352**:609-13.

Morgan 1999

Morgan MY. Alcoholic liver disease: natural history, diagnosis, prognosis, and prevention. In: Bircher J, Benhamou J-P,

McIntyre N, Rizzetto M, Rodés J editor(s). Oxford Textbook of Clinical Hepatology. Second Edition. Vol. 2, Oxford: Oxford Medical Publications, 1999:1185-238.

Powell 1968

Powell WJ Jr, Klatskin G. Duration of survival in patients with Laennec's cirrhosis. Influence of alcohol withdrawal, and possible effects of recent changes in general management of the disease. *American Journal of Medicine* 1968;**44**(3):406-20.

Poynard 1997

Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIR, METAVIR, CLINIVIR, and DOSVIR groups. *Lancet* 1997;**349**(9055):825-32.

Rojkind 1975

Rojkind M, Kershenobich D. Effect of colchicine on collagen, albumin and transferrin synthesis by cirrhotic rat liver slices. *Biochimica et Biophysica Acta* 1975;**378**:415-23.

Rubin 1968

Rubin E, Lieber CS. Alcohol-induced hepatic injury in non alcoholic volunteers. *New England Journal of Medicine* 1968;**278**(16):869-76.

Schiff 1997

Schiff ER. Hepatitis C and alcohol. *Hepatology* 1997;**26**(3 (Suppl 1)):39S-42S.

Sheron 1993

Sheron N, Bird G, Koskinas J, Portmann B, Ceska M, Lindley, et al. Circulating and tissue levels of the neutrophil chemotaxin interleukin-8 are elevated in severe acute alcoholic hepatitis, and tissue levels correlate with neutrophil infiltration. *Hepatology* 1993;**18**(1):41-6.

Shi 1998

Shi Q, Chen K, Morris-Natschke SL, Lee KH. Recent progress in the development of tubulin inhibitors as antimitotic antitumor agents. *Current Pharmaceutical Design* 1998;**4**(3):219-48.

Sørensen 1984

Sørensen TIA, Orholm M, Bentsen KD, Høybye G, Eghøj K, Christoffersen P. Prospective evaluation of alcohol abuse and alcoholic liver injury in men as predictors of development of cirrhosis. *The Lancet* 1984;**2**(8397):241-4.

Trinchet 1989a

Trinchet JC, Beaugrand M, Callard P, Hartmann DJ, Gotheil C, Nussgens BV, et al. Treatment of alcoholic hepatitis with colchicine. Results of a double blind randomized trial. *Gastroenterologie clinique et biologique* 1989;**13**:551-5.

Vickers 1998

Vickers A, Goyal N, Harland R, Rees R. Do certain countries produce only positive results? A systematic review of controlled trials. *Controlled Clinical Trials* 1998;**19**(2):159-66.

Warnes 1991

Warnes TW. Colchicine in primary biliary cirrhosis. *Alimentary pharmacology & therapeutics* 1991;**5**:321-79.

Wiley 1998

Wiley TE, McCarthy M, Breidi L, McCarthy M, Layden TJ. Impact of alcohol on the histological and clinical progression of hepatitis C infection. *Hepatology* 1998;**28**(3):805-09.

References to other published versions of this review

Rambaldi 2001a

Rambaldi A, Gluud C. Colchicine for alcoholic and non-alcoholic liver fibrosis and cirrhosis (Cochrane Review). *The Cochrane Library* 2001, Issue 3.

Rambaldi 2001b

Rambaldi A, Gluud C. Colchicine for alcoholic and non-alcoholic liver fibrosis or cirrhosis. *Liver* 2001;**21**(2):129-36. [MEDLINE: PMID: 11318982]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Akriviadis 1990

Methods	<p>Sample size: no justification.</p> <p>Generation of the allocation sequence: no information.</p> <p>Allocation concealment: adequate, performed using sealed envelopes.</p> <p>Blinding: adequate, double blind with identical placebo.</p> <p>Intention-to-treat: yes.</p> <p>Follow up: adequate, described, but more than 10% dropped out or were withdrawn.</p>
Participants	<p>Seventy-four patients (49 males and 23 females, being 41.3 ± 8.8 years in the colchicine group and 40.8 ± 9.4 years in control group) with acute alcoholic hepatitis. Each patient had a history of heavy ethanol abuse and an admission diagnosis of acute alcoholic hepatitis.</p> <p>Inclusion criteria: palpable hepatomegaly, serum bilirubin > 5 mg/dl, and one or more of the following: hepatic tenderness, fever above 100° F, and leukocytosis above 12,000/ mm³. Enrolment into the trial was no later than the tenth hospital day.</p> <p>Exclusion criteria: patients with improving liver tests or advanced cirrhosis (life treating infection, massive gastrointestinal haemorrhage, renal insufficiency or HBsAg positivity).</p>
Interventions	<p>Colchicine group: colchicine 1 mg every day.</p> <p>Control group: placebo.</p> <p>Duration of treatment: 30 days.</p> <p>Follow up: maximal four months.</p>
Outcomes	<p>Mortality.</p> <p>Complications.</p> <p>Liver biochemistry.</p> <p>Adverse events.</p>
Notes	<p>Letter to the trialist sent in February 2000.</p> <p>M. Angelico answered in February 2000.</p>

Akriviadis 1990 (Continued)

In contrast with the working hypothesis the 18-month interim analysis of biochemical and virological findings reported herein showed that the combination of colchicine and interferon-alfa was associated with unexpected deleterious effects compared to interferon-alfa monotherapy. This prompted us to interrupt the study at this stage.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Angelico 2000

Methods	<p>Sample size: no justification.</p> <p>Generation of allocation sequence: adequate, was computer made.</p> <p>Allocation concealment: adequate, performed using sealed envelopes.</p> <p>Blinding: not performed.</p> <p>Intention-to-treat: yes.</p> <p>Follow up: adequate, described but more than 10% dropped out or were withdrawn.</p> <p>Interim analysis: after 18 months.</p>
Participants	<p>Sixty-five patients (38 males and 27 females; mean age 48± 11 years).</p> <p>Inclusion criteria: biopsy proven HCV-RNA positive chronic hepatitis C with Ishak stage 1-5 and persistent ALT elevation > 1.5 times upper normal limit. Inclusion criteria was also age between 18 and 65 years.</p> <p>Liver biopsies were taken within six months before the treatment. More than 60% of the patients in both groups were infected with HCV genotype 1b.</p> <p>Exclusion criteria: HBV or HIV coinfection, alcohol or drug abuse, platelets count < 70 billion/l, leukocyte count < 3.000 cells/cubic mm, Ishak stage for fibrosis = 6, cirrhosis or other concomitant diseases.</p>
Interventions	<p>Colchicine group: colchicine, 1 mg of colchicine six days a week for one year plus interferon as above.</p> <p>Control group: no intervention and interferon (6 million international units (MIU) three times each week (t.i.w.) for four months), then followed in responders, by interferon 3 MIU t.i.w. for a further eight months.</p> <p>The primary end-point of the study was to assess the effects of either treatments on fibrosis progression after three years. This report presents the results of an interim analysis of clinical, biochemical and virological findings after 18 months of treatment (after the enrolment of 50% of patients, 29 patients per group).</p>
Outcomes	<p>Mortality.</p> <p>Liver related mortality.</p> <p>Complications.</p> <p>Biochemistry.</p> <p>Liver histology.</p> <p>Alcohol use.</p> <p>Adverse events.</p>
Notes	Letter to the trialist sent in February 2000.

Angelico 2000 (Continued)

M. Angelico answered in February 2000.

In contrast with the working hypothesis the 18-month interim analysis of biochemical and virological findings reported herein showed that the combination of colchicine and interferon-alfa was associated with unexpected deleterious effects compared to interferon-alfa monotherapy. This prompted us to interrupt the study at this stage.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Buligescu 1990

Methods	<p>Sample size: no justification.</p> <p>Generation of allocation sequence: unclear, no information.</p> <p>Allocation concealment: unclear, no information.</p> <p>Blinding: not performed.</p> <p>Intention to-treat analysis: not mentioned.</p> <p>Follow up: inadequate, not described.</p>
Participants	<p>Inclusion criteria: 200 patients with liver cirrhosis. Etiology not reported.</p> <p>Diagnostic assessment not stated. One hundred patients with liver cirrhosis were randomised to receive colchicine, another 100 patients to receive placebo.</p>
Interventions	<p>Colchicine group: colchicine 1 mg every day.</p> <p>Control group: no intervention.</p> <p>Mean duration of treatment and of follow up: 17.4 months (range 6-36).</p>
Outcomes	<p>Mortality.</p> <p>Alcohol use.</p> <p>Adverse events.</p>
Notes	<p>Letter to the trialist sent in February 2000.</p> <p>In the abstract from 1989, only 80 patients were reported to have entered into the control group, but in the abstract from 1990, 100 patients were reported to be in the control group. The outcomes were the same.</p> <p>Only published as abstract.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Colman 1998

Methods	<p>Sample size: no justification.</p> <p>Generation of allocation sequence: unclear, no information.</p> <p>Allocation concealment: unclear, no information.</p> <p>Blinding: adequate, double blind.</p> <p>Intention-to-treat: yes.</p> <p>Follow up: adequate, described but more than 10% dropped-out or were withdrawn.</p>
Participants	<p>Inclusion criteria: 129 patients with alcoholic liver cirrhosis. Ninety-nine patients were Pough grade A, 26 grade B, and 4 grade C.</p> <p>Diagnostic assessment not stated.</p>
Interventions	<p>Colchicine group: colchicine 1 mg every day.</p> <p>Control group: placebo.</p> <p>Mean duration of treatment and of follow up: 45.3 months (range 1-106).</p>
Outcomes	<p>Mortality.</p> <p>Liver biochemistry.</p> <p>Alcohol use.</p> <p>Adverse events.</p>
Notes	<p>Letter to the trialist sent in February 2000.</p> <p>Only published as abstract.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Cortez-Pinto 2002

Methods	<p>Sample size: a sample size of 86 patients was calculated to be required to show an improvement in survival, with a mean follow up of five years and a minimum follow up of three years. However, difficulties in enrolling such patients, and an interim analysis of the results led us to stop the study with a smaller sample.</p> <p>Generation of allocation sequence: adequate, computer generated.</p> <p>Allocation concealment: unclear, no information.</p> <p>Blinding: adequate, double blind with a placebo identical in appearance.</p> <p>Intention-to-treat: yes.</p> <p>Follow up: adequate, described but more than 10% dropped out or were withdrawn.</p>
---------	--

Cortez-Pinto 2002 (Continued)

Participants	<p>Inclusion criteria: consecutive ambulatory patients (49 males and 6 females; age 18 to 65 years) with biopsy proven alcoholic liver cirrhosis.</p> <p>Exclusion criteria: bilirubin > 10 mg/dl, Child-Pugh C, gastrointestinal bleeding 15 days prior the trial, refractory ascites, renal or cardiac failure, cancer, the presence of others liver disease.</p>
Interventions	<p>Colchicine group: colchicine 1 mg 5 days a week.</p> <p>Control group: placebo.</p> <p>Mean duration of treatment and of follow up in colchicine group: 19.5 ± 9 months.</p> <p>Mean duration of treatment and of follow up in control group: 16.1 ± 1 months.</p>
Outcomes	<p>Mortality. Liver related mortality. Complications. Biochemistry. Liver histology. Fibrosis markers. Alcohol use. Adverse events.</p>
Notes	Letter to the trialist sent in February 2000.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Gültepe 1994

Methods	<p>Sample size: no justification.</p> <p>Generation of allocation sequence: adequate, by random number tables.</p> <p>Allocation concealment: unclear, not described.</p> <p>Blinding: not performed, single blind (0). The study started as double blind but progressed as single blind.</p> <p>Intention-to-treat: not mentioned.</p> <p>Follow up: adequate, described, but more than 10% dropped out or were withdrawn.</p>
Participants	<p>Inclusion criteria: 43 cirrhotic patients (28 males and 15 females); mean age of 52 years (range 22-72) in colchicine group and 55 years (range 22-67) in control group. Aetiologies were (colchicine versus control) posthepatitic (17 versus 15 patients), alcoholic (1 versus 5 patients), and other (5 versus 0 patients).</p> <p>Exclusion criteria: among patients with liver cirrhosis those individuals with bilirubin > 10 mg/dl, albumin < 1.5 g/dl. Patients with severe concomitant disease, distant location, and age < 18 years.</p>
Interventions	<p>Colchicine group: colchicine 1 mg, 5 days week.</p>

Gültepe 1994 (Continued)

Control group:
placebo.

Mean duration of treatment and of follow up: 16 months (range 3-32) in the colchicine group and 14 months (range 5-28) in the control group.

Outcomes	Mortality. Liver related mortality. Biochemistry. Fibrosis markers. Liver histology. Alcohol use. Adverse events.
Notes	Letter to the trialist sent in February 2000. M Gültepe answered in August 2000. In the answer it is revealed that originally 55 patients were included with six withdrawals very early from the colchicine and the control group, respectively.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Kershenobich 1988

Methods	Sample size: no justification. Generation of allocation sequence: adequate, with random numbers. Allocation concealment: adequate, using coded supplies. Blinding: adequate, double blind, with identical and indistinguishable placebo. Intention-to-treat: yes. Follow up: adequate, described but more than 10% dropped-out or were withdrawn.
Participants	Inclusion criteria: 100 cirrhotic patients (49 males and 51 females; mean age of 50 years $\pm$ 1.6). Exclusion criteria: severe cirrhosis (recent hepatic encephalopathy, gastrointestinal bleeding (within 15 days), bilirubin > 10 mg/dl, serum albumin > 1.5 g/dl), severe concomitant disease, geographic reasons and age < 18 years.
Interventions	Colchicine group: colchicine 1 mg, 5 days week. Control group: placebo. Mean duration of treatment and of follow up: 4.7 years.
Outcomes	Mortality. Liver related mortality. Liver histology. Alcohol use.

Kershenobich 1988 (Continued)

Adverse events.

Notes	Letter to the trialist sent in February 2000.
-------	---

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Lin 1996

Methods	<p>Sample size: no justification.</p> <p>Generation of allocation sequence: adequate with random table.</p> <p>Allocation concealment: unclear, no information.</p> <p>Blinding: not performed.</p> <p>Intention-to-treat: not mentioned.</p> <p>Follow up: adequate, described but more than 10% dropped-out or were withdrawn.</p>
Participants	<p>Sixty-six patients (58 males and 8 females; mean age of 39.9 ± 9.1 years in the colchicine group and 39.7 ± 13.3 years in the control group) with chronic hepatitis B (HBsAg positive and elevated transaminases for at least six months). There were three patients in colchicine and two in the control group with HCV antibodies positivity.</p> <p>Exclusion criteria: liver cirrhosis, age < 25 years, renal insufficiency, idiosyncrasy to colchicine, pregnancy, cardiopulmonary decompensation, and patients who refused.</p>
Interventions	<p>Colchicine group: colchicine 1 mg, 5 days week.</p> <p>Control group: no intervention.</p> <p>Follow up max four years. Mean duration of treatment and of follow up 26.6 ± 14.4 in colchicine and 23.2 ± 14.1 months in control group.</p>
Outcomes	<p>Mortality.</p> <p>Liver related mortality.</p> <p>Biochemistry.</p> <p>Liver histology.</p> <p>Adverse events.</p>

Notes	Letter to the trialist sent in February 2000.
-------	---

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Morgan 2002

Methods	<p>Sample size: enrolment goal of 650 patients; power of 0.9 to detect 6 month prolongation in survival.</p> <p>Generation of allocation sequence: adequate, computer generated.</p> <p>Allocation concealment: adequate.</p> <p>Blinding: adequate, double blind with a placebo identical in appearance.</p> <p>Intention-to-treat: yes.</p> <p>Follow up:adequate.</p>
Participants	<p>It is 13 VA Medical Centers including patients with advanced alcoholic liver cirrhosis (Child B and Child C) from august 1994 to august 2000. At enrolment, groups did not differ in age, gender, Child's score, or routine laboratory tests. During treatment groups did not differ in medicine consumption or alcohol intake.</p> <p>Inclusion criteria: clinical diagnosis of alcoholic liver disease. Child-Pugh score of 7 or more (B or C). Liver biopsy demonstrating cirrhosis (if possible).</p> <p>Exclusion criteria: hepatitis B, hepatitis C, HIV positivity, or recent gastrointestinal bleeding.</p>
Interventions	<p>Colchicine group: colchicine 0.6 mg, bid.</p> <p>Control group: placebo.</p> <p>Additional treatment: all patients received one multivitamin pill daily.</p> <p>Duration of treatment: at least 24 months, maximum 72 months.</p>
Outcomes	<p>Mortality.</p> <p>Liver related mortality.</p> <p>Complications.</p> <p>Biochemistry.</p> <p>Liver histology.</p> <p>Fibrosis markers.</p> <p>Alcohol use.</p> <p>Adverse events.</p>
Notes	<p>Letter to the trialist sent in September 2004</p> <p>TR Morgan answered in September 2004.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Parise 1995

Methods	<p>Sample size: no justification.</p> <p>Generation of allocation sequence: adequate with random table.</p>
---------	---

Parise 1995 (Continued)

Allocation concealment: adequate, with sealed envelopes.

Blinding: adequate, double blind, with identical placebo.

Intention-to-treat: not mentioned.

Follow up: adequate, less than 10% dropped-out or were withdrawn.

Participants	<p>Inclusion criteria: 41 patients (36 males and 5 females; being 49.2 ± 9.9 months in the colchicine group and 47.8 ± 9.8 months in the control group) with biopsy proven or ultrasound, endoscopic and biochemical diagnosis of chronic alcoholic liver disease. There were four in the colchicine and three in the control group patients with HCV antibodies positivity.</p> <p>Exclusion criteria: hepatic encephalopathy stage 3-4, recent gastrointestinal bleeding (within 30 days), treatment resistant ascites, hepatorenal syndrome, concomitant other disease, all the state that can influence the protein synthesis, HBsAg positive patients.</p>
Interventions	<p>Colchicine group: colchicine 1 mg, five days week.</p> <p>Control group: placebo.</p> <p>Duration of the treatment and of follow up: 12 months.</p>
Outcomes	<p>Mortality. Liver related mortality. Complications. Biochemistry. Alcohol use. Adverse events.</p>
Notes	<p>Letter to the trialist sent in February 2000.</p> <p>ER Parise answered in May 2000.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Reinhardt 1986

Methods	<p>Sample size: no justification.</p> <p>Generation of allocation sequence: unclear, no information.</p> <p>Allocation concealment: unclear, no information.</p> <p>Blinding: adequate, double blind with identical placebo.</p> <p>Intention-to-treat: not mentioned.</p> <p>Follow up: adequate, described but more than 10% dropped out or were withdrawn.</p>
Participants	<p>Inclusion criteria: 74 patients with chronic liver disease of whom 38 had alcoholic liver disease. Three diagnoses groups had been formed with regard to the histological grades of fibrosis: chronic hepatitis, moderate liver cirrhosis, severe liver cirrhosis.</p>

Reinhardt 1986 (Continued)

Exclusion criteria: decompensated liver cirrhosis (gastrointestinal bleeding and hepatic encephalopathy in the last two weeks, bilirubin > 2mg/ dl), not compliant patient, concomitant non-hepatic disease.

Interventions	<p>Colchicine group: colchicine 1 mg, five days week.</p> <p>Control group: placebo.</p> <p>Duration of the treatment: 12 months in 53 patients.</p> <p>Duration of follow up: 12 months in 53 patients, 24 months in 43 patients, 36 months in 24 patients.</p>
Outcomes	<p>Mortality.</p> <p>Biochemistry.</p> <p>Fibrosis markers.</p> <p>Liver histology.</p>
Notes	<p>Letter to the trialist sent in February 2000.</p> <p>M Reinhardt answered in August 2000.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Sáinz 1992

Methods	<p>Sample size: no justification.</p> <p>Generation of allocation sequence: unclear, no information.</p> <p>Allocation concealment: unclear, no information.</p> <p>Blinding: not performed.</p> <p>Intention-to-treat: not mentioned.</p> <p>Follow up: adequate, described but more than 10% dropped-out or were withdrawn.</p>
Participants	<p>Inclusion criteria: 54 patients with alcoholic liver disease (liver cirrhosis and non-cirrhosis).</p> <p>Diagnostic assessment not stated.</p>
Interventions	<p>Colchicine group: colchicine 1 mg, five days week.</p> <p>Control group: no intervention.</p> <p>Mean duration of treatment and of follow up: 22.7 ± 18 months.</p>
Outcomes	<p>Mortality.</p> <p>Liver related mortality.</p> <p>Complications.</p> <p>Biochemistry.</p> <p>Fibrosis markers.</p> <p>Alcohol use.</p>

Sáinz 1992 (Continued)

Adverse events.

Notes Letter to the trialist sent in February 2000.
Only published as abstract.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Trande 1996

Methods Sample size: no justification.
Generation of allocation sequence: unclear, no information.
Allocation concealment: unclear, no information.
Blinding: not performed.
Intention-to-treat: not mentioned.
Follow up: inadequate, not described.

Participants Inclusion criteria: 85 patients with chronic active hepatitis C.
Diagnostic assessment not-stated.

Interventions Colchicine group:
colchicine, 1 mg of colchicine five days a week for one year plus interferon in the same dosage as above.
Control group:
no intervention and interferon (6 MIU x 3 months), then interferon (3 MIU x 3 months).
Mean duration of treatment and of follow up: 24 months.

Outcomes Mortality.
Liver related mortality.
Fibrosis markers.

Notes Letter to the trialist sent in February 2000.
E Villa answered in February 2000.
Only published as abstract.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Trinchet 1989

Methods	<p>Sample size: with a difference in alcoholic hepatitis scores (of two in the placebo group and of four in the colchicine group), 18 histological samples in each group were required using a one-side test with $\alpha = 5$ per cent and $\beta = 10$ per cent.</p> <p>Randomisation: adequate, stratified for presence or absence of cirrhosis in initial liver biopsy.</p> <p>Generation of allocation sequence: unclear, no information.</p> <p>Allocation concealment: adequate, sealed envelopes.</p> <p>Blinding: adequate, double blind with placebo of identical presentation.</p> <p>Intention-to-treat: not mentioned.</p> <p>Follow up: adequate, described but more than 10% dropped-out or were withdrawn.</p>
Participants	<p>Sixty-seven patients with histologically proven alcoholic hepatitis or alcoholic cirrhosis (38 males and 29 females with a mean age of 52 ± 8.5 years) were included.</p> <p>Exclusion criteria: hepatic encephalopathy, ascites, prothrombin activity $< 50\%$, platelet count < 100 billion/l, hepatocellular carcinoma, or refusal to participate.</p>
Interventions	<p>Colchicine group: colchicine 1 mg every day.</p> <p>Control group: placebo.</p> <p>Mean duration of treatment and of follow up: six months; patients were analysed at three and six months.</p>
Outcomes	<p>Mortality. Liver related mortality. Complications. Biochemistry. Fibrosis markers. Liver histology. Alcohol use. Adverse events.</p>
Notes	<p>Letter to the trialist sent in February 2000.</p> <p>J-C Trinchet answered in March 2000.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Wang 1994

Methods	<p>Sample size: yes, with 81% power and $\alpha = 5\%$ and minimal relevant difference in death rate of 40%, 50 patients in each arm of the trial were needed.</p> <p>Generation of allocation sequence: adequate, computer generated.</p> <p>Allocation concealment: adequate, using coded supplies.</p> <p>Blinding: adequate, double blind with identical placebo.</p>
---------	--

Wang 1994 (Continued)

Intention-to-treat: not mentioned.

Follow up: adequate, described but more than 10% dropped out or were withdrawn.

Participants	<p>One-hundred patients with HBsAg positive cirrhosis. Ninety-four males and six females with a mean age of 60 years in colchicine group (range 32-79) and 59 years (range 36-80) in the control group were included.</p> <p>Exclusion criteria: end-stage liver cirrhosis (serum albumin level below 2.5 g/dl or total bilirubin > 10 mg/dl, variceal bleeding and hepatic encephalopathy two weeks before recruitment into the trial, concomitant non-hepatic disease and patients who were unable to attend the clinic regularly).</p>
Interventions	<p>Colchicine group: colchicine 1 mg every day.</p> <p>Control group: placebo.</p> <p>Follow up: Maximal 51 months (range 15-51), median duration of treatment and of follow up 26 months.</p>
Outcomes	<p>Mortality. Liver related mortality. Complications. Biochemistry. Fibrosis markers. Liver histology. Alcohol use. Adverse events.</p>
Notes	Letter to the trialist sent in February 2000.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
A-Kader 2000	The study is observational (case series). Thirty-nine children with hepatic fibrosis of different aetiologies were given colchicine orally 25 ug/kg/day for six months.
Adhami 1998	The study is quasi-randomised according to age. Those with an even number of years got colchicine plus diuretics, and those with an uneven number of years got placebo plus diuretics. In order to assess the role of colchicine on survival of cirrhotic patients with mixed aetiologies, 52 patients were studied during a period of 11 years with colchicine 1 mg five times a week.
Afdhal 2002	The trial randomises two-hundred-fifty patients with advanced fibrosis and HCV positivity to colchicine (122 patients) or PEG-Intron (128 patients).
Albornoz-Plata 1991	The study is observational (case series). One hundred and twenty-four patients with liver cirrhosis were evaluated and compared with patients treated before. The majority of patients remained stable.

Study	Reason for exclusion
Bahgat 1985	The study is not randomised. Ninety-six patients with histologically-proven chronic active hepatitis were studied to evaluate different treatments. Patients were divided into the following groups: control, colchicine, corticosteroid, azathioprine, corticosteroid plus azathioprine, chlorambucil, 5-fluorouracil, isoprinosine. Results showed that patients put on any therapeutic regimen did either the same or worse than the control group.
Campollo 2001	The double blind trial randomises thirty patients with alcoholic liver fibrosis and cirrhosis to soy-bean lecithin or colchicine for 24 months.
Floreani 1998	The study is observational (case series). Nine biopsy-proven chronic hepatitis B patients entered the study. All of them had a major contraindication to interferon therapy or refused antiviral therapy. None of the patients experienced adverse events during the treatment.
Frysak 1996	The study is observational (case series). The authors evaluate more than 12 years of their own experience with the administration of colchicine to patients with cirrhosis of the liver. Colchicine did not produce apparent undesirable effect.
Goral 1992	The study is not randomised. All cases were non-alcoholic cirrhosis and serological markers of hepatitis B virus were positive. There were 27 patients in the colchicine group and 15 patients in the control group. There was no difference between therapy and control groups in the clinical, laboratory and histological findings. Diarrhea was seen in one case as an adverse event.
Kocak 1996	The study is observational (case series). Colchicine was given to 45 children with liver cirrhosis or fibrosis. Control liver biopsies revealed a minimal decrease in fibrous tissue in four patients, but in seven patients the histological findings had worsened.
Li 2003	The trial randomises fifty-six patients with liver fibrosis due to chronic hepatitis B into two groups: 30 patients to Da Ding Feng Zhu Decoction and 26 patients to colchicine.
Mancinella 1995	The study is observational (case series). Eighty geriatric patients with alcoholic liver fibrosis were treated with colchicine. The authors didn't observe any adverse event, but a lowering of white and platelet count in 2% of cases.
Mingxing 1983	The study is observational (case series). This study reports the results of colchicine to 31 cases of refractory viral hepatitis (11 being acute or subacute liver necrosis, eight acute heavy icteric hepatitis and 12 chronic active hepatitis). Twenty patients recovered, three improved and five did not improve. Three patients died of hepatic coma. Thrombocytopenia and hemorrhagic tendency were found in only one case on the fourth day of colchicine therapy, but turned into normal in a few days after discontinuation of colchicine.
Nak 1997	The study is observational (case series). One hundred-twenty-two patients with liver cirrhosis were studied prospectively. Sixty-one were given colchicine while 61 served as control group.
Nicolaescu 1986	The study is not randomised. A group of 70 patients with compensated inactive cirrhosis were followed for one to four years. Forty-one patients received colchicine (1 mg/day), and the other 29 served as control.
Simon 1991	The study is observational (case series). Twelve patients with viral chronic hepatitis were treated with colchicine one mg daily. After 20 months only two patients presented clinical and histological improvement of liver function. In the remaining group of patients deterioration of liver function and progression of the disease was observed.
Stancikova 1987	The study is observational (case series). The activities of cathepsin B and D in human liver biopsy specimens from cirrhotic alcoholic patients before and after one year of colchicine treatment were studied. The ratio of cathepsin B and D activity to hepatic hydroxyproline content was significantly reduced in cirrhotic livers. Colchicine treatment was followed by an increase in the levels of en-

Study	Reason for exclusion
	zymes investigated as well as by a significant rise in the ratio of cathepsin B and D activity to hepatic hydroxyproline content.
Tanriöğür 1992	The study is observational (case series). In this investigation the clinical, biochemical and histological effects of colchicine in childhood cirrhosis and fibrosis were studied. A total of 20 patients were treated with colchicine, and 18 patients were reported to be in the control group.

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

[Bui 1999](#)

Trial name or title	Reversal of fibrotic lesions of alcoholic liver disease.
Methods	
Participants	The abstract describes a preliminary report on seven patients.
Interventions	Control group: no intervention. Colchicine group: colchicine 1 mg every day.
Outcomes	Mortality. Liver related mortality. Complications. Biochemistry. Fibrosis markers. Liver histology. Alcohol use. Adverse events.
Starting date	It is a large five-year Veteran Administration Cooperative study, which started in 1997.
Contact information	Dr. Bui et al Department of Veteran Affairs and Department of Medicine University of Cincinnati Medical Center OH 45220 USA
Notes	Letter sent in February 2000.

[Collins 2000](#)

Trial name or title	Colchicine in the treatment of alcoholic cirrhosis of the liver.
Methods	
Participants	Alcoholic cirrhosis Pugh class B and C.
Interventions	Control group: placebo. Colchicine group:

Collins 2000 *(Continued)*

	colchicine.
Outcomes	Mortality. Liver related mortality. Liver biochemistry. Liver function. Liver histology. Nutritional assessments. Quality of life.
Starting date	April 1994. Randomisation closed November 2000.
Contact information	Joseph F Collins P.O. BOX 1010 Perry point, Maryland 21902 Phone (410) 642-2411, Ext. 5288
Notes	Letter sent in February 2000. Data analysis had to be ready before autumn 2001.

Floreani 2001

Trial name or title	Preliminary results of a two-center trial with colchicine for the treatment of chronic hepatitis B.
Methods	
Participants	The letter published in The American Journal of Gastroenterology describes a trial of 13 patients with chronic hepatitis B who had major contraindications to interferon therapy or refused the treatment.
Interventions	Control group: no intervention. Colchicine group: colchicine.
Outcomes	Mortality. Liver related mortality. Complications. Biochemistry. Fibrosis markers. Liver histology. Adverse events.
Starting date	It is a two-center trial with a follow-up of at least 12 months after the end of treatment period.
Contact information	Annarosa Floreani, M.D., Divisione di Gastroenterologia, Via Giustiniani, 2, 35128 Padova, Italy
Notes	

DATA AND ANALYSES

Comparison 1. Colchicine versus placebo or no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	15	1714	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.87, 1.16]
1.1 Alcoholic liver disease	6	928	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.92, 1.27]
1.2 Chronic hepatitis B	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.1 [0.51, 2.36]
1.3 Chronic hepatitis C	2	150	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Mixed aetiologies	6	536	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.50, 1.03]
2 Liver-related mortality	11	1237	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.88, 1.33]
2.1 Alcoholic liver disease	4	725	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.87, 1.42]
2.2 Chronic hepatitis B	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.1 [0.51, 2.36]
2.3 Chronic hepatitis C	2	150	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Mixed aetiologies	4	262	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.62, 1.52]
3 Ascites	2	132	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.15, 6.89]
3.1 Alcoholic liver disease	1	67	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.15, 6.89]
3.2 Chronic hepatitis C	1	65	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Variceal bleeding	6	388	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.51, 1.61]
4.1 Alcoholic liver disease	2	139	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.43, 6.46]
4.2 Chronic hepatitis B	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.26, 3.78]
4.3 Chronic hepatitis C	1	65	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.4 Mixed aetiologies	2	84	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.33, 1.44]
5 Hepatic encephalopathy	4	304	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.53, 1.87]
5.1 Alcoholic liver disease	2	139	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.60, 3.78]
5.2 Chronic hepatitis B	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.7 [0.29, 1.69]
5.3 Chronic hepatitis C	1	65	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Hepato-renal syndrome	3	204	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.27, 3.69]
6.1 Alcoholic liver disease	2	139	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.27, 3.69]
6.2 Chronic hepatitis C	1	65	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Total number of complications (variceal bleeding, hepatic encephalopathy,	7	442	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.74, 1.38]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
ascites, hepatorenal-syn-drome)				
7.1 Alcoholic liver disease	3	193	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.86, 1.92]
7.2 Chronic hepatitis B	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.40, 1.56]
7.3 Chronic hepatitis C	1	65	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.4 Mixed aetiologies	2	84	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.33, 1.44]
8 Bilirubin (mg/dl)	4	207	Mean Difference (IV, Random, 95% CI)	0.05 [-0.48, 0.58]
8.1 Alcoholic liver disease	2	104	Mean Difference (IV, Random, 95% CI)	2.83 [-0.97, 6.63]
8.2 Chronic hepatitis B	1	60	Mean Difference (IV, Random, 95% CI)	0.10 [-0.02, 0.22]
8.3 Mixed aetiologies	1	43	Mean Difference (IV, Random, 95% CI)	-0.40 [-0.54, -0.26]
9 AST (U/l)	4	207	Mean Difference (IV, Fixed, 95% CI)	-8.93 [-18.29, 0.43]
9.1 Alcoholic liver disease	2	104	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-24.46, 22.66]
9.2 Chronic hepatitis B	1	60	Mean Difference (IV, Fixed, 95% CI)	-7.90 [-20.63, 4.83]
9.3 Mixed aetiologies	1	43	Mean Difference (IV, Fixed, 95% CI)	-15.0 [-32.06, 2.06]
10 ALT (U/l)	3	168	Mean Difference (IV, Random, 95% CI)	-21.35 [-51.27, 8.57]
10.1 Chronic hepatitis B	1	60	Mean Difference (IV, Random, 95% CI)	-48.10 [-63.14, -33.06]
10.2 Chronic hepatitis C	1	65	Mean Difference (IV, Random, 95% CI)	15.0 [-5.93, 35.93]
10.3 Mixed aetiologies	1	43	Mean Difference (IV, Random, 95% CI)	-28.0 [-39.18, -16.82]
11 ALP (U/l)	2	103	Mean Difference (IV, Random, 95% CI)	7.54 [-11.07, 26.16]
11.1 Chronic hepatitis B	1	60	Mean Difference (IV, Random, 95% CI)	16.10 [10.66, 21.54]
11.2 Mixed aetiologies	1	43	Mean Difference (IV, Random, 95% CI)	-3.0 [-16.24, 10.24]
12 GGT (U/l)	2	67	Mean Difference (IV, Fixed, 95% CI)	14.96 [-52.68, 82.60]
12.1 Alcohol liver disease	1	32	Mean Difference (IV, Fixed, 95% CI)	1.0 [-386.62, 388.62]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.2 Mixed aetiologies	1	35	Mean Difference (IV, Fixed, 95% CI)	15.40 [-53.30, 84.10]
13 Serum albumin (g/dl)	4	176	Mean Difference (IV, Random, 95% CI)	0.03 [-0.22, 0.27]
13.1 Alcoholic liver disease	1	32	Mean Difference (IV, Random, 95% CI)	-0.40 [-0.85, 0.05]
13.2 Chronic hepatitis B	1	60	Mean Difference (IV, Random, 95% CI)	0.15 [0.08, 0.22]
13.3 Mixed aetiologies	2	84	Mean Difference (IV, Random, 95% CI)	0.09 [-0.33, 0.50]
14 Prothrombin (%)	3	145	Mean Difference (IV, Fixed, 95% CI)	0.21 [-7.04, 7.46]
14.1 Prothrombin (%) alcoholic liver disease	2	104	Mean Difference (IV, Fixed, 95% CI)	-2.55 [-11.13, 6.03]
14.2 Prothrombin (%) mixed etiologies	1	41	Mean Difference (IV, Fixed, 95% CI)	7.10 [-6.46, 20.66]
15 Prothrombin (seconds)	2	103	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.33, 0.09]
15.1 Chronic hepatitis B	1	60	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.32, 0.12]
15.2 Mixed aetiologies	1	43	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-2.41, 0.41]
16 White blood count (1.000 cells/ cubic mm)	1	72	Mean Difference (IV, Fixed, 95% CI)	1.0 [-3.67, 5.67]
16.1 Alcoholic liver disease	1	72	Mean Difference (IV, Fixed, 95% CI)	1.0 [-3.67, 5.67]
17 Collagen-peptidase	1	24	Mean Difference (IV, Fixed, 95% CI)	-14.21 [-61.60, 33.18]
17.1 Mixed aetiologies	1	24	Mean Difference (IV, Fixed, 95% CI)	-14.21 [-61.60, 33.18]
18 7S collagen (ng/ml)	1	60	Mean Difference (IV, Fixed, 95% CI)	-1.20 [-1.69, -0.71]
18.1 Chronic hepatitis B	1	60	Mean Difference (IV, Fixed, 95% CI)	-1.20 [-1.69, -0.71]
19 Prolidase (U/l)	1	43	Mean Difference (IV, Fixed, 95% CI)	-446.0 [-836.76, -55.24]
19.1 Mixed aetiologies	1	43	Mean Difference (IV, Fixed, 95% CI)	-446.0 [-836.76, -55.24]
20 PIIP (ng/ml)	3	135	Mean Difference (IV, Fixed, 95% CI)	0.10 [0.05, 0.15]
20.1 Alcoholic liver disease	1	32	Mean Difference (IV, Fixed, 95% CI)	8.0 [-16.03, 32.03]
20.2 Chronic hepatitis B	1	60	Mean Difference (IV, Fixed, 95% CI)	0.10 [0.05, 0.15]
20.3 Mixed aetiologies	1	43	Mean Difference (IV, Fixed, 95% CI)	-2.20 [-5.29, 0.89]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21 Liver biopsy improvement	4	168	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.56, 2.19]
21.1 Alcoholic liver disease	1	54	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.04, 3.49]
21.2 Chronic hepatitis B	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
21.3 Mixed aetiologies	2	84	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.64, 2.72]
22 Liver biopsy findings (hepatitis)	1	26	Mean Difference (IV, Fixed, 95% CI)	0.20 [-1.03, 1.43]
22.1 Score of alcoholic hepatitis	1	26	Mean Difference (IV, Fixed, 95% CI)	0.20 [-1.03, 1.43]
23 Liver biopsy findings (fibrosis)	1	26	Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.34, 0.94]
23.1 Score of alcoholic fibrosis	1	26	Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.34, 0.94]
24 Alcohol consumption	8	441	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.77, 1.38]
24.1 Alcoholic liver disease	3	129	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.71, 1.36]
24.2 Chronic hepatitis B	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
24.3 Chronic hepatitis C	1	65	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
24.4 Mixed aetiologies	3	147	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.62, 2.25]
25 Sustained biochemical response	1	65	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.06, 1.04]
25.1 Chronic hepatitis C	1	65	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.06, 1.04]
26 Sustained virological response	1	65	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.02, 1.20]
26.1 Chronic hepatitis C	1	65	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.02, 1.20]

Analysis 1.1. Comparison 1 Colchicine versus placebo or no intervention, Outcome 1 Mortality.

Analysis 1.2. Comparison 1 Colchicine versus placebo or no intervention, Outcome 2 Liver-related mortality.

Analysis 1.3. Comparison 1 Colchicine versus placebo or no intervention, Outcome 3 Ascites.

Analysis 1.4. Comparison 1 Colchicine versus placebo or no intervention, Outcome 4 Variceal bleeding.

Analysis 1.5. Comparison 1 Colchicine versus placebo or no intervention, Outcome 5 Hepatic encephalopathy.

Analysis 1.6. Comparison 1 Colchicine versus placebo or no intervention, Outcome 6 Hepato-renal syndrome.

Analysis 1.7. Comparison 1 Colchicine versus placebo or no intervention, Outcome 7 Total number of complications (variceal bleeding, hepatic encephalopathy, ascites, hepatorenal-syndrome).

Analysis 1.8. Comparison 1 Colchicine versus placebo or no intervention, Outcome 8 Bilirubin (mg/dl).

Analysis 1.9. Comparison 1 Colchicine versus placebo or no intervention, Outcome 9 AST (U/l).

Analysis 1.10. Comparison 1 Colchicine versus placebo or no intervention, Outcome 10 ALT (U/l).

Analysis 1.11. Comparison 1 Colchicine versus placebo or no intervention, Outcome 11 ALP (U/l).

Analysis 1.12. Comparison 1 Colchicine versus placebo or no intervention, Outcome 12 GGT (U/l).

Analysis 1.13. Comparison 1 Colchicine versus placebo or no intervention, Outcome 13 Serum albumin (g/dl).

Analysis 1.14. Comparison 1 Colchicine versus placebo or no intervention, Outcome 14 Prothrombin (%).

Analysis 1.15. Comparison 1 Colchicine versus placebo or no intervention, Outcome 15 Prothrombin (seconds).

Analysis 1.16. Comparison 1 Colchicine versus placebo or no intervention, Outcome 16 White blood count (1.000 cells/ cubic mm).

Analysis 1.17. Comparison 1 Colchicine versus placebo or no intervention, Outcome 17 Collagen-peptidase.

Analysis 1.18. Comparison 1 Colchicine versus placebo or no intervention, Outcome 18 7S collagen (ng/ml).

Analysis 1.19. Comparison 1 Colchicine versus placebo or no intervention, Outcome 19 Prolidase (U/l).

Analysis 1.20. Comparison 1 Colchicine versus placebo or no intervention, Outcome 20 PIIP (ng/ml).

Analysis 1.21. Comparison 1 Colchicine versus placebo or no intervention, Outcome 21 Liver biopsy improvement.

Study or subgroup	Colchicine n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: $Z=0.31(P=0.76)$					
Test for subgroup differences: Not applicable					
<div> <div>Favours colchicine</div> <div>0.0010.11101000</div> <div>Favours control</div> </div>					

Analysis 1.22. Comparison 1 Colchicine versus placebo or no intervention, Outcome 22 Liver biopsy findings (hepatitis).

Study or subgroup	Colchicine		Control		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
1.22.1 Score of alcoholic hepatitis							
Trinchet 1989	11	5.8 (1.3)	15	5.6 (1.9)		100%	0.2[-1.03,1.43]
Subtotal ***	11		15			100%	0.2[-1.03,1.43]
Heterogeneity: $\tau^2=0$; $\chi^2=0$, $df=0(P<0.0001)$; $I^2=100\%$							
Test for overall effect: $Z=0.32(P=0.75)$							
Total ***	11		15			100%	0.2[-1.03,1.43]
Heterogeneity: $\tau^2=0$; $\chi^2=0$, $df=0(P<0.0001)$; $I^2=100\%$							
Test for overall effect: $Z=0.32(P=0.75)$							
<div> <div>Favours colchicine</div> <div>-10-50510</div> <div>Favours control</div> </div>							

Analysis 1.23. Comparison 1 Colchicine versus placebo or no intervention, Outcome 23 Liver biopsy findings (fibrosis).

Study or subgroup	Colchicine		Control		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
1.23.1 Score of alcoholic fibrosis							
Trinchet 1989	11	3.6 (0.9)	15	3.3 (0.7)		100%	0.3[-0.34,0.94]
Subtotal ***	11		15			100%	0.3[-0.34,0.94]
Heterogeneity: Not applicable							
Test for overall effect: $Z=0.92(P=0.36)$							
Total ***	11		15			100%	0.3[-0.34,0.94]
Heterogeneity: Not applicable							
Test for overall effect: $Z=0.92(P=0.36)$							
<div> <div>Favours colchicine</div> <div>-10-50510</div> <div>Favours control</div> </div>							

Analysis 1.24. Comparison 1 Colchicine versus placebo or no intervention, Outcome 24 Alcohol consumption.

Study or subgroup	Colchicine n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.24.1 Alcoholic liver disease					
Cortez-Pinto 2002	9/20	13/23		26.14%	0.8[0.44,1.45]
Sáinz 1992	16/28	15/26		33.63%	0.99[0.63,1.57]
Trinchet 1989	9/16	7/16		15.13%	1.29[0.64,2.6]
<div> <div>Favours colchicine</div> <div>0.10.20.512510</div> <div>Favours control</div> </div>

Analysis 1.25. Comparison 1 Colchicine versus placebo or no intervention, Outcome 25 Sustained biochemical response.

Analysis 1.26. Comparison 1 Colchicine versus placebo or no intervention, Outcome 26 Sustained virological response.

Comparison 2. Adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serious adverse events	11	863	Risk Ratio (M-H, Fixed, 95% CI)	8.38 [1.08, 65.22]
1.1 Alcoholic liver disease	4	248	Risk Ratio (M-H, Fixed, 95% CI)	8.38 [1.08, 65.22]
1.2 Chronic hepatitis B	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Chronic hepatitis C	1	65	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Mixed aetiologies	5	450	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Non-serious adverse events	11	863	Risk Ratio (M-H, Fixed, 95% CI)	4.35 [2.16, 8.77]
2.1 Alcoholic liver disease	4	248	Risk Ratio (M-H, Fixed, 95% CI)	3.64 [1.24, 10.71]
2.2 Chronic hepatitis B	1	100	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.25, 101.58]
2.3 Chronic hepatitis C	1	65	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.01, 4.39]
2.4 Mixed aetiologies	5	450	Risk Ratio (M-H, Fixed, 95% CI)	9.03 [2.51, 32.42]

Analysis 2.1. Comparison 2 Adverse events, Outcome 1 Serious adverse events.

Analysis 2.2. Comparison 2 Adverse events, Outcome 2 Non-serious adverse events.

Comparison 3. Sensitivity analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality and duration of treatment	15	1714	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.87, 1.16]
1.1 Duration of treatment less than 18 months	7	596	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.57, 1.56]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Duration of treatment of at least 18 months	8	1118	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.87, 1.17]
2 Mortality - worst case scenario	15	1714	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.83, 1.07]
2.1 Worst case scenario	15	1714	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.83, 1.07]
3 Colchicine versus placebo or no intervention	15	1714	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.87, 1.16]
3.1 Colchicine versus placebo	10	1244	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.88, 1.17]
3.2 Colchicine versus no intervention	5	470	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.33, 1.88]
4 Mortality and methodological quality	15	1714	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.87, 1.16]
4.1 Trials with high methodological quality	8	1051	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.86, 1.16]
4.2 Trials with low methodological quality	7	663	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.69, 1.57]

Analysis 3.1. Comparison 3 Sensitivity analyses, Outcome 1 Mortality and duration of treatment.

Analysis 3.2. Comparison 3 Sensitivity analyses, Outcome 2 Mortality - worst case scenario.

Analysis 3.3. Comparison 3 Sensitivity analyses, Outcome 3 Colchicine versus placebo or no intervention.

Analysis 3.4. Comparison 3 Sensitivity analyses, Outcome 4 Mortality and methodological quality.

APPENDICES

Appendix 1. Search Strategies

Database	Search performed	Search strategy
The CHBG Controlled Trials Register (on ProCite) and The Cochrane Central Register of Controlled Trials (CENTRAL) on The Cochrane Library	October 2004; CLib Issue 3 2004	We searched both registers with the text word 'colchicine' (288 records).
Web of Science	September 2004	colchicine and cirrhosis (253 records) colchicine and fibrosis (161 records)
MEDLINE	September 2004	No. Records Request 1 10688 explode "Colchicine"/ all subheadings 2 13039 colchicine 3 13871 #1 or #2 4 44361 explode "Liver-Cirrhosis"/ all subheadings 5 88579 explode "Hepatitis"/ all subheadings 6 8634 explode "Fibrosis"/ all subheadings 7 130706 #4 or #5 or #6 8 571780 liver

(Continued)

9 2729627 disease*
10 260782 hepati*
11 280786 fibro*
12 58151 cirrho*
13 587946 liver disease* or hepati* or fibro* or cirrho*
14 130342 #7 and #13
15 256 #3 and #14
16 341961 random*
17 97647 placebo*
18 147741 blind*
19 13178 meta-analysis
* 20 50 #15 and (random* or placebo* or blind* or meta-analysis)

EMBASE	September 2004	No. Records Request
		1 11178 explode "Colchicine"/ all subheadings
		2 13306 colchicine
		3 31840 explode "Liver-Cirrhosis"/ all subheadings
		4 58580 explode "Hepatitis"/ all subheadings
		5 34501 explode "Fibrosis"/ all subheadings
		6 114324 #3 or #4 or #5
		7 13306 #2 or #1
		8 406018 liver
		9 1713688 disease*
		10 189597 hepati*
		11 216200 fibro*
		12 39584 cirrho*
		13 428144 liver disease* or hepati* or fibro* or cirrho*
		14 279071 random*
		15 114277 placebo*
		16 125932 blind*
		17 21452 meta-analysis
		18 399955 random* or placebo* or blind* or meta-analysis
		19 702 #6 and #7
		20 691 #19 and #13
		* 21 100 #20 and #18

WHAT'S NEW

Date	Event	Description
17 October 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

AR drafted and revised the protocol, coordinated the identification of studies, selected trials for inclusion, performed data extraction, and drafted the review. CG performed trial selection and data extraction and checked and revised all the processes. Both are guarantors for the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- The Copenhagen Trial Unit, Denmark.

External sources

- The 1991 Pharmacy Foundation, Denmark.
- The Copenhagen Hospital Corporation's Research Grant on Getting Research into Practice (GRIP), Denmark.
- The Danish Medical Research Council's Grant on Getting Research into Practice (GRIP), Denmark.

NOTES

We have contacted the following companies in order to obtain additional data, published or unpublished: Aventis, Celafar (Italy), Novopharm (Canada), Quimica Y farmacia (México), Merck (USA), IE Ulagay (Turkey), Abbott Laboratories (U.S.A.).

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Inflammatory Agents [*therapeutic use]; Colchicine [*therapeutic use]; Liver Cirrhosis [*drug therapy] [mortality]; Liver Cirrhosis, Alcoholic [drug therapy] [mortality]; Randomized Controlled Trials as Topic

MeSH check words

Humans