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Review Article

Current Concept of Management of Alcoholic Hepatitis

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Abstract

Alcohol is in use probably since ancient civilization era in different parts of the world. The harmful use of alcohol causes more than 200 diseases. Alcoholic hepatitis (AH) represents the most severe manifestation of alcohol-associated liver disease. Severe AH is associated with a high short-term mortality of up to 50% at 3 months. Emerging and promising treatment approaches for AH include anti-inflammatory agents (e.g., canakinumab), modifications of the gut-liver axis (e.g., through fecal microbiota transplantation or bacteriophages), epigenetic modulation, and drugs targeting liver regeneration (e.g., interleukin-22 agonists or granulocyte colony-stimulating factor). Growing evidence confirms the benefits of early liver transplantation in selected patients with severe AH, who do not respond to medical therapy.

Key words: Alcohol use disorder, Alcoholic Hepatitis, Early liver transplantation, Liver disease

INTRODUCTION

Alcohol is in use probably since the ancient civilization era in different parts of the world. Ancient Ayurvedic texts described both the beneficial uses and the bed effects of intoxication and alcoholic diseases. Alcohol was considered a medicine if consumed in moderation, but a poison if consumed in access. The discussion is still on.

Alcohol use may cause more than 200 diseases and conditions. Worldwide, harmful use of alcohol causes more than 3 million deaths every year. This is around 5.3% of all deaths. Apart from disease conditions, the harmful use of alcohol is responsible for social and economic losses to individuals and society at large.

Alcoholic liver disease (ALD) is the most prevalent type of chronic liver disease worldwide and it has increased exponentially over the last decade. ALD can progress from alcoholic fatty liver (AFL) to alcoholic steatohepatitis (ASH), Chronic ASH eventually leads to fibrosis and cirrhosis, and in some cases, hepatocellular carcinoma (HCC). In addition, severe ASH (with or without cirrhosis) can lead to alcoholic hepatitis (AH), which is an acute clinical presentation of ALD that is associated with liver failure and high mortality.[1]

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SIGNIFICANT ALCOHOLISM

There is no international consensus as to the amount of alcohol considered "Significant" or "Harmful."

Daily consumption of 30–50 g of alcohol for over 5 years can cause ALD. Steatosis can occur in 90% of patients who drink over 60 g/day, and cirrhosis occurs in 30% of individuals with long-standing consumption of more than 40 g/day.

The Asia Pacific Association of Study of Liver (2017) guideline has given more useful conservative alcohol threshold which is usually followed.

Men: 2 standard drinks/day or 140 g/week and Women: 1 standard drink/day or 70 g/week.

Definition of one alcoholic drink as per the Centers for Disease Control and Prevention:

12 oz beer (5% alcohol), 8 oz malt liquor (7% alcohol), 5 oz wine (12% alcohol), or 1.5 oz 80-proof "hard-liquor" (40% alcohol).

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TERMINOLOGY OF ALCOHOL-RELATED LIVER DISEASES

1. Alcohol use disorder (AUD) is a medical condition characterized by an impaired ability to stop or control alcohol use despite adverse social, occupational, or health consequences. It encompasses the conditions that some people refer to as alcohol abuse, alcohol dependence, alcohol addiction, and the colloquial term, alcoholism.
2. Alcohol-associated liver disease (ALD) includes a wide range of disease entities resulting from harmful alcohol use and is one of the most prevalent causes of advanced liver disease worldwide. At present, it is the most common cause of cirrhosis in many countries. The spectrum of ALD encompasses AFL, alcohol-associated hepatitis with or without progressive fibrosis, cirrhosis, and its related complications, as well as HCC.
3. AH represents the most severe syndrome of all alcohol-induced liver pathologies and is characterized by a sudden onset of jaundice and clinical signs of hepatic decompensation, along with an intense systemic inflammatory response and high short-term mortality. It can occur as a first presentation of earlier asymptomatic ALD or as an exacerbation of pre-existing chronic liver disease. AH frequently triggers acute decompensation or acute-on-chronic liver failure.

HISTOLOGIC STAGES OF ALCOHOLIC LIVER DISEASE[2]

1. AFL or Steatosis – At this stage, fat accumulates in the liver parenchyma
2. AH – Inflammation of liver cells takes place at this stage, and the outcome depends on the severity of the damage
3. Alcoholic Cirrhosis – Liver damage at this stage is irreversible and leads to complications of cirrhosis and portal hypertension.

DEFINITION OF AH

AH typically occurs acutely in patients with heavy and prolonged alcohol consumption and is characterized by new-onset jaundice, malaise, right upper abdominal pain (tender) hepatomegaly, fever, and laboratory signs of mild-to-moderate hepatocyte injury and systemic inflammatory response. AH represents the most severe manifestation of alcohol-associated liver disease. Severe AH is associated with a high short-term mortality of up to 50% at 3 months [Figure 1].

PATHOPHYSIOLOGY [FIGURE 2]

Alcohol metabolism by the liver is primarily through two enzymes:
1. Alcohol dehydrogenase
2. Aldehyde dehydrogenase

Alcohol dehydrogenase converts alcohol into acetaldehyde, and aldehyde dehydrogenase converts acetaldehyde into acetate. The metabolism of alcohol increases the production of NADH by reducing NAD in the body. This shifting of metabolic balance toward the production of NADH leads to the formation of glycerol phosphate, which combines with the fatty acids and becomes triglycerides, which accumulate within the liver. When lipid oxidation (lipolysis) stops due to alcohol consumption, fats accumulate in the liver and lead to "fatty liver disease."

Continued alcohol consumption brings the immune system into play. Interleukins (ILs) with the help of neutrophils

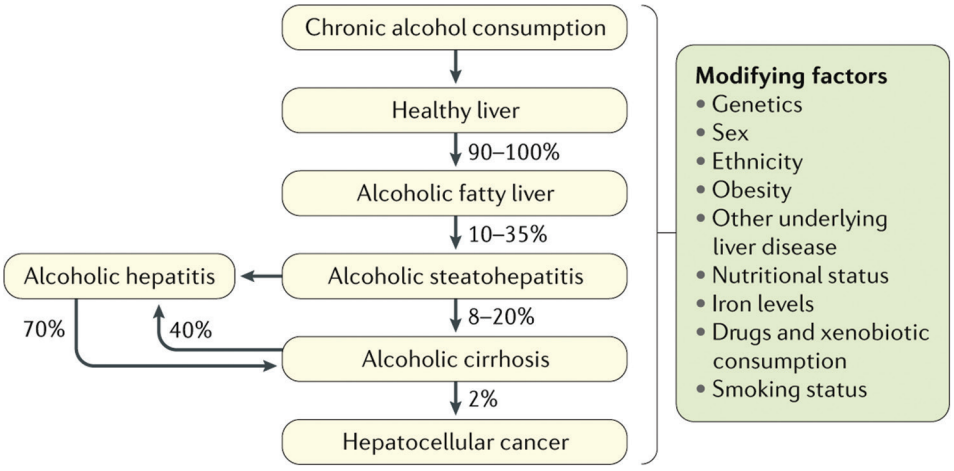

Figure 1: Progression of alcoholic liver disease

attack the hepatocytes, and swelling of the hepatocytes known as the "alcoholic hepatitis" takes place.

Ongoing liver injury leads to irreversible liver damage, the cirrhosis of the liver.

Most individuals consuming >40 g of alcohol per day develop acute fatty liver. However, only some of them will develop more advanced diseases. Genetic, epigenetic, and non-genetic factors might explain the considerable inter-individual variation in ALD phenotype [Figure 1].

CLINICAL PRESENTATION OF AH [FIGURE 3][3]

AH typically presents with new-onset jaundice, upper abdominal pain, malaise or fatigue, and sometimes, fever. More severe patients can have ascites, edema, tachycardia, loss of appetite, weight loss, nausea, and confusion.

Most of the patients got a history of heavy chronic alcohol use, which continued until <8 weeks before the onset of jaundice. Usually, this describes a history of discontinuation of alcohol days or weeks before the onset of symptoms.

General physical examination typically shows jaundice, hepatomegaly, splenomegaly, spider telangiectasias, Dupuytren contractures, testicular atrophy, decreased libido, parotid and lacrimal gland enlargement, white nails, Muecke lines, asterixis, and features of portal hypertension such as ascites, pedal edema, encephalopathy, and caput-medusae.

The cardinal sign is the rapid onset of jaundice. Other signs and symptoms include fever, ascites (SAAG [serum-ascites albumin gradient] >1.1), and proximal muscle loss. Patients presenting with severe AH may have encephalopathy.

INVESTIGATIONS

1. Complete blood count to rule out the infection and complications of cirrhosis such as anemia, thrombocytopenia, and a leukemoid reaction in AH.
2. Markers for Infection: AH and infection can be closely associated and need differentiation for management. An increase in inflammatory markers with leukocytosis, neutrophilia, and elevated C-reactive protein levels is of high significance. Microbiological testing testings are also of paramount importance

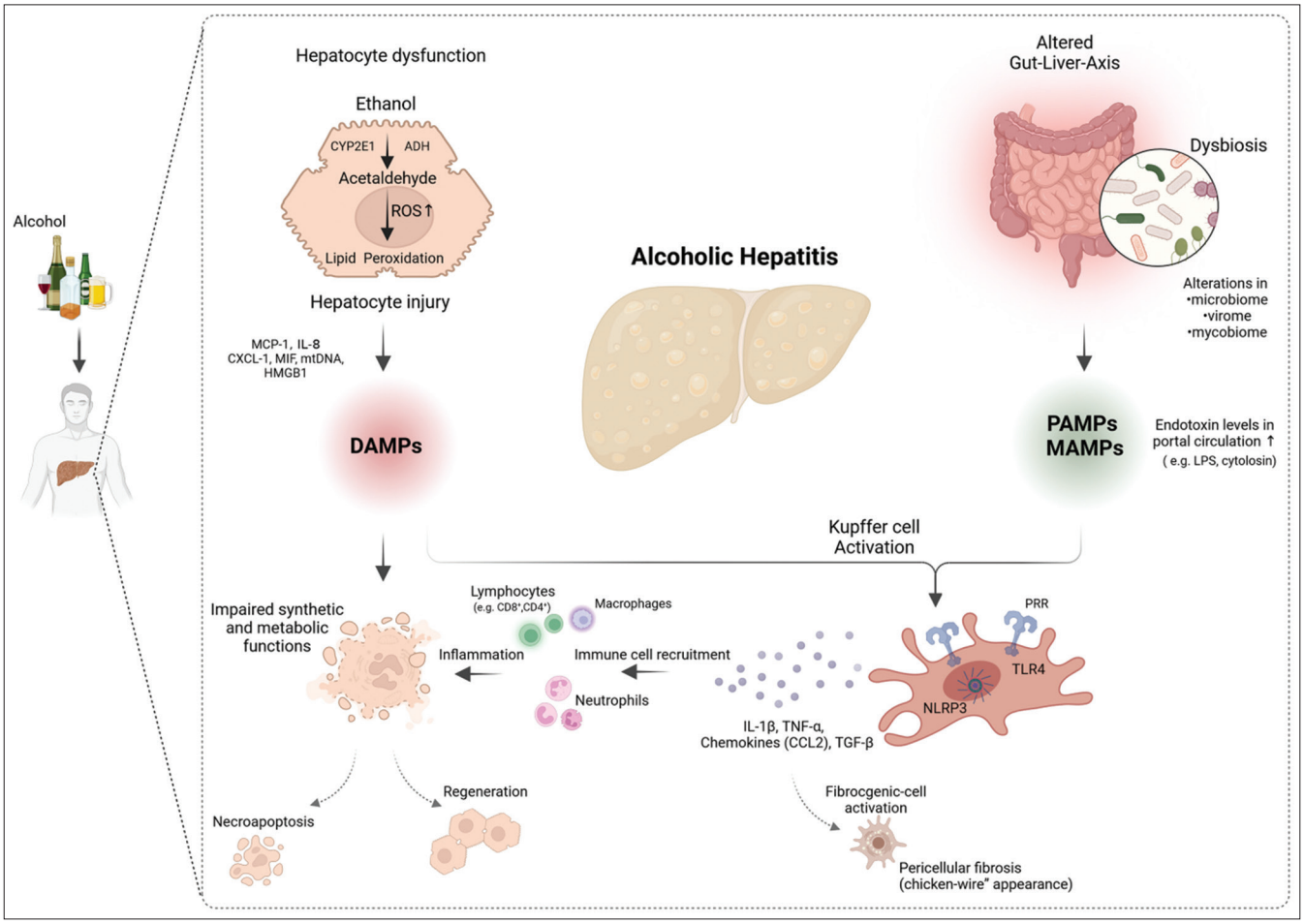

Figure 2: Pathophysiology of alcohol-associated hepatitis

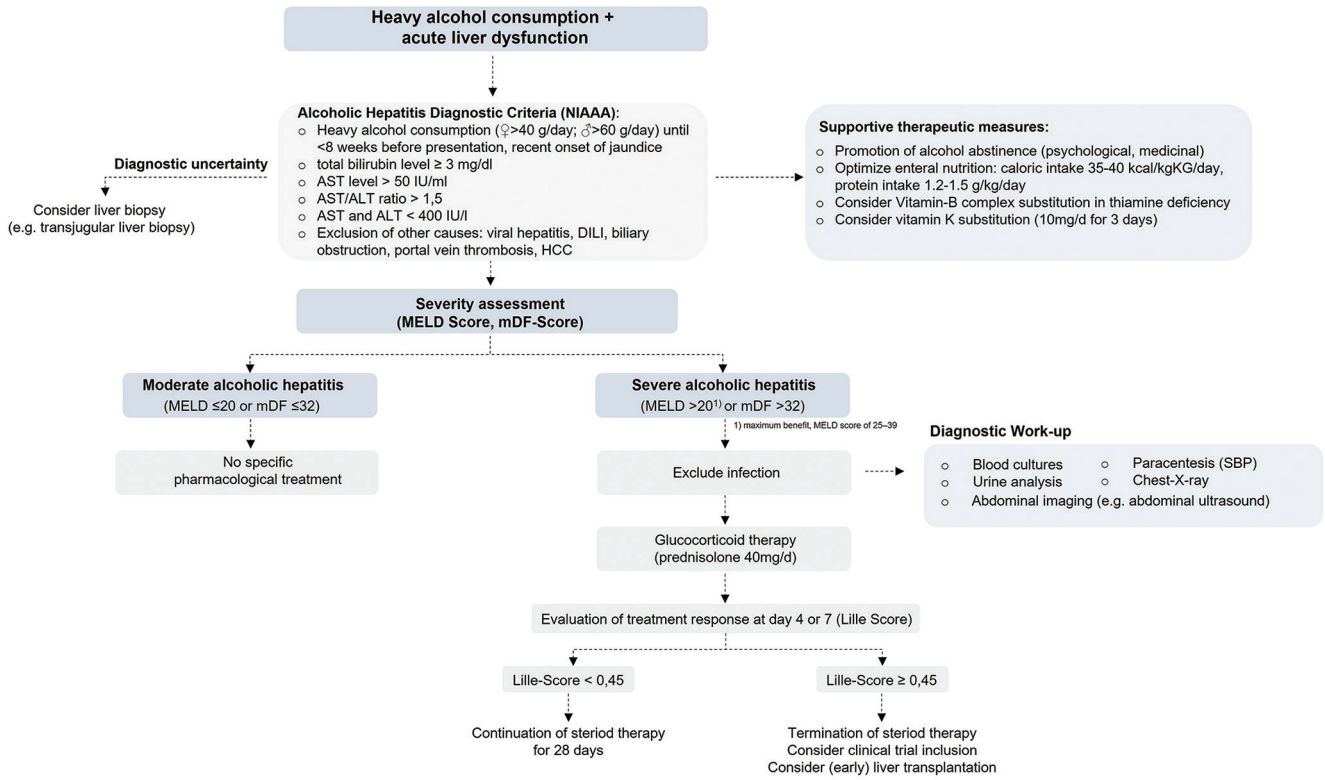

Figure 3: Algorithm for the diagnosis and management of alcohol-associated hepatitis (Kasper *et al.*)

3. Liver Function Tests: Increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels (AST/ALT ratio >1.5) with AST levels >50 IU/mL, whereas the absolute values of AST or ALT usually do not exceed values of 300–400 U/L. Furthermore, Often there is elevated serum bilirubin levels (>3 mg/dL). There is hypoalbuminemia and hypertriglyceridemia, and gamma-glutamyl transpeptidase is usually raised. Prothrombin time and INR (to assess liver synthetic function): An elevated value indicates more severe disease.
4. Abdominal imaging: Liver imaging by ultrasonography, elastography, or MRI should be performed in all patients with suspected AH to rule out other causes of liver disease, including biliary obstruction, liver malignancies, or infectious complications.
5. Basic metabolic profile should be performed for renal failure and electrolyte disturbance (low levels of potassium, magnesium, and phosphorus).
6. Ascitic fluid SAAG should be calculated to assess the reason for ascites if present.
7. Screening blood tests for other causes of chronic liver disease include viral hepatitis.
8. Endoscopy to look for esophageal varices due to portal hypertension in patients with cirrhosis.
9. Liver biopsy can lead to a definitive diagnosis in cases where the diagnosis is uncertain. Liver biopsy has a risk of complications, including life-threatening hemorrhage, so it is reserved for cases where the results of a biopsy can make a difference in the treatment plan.

CURRENT MANAGEMENT APPROACHES OF AH

All patients with suspected AH should be hospitalized for a comprehensive evaluation to confirm the diagnosis, assess disease severity, screen for infections, and determine treatment modality. Alcohol abstinence, optimal nutrition, corticosteroids, and prevention of infections are currently the mainstays of treatment for AH [Figure 4].

Alcohol Abstinence

Complete abstinence from alcohol is one of the most important factors in the long-term prognosis of patients with AH. Unfortunately, alcohol abstinence is only achieved in a minority of patients with AH.

Nutrition

Patients with AH often present with malnutrition, which is another major determinant of mortality. Patients with AH with a daily caloric intake of <21.5 kcal/kg of body weight seem to have a worse prognosis. Unlike earlier

thought, increasing daily protein intake of 1.2–1.5 g/kg body weight with a total calorie intake of 30–40 kcal/kg body weight/ day is generally recommended. Interestingly, an intensive enteral nutrition regimen through a nasogastric tube had no additional survival benefit at 6 months when compared to routine oral nutrition. Supplementation of zinc may be considered in patients with AH, as zinc deficiency is common in patients with ALD, and studies have demonstrated that zinc supplementation protects against alcohol-induced liver injury and is critical for the maintenance of intestinal barrier.

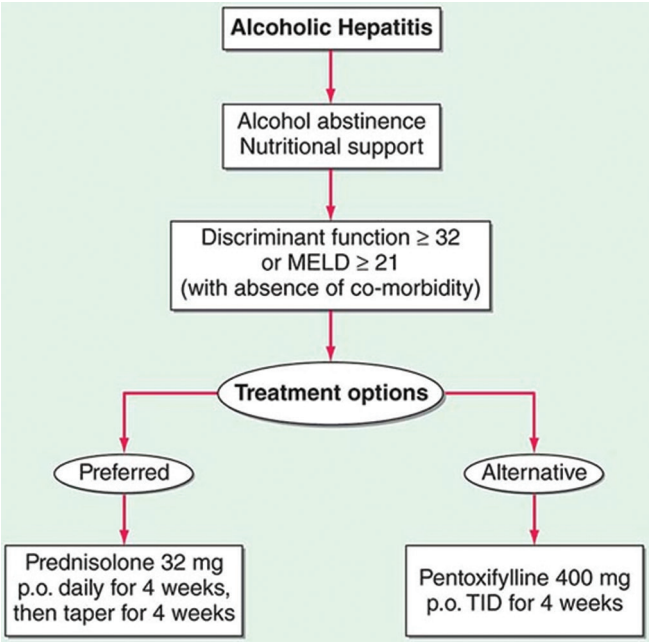

Figure 4: Treatment algorithm of alcoholic hepatitis

Glucocorticoid Treatment

In patients with severe AH (MDF ≥32 or Model for End-Stage Liver Disease score >20), glucocorticoid treatment should be initiated.

Oral prednisolone, 40 mg/d, is the recommended dose. For patients unable to receive oral medication, intravenous methylprednisolone (32 mg/d) is recommended. Uncontrolled infection or sepsis, gastrointestinal bleeding, and the presence of severe kidney injury (serum creatinine >2.5 mg/dL) are contraindication to corticosteroid therapy.

Whether prophylactic antibiotic administration can improve prognosis in severe AH in the absence of infection remains unclear.

Pentoxifylline

Patients who have got contraindications to steroids may receive pentoxifylline (400 mg orally, 3 times a day for 28 days).

Emerging Treatment Options[4]

New potential therapeutic targets include (i) inflammatory cytokine antagonism, (ii) modification of the gut-liver axis, (iii) reducing oxidative stress, and (iv) improving liver tissue regeneration [Figure 5].

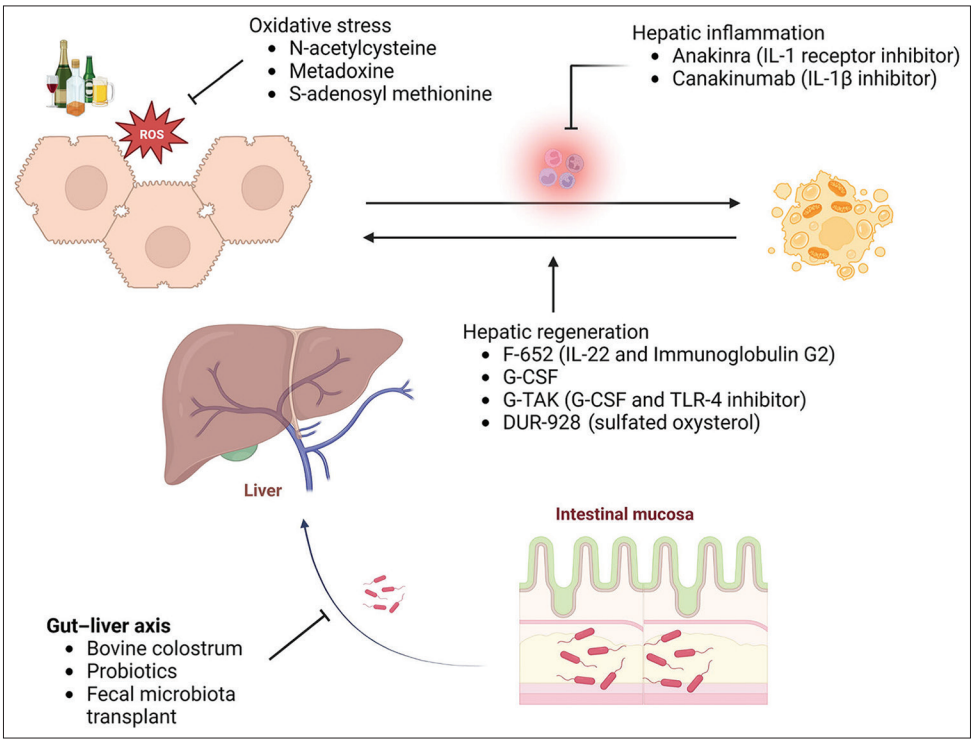

Figure 5: Emerging treatment options of alcoholic hepatitis (Yoon and Kim)

Anti-inflammatory Agents

Due to the extensive role of immune-mediated inflammation, anti-inflammatory therapies and immunomodulatory agents are promising approaches to controlling hepatic inflammation in AH. A cytokine of particular importance in the pathogenesis of AH is IL-1.

It is suggested that treatment with the IL-1 receptor antagonist anakinra could be of good benefit in AH. However, recent studies are not promising.

However, another IL-1β antibody canakinumab is highly promising.

Chemokine receptor antagonists, such as the dual CCR2/CCR5 antagonist cenicriviroc, may also represent a potential anti-inflammatory treatment option in AH.

Another innovative therapeutic approach is the inhibition of so-called super-enhancers (transcription-regulating genomic elements).

Tumor necrosis factor (TNF)α is another important mediator in the inflammatory response of alcohol-related liver injury. TNFα inhibitors (e.g., infliximab, etanercept) have not been shown to be effective in the treatment of AH. Inhibition of TNFα showed adverse effects and was associated with higher mortality and a higher rate of infectious complications in AH.

Modification of the Gut Liver Axis

Alcohol-induced dysbiosis is associated with increased intestinal permeability and increased bacterial translocation, which are critical for the development and progression of AH. Therefore, modifications of the dysfunctional gut-liver axis represent another attractive therapeutic target. Potential approaches include fecal microbiome transplantation, administration of oral non-absorbable antibiotics, administration of probiotics, or treatment with bacteriophages.

Reducing Oxidative Stress

Reactive oxygen species, which cause oxidative stress and hepatocellular damage, are also centrally involved in the pathogenesis of AH. Thus, drugs that can reduce oxidative stress (e.g., N-acetylcysteine, metadoxine) represent further promising therapeutic strategies.

Combination of intravenous NAC with corticosteroids was associated with a reduced rate of infections and 1-month mortality. Metadoxine is able to restore intrahepatic glutathione reserves and also showed survival benefits.

Targeting Liver Tissue Regeneration

Inadequate regenerative capacity due to acute hepatocellular injury is another feature in the pathogenesis of AH and correlates with poor outcomes. Therapeutic agents with pro-regenerative hepatoprotective properties include granulocyte-colony stimulating factor (G-CSF) and IL-22 agonists. G-CSF comprises both a pro-regenerative capacity, which boosts proliferation in progenitor and parenchymal cells and immunomodulatory properties to maintain an adequate pathogen response.

Therefore, G-CSF administration has been proposed as a therapeutic option for AH. However, there are contradictory results.

IL-22 exhibits anti-apoptotic, anti-oxidative, anti-steatotic, and pro-proliferative effects, which may reduce hepatic inflammation and promote hepatic regeneration in AH.

Early Liver Transplantation (LT) for Alcohol-Associated Hepatitis[5]

The role of LT in patients with AH remains controversial. Despite high mortality rates, most patients are not eligible for LT, as the majority of regulations for liver transplantation require alcohol abstinence for at least 6 months before LT due to ALD.

However, recently early liver transplantation is emerging as a treatment option for severe alcohol-associated hepatitis refractory to pharmacotherapies. Rates of early liver transplantation for alcohol-associated hepatitis are increasing with significant heterogeneity in practices across the globe. Recent studies have demonstrated a substantial survival benefit in patients transplanted for AH with improved outcomes in early versus late transplantation, first versus prior hepatic decompensation, and post-transplant abstinence/delayed relapse versus early return to alcohol use. Additional research is needed to evaluate its long-term outcomes, optimize candidate selection, and understand the treatment of AUD post-transplant.

FOLLOW-UP

Relapse prevention (RP) in alcohol dependence is a strategy for reducing the likelihood and severity of relapse after the cessation of alcohol use. RP is done using a combination of pharmacotherapy and a cognitive behavioral approach with the goal of identifying and addressing high-risk situations for relapse and assisting individuals in maintaining abstinence. Alcohol abstinence achieved by psychosomatic intervention is the best treatment for all stages of ALD.

Screening for HCC with ultrasonography every 6 months with alpha-fetoprotein analysis is important. Endoscopic evaluation for esophageal varices in those with cirrhosis is also required during follow-up.

In the Western world, chronic alcoholics are more prone to develop hepatotoxicity from acetaminophen, so dosing should not exceed more than 2000 mg/day. An average person can tolerate up to 4000 mg of acetaminophen per day.

Treatment of coexisting liver diseases such as hepatitis B and C viral infections is equally required.

CONCLUSION

The global strategy to reduce the harmful use of alcohol and its associated health and social burden is a public health priority. Global action plan for the prevention and control of non-communicable diseases 2013–2020 provides a new set of enabling and focused recommended actions to reduce the harmful use of alcohol.

Emerging and promising treatment approaches for AH include anti-inflammatory agents (e.g., canakinumab), modifications of the gut-liver axis (e.g., through fecal microbiota transplantation or bacteriophages), epigenetic modulation, and drugs targeting liver regeneration (e.g., IL-22 agonists or G-CSF).

Growing evidence confirms the benefits of early liver transplantation in selected patients with severe AH, who do not respond to medical therapy.

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