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Authors' contributions

M Papatheodoridi: Drafting of the initial manuscript; Approval of the final version of the manuscript. G Papatheodoridis: Conception and revision of the manuscript; Approval of the final version of the manuscript.

Supplementary data

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I shall be released (from infinite HBV nucleos(t)ide analog therapy): Japanese experience

To the Editor:

We read with great interest the article by Berg *et al.*[1] titled "The times they are changing: A refined proposal for finite HBV nucleos(t)ide analog therapy." The authors proposed that HBV relapse after nucleos(t)ide analog (NA) discontinuation could improve rates of HBsAg seroclearance according to the "stop-to-cure" approach. Therefore, reliable biomarkers to identify patients who could say "I shall be released" (from infinite NA therapy) are indispensable.

In Japan, the HBcrAg assay has been covered by national insurance and has been performed in clinical practice since 2008. It involves the measurement of serum levels of all antigens transcribed from the pre-core/core gene, composed of a 22 kDa pre-core protein, hepatitis B core, and e-antigens. Serum HBcrAg levels can help predict hepatocellular carcinoma development and assess the risk of post-treatment relapse. Patients with persistently high on-treatment HBcrAg levels were more likely to develop hepatocellular carcinoma despite sustained HBV DNA suppression in response to long-term NA treatment.[2] In the Japan Society of Hepatology Guidelines,[3] a model to predict relapse after discontinuation of NA therapy, by scoring HBcrAg and HBsAg levels, has been proposed for patients treated with NA for ≥2 years, with negative HBeAg and undetectable HBV DNA levels. Both HBcrAg and HBsAg are surrogate markers of covalently closed circular DNA (cccDNA) in the liver. However, as HBcrAg includes HBeAg, the HBcrAg assay has limited sensitivity in HBeAg-negative patients, although a novel, approximately 10-fold more sensitive HBcrAg assay has recently been introduced.[4,5] In HBeAg-positive patients, HBeAg is the dominant component of HBcrAg, but in HBeAg-negative patients, it is unclear which component is dominant – the 22 kDa protein or the hepatitis B core protein. Moreover, as HBsAg may be expressed from both cccDNA and integrated viral DNA sequences,[6] quantitative HBsAg levels correlate with the transcriptional activity of cccDNA less significantly than HBcrAg level.[7] HBcrAg and HBsAg measurements can play complementary roles because their production is regulated by

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alternative enhancer–promoter systems in the HBV genome. Although the risk-assessment model in the guidelines[3] was developed based on data from a small Japanese study, a recent multi-ethnic, multicenter cohort study validated that serum HBcrAg and HBsAg levels were independent predictors of off-treatment relapse in both Asian and non-Asian patients.[8]

When the aforementioned criteria are met, NA cessation may be considered in the low-risk patients with HBsAg of <80 IU/ml and HBcrAg of <3.0 log U/ml, according to the Japan Society of Hepatology Guidelines,[3] because the predicted relapse rate is 10%–20%. In contrast, moderate-risk patients, *e.g.* those with a HBsAg level of ≥80 and <800 IU/ml and HBcrAg level of ≥3.0 and <4.0 log U/ml, had a higher risk of off-treatment relapse of approximately 50%. In such patients, switching sequential therapy from NA to interferon-α may be indicated for safe NA cessation. A nationwide prospective study showed that combined HBcrAg and HBsAg levels at NA cessation helped predict off-treatment relapse for patients who switched to interferon-α[9]; however, the number of patients was limited (n = 95), and these results need to be validated in larger studies.

However, most patients and physicians prefer infinite NA therapy because of the fear of viral relapse and to avoid the need for more intensive monitoring off-treatment. In Japan, a medical expense subsidy system for patients with viral hepatitis was introduced in 2008.[10] The range of coverage has been expanding from patients treated with interferon to those on oral antivirals, including drug prices and examination expenses. Using the specific subsidy system supported by the national and prefectural governments, patients themselves pay 10,000–20,000 Japanese yen (75–150 euro) each month to cover all medical expenses. This established financial support is another reason why patients prefer infinite NA therapy. In Japan and other countries where healthcare and medications are fully subsidized, there may be little financial incentive to stop therapy. However, it is more crucial to establish the "stop-to-cure" strategy in resource-limited countries where HBV is prevalent.

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Conflict of interest

The authors declare no conflicts of interest pertaining to this work.

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Authors' contributions

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