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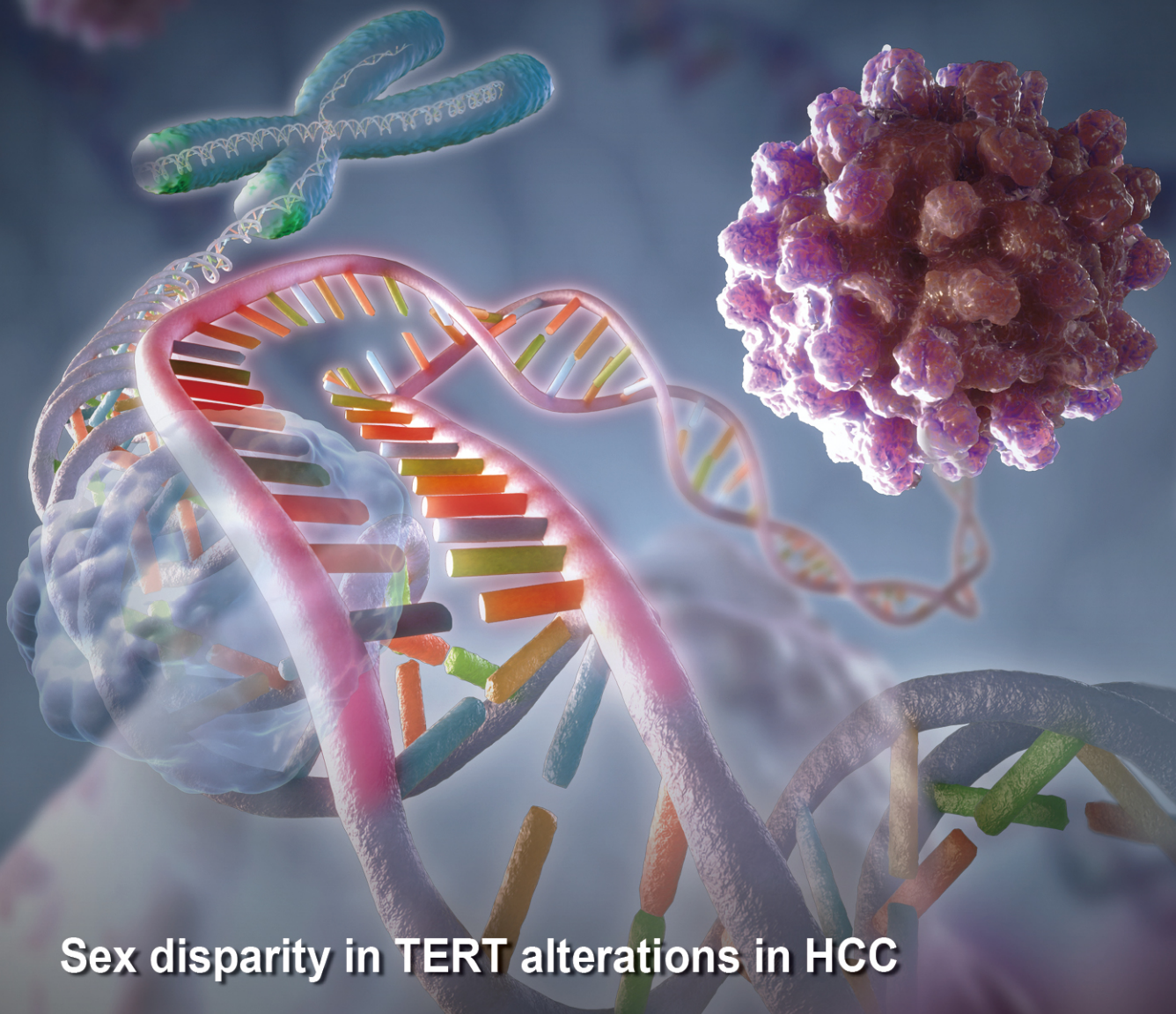

Sex disparity in TERT alterations in HCC

Economic evaluation of hepatitis C elimination
GOLM1 promotes MASH-related gallstone formation
Molecular characterization of sarcomatoid HCC

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Editorial

Momentum towards simplifying and expanding treatment for chronic hepatitis B: The body of evidence continues to grow: Editorial on "Antiviral therapy for chronic hepatitis B with mildly elevated aminotransferase: A rollover study from the TORCH-B trial"

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Chronic hepatitis B (CHB) infection remains a leading cause of hepatocellular carcinoma (HCC) and liver-related deaths globally. Nearly 300 million individuals are chronically infected with hepatitis B virus (HBV), among whom only a fraction have been diagnosed and linked to successful treatment.[1] The beneficial effect of CHB antiviral therapies in sustained suppression of HBV viral replication, leading to reduced long-term risks of disease progression and HCC, is robust.[2-4] Despite these robust data, there remain contradictory guidelines and recommendations regarding "treatment-eligibility," which in many cases are based on complex algorithms that incorporate various factors such as an individual's age, country of origin, family history, comorbidities, liver disease severity, HBV e antigen status, alanine aminotransferase (ALT) levels, and HBV viral load.[5-7] While not the only factor, the complexities of these existing guidelines, in part, contribute to potential gaps in timely CHB treatment. However, there is building momentum to simplify and expand CHB treatment criteria,[8-11] fueled by the growing body of evidence demonstrating clinical benefit of treating individuals with CHB who are outside of current "treatment-eligibility."

In this issue of *Clinical and Molecular Hepatology*, Hsu et al. performed an open-label extension phase study of the TORCH-B trial,[12] which enrolled adults with CHB who had serum HBV DNA >2,000 IU/mL and ALT levels between one to two folds of the upper limit of normal across six hospitals in Taiwan who were randomized to treatment with placebo or tenofovir disoproxil fumarate (TDF). The current study evaluated outcomes of patients that were rolled over to open-label treatment with TDF for 3 years. Among

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a total of 146 enrolled patients, 123 had paired biopsies before and after treatment to assess histological changes. The investigators observed that 60.2% (n=64) of patients experienced improvement in Ishak fibrosis score and 47.2% (n=58) experienced improvement in Knodell necroinflammation score. As expected, patients who switched from placebo to open-label TDF therapies also experienced significant improvements in virological and biochemical outcomes. While the length of follow up limited the ability to assess for clinical outcomes such as incidence of cirrhosis or HCC, the strength of this study is the demonstration of objective meaningful histological improvement resulting from antiviral therapy in CHB patients with only minimally elevated ALT and hence "ineligible" for treatment based on many existing guidelines.

These data add to the growing body of evidence supporting the benefits of antiviral therapy in CHB patients outside of current "treatment-eligibility" criteria. For example, Huang et al.[13] performed a retrospective multi-center, multi-national cohort study of 3,366 adults with CHB, among whom 1,303 were in the indeterminate phase and hence not "eligible" for antiviral therapy. Over a 10-year follow up, 52.7% of patients remained in the indeterminate phase, whereas 21.7% of patients transitioned into the immune active phase. Compared to those remaining in the inactive phase, those who remained in the indeterminate phase had 14 times higher risk of HCC (4.6% vs. 0.5%, aHR 14.1, *P*=0.03), which was even higher among patients who were age 45 years and older (aHR 18.4, *P*=0.005). Similarly, Sinn et al.[14] performed a retrospective multi-center study of 3,624 adults with untreated CHB. During a median follow up of 4.6 years, 161 patients developed HCC. Most striking, among the patients who developed HCC, 64.0%, 46.0%, and 33.5% did not meet CHB treatment eligibility criteria according to guidelines by the Asian Pacific Association for the Study of the Liver (APASL), the American Association for the Study of Liver Diseases (AASLD), and European Association for the Study of the Liver (EASL). Furthermore Y.S. Lim and others have also published extensively on the non-linear relationship of baseline HBV viral load on the long-term risks of HCC, arguing for the consideration of earlier initiation of antiviral therapy that is tailored to HBV DNA levels.[15-17] These studies and others continue to add to the growing body of evidence that implementing treatment even in so-called "ineligible" patients may still confer lasting benefit in reducing morbidity and mortality. While it is true that long-term risks of cirrhosis and HCC in the indeterminate phase are lower than those in the immune active phases, with the availability of safe and highly effective antiviral therapies, one has to question what degree of risk is acceptable. The emerging data from investigators such as Hsu et al.[18] prompts us to reassess this question of acceptable risk and continues to make a convincing case towards expanding treatment for CHB.

Conflicts of Interest

The author has no conflicts to disclose.

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Abbreviations:

ALT, alanine aminotransferase; CHB, chronic hepatitis B; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; TDF, tenofovir disoproxil fumarate

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