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Understanding alcohol-associated liver disease: a focus on alcohol-associated hepatitis

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Patients living with steatotic liver diseases continue to face significant unmet medical needs. As drug development sponsors are increasingly focusing on innovative products to address these diseases, a basic understanding of the landscape is useful.

The purpose of this white paper is to increase awareness of alcohol-associated liver disease and the serious complications of alcohol-associated hepatitis and acute-on-chronic liver failure. Drug development sponsors will learn about the challenges of advancing clinical studies in this indication along with potential mitigation strategies.

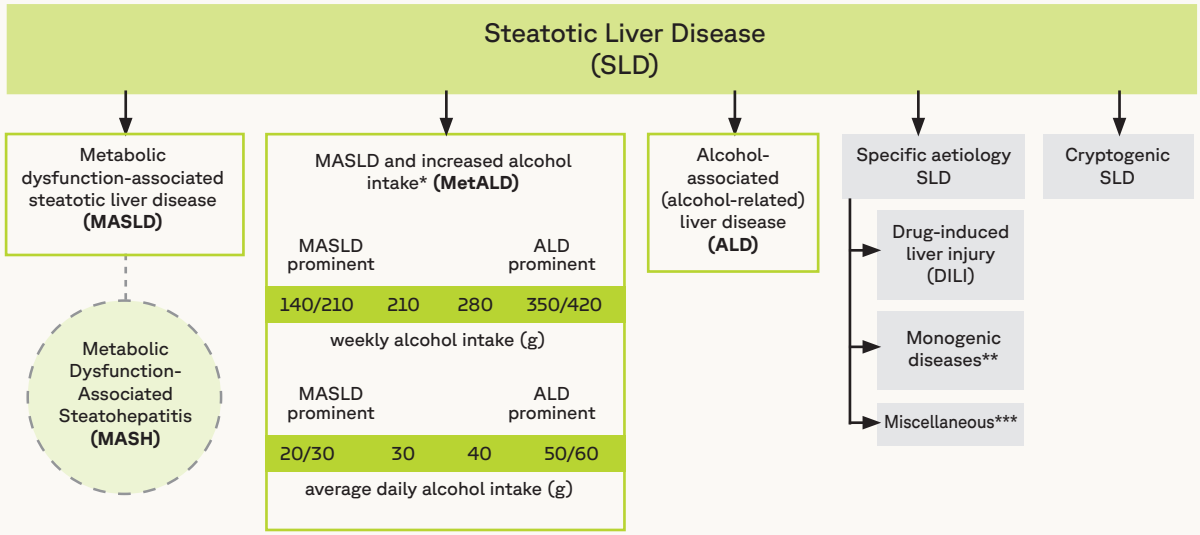
Understanding alcohol-use disorder (AUD) and the new classification of steatotic liver diseases

Alcohol-use disorder (AUD) continues to be a major cause of liver disease and liver-related complications/hospitalizations and death throughout the world. According to the DSM-5 definition, any patient meeting two of 11 of the published criteria within a 12-month period would receive a diagnosis of AUD. Severity is dependent upon the number of criteria met.[1]

Approximately 50% of deaths due to liver disease globally are attributed to alcohol use. Additionally, for those patients with alcohol use disorder, approximately 35% will develop some form of alcohol-associated liver disease (ALD).[2] The continuum of AUD ranges from simple steatosis to the development of chronic liver disease characterized by metabolic-related steatohepatitis, fibrosis, cirrhosis, and liver failure including the development of hepatocellular carcinoma, a serious complication of advanced ALD. The rapidity with which these complications develop varies and may in part be due to additional comorbid medical conditions as well as environmental conditions.

Alcohol-associated liver disease (ALD) is categorized under the umbrella of the recently adopted term, "steatotic liver disease." [3] New nomenclature is now used for a spectrum of steatotic liver diseases: the previous terminology of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH) has been replaced by metabolic dysfunction-associated steatotic liver disease (MASLD/MASH); metabolic and alcohol-related steatotic liver disease (MetALD) was selected to describe those individuals with MASLD who consume more than 140-350 g/week and 250-420 g/week of alcohol for females and males respectively. This new nomenclature has been widely supported by the hepatology community and hopefully will be less stigmatizing, allowing for a more accurate diagnosis of a patient's underlying steatotic liver disease etiology (see Figure 1).

Figure 1. Classification of steatotic liver diseases



From Rinella ME, Lazarus JV, Ratziu V et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *Hepatology.* 2023; 79:1542-1556.
*Weekly intake 140–350 g female, 210–420 g male (average daily 20–50 g female, 30–60 g male). **e.g., Lysosomal acid lipase deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism. ***e.g., HCV, malnutrition, celiac disease, human immunodeficiency virus (HIV)

In contrast to those with simple MetALD, a subset of individuals consuming heavy amounts of alcohol can develop a more severe form of MetALD. This severe form of liver injury, called alcohol-associated hepatitis (AH) is an important etiology of acute-on-chronic liver failure (ACLF), both in the U.S. as well as in Europe and globally. Important in the definition of ACLF is the absence of a new hepatic decompensation event, as well as evidence of acute liver failure (with/without a history of underlying liver disease). It is characterized by the existence of organ system failure(s) and a high risk of short-term mortality. ACLF can frequently be precipitated by an infection, inflammation or dysfunction of the immune system and is a systemic disease. Further discussion of ACLF is beyond the scope of this article and may be addressed in a future publication.

MetALD and alcoholic-associated hepatitis

Susceptibility to the development of the more aggressive form of MetALD is presently unknown but thought to be associated with both environmental, genetic and epigenetic factors. Genetic factors such as the presence of the PNPLA3 gene, seen frequently in Hispanic populations, have been shown to be associated with disease severity among those with the diagnosis of alcoholic-associated hepatitis (AH).[2] Gender differences have also been described, with women being more prone to the development of alcohol injury and cirrhosis.[4] Younger women now constitute a group of patients more frequently being referred for liver transplantation evaluation in the U.S. due to excessive alcohol use.[5]

The pathogenesis of AH is poorly understood, and a detailed description of recent developments is beyond the scope of this white paper. Briefly, the gut-liver axis alteration of the microbiome, disruption of tight junctions increasing gut permeability, and increased production of mitochondrial DAMPs (damage-associated molecular patterns) and PAMPs (pathogen-associated molecular patterns) all likely play a role. Additionally, hepatic metabolism of acetaldehyde, resulting in the development of reactive oxygen species (ROS) and lipid peroxidation, causes hepatocyte injury; in some patients this injury leads to the development of portal hypertension, liver failure, severe immune system alteration with sepsis, acute on chronic liver failure, multiorgan failure and death unless liver recovery occurs. Presently, urgent liver transplantation is the only modality that improves the prognosis for patients not responding to medical therapy.[6]

Abnormal hepatic lipoprotein and cholesterol metabolism are present in patients with MetALD and AH, causing the accumulation of lipoprotein Z particles (LP-Z) in the serum. *In vitro*, LP-Z particles exert hepatotoxicity and may contribute to the pathogenesis of the disease.[7] The association of significant hepatotoxicity with these abnormal LP-Z particles require further study, and, if validated further, could potentially be identified as a key contributor to the pathogenesis of AH. Their detection could allow for early diagnosis of AH and have prognostic implications for the disease as well.

Diagnosis, potential biomarkers and current medical treatment

The National Institute on Alcohol Abuse and Alcoholism (NIAAA)-funded Alcoholic Hepatitis Consortia has proposed criteria for the clinical definition of AH.[8] The absence of other causes of liver disease, as well as the absence of biliary obstruction are important to document prior to consideration of the diagnosis of AH. Liver biopsy, although preferable, is invasive, costly and may not be feasible in patients with such severe liver disease due to underlying comorbidities, coagulation disorders, etc. There is clear interest in the development of non-invasive diagnostic and prognostic biomarkers to augment clinical decision-making in AH. In addition to LP-Z particles discussed above, cytokeratin-18 fragments may be useful to correlate disease severity as well as possible response to steroid therapy.[9] Pro-C3 may also be useful to predict liver-related events in ALD and AH.[10] Although some patients can spontaneously recover after alcohol abstinence, for others the disease progression will require urgent liver transplantation to avert the high risk of death. To date, there are no significant advances in medical therapy to treat this disease.

Corticosteroids have been shown to have a short-term beneficial effect in patients with severe AH, with no significant impact on 60–90-day mortality and are most beneficial in patients with Model for End-stage Liver Disease (MELD) scores of ≥20. Maximum benefit has been noted in those with MELD scores of 25-39.[11] Due to the underlying immune system dysfunction and presence of infection in many patients presenting with AH, steroids are frequently not able to be utilized. Increased infection rates have also been seen to occur during steroid treatment.[12] Although

granulocyte-colony stimulating factor (G-CSF) plus standard medical therapy were associated with an improvement in three-to-six-month survival and reduced infections in one study, a more recent study failed to show a benefit.[13] Since malnutrition is also highly prevalent in this patient population, nutritional assessment and provision of adequate protein and calories are part of the medical regimen.

A focus on clinical trials, challenges and future directions for alcoholic-associated hepatitis

There are still no FDA-approved pharmacological therapies for treating patients with alcoholic-associated hepatitis. Cessation of drinking (i.e., abstinence) is an integral part and first-line therapy for all aspects of the disease. Liver transplantation remains the life-saving strategy for patients with end-stage alcohol-related liver disease and those with ACLF related to alcohol use.[14] However, clinical guidelines to standardize the definition of the patients to be randomized to an ACLF trial, as well as the surrogate endpoints that can potentially lead to a reduction in the number of patients requiring a liver transplant through an accelerated approval path, are clearly warranted.

Clinical studies in AH pose several challenges, including some of the following:

- **Inclusion of the appropriate patients:** It is helpful to enroll patients most likely to avoid recidivism (for example, patients with family support, individuals that do not have multiple convictions of driving under the influence (DUI), those with meaningful employment and a purpose to live, etc.)
- **Applying the appropriate model:** While no individual model has shown to be superior, the use of Maddrey's discriminant function, MELD score, and/or the Lille model can support early identification of patients with a high likelihood of short-term mortality[14]
- **Patient retention:** To avoid significant drop-out rates and retain subjects in the trial after discharge from the hospital, ongoing communication with the site, patients and their family members needs to be part of the strategy
- **Operations and communications:** Conducting a clinical trial in an intensive care unit poses operational challenges. Development and maintenance of a communication plan between the study team and ICU staff is essential to outline each member's role and responsibility
- **Data quality and study safety:** Drug development sponsors must understand each hospital's HIPAA policy. Access to the subject's electronic medical records must also be planned and established prior to study start to ensure data quality and study safety

Looking ahead to improve the drug development landscape in AH

Future directions in AH should focus on the development of targeted medical therapies to treat the disease, as well as the development of better diagnostic and prognostic biomarkers for earlier identification of AH. Defining those patients who might potentially respond to medical therapy should also be a focus of future research. For those requiring urgent liver transplantation, it is critically important to focus on the development of more standardized criteria for evaluation, duration of recidivism before transplantation and maintenance afterward. Adequate mental health resources are also integral to long-term success by identifying and treating an underlying alcohol use disorder prior to its progression.

Learn how Fortrea is committed to improving the lives of patients as we advance the field of liver disease research through cutting-edge clinical trials and innovative treatments. https://www.fortrea.com/scientific-expertise/by-therapeutic-or-specialty-areas/hepatology.html.

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