Closing the Stable Door After the Horse Has Bolted: Should We Be Treating People With Immune-Tolerant Chronic Hepatitis B to Prevent Hepatocellular Carcinoma?

More than 257 million people, or 3.2% of the world's population, are estimated to be living with chronic hepatitis B infection (CHB).[1] Without treatment, for every 100 persons infected with CHB, 25 will develop cirrhosis and ≤5 people will develop liver cancer.[2] In 2015 alone, >700,000 deaths were directly attributable to CHB infection and many of these deaths could have been prevented with appropriate treatment.[1,3] In addition to liver-related morbidity and mortality, CHB has a major impact on the overall health of individuals and societies through its effects on quality of life, stigma, reduced societal participation, and personal financial security, with flow-on effects for national economies.[4]

Prevention of HCC is now the major clinical challenge for the field. International CHB management guidelines currently recommend nucleos(t)ide analogue (NA) therapy for people with a high HBV DNA level and at least moderate liver fibrosis and/or inflammation,[3,5] based on strong evidence that viral suppression prevents liver fibrosis progression, cirrhosis, and liver failure and decreases the risk of hepatocellular carcinoma (HCC).[6,7] The association between viral suppression and HCC risk reduction is potentially both direct by decreasing genomic integration through reduced infection of new hepatocytes and progressive depletion of hepatocytes with cccDNA integration as shown in murine models,[8,9] and indirect, by preventing liver fibrosis and cirrhosis, the strongest risk factor for HCC.[6] The recent European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) guidelines have also expanded their previous treatment criteria to include consideration of treatment in people aged >30 years (EASL) or >40 years (AASLD) with a viral load of >2000 IU/mL, even in the absence of significant fibrosis or an increased alanine aminotransferase (ALT) level in recognition of the higher risk of HCC with advancing age after 30 years.[3,10,11]

Importantly, even when guideline-based CHB management is rigorously followed in well-resourced settings, HCC incidence is not completely prevented. Long-term follow-up of patients treated with NA in accordance with current guidelines show that, although treatment significantly decreases HCC risk, there remain incident HCC cases in older patients on long-term NA therapy (annual risk in non-cirrhotic patients of 0.5%–1.4%, risk in patients with cirrhosis of 0.7%–5.0%).[11] The recent observation that the rate of incident HCC decreases after 5 years of NA therapy suggests that a longer duration of therapy has a cumulative benefit and raises the important question of whether starting treatment earlier might decrease HCC risk further.[12] Furthermore, even in high-income countries, diagnosis and referral rates are low and many patients are not followed adequately to identify transitions to active disease, leading to further delays in therapy initiation.[13]

Circumstantial evidence suggests that early viral suppression may improve clinical outcomes. Natural history studies in older patients have shown that HBV-related HCC risk is strongly associated with viral load.[14] The REVEAL study was a long-term prospective cohort study in Taiwan that demonstrated the relationship between HBV DNA level and long-term risk of HCC and suggested that persistent viremia was a critical driver of HCC risk.[14,15] Most study participants were older and negative for hepatitis B e antigen (HBeAg), not young people in the immune-tolerant phase (defined as HBeAg positive, with normal ALT levels and a high viral load).[14] A recent retrospective cohort study by Kim et al[16] compared clinical outcomes in 413 HBeAg-positive immune-tolerant patients who did not meet the treatment criteria with outcomes in 1497 immune active patients (HBeAg positive with high ALT) who received NA treatment. Patients in the immune-tolerant phase who remained untreated had a 2–3 times higher risk of HCC, liver transplantation, or death compared with patients in the immune clearance phase who were started on NA therapy. Although there are limitations to this retrospective dataset—the median age of immune-tolerant patients was older (38 years), 26% had HBV DNA levels of $<10^7$ IU/mL and ALT levels were not normal in all subjects suggesting a cohort in transition to the immune active phase—the data do suggest significant risk of HCC among patients traditionally considered to have immune-tolerant disease.

Changes in our understanding of HBV immunovirology also point to the potential benefit of treating early. Emerging data suggest that liver carcinogenesis in CHB may start during the immune-tolerant phase of CHB. Integration of HBV DNA into the host genome of infected hepatocytes is thought to be a key event driving oncogenesis.[17,18] HBV genomic integration, associated with clonal hepatocyte expansion, can be detected frequently in young patients with immune-tolerant disease.[16,17] The frequency of integration events is proportional to HBV viral load,[18,19] and is detectable in the immune-tolerant phase[17] at rates comparable with later phases of disease and is associated with higher risk of HCC development and HCC-related death. It is reasonable to argue that these pro-oncogenic events must accumulate over the lifetime of infection, and that current treatment paradigms allow decades of oncogenic opportunity. Moreover, the concept of immune tolerance itself is now being challenged. HBV-specific T-cell responses,

hepatic necroinflammatory activity,[20] and circulating HBV variants associated with progression to HBeAg-negative disease are detectable in young immune-tolerant patients.[21] Early introduction of NA therapy would seem a logical approach to decrease the risk of HCC by potentially decreasing the probability of viral integration in the host genome; and to prevent liver fibrosis progression. In the era of viral hepatitis elimination, it is timely to rethink our current CHB treatment strategy and address the evidence gaps through high-quality clinical trials to decrease CHB-related HCC. Should young patients in the immune-tolerant phase of CHB be offered treatment? Should we be offering treatment to all?

Such an approach would simplify assessment and treatment algorithms. The assessment and management of CHB is complicated: the phase of disease and treatment eligibility are defined by multiple clinical tests, including serum biochemistry, HBV serology, HBV DNA level, and in some cases liver histology. Further, the natural history of CHB is variable and dynamic, necessitating long-term follow-up. In many low- and middle-income countries with a high CHB prevalence, the tests required to diagnose, monitor, and determine treatment eligibility in accordance with guidelines are inaccessible, poorly resourced, or unaffordable; the annual costs of NA treatment are now lower than the costs of disease monitoring in many countries.[22] Even in developed economies, the current complexity requires specialist involvement, despite the fact that models of care must shift to the primary care setting to meet targets for diagnosis and treatment.[1] Therefore, there are significant barriers to linkage, treatment, and retention in care for patients with CHB.[1] Identification and linkage to care of all people living with CHB globally has already been identified as the major challenge facing the field to achieve hepatitis B elimination.[1] Simplified CHB disease assessment, monitoring, and treatment strategies are therefore needed to drive progress toward achieving the 2030 CHB elimination targets from the World Health Organization. The vast majority of young people in the immune-tolerant phase are unlikely to have advanced fibrosis; commencing NA treatment in this group would potentially prevent most long-term sequelae and mitigate the need for ongoing fibrosis assessment and monitoring.[1] HCC predictive scores such as PAGE-B[23] and REACH-B[24] have already identified a subpopulation of people on NA therapy for whom the risk of HCC is so low that HCC surveillance falls below the cost-effectiveness threshold; although not validated in immune-tolerant individuals, the majority of people living with CHB who are in the immune-tolerant phase would be classified as low risk for HCC using these scores. Finally, broadening current treatment criteria to include young people in the immune-tolerant phase of CHB is likely to decrease rates of horizontal and vertical transmission (treatment as prevention). The susceptible pool remains unacceptably high. Despite a highly effective vaccine for hepatitis B,[25] global coverage of full course hepatitis B vaccination is 84% and only 38% are estimated to receive timely birth dose.[1]

The HBV management landscape has evolved markedly over the past decade. Two of the first-line NA for the treatment of CHB—entecavir (ETV) and tenofovir disoproxil fumarate (TDF)—are now available as generics, dramatically decreasing costs. The price of TDF in some low- and middle-income countries is as low as $3 per month, significantly less than the cost of an annual HBV DNA level using polymerase chain reaction technology.[22] Both ETV and TDF are highly potent antiviral agents with very high barriers to resistance; for ETV, rates of resistance development have been reported to be 1.2% at 5 years in patients who were treatment naïve at the time ETV was started, and to date no resistance to TDF has been reported with >8 years of reported experience from patients enrolled in the registration studies.[3] The efficacy of TDF compared with combination TDF plus emtricitabine in immune-tolerant patients has been evaluated in a prospective study.[26] Although HBeAg and hepatitis B surface antigen seroconversion were rare after 4 years, sustained viral suppression was observed.[26] Importantly, no evidence of virologic resistance was detected in patients with ongoing low levels of viral replication by viral genotypic or phenotypic analyses.[26] The safety profile of both agents is very good. Long-term adverse events with ETV are very rare and toxicity monitoring is not routinely recommended. TDF has been associated very rarely with renal and bone adverse events.[3] A new formulation of tenofovir, the prodrug tenofovir alafenamide, has recently been licensed that has lower risk of renal and bone adverse events than TDF.[3] Therefore, the field now has suitable agents for long-term use that are very effective and with good long-term safety data from clinical trials out to 12 years in patients with CHB[27] and extensive long-term safety data from the use of tenofovir in people living with HIV.[28] Although long-term treatment compliance is an important concern owing to the risk of viral resistance and hepatitis B flares, this is also the case for other chronic infectious diseases including HIV and should not be a reason to withhold treatment. Instead, investment in strategies to improve linkage to care and treatment compliance is needed based on evidence from the local context, such as effective community education, integration of HBV treatment programs within existing chronic disease programs, and coverage of treatment cost under the Universal Health Care package to reduce the cost burden of treatment.[22,29] Such investment will be required to improve linkage to care rates to achieve World Health Organization hepatitis B elimination targets,[1] regardless of changes to treatment eligibility.

Given this context, we believe it is timely to consider planning a study and gathering all available global data evaluating the clinical benefit of early NA therapy for patients in the immune-tolerant phase of CHB. The target population should be young, HBeAg-positive with high HBV DNA levels ($>10^7$ IU/mL) and normal serum ALT levels. Although an argument could be made to consider treating children given the observation that integration

occurs early in CHB, for pragmatic reasons participants would likely be aged 18–30 years. A randomized, controlled trial with a control population monitored per current guidelines, and commenced on antiviral therapy at the time of progression to active hepatitis, defined by ALT flare would provide the best evidence to guide our decisions. The primary outcome of interest is HCC incidence; other surrogate endpoints, such as ALT flare, are unlikely to suffice for key regulatory bodies globally to approve expansion of current treatment criteria. Cost-effectiveness would be a key secondary endpoint, compared with management in accordance with current guidelines. Such a study could determine whether treatment must be lifelong or until HBeAg seroconversion is achieved to reduce HCC incidence and remain cost effective. However, in many countries where long-term monitoring of a large HBV affected population is challenging and in the absence of World Health Organization prequalified HBeAg point-of-care assays, it is likely that lifelong treatment will be a simpler strategy to implement in low-resource settings.

Study design will be challenging. There are several practical obstacles to conducting such a study. Given the low rates of HCC in this population in the short to medium term, a very large sample size and prolonged period of follow-up will be required.[16,26] Patient retention is likely to be challenging given that young people are often mobile and have competing priorities. Tenofovir alafenamide is the only NA still patent protected. The patent will expire in the next 5–10 years, making it challenging for industry to directly support such a study. HBV cure strategies are in active development. If these succeed in the next 5–10 years, then the concept of lifelong long-term suppression is likely to become obsolete.

Despite these challenges, a longitudinal study evaluating the benefit of early treatment would be seminal for informing clinical practice and improving patient outcomes. This was the approach taken for HIV, with the INSIGHT START study demonstrating the clinical benefit of treatment initiation for all HIV-positive people regardless of $CD4^+$ count, which is now incorporated into clinical guidelines.[30]

Are there alternatives to conducting a prospective study? Opportunities may exist to collect data within the context of national hepatitis campaigns currently being planned in low- and middle-income countries. In Uzbekistan, the government is working to eliminate viral hepatitis. A novel demonstration program is making hepatitis testing and treatment available to the whole population using a scalable and sustainable funding mechanism, where patients who can afford discounted treatment subsidize treatment for those less able to afford it. In this model, monitoring is more costly than a treat-all approach; therefore, all hepatitis B surface antigen-positive individuals will be treated indefinitely. The program will be implemented in a stepwise manner across the country; therefore, evaluation of outcomes and costs in the treat-all population could be compared with regions with treatment given in accordance with EASL guidelines. Certainly, there will be logistical challenges to such a large undertaking, but this type of "practical" study may be more realistic than a classical industry-sponsored clinical trial.

Additionally, opportunities exist to examine previously collected cohort and natural history data and to use modelling to examine the likely impact, effectiveness, and cost effectiveness of such an approach and use new statistical techniques to look for evidence of causation. Regardless of the approach used to guide our decisions on when to start therapy, community consultation exploring attitudes toward lifelong therapy starting at a young age will be vital and must be undertaken.

Finally, given the practical challenges to collecting prospective data, is it possible for guidelines to expand treatment indications ahead of the evidence? We would strongly advocate for prospective studies to justify changes to policy, but acknowledge that clinical care can move ahead of the data at times where there is compelling rationale. The recommendation that treatment be considered for people with persistent immune-tolerant CHB over the age of 30 years is a recent example of this phenomenon.

HBV cure strategies are in active development. If these succeed in the next 5–10 years, then the concept of lifelong long-term suppression will be rendered obsolete. However, we know from the development of direct-acting antivirals for hepatitis C cure that affordable access to antivirals on-patent is slow, particularly for low- to middle-income countries who shoulder the greatest burden of HBV-related HCC.[1] Investment in treatment programs for immune-tolerant patients now will facilitate the roll-out and rapid scale-up of curative therapy when it becomes available.

Conclusion

It is logical that the carcinogenic risk of HBV starts from the time of infection, is cumulative, and is driven by integration events associated with high-level viral replication, as well as progressive fibrotic liver damage. Early viral suppression is likely to minimize the risk of HCC by reducing integration and preventing cirrhosis. Treatment for all would also simplify clinical management algorithms, promoting public health interventions for control of CHB. In an era where effective NA are cheap and safe, there is a need to define the benefit of a "treat-all" approach for immune-tolerant patients. The challenge for the field is how best to do this.

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Conflicts of interest
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