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Treatment of severe alcoholic hepatitis: a systematic review

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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-a) 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).

146 Canakinumab is a human immunoglobulin blocking interleukin-1beta[28]. An ongoing RCT
147 (n=56) is comparing Canakinumab to placebo, with survival at 90 days being a secondary
148 outcome measure (NCT03775109). Enrollment was completed in November 2020 and the
149 study is estimated to be finished in January 2021.
150
151 One RCT compared emricasan, a pan-caspase inhibitor, to placebo in patients with sAH and a
152 contraindication for corticosteroids. It was stopped prematurely, after including 5 patients,
153 due to concern for high systemic drug levels (NCT01912404).
154
155 Selonsertib is an inhibitor of apoptosis signal-regulating kinase 1 (ASK1), which mediates pro-
156 inflammatory and pro-fibrotic changes in the liver[29]. One RCT investigated the addition of
157 selonsertib to prednisolone in 99 patients with biopsy-proven sAH (NCT02854631, P. Mathurin
158 et al. Abstract 13, Annual Meeting of the AASLD, San Francisco, November 2018). No
159 differences were seen between both groups for infection-rate and survival at 28 days or 8 weeks.
160

Anti-oxidants

162
163 There are several pathways in the pathology of sAH that contribute to the generation of reactive
164 oxygen species and to the development of oxidative stress. These pathways include apoptosis
165 and necrosis of cells, inflammatory signaling and recruitment of inflammatory cells,
166 mitochondrial dysfunction and metabolism of alcohol[8].
167

N-acetylcysteine

169
170 N-acetylcysteine (NAC) is an antioxidant administered to patients with acute liver failure [30],
171 with its thiol group being able to reduce levels of free radicals.
172 One RCT (n=52) compared NAC versus placebo in biopsy-proven sAH. This study reported
173 no survival benefit at 1 or 6 months[31]. A second RCT (n=70) applied NAC in combination
174 with a cocktail of anti-oxidants compared to a placebo cohort. The obtained results did not show
175 any survival advantage after 6 months[32]. A third RCT (n=101) compared prednisolone versus
176 a combination of NAC with a cocktail of anti-oxidants and found a significantly higher survival
177 in the prednisolone treated group at 28 days[33]. No difference was found at 1 year follow-up.
178 Two RCT's (n=59) examined the addition of NAC to PTX and G-CSF respectively, however
179 both studies showed no survival benefit (B. Patel, abstract L09, 53rd Annual Conference of the
180 Indian Society of Gastroenterology, November 2012)[34]. A last RCT (n=174), with biopsy-
181 proven sAH, examined the addition of NAC to prednisolone compared with prednisolone
182 monotherapy and found a significantly improved survival in the NAC-prednisolone group at 28
183 days (but not at 3 months or 6 months). This result was associated with a lower infection rate
184 and reduced occurrence of hepatorenal syndrome [35].
185 There are two ongoing RCT's examining the role of NAC in sAH. The first (n=170) study is
186 assessing the effect of the addition of NAC to standard of care on the survival at 6 months
187 (ChiCTR2000030583). The other trial (n=42) is evaluating the effect of the addition of NAC
188 to prednisolone on survival at 28 and 90 days. (NCT03069300).
189 In conclusion, although some studies demonstrated efficacy in aforementioned trials, there is
190 currently insufficient evidence to conclude that NAC improves survival in patients with sAH.
191 The results of the 2 ongoing trials are awaited.
192

Pentoxyfilline

194

Pentoxifilline (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 pentoxifilline (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 serotonine 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 pentoxyfilline (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

293   G-CSF to combination therapy (NCT04066179). The third trial (n=78, USA, survival at 3
294   months) compares G-CSF to standard medical treatment (NCT02776059). The last ongoing
295   trial (n=268, South-Korea) investigates the effect of G-CSF in partial responders (survival at 6
296   months) and null responders (survival at 2 months)[58].
297   In conclusion, G-CSF is a promising therapy that possibly improves 90-day survival in patients
298   with SAH. However, none of the aforementioned data were gathered in a Western population.
299   To note is that an RCT examining G-CSF in ACLF in a Western population found no survival
300   benefit in the sub-analysis of the patients with AH (Engelmann et al, abstract 17, AASLD,
301   November 2019). However, it has been reported that the presence of ACLF in patients with
302   SAH is associated with a detrimental effect on survival[21]. Therefore, additional data are
303   needed before conclusive recommendations can be set for the use of G-CSF in the Western
304   population.
305

306   ## Early liver transplantation

307

308   Liver transplantation is used as a rescue-treatment in several etiologies leading to (acute) liver
309   failure[30]. However, until recently liver transplantation in sAH patients was only performed
310   after a period of abstinence (mostly 6 months) in most centers. After the publication of a trial
311   showing a significantly improved survival in highly selected corticosteroid non-responders
312   undergoing an early liver transplantation compared to those not, more centers started with early
313   liver transplantation (ELT)[59].
314   Two systematic reviews, using mostly retrospective data, found 1) a significantly improved
315   survival of sAH corticosteroid non-responders after ELT (i.e. within the 6 month interval after
316   diagnosis) compared to solely medical treatment; 2) a comparable post-transplant survival after
317   ELT for sAH and transplantation for alcoholic cirrhosis after 6 months abstinence and 3) a
318   comparable rate of alcohol relapse[60,61].
319   Recently, preliminary results of the Quicktrans study were presented (A. Louvet et al, Abstract
320   6, AASLD, November 2020). In this prospective, controlled trial, it was shown that
321   corticosteroid non-responders who underwent an ELT (based on a dedicated score using social
322   and addiction parameters) had a 2-year survival of 82.8% versus 28.2% (p<0.001) for non-
323   responders who received only medical treatment. The alcohol relapse rate and heavy drinking
324   relapse were both significantly higher (33.8% and 22.1% respectively) compared to patients
325   who were transplanted for alcoholic cirrhosis (24.7% and 5.4% respectively).
326   In conclusion, ELT greatly improves the survival of extreme highly selected patients with sAH
327   non-responding to medical treatment. However, even in this highly selected population alcohol
328   relapse is more prevalent and remains a concern. Additional long-term data are needed on the
329   rate of relapse and its consequences on patient and graft survival. In addition, there appears to
330   be a higher risk for aspergillosis after ELT, with 5 out of 26 patients (of which 4 died)
331   developing invasive aspergillosis within two weeks after transplantation in the 2011 trial[59].
332

333   ## Other therapies

334

335   Amlodipine, a calcium channel antagonist, has shown a hepatoprotective effect in animal
336   models of ALD[62]. One RCT (n=52) compared amlodipine versus placebo in AH[62]. No
337   difference was found in survival after 28 days in the subanalysis of the patients with sAH
338   (n=29).
339

340   DUR-928 (25HC3S) is a sulfated oxysterol that epigenetically modifies gene activity. After
341   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

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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

Anti-inflammatory therapies
- Methylprednisolone
- Canakinumab

Other therapies
- DUR-928

LIVER

Boosting liver regeneration
- Granulocyte colony stimulating factor
- Pegfiltrastim

Anti-oxidants
- N-acetylcysteïne

Anti-inflammatory therapies
- Amoxicilline-clavulanic acid
- Anakinra + Zinc
- Ciprofloxacin

Other therapies
- Omega-5 fatty acid

PORTAL VEIN

INTESTINAL BARRIER

GUT

LUMEN

Modulation of gut-liver axis
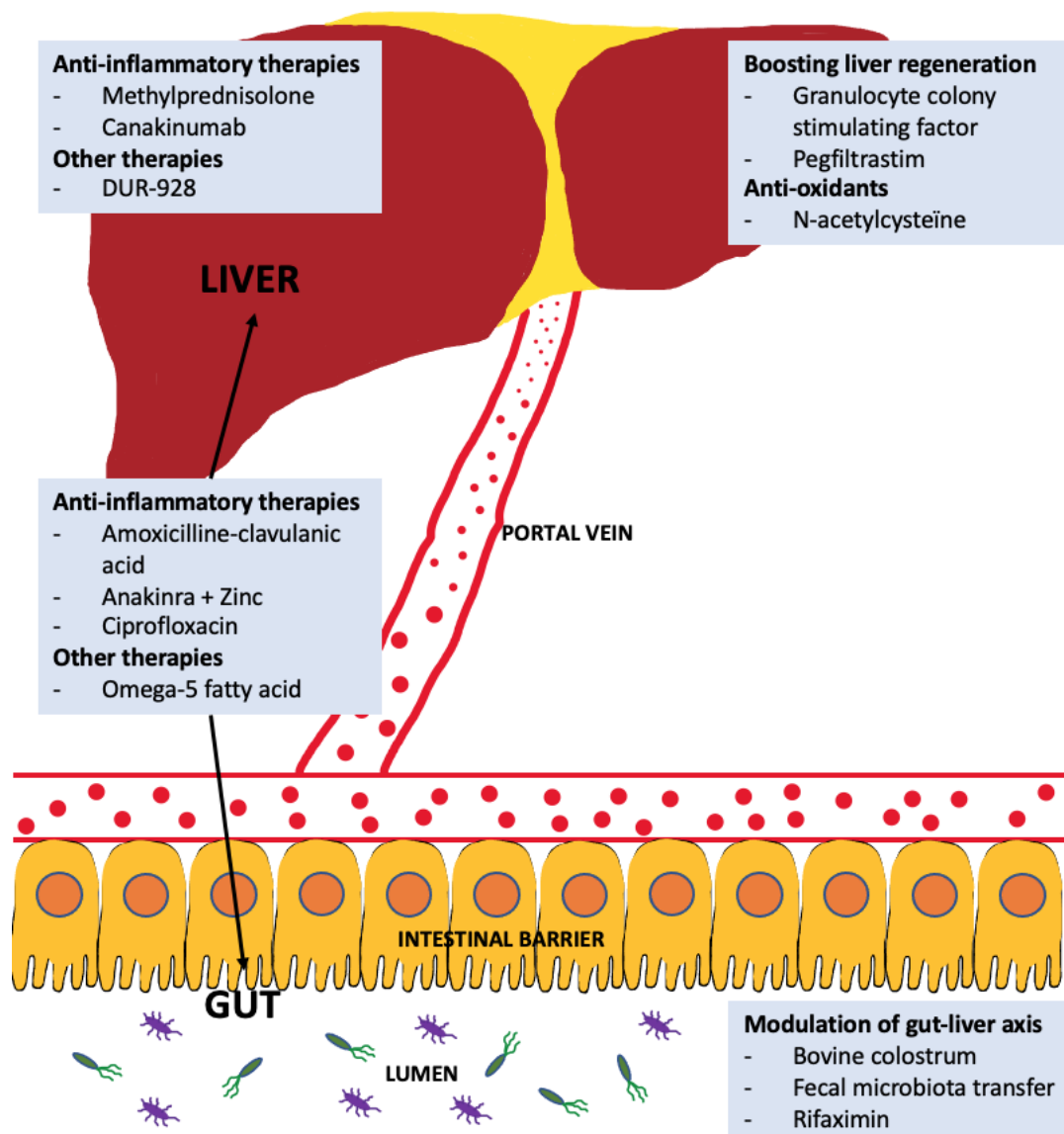- Bovine colostrum
- Fecal microbiota transfer
- Rifaximin

Table 2

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
Pegfiltrastim	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	0S 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=pentoxyfilline; Pred=prednisolone; SMT=standard medical treatment; PT= post-transplant; UK= United Kingdom; USA=United Stated of America
* Not a RCT but a prospective, controlled trial.

Highlights

- Severe alcoholic hepatitis has a high short-term mortality of 20-50%
- Meta-analytic analyses show that corticosteroids are associated with an improved survival at 28 days, but not beyond this period
- Due to lack of effective and safer alternatives, corticosteroids remain the first choice of treatment
- Granulocyte colony stimulating factor might improve 90-day survival, but this observation needs confirmation in Western populations
- Early liver transplantation (ELT) greatly improves survival in highly selected patients with severe alcoholic hepatitis patients who failed to respond to corticosteroids, but longer-term data after ELT are needed
- Predicting corticosteroid response, uniformity in clinical trial design and preventing alcohol relapse are the current unmet needs in the field of severe alcoholic hepatitis

COPHAR

Leuven, June 9, 2021

Dear Editor,

We thank the reviewers for their positive and constructive comments on the manuscript: *"Treatment of severe alcoholic hepatitis: a systematic review"* We have adapted the manuscript according to the comments. Our responses are given in a point-by-point manner below. We hope that the manuscript in its current form is suitable for publication in *Current Opinion in Pharmacology.*

Sincerely,

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1. When discussing infliximab and other anti-inflammatory therapies, please provide some background and references about the role of IL-1, IL-1ß and TNFα in severe alcoholic hepatitis and in the involvement of liver tissue damage.
   Added, cfr. line number 62-68

2. Similarly, when discussing approaches for the modulation of gut-liver axis, please provide a short background on the role of microbiome in severe alcoholic hepatitis. In this regard, please see the work of Wrzosek et al. showing that microbiota tryptophan metabolism induces aryl hydrocarbon receptor activation and improves alcohol related injury in a murine model of alcohol induced liver damage (PMID 33004548).
   Added, cfr. line number 238-245. Also a short background was provided for the anti-oxidants section, cfr. line number 163-166.

3. I would suggest the Authors provide a figure/cartoon representing the different categories of treatments/therapeutic options under evaluation in clinical trials.
   Figure added, see figure 1

4. Paragraph on 'boosting liver regeneration': "In conclusion, G-SCF…' please correct the spelling.
   Changed, line number 294.

5. Table 1, selonsertib row: Please correct 'Switserland' spelling.
   Changed, cfr table 1v2.

Note: All changes are marked in yellow in the manuscript.

Supplementary Figure 1

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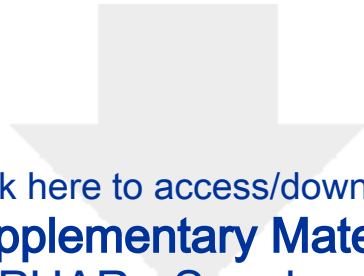
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