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LETTER TO THE EDITOR

HBsAg levels as a guide for finite treatment duration of chronic hepatitis B

KEYWORDS
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Relapse

To the Editor,

Discontinuation of nucleos(t)ide analogues (NAs) therapy remains one of the most controversial issues in the management of chronic hepatitis B (CHB). New HBV EASL guidelines suggest that NA discontinuation may be considered in selected non-cirrhotic HBeAg-negative and HBeAg-positive patients if close post-treatment monitoring is guaranteed [1]. But, when to stop treatment and in whom remains unclear. Two current options for finite NAs treatment duration in CHB patients with long-term on-treatment virologic remission are discussed herein. The first optionis based on the so-called ''stop-and-wait tactics'', in which a sudden virologic relapse with ALT flare may trigger (if untreated) an immune-mediated clearance of HBV-infected hepatocytes and subsequent HBsAg loss and cure [2,3]. The second option is based on different surrogate markers (HBsAg levels and/or on-treatment HBsAg kinetics, anti-HBc quantification, among others) that enable the selection of eligible patients with high probability of durable off-treatment remission [4—6]. Therefore, the identification of strong predictors of sustained virologic and clinical remission and the selection of patients who can safely discontinue therapy is urgently needed.

The end of treatment quantitative HBsAg level (EoT qHBsAg) is now considered one of the most accessible and promising predictors, but the suitable cut-off value remains unclear. Most studies demonstrating different predictive EoT qHBsAg level cut-off performed in Asian patients whose viral genotype was either type B or C [7—9]. The extrapolation of Asian data to the Western population (with predominant HBV genotype D or A) requires validation.

This study aimed to evaluate EoT qHBsAg levels as the predictors of off-therapy relapse or stable virologic remission after long-term NAs treatment in CHB patients. We monitored 36 patients (all Caucasian) with CHB and compensated liver disease who discontinued long-term NAs therapy (Table 1). The stopping rules criteria were: patients desire to cease NAs treatment and agreement to remain under close follow-up; duration of treatment with NAs for > 36 months; on-treatment undetectable HBVDNA (< 150 IU/mL) for > 24 months; and HBeAg lost with at least 12 months of consolidation therapy thereafter (for HBeAg-positive patients).

Liver stiffness (LS) was evaluated via FibroScan before, during and at the end of treatment. LS declined in most of the patients (86%) by a mean value of 2 kPa (range: 0.7 — 5.3). LS significantly declined from mean values of 13.7 (range: 9.4 — 18.5) to 10.5 (range: 6.5 — 14.5) kPa in patients with moderate-severe fibrosis (> 9 kPa) ($P < 0.0001$). Eight (29%) patients with a baseline value of LS > 9 kPa switched to a LS value of < 9 kPa at EoT.

After the cessation of NAs therapy, the patients were followed up every 3 months for the first 12 months and thereafter every 6 months over the next 12 months. Additional biweekly visits were arranged if their ALT levels increased by more than 2 from the upper limit of normal (ULN). Serum HBsAg quantification was tested at the cessation of NAs therapy, at month 12, and at the end of follow-up. We assessed the clinical outcome as non-relapse (HBVDNA < 300 IU/mL), virologic relapse (HBVDNA > 300 IU/m and normal ALT or AST levels) and clinical relapse (HBVDNA > 2000 IU/ml and ALT or AST > 2ULN on 2 sequential tests 1-2 months apart).

During a 24-months follow-up after the cessation of NAs therapy, virologic and clinical relapse was documented in 9 (25%) and 14 (39%) patients, respectively. The cumulative rate of virologic and clinical relapse was 13.9% and 16.6%, 25% and 30.5%, 25% and 39%, and 25% and 39% in 6, 12, 18 and 24 months after the cessation of NAs therapy, respectively. In the patients with clinical relapse the mean time between the reappearance of viraemia and ALT or AST elevation above 2 ULN was 20.4 ± 4.6 weeks. The mean viral load during follow-up in the clinical relapsers was significantly higher than in the virologic relapsers (6.34 ± 1.82 vs. 3.86 ± 0.71 $\log_{10}$/IU/mL, respectively, $P < 0.0001$). No patients with relapse died, developed jaundice or

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Table 1 Clinical characteristics of study population (n=36).

Characteristics	
At NAs discontinuation	
Male sex, *n* (%)	27 (75.0%)
Age, years, mean ± SD	38.8±14.3
F3/F4 fibrosis, *n* (%)	4 (11%)
Type of NAs therapy, *n* (%)	
entecavir	26 (72.2%)
tenofovir disoproxil fumarate	4 (11.1%)
telbivudine	6 (16.7%)
Duration of NAs therapy, months, mean ± SD (min—max)	77.4 ± 23.5 (36—96)
Duration of on-NAs viral remission, months, mean ± SD (min—max)	41.4 ± 19.7 (24—84)
Liver stiffness, mean±SD (min-max), kPa	9.14 ± 2.31 (5.5—14.5)
HBsAg level, $\log_{10}$/IU/mL, mean±SD (range)	3.29 ± 0.90 (0.69—4.42)
in patients with baseline HBeAg	3.35 ± 0.84
in HBeAg-negative patients	3.25 ± 0.79
HBsAg level, *n* (%)	
< 500 IU/ml	7 (19%)
500—5000 IU/mL	14 (39%)
> 5000 IU/mL	15 (42%)
Before NAs therapy	
ALT, U/L, mean±SD (min-max)	125 ± 87 (44—257)
HBVDNA level, $\log_{10}$/IU/mL, mean ± SD (min—max)	7.43 ± 1.49 (3.92—9.08)
Liver stiffness, mean±SD (min—max), kPa	10.85 ± 3.21 (6.7—18.5)
HBeAg-positive, *n* (%)	5 (13.9%)
HBV genotype D, *n* (%)	21 (91.3%)[a]

[a] HBV genotyping was performed in 23 cases.

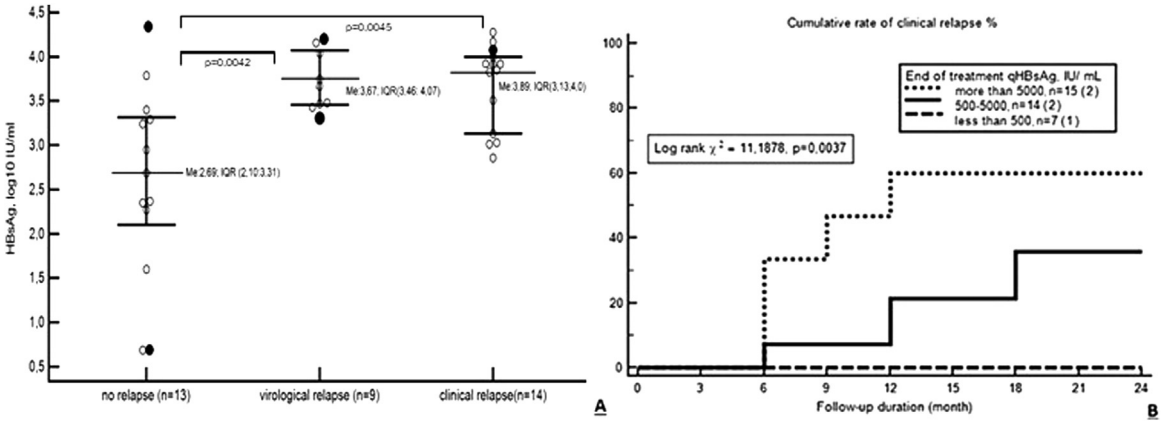

Figure 1 End of treatment qHBsAg levels predicts outcome after NAs therapy discontinuation. A. Individual values of EoT qHBsAg levels were plotted in for patients with non-relapse, virologic and clinical relapse. Solid figures indicate patients with HBeAg before treatment; horizontal lines and bars represent the median and interquartile range (IQR), respectively. B. Kaplan-Meier analyses of cumulative rate of clinical relapse according to EoT HBsAg levels. Patients with baseline HBeAg indicated in brackets.

decompensation during follow-up. The patients with non-relapse had lower EoT qHBsAg (median: 2.69 vs. 3.67 and 3.89 Log_{10}/IU/mL, $P < 0.005$) than those with virologic or clinical relapse (Fig. 1A). The EoT mean HBsAg level (3.35 and 3.25 $\log_{10}$/IU/ml, respectively) and relapse patterns during follow-up were similar in all of the patients irrespective of their pre-treatment HBeAg status.

In a multivariable Cox regression model, including different variables (age, sex, baseline ALT and HBVDNA levels, the presence of HBeAg, the duration of treatment and on-treatment viral remission, changes in LS during therapy and EoT qHBsAg), only EoT qHBsAg ($P = 0.002$, 95% CI 0.218—0.873) demonstrated a significant association with non-relapse. When the patients were grouped according to their EoT qHBsAg levels, no virologic or clinical relapse occurred in those with ≤ 500 IU/mL compared to a high rate of clinical relapse in those with level 500—5000 IU/mL (35.7%) and above 5000 IU/mL (60%) (Fig. 1B). There was a significant difference among these three groups ($P = 0.0037$). The patients with EoT qHBsAg < 500 IU/mL showed a

significant reduction in qHBsAg levels (median: −1.311) and the patients with non-relapse demonstrated stable qHBsAg levels (median: −0.05) during follow-up. In two patients with EoT qHBsAg < 500 IU/mL, the HBsAg levels dropped below the lower limit of detection (< 0.05 IU/mL) during follow-up.

Little is known about the safety and predictors off-treatment remission in Caucasian patients with predominant genotype D HBV who discontinued NA therapy. A recently published Greek study demonstrated that long-term NAs treatment can be safely discontinued in non-cirrhotic HBeAg patients [10]. Lower EoT HBsAg levels in the Greek study were not associated with the probability of relapse, but were associated with subsequent HBsAg loss. Our results are in line with previous studies of Asian patients in which a low EoT qHBsAg levels was associated with a higher likelihood off-treatment remission and HBsAg loss [4,7—9]. Despite a very strong virologic relapse definition (> 300 IU/mL), the results of our study showed a lower virologic and clinical relapse rate over 2 years compared to previous studies [7—11]. The origin of the discrepancy may be caused by the long mean treatment duration time (77.4 ± 23.5 months) and differences in the population (Caucasian race, genotype D HBV) in our study. The majority of virologic and clinical relapses in our study occurred in the first 12 months of follow-up (100% and 79%, respectively), which is in line with previous reports [10, 20]. Our study also found that the HBsAg levels post-therapy was a stable or decreased in patients with non-relapse. We can speculate that the patients who had any decline of HBsAg levels from the end of treatment during post-treatment had a lower virological and clinical relapse rates.

This study had several limitations. First, the study cohort was small and the follow-up time relatively brief, so further large-scale studies are needed to confirm the results. Second, there were no baseline and on-treatment HBsAg levels to assess the serum HBsAg kinetics. Third, there was a limited number of tenofovir-treated patients ($n = 4$) and thus, it is unclear whether the same HBsAg cut-offs are applicable for those who have discontinued tenofovir therapy.

In a 24-months follow-up study of patients with CHB who stopped nucleos(t)ide analogue therapy, EoT qHBsAg levels was associated with low risk of virologic and clinical relapse. EoT qHBsAg levels might be used to select patients eligible for the safe discontinuation of nucleos(t)ide analogue therapy.

Author's contribution

Dzhamal Abdurakhmanov: study design, data acquisition and analysis, manuscript drafting and critical revision of the manuscript; Elhan Ibragimov, Teona Rozina, Elena Nikulkina and Natalya Mazurchik: study design, data acquisition and critical revision of the manuscript

All authors read, edited, and approved the final draft submitted.

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Disclosure of interest

The authors declare that they have no competing interest.

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