Editorial

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Alcohol-related liver disease: Time for action

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The overall landscape of clinical hepatology has markedly evolved in the last few years. Recent major advances in the management of viral hepatitis B and C with highly effective therapies are decreasing the proportion of patients with viral-related end-stage liver disease in many countries.[1] Consequently, increasing attention is being paid to fatty liver diseases (both alcohol-related liver disease [ALD] and non-alcoholic fatty liver disease [NAFLD]) as the main current and future driver of liver-related health burdens. While NAFLD is probably the main cause of mild liver disease globally, ALD remains the main cause of liver-related mortality worldwide.[2] Despite its huge health and economic burden, ALD has traditionally received little attention compared to other types of liver diseases. However, in the last years there has been renewed public and research interest in this prevalent cause of severe liver disease. Epidemiological studies have revealed an alarming increase in alcohol intake and ALD in emerging countries, and recent evidence supports the notion that binge drinking in youth precedes the development of cirrhosis in adulthood.[3] These studies have stimulated policymakers to take more active measures to reduce alcohol-related harm. From a clinical standpoint, there is a clear need to perform clinical trials to treat alcohol use disorder (AUD) in the setting of ALD, as highlighted in a recent review by Addolorato *et al.* in *Journal of Hepatology*.[4] New non-invasive tools are increasingly being used to detect significant, albeit subclinical, liver disease among patients with an AUD. Moreover, there are encouraging new results from novel targeted therapies to treat alcoholic hepatitis (AH), the most devastating clinical form of ALD that urgently needs effective therapeutic advances.[5] Important clinical trials assessing treatments for patients with severe AH are underway. For patients with life-threatening AH, there is a current trend to offer early transplantation to highly selected patients.[6] In order to develop targeted therapies, numerous laboratories around the world are uncovering novel cellular and molecular mechanisms of ALD including the role of innate immunity and the gut-liver axis.[7] New animal models of ALD have been developed, and several groups are working on developing a model of true AH mimicking the human disease (*i.e.* jaundice, advanced fibrosis, *etc.*).[8] All of these advances are attracting a new generation of clinicians and scientists to work collaboratively to beat ALD.

Following recent supplements on viral hepatitis B and C as well as NAFLD, the *Journal of Hepatology* commissioned the current supplement to review the current efforts to prevent, diagnose and treat ALD. The four co-editors of this supplement discussed and agreed on ten main topics that cover the most relevant aspects of ALD, ranging from public health policies, molecular mechanisms and clinical topics, such as non-invasive diagnosis, hepatocellular carcinoma and liver transplantation. Two important topics (*i.e.* management of AUD and genetic predisposition to ALD) were not included as they were recently covered by excellent reviews in the *Journal of Hepatology*.[4,9]

Because primary prevention is the most cost-efficient strategy to beat a given disease, the first chapter of this supplement by Theresa Hydes, William Gilmore, Nick Sheron and Ian Gilmore discusses the current health policies and their impact on the burden of alcohol misuse and ALD.[10] Next, we devoted three chapters to review recent advances in the molecular mechanisms of ALD that have yielded the identification of novel druggable therapeutic targets. Gavin Arteel and Min Yao review the effects of alcohol on lipid metabolism; Bin Gao, Maleeha F. Ahmad, Hide Tsukamoto and Laura Nagy discuss the cellular and molecular drivers of hepatic inflammation and Bernd Schnabl, Apurva Pande and Shiv K. Sarin summarise data indicating a new role for the microbiome as a driver of ALD and also as a potential site for therapeutic intervention.[11–13] The cellular mechanisms of liver fibrosis are discussed by two expert pathologists, Karoline Lackner and Dina Tiniakos, who also highlight the need for systemic staging systems for fibrosis in patients with ALD.[14] From the clinical standpoint, Sebastian Mueller, Gyongyi Szabo and Christophe Moreno discuss new non-invasive diagnosis and biomarker tools in ALD including elastography and miRNA.[15] The prevalence, need for screening, and specific drivers of hepatocellular carcinoma in the setting of ALD are discussed by Pierre Nahon and Nathalie Ganne.[16] The following two chapters are devoted to discussing current efforts to treat AH, as well as to propose novel endpoints in order to aid researchers in designing clinical trials. The current trials for AH and novel therapeutic targets are summarised by Vijay Shah and Ashwani Signal, while the endpoints and patient stratification in clinical trials for AH are described by Philippe Mathurin and Mike Thursz.[17,18] Thierry Gustot, and Rajiv Jalan then discuss the recently defined clinical entity of acute-on-chronic liver failure, focussing on its pathophysiology, prognosis and management in the context of ALD.[19] Finally, AH is an increasingly relevant novel indication for early

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liver transplantation, which is discussed by experts who have very active transplant programmes (*i.e.* John Cameron, Michael Lucey and Gene Im) ALD.[20]

In conclusion, this commissioned supplement intends to provide an updated review of the current efforts by the scientific liver community to prevent the development of ALD, identify novel therapeutic targets, perform non-invasive diagnosis of early forms, determine an accurate disease stage and treat the most advanced forms medically and/or by liver transplantation. After decades of being relatively overlooked, the field of ALD is receiving increasing attention and consequently there are more novel advances that should yield improvements in the prevention, diagnosis and management of this prevailing cause of severe liver disease.

References

[1] Kim D, Li AA, Gadiparthi C, Khan MA, Cholankeril G, Glenn JS, et al. Changing trends in etiology-based annual mortality from chronic liver disease, from 2007 through 2016. Gastroenterology 2018;155, 1154–63. e3.

[2] Stein E, Cruz-Lemini M, Altamirano J, Ndugga N, Couper D, Abraldes JG, et al. Heavy daily alcohol intake at the population level predicts the weight of alcohol in cirrhosis burden worldwide. J Hepatol 2016;65:998–1005.

[3] Seitz HK, Bataller R, Cortez-Pinto H, Gao B, Gual A, Lackner C, et al. Alcoholic liver disease. Nat Rev Dis Primers 2018;4:16.

[4] Addolorato G, Mirijello A, Barrio P, Gual A. Treatment of alcohol use disorders in patients with alcoholic liver disease. J Hepatol 2016;65:618–630.

[5] Singal AK, Shah VH. Therapeutic strategies for the treatment of alcoholic hepatitis. Semin Liver Dis 2016;36:56–68.

[6] Marot A, Dubois M, Trepo E, Moreno C, Deltenre P. Liver transplantation for alcoholic hepatitis: a systematic review with meta-analysis. PLoS ONE 2018;13 e0190823.

[7] Poole LG, Dolin CE, Arteel GE. Organ-organ crosstalk and alcoholic liver disease. Biomolecules 2017;7.

[8] Mandrekar P, Bataller R, Tsukamoto H, Gao B. Alcoholic hepatitis: Translational approaches to develop targeted therapies. Hepatology (Baltimore, MD) 2016.

[9] Stickel F, Moreno C, Hampe J, Morgan MY. The genetics of alcohol dependence and alcohol-related liver disease. J Hepatol 2017;66:195–211.

[10] Hydes T, Gilmore W, Sheron N, Gilmore I. Treating alcohol-related liver disease from a public health perspective. J Hepatol 2019;70:223–236.

[11] You M, Arteel G. Effect of ethanol on lipid metabolism. J Hepatol 2019;70:237–248.

[12] Gao B, Ahmad MF, Nagy LE, Tsukamoto H. Inflammatory pathways in ASH. J Hepatol 2019;70:249–259.

[13] Schnabl B, Pande A, Sarin SK. Microbiome as a therapeutic target in alcoholic liver disease. J Hepatol 2019;70:260–272.

[14] Lackner K, Tiniakos D. Fibrosis and alcohol-related liver disease. J Hepatol 2019;70:294–304.

[15] Mueller S, Szabo G, Moreno C. Non-invasive diagnosis and biomarkers in ALD. J Hepatol 2019;70:273–283.

[16] Ganne-Carrie N, Nahon P. Hepatocellular carcinoma in the setting of alcohol-related liver disease. J Hepatol 2019;70:284–293.

[17] Singal A, Shah V. Current trials and novel therapeutic targets for alcoholic hepatitis. J Hepatol 2019;70:305–313.

[18] Mathurin P, Thursz M. End-points and patients stratification in clinical trials for alcoholic hepatitis. J Hepatol 2019;70:314–318.

[19] Gustot T, Jalan R. Acute-on-chronic liver failure in patients with ALD. J Hepatol 2019;70:319–327.

[20] Cameron J, Lucey M, Im G. Liver transplantation for alcoholic hepatitis. J Hepatol 2019;70:328–334.