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Systematic review: pentoxifylline for the treatment of severe alcoholic hepatitis

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SUMMARY

Background
Acute alcoholic hepatitis (AH) is a severe manifestation of alcoholic liver disease with a grave prognosis. Pentoxifylline, an oral antitumour necrosis factor agent, has been reported to reduce mortality and incidence of hepatorenal syndrome (HRS) in severe alcoholic hepatitis (SAH).

Aim
To summarise evidence for the use of pentoxifylline in SAH.

Methods
A literature search was undertaken using MeSH terms 'hepatitis, alcoholic' and 'pentoxifylline' using the set operator AND. We included randomised controlled trials examining pentoxifylline in SAH, published as abstracts or full manuscripts. Risk ratios (RRs) were calculated for pooled data using random effects modelling. Risk of bias was assessed using Cochrane group criteria and quality of trials assessed using 'Consolidated Standards of Reporting Trials' CONSORT guidelines.

Results
Ten trials including 884 participants were included, from six papers and four abstracts. There was significant heterogeneity between trials regarding control groups and trial end-points. Treatment was given for 28 days in all trials except one. Pooling of data showed a reduced incidence of fatal HRS with pentoxifylline compared with placebo (RR: 0.47, 0.26–0.86, $P = 0.01$), but no survival benefit at 1 month (RR: 0.58, 0.31–1.07, $P = 0.06$). There were no significant differences between treatment groups in trials of pentoxifylline vs. corticosteroid, or vs. combination therapy.

Conclusions
Pentoxifylline appears superior to placebo in prevention of fatal HRS and thus may be effective treatment of SAH when corticosteroids are contraindicated. However, multiple trials have failed to show conclusive superiority of either pentoxifylline or corticosteroids.

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INTRODUCTION

Alcoholic liver disease (ALD) comprises a spectrum from steatosis to cirrhosis and hepatocellular carcinoma.[1] Alcoholic hepatitis (AH) is an acute manifestation of ALD characterised by a clinical syndrome of jaundice, malaise and often liver failure.[2] Prevalence is difficult to estimate as clear data are lacking: incidence rose over the last decade in Denmark from 37 to 46 cases/1 000 000 and 24–34 cases/1 000 000 in men and women respectively.[3] Severe alcoholic hepatitis (SAH) – usually defined using Maddrey's discriminant function (DF)[4] – has a 28-day mortality of up to 35%[5] without treatment.

Multiple agents have been trialled for the treatment of SAH,[6] but few agents have shown any promise. After several trials, meta-analysis of patient level data demonstrated a short-term survival benefit with corticosteroids in SAH,[5] which are now recommended for use by specialist societies.[1, 7] However, side effects of corticosteroids and the high risk of fatal gastrointestinal (GI) bleeding and sepsis in patients with SAH[8–10] preclude their use in some patients.

Serum levels of tumour necrosis factor-α (TNF-α) are raised in ALD, and AH in particular.[11, 12] Although inhibition of TNF-α with monoclonal antibody infliximab[13] or soluble TNF receptor etanercept[14] increased mortality, pentoxifylline, an oral anti-TNF agent via inhibition of phosphodiesterase,[15] was suggested to be useful in preventing hepatorenal syndrome (HRS) in SAH in 1991 by McHutchison *et al.*[16] Several trials have subsequently investigated the use of pentoxifylline in SAH with varying results. The American Association for the Study of Liver Disease (AASLD) guidelines recommend the use of pentoxifylline for SAH, especially if there are contraindications to corticosteroids.[1] The European Association for the Study of the Liver (EASL) guidelines recommend pentoxifylline be used if sepsis precludes the use of corticosteroids.[7]

A meta-analysis of pentoxifylline for SAH by the Cochrane group in 2009 analysed trial data from a total of 336 patients.[17] This showed a statistically significant reduction in mortality with pentoxifylline in SAH. This conclusion was not supported by trial sequential analysis, which prevented firm conclusions being drawn. There are also minor but important problems with the meta-analysis: an abstract interpreted as comparing pentoxifylline to placebo was revealed in the full paper to be a trial of pentoxifylline and prednisolone vs. prednisolone alone. In addition, meta-analysed trials reported mortality at different time points (mean time to death, 28-day mortality and 2-month mortality), but these were all regarded as a single, comparable outcome. There can be methodological problems with meta-analysis of small data sets,[18] which may limit validity. Since this meta-analysis was published, five studies (including 548 participants) have reported on the use of pentoxifylline in SAH.

This systematic review examines the use of pentoxifylline for treatment of SAH, through evaluation of prospective randomised controlled trials and with regard to 28-day and 6-month mortality, and incidence of HRS.

METHODS

A review protocol was established regarding search strategy and data extraction. This protocol is not available publicly. Trials published as full papers or abstracts since 1947 were searched for using PubMed/Medline and EmBase. Clinical trial registries (http://www.clinicaltrialsregister.eu, http://www.clinicaltrials.gov and http://www.who.int/ictrp/search/en) were searched with the same protocol to identify suitable trials and investigators contacted if a trial appeared relevant. The literature search was performed using the MeSH terms 'hepatitis, alcoholic' and 'pentoxifylline' using the set operator AND. No limits were applied. Search results were examined with regard to title and abstract and suitable trials identified. References of relevant studies were searched for other suitable trials. Studies were included if they were prospective randomised controlled trials with at least 28 days of follow-up, examining the use of pentoxifylline in SAH. This systematic review is reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses PRISMA guidelines.[19]

Data synthesis and analysis

Data were extracted from reports by four authors independently (RP, MJA, CC and IAR) using a preprepared spreadsheet and inconsistencies between authors agreed by consensus. The following data were extracted from each trial: year of trial, location, definition of SAH, characteristics of participants, dose of pentoxifylline, nature of control/placebo, number of subjects, number of subjects treated with pentoxifylline/placebo, mortality at 28 days and/or 6 months, number of patients with incident HRS. Effect estimates for outcomes were analysed with Fisher's exact test (SPSS v21; IBM, Armonk, New York, NY, USA). Where possible, data for outcomes were pooled and a RR calculated using a random effects model [Review Manager v5 (The Nordic Cochrane Centre, The Cochrane Collaboration 2012, Copenhagen,

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Denmark), available from the Cochrane Collaboration website http://www.cochrane.org]. Risk of bias was assessed using Cochrane Review guidelines.[20] Quality of included trials was assessed using 'Consolidated Standards of Reporting Trials' (CONSORT) guidelines for reporting of randomised controlled trials[21] and reporting of randomised trials as abstracts.[22]

RESULTS

The literature search identified 302 trial reports through database searching and four additional records after searching through references and clinical trial registries. After removing duplicate records, 21 trials were screened and 12 assessed for eligibility. Two trials were excluded – one was a retrospective trial[23] and another was a trial of pentoxifylline as rescue therapy after failure of prednisolone.[24] A total of 10 trials were included in the review (Figure 1). Characteristics of included trials are shown in Table 1. A summary of trial outcomes is shown in Table S3.

Quality of trials and risk of bias

Risk of bias was assessed using criteria specified by the Cochrane group. Risk of bias was high in some papers[25–27] and low in others[28–30] (Table 2). CONSORT guidelines were used to assess the quality of trials (Tables S1 and S2). Earlier trials and those reported as abstracts were generally of lower quality than later trials and those published as full papers and hence were at greater risk of bias. Some trials, in particular De *et al.*'s[25] trial and Garcia *et al.*'s[26] trials, had serious flaws in their methodology and/or reporting and were considered at high risk of bias.

Methodological differences between trials

There was significant heterogeneity between trials with regard to methodology. AH was defined by clinical

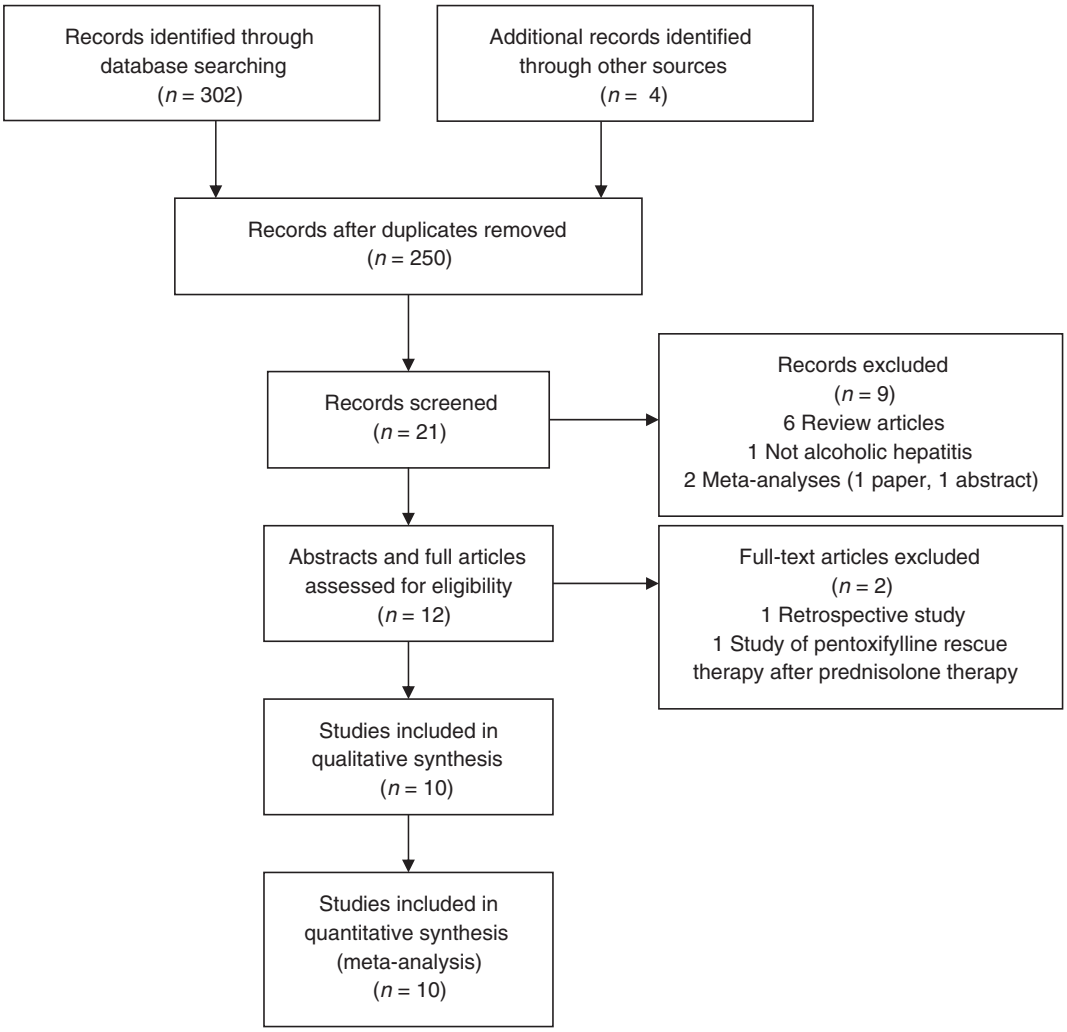

Figure 1 | Flow diagram.

Table 1 | Trial characteristics

First author	Year	Type of publication	Country	Number of participants	Inclusion criteria	Exclusion criteria	Histology	Dose of PTX	Control	Outcome measures	Follow-up
Pentoxifylline vs. placebo											
McHutchison *et al.*[16]	1991	Abstract	USA	22 (12 PTX, 10 control)	1. Biopsy proven AH 2. Bilirubin >10 mg/dL 3. Elevated PT 4. Fever 5. Tender hepatomegally	Active infections	Yes	1200 mg o.d.	Placebo	1. Biochemical improvement 2. TNF levels 3. Renal impairment, fever, 4. Mortality.	28 days
Akriviadis *et al.*[28]	2000	Paper	USA	101 (49 PTX, 52 control)	1. Jaundice 2. DF ≥32 3. 1 or more of • Tender hepatomegaly, • Fever • Leukocytosis • Hepatic encephalopathy • Hepatic systolic bruit	1. Concomitant bacterial infections 2. Active gastrointestinal haemorrhage 3. Severe cardiovascular/pulmonary disease 4. Decreasing serum bilirubin or rapid improvement of other liver tests 5. Evidence of advanced alcoholic cirrhosis.	No	400 mg t.d.s.	B12 tablets 500–1000 μg t.d.s.	Primary endpoints 1. Short-term survival 2. Progression to HRS Secondary endpoints 1. Laboratory parameters 2. Complications of liver disease	6 months
Peladagu *et al.*[31]	2006	Abstract	India	30 (14 PTX, 16 control)	Maddrey >32 or encephalopathy	Not described	No	Not specified	Placebo	1. Mortality 2. HRS	28 days
Sidhu *et al.*[32]	2006	Abstract	India	50 (25 PTX, 25 control)	Maddrey >32	Not described	No	400 mg t.d.s.	Placebo	1. 28 day survival 2. Laboratory parameters	28 days
Trials of pentoxifylline versus corticosteroid											
De *et al.*[25]	2009	Paper	India	68 (34 PTX, 34 control)	1. DF≥32 2. Alcohol>50 g/d 3. AST:ALT>2:1 4. AST <500 5. ALT <200	1. Acute or chronic viral (inc HIV) 2. Autoimmune liver disease 3. Wilsons 4. Abstinence in last month 5. Infection 6. GI bleeding 7. Severe HRS 8. Pancreatitis 9. Severe disease in last three months	No	400 mg t.d.s.	Prednisolone 40 mg o.d. for 4 weeks + placebo t.d.s.	Not stated. Death and morbidity reported.	12 months
Kim *et al.*[27]	2011	Paper	South Korea	69 (33 PTX, 36 control)	1. Alcohol > 40 g/day 2. Biochemical features of severe AH	1. Other liver disease including HIV 2. Sepsis 3. SBP 4. GI bleeding 5. Pancreatitis 6. Malignancy	No	400 mg t.d.s.	Prednisolone 40 mg o.d.	1. 28 day survival 2. Changes in liver function 3. Morbidity	6 months
Garcia *et al.*[26]	2012	Paper	Mexico	60 (30 PTX, 30 control)	1. DF >32 2. Jaundice 3. No biliary obstruction on US 4. AST/ALT > 2 5. No active infection	1. Pregnancy 2. Serious bacterial infection 3. Neoplasia 4. Previous diagnosis of chronic or degenerative disease 5. Hypertension (level not defined) 6. Heart disease 7. Lung disease 8. HIV 9. Substance misuse 10. Previous use of steroids	No	400 mg t.d.s.	Prednisolone 40 mg	1. 28 day mortality 2. Incidence of HRS	28 days
Trials of pentoxifylline and corticosteroid versus corticosteroid alone											
Lebrec *et al.*[29]	2010	Paper	France	55 (26 PTX, 29 placebo)	1. Child-Pugh class C cirrhosis 2. Aged over 18 years 3. DF >32	1. Pregnancy 2. Anticoagulants or non-corticosteroid immunosuppressives 3. Hypertension 4. Severe coronary artery disease 5. HIV 6. Hypersensitivity to pentoxifylline 7. Liver transplantation 8. Received PTX within 3 months of study 9. Advanced hepatocellular carcinoma 10. Ilnesses with a life expectancy of < 1 month 11. Patients who could not be regularly followed up	Yes	400 mg t.d.s. Prednisolone 40 mg o.d.	Placebo Prednisolone 40 mg o.d.	Primary end points 1. Mortality at 2 months Secondary end points 1. Mortality at 6 months 2. Development of complications: 3. Bacterial infections, 4. Renal insufficiency 5. Hepatic encephalopathy 6. Gastrointestinal haemorrhage	6 months
Mathurin *et al.*[33]	2012	Abstract	France	270 (133 PTX, 137 control)	1. DF >32 2. Biopsy proven alcoholic hepatitis	1. HRS or creatinine>221 umol/L 2. Severe extra-hepatic comorbidities 3. Malignancy 4. GI bleeding 5. Pancreatitis 6. Infection 7. Treatment with trial drugs in past year	Yes	400 mg t.d.s. + Prednisolone 40 mg o.d.	Prednisolone 40 mg o.d.	6 month survival (2) HRS	6 months
Sidhu *et al.*[30]	2011	Paper	India	70 (36 PTX, 34 control)	1. DF >32 2. AH as first decompensating event	1. Chronic jaundice 2. Infection 3. GI bleeding 4. Renal failure 5. Pancreatitis 6. Pre-existing end stage liver disease	No	400 mg t.d.s. + prednisolone 40 mg o.d.	Prednisolone 40 mg o.d.	1. Six month survival 2. Lille score	6 months

Table 2 | Assessment of risk of bias in trials

	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data assessed	Free of selective reporting	Free of other bias
McHutchinson *et al.*[16]	?	?	?	Yes	?	?
Paladugu *et al.*[31]	?	?	?	Yes	?	?
Sidhu *et al.*[32]	?	?	?	Yes	?	?
Akriviadis *et al.*[28]	Yes	Yes	Yes	Yes	Yes	Yes
De *et al.*[25]	Yes	No	No	No	No	Yes
Kim *et al.*[27]	?	?	?	No	?	?
Garcia *et al.*[26]	No	No	No	No	Yes	Yes
Lebrec *et al.*[29]	Yes	Yes	Yes	Yes	Yes	Yes
Sidhu *et al.*[30]	Yes	Yes	Yes	Yes	Yes	Yes
Mathurin[33]	?	?	?	Yes	Yes	Yes

parameters in most trials; three used biopsy to confirm the diagnosis. In all trials, severe disease was defined as Maddrey's DF score of greater than 32. Some trials excluded patients who exhibited a spontaneous improvement in liver function in the first few days of admission, whilst patients with cirrhosis were excluded from other trials. Many trials included incidence of HRS as an outcome measure; however, this was not defined in any reports and consequently it is unknown whether this outcome is comparable between trials.

Trials comparing pentoxifylline with placebo

Four trials comparing pentoxifylline with placebo have been reported: three abstracts[16, 31, 32] and one paper.[28]

McHutchinson *et al.*[16] treated 12 patients with biopsy-proven SAH with pentoxifylline for 10 days and compared them to 10 patients treated with placebo. Severity was defined by DF >32. Patients were given 1200 mg of pentoxifylline daily or placebo for 10 days. One of 12 treated patients died at 30 days of follow-up compared with 3 of 10 controls (P = N.S.). Reduction in mortality was attributed to reduced incidence of renal impairment, as measured by creatinine levels after 10 days of treatment (mean creatinine in pentoxifylline group 1.0 ± 0.5 mg/dL vs. 3.2 ± 1.2 mg/dL in controls). Side effects of medications were not reported.

Paladugu *et al.*[31] randomised 30 participants to pentoxifylline (14 patients) or placebo treatment (16 patients) for 4 weeks. Reported outcomes were 28-day mortality, and cause of death. Incidence of HRS – which was not defined – was only reported if it was fatal. Four patients treated with pentoxifylline died (28.6%), compared with seven control patients (43.8%) (P = 0.09). Fatal HRS was observed in two participants treated with pentoxifylline and six control patients (50% vs. 87.5% of deaths, P = 0.10, 14% vs. 37.5% of all participants). Side effects or harms of treatment were not reported.

Sidhu *et al.*[32] reported a trial of 50 patients randomised to pentoxifylline (25 patients) or placebo (25 patients) for 28 days. Outcomes were 28-day mortality and biochemical parameters. The placebo group had significantly higher creatinine at randomisation. Six patients died in pentoxifylline group (24%) compared with 10 patients in the control group (40%). Fatal HRS was proportionally more common in the pentoxifylline group: five patients (83% of deaths, 20% of participants), compared with six control patients (60% of deaths, 24% of participants). Harms of treatment were not reported.

Akriviadis *et al.*[28] reported a trial of 102 patients randomised to treatment with pentoxifylline 400 mg t.d.s. or placebo (vitamin B12 tablets were used as placebo) for 28 days. All patients had a DF greater than 32. Of note, patients with rapid spontaneous improvement in bilirubin or other liver function were excluded, as were patients with evidence of advanced cirrhosis. Patients were followed up for 6 months. Survival and incident HRS were the primary outcome measures, although a range of biochemical data was also reported. A patient in the pentoxifylline group dropped out after three tablets and was excluded from analysis, despite intention-to-treat analysis being stated in the methodology. Baseline renal impairment (serum creatinine >2.4 mg/dL) was more common in the control group (six patients vs. three patients), but this was not statistically significant (P = 0.22). This trial found decreased 6-month mortality in the pentoxifylline group (12/49 patients, 24.5%) compared with controls (24/52, 46.1%), (RR, risk ratio: 0.59, 95% CI: 0.35–0.97, P = 0.037). HRS occurred on a background of renal failure in 2/49 pentoxifylline patients and 4/52 control patients. New onset HRS occurred in 4/49 pentoxifylline patients and 18/52

control patients (8.2% vs. 18%) (RR: 0.32, 0.13–0.79, $P = 0.0015$). HRS was therefore observed in a total of 6/49 (12.2%) participants treated with pentoxifylline and 22/52 (42.3%) of controls. Of note, seven patients in the pentoxifylline group discontinued treatment after only 4–9 days due to side effects: severe GI side effects, headache, epigastric pain and rash were reported. GI side effects were also common in participants who completed treatment.

Mortality data were pooled from the three trials reporting 28-day outcomes.[16, 31, 32] This showed an overall RR for mortality of 0.43 (95% CI: 0.18–1.05, $P = 0.06$) (pentoxifylline vs. control; Fig. S1). HRS data were pooled regarding incidence of fatal HRS as this was the only outcome consistently reported: RR for incidence of HRS was 0.47 (0.26–0.86, $P = 0.01$; Fig. S2) (Table 3).

Trials comparing pentoxifylline with corticosteroid

Three trials have compared pentoxifylline with prednisolone; two as papers[25] and one in an interim report.[27] One trial reported 28-day outcomes, two reported both 28-day and 6-month outcomes.

De *et al.*[25] conducted a randomised trial of pentoxifylline (400 mg t.d.s.) vs. prednisolone (40 mg o.d.). After 4 weeks, the study was unblinded and prednisolone was tapered by 5 mg/week. Pentoxifylline was continued until 8 weeks – thus full dose of pentoxifylline is compared to lower dose prednisolone. Diagnosis of AH was made on clinical and biochemical grounds; biopsy was not used. Severity was defined by DF >32 and an AST/ALT ratio >2, with absolute values of AST <500 IU/L and ALT<200 IU/L. A total of 70 patients were enrolled, 34 in the pentoxifylline group and 36 in the prednisolone group. Although intention-to-treat analysis was stated, two patients who withdrew from the prednisolone group and one patient in the pentoxifylline group who was lost to follow-up were excluded from analysis. Furthermore, patients who returned to alcohol consumption (one in the pentoxifylline group, two in the prednisolone group) were excluded from further analysis. Outcomes were not stated in the methodology, but several were reported: deaths, mode of death, side effects, baseline features of those who died and evolution of various clinical scoring systems. At 28 days, 2 of 34 patients had died in the pentoxifylline group (5.8%) and 7/34 (20.5%) in the prednisolone group. Six-month mortality was 5/34 (14.7%) in pentoxifylline group and 12/34 (35.3%) in the prednisolone group ($P = 0.04$). No patients on pentoxifylline developed HRS (not defined), whereas six patients on prednisolone did. This trial, with inadequate blinding, analysis and reporting, concluded that pentoxifylline was superior to prednisolone in the treatment of SAH. Common adverse side effects of pentoxifylline were GI, sepsis occurred in two patients and encephalopathy was noted in two patients.

Kim *et al.*'s[27] study is ongoing; an interim analysis was published in 2011. A total of 78 patients with clinically diagnosed AH (alcohol history of >40 g/day and clinical and biochemical features of AH) were included without biopsy. Severity was defined by DF >32. Patients were randomised into two groups: one of whom received 40 mg prednisolone for 4 weeks (41 patients); the other received 400 mg pentoxifylline t.d.s. for 4 weeks (33 patients). Randomisation procedure and whether the trial was blinded were not reported. Survival, liver function and complications at 28 days after starting therapy were stated as outcome measures. Patients who completed therapy were analysed: five dropouts from the prednisolone group and four from the pentoxifylline group were not included in analysis. In the pentoxifylline group, 8/33 (24%) patients died, compared to 3/36 (8%) patients

Table 3 | Pooled outcome data: risk ratio (RR) for mortality and incidence of hepatorenal syndrome (HRS) (random effects modelling, I^2: heterogeneity)

	28-day mortality RR (95% CI)	I^2 (%)	*P*-value	6-month mortality RR (95% CI)	I^2 (%)	*P*-value	Incidence of HRS RR (95% CI)	I^2 (%)	*P*-value
Pentoxifylline vs. placebo	0.58 (0.31–1.07)	0	0.06				0.47 (0.26–0.86)*	0	**0.01**
Pentoxifylline vs. corticosteroid	0.88 (0.30–2.57)	67	0.86						
Pentoxifylline and corticosteroid vs. corticosteroid	0.93 (0.56–1.54)	0	0.78	0.94 (0.76–1.17)	0	0.88	0.73 (0.41–1.32)	0	0.30

* Incidence of fatal HRS.

Results in bold considered statistically significant.

in the prednisolone group (*P*-value not given). One patient in each group developed fatal HRS (not defined). Common adverse effects in the pentoxifylline group were diarrhoea, epigastric pain and general weakness.

Garcia *et al.*[26] published a report of a trial in Mexico, comparing pentoxifylline to prednisolone. Sixty patients were randomised to 400 mg of pentoxifylline t.d.s. or 40 mg of prednisolone o.d. for 28 days. AH was defined by clinical findings and biochemical parameters; biopsy was not used. Severity was defined with DF, only patients with a score greater than 32 were included. Patients with spontaneous improvement in liver function were included, as were patients with cirrhosis. HRS was not defined. Patients who did not complete treatment were not included in analysis – although there were apparently no drop-outs, elimination criteria were given: diagnosed of diabetes mellitus during follow-up, systemic arterial hypertension and patients who did not complete treatment. There was no difference in 28-day mortality: 12/30 (40%) in the pentoxifylline group and 16/30 (54.4%) in the prednisolone group ($P = 0.30$). Incidence of HRS is reported as 9/30, 6/30 and 10/30 in the pentoxifylline group, and 13/30 and 14/30 in the prednisolone group. There are methodological problems with this study, specifically with regard to reporting of results. Side effects of treatment were not detailed, but described as similar between groups.

Data were pooled from all three trials for 28-day mortality (Fig. S3). Pooled RR was 0.88 (0.30–2.57, $P = 0.86$) for 28-day mortality (Table 3). Data for 6-month mortality and incidence of HRS were not suitable for pooled analysis.

Trials comparing pentoxifylline and corticosteroid dual therapy with corticosteroid monotherapy

Three trials compared pentoxifylline, in combination with corticosteroid, with corticosteroid monotherapy. Two of these set out to examine this problem in SAH specifically;[30, 33] the other was a trial of patients with cirrhosis that included a sub-group of patients with SAH.[29] The latter was included in the Cochrane meta-analysis as a trial of placebo vs. pentoxifylline, as the original published abstract did not include such detail.

The trial by Lebrec *et al.*[29] was a randomised, placebo-controlled double-blinded trial of 335 patients with Child-Pugh class C cirrhosis. Patients received 400 mg of pentoxifylline t.d.s. or placebo. A subset of 133 patients had biopsy-proven AH of whom 55 had a DF greater than 32. AH was not defined. All of these patients received corticosteroid therapy in addition to trial drugs: 26 received corticosteroid and pentoxifylline; 29 received corticosteroid and placebo. Patients were randomised by a computer-generated sequence. Intention-to-treat analysis was used. Outcomes reported for the subset of patients with SAH were 2- and 6-month mortality. The probability of survival did not differ between pentoxifylline and placebo groups: 84.6% (70.8–98.5%) vs. 86.2% (73.7–98.8%), respectively, at 2 months ($P = 0.84$) and 76.9% (60.7–93.1%) vs. 79.3% (64.6–94.1%), respectively, at 6 months ($P = 0.82$). Adverse events of pentoxifylline were GI: diarrhoea, vomiting and epigastric pain.

Sidhu *et al.*'s[30] randomised, double-blinded controlled trial included 70 patients randomised to corticosteroids (prednisolone 40 mg o.d.) and pentoxifylline (400 mg t.d.s.) or corticosteroid alone for 28 days. AH was defined as a history of alcohol intake >80 g/day in males and 60 g/day in females, with jaundice, fever, hepatomegaly, bilirubin >5 mg/dL (85 μmol/L) AST:ALT ratio >2:1 with absolute values of AST <500 IU/L and ALT <300 IU/L. Biopsy was not performed. Severity was defined by DF >32. Patients were included if they had SAH and had no previous history of hepatic decompensation. Outcomes investigated were 6-month survival, and response to treatment (as defined by Lille score[34]). Twenty-eight-day survival was also reported. Intention-to-treat analysis was used. In common with some other trials, patients with a spontaneous improvement in liver function over the first 5–7 of admission were not included. The results showed no significant difference at 28 days (mortality 10/36 in combination group vs. 9/34 in corticosteroid group, $P = 1.00$) or 6 months (25/36 in combination group and 26/34 in corticosteroid group, $P = 0.360$). Incidence of HRS was not reported. Adverse events experienced in the combination group were predominantly GI – epigastric pain, vomiting and diarrhoea. GI bleeding occurred in three patients in combination group and two patients in the corticosteroid group.

Mathurin[33] conducted a randomised, double-blinded controlled trial comparing pentoxifylline and prednisolone to prednisolone alone. A total of 270 patients were included, 137 treated with combination therapy and 134 with prednisolone alone. Pentoxifylline was given at 400 mg t.d.s., prednisolone at 40 mg o.d., each for 28 days. Patients had biopsy-proven AH, severity was defined by DF >32. Intention-to-treat analysis was performed. Primary outcome was 6-month survival; secondary outcomes were incidence of HRS and response to therapy as defined by the Lille score. In addition, 28-day survival was also reported.[35] No differences were seen

between groups with regard to 28-day survival (119/133 vs. 120/137), 6-month survival (93/133 vs. 95/137, $P = 0.9$), incidence of HRS (undefined) (9.1% vs. 10.3%, $P = 0.75$) or response to therapy. Numbers of adverse events in each group were similar (70 with pentoxifylline, 88 with prednisolone, $P = 0.77$).

Data were pooled for 28-day mortality from Sidhu *et al.*[30] and Mathurin,[33] (Fig. S4) for 6-month mortality from all three trials (Fig. S5) and for incidence of HRS from Sidhu *et al.*[30] and Mathurin (Fig. S6).[33] Pooled RR for 28-day mortality, 6-month mortality and incidence of HRS was 0.93 (0.56–1.54, $P = 0.78$), 0.94 (0.76–1.17, $P = 0.88$) and 0.73 (0.41–1.32, $P = 0.30$) respectively (Table 3).

CONCLUSION

SAH is a devastating manifestation of ALD. Pentoxifylline has been shown to reduce mortality in some trials, possibly through reduced incidence of HRS. A Cochrane review by Whitfield *et al.*[17] found a significant positive effect of pentoxifylline on survival in SAH, but further data were required for a reliable result. Further studies have since more than doubled the number of patients with SAH treated experimentally with pentoxifylline. However, there is significant heterogeneity between these trials, and the role of pentoxifylline remains uncertain. Further data are needed for firm conclusions to be drawn. It seems likely that pentoxifylline is superior to placebo with regard to reducing incidence of fatal HRS, but evidence to date does not show any benefits in mortality. There is no clear evidence of superiority of pentoxifylline or prednisolone. This finding has implications for clinicians managing patients with SAH.

Trials included in this review are often limited by poor methodology and consequent high risk of bias. The size and quality of trials of pentoxifylline has generally improved over time with rigorous randomisation and analysis although this is not universal. Recent trial data are thus more reliable. Of note, these trials have tended to find no evidence of benefit of pentoxifylline.[29, 30, 33] Heterogeneity of trials may mask an effect of pentoxifylline in certain cohorts – for example, Akriviadis demonstrated a mortality benefit of pentoxifylline after exclusion of spontaneously improving patients and those with cirrhosis. The lack of a definition of HRS in these trials makes interpretation of results difficult. A useful definition is provided by the International Club of Ascites,[36] which should be used in future studies.

Initial trials tended to compare pentoxifylline with placebo, whereas recent trials have used active control groups. As there seems to be little evidence of the superiority of one treatment to another, in practice, choice of agent may rest on the side effect profile. Although rarely addressed in detail in these trials, the side effect profile of pentoxifylline may be preferable to that of corticosteroids. An alternative approach is to use one treatment after failure of another. Louvet *et al.*[24] examined the use of pentoxifylline in nonresponders to corticosteroid therapy and found no survival benefit, although such a group of patients has an extremely poor prognosis.

This review emphasises the need for large, well-conducted trials to provide definitive evidence for the treatment of SAH. The STOPAH (steroids or pentoxifylline in alcoholic hepatitis) trial is currently recruiting patients with SAH in the UK, and aims to randomise 1200 participants to placebo, pentoxifylline, prednisolone or combination therapy.[37] The primary end-point of this study is 28-day mortality. This trial, powered to provide conclusive evidence for relative effect of these treatments, will be the largest to date in this field.

SAH remains a challenge to treat. Despite trials of several different agents, there has been no significant advance in therapy for many years. Future trials may provide definitive evidence, but at present, evidence regarding pentoxifylline is inconclusive. It is probably superior to placebo, but trials to date have not demonstrated superiority or inferiority to corticosteroid. Clinicians managing SAH should be aware of the relative paucity of data on which the use of pentoxifylline is based.

AUTHORSHIP

Guarantor of the article: Dr R Parker.

Author contributions: RP developed the idea for this review, designed the protocol, performed literature search, analysed data and wrote the manuscript. IAC, MJA, CC performed literature search, reviewed and edited the manuscript. DDH reviewed and edited the manuscript. All authors have approved the final version of this article, including the authorship list.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Pentoxifylline vs. placebo, 28-day mortality.

Figure S2. Pentoxifylline vs. placebo, incidence of fatal HRS.

Figure S3. Pentoxifylline vs. prednisolone, 28-day survival.

Figure S4. Pentoxifylline vs. combination therapy, 28-day survival.

Figure S5. Pentoxifylline vs. combination therapy, 6-month survival.

Figure S6. Pentoxifylline vs. combination therapy, incidence of HRS.

Table S1. Quality of trials published as full manuscripts assessed by CONSORT criteria.

Table S2. Quality of trials published as abstracts assessed by CONSORT guidelines.

Table S3. Outcomes: 28-day mortality, 6-month mortality and incidence of HRS (%) (analysed with Fisher's exact test).

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