DYNAMICS IN QUANTITATIVE HBsAg VALUES DURING THERAPY WITH NUCLEOTIDE/ NUCLEOSIDE ANALOGUES (NUCs)

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ABSTRACT

Introduction: *Chronic hepatitis B infection remains a global health challenge, with nucleotide/nucleoside analogs (NUCs) as a primary treatment option.*

Materials and methods: *A retrospective analysis was conducted on 337 patients treated with NUCs over a 5-year period. Quantitative HBsAg values were determined at baseline and at 3 and 5 years after starting the treatment. Quantitative HBsAg values were determined at the beginning, prior to initiating antiviral therapy, and at 3 and 5 years after starting the treatment.*

Results: *The results demonstrated a significant association between quantitative HBsAg values and liver cirrhosis, with higher baseline values observed in patients with cirrhosis. Furthermore, a faster decline in HBsAg titer during treatment was observed in HBeAg-positive patients compared to HBeAg-negative patients.*

Conclusion: *Our findings support the use of quantitative HBsAg as an important marker for monitoring liver disease progression and individual risk assessment in chronic hepatitis B patients treated with NUCs. Further research is needed to optimize treatment strategies based on quantitative HBsAg levels and other surrogate markers.*

Keywords: *Hepatitis B, HBsAg, therapy, NUC, decline.*

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Introduction

Viral hepatitis B occurs as an acute infectious disease with liver function impairment. The disease can be fulminant or chronic. Despite mandatory HBV vaccinations since 1992, which significantly lowered infection rates, high-risk groups and areas with elevated infection incidences persist. Approximately 350 million individuals globally are infected with hepatitis B virus (HBV). In Bulgaria, the prevalence of HBV infection ranges from 2 to 4% within the population[2,3]. Using existing treatment methods, the virus's replication is halted in the majority of patients, but complete eradication is not achieved. The diverse outcomes and disease progression in patients treated with nucleotide/nucleoside analogues (NUCs) imply that factors beyond negative HBV DNA are involved. Identifying and understanding these factors will enhance diagnostic and therapeutic approaches and improve treatment predictions. It is established that not only HBeAg and anti-HBe status, initial viremia, liver damage extent, but also the duration and kind of antiviral therapy are crucial for therapy outcomes. In this context, quantitative HBsAg serves as an effective non-invasive prognostic indicator for assessing therapy effectiveness.

Aim

The objective of this study was to examine the correlation between quantitative HBsAg as a non-invasive marker for cccDNA evaluation and baseline

viremia, liver damage extent, HBeAg and anti-HBe status, as well as the kind of antiviral treatment over a five-year period.

Materials and methods

A retrospective analysis was carried out on the fluctuations in quantitative HBsAg levels in a total of 337 chronic viral hepatitis B patients undergoing antiviral treatment with nucleotide/nucleoside analogues (NUCs) for a duration of 5 years. Quantitative HBsAg values were determined at the beginning, prior to initiating antiviral therapy, and at 3 and 5 years after starting the treatment, using electrochemiluminescence immunoassay. HBV-DNA was tested through quantitative real-time PCR. Other hepatotropic viruses were ruled out by testing for anti-HDV and anti-HCV antibodies.

Quantitative HBsAg values were compared to baseline viremia, liver damage extent, HBeAg and anti-HBe status, and the type of antiviral treatment. The statistical data were analyzed using SPSS version 25.0, employing descriptive statistics, correlation analysis, the Mann-Whitney test, and the Kolmogorov-Smirnov test. P values less than 0.05 were deemed statistically significant.

Results

In the study, we included a total of 337 patients with chronic viral hepatitis B with an average age of 54.32 years. ±12.14 years. The mean value of quantitative HBsAg at baseline in the group was 9656.60 IU/ml±30334.21 IU/ml, its value at the 3rd year from the start of treatment with nucleotide/nucleoside analogs (NUCs) was 4803.89 IU/ml±9967.72 IU/ml, and on the 5th-3746.70 IU/ml±8262.21 IU/ml. The initial viral load in the subjects was 477973958.6 cop/ml±1292802277 cop/ml (Table 1). There was no statistically significant correlation discovered between quantitative HBsAg and HBV DNA values.

Additionally, no statistical connection was observed between the rate of HBV DNA negativation and the values of quantitative HBsAg. Of the subjects studied, 229 were men (68%) and 108 (32%) were women, and it was found that the initial titer of quantitative HBsAg was higher in men, but subsequently they showed a slower decline in the values of 3 and 5th year of treatment (Figure 1). However, no statistically significant correlation was found between gender and quantitative HBsAg titer.

Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
Age:	337	29	79	54,32	12,137
Baseline HBsAg:	337	3	380000	9656,60	30334,209
3rd year HBsAg:	337	0	99704	4803,89	9967,723
5th year HBsAg:	337	0	87255	3746,70	8262,207
HBV DNA (cop/ml):	337	10	8990000000	477973958,6	1292802287
Valid N (listwise):	337				

Table 1: Mean values of quantitative HBsAg-baseline, 3rd and 5th year after initiation of antiretroviral therapy and baseline HBV DNA.

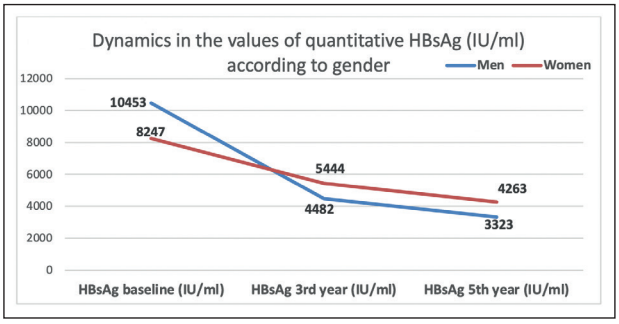

Figure 1: Dynamics in quantitative HBsAg values - baseline, 3rd and 5th year after initiation of antiviral therapy by gender.

Based on the severity of liver damage, patients were categorized into two groups. The first group consisted of patients with chronic hepatitis (Fibrosis stages F1-F3 as evaluated by Metavir) - n=258 (77%), while the second group- patients with Fibrosis stage F4 or those with clinical indications of liver cirrhosis - n=79 (23%). Higher baseline quantitative HBsAg values were observed in the cirrhosis group compared to those with chronic hepatitis.

Furthermore, a quicker decline and a more significant difference in baseline quantitative HBsAg values were seen at 3 and 5 years from the onset of treatment in cirrhotic compared to those with chronic hepatitis (Figure 2).

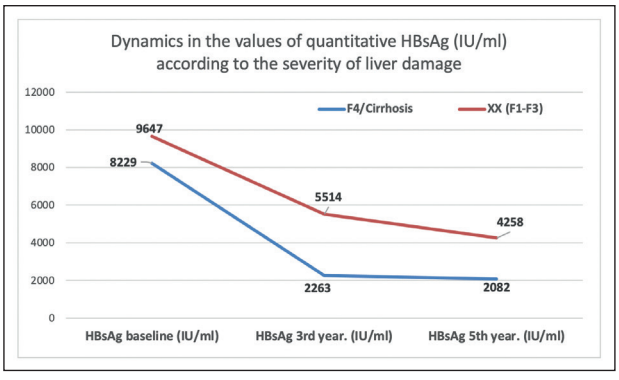

Figure 2: Dynamics in quantitative HBsAg values - baseline, 3rd and 5th year after initiation of antiviral therapy in relation to the severity of liver damage.

A significant correlation was shown between baseline quantitative HBsAg values and the presence

or absence of liver cirrhosis (Table 2). The same was confirmed for quantitative HBsAg values at 3 and 5 years of treatment, with r=0.143, P=0.001 and r=0.180, P=0.001, respectively.

In the group of patients with chronic hepatitis, a positive correlation was identified between baseline quantitative HBsAg values and the baseline level of HBV DNA (r=0.208, P=0.017 Pearson). However, this correlation was not observed in patients with liver cirrhosis.

Correlations			Baseline HBsAg	Severity of liver disease
Kendall's tau_b	Baseline HBsAg	Correlation Coefficient	1,000	,117**
		Sig. (2-tailed)	.	,009
		N	337	337
	Severity of liver disease	Corelation Coefficient	,117**	1,000
		Sig. (2-tailed)	,009	.
		N	337	337
Spearman's rho	Baseline HBsAg	Correlation Coefficient	1,000	,143**
		Sig. (2-tailed)	.	,009
		N	337	337
	Severity of liver disease	Correlation Coefficient	,143**	1,000
		Sig. (2-tailed)	,009	.
		N	337	337

Table 2: Correlation between baseline quantitative HBsAg values and severity of liver damage.

Among the participants studied, 270 were HBeAg(+) positive (80%) and 67 (20%) were HBeAg(-) negative.

It was found that quantitative HBsAg values at baseline and at 3 and 5 years were significantly higher in HBeAg positive patients, along with a faster decline in HBsAg titer during treatment (Figure 3). However, no statistically significant correlation was observed between HBeAg carrier status and quantitative HBsAg titer.

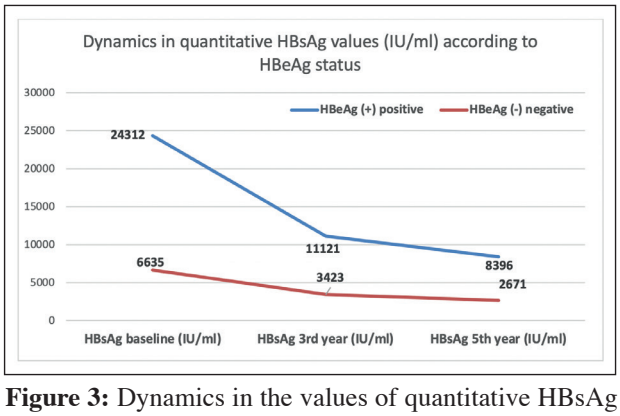

Figure 3: Dynamics in the values of quantitative HBsAg - baseline, on the 3rd and 5th year after the initiation of anti-inflammatory therapy in relation to HBeAg - status.

Based on the type of antiviral treatment using nucleotide/nucleoside analogues, patients were divided into three groups:

• Group 1 - Tenofovir in a daily dose of 245 mg/day n = 230 (68%);

• Group 2 - Lamivudine in a daily dose of 100 mg/day n = 68 (20%);

• Group 3 - Entecavir in a daily dose of 0.5 mg/day n = 39 (12%).

Significantly higher values of quantitative HBsAg were found at baseline, at 3 and 5 years in the group of patients treated with Tenofovir compared to the other 2 groups, P=0.001, as well as a faster decline in the titer during treatment (Figure 4).

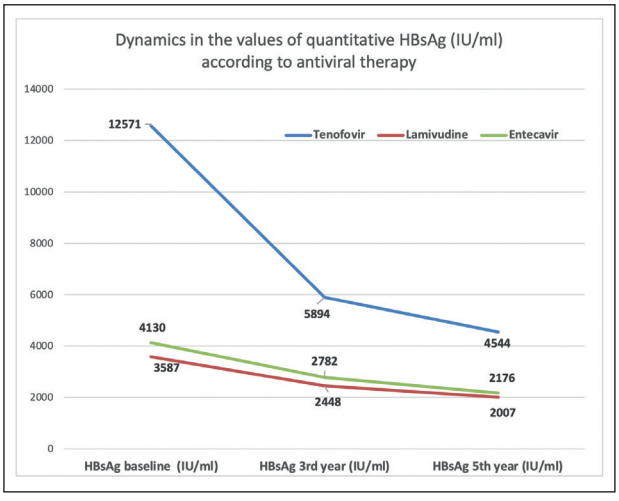

Figure 4: DDynamics in the values of quantitative HBsAg - baseline, 3rd and 5th year after the initiation of antiviral therapy according to the type of antiviral therapy.

Discussion

Our findings align with numerous previous studies that demonstrate a significantly faster decrease in quantitative HBsAg titer during therapy with NUCs in HBeAg-positive patients compared to HBeAg-negative patients[8-10].

In 2013, Xun and colleagues established that in untreated HBeAg-positive patients, there was a negative correlation between serum HBsAg and the histological stage of fibrosis (r=-0.533). Patients with advanced fibrosis had a mean value of quantitative HBsAg at 3.79 log IU/mL, compared to 4.47 log IU/mL in those without advanced fibrosis. The authors suggest that lower baseline values of quantitative HBsAg could serve as a marker for the presence of advanced fibrosis in these patients[11].

A comparable observation was made in another study that assessed liver fibrosis based on the Ishak classification. Consequently, it was demonstrated

that HBeAg-positive patients with liver fibrosis <1 according to Ishak had a significantly higher titer of serum HBsAg compared to those with fibrosis >1[12]. Despite the availability of numerous surrogate markers for advanced fibrosis, the inverse relationship between HBsAg values and the extent of liver fibrosis should be taken into account.

In contrast to the significant suppression of serum HBV DNA, nucleotide/nucleoside analogs (NUCs) have a limited impact on serum HBsAg, particularly for HBeAg-negative patients[13]. In a 2014 study involving 121 patients treated with Tenofovir, a decrease in baseline HBsAg of ≥1.0 log was reported at the fifth year of therapy initiation for only 36.4% of HBeAg-positive and merely 20% of HBeAg-negative patients[14].

Extending the duration of antiviral therapy further slows the decline in serum HBsAg levels[15]. It has been demonstrated that the decline rate depends on the baseline HBsAg level, as patients with a higher baseline HBsAg >3 log IU/mL experienced a faster decline in the third year of antiviral therapy than those with baseline HBsAg levels <3 log IU/mL (0.155 vs. 0.039 log IU/mL/year)[15]. The lack of a suppressive effect on HBsAg synthesis in patients treated with NUCs can be attributed to their mechanism of action, as they only inhibit DNA polymerase and do not affect the remaining stages of viral replication. Consequently, the associated cccDNA transcriptional activity is preserved. This explains the difference in the suppression of serum HBV-DNA and HBsAg[17]. Various studies have indicated that different NUCs have distinct effects on the decline of serum HBsAg, with the most pronounced effect for Tenofovir and the weakest for Lamivudine[18-23].

Boglione and colleagues tracked the dynamics of serum HBsAg levels in 134 HBeAg-negative patients undergoing antiviral therapy for a two-year period. They reported a significantly faster decline in quantitative HBsAg values for patients treated with Tenofovir compared to other NUCs[21].

Conclusion

In contemporary management of chronic hepatitis B virus infection, once permanently undetectable serum levels of HBV DNA and normalized aminotransferase values are achieved, the quantitative HBsAg titer remains a crucial surrogate marker for monitoring the progression of liver disease. Investigating this marker will enable a more accurate individual evaluation of the risk of liver damage progression in patients undergoing therapy with NUCs.

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