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Review Article

Role of inflammation in alcoholic liver diseases and its management

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ABSTRACT

Alcoholic liver disease (ALD) weighs a heavy health burden in India with 76% increase in disability-adjusted life years (DALYs) through 1990 to 2016. This review examines the role of inflammation in its pathogenesis and management approaches for the same. The pathophysiology of ALD involves various mechanisms such as increased gut permeability, oxidative stress and activation of inflammatory cascade, where tumor necrosis factor-alpha (TNF-α) plays a central role. Due to these varied mechanisms, the clinical presentation also varies, ranging from asymptomatic fatty liver to severe cirrhosis. As such, the management strategies range from alcohol abstinence and nutritional support to pharmacological interventions. For inflammation-predominant ALD phenotypes such as alcoholic hepatitis, corticosteroids are often used as the primary therapy. Other agents, including S-adenosylmethionine (SAMe), pentoxifylline and N-acetylcysteine, show promise in targeting the inflammatory pathogenesis of ALD. SAMe is a more specific option for targeting inflammation, while N-acetylcysteine is best used where its potent anti-oxidant activity is desired. Ultimately, liver transplantation offers the terminal option for end-stage disease, with considerations for inflammation to subside before it can be done. This review highlights the complex inflammatory mechanisms underlying the ALD spectrum and discusses various multimodal approaches for incorporating various treatment strategies.

Keywords: Alcoholic liver disease, Inflammation, Tumor necrosis factor-alpha, Corticosteroids, S-adenosylmethionine, N-acetylcysteine

INTRODUCTION

ALD encompasses a clinical-histologic spectrum, comprising fatty liver, alcoholic hepatitis, and cirrhosis with associated complications. Diagnosis involves documenting chronic heavy alcohol use while excluding other potential causes of liver disease.[1] Advancing through different stages uncovers specific hurdles that show how deeply alcohol affects us. Fat accumulation triggers steatosis, hepatitis causes inflammation, and the degree of damage determines the result. This irreversible stage, which culminates in cirrhosis, causes difficulties.[2] Acute-on-chronic liver failure (ACLF) occurs in patients with chronic liver diseases, characterized by acute decompensation, organ failures, and a high risk of short-term mortality.[3] In the case of acute alcoholic liver disease (AALD), symptoms, notably jaundice, manifest abruptly, often in patients without prior indications of liver disease. Nonetheless, certain individuals may experience recurrent acute episodes.[4] Chronic and prolonged alcohol consumption poses a widespread healthcare challenge. The duration and quantity of alcohol use are the primary risk factors for the development of ALD. The kind of beverage and drinking behaviour have a secondary influence in influencing the risk of ALD. In the context of severe alcohol-associated liver disease, men face a threshold risk with an intake of less than 60–80 g per day of alcohol over 10 years. In contrast, women appear to be at an elevated risk of similar liver injury with an alcohol consumption range of 20–40 g per day.[5] WHO defines binge drinking as the consumption of more than 5 standard drinks for men and more than 4 for women within a 2-hour period. Although binge drinking alone may not directly

cause liver disease, it expedites fibrosis progression and cirrhosis development, particularly in individuals with obesity and metabolic syndrome.[6] Group discussions with Indian specialists were planned to improve understanding of the ALD burden in India, Diagnosis pathophysiology with emphasis on inflammation, and management of IBS. This review provides an overview of relevant literature about ALD burden in India, Diagnosis and pathophysiology and tries to take a holistic view at this disorder.

EPIDEMIOLOGY

Alcohol-related disorders constitute a huge worldwide health concern, with cirrhosis of the liver emerging as a major cause. This issue imposes a significant financial strain on health-care systems across the world. The recent findings from the Global Burden of Disease Study highlight a similar alarming trend in India, where alcohol-related factors rank among the top 10 causes of disability-adjusted life years (DALY) in 2016, exhibiting a concerning 76% increase since 1990. Various series focusing on cirrhosis and liver transplant cases in India underscore alcohol as the predominant cause of cirrhosis. The incidence of alcohol-related liver disease is witnessing a steep and worrisome rise in India, attributed largely to escalating quantities and prolonged durations of alcohol consumption, often initiated at an early age. Notably, this surge impacts a predominantly young demographic in their peak productive years, thereby exerting a negative socioeconomic influence on society.[7] In a study conducted in eastern India, Singh et al revealed that half of the individuals diagnosed with alcoholic liver disease initiated alcohol consumption before reaching the legally permissible drinking age.[8] In a study published by Ray in 2014 from Kolkata observed a parallel increase in the prevalence of alcohol-related chronic liver disease (CLD) in his study, noting a surge from 22% in 2003 to 42% in 2011.[9] Additionally, Nand et al conducted a study involving 149 patients, with 74% of them having a drinking history of $\\le$20 years. This observation further underscores the tendency of Indians to develop liver disease in a shorter duration compared to Western populations.[10]

RISK FACTORS[11]

Alcohol

The amount, duration, type, and pattern of intake of alcohol, along with dietary influences are important[53]. Studies highlight the pivotal role of quantity and duration of alcohol intake, suggesting a cirrhogenic dose of 80 g/day, albeit lower thresholds, particularly in women. Consistently consuming at least 30 gm/day for women and 50 gm/day for men over 5 years is associated with the development of clinically significant liver disease. Additionally, the choice of alcohol type contributes to risk variation, with wine-only drinkers displaying a lower risk profile.[11]

Gender

Gender represents a significant factor, with women exhibiting a higher relative risk of ALD irrespective of the alcohol intake amount. This susceptibility is attributed to a lower volume of distribution, leading to elevated blood alcohol levels. Furthermore, estrogen's involvement in enhancing gut permeability is proposed as a contributing factor to this vulnerability.[11]

Chronic viral hepatitis

Persistent viral hepatitis, especially hepatitis C, acts synergistically with alcohol, resulting in heightened apoptotic cell death and accelerated fibrosis. The influence of coexisting Hepatitis B infection remains uncertain, with conflicting evidence emerging on its effects.[10]

Comorbidities

Metabolic comorbidities, including diabetes and obesity, exert an influence on the risk of ALD[65]. The term "BASH," denoting both alcoholic and NASH, signifies the coexistence of fatty liver disease in individuals with alcohol consumption below the specified thresholds for NAFLD.[11]

Genetic and epigenetic factors

Genetic and epigenetic factors may help explain the phenomenon where only 10% of individuals with excessive alcohol consumption progress to cirrhosis. Notably, polymorphisms in the patatin-like phospholipase domain-containing protein 3 (PNPLA3), particularly the 148M variant, have been extensively examined and associated with an elevated risk.[11]

PATHOPHYSIOLOGY OF ALD

As previously discussed, genetics is one of the host variables that increase the risk of ALD. While metabolic alterations play an important part in AFL, epigenetic changes, oxidative stress, and inflammation also contribute to ALD. These variables predominantly affect hepatocytes, but they also regulate hepatic stellate cells (HSCs).[12] HSCs are central to the onset, advancement, and reversal of liver fibrosis. They release fibrogenic factors that stimulate portal fibrocytes, fibroblasts, and bone marrow-derived myofibroblasts to generate collagen, thereby driving fibrosis.[11]

Gut permeability

Chronic alcohol abuse is associated with increased intestinal permeability and alterations in gut microbiota, leading to the release of pro-inflammatory cytokines and liver inflammation. Furthermore, chronic alcohol exposure leads to gut permeability, allowing gut-derived lipopolysaccharides to enter the liver and trigger an inflammatory response.[13] This "leaky gut" phenomenon is

a necessary cofactor for the development of chronic liver injury in heavy drinkers.[14] Ethanol and its metabolic derivatives disrupt epithelial tight junctions, increasing paracellular permeability to macromolecules and contributing to endotoxemia and liver damage.[15]

Acetaldehyde and oxidative stress

Acetaldehyde, a highly toxic and carcinogenic byproduct of alcohol metabolism, is formed via the cytochrome P450 2E1 (CYP2E1) and alcohol dehydrogenase pathways. Chronic alcohol drinking activates CYP2E1, resulting in an additional pathway for alcohol oxidation. Acetaldehyde harms cellular structures such as mitochondria and promotes the production of neoantigens. Beyond acetaldehyde's direct toxicity, alcohol use causes oxidative stress, which is mediated by reactive oxygen species (ROS). ROS may affect proteins, DNA, and lipids, causing functional and structural changes. Lipid peroxidation products, such as 4-hydroxynonenal and malondialdehyde, lead to the production of carcinogenic DNA adducts.[12] ROS generation in alcohol-induced oxidative stress is aided by CYP2E1 activation or alcohol-induced inflammation. Chronic alcohol use increases CYP2E1 activity, which boosts ROS generation via increased electron leakage. Inflammation, particularly in alcoholic hepatitis, enhances ROS formation. Alcohol also increases nitrosative stress, which is caused by reactive nitrogen species.[12] In animal models, CYP2E1 overexpression worsens alcoholic liver disease (ALD), but inhibition has therapeutic effects. Patients with ALD have a link between hepatic CYP2E1 expression, etheno-DNA adducts, and fibrosis severity. Chronic alcohol intake weakens the antioxidant defence system, in part because of acetaldehyde-mediated glutathione degradation. However, the adaptive response involves overexpression of the transcription factor Nrf2, which controls cytoprotective enzymes, providing a defensive mechanism against oxidative stress generated by CYP2E1.[12]

INFLAMMATION AND TUMOR NECROSIS FACTOR-ALPHA (TNF*α*)

Inflammation in ALD is closely associated with the production of proinflammatory cytokines, particularly TNF- α. TNF- α is a key mediator in the pathogenesis of ALD, and its production is induced by the activation of the CD14/TLR4 pathway in response to endotoxin. This activation leads to downstream signaling resulting in the production of proinflammatory cytokines, particularly TNF- α, which then provoke hepatocellular injury and death, leading to ALD. The role of TNF- α in ALD has been highlighted in various studies. For instance, it has been shown that TNF- α is a key factor in the development of new approaches to treatment for ALD, and its inhibition has been found to be effective in preventing inflammation and necrosis in animal models of alcohol feeding. Additionally, anti-TNF- α antibodies have been demonstrated to attenuate hepatic necrosis and inflammation caused by chronic exposure to ethanol in rats. Furthermore, the use of anti-TNF-α antibody infliximab has been found to be effective in severe ALD patients.[17] The relationship between TNF-α and inflammation in ALD is further supported by the association of platelet aggregation activity with the disease. Studies have shown that plasma ADAMTS13 activity, which is inversely proportional to TNF- α, decreases in ALD or severe alcoholic hepatitis (AH). Moreover, treatment with pentoxifylline, an inhibitor of TNF- α synthesis, has been found to improve the survival of patients with severe AH.[18] In summary, the pathophysiology of ALD involves the activation of inflammatory responses, particularly the production of TNF- α, which plays a crucial role in the development and progression of the disease. Understanding the role of TNF-α and its association with inflammation is essential for the development of new therapeutic approaches for ALD.[17-19] Key insights from expert recommendations suggest that chronic alcohol intake initiates various mechanisms contributing to disease progression. These mechanisms include the formation of acetaldehyde, increased NADH production leading to metabolic stress, impaired antioxidant mechanisms resulting in oxidative stress and lipid peroxidation, and disruption of the gut barrier leading to inflammation. TNF- α emerges as a critical cytokine involved in alcoholic liver disease pathophysiology, regulating immune responses, cell survival, proliferation, and metabolic processes[111]. Excessive alcohol consumption exacerbates these pathways, culminating in alcoholic hepatitis characterized by a systemic inflammatory response and liver fibrosis. Notably, while the majority of individuals with excessive alcohol intake develop alcohol fatty liver, a subset progresses to alcoholic steatohepatitis, distinct from alcoholic hepatitis, which may evolve from this condition.

MANIFESTATION OF ALD

ALD can lead to a wide range of extrahepatic manifestations involving various organ systems[115]. These manifestations are often overlooked by hepatologists and physicians focused on managing life-threatening complications of ALD.[19] Patients with ALD can experience gastrointestinal tract issues, central and peripheral nervous system disorders, cardiovascular problems, musculoskeletal abnormalities, disruptions in nutritional status, endocrine abnormalities, hematological abnormalities, and immune dysfunction.[20] Other manifestations, like alcoholic cardiomyopathy and malignancies, have prognostic significance and increase the risk of morbidity and mortality.[21] It is crucial for healthcare providers to have a clear understanding and awareness of these extrahepatic manifestations to ensure proper management of patients with ALD.[21]

Hepatic manifestations

ALD can manifest in various ways in the liver. These manifestations include steatosis (fatty liver), inflammation, fibrosis, and cirrhosis.[20] Steatosis is the

initial manifestation and is reversible, but it indicates ongoing metabolic stress on the liver.[23] Inflammation is a key feature of ALD, involving innate immune mechanisms and the release of TNF α by Kupffer cells.[24] Fibrosis, mediated by hepatic stellate cells, is driven by inflammation and is a progressive stage of ALD.[21] Cirrhosis is the most severe form of ALD, characterized by extensive fibrosis and irreversible liver damage.[26] These liver manifestations of ALD can have significant clinical implications and can lead to complications such as hepatocellular carcinoma and liver-related deaths. Early diagnosis and management of ALD are crucial to prevent disease progression and improve patient outcomes.

Gastrointestinal tract

Alcohol affects the upper gastrointestinal (UGI) tract, causing inflammation, motility impairment, and changes in gastric acid secretion. In individuals with Alcohol Use Disorder (AUD), there's an elevated risk of gastro-esophageal reflux disease (GERD), reflux esophagitis, and Barrett's esophagus. Advanced ALD patients, especially those with alcoholic hepatitis and cirrhosis, face an increased risk of UGI bleeding, often associated with higher mortality. Peptic ulcer disease prevalence is elevated in AUD patients, contributing to higher rebleeding rates and mortality. ALD is linked to an increased risk of stomach cancer, leading to decreased survival rates.[20]

Pancreatic disorders

Excessive alcohol intake, particularly over 80 g/day for 6-12 years, can lead to chronic pancreatitis through chronic inflammation and fibrosis. Alcohol-related chronic pancreatitis coexists with ALD, with a pooled prevalence of 16.2% in ALD patients and 21.5% in chronic pancreatitis cases. Patients with ALD and chronic abdominal pain should be evaluated for concurrent alcohol-related chronic pancreatitis, and moderate to excessive alcohol use (>3 drinks/day) is associated with an increased risk of pancreatic cancer.[20]

Neurological manifestations

Alcohol-related neurologic complications in ALD involve both nutritional deficiency-induced effects on the central nervous system and structural changes from liver cirrhosis-related portosystemic shunting. Acute Alcohol Intoxication, a harmful condition following significant alcohol ingestion, manifests with behavioural changes, cardiovascular effects, and metabolic alterations. Alcohol Withdrawal Syndrome may occur upon reducing chronic alcohol intake, ranging from mild tremors to severe delirium tremens. Wernicke's encephalopathy, caused by thiamine deficiency, requires urgent treatment to prevent serious neurological sequelae. Korsakoff Syndrome, associated with malnutrition and thiamine deficiency, presents as chronic neuropsychiatric impairment. Alcohol-related Dementia results from prolonged alcohol use and features multifactorial pathophysiology, often showing limited response to thiamine supplementation. Alcohol-related Cerebellar Degeneration, a common cause of acquired ataxia, involves toxic alcohol effects, thiamine deficiency, and impaired blood-brain barrier. Neurologic complications underscore the diverse impact of alcohol on the central nervous system, emphasizing the importance of early identification and intervention.[20]

Peripheral nervous system

Prolonged alcohol consumption leads to a high prevalence of peripheral neuropathy in patients with alcohol use disorder, affecting both small and large nerve fibers, including autonomic fibers. The condition's pathogenesis involves direct alcohol toxicity, nutritional deficiencies (especially thiamine and vitamin B12), cirrhosis-related neuropathy, and impurities in alcoholic beverages. Symptoms primarily manifest in the lower extremities, presenting as sensory issues like paraesthesia and numbness, with less frequent motor features. Management includes alcohol abstinence and vitamin supplementation, particularly vitamin B complex.[20]

Autonomic dysfunction

Alcohol-induced autonomic dysfunction, affecting both sympathetic and parasympathetic systems, is prevalent among individuals with AUD, with parasympathetic involvement observed more frequently. Its presence holds prognostic significance, correlating with increased mortality risk in ALD patients. The prevalence varies widely (0-73%) among chronic alcohol abusers, primarily linked to lifetime cumulative alcohol dose. Erectile dysfunction, heart rate variability issues, abnormal sympathetic skin response, and gastrointestinal symptoms are common. Treatment options are limited, with abstinence showing variable recovery. Cardiovascular manifestations, including atherosclerosis, arterial hypertension, myocardial damage, and arrhythmias, are significant consequences of chronic alcohol consumption.[20]

Cardiovascular manifestations

Excessive alcohol consumption significantly impacts the cardiovascular system, increasing the risk of atherosclerosis, arterial hypertension, myocardial damage, and arrhythmias. Alcoholic cardiomyopathy, a toxic-induced dilated cardiomyopathy, leads to heart failure, with symptoms emerging in later stages. Recovery is possible with abstinence and cardiac risk factor control, but in severe cases, cardiac transplantation may be the only option. Atrial fibrillation, a common sustained arrhythmia, is associated with increased morbidity and mortality in alcohol consumers. The risk is dose-dependent, and alcohol-induced arrhythmogenic changes contribute to its development, worsening prognosis in persistent alcohol users. Further studies are needed to address the

epidemiology, diagnostics, and therapeutic targets for alcoholic cardiomyopathy.[20]

Nutrition

Harmful alcohol abuse commonly leads to protein-energy malnutrition in all stages of ALD, impacting prognosis, especially in alcoholic hepatitis. Malnutrition's multifactorial pathophysiology involves factors such as loss of appetite, inflammatory cytokines, intestinal dysmotility, malabsorption, and impaired energy metabolism. The upregulation of cytokines suppresses appetite, and alcohol-induced effects on gut motility and immunity contribute to malabsorption. Alcoholic hepatitis patients experience a hypermetabolic state, leading to protein and calorie depletion. While early oral nutritional support shows some survival benefits, an ideal nutritional regimen is yet to be established for effective ALD management. Timely diagnosis allows implementing treatment strategies to mitigate adverse outcomes.[20]

Endocrine abnormalities

AUD impacts the endocrine system directly and through hepatocyte dysfunction in ALD. It disrupts the hypothalamic–pituitary axis, causing stress intolerance, reproductive dysfunction, and thyroid abnormalities. Additionally, chronic alcohol use is linked to low testosterone levels, bone density loss, and altered thyroid function, while ALD can lead to impaired glucose tolerance and hepatogenous diabetes mellitus.[20]

Hematological malignancies

Alcohol-induced hematological changes include bone marrow suppression, leading to ineffective blood cell production, and liver-related metabolic alterations exacerbating nutritional deficiencies. These manifest as macrocytosis, megaloblastic anemia, thrombocytopenia, and impaired immunity, with potential rebound effects upon abstinence. Iron overload further complicates liver cirrhosis in alcohol-related liver disease.[20]

Musculoskeletal complications

Alcoholism significantly contributes to osteopenia and osteoporosis, affecting 35.9% of patients with alcohol-related liver disease. Hepatic osteodystrophy, encompassing osteomalacia, osteopenia, and osteoporosis, elevates fracture risk in these patients. Non-traumatic osteonecrosis of the femoral head is also linked to alcohol and steroid abuse in chronic liver disease. Additionally, patients with alcohol-related liver disease frequently experience sarcopenia, attributed to hepatocellular dysfunction and direct alcohol toxicity on muscle tissue, worsening survival and quality of life. Alcoholic myopathy, characterized by muscle weakness and atrophy, is a common complication, with abstinence being the primary therapy.

CLINICAL PRESENTATION OF ALD

The clinical presentation of ALD can vary. Typically, ALD is associated with indirect/unconjugated hyperbilirubinemia and elevated aminotransferases. However, there are cases where ALD can present with mainly direct/conjugated hyperbilirubinemia and relatively low aminotransferases. Imaging tests should be pursued to rule out obstructive etiologies, but invasive tests and liver biopsies are not indicated in typical clinical settings.[27] Chronic and heavy alcohol consumption is commonly observed in AUD, which often leads to ALD. The progression of ALD involves the interplay of several pathways, including nutritional alterations. However, there are major gaps in the characterization and understanding of the clinical presentation of early-stage ALD. Laboratory biomarkers, including liver injury and drinking history markers, as well as nutrition status, play a role in the development and progression of early-stage ALD.[28] ALD can also present with solitary hyperbilirubinemia without substantial hepatic abnormalities. Patients with ALD are more likely to develop bacterial and invasive fungal infections, which are linked with more severe systemic inflammation and a higher mortality rate.[29] The clinical presentation of ALD can range from never-decompensated ALD to the life-threatening decompensated phenotype known as AH. AH patients present with worse liver function compared to never-decompensated ALD patients, and features such as bilirubinostasis, severe fibrosis, and ductular reaction are more prominent in AH.[30] Clinical presentation of ALD and non-alcoholic fatty liver disease (NAFLD) depends on the stage of liver disease. Most NAFLD patients are asymptomatic and diagnosed during routine health check-ups, while ALD requires a significant history of alcohol intake supported by radiological and biochemical tests.

DIAGNOSTIC WORKUP

The diagnostic workup of alcoholic liver disease includes several components. Firstly, a diagnosis of ALD requires information on the history of excessive alcohol consumption, along with blood tests such as Gamma-glutamyl Transferase (GGT), Aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and mean corpuscular volume.[32] These blood tests help in assessing liver function and damage. Additionally, imaging studies like abdominal ultrasound or transient elastography can be useful in evaluating the severity of ALD.[33] Liver biopsy may also be performed to confirm the diagnosis and provide prognostic value.[34] In terms of genetics, studies have shown that certain genetic variants are associated with alcoholic liver disease, such as PNPLA3, TM6SF2, and HSD17B13.[35] Overall, a comprehensive diagnostic approach involving history, blood tests, imaging studies, and genetic factors can help in diagnosing and evaluating the severity of alcoholic liver disease.

Expert suggestions are as follows (a) diagnosis of ALD relies on assessing alcohol consumption history and

laboratory findings; (b) liver biopsy may be indicated in select cases for confirming ALD diagnosis and assessing disease severity; (c) non-invasive methods like liver stiffness measurement (LSM) offer valuable insights into liver fibrosis; (d) genetic polymorphisms influence ALD progression and treatment response; (e) histological findings may not always correlate with clinical severity, impacting the role of liver biopsy; (f) liver biopsy remains relevant in specific scenarios such as ACLF; (g) caution is warranted when considering steroid therapy in ACLF patients, given limited efficacy and potential harm; and (h) comprehensive evaluation incorporating clinical assessment, non-invasive testing, and selective use of liver biopsy is crucial for effective ALD management.

GOALS OF THERAPY IN ALCOHOLIC LIVER DISEASE

The goals of therapy in ALD include achieving and maintaining alcohol abstinence, providing nutritional support, managing alcohol withdrawal syndrome (AWS), preventing and treating complications, and improving long-term outcomes. Abstinence from alcohol is crucial in the treatment of ALD and should be accompanied by support measures such as nutritional assessment and supplementation.[36,37] Combining psychosocial therapy, such as cognitive behavioral therapy, with appropriate pharmacological treatments can aid in achieving and maintaining alcohol abstinence.

Reducing inflammation is pivotal in managing ALD due to its central role in disease development and progression. In ALD, hepatic inflammation arises from inflammatory mediators and neutrophil infiltration. Targeting these mediators can mitigate liver inflammation and damage. However, excessive inflammation inhibition may hinder liver regeneration and worsen bacterial infections in severe ALD. Therefore, a balanced approach incorporating immunosuppression, hepatoprotection, and anti-bacterial strategies may be necessary for severe ALD treatment, given the intricate interplay of inflammatory processes in the disease.[38]

MANAGEMENT OF ALD

Alcohol abstinence and lifestyle management

In managing alcoholic liver disease, lifestyle adjustments such as alcohol cessation and weight reduction through diet and exercise are paramount. A holistic approach, incorporating abstinence from alcohol, weight management, and nutritional assistance, is imperative for effective long-term management of the condition.[39] Experts recommend strict abstinence from alcohol consumption for patients with severe ALD to mitigate risks of variceal bleeding, HCC development, and mortality. Fatty liver, a common manifestation, shows reversibility in over 90% of patients within four to six weeks of alcohol cessation.[40]

Nutritional therapy

Nutritional therapy emerges as a promising intervention in the management of chronic alcohol abuse, addressing the deficiency of essential macro and micronutrients prevalent in affected individuals. Studies have underscored the significance of adequate caloric intake, recommending a range of 35-40 kilocalories per kilogram of body weight, along with a protein intake of 1.5-2 g/kg of BW to mitigate mortality and infection risks.[41] Additional strategies include optimizing meal frequency, incorporating protein-rich nighttime snacks, and devising personalized dietary plans.[42] Supplementation with β-carotene, vitamins A, C, and E, zinc, and selenium holds considerable importance in combating the oxidative stress inherent in ALD. Importantly, both abstinence from alcohol and nutritional assessment or intervention are established therapeutic modalities applicable across all stages of the disease.[43]

PHARMACOLOGICAL TREATMENT

Steroids

Corticosteroids, such as prednisolone (40 mg/day) or methylprednisolone (32 mg/day) for 28 days, show short-term survival benefits in ALD. However, long-term mortality benefits are inconclusive, with 30%-40% of patients showing non-responsiveness.

Caution is warranted in patients with active viral infections, including hepatitis C, due to potential exacerbation of viral replication. Monitoring for sepsis and initiating antibiotic prophylaxis is recommended, as corticosteroid therapy carries an increased risk of sepsis and gastrointestinal bleeding. Discontinuation is advised in non-responsive cases, particularly in patients with a Lille score ≥0.56. Patients with massive ascites should avoid corticosteroids, while those with jaundice and coagulopathy may benefit. Treatment cessation after one week of no improvement reduces the risk of infection due to immunosuppression.[41]

Thiamine

Thiamine supplementation has shown potential for the treatment of ALD by reversing alcohol-induced toxicity and improving liver function. Studies have demonstrated that thiamine can alleviate hyperuricemia, gut barrier dysfunction, and inflammation activity in ALD patients.[44] Thiamine supplementation, either orally or intravenously, can increase thiamine blood levels and improve cognitive function in patients with AUD.[45]

Thiamine has also been found to reverse alcohol-induced toxicity by restoring liver and brain enzyme activities, reducing inflammatory markers, and promoting faster regeneration of hepatic and neuronal damage. Thiamine supplementation may be beneficial in preventing oxidative damage caused by chronic alcohol intake and could be considered as part of the treatment for ALD.

Benzodiazepines (BZDs)

BDZs are the drugs of choice for preventing alcohol withdrawal syndrome (AWS) in patients with alcoholic liver disease. Different treatment regimens and choice of BDZ can significantly affect the exposure of patients to these drugs.[47] Among the various benzodiazepines, lorazepam is considered the safest choice for this population.[48] However, their use in long-term treatment of alcoholism is not recommended due to their dependency-producing potency. while benzodiazepines are important in the management of AWS in ALD patients, their place in the therapeutic algorithm should be carefully considered, and their long-term use should be avoided.

Pentoxifylline

Pentoxifylline induces the production of tumor necrosis factor, rendering it a therapeutic option for alcoholic hepatitis. A double-blind, randomized controlled trial demonstrated a significantly lower mortality rate among patients with severe alcoholic hepatitis treated with pentoxifylline compared to controls (p=0.037). In this study, the incidence of alcoholic hepatitis was significantly lower in the group treated with pentoxifylline compared to the control group (8.2% verses 34.6%, p=0.0015), suggesting that its hepatoprotective role may contribute to reduced mortality rates. However, subsequent combination therapy of pentoxifylline with steroids or rescue therapy with pentoxifylline following steroid therapy showed no significant effect compared to steroid monotherapy. Moreover, in the STOPAH study, pentoxifylline therapy did not improve 28-day mortality rates (odds ratio 1.07; p=0.69). Singh et al.'s network meta-analysis suggested a survival improvement effect of pentoxifylline, albeit with low evidence levels, while other meta-analyses found no reduction in mortality rates with pentoxifylline. Conversely, a meta-analysis conducted by domestic researchers demonstrated a preventive effect of pentoxifylline on worsening renal function, suggesting the need for further research on the role of pentoxifylline in severe alcoholic hepatitis.[50]

N-acetylcysteine (NAC)

Oxidative stress is known to play a significant role in patients with alcoholic hepatitis. Initial studies using antioxidant therapies such as NAC and vitamin E in severe alcoholic hepatitis patients showed no improvement in prognosis. Subsequent multicenter studies in France found that combination therapy of NAC and steroids did not show a significant difference in 3-month and 6-month survival rates compared to steroid monotherapy (p=0.06, p=0.07), but did show an improvement in 1-month survival (8% vs. 24%, p=0.006) and a significantly lower incidence of hepatic encephalopathy (22% vs. 9%, p=0.02).[51] Additionally, network meta-analysis demonstrated evidence of improved 1-month survival with the combination therapy of steroids and NAC at a moderate level.[52] Therefore, while NAC holds promise as an adjunct therapy to steroids for improving survival in severe alcoholic hepatitis, further research is needed before its widespread clinical adoption.[49]

S-adenosylmethionine (SAMe)

SAMe emerges as a promising antioxidant for ALD treatment, as evidenced by its restoration of ethanol-induced mitochondrial dysfunction and attenuation of liver injury in animal models exposed to ethanol and other hepatotoxins. The typical dose is 400-1600 mg orally per day divided into three to four doses.

SAMe plays a crucial role in liver function, serving as a precursor of cysteine, a component of glutathione, a vital antioxidant. It also acts as a major methyl group donor in transmethylation reactions and regulates gene expression in hepatocytes by promoting liver-specific y methionine adenosyltransferase 1A (MAT1A) gene expression while inhibiting non-liver-specific MAT2A gene expression. Additionally, SAMe influences hepatocyte response to growth factors and cytokines. Impaired SAMe synthesis, observed in MAT1A knockout mice and patients with alcoholic cirrhosis, leads to liver injury and steatohepatitis. Chronic alcohol consumption reduces SAMe synthesis by inactivating liver-specific MAT, resulting in decreased liver-specific MAT activity, oxidant stress, and depleted glutathione levels. SAMe treatment has shown to improve survival rates in patients with alcoholic cirrhosis, possibly by preventing liver injury. Oxidation of a cysteine residue at position 121 by free radicals is proposed as a mechanism for liver-specific MAT inactivation.[53]

SAMe supplementation restores mitochondrial glutathione levels and mitigates liver injury associated with SAMe deficiency, glutathione depletion, and oxidant stress. SAMe administration also prevents liver tumor formation by enhancing DNA methylation.[52] SAMe potentially mitigates alcohol-induced liver disease by serving as a glutathione precursor, repairing mitochondrial glutathione transport, counteracting proinflammatory cytokines, and enhancing DNA methylation.[52]

Proteomic analysis has revealed that SAMe supplementation preserves proteins involved in key mitochondrial energy conserving and biosynthetic pathways, demonstrating its potential as a candidate for treatment of alcoholic liver disease.[54] SAMe has also been found to significantly reduce hepatic injury and fibrosis through inhibition of oxidative stress and hepatic stellate cell activation.[55]

Liver transplantation

Liver transplantation is a valuable option for patients with life-threatening ALD, particularly in cases of unresponsive alcoholic hepatitis.[56] Despite concerns about relapse, careful evaluation and selection of patients can lead to successful outcomes, with survival rates like non-alcoholic patients.[57] However, post-transplantation, ALD patients

are at increased risk of cardiovascular disease and aerodigestive tract cancers, highlighting the need for ongoing care and support.[54]

Expert suggestions on pharmacological management of ALD are as follows- (a) current therapy options for alcoholic liver disease include alcohol cessation, pharmacological treatments such as baclofen and acamprosate, lifestyle changes, and, in severe cases, corticosteroids; (b) alcohol abstinence is a cornerstone of management and should be recommended in all patients with alcoholic liver disease; (c) pharmacological treatments like baclofen, acamprosate, and topiramate are effective in preventing alcohol relapse and should be considered in patients with alcohol use disorder; (d) lifestyle changes, including smoking cessation, reduction of body weight, and nutritional support with adequate calorie and protein intake, improve survival and reduce the risk of hepatic encephalopathy and infections; (e) corticosteroids have been used in the management of alcoholic hepatitis, but their benefits are limited and may be associated with risks such as infections and organ failure; (f) fentoxifylline, although not associated with significant improved survival, may reduce the risk of acute kidney injury and hepatorenal syndrome in patients with alcoholic hepatitis' (g) NAC has shown early short-term improvement in treatment outcome when used in combination with steroids, but its long-term effects are inconsistent; (h) SAMe supplementation replenishes antioxidant levels, modulates inflammatory cytokines, and improves clinical and biochemical parameters in alcoholic liver disease patients. SAMe has also been shown to elevate mood by regulation of liver-produced inflammatory cytokines in cerebral tissue; (i) the development of novel drugs targeting different pathways involved in the progression of alcoholic liver disease is crucial to improve patient outcomes and reduce mortality rates; and (j) further research and clinical trials are essential to identify and validate new therapeutic targets and drug candidates for the management of alcoholic liver disease.

CONCLUSION

The management of alcoholic liver disease requires an understanding of its inflammatory pathophysiology and a multi-faceted approach. Alcohol abstinence remains the cornerstone of treatment. Addressing the inflammatory component through various pharmacological interventions is quintessential for improving long term outcome in ALD. Current evidence supports the use of emerging therapies targeting specific inflammatory pathways such as SAMe. The role of nutritional support and lifestyle modifications cannot be understated. Early identification and intervention in high-risk patients, along with better strategies to maintain alcohol abstinence, are essential for improving long-term outcomes. As our understanding of the inflammatory mechanisms in ALD continues to evolve, more targeted and effective therapeutic approaches may emerge.

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