Current Opinion in Pharmacology

Treatment of severe alcoholic hepatitis: a systematic review

--Manuscript Draft--

Manuscript Number:	COPHAR-D-21-00021R1
Full Title:	Treatment of severe alcoholic hepatitis: a systematic review
Article Type:	SI: 61 Gastrointestinal (2021)
Short Title:	Treatment of sAH: a systematic review
Keywords:	Severe alcoholic hepatitis; treatment; systematic review
Corresponding Author:	Jef Verbeek UZ Leuven: Katholieke Universiteit Leuven Universitaire Ziekenhuizen Leuven BELGIUM
Corresponding Author's Institution:	UZ Leuven: Katholieke Universiteit Leuven Universitaire Ziekenhuizen Leuven
Corresponding Author E-Mail:	jef.verbeek@uzleuven.be
First Author:	Lukas Van Melkebeke, MD
Order of Authors:	Lukas Van Melkebeke, MD Hannelie Korf, PhD Emmanuel A. Tsochatzis, MD, PhD Schalk van der Merwe, MD, PhD Frederik Nevens, MD, PhD Jef Verbeek, MD, PhD
Abstract:	Severe alcoholic hepatitis is the most severe form of alcohol-related liver disease. Corticosteroids remain the first choice of treatment. However, they are only effective in a subset of patients and are associated with an increased infection risk. Furthermore, non-responders to corticosteroids have a poor prognosis with a mortality of 70% over 6 months. As such, there is a high need for a more personalized use of corticosteroids and the development and identification of alternative therapeutic strategies. In this review, we summarize the recent and ongoing randomized controlled trials concerning the treatment of severe alcoholic hepatitis.
Author Comments:	No comments

Treatment of severe alcoholic hepatitis: a systematic review

Lukas Van Melkebeke^{1,2}, Hannelie Korf¹, Emmanuel A. Tsochatzis³, Schalk van der Merwe^{1,2}, Frederik Nevens^{1,2}, Jef Verbeek^{1,2}

1. Laboratory of Hepatology, Department of Chronic Diseases and Metabolism, Catholic University of Leuven, Belgium
2. Department of Gastroenterology & Hepatology, University Hospitals Leuven, Leuven, Belgium
3. UCL Institute for Liver and Digestive Health, Royal Free Hospital and UCL, London. United Kingdom

Corresponding author: Jef Verbeek, MD, PhD, Herestraat 49, 3000 Leuven, Leuven, Belgium; jef.verbeek@uzleuven.be

Treatment of severe alcoholic hepatitis: a systematic review

Abstract

Severe alcoholic hepatitis is the most severe form of alcohol-related liver disease. Corticosteroids remain the first choice of treatment. However, they are only effective in a subset of patients and are associated with an increased infection risk. Furthermore, non-responders to corticosteroids have a poor prognosis with a mortality of 70% over 6 months. As such, there is a high need for a more personalized use of corticosteroids and the development and identification of alternative therapeutic strategies. In this review, we summarize the recent and ongoing randomized controlled trials concerning the treatment of severe alcoholic hepatitis.

Introduction

Alcohol-related liver disease (ALD) is the most frequent cause of advanced chronic liver disease worldwide, contributing to 47.9% of all liver cirrhosis-related deaths globally[1]. Alcoholic hepatitis (AH) is an acute form of ALD that ranges from mild to severe disease states and usually presents on a background of cirrhosis [2]. Severe alcoholic hepatitis (sAH) is defined as a Maddrey discriminant function (MDF) of > 32 and/or a model for end-stage liver disease (MELD)-score of more than 20 in a patient with a recent onset of jaundice and a chronic alcohol use disorder [3]. sAH is the most severe manifestation of ALD with a 28-day mortality of 20-50% [1].

ALD has a complex pathogenesis, involving multiple mechanistic pathways[4]. Recent translational studies have demonstrated a key role for the innate immunity and the gut-liver axis in propagating hepatocellular inflammation and fibrosis[5]. In AH, systemic inflammation and hepatocellular degeneration are major contributors to liver- and multi-organ failure[5]. Therapeutic strategies for sAH therefore can be categorized based on their mode of action: 1) anti-inflammatory therapies, 2) anti-oxidants, 3) therapies modulating the gut-liver axis and 4) therapies boosting liver regeneration[6].

Despite the high mortality of sAH, only limited therapeutic options exist at this point, resulting in an important unmet need. In recent years, several new therapies have been investigated in the treatment of sAH and multiple clinical trials are ongoing. Here, we provide an overview of the treatment modalities for sAH, with a special focus on clinical trial results published from 2018 onwards (Table 1) and on ongoing randomized clinical trials (Table 2).

Material and methods

Study selection

A systematic literature search (supplementary figure 1) was carried out using MEDLINE, Web of Science, Embase, the Cochrane Library, the International Clinical Trials Register, ClinicalTrials.gov and EudraCT (a detailed search query for each database is provided in supplementary figure 2). We included studies assessing therapies for severe AH. Only randomized controlled trials (RCT) or systematic reviews were included. Randomized controlled trials were included as full text articles and meeting abstracts, systematic reviews

only in full text format. For randomized controlled trials there was no publication year restriction, while systematic research articles were only included starting from 23/04/2015 (publication date of the landmark trial by Thursz et al.[7]). Only studies reporting survival as primary or secondary endpoint were included. Included studies defined sAH as AH with a Maddrey-score of > 32, a MELD-score of > 20 or concomitant hepatic encephalopathy. There were no language restrictions. Animal studies were excluded.

All registered studies published until the 23rd of November 2020 were included. This resulted in 3085 unique references (5036 references before duplicate removal). All records were screened in two stages. After title and abstract screening 248 references remained. Afterwards, a full-text screening resulted in 66 references, consisting of 43 full text articles, 6 meeting abstracts and 17 ongoing registered clinical trials.

Anti-inflammatory therapies

Inflammation plays a pivotal role in the pathogenesis of SAH. In the gut, alcohol-induced dysbiosis and bacterial translocation lead to the accumulation of pathogen-associated molecular patterns (PAMPs) in the portal circulation. On the other hand, heavy alcohol use and its metabolites damage hepatocytes resulting in the release of danger-associated molecular patterns (DAMPs). The combination of PAMPs and DAMPS results in Toll-like receptor 4 (TLR4) and NRP3 inflammasome-mediated inflammatory responses in the liver, with a central role for tumor necrosis factor alpha (TNF- α) and interleukin 1 (IL-1), especially interleukin 1beta[5,8].

Corticosteroids

As first-line agent in the treatment of sAH, current guidelines recommend the use of prednisolone, a corticosteroid with broad anti-inflammatory and immunosuppressive actions[3]. We identified 6 RCT's comparing corticosteroids to placebo. Two RCT's (n=127) showed a significantly improved survival at 28 days[9,10] and one of those also at 1 year[10]. On the contrary, four RCT's (n=689) found no significant survival benefit at 28 days[7], 2 months[11], 3 months[7] or 1 year[7,12], with the largest RCT (n=546) finding a trend towards improved survival at 28 days[7]. Only 2 out of these 6 RCT's that compared corticosteroids to placebo, solely included patients with biopsy-proven sAH. The first study [10] showed a significantly improved survival at 28 days and one year, the other[13] showed no effect on survival at 28 days. Notably however, in the latter study, prednisolone was administered atypically (1g for 3 days).

The evidence supporting the use of corticosteroids is primarily based on meta-analytic data. Out of 6 meta-analyses, 4 showed a significant survival benefit of corticosteroid treatment at 28 days[14–17], while two studies failed to show improved survival [18,19]. None of the meta-analyses found improved survival beyond the first 28 days period. The negative results in two meta-analyses can possibly be explained by the study design. One of the negative analyses studied the effect of corticosteroids at the end of corticosteroid treatment, what is not always equal to a 28 day-period and also included studies performed more than 30 years ago, when the death rates in the placebo arms were significantly higher than today [19]. The other negative systematic review was an attempted network meta-analysis[18].

One ongoing trial is examining the effect of prednisolone, compared to placebo, in 140 patients with biopsy-proven sAH. Endpoints in this regard are improvement of liver function (defined as a 10% decrease in MDF) and bilirubin at day 7 (EudraCT2016-005136-16).

Taken together, current evidence suggests that treatment with prednisolone marginally improves the survival of at least a subset of sAH patients at 28 days, but not beyond this period. Whether corticosteroids improve the short-term survival of patients with sAH complicated by acute-on-chronic liver failure (ACLF) is unclear [20]. Current data suggest a lower rate of response in patients with ACLF grade 2 and 3 (42 and 8% respectively)[7,21].

The combination of prednisolone with prophylactic antibiotics could possibly reduce the infection rate. Around 25% of patients presenting with sAH have an infection and an additional 25% develops an infection within 3 months[22]. One study investigating the effect of the addition of ciprofloxacin to prednisolone on survival after 1, 3 and 6 months was temporarily halted in 2017, after the inclusion of only 22 patients in 3 years. No intermediate results were found (EudraCT2013-003727-11). Another study (n=280) will examine the effect of adding amoxicillin-clavulanic acid to prednisolone therapy on the survival at 2 months in patients with sAH (NCT02281929).

Extracorporeal liver assist device

The extracorporeal liver assist device (ELAD) uses a special hepatoblastoma cell line (the HepG2/C3A cell line), that produces anti-inflammatory, antiapoptotic and anti-oxidant cell products[23]. Its use in sAH is based on the assumption that by providing hepatocellular support, the impaired liver cells can recover, inhibiting further degeneration and enabling recovery of the patient [23]. However, an RCT (n=203) comparing ELAD and standard of care showed no difference in overall survival at 28 and 91 days [23]. In the subgroup analysis of patients with a MELD < 28 (n=120), the therapy was associated with a trend toward higher survival at 91 days. Therefore, a new RCT was initiated examining the role of ELAD in the subgroup of sAH patients with a MELD <30 (NCT02612428). This trial was terminated after enrolling 151 patients when an intermediate analysis showed no improvement of survival at 90 days.

Infliximab

Infliximab is a monoclonal antibody that binds to soluble and transmembrane forms of TNF- α and consequently disrupt its downstream pro-inflammatory signaling cascade [24]. One RCT compared infliximab (3 doses at weeks 0, 2, and 4) to prednisolone in patients with biopsy-proven sAH (n=36)[25]. The study was stopped prematurely due to a significantly higher infection rate and a trend to higher mortality in the infliximab-group. Nevertheless, based on a case series, a systematic review of infliximab found that treatment with a single dose lowered the infection- and the mortality rate compared to a triple-dose infliximab regimen [26]. However, there are no ongoing trials investigating a single dose of infliximab for the treatment of sAH.

Other anti-inflammatory therapies

One RCT (n=104) compared the combination of anakinra (an interleukin 1 inhibitor), PTX and zinc (zinc deficiency contributes to an impaired gut-barrier) with prednisolone[27]. The results showed no significant difference in survival at 28 days, but a trend towards improved survival was detected at 180 days. A follow-up study (n=258) started in July 2020 that compares the combination of anakinra and zinc to prednisolone on survival at 90 days (NCT04072822).

Canakinumab is a human immunoglobulin blocking interleukin-1beta[28]. An ongoing RCT (n=56) is comparing Canakinumab to placebo, with survival at 90 days being a secondary outcome measure (NCT03775109). Enrollment was completed in November 2020 and the study is estimated to be finished in January 2021.

One RCT compared emricasan, a pan-caspase inhibitor, to placebo in patients with sAH and a contraindication for corticosteroids. It was stopped prematurely, after including 5 patients, due to concern for high systemic drug levels (NCT01912404).

Selonsertib is an inhibitor of apoptosis signal-regulating kinase 1 (ASK1), which mediates pro-inflammatory and pro-fibrotic changes in the liver[29]. One RCT investigated the addition of selonsertib to prednisolone in 99 patients with biopsy-proven sAH (NCT02854631, P. Mathurin et al. Abstract 13, Annual Meeting of the AASLD, San Francisco, November 2018). No differences were seen between both groups for infection-rate and survival at 28 days or 8 weeks.

Anti-oxidants

There are several pathways in the pathology of sAH that contribute to the generation of reactive oxygen species and to the development of oxidative stress. These pathways include apoptosis and necrosis of cells, inflammatory signaling and recruitment of inflammatory cells, mitochondrial dysfunction and metabolism of alcohol[8].

N-acetylcysteine

N-acetylcysteine (NAC) is an antioxidant administered to patients with acute liver failure [30], with its thiol group being able to reduce levels of free radicals.

One RCT (n=52) compared NAC versus placebo in biopsy-proven sAH. This study reported no survival benefit at 1 or 6 months[31]. A second RCT (n=70) applied NAC in combination with a cocktail of anti-oxidants compared to a placebo cohort. The obtained results did not show any survival advantage after 6 months[32]. A third RCT (n=101) compared prednisolone versus a combination of NAC with a cocktail of anti-oxidants and found a significantly higher survival in the prednisolone treated group at 28 days[33]. No difference was found at 1 year follow-up. Two RCT's (n=59) examined the addition of NAC to PTX and G-CSF respectively, however both studies showed no survival benefit (B. Patel, abstract L09, 53rd Annual Conference of the Indian Society of Gastroenterology, November 2012)[34]. A last RCT (n=174), with biopsy-proven sAH, examined the addition of NAC to prednisolone compared with prednisolone monotherapy and found a significantly improved survival in the NAC-prednisolone group at 28 days (but not at 3 months or 6 months). This result was associated with a lower infection rate and reduced occurrence of hepatorenal syndrome [35].

There are two ongoing RCT's examining the role of NAC in sAH. The first (n=170) study is assessing the effect of the addition of NAC to standard of care on the survival at 6 months (ChiCTR2000030583). The other trial (n=42) is evaluating the effect of the addition of NAC to prednisolone on survival at 28 and 90 days. (NCT03069300).

In conclusion, although some studies demonstrated efficacy in aforementioned trials, there is currently insufficient evidence to conclude that NAC improves survival in patients with sAH. The results of the 2 ongoing trials are awaited.

Pentoxifylline

Pentoxifylline (PTX) is a non-selective phosphodiesterase inhibitor with vasodilating and anti-inflammatory properties.

We identified 4 RCT's comparing PTX versus placebo, of which three (n=625)[7,36] (Paladugu et al., Asian Pacific Digestive Week, November 2006) were negative and one positive (n=101)[37] regarding survival at 28 days. However, no survival benefit was found at 90 days or 1 year[7]. Another 4 RCT's compared the combination of PTX and prednisolone versus prednisolone alone (n=902), however all of these failed to improve survival.[7,38–40]. Notably, only two of the latter 4 negative RCT's included only patients with biopsy-proven sAH[39,40].

As a follow up after the last RCT, five systematic reviews were published with the scope of examining PTX efficacy. None of these systematic reviews found a survival benefit of PTX in comparison with placebo or in addition to corticosteroids at any timepoint [14–16,18,41]. One systematic review, that included several older RCT's (that also included moderate AH), found significantly less hepatorenal syndrome (HRS) in patients treated with PTX[16], while another systematic review found no effect on HRS[15].

Five RCT's compared prednisolone to pentoxifylline (PTX). Two RCT's (n=195) found no difference in survival[42,43]. Two RCT's (n=142), of which one in corticosteroid non-responders, implicated a survival benefit in PTX-treated patients[44,45]. Another RCT (n=121) found improved survival for prednisolone treated patients[46]. Of note, none of these trials exclusively included patients with biopsy-proven sAH.

Five systematic reviews compared prednisolone to PTX. Four found no significant difference in survival between these two therapies[14–16,18]. One systematic review of individual data found a significant survival advantage for prednisolone at 28 days (compared to PTX), but not at 6 months[17].

We can conclude that PTX does not improve survival in patients with sAH, while the effect on HRS is unclear.

Other anti-oxidants

Metadoxine is a precursor of glutathione, but also a selective antagonist of the serotonin receptor 5-HT 2B. One RCT (n=135) examined the addition of metadoxine to PTX or prednisolone[43]. It found that the addition of metadoxine improved 3 month and 6 month survival, possibly caused by a significantly improved alcohol abstinence in the metadoxine-group.

S-adenosyl-methionine (SAME) is a precursor for the synthesis of glutathione. One RCT (n=40) investigated the addition of SAME to prednisolone [47]. Survival at 28 days was not significantly different between the two groups.

Modulation of gut-liver axis

Growing evidence suggests that the gut-liver axis plays a major role in ALD and represents a potential target for therapy [5]. DNA metagenomic sequencing and bacterial rRNA sequencing have revealed severe dysbiosis in ALD [48]. A major mechanism by which gut microbiota influence the development of alcohol-related liver disease is through a leaky intestinal barrier. This permits translocation of viable bacteria and microbial products to the liver, where they induce and promote inflammation, as well as contribute to hepatocyte death and the fibrotic response. For

example, recently it has been shown that microbiota tryptophan metabolism induces aryl hydrocarbon receptor activation and improves alcohol related injury in a murine model of alcohol induced liver damage [49]. In addition to changes in the metabolic function of the intestinal microbiota, gut dysbiosis is associated with changes in bile acid composition and circulation during onset and progression of alcohol-related liver disease[50].

Bovine colostrum has been shown to decrease the level of lipopolysaccharides in the systemic circulation in animal studies. One RCT (n=57) comparing the use of hyperimmune bovine colostrum as adjuvant to corticosteroid therapy showed no improved survival at 180 days (NCT01968382). Another trial (n=174) comparing bovine colostrum with placebo is still ongoing (NCT02473341).

One RCT examined the role of fecal microbiota transfer (FMT) in 30 steroid ineligible patients in comparison with pentoxifylline (NCT 02458079, C. Philips et al. Abstract 1410, Annual Meeting of the AASLD, Boston MA, November 2016). Survival at 3 months was significantly higher in patients treated with FMT. A larger RCT (n=112) from the same research group compared FMT to steroid therapy and completed its enrollment in March 2019 (NCT03091010). The primary outcome measure is survival at 3 months. The data of the first trial are promising, but due to its small size, the results of the second trial will have to be awaited before a correct assessment can be made about the role of FMT in sAH.

Protein malnutrition is present in most of the patients with sAH and is associated with an impaired survival[51]. Two RCT's (n=208) examined the effect of intensive enteral feeding (compared to placebo and prednisolone) but found no effect on survival at 6 months or 1 year[51,52]. A third RCT (n=54), investigating the effect of parenteral amino acid supplementation was also negative[53]. However, adequate nutrition remains a cornerstone of the treatment of patients with sAH, with a target of 35-40 kcal/kg and a daily protein intake of 1.2-1.5 g/kg[3]. The use of enteral feeding, if necessary, is strongly recommended. However, their early removal by patients remains an important issue[3].

One ongoing trial examines the effect of gut decontamination with rifaximin on the infection and survival rate at 90 days, however no results are available up to date and its recruitment status is unknown (NCT02116556).

Boosting liver regeneration

Granulocyte colony stimulating factor (G-CSF) is a glycoprotein that stimulates the bone marrow to produce and release neutrophils and CD34⁺ stem cells in the bloodstream, possibly inducing liver regeneration[54]. Three Asian RCT's (n=153) have investigated the addition of G-CSF to PTX or standard medical treatment. All showed a significant survival advantage in the G-CSF group at 90 days[34,55](A. Sharma, Abstract P0679, United European Gastroenterology Week, October 2017). Another RCT (n=28) compared G-CSF with placebo in corticosteroid non-responsive, biopsy-proven, sAH patients. It found a significantly improved survival at 90-days[56].

Two systematic reviews also found a significantly improved survival at 90 days in sAH patients treated with G-CSF compared to placebo or PTX[54,57].

Four ongoing trials are currently investigating the role of G-CSF in sAH patients. The first trial (n=100, India, survival at 3 months) compares G-CSF to standard medical treatment (NCT03703674). The second (n=126, India, survival at 3 months) compares prednisolone to

G-CSF to combination therapy (NCT04066179). The third trial (n=78, USA, survival at 3 months) compares G-CSF to standard medical treatment (NCT02776059). The last ongoing trial (n=268, South-Korea) investigates the effect of G-CSF in partial responders (survival at 6 months) and null responders (survival at 2 months)[58].

In conclusion, **G-CSF** is a promising therapy that possibly improves 90-day survival in patients with SAH. However, none of the aforementioned data were gathered in a Western population. To note is that an RCT examining G-CSF in ACLF in a Western population found no survival benefit in the sub-analysis of the patients with AH (Engelmann et al, abstract 17, AASLD, November 2019). However, it has been reported that the presence of ACLF in patients with SAH is associated with a detrimental effect on survival[21]. Therefore, additional data are needed before conclusive recommendations can be set for the use of G-CSF in the Western population.

Early liver transplantation

Liver transplantation is used as a rescue-treatment in several etiologies leading to (acute) liver failure[30]. However, until recently liver transplantation in sAH patients was only performed after a period of abstinence (mostly 6 months) in most centers. After the publication of a trial showing a significantly improved survival in highly selected corticosteroid non-responders undergoing an early liver transplantation compared to those not, more centers started with early liver transplantation (ELT)[59].

Two systematic reviews, using mostly retrospective data, found 1) a significantly improved survival of sAH corticosteroid non-responders after ELT (i.e. within the 6 month interval after diagnosis) compared to solely medical treatment; 2) a comparable post-transplant survival after ELT for sAH and transplantation for alcoholic cirrhosis after 6 months abstinence and 3) a comparable rate of alcohol relapse[60,61].

Recently, preliminary results of the Quicktrans study were presented (A. Louvet et al, Abstract 6, AASLD, November 2020). In this prospective, controlled trial, it was shown that corticosteroid non-responders who underwent an ELT (based on a dedicated score using social and addiction parameters) had a 2-year survival of 82.8% versus 28.2% (p<0.001) for non-responders who received only medical treatment. The alcohol relapse rate and heavy drinking relapse were both significantly higher (33.8% and 22.1% respectively) compared to patients who were transplanted for alcoholic cirrhosis (24.7% and 5.4% respectively).

In conclusion, ELT greatly improves the survival of extreme highly selected patients with sAH non-responding to medical treatment. However, even in this highly selected population alcohol relapse is more prevalent and remains a concern. Additional long-term data are needed on the rate of relapse and its consequences on patient and graft survival. In addition, there appears to be a higher risk for aspergillosis after ELT, with 5 out of 26 patients (of which 4 died) developing invasive aspergillosis within two weeks after transplantation in the 2011 trial[59].

Other therapies

Amlodipine, a calcium channel antagonist, has shown a hepatoprotective effect in animal models of ALD[62]. One RCT (n=52) compared amlodipine versus placebo in AH[62]. No difference was found in survival after 28 days in the subanalysis of the patients with sAH (n=29).

DUR-928 (25HC3S) is a sulfated oxysterol that epigenetically modifies gene activity. After promising results in a phase 2a clinical trial examining the effect of DUR-928 in patients with

sAH (n = 19, NCT03432260), a large RCT (n=300) will start in the near future comparing DUR-928 with placebo (NCT04563026).

Omega-5 fatty acid, an agonist of peroxisome proliferator-activated receptor gamma (PPARG), reduces lipid peroxidation. One ongoing trial (n=40) is currently examining the effect of the addition of omega-5 fatty acid to prednisolone on 30-day survival (NCT03732586).

Conclusion and future perspectives

In this review, we investigated the recent and ongoing RCT's concerning the treatment of sAH. In the absence of effective alternatives, corticosteroids, although suboptimal, remain the most applied treatment with the most robust evidence. Its use is associated with a modest survival benefit at 28 days but not after longer follow-up. Furthermore, only a subset of patients (55%) respond to corticosteroid treatment [63]. In addition, corticosteroids cannot be administered to patients with active uncontrolled infection and gastro-intestinal bleeding. Moreover, corticosteroids increase the risk of acquiring an infection in these patients who are already at risk for infection due to their progressive underlying liver disease. Being able to predict which sAH patients will benefit from corticosteroids, preferentially at the time of presentation, could at least alleviate these concerns and is also the subject of ongoing translational research in our center. The combination of corticosteroids with antibiotics to prevent infectious complications is an additional strategy that is currently under investigation.

Of the discussed pharmacological therapies under investigation, granulocyte-colony stimulating factor is the most promising one, possibly improving survival at 3 months. However, additional data in a Western population are needed before a recommendation can be made. Another interesting option is fecal microbiota transfer, however, also in this treatment option further investigation is required.

In highly selected corticosteroid non-responders, ELT is the most promising treatment leading to a significant survival benefit. It is important to emphasize that only a small fraction of patients are eligible for this option based on very strict psychosocial selection criteria. Longer-term results about alcohol relapse after ELT are needed to assess their impact on patient and graft survival.

Because of the suboptimal efficacy of corticosteroids and the liver donor shortage, continued efforts to optimize current treatment options and assess novel therapeutic agents are necessary. One particular challenge in the field is the uniformity in trial design and study patient selection[64]. This should facilitate therapeutic development in (subsets) of sAH patients and comparison between trials. Last, but not least, the outcome of patients with sAH beyond 3 months is primarily determined by the fact whether alcohol abstinence is maintained. Therefore, also additional research on strategies preventing and detecting alcohol relapse is urgently needed.

Acknowledgments

Funding: This work was supported by the Research Foundation of the Flemish Government (FWO) [grant number 1110121N].

References

1. Sarin SK, Sharma S: **Predictors of steroid non-response and new approaches in**

severe alcoholic hepatitis. *Clin Mol Hepatol* 2020, **26**:639–351.

2. Yadav DK, Zhang Q, Bai X, Li E, Liang T: **Liver Transplantation for Alcohol-Related Liver Disease (ARLD): An Update on Controversies and Considerations.** *Can J Gastroenterol Hepatol* 2020, **2020**.
3. Thursz M, Gual A, Lackner C, Mathurin P, Moreno C, Spahr L, Sterneck M, Cortez-Pinto H, Association for the Study of the Liver E: **EASL Clinical Practice Guidelines: Management of alcohol-related liver disease.** *J Hepatol* 2018, **69**:154–181.
4. Seitz HK, Bataller R, Cortez-Pinto H, Gao B, Gual A, Lackner C, Mathurin P, Mueller S, Szabo G, Tsukamoto H: **Alcoholic liver disease.** *Nat Rev Dis Prim* 2018, **4**:1–22.
5. Argemi J, Ventura-Cots M, Rachakonda V, Bataller R: **Alcoholic-related liver disease: pathogenesis, management and future therapeutic developments.** *Rev Esp Enferm Dig* 2020, **112**:869–878.
6. Singal AK, Shah VH: **Current trials and novel therapeutic targets for alcoholic hepatitis.** *J Hepatol* 2019, **70**:305–313.
7. Thursz MR, Richardson P, Allison M, Austin A, Bowers M, Day CP, Downs N, Gleeson D, MacGilchrist A, Grant A, et al.: **Prednisolone or Pentoxifylline for Alcoholic Hepatitis.** *N Engl J Med* 2015, **372**:1619–1628.
8. Louvet A, Mathurin P: **Alcoholic liver disease: Mechanisms of injury and targeted treatment.** *Nat Rev Gastroenterol Hepatol* 2015, **12**:231–242.
9. Carithers RL, Herlong F, Diehl AM, Shaw EW, Combes B, Fallon HJ, Maddrey WC: **Methylprednisolone therapy in patients with severe alcoholic hepatitis. A randomized multicenter trial.** *Ann Intern Med* 1989, **110**:685–690.
10. Mathurin P, Duchatelle V, Ramond MJ, Degott C, Bedossa P, Erlinger S, Benhamou JP, Chaput JC, Rueff B, Poynard T: **Survival and prognostic factors in patients with severe alcoholic hepatitis treated with prednisolone.** *Gastroenterology* 1996, **110**:1847–1853.
11. Depew W, Boyer T, Omata M, Redeker A, Reynolds T: **Double-blind controlled trial of prednisolone therapy in patients with severe acute alcoholic hepatitis and spontaneous encephalopathy - PubMed.** *Gastroenterology* 1980, **78**:524–529.
12. Mandal S, Mani S, Chatterjee S, Bhattacharya K, Bhattacharya R, Sau D, Mondal S, Sil K, De B: **Pentoxifylline plus prednisolone versus pentoxifylline only for severe alcoholic hepatitis: A randomized controlled clinical trial.** *Ann Med Health Sci Res* 2014, **4**:810.
13. Theodossi A, Eddleston ALWF, Williams R: **Controlled trial of methylprednisolone therapy in severe acute alcoholic hepatitis.** *Gut* 1982, **23**:75–79.
14. Singh S, Murad MH, Chandar AK, Bongiorno CM, Singal AK, Atkinson SR, Thursz MR, Loomba R, Shah VH: **Comparative Effectiveness of Pharmacological Interventions for Severe Alcoholic Hepatitis: A Systematic Review and Network Meta-analysis.** *Gastroenterology* 2015, **149**:958-970.e12.
15. Njei B, Do A, Mccarty TR, Fortune BE: **Corticosteroids versus pentoxifylline for severe alcoholic hepatitis.** *J Clin Gastroenterol* 2016, **50**:871–881.
16. Lee YS, Kim HJ, Kim JH, Yoo YJ, Kim TS, Kang SH, Suh SJ, Joo MK, Jung YK, Lee BJ, et al.: **Treatment of Severe Alcoholic Hepatitis with Corticosteroid, Pentoxifylline, or Dual Therapy.** *J Clin Gastroenterol* 2017, **51**:364–377.
17. Louvet A, Thursz MR, Kim DJ, Labreuche J, Atkinson SR, Sidhu SS, O’Grady JG, Akriviadis E, Sinakos E, Carithers RL, et al.: **Corticosteroids Reduce Risk of Death Within 28 Days for Patients With Severe Alcoholic Hepatitis, Compared With Pentoxifylline or Placebo—a Meta-analysis of Individual Data From Controlled Trials.** *Gastroenterology* 2018, **155**:458-468.e8.

18. Buzzetti E, Kalafateli M, Thorburn D, Davidson BR, Thiele M, Gluud LL, Del Giovane C, Askgaard G, Krag A, Tsochatzis E, et al.: **Pharmacological interventions for alcoholic liver disease (alcohol-related liver disease): An attempted network meta-analysis.** *Cochrane Database Syst Rev* 2017, **2017**.
19. Pavlov CS, Varganova DL, Casazza G, Tsochatzis E, Nikolova D, Gluud C: **Glucocorticosteroids for people with alcoholic hepatitis.** *Cochrane Database Syst Rev* 2019, doi:10.1002/14651858.cd001511.pub4.
20. Avila MA, Dufour JF, Gerbes AL, Zoulim F, Bataller R, Burra P, Cortez-Pinto H, Gao B, Gilmore I, Mathurin P, et al.: **Recent advances in alcohol-related liver disease (ALD): Summary of a Gut round table meeting.** *Gut* 2020, **69**:764–780.
21. Sersté T, Cornillie A, Njimi H, Pavesi M, Arroyo V, Putignano A, Weichselbaum L, Deltenre P, Degré D, Trépo E, et al.: **The prognostic value of acute-on-chronic liver failure during the course of severe alcoholic hepatitis.** *J Hepatol* 2018, **69**:318–324.
22. Karakike E, Moreno C, Gustot T: **Infections in severe alcoholic hepatitis.** *Ann Gastroenterol* 2017, **30**:152–160.
23. Thompson J, Jones N, Al-Khafaji A, Malik S, Reich D, Munoz S, MacNicholas R, Hassanein T, Teperman L, Stein L, et al.: **Extracorporeal cellular therapy (ELAD) in severe alcoholic hepatitis: A multinational, prospective, controlled, randomized trial.** *Liver Transplant* 2018, **24**:380–393.
24. Subedi S, Gong Y, Chen Y, Shi Y: **Infliximab and biosimilar infliximab in psoriasis: Efficacy, loss of efficacy, and adverse events.** *Drug Des Devel Ther* 2019, **13**:2491–2502.
25. Naveau S, Chollet-Martin S, Dharancy S, Mathurin P, Jouet P, Piquet MA, Davion T, Oberti F, Broët P, Emilie D: **A Double-Blind Randomized Controlled Trial of Infliximab Associated with Prednisolone in Acute Alcoholic Hepatitis.** *Hepatology* 2004, **39**:1390–1397.
26. Majeed MB, Agrawal R, Attar BM, Abu Omar Y, Gandhi SR: **Safety and Efficacy of Infliximab in Severe Alcoholic Hepatitis: A Systematic Review.** *Cureus* 2019, **11**.
27. Dasarathy S, Mitchell MC, Barton B, McClain CJ, Szabo G, Nagy LE, Radaeva S, McCullough AJ: **Design and rationale of a multicenter defeat alcoholic steatohepatitis trial: (DASH) randomized clinical trial to treat alcohol-associated hepatitis.** *Contemp Clin Trials* 2020, **96**.
28. Schenk KM, Reuss JE, Choquette K, Spira AI: **A review of canakinumab and its therapeutic potential for non-small cell lung cancer.** *Anticancer Drugs* 2019, **30**:879–885.
29. Harrison SA, Wong VWS, Okanoue T, Bzowej N, Vuppalanchi R, Younes Z, Kohli A, Sarin S, Caldwell SH, Alkhouri N, et al.: **Selonsertib for patients with bridging fibrosis or compensated cirrhosis due to NASH: Results from randomized phase III STELLAR trials.** *J Hepatol* 2020, **73**:26–39.
30. Khan R, Koppe S: **Modern Management of Acute Liver Failure.** *Gastroenterol Clin North Am* 2018, **47**:313–326.
31. Moreno C, Langlet P, Hittelet A, Lasser L, Degré D, Evrard S, Colle I, Lemmers A, Devière J, Le Moine O: **Enteral nutrition with or without N-acetylcysteine in the treatment of severe acute alcoholic hepatitis: A randomized multicenter controlled trial.** *J Hepatol* 2010, **53**:1117–1122.
32. Stewart S, Prince M, Bassendine M, Hudson M, James O, Jones D, Record C, Day CP: **A randomized trial of antioxidant therapy alone or with corticosteroids in acute alcoholic hepatitis.** *J Hepatol* 2007, **47**:277–283.
33. Phillips M, Curtis H, Portmann B, Donaldson N, Bomford A, O'Grady J: **Antioxidants versus corticosteroids in the treatment of severe alcoholic hepatitis - A**

- randomised clinical trial. *J Hepatol* 2006, **44**:784–790.
34. Singh V, Keisham A, Bhalla A, Sharma N, Agarwal R, Sharma R, Singh A: **Efficacy of Granulocyte Colony-Stimulating Factor and N-Acetylcysteine Therapies in Patients With Severe Alcoholic Hepatitis.** *Clin Gastroenterol Hepatol* 2018, **16**:1650-1656.e2.
 35. Nguyen-Khac E, Thevenot T, Piquet M-A, Benferhat S, Gorla O, Chatelain D, Tramier B, Dewaele F, Ghrib S, Rudler M, et al.: **Glucocorticoids plus N -Acetylcysteine in Severe Alcoholic Hepatitis .** *N Engl J Med* 2011, **365**:1781–1789.
 36. Sidhu SS, Goyal O, Singla M, Bhatia KL, Chhina SR, Sood A: **Pentoxifylline in severe alcoholic hepatitis: a prospective, randomised trial.** *J Assoc Physicians India* 2012, **60**:20–22.
 37. Akriviadis E, Botla R, Briggs W, Han S, Reynolds T, Shakil O: **Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: A double-blind, placebo-controlled trial.** *Gastroenterology* 2000, **119**:1637–1648.
 38. Sidhu SS, Goyal O, Singla P, Gupta D, Sood A, Chhina RS, Soni RK: **Corticosteroid plus pentoxifylline is not better than corticosteroid alone for improving survival in severe alcoholic hepatitis (COPE Trial).** *Dig Dis Sci* 2012, **57**:1664–1671.
 39. Lebrec D, Thabut D, Oberti F, Perarnau JM, Condat B, Barraud H, Saliba F, Carbonell N, Renard P, Ramond MJ, et al.: **Pentoxifylline Does Not Decrease Short-term Mortality but Does Reduce Complications in Patients With Advanced Cirrhosis.** *Gastroenterology* 2010, **138**.
 40. Mathurin P, Louvet A, Duhamel A, Nahon P, Carbonell N, Boursier J, Anty R, Diaz E, Thabut D, Moirand R, et al.: **Prednisolone with vs without pentoxifylline and survival of patients with severe alcoholic hepatitis: A randomized clinical trial.** *JAMA - J Am Med Assoc* 2013, **310**:1033–1041.
 41. Louvet A, Thursz MR, Kim DJ, Labreuche J, Atkinson SR, Sidhu SS, O'Grady JG, Akriviadis E, Sinakos E, Carithers RL, et al.: **Corticosteroids Reduce Risk of Death Within 28 Days for Patients With Severe Alcoholic Hepatitis, Compared With Pentoxifylline or Placebo—a Meta-analysis of Individual Data From Controlled Trials.** *Gastroenterology* 2018, **155**:458-468.e8.
 42. García JRG, Hernández GS, López AM, Barrera CIE, Vargas LS: **Pentoxifilina versus esteroide en la sobrevivencia a corto plazo en hepatitis aguda alcohólica severa.** *Med Interna México* 2012, **28**:227–233.
 43. Higuera-De La Tijera F, Servín-Caamaño AI, Serralde-Zúñiga AE, Cruz-Herrera J, Pérez-Torres E, Abdo-Francis JM, Salas-Gordillo F, Pérez-Hernández JL: **Metadoxine improves the three- and six-month survival rates in patients with severe alcoholic hepatitis.** *World J Gastroenterol* 2015, **21**:4975–4985.
 44. Arredondo-Andrade SA, Elizalde-Barrera CI, Vargas-Ayala G: **Hepatitis alcohólica grave: pentoxifilina como tratamiento de rescate en pacientes que no responden a esteroides.** *Med Int Méx* 2014, **30**:32–42.
 45. De BK, Gangopadhyay S, Dutta D, Baksi S Das, Pani A, Ghosh P: **Pentoxifylline versus prednisolone for severe alcoholic hepatitis: A randomized controlled trial.** *World J Gastroenterol* 2009, **15**:1613–1619.
 46. Park SH, Kim DJ, Kim YS, Yim HJ, Tak WY, Lee HJ, Sohn JH, Yoon Ki Tae, Kim IH, Kim HS, et al.: **Pentoxifylline vs. corticosteroid to treat severe alcoholic hepatitis: a randomised, non-inferiority, open trial - PubMed.** *J Hepatol* 2014, **61**:792–798.
 47. Tkachenko P, Maevskaya M, Pavlov A, Komkova I, Pavlov C, Ivashkin V: **Prednisolone plus S-adenosil-l-methionine in severe alcoholic hepatitis.** *Hepatol Int* 2016, **10**:983–987.

48. Szabo G: **Gut-liver axis in alcoholic liver disease.** *Gastroenterology* 2015, **148**:30–36.
49. Wrzosek L, Ciocan D, Hugot C, Spatz M, Dupeux M, Houron C, Lievin-Le Moal V, Puchois V, Ferrere G, Trainel N, et al.: **Microbiota tryptophan metabolism induces aryl hydrocarbon receptor activation and improves alcohol-induced liver injury.** *Gut* 2020, doi:10.1136/gutjnl-2020-321565.
50. Sarin SK, Pande A, Schnabl B: **Microbiome as a therapeutic target in alcohol-related liver disease.** *J Hepatol* 2019, **70**:260–272.
51. Moreno C, Deltenre P, Senterre C, Louvet A, Gustot T, Bastens B, Hittelet A, Piquet MA, Laleman W, Orlent H, et al.: **Intensive Enteral Nutrition Is Ineffective for Patients with Severe Alcoholic Hepatitis Treated with Corticosteroids.** *Gastroenterology* 2016, **150**:903-910.e8.
52. Cabré E, Rodríguez-Iglesias P, Caballería J, Quer JC, Sánchez-Lombrana JL, Parés A, Papo M, Planas R, Gassull MA: **Short- and long-term outcome of severe alcohol-induced hepatitis treated with steroids or enteral nutrition: A multicenter randomized trial.** *Hepatology* 2000, **32**:36–42.
53. Mezey E, Caballeria J, Mitchell MC, Parés A, Herlong HF, Rodés J: **Effect of parenteral amino acid supplementation on short-term and long-term outcomes in severe alcoholic hepatitis: a randomized controlled trial - PubMed.** *Hepatology* 1991, **14**:1090–1096.
54. Marot A, Singal AK, Moreno C, Deltenre P: **Granulocyte colony-stimulating factor for alcoholic hepatitis: A systematic review and meta-analysis of randomised controlled trials.** *JHEP Reports* 2020, **2**:100139.
55. Singh V, Sharma AK, Narasimhan RL, Bhalla A, Sharma N, Sharma R: **Granulocyte colony-stimulating factor in severe alcoholic hepatitis: A randomized pilot study.** *Am J Gastroenterol* 2014, **109**:1417–1423.
56. Shashtry SM, Sharma MK, Shashtry V, Pande A, Sarin SK: **Efficacy of Granulocyte Colony-stimulating Factor in the Management of Steroid-Nonresponsive Severe Alcoholic Hepatitis: A Double-Blind Randomized Controlled Trial.** *Hepatology* 2019, **70**:802–811.
57. Baig M, Walayat S, Dhillon S, Puli S: **Efficacy of Granulocyte Colony Stimulating Factor in Severe Alcoholic Hepatitis: A Systematic Review and Meta-Analysis.** *Cureus* 2020, **12**.
58. Cho Y, Park YS, Kim HY, Kim W, Lee HJ, Kim DJ: **Efficacy of granulocyte colony stimulating factor in patients with severe alcoholic hepatitis with partial or null response to steroid (GRACIAH trial): Study protocol for a randomized controlled trial 11.** *Trials* 2018, **19**.
59. Mathurin P, Moreno C, Samuel D, Dumortier J, Salleron J, Durand F, Castel H, Duhamel A, Pageaux G-P, Leroy V, et al.: **Early Liver Transplantation for Severe Alcoholic Hepatitis.** *N Engl J Med* 2011, **365**:1790–1800.
60. Al-Saeedi M, Barout MH, Probst P, Khajeh E, Weiss KH, Diener MK, Mehrabi A: **Meta-analysis of patient survival and rate of alcohol relapse in liver-transplanted patients for acute alcoholic hepatitis.** *Langenbeck's Arch Surg* 2018, **403**:825–836.
61. Marot A, Dubois M, Trépo E, Moreno C, Deltenre P: **Liver transplantation for alcoholic hepatitis: A systematic review with meta-analysis.** *PLoS One* 2018, **13**:e0190823.
62. Bird GL a., Prach AT, McMahon AD, Forrest JA h., Mills PR, Danesh BJ: **Randomised controlled double-blind trial of the calcium channel antagonist amlodipine in the treatment of acute alcoholic hepatitis.** *J Hepatol* 1998, **28**:194–198.

- 590 63. Louvet A, Naveau S, Abdelnour M, Ramond M-J, Diaz E, Fartoux L, Dharancy S,
591 Texier F, Hollebecque A, Serfaty L, et al.: **The Lille model: a new tool for**
592 **therapeutic strategy in patients with severe alcoholic hepatitis treated with**
593 **steroids.** *Hepatology* 2007, **45**:1348–54.
- 594 64. Mathurin P, Thursz M: **Endpoints and patient stratification in clinical trials for**
595 **alcoholic hepatitis.** *J Hepatol* 2019, **70**:314–318.
- 596
- 597

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Figure 1. Therapies currently investigated in severe alcoholic hepatitis in RCT's

Table 2. Ongoing RCT's in severe alcoholic hepatitis

Treatment	Study design	n	Primary endpoint	Results/status (last update)	Country	ID
Anti-inflammatory therapies						
Amoxicillin-clavulanic acid	Amoxicillin-clavulanic acid (1g/125mg 3/d, 30d) + pred vs pred	Est: 280	OS 60d	Active, not recruiting (2019)	France	NCT02281929
Anakinra + Zinc	Anakinra (100mg, 14d) + Zinc (220mg, 90d) + pred vs pred	Est: 258	OS 90d	Recruiting (2020)	USA	NCT04072822
Canakinumab	Canakinumab 3mg/kg at d1 +- d28 vs placebo	56	Histological improvement 28d	Enrollment completed (2020)	United Kingdom	NCT03775109 EudraCT2017-003724-79
Ciprofloxacin	Ciprofloxacin (2x500mg/d) vs placebo	22	OS 28d OS 3m OS 6m	Temporarily halted (2017)	Finland	NCT02326103 EudraCT2013-003727-11
Methyl-prednisolone	Methyl-prednisolone (32mg, 28d) vs placebo	Est: 140	OS 90d	Ongoing (2017)	Belgium, France	NCT03160651 EudraCT2016-005136-16
Anti-oxidants						
NAC	NAC + SMT vs SMT	Est: 170	Survival	Recruiting (2020)	China	ChiCTR 2000030583
NAC	NAC (5d) + pred vs pred	Est: 42	Monocyt oxidative burst (24h)	Recruiting (2020)	United Kingdom	NCT03069300
Modulation of gut-liver axis						
Bovine colostrum	Bovine colostrum vs placebo	Est: 174	OS 3m	Recruiting (2020)	India	NCT02473341
FMT	FMT vs pred	112	OS 3m	Enrollment completed (2020)	India	NCT03091010
Rifaximin	Rifaximin (1200mg/d, 90d) + pred, vs pred	29	Bacterial infections 90d	Unknown (2016)	Spain	NCT02116556
Boosting liver regeneration						
G-CSF	Null responder: G-CSF (5 µg/kg) vs placebo Partial responder: G-CSF (5 µg/kg) + pred vs pred	Est: 268	OS 2m (null responder) OS 6m (partial responder)	Recruiting (2020)	Republic of Korea	NCT02442180
G-CSF	G-CSF (5 µg/kg 2/d, 5d) vs placebo	Est: 100	OS 3m	Unknown (2018)	India	NCT03703674
G-CSF	G-CSF (300 µg, 7d) + pred vs G-CSF vs pred	Est: 126	OS 90d	Recruiting (2019)	India	NCT04066179
Pegfilgrastim	Pegfilgrastim 6mg + SMT vs SMT	Est: 78	OS 90d	Recruiting (2020)	USA	NCT02776059
Other therapies						
DUR-928	DUR-928 (30mg) vs DUR-928 (90mg) vs placebo	Est: 300	OS 90d	Not yet recruiting (2020)	USA	NCT04563026
Omega-5 fatty acid	Omega-5 + pred vs pred	Est: 40	OS 30d	Recruiting (2020)	Mexico	NCT03732586

FMT = fecal microbiota transfer; G-CSF = granulocyte colony stimulating factor; NAC = N-acetylcysteine; OS = overall survival; Pred = prednisolone; SMT = standard medical treatment; USA: United States of America

Table 1. RCT's completed since 01/2018

Treatment	Study design	n	Results	All biopsy-proven	Country	Reference
Anti-inflammatory therapies						
Anakinra + PTX + Zinc	Anakinra (100mg/d, 14d) + PTX (3x400mg/d, 28d) + Zinc (220mg, 180d) vs pred	103	Negative OS 30d: HR 0.91, p 0.85 OS 90d: HR 0.69, p 0.28 OS 180d: HR 0.69, p 0.26	No	USA	Dasarathy et al.[26]
ELAD	ELAD vs SMT	151	Negative OS 91d (HR 0.91, p 0.76)	No	Austria, Germany, Ireland, Spain, UK, USA	NCT02612428
Selonsertib	Selonsertib (18mg/d) + pred vs pred	99	Negative OS 28d: HR 1.06, p 1.00 OS 8w: HR 3.34, p 0.06	yes	Austria, Belgium, France, Switzerland , UK, USA	NCT02854631
Modulation of gut-liver axis						
Bovine colostrum (IMM 124-E)	IMM 124-E (2400mg/d) vs IMM 124-E (4800mg/d) vs placebo	57	Negative Mortality at 180d: 10% in placebo group versus 27,8% (2400mg/d) and 10,5% (4800mg/d).	No	USA	NCT01968382
Boosting liver regeneration						
G-CSF & NAC	Group A: G-CSF (2x5 µg/kg/d, 5d) + NAC (5d) + PTX 3x400mg, 28d) vs Group B: G-CSF + PTX vs Group C: PTX	57	Positive OS 90d A vs C: HR 0.45, p 0.37 OS 90d B vs C: HR 0.16, p 0.0001 OS 90d A vs B: HR 2.84, p 0.11	No	India	Singh et al.[33]
G-CSF	G-CSF (5 µg/kg 12 doses/4w) vs placebo in CNS	28	Positive OS 28d (HR 0.75, p 0.69) OS 90d (HR 0.50, p 0.04)	Yes	India	Shasthry et al.[52]
Early Liver Transplantation						
ELT	Group A: ELT in CNS vs Group B: LT in AC vs Group C: SMT in CNS	284	Mixed OS (PT) 2y A vs B: 89.7% vs 88.1%, p NS OS 2y A vs C: 82.8% vs 28.2%, p<0.001 AR 2y A vs B: 33.8% vs 24.7%, non-inferiority B not proven	Yes	Belgium, France	NCT01756794*

AC= alcoholic cirrhosis patients, more than 6 months abstinent; AR= alcohol relapse; CNS=corticosteroid non-responders; ELAD= extracorporeal liver assist device; ELT:early liver transplantation; G-CSF=granulocyte colony-stimulating factor; LT=liver transplantation; NAC=n-acetylcysteine; OS=overall survival; PTX=pentoxifylline; Pred=prednisolone; SMT=standard medical treatment; PT= post-transplant; UK= United Kingdom; USA=United States of America

* Not a RCT but a prospective, controlled trial.

[Click here to access/download](#)

Supplementary Material

Review - COPHAR - Supplementary 1.docx

[Click here to access/download](#)

Supplementary Material

Review - COPHAR - Supplementary 2.docx

[Click here to access/download](#)

Annotated references

Review - COPHAR - Annotated referencesv2.docx