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Past, Present and Future Therapies for Alcohol-Associated Hepatitis

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Abstract

Purpose: Alcohol-associated hepatitis (AH) is a unique presentation of cholestatic steatohepatitis with liver dysfunction and malaise preceded by heavy alcohol intake. While it exists on a spectrum, in its most severe form 28-day mortality approaches 50%. Clinical trials of therapeutic interventions over the last 50 years have yielded few durable therapies, none of which convey benefit beyond the short term.

Methods: A qualitative systematic review was performed via searches of PubMed, International Clinical Trials Registry Platform and ClinicalTrials.gov for therapeutic interventions for AH.

Findings: Prior to 2005, clinical trial results for AH were identified within PubMed. From 2005-present, trials were well catalogued within online registries and included information regarding trial status (e.g. complete, terminated, actively enrolling). Most clinical trials for AH have utilized existing medications broadly targeting pathogenic themes of AH (inflammation, cell death, etc.) in an off-label manner. The trend of initially promising pilot studies answered by larger trials demonstrating lack of efficacy or safety signals have ended the hopes of many new therapeutics. The emergence of theragnostics to identify patients who may benefit from existing therapies and trials of agents with novel mechanisms of action, including epigenetic modifications and hyaluronic acid signaling, targeted to AH pathogenesis are currently under investigation. Implications: This review of AH treatments details the historical interventions and clinical trials that have led to the current treatment algorithm and active studies shaping the therapeutic pipeline for AH.

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Author contributions:

SC: writing - original draft, review and editing

LLJ: conceptualization, data curation, writing - original draft, review and editing

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Keywords

Clinical trials; corticosteroids; alcoholic hepatitis

Introduction:

While Mallory provided the first histopathology description of AH in 1911 [1], in the 1938 British Medical Journal article “The Physical Basis of Biliousness” Sir Arthur Hurst MD coined the phrase *alcoholic hepatosis* to describe a man’s symptoms “the morning after the night before” a bout of heavy alcohol drinking [2]. This passage appears to be one of the first to describe the severe, acute presentation of AH however there were no recommendations for treating the patient. Despite its rising prevalence, when compared to other diseases with high mortality such as cancer, little therapeutic progress has been made in the treatment of AH. For perspective, since 1970 over 130 new therapeutics have been Food and Drug Administration (FDA) approved for treating malignancies [3]. Over the same time frame, there have been no FDA approvals for AH, per se, but rather treatment algorithms have been developed using repurposed medications. Since 1979, corticosteroids have remained at the forefront of AH therapies yet show only modest improvement in one month survival [4, 5]. Dozens of historical clinical trials in patients with AH have shown no survival benefit or have proven non-superior to corticosteroids. Many of these trials were performed in an era when clinical trials were less rigorous. For historical vitamin and supplement trials, the quality, purity and sourcing of study drug can often not be verified. Additionally, some historical trials provide scant details of informed consent, blinding or randomization. Few included females, perhaps due to an era in which the FDA restricted females of childbearing age from participating in trials [6]. Patient selection requiring liver biopsy for the diagnosis of AH may have selected for individuals who were less severely ill. Lastly, early studies on individuals with AH must also be viewed from the perspective that this population has historically been marginalized due to stigma associated with alcohol use disorder [7, 8]. While progress has been made in reducing the stigma [9], AH remains a condition of despair and access to trials as well as patient retention are persistent challenges. In the last decade, there has been progress aimed at rationale clinical trial design for AH [10, 11] as well as in the standard of care of patients with AH. This review is not an all-inclusive summary of AH clinical trials but rather aims to provide a historical framework for the current landscape and future trajectory of selected AH therapeutics.

Methods:

A qualitative systematic review was performed via searches of PubMed, International Clinical Trials Registry Platform and ClinicalTrials.gov for therapeutic interventions for alcohol-associated hepatitis.

Results:

The Mainstays: Nutrition and Corticosteroids

Nutrition: Malnutrition is nearly universal, associates with worse prognosis and plays a role in the pathophysiology of AH [12–14] yet few studies involving AH patients inform nutrition guidelines. The current guideline-based recommendations pertaining to nutrition of patients with AH [15–18] are derived from recommendations for patients with all chronic liver diseases and include a caloric target of 35 to 40 Kcal/kg bw per day and a protein intake of 1.2 to 1.5 g/kg bw per day [19]. The most informative clinical trials to date of AH patients [20, 21] compared enteral nutrition (EN) delivered via nasogastric tube (NGT) to corticosteroids and must be framed by the knowns and unknowns of the respective eras. The Cabre study, performed in 2000 [20], was prior to the knowledge derived from the Lille score described in 2007 [22]. Cabre and colleagues found equivalent 28-day survival in EN and corticosteroid treated patients, with steroid-treated patients more often succumbing to infections in the 6 weeks following their initial 28 day survival [20]. The conclusions of the trial may have been very different had Lille criteria been described and utilized, with some patients stopping steroids at day 7 (or even day 4). The Moreno trial, performed in the post-Lille era [21], was more robust in numbers and multicenter design however it lacked the 2016 National Institute on Alcohol Abuse and Alcoholism (NIAAA) criteria for AH diagnosis [10]. Patient selection utilized biopsy, which tends to select for a population of less sick individuals who can withstand the procedural risk. Patients with severe AH were treated with IV methylprednisolone and randomized to EN for 14 days or conventional nutrition (*ad lib* by mouth). The study concluded that intensive EN for 14 days was equivalent to conventional nutrition in regards to 6 month survival and also importantly revealed that patients consuming < 21.5 kcal/kg bw per day, regardless of the route, had higher mortality at 6 months (62.9 vs. 34.2%, P<0.001) [21]. Almost 50% of the patients in the EN arm did not complete the 14-day course due to tube intolerance perhaps contributing to the results of the study.

A small trial comparing nil by mouth (N=10) to nasogastric feeding (N=12) for the first 4 days following ligation- or sclerotherapy-stabilized variceal hemorrhage showed no differences in rates of re-bleeding, nutritional status, length of stay [23] though a larger trial may provide reassurance of current practice. Regarding location of enteral feeding, gastric and jejunal tube placement have equally efficacious caloric delivery for this population, demonstrated by a simple but well-designed clinical trial [24]. Finally, in situations where barriers exist to enteral feeding, a small but reassuring study of parenteral nutrition was performed and did not worsen mortality in moderate or severe AH patients but unfortunately also showed no survival benefit [25]. Interestingly, peripheral nutrition appeared to cause less exacerbation of ascites and encephalopathy thus may be favorable in some patients [25]. Moving forward, nutrition trials utilizing NIAAA diagnostic criteria for patient selection [10], refined criteria for steroid-eligible patients [26] and Lille criteria for steroid discontinuance [27] without trepidation of using feeding tubes or parental nutrition will allow for better determination of nutrition goals for AH patients.

Corticosteroids: In the 1950s, a publication within the Annals of Internal Medicine suggested that hormones from the adrenal cortex may be helpful in the treatment of liver disease [28]. It wasn't until 1961 that an article titled *Acute Alcoholic Hepatitis* was published within the British Medical Journal recommending a treatment algorithm including abstinence from alcohol, bedrest, intensive nutrition, and high dose B vitamins [29]. A decade later, the first randomized controlled trial (RCT) evaluating corticosteroids in the treatment of 20 patients with AH was published and failed to show benefit [30]. In the 50+ years following, the efficacy of corticosteroids beyond the short term continues to be controversial, though patient selection and discontinuation criteria have informed their optimal use. A Cochrane review of 16 RCTs showed no difference between corticosteroids and placebo in all-cause mortality, health-related quality of life, and serious adverse events [31] while the STOPAH trial, the largest multicenter RCT of AH patients to date, showed favorable results for corticosteroids. This trial included 1,103 severe AH patients randomized to prednisolone or placebo for 28 days and demonstrated a trend for mortality benefit with corticosteroids (13.8 vs. 18%, P=0.056). The effects of corticosteroids were potentially dampened by overall lower mortality than prior studies, possibly reflecting improved management of patients with decompensated liver disease [4]. Two additional metanalyses have added support for the use of corticosteroids in AH: The first analyzed 3 randomized placebo-controlled clinical trials demonstrating positive results of corticosteroids, with 1-month survival of 84.6% versus 65.1% [32] and the second study, which did include the STOPAH data, concluded that corticosteroids were effective in reducing short-term mortality by 36% [5] thus placing corticosteroids at the cornerstone of modern AH therapeutics.

Given the increased risk of infection with corticosteroid use in this population, studies refining their use including prediction of patients who will benefit from them or who will spontaneously improve without them as well as the optimal duration for use have framed the current treatment guidelines. Maddrey's discriminant function [33] was historically used to identify the population of patients most likely to respond to corticosteroids but Model of End-Stage Liver Disease (MELD) score is now recommended for determining who should receive steroids. A recent worldwide retrospective multicenter cohort of patients with severe AH showed that a 28-day course of steroids is beneficial in patients with MELD scores ranging between 21–39, with limited benefit in those in the 40–50 range and no benefit above a MELD score of 50 [26]. In predicting patients likely to improve without steroids, the kinetics of a patient's serum bilirubin may be employed. A recent study stratifying 426 AH patients by change in serum bilirubin as "fast fallers," "static" and "rapid risers" revealed that fast fallers most improve without steroids and have superior 90-day survival [34], however as the stratification is made 7 days post admission, putting this scoring system into practice may be challenging.

Prediction of steroid responders using advanced molecular techniques has also emerged in the last 5 years. While single markers such as cytokeratin-18 [35] have shown prognostic and theragnostic potential in AH, multimarker transcriptomics related to immunity and the mitochondrial electron transport chain appear to have potential to predict severe AH patients

who will be steroid non-responders [36]. Further, the predictive capacities of liver biopsy as well as circulating metabolites and macrovesicles have been explored [37]

In terms of steroid duration, 28-day treatment courses of corticosteroids are standard for responders though the rationale for this duration in the earliest clinical trials was not provided. One could surmise that 28 days was convenient as this duration became the accepted course of care for inpatient stays for alcohol and substance rehabilitation. 30 days also defines a “short” course of steroids for which long term side effects may be avoided [38] though infections from steroids are common and convey risk for poor outcomes extending beyond the treatment course [39]. The Lille model provides guidance for continuing or stopping steroids following 7 days of treatment [40] and more recent studies have shown that utilizing Lille score at day 4 is equally accurate [27, 41].

Finally, the use of prednisolone over prednisone has been favored for AH and early studies showing that prednisolone does not require hepatic conversion are often cited as the rationalization behind this [42, 43]. Most interesting is the better-than-expected outcomes of patients within the AlcHepNet trial, which utilized IV methylprednisolone rather than PO formulations [44]. Head-to-head trials of IV corticosteroid formulations, prednisolone and prednisone have not been performed but may be informative. In summary, corticosteroids have been studied extensively yet have limited utility in patients with alcohol-associated hepatitis, underscoring the need for new therapies.

Foundational work

Metabolic studies on animal models have suggested that modifying the endocrine axis could improve hepatic function [45]. Two initially favorable trials of insulin and glucagon were later answered by additional trials showing lack of survival benefit [46–49] and thyroid blockade with propylthiouracil was likewise found to have no efficacy in AH [50, 51]. Trials of the anabolic steroid oxandrolone showed favorable signals [52, 53] but studies waned in the mid 1990’s and it was not integrated into practice. Small trials of Vitamin E [54] and antioxidant cocktails [55] [56] also proved non-beneficial. A milestone in clinical trials for AH was the first use of a monoclonal antibody (i.e. biologic) targeting the inflammatory cytokine Tumor Necrosis Factor (TNF)-alpha. Given its efficacy in Crohn’s disease and rheumatoid arthritis and the protection that TNF-alpha knockout mice showed against alcohol-induced liver injury [57], studies commenced examining infliximab for AH. While a pilot study showed promise [58], a subsequent RCT [59] was stopped early due to safety signal. An open label trial that followed demonstrated a remarkable 89% 1-month survival with a single dose of infliximab in AH patients [60] however no studies have followed. Etanercept, a soluble TNF receptor targeting TNF-alpha, and beta was the second biologic used in clinical trials for AH and failed to show efficacy [61, 62].

Pentoxifylline (PTX): PTX is a nonselective phosphodiesterase (PDE) inhibitor and potent inhibitor of TNF-alpha secretion, both of which are implicated in the pathogenesis of AH [63]. The first trial of PTX was presented as an abstract in 1991 [64] describing 22 patients, 12 treated with PTX and 10 controls with 8.3% and 30% 30 day mortality rates respectively. These positive data were followed by a RCT 9 years later: 101 patients with severe AH

received 28 days of PTX (400 mg, 3 times daily) or vitamin B 12 tablets (selected as a “placebo”) and demonstrated a remarkable 180-day survival curve showing nearly 80% survival for the PTX arm compared to 50% survival in the placebo arm [65]. While this and other initial studies of PTX showed efficacy, the large STOPAH trial demonstrated no 28-day survival benefit [4] and further studies have shown lack of signal as a salvage therapy for steroid non-responders [22] or as an adjuvant therapy to corticosteroids [66, 67]. The number of trials on PTX have allowed for a metanalysis assuring overall non-benefit of PTX [5] yet many providers continue to use it for AH citing a paucity of available therapies, as well as its availability, safety profile and signal for reducing incidence of hepatorenal syndrome [65, 68, 69]. The conditional recommendation of PTX has since been removed from most treatment algorithms for AH. Given recent studies demonstrating that selective PDE inhibition, particularly that of PDE4, shows efficacy in AH [63, 70], future clinical studies may be considered with specific PDE4 agents.

Era of modern trials

Antibiotics: Given the incidence of infections in AH patients, particularly following corticosteroid treatment, as well as the common initiation of empiric antibiotics in AH patients given their frequent presentation with SIRS criteria, recent trials studying the utility of antibiotics in AH have been informative. Reduction of gut bacteria using rifaximin [71, 72], amoxicillin-clavulanate [73] and the combination of meropenem, vancomycin, and gentamycin [74] have not shown clinically significant benefit in AH patients. *Metadoxine:* A complex compound of pyridoxine (a vitamin B 6 precursor) and pyrrolidone carboxylate with multiple proposed mechanisms has shown promise in 2 open label studies published in 2014 and 2015 [75, 76], demonstrating improvements in 90 day and 6-month survival though a RCT has not yet been performed. *Anakinra:* Anakinra, an IL-1 receptor antagonist which blocks IL-1α and IL-1β signaling showed remarkable preclinical efficacy in a mouse study of alcohol induced liver injury [77] but failed to show survival benefit in the recently published multisite AlcHepNet RCT [44]. No further studies of anakinra are in progress. *IL-22:* F-652 human interleukin 22 (IL-22) and human Immunoglobulin G2 (IgG2)-Fc was studied in open label format with interesting exploratory endpoints but no survival benefit was demonstrated [78]. There appears to be no further studies in process.

Granulocyte Colony-Stimulating Factor (G-CSF): G-CSF is a glycoprotein believed to recruit bone-marrow derived stem cells, allowing for hepatocyte cell regeneration by differentiation of bone marrow precursor cells into hepatocytes. The initial study examining G-CSF for the treatment of severe AH in 2008 showed increased CD34+ cells (markers of hematopoietic stem cells) as well as hepatocyte progenitor cells on histologic liver biopsy evaluation. However, there were no significant improvements in liver function [79]. The first clinic trial of G-CSF in AH was reported in 2014 [80] and several subsequent studies have allowed for meta-analyses showing a 90-day survival benefit in studies performed in Asia with a trend for increased mortality found in 2 studies performed in Europe. It has been proposed that study design variability accounted for mixed results [81]. Two subsequent studies since the latest metanalysis have demonstrated the same hemispheric trend. A trial performed in the US revealed that the combination of G-CSF and prednisolone has equivalent 90 day survival compared to prednisolone alone (0.73 vs 0.83 $p > 0.05$) [82]

while another study from Asia comparing G-CSF alone (N=42), prednisolone alone (N=42), and the combination of G-CSF + prednisolone (N=42) showed 64.3%, 78.6% and 88.1% 90 day survival respectively (p =0.03) [83].

Promising Leads

N-Acetylcysteine (NAC): NAC has been traditionally used for the treatment and prevention of acetaminophen-induced liver injury due to its ability to restore glutathione and enhance hepatic perfusion. The first report of NAC in AH patients was described in a 1991 *New England Journal of Medicine* article reporting its benefits primarily in acetaminophen overdose however 2 patients with AH were included within the study [84]. NAC has been studied in tandem with and compared against corticosteroids. While initial studies of NAC showed limited efficacy, study designs including NAC within “antioxidant-cocktails” may have obscured benefit. The number of NAC studies accumulating over the years has allowed for a robust network-metanalysis revealing that IV NAC in combination with corticosteroids yielded a remarkable 85% risk reduction of death from AH at 28 days [85] leading to the addition of IV NAC into recent American College of Gastroenterology guidelines for the treatment of AH [86]. Multiple RCTs of NAC are currently in progress.

Fecal microbiota transplant: In the 1951 journal article titled “Dietetics in alcoholic hepatitis; therapeutic role of cheese” published within *Semaine des hôpitaux de Paris* may represent the first publication of the positive effects of microbiome modulation for AH [87]. While probiotics have been employed in trials, effects may have been dampened by sample size and patient selection [88, 89]. The first fecal microbiota transplantation (FMT) trial published in 2017 of 8 subjects with AH having contraindications to steroid therapy showed encouraging results [90] and has since been followed by a RCT comparing FMT (N=55) to prednisolone (N=57) with improved 90-day survival in the FMT arm compared to the prednisolone arm (75% vs 57% p=0.044) [91]. As infections from FMT donor stool [92] have led to several FDA alerts, the risks and benefits of FMT must be considered in this relatively immunocompromised patient population. With the recent FDA approval of Rebyota for recurrent C. difficile, the field is theoretically open to its off-label use in AH however drug cost of approximately $9,000 USD per treatment will likely limit the practice.

Unfinished studies: Several concluded or terminated trials populate clinical trial registries. Among these include emricasan (NCT01912404), DS102 (NCT03452540), vitamin C infusion (NCT03829683), mycophenolate/pilonacept (NCT01903798) and selonsertib (NCT02854631). While data are uploaded demonstrating indications for these unfinished or early terminated studies, peer-reviewed publications with the investigator’s insights have yet to evolve from these. While other endpoints appeared favorable, there was a lack of survival benefit for the IL-1 beta target Canakinumab recently shared in abstract form however the complete trial results have yet to be published [93]

Looking Forward

Sulfated oxysterol (DUR-298): The first Phase 2a clinical trial of this epigenetic modulator was published in 2023 [94] revealing improvement in MELD score. Results are awaited from a recently completed Phase 2b trial (NCT04563026). *Bovine Colostrum:*

Bovine colostrum, derived from cow milk and rich in immunoglobulins believed to have benefit on gut barrier function and abrogation of endotoxemia, was used “in extremis” and published in a 2015 abstract [95] showing a positive signal. Additional work is in progress (NCT02473341). *HA35:* Clinical work has demonstrated increased circulating hyaluronic acid (HA) in patients with liver disease [96–98] and preclinical studies of small-specific sized HA (HA35) demonstrate this molecule preserves the intestinal barrier and decreases hepatocyte apoptosis in a mouse model of alcohol-induced liver injury [99]. A study of HA35 is underway in patients with moderate AH (NCT05018481).

Discussion/conclusions:

Nearly 90 years ago, Sir Arthur Hurst wrote, “alcohol is the commonest cause of liverishness” [2] and unfortunately his statement remains true to this day. Therapeutic advances for AH have come at a slow pace when compared to other common conditions carrying high mortality and as such severe AH remains a condition that is difficult to treat. While small early trials with design flaws intrinsic to their era may be viewed now as failed studies, their dissemination was critical as they have allowed for larger metanalysis and informed future therapeutic efforts. Cases in point are the dissolution of PTX and adoption of IV NAC in guideline-based care for AH. Corticosteroids remain the pharmacological treatment of choice for severe AH and recent studies have revealed that control arms utilizing steroids have shown better than expected survival when compared to historical cohorts of patients. This may be from improved medical care of AH patients. The demographics of AH have also shifted, with increasing presentations of females and young adults particularly coinciding with the COVID pandemic [100]. These younger patients may present with more physiologic reserves. Nevertheless, AH remains a deadly disease with limited treatment options despite the work that investigators have invested (Figure 1). The commitment of the NIAAA and persistence of investigators in modernizing AH clinical trials cannot be understated and allow for a new era of emerging AH therapies to begin.

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Abbreviations

AH	Alcohol-Associated Hepatitis
EN	Enteral Nutrition
FDA	Food and Drug Administration
FMT	Fecal Microbiota Transplant
G-CSF	Granulocyte Colony-Stimulating Factor
HA	Hyaluronic Acid
MELD	Model for End-Stage Liver Disease

NAC	N-Acetylcysteine
NGT	Nasogastric Tube
NIAAA	National Institute on Alcohol Abuse and Alcoholism
PDE	Phosphodiesterase
PTX	Pentoxifylline
RCT	Randomized Controlled Trial
TNF	Tumor Necrosis Factor

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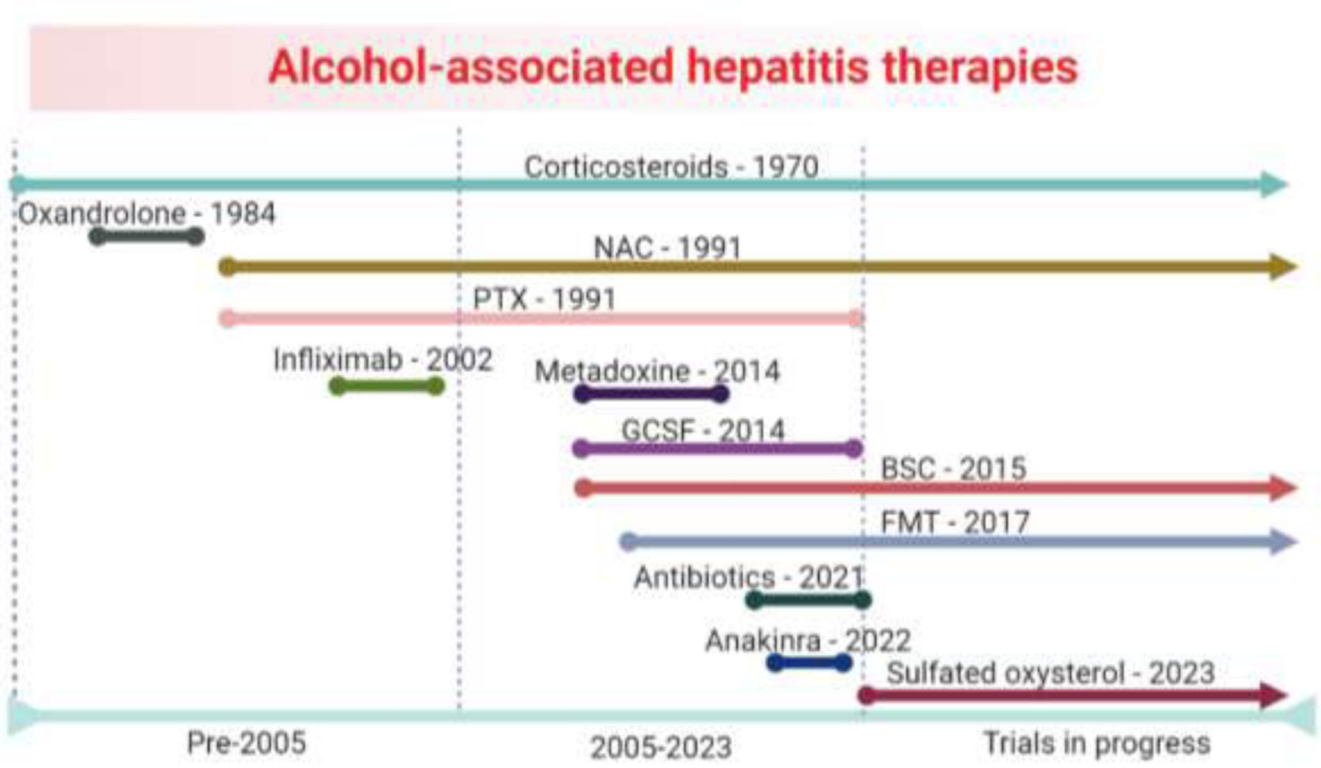

Figure 1: Timeline of alcohol-associated hepatitis therapies.

Selected therapies with the year of their first published clinical trial are shown. BSC, bovine serum colostrum; FMT, fecal microbiome transplantation; GCSF, granulocyte colony stimulating factor; NAC, N-acetylcysteine; PTX, pentoxifylline.