HBsAg loss in chronic hepatitis B: pointers to the benefits of curative therapy

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Hepatitis B surface antigen (HBsAg) clearance is a relatively rare outcome during the complex natural history of chronic hepatitis B [1]. The estimated annual incidence of clearance of HBsAg is 1–2 % in Asian and in Western populations [2]. Annual rates of HBsAg loss in HBeAg-negative patients may be higher in those with lower levels of hepatitis B replication, minimal hepatitis and normal serum aminotransferases [3]. Hepatitis B genotype and mode of acquisition may influence the rate of HBsAg loss. Spontaneous seroclearance of HBsAg is thought to be beneficial, and to confer an improved outlook; thus HBsAg concentrations and loss may be a useful biomarker of prognosis in patients with chronic hepatitis B [4]. HBsAg loss may also occur, although relatively rarely, after interferon-alpha treatment or nucleoside analogue anti-viral therapy [5–7]. Likewise, the prognosis is improved, and thus HBsAg loss, rather than merely HBV DNA suppression, has become an important goal of potential curative therapies for hepatitis B.

However, patients who have become HBsAg negative can nonetheless develop hepatocellular carcinoma (HCC), although the risk is diminished compared to those with persistent HBsAg positivity [8]. The risk of HCC is greater in those with established cirrhosis or older age. It should be remembered that the lack of detectable HBsAg in serum depends upon the sensitivity of the assay [9]. HBsAg loss is usually durable. It is recognised that intrahepatic HBV genomes may persist in HBsAg-negative individuals: both covalently closed circular (ccc) DNA and integrated

hepatitis B viral genomes may persist in the liver after HBsAg clearance from serum [10]. Consequently, reactivation may occur either spontaneously, and importantly, after chemotherapy in patients with hematological and solid malignancies, or after immunosuppression in HBsAg negative, anti-HBc positive persons [11].

In this study from New Zealand Lim and colleagues [12] report the long-term rates of HBsAg loss and outcomes, particularly HCC, in a cohort from the eastern Bay of Plenty in North Island in New Zealand. They also assessed the predictive value of baseline HBsAg levels compared to HBV DNA in predicting long-term HBsAg loss. The study examined a community cohort in which 572 patients with chronic hepatitis B were identified and followed for a prolonged period of 28 years. The database was established in 1984, after 93 % of 8,514 persons over the age of 6 months were tested for current and past hepatitis B infection. Seventy-nine percent of the cohort were Polynesian, 21 % Caucasian and 63 % were male. In this cohort, 6.1 % were confirmed as having chronic hepatitis B, and at the outset of the study, 48 % were HBeAg-positive. All were entered into a long-term follow-up study, with six monthly blood tests. The median age of the participants in the study at enrolment was 17 years. The predominant genotype in this population is C and D. Interestingly in 79 % of the cohort, serum alanine aminotransferases were normal but only 11 % had HBV DNA concentration of less than 2000 IU/mL at baseline. Spontaneous HBsAg loss had occurred in 145/572 individuals (33 %) after 12,702 person-years of follow-up. The majority had developed anti-HBs. No HCC has been observed following HBsAg loss in the cohort after a median follow-up of 72 months. The main predictors of HBsAg loss were older age and a lower baseline HBsAg; in particular, the HBsAg level hazard ratio for HBsAg loss over 28 years was 2.7 for HBsAg concentrations of 1000–10,000 IU/mL, 6.7

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for concentrations of 100–1000 IU/mL but 9.4 for HBsAg concentrations of <100 IU/mL (compared to HBsAg concentrations >10,000 IU/mL). The annual rate of loss of HBsAg in patients with HBsAg levels below 100 IU/mL was 5.7 % compared to 0.5 % in persons with HBsAg concentration of >10,000 IU/mL. Seventeen percent of those with HBsAg loss were originally HBeAg-positive in 1984.

Quantitation of HBsAg thus offers an opportunity to predict outcome. The analysis self-fulfils a prophecy that lower HBsAg levels are associated with a greater likelihood of HBsAg becoming undetectable in serum during follow-up [13]. It is remarkable that only 25 patients (4 %) of the entire HBsAg positive cohort had received anti-viral therapy by 2012. The reason given by the authors was that antiviral therapies were not available. (None of those treated with anti-viral therapy lost HBsAg). The very low rate of treatment in this cohort is somewhat surprising: does this point to the possibility that a high proportion of individuals in this community study had what was considered inactive disease, not meriting anti-viral therapy? Thus this interesting and unique study from New Zealand largely reflects events in an untreated population, but the analysis may also have selected for a population that did not require treatment because of relatively inactive disease. The data indicate that clinical outcomes were particularly favourable in those in whom HBsAg clearance had occurred at a relatively young age. Liver stiffness measurements obtained by transient elastography were significantly lower if HBsAg loss occurred in those younger than 40 compared to those older than 40 years.

The REVEAL studies demonstrated a linear reduction in HCC risk with reductions in HBV DNA levels. Newer predictive models incorporating baseline HBsAg as well as HBV DNA to examine the probability of later disease or the risk of HCC are being developed [14]. This unique data from New Zealand provides important outcomes from a prolonged follow-up study, in a sizeable cohort of HBsAg positive persons, but leaves open several important questions of the mechanisms of HBsAg clearance. The data do not clarify the serial, longitudinal declines in HBsAg concentrations during the phases of the natural history of the disease, and the absence of serial measurements in the analysis does not clarify any decline in HBsAg concentrations during a stepwise process of spontaneous decreases in HBV-DNA concentrations, or seroconversion from HBeAg-positive disease to anti-HBe disease, and eventual HBsAg loss in the HBeAg positive cohort. For example, did the kinetics of HBsAg loss differ, perhaps as a result cell turnover, during the immune active phase in the HBeAg positive patients with high and then lowered levels of HBV replication compared to those with anti-HBe positive disease [15]. Can HBsAg loss be predicted after HBeAg loss [16]?

As we attempt to develop curative immune-modulatory and molecular therapies for hepatitis B, it will be important

to better understand the in situ molecular intrahepatic virological (and immunological) events that presage and accompany a decline in HBsAg concentrations [17, 18]. cccDNA is the transcriptional template for transcription of viral RNA, and the relative resistance of cccDNA to treatment with chain terminators precludes cure in most patients treated with nucleoside analogue therapy. Hepatocyte turnover is a factor in cccDNA decay: Does cccDNA persist in the nucleus of infected cells without amplification to multiple copies in patients losing HBeAg and then HBsAg? What continued transcription occurs from integrated viral genomes? In patients with spontaneous, albeit slow declines in HBsAg concentrations, is the absolute quantity and reservoir of cccDNA stable, but transcription from cccDNA silenced by epigenetic modification [19]? Does all cccDNA chromatin require clearance for a cure of hepatitis B, or do most individuals continue to replicate low threshold levels that are insufficient to express detectable HBsAg and thus result in a slowing of the disease? To what extent do the molecular events reflect control by immunological targeting, or conversely do molecular changes lead to a reduction of the high HBsAg antigen load to allow restoration of T cell activation and recovery from a dysfunctional immune response? What are the influences of HBV genotype on these events? Critical surrogates of cccDNA function and concentration are required.

Several recent studies have indicated that HBsAg seroconversion occurring in those who are older or who have advanced fibrosis and cirrhosis are still at risk of HCC, although that risk is lowered [20]. Patients with cirrhosis on continuous antiviral therapy require ongoing surveillance; such surveillance is deemed generally “cost-effective” if the expected annual incidence exceeds an accepted threshold, so that surveillance at 6 months intervals is usually required. The data in this population point to a guideline whereby the burden of continuous imaging and surveillance for HCC may be refined. The data from this analysis suggest that patients who have cleared HBsAg could have transient elastography or other measure of hepatic fibrosis; patients with advanced fibrosis, or cirrhosis will require ongoing surveillance for HCC whereas HBsAg loss in patients with lesser degrees of fibrosis may not require ongoing surveillance. Perhaps HBsAg loss at a young age may allow an extension of surveillance intervals in younger patients with cirrhosis prior to therapy [21].

Importantly the study provides indirect evidence that new curative therapies that result in loss, or diminution, of HBsAg will improve clinical outcomes [14]. The data indicate that HBsAg clearance can occur after a prolonged period of disease, but to improve clinical outcomes we will need to seek to cure active hepatitis at an age well before the onset of severe fibrosis, to limit the consequences of

necro-inflammatory change in the liver and intrahepatic events accompanying HBV DNA into the host chromosome. Such a strategy, and the means to effect loss of HBsAg at a young age, will reduce the residual likelihood of cirrhosis and of HCC and result in true cures of chronic hepatitis B.

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