Chapter 9

Response-Guided Therapy Based on the Combination of Quantitative HBsAg and HBV DNA Kinetics in Chronic Hepatitis B Patients

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Abstract

Chronic hepatitis B (CHB) remains a difficult-to-treat disease because no current treatments provide an optimal virological and immunological control, there is a high rate of relapse following any antiviral therapy, and there are no identified clinical useful treatment stopping rules, especially in hepatitis B e antigen (HBeAg)-negative patients treated with nucleoside or nucleotide analogues (NUCs). Taking into account the limited options of antiviral drugs, the response-guided therapy seems to be the best approach for optimization of treatment response. Hepatitis B surface antigen (HBsAg) can be considered a surrogate marker of HBV immune control during antiviral therapy, regardless of virological response reflected by serum HBV DNA. Thus, the decrease of HBV DNA level represents a reduction of viral replication, while serum HBsAg decline signifies a reduction of messenger RNA translation. The most important on-treatment predictors of the antiviral treatment response, especially Peg-IFN α-2a, are the quantitative HBsAg and HBV DNA evolution during therapy. A combination of no HBsAg decline and <2 log10 IU/mL decrease of HBV DNA seems to be a predictor of nonresponse in European HBeAg-negative patients with genotype D. The reduction of HBsAg levels during NUCs treatment in HBeAg-positive patients may identify cases with subsequent HBeAg or HBsAg loss.

Keywords: chronic hepatitis B, antiviral treatment strategy, quantitative HBsAg, algorithm of chronic hepatitis B treatment

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1. Introduction

Worldwide, hepatitis B virus (HBV) infection has a high prevalence (350–400 million people are chronic HBV surface antigen carriers) and an increased morbidity and mortality (0.5–1 million deaths annually) [1]. To date, chronic hepatitis B (CHB) remains a difficult-to-treat disease due to the inability to achieve an optimal viral and immunological control with the available treatments, the high rate of relapse following any antiviral therapy and the absence of clinically useful predictors of sustained serological and viral responses.

Although existing potent nucleoside and nucleotide analogues (NUCs) with high genetic barriers have improved patient prognosis via suppression of viral load, there are still concerns that need to be addressed such as the need for long-term therapy, reactivation of the disease after cessation of therapy, hepatocellular carcinoma (HCC) risk persistence and the low rate of hepatitis B surface antigen (HBsAg) seroconversion.

In the last years, many published studies assessed the role of serum HBsAg quantification as predictor of treatment response in CHB patients treated mainly with pegylated interferon (Peg-IFN)-based regimens [2]. Some authors have proposed an early stopping rule using the combination between serum HBsAg and HBV DNA levels for hepatitis B e antigen (HBeAg)-negative CHB patients treated with Peg-IFN α-2a [2, 3].

2. Natural history of chronic hepatitis B

CHB is distinguished in five different phases according to HBeAg status, HBV DNA level, HBsAg status, alanine aminotransferase (ALT) level and histologic damages [1, 4]. Thus, the five evolutionary phases are as follow: the "immune-tolerant" phase, the "immune-active" HBeAg-positive phase, the "inactive HBV carrier" state, the "immune-escape" HBeAg-negative phase and the HBsAg-negative phase or "occult" HBV infection phase [1, 4]. In the evolution of chronic HBV infection, a patient may pass through each phase consecutively, especially after vertical transmission of the virus. Also, some phases are not identifiable in every patients, either because it may not be an obligatory step in the overall natural course of the infection or because it is of very short duration [5]. This feature seems to be dependent on age at the time of infection and the host immune reactivity against the virus.

The "immune-tolerant" phase is recognized usually in perinatally HBV-infected patients, which may last for about one to four decades in different populations and individuals [4, 5]. There is a highly replicative phase of the virus denoted by the presence of the HBeAg and high levels of HBV DNA (>2 × 10^7 IU/mL) in the serum despite a low inflammatory reaction reflected by normal ALT levels (<19 U/L for females and <30 U/L for males) and mild or no liver inflammation and no or slow progression of fibrosis [1, 2, 4, 5].

The "immune-active" phase, in which the immune system is trying to eliminate the virus, is defined by the HBeAg positivity in conjunction with high or fluctuating serum HBV DNA levels, persistent or intermittent elevation of ALT levels and active inflammation with accelerated

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progression of fibrosis compared to the previous phase [1, 2, 5]. The hallmark of transition to the inactive phase of chronic HBV infection is the HBeAg seroconversion achieved in the natural course of the disease or therapeutically induced.

The "inactive HBV carrier" state represents the most desirable phase of the disease for HBsAg-positive patients. It is characterized by absence of HBeAg, positive anti-HBe, persistently normal ALT values, low or undetectable HBV DNA (usually <2000 IU/mL) and mild or no inflammatory reaction on liver histology [1, 2, 5]. In clinical practice, one of the main issues is to distinguish between truly inactive HBV carriers and HBeAg-negative active CHB phase. It is well known that HBeAg-negative CHB patients could have intermittent normal transaminases and relatively low level of viral replication. However, these patients often have a long-term chronic HBV infection with advanced fibrosis score and a high probability of progression in the absence of treatment intervention. Considering that, we reinforced the recommendation to regularly check these patients based on individual clinical and biological characteristics.

The "immune-escape" phase may follow either by a spontaneous HBeAg seroconversion to anti-HBe (10–30%) or by reactivation of HBV replication and exacerbations of hepatitis following years of persistent inactive carrier state (10–20%) [1, 2, 5]. Moreover, this phase is defined by a fluctuating evolution of the disease activity with intermittent increase in ALT and HBV DNA serum levels [2]. Most of the patients harbor a pre-core or core promoter HBV variants which are unable to express or express low levels of HBeAg [1, 2].

The "occult" HBV infection phase follows after HBsAg disappearance and represents the persistence of minimum viral replication with detectable HBV DNA into the liver and no or low levels of HBV DNA in serum (<200 IU/mL) [1]. The clinical relevance of this phase is explained by the increasing number of patients who need immunosuppressive or cytotoxic therapy. Thus, to avoid the reactivation of the HBV replication, all guidelines recommend checking for HBsAg, immune globulins G (IgG) anti-HBc, anti-HBs, ALT and HBV DNA serum levels in conjunction with preemptive antiviral therapy depending on the blood test results and type of immunosuppressive agent [1, 2, 5, 9].

3. Treatment objective

As HBV cannot be truly eliminated with available treatment due to the persistence of covalently closed circular (ccc) DNA into the nuclei of the hepatocytes, the current goal of therapy in patients with CHB is improving the quality of life and prolonging their life expectancy by preventing the progression of the disease to the cirrhosis, decompensated cirrhosis, end-stage liver disease, hepatocellular carcinoma (HCC) and deaths [1, 2]. One of the efficient strategies to reach this goal is achieving and maintaining indefinitely the complete inhibition of viral replication. HBsAg loss and anti-HBs seroconversion, events rarely achieved nowadays, represent the ultimate aim of any antiviral treatment strategy and reflect especially the immune control of the virus without need for further medication, except decompensated cirrhosis or necessity of cytotoxic/immunosuppressive prolonged treatment [4].

Virtually, all patients diagnosed with chronic HBV infection are potential candidates for antiviral therapy. However, considering that current antiviral cannot completely eradicate the virus, all international guidelines agree that treatment is not required in the immune-tolerant phase and inactive carrier state of chronic HBV infection [1, 2, 5, 6]. In addition, it has been proved that patients with CHB who persist for years in immune-tolerant phase or inactive carrier state do not register a significant disease progression and the likelihood of response, in particular HBeAg seroconversion, is very low (<5%) [6, 7]. Nevertheless, even in these populations some controversy still remains about the risk of developing HCC and the risk of virus transmission into the population, respectively. The REVEAL (Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer) study has been concluded that persistently high serum HBV DNA levels are associated with increased risk of cirrhosis, HCC and liver-related death. On the other hand, 67% of populations in this study were older than age 39 [8]. For all these reasons some experts have proposed that immune-tolerant patients older than age of 40 should receive antiviral treatment, especially if they have elevated HBV DNA (>10^6 IU/mL) and significant necroinflammation or fibrosis [2, 6]. Given that HBV infection is a chronic and dynamic condition, having the possibility of crossing a stage to the other and vice versa, regular monitoring is critical in patients without indication for antiviral therapy at a single-point assessment, in order to identify the best timing for treatment intervention [6].

From the clinical perspective, usually the decision to initiate the antiviral treatment in patients diagnosed with HBV infections is made by taking into consideration several important parameters: clinical status, ALT and HBV DNA levels, HBeAg status and the severity of liver inflammation and fibrosis [1, 2, 5, 6]. Indications for treatment may also depend on age, familial history of HCC, coinfection with other viruses, immunosuppression conditions, planning to become pregnant within the next 2–3 years in female patients [1, 6]. There are some absolute indications for antiviral treatment necessity such as HBV infection–associated life-threatening liver disease: acute liver failure or severe acute hepatitis (prolonged jaundice and coagulation abnormality), decompensated cirrhosis, severe exacerbation of CHB as well as for preventing reactivation in patients receiving immunosuppressive therapy, regardless of HBV DNA and ALT levels [1, 2, 5, 6]. In patients with compensated cirrhosis, we follow the European Association for the Study of the Liver (EASL) guideline which recommends antiviral treatment when the serum HBV DNA is detectable, irrespective of ALT levels [1]. In supporting of this approach, we mention the availability of potent NUCs with high genetic barrier to resistance along with slowing the progression of the disease to decompensated cirrhosis, end-stage liver disease and death. In noncirrhotic CHB patients, the treatment is generally recommended when they have a serum HBV DNA levels above 2000 IU/mL, persistently increased ALT levels above upper limit of normal (ULN) and/or histologic assessment showing moderate/severe inflammation or fibrosis [1, 6]. However, there are slight differences between the guidelines regarding the cutoff for HBV DNA and ALT values and the need for liver biopsy in order to establish the indication for antiviral treatment.

The EASL guideline recommends an HBV DNA cutoff value of 2000 IU/mL for initiating treatment, irrespective of HBeAg status [1]. The American Association for the Study of Liver Disease (AASLD) and Asian Pacific Association for the Study of the Liver (APASL) guidelines suggest an HBV DNA level of 20,000 IU/mL for HBeAg-positive patients and 2000 IU/mL for

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HBeAg-negative patients [2]. All international guidelines agree that, for patients who fulfill the criteria for HBV DNA, treatment should be recommended whenever the ALT levels are above 2×ULN or less than 2×ULN, even in normal range, whether are evidences for moderate/severe inflammation or fibrosis [1, 2, 5].

4. Antiviral treatment strategy with available options: Peg-IFN and NUCs

To date, there are currently available two different classes of antiviral agents for treatment of CHB patients: IFN-α (conventional or pegylated) and oral drugs (NUCs) [4]. Despite the availability of seven approved drugs, only three of them are preferred as first-line options in the international American and European guidelines, as follow: Peg-IFN α-2a, entecavir (ETV) and tenofovir (TDF). Obviously, each of these agents is selected based on patient characteristics, considering that neither IFN nor NUCs are the best treatment options in any clinical condition. Thus, baseline as well as on-treatment predictive markers are needed to identify which patients benefit most from a finite course of IFN treatment or indefinite treatment with oral NUCs.

Both IFN-alfa and NUCs have different mechanisms of action in order to achieve the predefined goals of treatment in CHB patients: ALT normalization, suppression of viral replication, HBeAg and HBsAg seroconversion [9]. In addition, the reduction of the risk of progression to cirrhosis and HCC are among the desired therapeutic objectives [9].

IFN is a pro-inflammatory cytokine with dual mechanism of action, both antiviral and immunomodulatory activities, enhancing host immunity defense against HBV, which may lead to a sustained off-therapy response known as immune control [5, 6, 9]. Although the antiviral potency of IFN (Peg-IFN, respectively) is modest, the international guidelines have positioned it in the first-line treatment option, considering the major advantages associated with usage of this drug: finite duration of therapy, immunomodulatory effect with the potential to increase the chance of HBeAg and HBsAg seroconversion as well as a long-term immune control of the disease at least in a well-selected population [1, 2, 5, 10]. In addition, the National Institute for Health and Care Excellence (NICE) guideline for CHB recommend that a 48-week course of Peg-IFN α-2a should be offered as first-line treatment in adults with HBeAg-positive and-negative CHB and compensated liver disease [10].

It has been identified pretreatment predictors of IFN/Peg-IFN α-2a response in HBeAg-positive CHB patients: young age, high serum ALT levels (>2×ULN), low viral load, HBV genotype A and B, high histologic activity index and wild-type pre-core and basal-core promoter sequence [6, 9]. In HBeAg-negative patients, there were no such well-defined baseline predictors of IFN treatment [6]. From the clinical point of view, the presence of these baseline predictors in an individual patient with CHB does not assure the response to a 48-week course of Peg-IFN treatment. For this reason, of great significance are early predictive factors, such as ALT flares and quantitative HBsAg decline at 12 and 24 weeks during treatment [11–13].

On the other hand, there are some limitations of IFN-based treatment in CHB due to the parenteral weekly administration, the broad spectrum of side effects and the restriction of

administration in several circumstances of the disease according to licensed indications (e.g., decompensated cirrhosis, uncontrolled psychiatric illness, pregnancy, hematologic neoplasia with need for cytotoxic or immunosuppressive treatment) [14].

NUCs, known as drugs with direct antiviral mechanism of action, targeting the HBV polymerase, represent another major class available in the therapeutic armamentarium of CHB. These antiviral drugs have become the mainstay therapy in CHB given the oral administration, the easy management, the absence of contraindications to start treatment, the high antiviral potency and a narrow spectrum of side effects [6, 9]. Among the available NUCs, lamivudine (LAM), telbivudine (LdT) and adefovir (ADV) are no longer recommended as first-line monotherapy because of the resistance concerns, while ETV and TDF are ranked by all international guidelines in the pole position of antiviral treatment [1, 2, 5].

Mitochondrial toxicity is a potential side effect of any NUCs, but fortunately is very rare event. There are reported specific side effects for each NUC, such as myopathy and neuropathy related to LdT, lactic acidosis related with administration of ETV in patients with severely impaired liver function and renal dysfunction and bone mineral density impairment in patients treated with ADV and TDF [6].

ETV and TDF suppress viral replication in over 90% of CHB patients within a defined period of time (months to years), although undetectable HBV DNA is much faster achieved when the baseline viral load is lower [9]. Furthermore, HBeAg seroconversion rate increase over time with around 40% in Asian studies and 20% of HBeAg-positive, genotype A, patients from Europe, respectively, while HBsAg seroconversion occurs in approximately 3–10% of all CHB patients over 5 years of follow-up [6, 9]. Despite the inability of NUCs to act directly on the cccDNA, the level of the intrahepatic cccDNA seems to decrease over prolonged treatment with NUCs, as the nuclear replenishment with new chains of viral DNA is interfered by blocking the transcription of pregenomic viral RNA. It is estimated that with current NUCs treatment, the median number of years needed to clear HBsAg is 52.2 years [15]. The similar study predicted a median time for HBsAg loss of 36 years in HBeAg-positive and 39 years in HBeAg-negative HBV infection, respectively [16]. High baseline ALT level seems to be the most important pretreatment predictor of response to NUC treatment in HBeAg-positive patients [6]. In the HBeAg-negative CHB patients, there have not been defined baseline predictors of treatment with NUCs [6]. Unlike Peg-IFN treatment, it has not been demonstrated that HBV genotype could influence the NUCs treatment response [6].

The long-term completely viral suppression is associated with liver histology improvement and in some patients even with reversion of cirrhosis over a treatment period of 5 years [17, 18]. The impact of long-term treatment with NUCs on HCC risk is questionable. At least from the theoretically point of view, the inhibition of viral replication could decrease the cumulative incidence of HCC, considering that HBV DNA levels have been identified as an independent risk factor for HCC occurrence [8]. Thus, there have been published some studies which established that long-term treatment with potent NUCs have been linked to the reduction of the incidence of HCC [19, 20]. On the opposite, the risk of HCC could not be eliminated with any available treatments because of the truncated sequences of HBs genes integrated in the DNA of the infected hepatocytes, which is believed to be associated with carcinogenesis.

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However, it is still unresolved issue related to the NUCs treatment in CHB, such as the safety of long-term usage of these antivirals, the extent of the optimal duration of treatment and when the treatment discontinuation is suitable [21]. Despite the highest antiviral efficacy, NUCs do not have immunomodulatory effects and induce only a transient increase of immune activity, being unlikely to provide a sustained off-treatment control of viral replication [21]. Thus, treatment with NUCs is indefinite in most cases. It has been proposed that the best and safest endpoint for NUCs discontinuation in any CHB patient is HBsAg seroconversion, defined as HBsAg loss and anti-HBs appearance at a level over 100–200 IU/mL [9]. However, around 30% of patients who achieve HBsAg loss during NUCs treatment do not develop anti-HBs even with prolongation of antiviral treatment [9]. According to the guidelines, the NUCs treatment endpoints in CHB patients are different depending on the HBeAg status. In HBeAg-positive CHB, it seems reasonable to discontinue the NUCs treatment in noncirrhotic patients who undergone HBeAg seroconversion and who have maintained the undetectable HBV DNA at least 1 year thereafter, although approximately 50% relapse [1, 9]. On the other hand, indefinite treatment with NUCs is necessary for HBeAg-negative patients and HBeAg-positive patients who do not develop anti-HBe seroconversion [1]. The same approach is recommended in patients with cirrhosis irrespective of HBeAg status or anti-HBe seroconversion on treatment [1]. In some instances, discontinuations could be attempted in HBeAg-negative patients after treatment for at least 2 years (preferably 4–5 years) with undetectable HBV DNA documented on three separate occasions, 6 months apart [5, 9]. Once it has been decided to stop the NUC-based treatment, regular monitoring of virological and biochemical parameters is mandatory, considering that there are potential life-threatening clinical consequences associated with NUCs discontinuation such as hepatitis flare and hepatic decompensation [9].

5. Response-guided therapy based on serum HBsAg and HBV DNA kinetics

One of the modern and cost-efficient concepts in the management of CHB in terms of antiviral treatment is "response guided therapy" depending on the kinetics of the serum HBsAg and HBV DNA levels during treatment. In the current international guidelines, there are some validated rules that support either continuation of antiviral regimen, based on a positive prediction of response, or contrary, cessation/switching therapy to another regimen, depending on a high negative prediction of sustained response.

The clinical relevance of quantitative serum HBsAg arises from the correlation with the intrahepatic amount and transcriptional activity of cccDNA, the main replicative template of HBV [22–24]. It is assumed that quantitative HBsAg could be used as a surrogate marker for immune control of the virus, regardless of the HBV DNA response during treatment and thereafter [23]. A HBV DNA decline directly reflects a reduction of viral replication, while serum HBsAg decline signifies a reduction of transcriptional activity of intranuclear cccDNA and integrated DNA sequences [24, 25].

Several studies have been published to identify the useful surrogate markers for selecting the initial antiviral regimen, for guiding the treatment as well as for early prediction of the favorable or unfavorable outcome [4]. These markers have been stratified as pretreatment

and on-treatment predictors. The majority of the studies have investigated the significance of HBsAg and HBV DNA levels as the most powerful predictive factors for antiviral treatment response. It is well known that the most important decrease of HBsAg levels occurred during the Peg-IFN treatment because of the dual mechanism of action, including the modulation of the immune activity. On the other hand, the long-term treatment with NUCs induces only a minimal reduction of serum HBsAg, especially in HBeAg-positive patients. Thus, the HBsAg quantification has various benefits in the management of CHB patients depending on the HBeAg status and the antiviral treatment.

Quantification of HBsAg levels can be used to guide the treatment with Peg-IFN α-2a. In addition, different studies proposed the role of HBsAg level as a "stopping rule" at week 12 of Peg-IFN treatment in both HBeAg-positive and HBeAg-negative patients [5].

In HBeAg-positive CHB patients with genotype A and D, an absence of any HBsAg decline at 12 weeks of Peg-IFN treatment has been associated with a negative predictive value (NPV) of 97% for sustained response [26]. Moreover, in HBeAg-positive, genotype B and C chronic HBV infections, it has been observed that a level of HBsAg over 20,000 IU/mL at 12 weeks of treatment with Peg-IFN could predict a low chance of HBeAg seroconversion [1, 5]. Thus, the European and Asian guidelines have proposed an early stopping rule in CHB, HBeAg-positive patients, who do not achieve any HBsAg decline or who have an HBsAg levels over 20,000 IU/mL after 12 weeks of Peg-IFN-based treatment [1, 5]. Also, a level of HBsAg over 20,000 IU/mL at 24 weeks could be applied as another stopping rule, irrespective of HBV genotype [27]. Overall, around 20–30% of the HBeAg-positive patients would be eligible for an early stopping of treatment with Peg-IFN, at 12/24 weeks, due to the high negative prediction of the sustained response after 48 weeks course of standard of care [9]. On the other hand, it has been proved that HBeAg seroconversion rates 6 months posttreatment were significantly higher in patients with HBsAg <1500 IU/mL at weeks 12 and 24 (56.7 and 54.4%, respectively) versus patients with HBsAg <20,000 IU/mL (16.3 and 15.4%, respectively) [28]. Another on-treatment positive predictor is based on HBV DNA decline at 12 weeks. An HBV DNA level less than 20,000 IU/mL has been associated with 50% chance of anti-HBe seroconversion [29].

In HBeAg-negative genotype D patients treated with Peg-IFN α-2a, it has been validated a stopping rule depending on a combination of HBsAg and HBV DNA assessment at 12 weeks. According to this rule, we can identify early, with a NPV of 100%, all CHB, HBeAg-negative, genotype D patients who will not achieve sustained response at 48 or 96 weeks of treatment with Peg-IFN α-2a [30]. A less than 10% decline of HBsAg levels at 12 weeks for patients with nongenotype D infections and at 24 weeks for genotype D has been shown to be associated with 16% probability of treatment response at 1 year posttherapy [31]. Similar to HBeAg-positive patients, approximately 50% of HBeAg-negative CHB patients with an HBV DNA decrease <20,000 IU/mL at 12 weeks during Peg-IFN treatment would achieve a sustained off-treatment response [1].

In 2013, we published a Romanian real-life small cohort study which included 57 patients with CHB treated 48 weeks with Peg-IFN α-2a and followed for another 24 weeks. The majority of patients had HBeAg-negative CHB (68%, $n = 39$) and genotype D (approximately 80%). During treatment, patients who achieved sustained response showed a marked decrease in

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serum HBsAg in comparison with non-responders (mean decrease of 1.06 ± 1.3 $\log_{10}$ IU/mL versus 0.04 ± 0.5 $\log_{10}$ IU/mL at 48 weeks, $p = 0.005$). On therapy, HBV DNA reduction >2 $\log_{10}$ IU/mL with any decrease of HBsAg level at week 12 had a positive predictive value (PPV) of 80% (95% CI: 51.91–95.43%) for sustained response, while HBV DNA decline <2 $\log_{10}$ IU/mL without any decline of HBsAg had a NPV of 85.71% (95% CI: 42.23–97.63%) for sustained response. One interesting findings of our study showed that relapsers had the same HBsAg declining profile as non-responder patients [3].

Considering that the rate of virological relapse after cessation of NUCs treatment is estimated to be 50%, the decline of HBsAg may help identify patients in whom treatment can be safely stopped without a high risk of relapse. Together with serum ALT and HBV DNA assessment, HBsAg quantification has been proposed as a clinically useful tool to monitor treatment responses during NUCs treatment, especially the prediction of future HBsAg loss [4].

The magnitude of HBsAg reduction during NUCs treatment could also predict the later HBsAg loss [4]. An HBsAg decline more than 1 $\log_{10}$ IU/mL after 1 year of oral antiviral treatment in HBeAg-positive CHB patients have been shown to predict the HBsAg loss [32].

Lower HBsAg levels at the end of treatment were predictive for later HBsAg loss, as well as for maintenance of HBV suppression after discontinuation of long-term NUCs treatment [4].

In HBeAg-positive CHB patients, an HBsAg levels <100 IU/mL was highly predictive of sustained response at 2 years off treatment [33]. In a recent Asian study, it has been showed that post-treatment virological relapse rate was significantly higher in patients over 50 years old and in patients with an HBsAg level >2 $\log_{10}$ IU/mL at the ETV cessation [34]. In the same study, an HBsAg level of 2.5 $\log_{10}$ IU/mL at HBeAg seroconversion has been established as an optimal cutoff for prediction of post-treatment virological relapse [34]. Thus, patients aged <50 years who achieved an HBsAg level <2.5 $\log_{10}$ IU/mL at HBeAg seroconversion had the lowest rate of relapse, 5% respectively [34]. In HBeAg-positive CHB patients treated with ETV, a serum HBsAg level below 2.5 $\log_{10}$ IU/mL at HBeAg seroconversion could be a useful predictor of post-treatment virological relapse [34].

Although previous studies have shown that quantitative HBsAg levels could be a useful predictor of relapse after cessation of treatment with NUCs in HBeAg-negative patients, in other recent prospective studies, neither HBsAg level at the end of treatment nor the kinetics of HBsAg were not able to predict the off-treatment relapse [35]. However, at the end of treatment, both HBsAg ≤2 $\log_{10}$ IU/mL and reduction by >1 $\log_{10}$ IU/mL from baseline were associated with a sustained virological response, defined as HBV DNA <200 IU/mL 12 month posttreatment [36].

6. Other clinical benefits of serum HBsAg quantifications in management of chronic hepatitis B

Since its discovery, besides the using of qualitative HBsAg as a diagnostic marker, there have been identified several roles of HBsAg in the management of chronic HBV infections, as follows.

6.1. Defining different phases of CHB

It is well known that HBsAg levels vary during the natural history of chronic HBV infections [3]. The highest values of HBsAg are reported in immune-tolerant phase (5.0 $\log_{10}$ IU/mL for HBsAg) and progressively decrease in "immune-active" phase (medium level of 3.0–4.0 $\log_{10}$ IU/mL) [24, 37, 38]. The lowest values of HBsAg levels have been reported in the "inactive carrier state" [24, 38]. Moreover, there is a variability of the quantitative HBsAg across different viral genotypes [3]. Patients with genotype A and D have the highest mean value of serum HBsAg (4.5 $\log_{10}$ IU/mL) compared to genotypes B and C (4.3 $\log_{10}$ IU/mL and 3.8 $\log_{10}$ IU/mL, respectively) [32, 39].

From the clinical point of view, combining a single-point determination of HBsAg <1500 IU/mL and HBV DNA <2000 IU/mL may identify "true inactive carriers" with a NPV of 96.7% for genotype D CHB patients [40]. This strategy could be useful especially in HBeAg-negative CHB patients with an HBV DNA level around 2000 IU/mL and normal transaminases, considering that in some patients is difficult to distinguish between active HBeAg-negative hepatitis and inactive carriers.

6.2. Predictor of liver fibrosis

Both HBV DNA and HBsAg levels have a declining evolution as long as liver disease progress from the immune-tolerant status to the active hepatitis and cirrhosis in HBeAg-positive patients [41]. Although previous studies showed that HBV DNA level could predict the risk of cirrhosis and HCC, it has been proved a poor correlation between HBsAg level and HBV DNA across different phases of the chronic HBV infection [8, 41]. Given that ALT measurement is a suboptimal marker for prediction of significant liver disease, it is recommended to have, as accurate as possible, an estimation of fibrosis and inflammation based on a reliable tool in order to decide antiviral treatment indication [42]. Nowadays, liver biopsy became rarely used in evaluation of patients with chronic hepatitis viral diseases due to the risk of the procedure, inter- and intraobservers variability, costs, as well as the availability of several noninvasive tests. All international guidelines agree that any HBV carriers who fulfill the criteria of HBV DNA have indication of antiviral treatment, whether there are evidences of significant necroinflammation and/or moderate/severe fibrosis [1, 2, 5]. Transient elastography, an imaging noninvasive test for assessing liver fibrosis, has a low accuracy in distinguished between intermediate stages of fibrosis (F1–F3). Also, the results are influenced by some confounding factors such as steatosis, ALT elevation [43].

There is emerging evidence suggesting association between HBsAg level and liver fibrosis stage in HBeAg-positive CHB patients. It has been proposed different cutoff levels of HBsAg for prediction of liver fibrosis among HBeAg-positive patients. Thus, serum HBsAg over 100,000 IU/mL was 100% predictive of insignificant fibrosis in patients with ALT below 2×ULN [42]. In HBeAg-positive patients with ALT ≤2×ULN, an HBsAg level over 25,000 IU/mL has been proved to be the best independent predictor of insignificant liver fibrosis (PPV of 92.7%, odds ratio 9.042) [42]. Based on these results, it has been suggested that HBeAg-positive patients with ALT ≤2×ULN and HBsAg ≥ 25,000 IU/mL could be followed

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without the need of liver biopsy [42]. On the other hand, there are evidences which support that lower serum levels of HBsAg are associated with more severe liver fibrosis in HBeAg-positive CHB patients [41]. A cutoff of 4.7 $\log_{10}$ IU/mL predicted moderate to advanced fibrosis (F2-F4) in HBeAg-positive patients, with an accuracy of 89% and a NPV of 91% [41]. Thus, a single-point baseline assessment of HBsAg level in HBeAg-positive chronic HBV-infected patients could become an accurate surrogate marker for distinguish moderate to advanced fibrosis from no or mild fibrosis [41]. However, in HBeAg-negative patients, there were no reported significant differences in serum HBsAg levels between patients with moderate to severe fibrosis and those with no or mild fibrosis [41].

6.3. Predictor of HCC

One of the remaining concerns in the management of CHB patients is the individual prediction of the HCC risk. There is very well known that the risk of HCC cannot be eliminated with any available therapy because of integrated sequences of viral DNA into the host genome. Even in cases of acute HBV naturally resolved infections the risk of HCC is estimated to be very low but higher compared to the general populations. The REVEAL study showed that viral replication is the major driver of disease progression and is an individual risk factor for HCC occurrence in patients with baseline HBV DNA ≥2000 IU/mL [8]. From the clinical practice point of view, it is very important to identify risk factors for HCC in an individual with CHB in order to adjust our HCC screening strategy. There are preliminary data which suggest an existing correlation between higher HBsAg level and an increased risk of HCC appearance [44]. From the clinical point of view, a particular interest would be in noncirrhotic patients with low level of HBV DNA (<2000 IU/mL) in whom the risk of HCC is difficult to be estimated. Thus, in HBeAg-negative patients with HBV DNA <2000 IU/mL an HBsAg level ≥1000 IU/mL has been has been identified as a new independent risk factor of HCC with a hazard ratio of 13.7 (95% CI: 4.8–39.3) compared to patients with HBsAg level <1000 IU/mL [44]. Moreover, HBV DNA has not been associated with HCC risk in these patients. Contrary, in HBeAg-negative patients with HBV DNA level above 2000 IU/mL, the HCC risk has not been proved to be linked to serum HBsAg levels [44]. These data support the role of HBsAg as a complementary tool by the side of HBV DNA in predicting the risk of HCC occurrence. According to the existing evidences, high risk factors for HCC related to HBV chronic infection include male gender, age over 50 years, HBV genotype B and C, pre-core and basal-core promoter HBV variants, pre-S deletion mutants, high serum of ALT, HBV DNA ≥ 2000 IU/mL and last but not least HBsAg ≥1000 IU/mL in low viremic HBeAg-negative patients [45].

7. Conclusions

In summary, there have been identified several clinical benefits of using quantitative HBsAg in the management of CHB. In case of IFN-based treatment, the most important role of HBsAg measurement is attributed to the highest NPV for sustained post-treatment response. Thus, in routinely clinical practice, different early stopping rules after 12 weeks of treatment can be used, depending on the HBeAg status. In HBeAg-positive CHB patients, Peg-IFN should be stopped

after 12 weeks whether HBsAg does not decline more than standard error or HBsAg level is above 20,000 IU/mL. In HBeAg-negative CHB patients, an absence of HBsAg reduction combined with a less than 2 $\log_{10}$ IU/mL decline of HBV DNA at week 12 of treatment should be used as another stopping rule. On the other hand, in NUCs treatment, the exact roles of the HBsAg have not been defined yet. However, one of the proposed roles of HBsAg quantification during long-term NUCs therapy is identifying those patients in whom treatment discontinuation can be safely decided. Moreover, there are robust evidences that support the role of HBsAg quantification as a useful tool for identification of true inactive HBV carriers, for distinguishing between HBeAg-positive patients with moderate to advanced fibrosis and no or mild fibrosis, as well as for predicting the risk of HCC occurrence especially in HBeAg-negative low viremic patients.

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