Chronic HBV Infection: Interferon Therapy and Long-Term Outcomes

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Abstract

Chronic hepatitis B infection affects around 240 million people worldwide, with long-term morbidity such as cirrhosis and hepatocellular carcinoma. Interferon treatment enhanced HBsAg seroclearance. Pegylated interferon induced a 10-15% yearly rate of HBsAg seroclearance in patients who developed sustained virological response in clinical trials. By contrast, treatment with nucleos (t) ides analogues did not significantly affect the rate of HBsAg seroclearance, especially in patients with hepatitis B e antigen (HBeAg) - negative disease. Recently, it has been shown that a significantly greater proportion of patients receiving tenofovir plus pegylated-interferon for 48 weeks had HBsAg loss than those receiving tenofovir or pegylated-interferon alone. HBsAg clearance is the closest to cure outcome, and there is increasing interest in HBsAg quantification. Quantification of serum HBsAg has also been recently shown to be a promising tool for monitoring virologic response in HBeAg-negative patients treated with pegylated interferon. This chapter reviews Interferon therapy and long-term outcomes.

Keywords

HBV cure • Immune therapy • cccDNA • HBs quantification

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Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
cccDNA	Covalently closed circular DNA
CHB	Chronic hepatitis B
ETV	Entecavir
HBeAg	HBe antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
IFN	Interferon
NAs	Nucleos(t)ide analogues
NI	Nucleoside inhibitors
NNI	Non-nucleoside inhibitors
PEG-IFN	Pegylated interferon
QD	Once daily
TDF	Tenofovir

1 Introduction

Chronic hepatitis B (CHB) infection affects over 240 million people worldwide, with long-term morbidity such as cirrhosis and hepatocellular carcinoma (HCC) accounting for around 600,000 deaths annually (World Health Organization 2012). HCC is one of the most frequent cancers in many countries, especially Africa, the Middle East, and Asia. Fibrosis is the most important prognosis predictor of survival (Marcellin et al. 2002; Asselah et al. 2014). HBV research and development programs aim to achieve an HBV cure. Interferon is the only immune-modulator treatment approved for HBV infection. This review will summarize results from interferon therapies, prediction of treatment response, and long-term outcomes.

2 HBV Current Therapy

The goal of therapy for CHB is to improve quality of life and survival by preventing progression of the disease (European Association for the Study of the Liver 2012; Sarin et al. 2016; Terrault et al. 2016). Previously, HBV DNA suppression with long-term lamivudine (LAM) has been associated with a reduction in the incidence of hepatic decompensation and HCC (Lai et al. 1998; Liaw et al. 2004). Treatment goals can be achieved by sustained suppression of HBV replication, thereby reducing necro-inflammation and reducing the risk of fibrosis progression. Suppression of HBV replication is critical and has to be maintained. Currently, there are two

Table 10.1 Advantages and limits of pegylated-interferons and analogue therapies

	PEG-IFN	Nucs
Advantages	• Finite duration • Absence of resistance • Higher rates of anti-HBe and anti-HBs seroconversion with 12 months of therapy	• Potent antiviral effect • Good tolerance • Oral administration
Disadvantages	• Moderate antiviral effect • Inferior tolerability • **Risk of adverse events** • Subcutaneous injections	• Duration • Risk of resistance • Unknown long-term safety

main treatment strategies for both hepatitis "e" (HBe) antigen positive (HBeAg+ve) and antigen negative (HBeAg−ve) (Table 10.1).

A finite treatment course of interferon (IFN) alpha/pegylated IFN (PEG-IFN) and long-term therapy with nucleoside/nucleotide analogues (NAs) are the currently approved treatments for chronic hepatitis B. A 1-year treatment with PEG-IFN offers the potential for immune-mediated control of HBV infection, with higher rates of HBe seroconversion and the possibility of off-treatment viral suppression and with loss of hepatitis B surface antigen (HBsAg) in a proportion of patients who maintain undetectable HBV DNA. However, PEG-IFN needs to be administered by subcutaneous injection and is associated with frequent side effects such as depression; it is also contraindicated in patients with decompensated cirrhosis or relevant autoimmune disease, during pregnancy.

In contrast, NAs suppress HBV via direct antiviral activity, and if compliance to treatment is good, more than 95% of patients treated with the newer, highly potent NAs tenofovir (TDF) and entecavir (ETV) achieve virological remission. NAs are administered orally, and tolerance is favorable, although the safety of these drugs over lifelong therapy is unknown. Regarding the risk of drug resistance, although common with earlier less potent NAs such as LAM and adefovir (ADV), resistance has become considerably less of a problem with the highly potent NAs TDF and ETV.

Long-term clinical data up to 6 years and beyond are emerging for the newer NAs that are providing reassuring data on their efficacy and safety. There is cumulative evidence that complete long-term suppression of HBV replication by the most potent drugs (ETV and TDF) results in an improved long-term outcome with a decreased risk of progression to cirrhosis and complications such as liver failure, HCC, and improved survival. In addition, a recent study assessing liver histology in patients treated with TDF for 5 years demonstrated that fibrosis regressed in most patients (Marcellin et al. 2013a; Marcellin and Asselah 2013). Moreover, unlike what is generally believed, the reversal of cirrhosis was observed during treatment in 75% of patients with cirrhosis, probably associated with a decreased risk of HCC and improved survival. Further long-term data are emerging from studies using newer potent NAs in routine clinical practice confirming safety and efficacy of these agents in the "real-world" setting.

3 The Importance of Fibrosis as Prognosis Factor

Fibrosis is the most important prognosis predictor of survival (Marcellin et al. 2002; Asselah et al. 2014). Therefore, patients with advanced fibrosis may be prioritized for treatment. Several new markers are developed to assess fibrosis.

For instance, we developed a simple scoring system to determine the severity of fibrosis in patients with genotype B or C HBV infection who are hepatitis B e antigen positive (Marcellin et al. 2015). We developed two prediction scoring systems (PSs). PS1 analyzed data on HBV genotype (B vs. C), patient age (<30 years vs. ≥30 years), level of hepatitis B surface antigen (≤17,500 IU/mL vs. >17,500 IU/mL), and level of alanine aminotransferase (≤3-fold vs. >3-fold the upper limit of normal). PS2 analyzed data on only age and level of hepatitis B surface antigen. Our system differentiated patients with no or mild fibrosis (F0–F1) from those with marked or severe (F2–F4) fibrosis with a high PPV. The high level of specificity for the identification of nonsevere fibrosis (F0–F2) limits the risk of overlooking patients with severe fibrosis (F3–F4).

In another study, the expression of 13 fibrosis-related microRNAs (miRNAs) (miR-20a, miR-21, miR-27a, miR-27b, miR-29a, miR-29c, miR-92a, miR-122, miR-146a, miR-155, miR-221, miR-222, and miR-224) was analyzed in 194 serums and 177 liver biopsies of patients with either CHB or CHC to develop models to diagnose advanced fibrosis and cirrhosis (Metavir F3–F4) (Appourchaux et al. 2016). In CHB patients, the model (serum miR-122, serum miR-222, platelet count, and alkaline phosphatase) was more accurate than APRI and FIB-4 to discriminate in between mild and moderate fibrosis (F1–F2) and F3–F4 (AUC of CHB model, 0.85, vs. APRI, 0.70, and FIB-4, 0.81). In CHC patients, the model (hepatic miR-122, hepatic miR-224, platelet count, albumin, and alanine aminotransferase) was more accurate than both APRI and FIB-4 to discriminate in between patients with F3–F4 and F1–F2 (AUC of the CHC model = 0.93 vs. APRI, 0.86, and FIB-4, 0.79). Most of the miRNAs tested were differentially expressed in patients with CHB and CHC. In particular, serum miR-122 was 28-fold higher in patients with CHB than in those with CHC. Both CHB and CHC models may help for the diagnosis of advanced fibrosis and cirrhosis (F3–F4).

4 Pegylated IFN (PEG-IFN): Results

The efficacy of PEG-IFN-α2a in HBeAg-positive and HBeAg-negative patients has been established in two large pivotal trials including 814 and 552 patients, respectively (Lau et al. 2005; Marcellin et al. 2004), and similar efficacy has been reported with the use of PEG-IFN-α2b (Buster et al. 2008). In both studies, PEG-IFN-α2a monotherapy, the combination of PEG-IFN-α2a plus lamivudine, and lamivudine monotherapy were compared during a 48-week treatment course. At the end of a 6-month posttreatment follow-up period, HBeAg seroconversion rates were 32%, 27%, and 19%, respectively, in the HBeAg-positive study (Lau et al. 2005), and serum HBV DNA levels were <400 copies/mL in 19%, 20%, and 7% of patients, respectively, in the HBeAg-negative study (Marcellin et al. 2004).

Interestingly, HBsAg seroconversion is achieved with a high steady rate in patients responding to interferon and associated with excellent outcome (Moucari et al. 2009a).

More recently, long-term follow-up data were reported for a subgroup of patients enrolled in the HBeAg-negative trial (Marcellin et al. 2009, 2013b). Interestingly, sustained off-treatment response (HBV DNA < 400 copies/mL) was maintained in 18% of patients treated with PEG-IFN-α2a. Importantly, HBsAg clearance occurred with a high steady rate (>10% per year) in sustained virological responders—reaching 64% at 5-year posttreatment.

5 PEG-IFN: Pretreatment Prediction

Selecting patients with the highest probability of achieving a response to PEG-IFN is essential to optimize its use and help the clinician decide whether to begin a finite course of 48 weeks of PEG-IFN.

6 HBV Genotype

HBV genotype A responds better to IFN when compared to other genotypes. A significant correlation between viral genotype and sustained HBeAg loss was found in HBeAg-positive patients in large multicenter trials of PEG-IFN, with the highest rates of HBeAg clearance at the end of follow-up in genotype A (47%), followed by B (44%), C (28%), and D (25%) (Flink et al. 2006). The meta-analysis clearly shows that genotype A is the most responsive to treatment in HBeAg-positive patients (Wiegand et al. 2008). Similar results have been reported in HBeAg-negative patients. The multicenter study by Bonino et al. including 518 HBeAg-negative patients has shown that genotype is significantly predictive of the efficacy in patients treated with IFN (Bonino et al. 2007).

7 HBV Viral Load

A low serum HBV DNA is predictive of HBe seroconversion. In HBeAg-positive patients, a low HBV DNA load (below 2×10^8 IU/mL) is predictive of anti-HBe seroconversion (Lau et al. 2005).

8 HBsAg Level (Quantification)

A low HBsAg level is predictive of response. Baseline HBsAg levels are reliable predictors of SVR, and current data confirm that baseline levels are good predictors of response. Baseline HBsAg levels are significantly lower in patients who achieve an SVR than in non-responders, both in HBeAg-positive and HBeAg-negative patients (Chan et al. 2010; Martinot-Peignoux et al. 2015).

9 Quantitative Hepatitis B Core-Related Antigen (qHBcrAg)

Quantitative hepatitis B core-related antigen (qHBcrAg) has been proposed as an additional marker to quantitative HBsAg (qHBsAg), for the management of chronic hepatitis B (Martinot-Peignoux et al. 2016). A recent study aimed to evaluate baseline combination of qHBsAg and qHBcrAg for the identification of patients that could benefit from pegylated interferon (PEG-IFN) alpha-2a-based therapy. Baseline qHBsAg is predictive of HBsAg loss. Both markers could be used, separately or in combination, for PEG-IFN-based "precision therapy." Our results emphasize that the combination of PEG-IFN alpha-2a plus TDF with 53% of SR might be an alternative to finite therapy.

10 Other Predictors: Genomics

The impact of IFNL3 (IL28B) polymorphism on response to interferon (IFN) treatment in patients infected with hepatitis B virus (HBV) is controversial (Lampertico et al. 2013; Holmes et al. 2013). We aimed to investigate whether IFNL3 polymorphism (rs12979860) influences the long-term response of chronic hepatitis B (CHB) treatment to conventional IFN (Zhang et al. 2014). No significant relationship between IFNL3 rs12979860 and fibrosis stage was observed ($P = 0.85$). IFNL3 genotype was neither associated with SVR nor with HBeAg seroconversion and long-term HBsAg seroconversion in HBeAg-positive CHB patients responding to IFN therapy.

Recently, Wu et al. investigated liver gene expression profiles to reveal the molecular basis associated with chronic hepatitis B and IFNα treatment response in CHB patients (Wu et al. 2016). Expression profiles were compared between seven paired liver biopsy samples taken before and 6 months after successful IFNα treatment or between pretreatment biopsy samples of 11 IFNα responders and 11 nonresponders. A total of 132 differentially upregulated and 39 downregulated genes were identified in the pretreated livers of CHB patients. The upregulated genes were mainly related to cell proliferation and immune response, with IFNγ and B cell signatures significantly enriched. Lower intrahepatic HBV pregenomic RNA levels and 25 predictive genes were identified in IFNα responders. The predictive gene set in responders significantly overlapped with the upregulated genes associated with the pretreated livers of CHB patients. The mechanisms responsible for IFNα treatment responses are different between HBV and HCV patients. HBV infection evokes significant immune responses even in chronic infection. The upregulated genes were predictive of responsiveness to IFNα therapy, as are lower intrahepatic levels of HBV pregenomic RNA and pre-activated host immune responses.

HBV DNA levels at weeks 12 and 24 cannot be used to develop a stopping rule similar to that for hepatitis C. A lack of decrease in HBsAg and a serum HBV DNA decrease of less than 2 $\log_{10}$ IU/mL have a strong negative predictive value for SVR

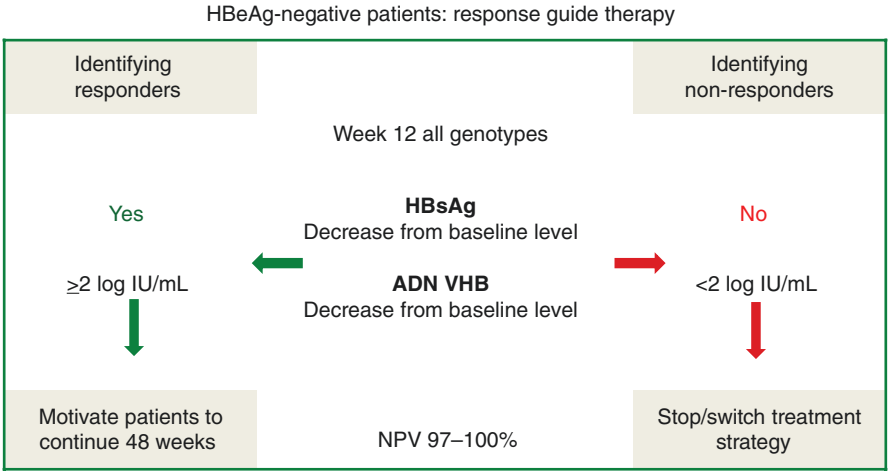

Fig. 10.1 Week-12 stopping rule for HBeAg-negative patients receiving PEG-IFN therapy

(Chan et al. 2010; Martinot-Peignoux et al. 2015; Moucari et al. 2009b; Brunetto et al. 2009). A week-12 response guide algorithm based on HBsAg kinetics has been proposed. Treatment should be discontinued or switched in patients without or with a limited decrease in HBsAg and/or a decrease in HBV DNA < 2 $\log_{10}$ IU/mL at week 12 (Fig. 10.1).

11 Major Recent Advances

11.1 Combination Therapy (TDF Plus PEG-IFN)

In a recent study, HBsAg loss was evaluated in patients receiving the combination of TDF and PEG-IFN for a finite duration (Marcellin et al. 2016). In an open-label, active-controlled study, 740 patients with CHB were randomly assigned to receive TDF plus PEG-IFN for 48 weeks (group A), TDF plus PEG-IFN for 16 weeks followed by TDF for 32 weeks (group B), TDF for 120 weeks (group C), or PEG-IFN for 48 weeks (group D) (Fig. 10.2a–c). At week 72, 9.1% of subjects in group A had HBsAg loss compared with 2.8% of subjects in group B, none of the subjects in group C, and 2.8% of subjects in group D. A significantly higher proportion of subjects in group A had HBsAg loss than in group C ($P < 0.001$) or group D ($P = 0.003$). However, the proportions of subjects with HBsAg loss did not differ significantly between group B and group C ($P = 0.466$) or group D ($P = 0.883$). HBsAg loss in group A occurred in hepatitis B e antigen-positive and hepatitis B e antigen-negative patients with all major viral genotypes.

Finally, a significantly greater proportion of patients receiving TDF plus PEG-IFN for 48 weeks had HBsAg loss than those receiving TDF or PEG-IFN alone.

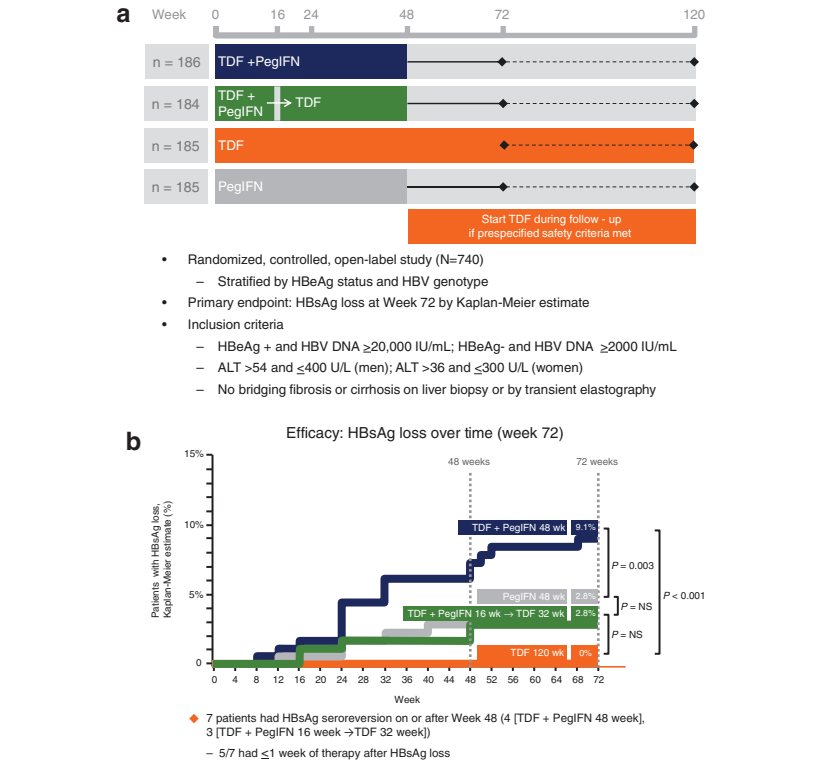

Fig. 10.2 Combination therapy with pegylated interferons plus tenofovir. (**a**) Trial design. (**b** and **c**) Results. At week 72, 9.1% of subjects in group A had HBsAg loss compared with 2.8% of subjects in group B, none of the subjects in group C, and 2.8% of subjects in group D. A significantly higher proportion of subjects in group A had HBsAg loss than in group C ($P < 0.001$) or group D ($P = 0.003$). However, the proportions of subjects with HBsAg loss did not differ significantly between group B and group C ($P = 0.466$) or group D ($P = 0.883$). Error bars represent 95% confidence intervals

11.2 HBsAg Quantification: A New Tool for HBV Monitoring

Quantifying HBsAg is certainly an important new tool for predicting the severity of disease, to distinguish inactive carriers from patients with HBeAg-negative chronic active hepatitis and thus help tailor follow-up and treatment management (Martinot-Peignoux et al. 2014, 2013). In addition, a decline in quantitative HBsAg during therapy is a strong predictor of SVR after PEG-IFN therapy and of the probability of HBsAg loss, which is the ultimate goal of therapy. In patients treated with analogues, a decline in HBsAg levels is also a predictor of HBsAg loss, allowing therapy to be discontinued.

Conclusion

HBsAg clearance is the closest to cure outcome as one can expect to achieve in hepatitis B. Support for this comes from natural history studies demonstrating increased length of survival, lower rates of hepatic decompensation, reduction in incidence of hepatocellular carcinoma, and regression of liver fibrosis. HBsAg seroclearance may occur spontaneously at a yearly incidence of 1–2%, preceded usually by a long period of inactive disease. Interferon treatment enhanced HBsAg seroclearance by approximately threefold in western studies and sixfold in Asian studies compared with non-treated patients. Pegylated interferon induced a 10–15% yearly rate of HBsAg seroclearance in patients who developed sustained virological response in clinical trials. By contrast, treatment with nucleos(t)ides analogues did not significantly affect the rate of HBsAg seroclearance, especially in patients with hepatitis B e antigen (HBeAg)-negative disease. Quantification of serum HBsAg has also been recently shown to be a promising tool for monitoring virological response in HBeAg-negative patients treated with pegylated interferon.

There is increasing research in the field of HBV infection. The new goal of HBV therapy is to achieve "functional cure" or even "absolute cure" with HBsAg loss/seroconversion and clearance of cccDNA. New drugs aimed to decrease or eliminate cccDNA and/or HBsAg.

Conflicts of Interest Tarik Asselah is a speaker and investigator for BMS, Boehringer Ingelheim, Tibotec, Janssen, Gilead, Roche, and MSD.

Patrick Marcellin is a speaker and investigator for BMS, Boehringer Ingelheim, Tibotec, Janssen, Gilead, Roche, and MSD.

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