Hepatol Int (2009) 3:425–433
DOI 10.1007/s12072-009-9140-3

REVIEW ARTICLE

HBeAg seroconversion as an important end point in the treatment of chronic hepatitis B

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Received: 5 May 2009 / Revised: 3 June 2009 / Accepted: 10 June 2009 / Published online: 24 June 2009

Abstract During the natural history of chronic hepatitis B virus (HBV) infection, the loss of serum hepatitis B e antigen (HBeAg) and the development of anti-HBe antibodies (HBeAg seroconversion) mark a transition from the immune-active phase of disease to the inactive carrier state. This review examines the evidence from natural history and cohort studies on the relationship between HBeAg seroconversion and disease progression. The role of HBeAg seroconversion as an important milestone in the management of HBeAg-positive patients with chronic hepatitis B (CHB), as well as the advantages and disadvantages of administering a finite course of therapy for HBeAg-positive CHB, is also discussed. The evidence from natural history and cohort studies indicates that spontaneous or treatment-induced HBeAg seroconversion is associated with lower rates of disease progression to cirrhosis and hepatocellular carcinoma, a potential of hepatitis B surface antigen seroconversion, and improved survival rates. Updated guidelines developed by major liver associations recommend stopping oral therapy for HBeAg-positive patients who achieve sustained HBeAg seroconversion with polymerase chain reaction-undetectable HBV-DNA on two separate occasions for 6 or more months apart, taking into consideration the individual's clinical and virologic response to therapy, as well as the severity of liver disease. Thus, early induction of HBeAg seroconversion with interferon-based therapy or oral nucleos(t)ide analogues has important clinical and socioeconomic implications for the management of CHB.

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Keywords HBeAg seroconversion · Hepatitis B virus · Chronic hepatitis B · Nucleoside analogue · Interferon alfa

Introduction

Chronic hepatitis B virus (HBV) infection continues to be a significant cause of liver-related morbidity and mortality, affecting more than 350 million people worldwide [1]. In regions of high HBV endemicity, such as the Asian-Pacific region where most individuals acquire the infection at birth or early in life, it is estimated that up to 40% of individuals with chronic hepatitis B (CHB) will progress to cirrhosis, end-stage liver disease, or hepatocellular carcinoma (HCC) during their lifetime [2, 3]. Seropositivity for hepatitis B e antigen (HBeAg), a surrogate marker of active viral replication, has been shown to be a significant risk factor for the development of cirrhosis and HCC [4–7]. Spontaneous loss of HBeAg and development of antibodies to HBeAg (anti-HBe), referred to as HBeAg seroconversion, are associated with low HBV-DNA levels and clinical remission of liver disease in the majority of patients [8–11]. Earlier HBeAg seroconversion, or a shorter HBeAg-positive phase, is associated with a higher chance of sustained remission, lower rate of HBeAg reversion, and slower progression of liver disease and even increased hepatitis B surface antigen (HBsAg) seroclearance [10–14].

Since highly sensitive HBV-DNA assays became available to measure HBV replication directly, rapid and durable suppression of HBV replication below the level of detection by polymerase chain reaction (PCR)-based assay has become the primary clinical goal for the treatment of CHB [15–18]. Studies have shown that profound and sustained suppression of HBV replication is a critical factor in

achieving the goals of anti-HBV therapy, including improvement of liver histology and reduction in liver disease progression [4–7, 19–24]. However, HBeAg seroconversion is still considered to be an important end point in the management of HBeAg-positive patients with CHB. Guidelines published by major liver associations, as well as other expert groups, recommend consideration of a finite period of oral therapy in HBeAg-positive patients who have undergone HBeAg seroconversion [15–17].

This review examines the evidence from recent studies that demonstrate a relationship between HBeAg seroconversion and long-term clinical outcomes. The factors that affect HBeAg seroconversion are also discussed. In addition, the rationale for HBeAg seroconversion in association with PCR-undetectable serum HBV-DNA levels as an important treatment goal in patients with HBeAg-positive CHB is also reviewed.

Natural course of disease and HBeAg seroconversion

Chronic HBV infection is a dynamic state of complex interactions involving the virus, the hepatocyte, and the host's immune response. The nature of these interrelationships, together with the influence of various external factors, ultimately determines disease severity and progression [25–27]. Accordingly, the natural course of chronic HBV infection consists of distinct phases: an immune-tolerant phase, an immune clearance phase, and an inactive or residual phase [28]. The patient's serologic profile with respect to HBV-DNA, HBsAg, and HBeAg levels changes with transition through the different phases of CHB. Patients in the immune-tolerant phase are usually young, HBeAg seropositive, and have high viral loads ($>10^6$ to 10^7 IU/ml or 10^7 to 10^8 copies/ml), yet normal serum alanine aminotransferase (ALT) levels and few clinicopathologic changes. Individuals with perinatal acquisition of HBV typically have a prolonged immune-tolerant phase that can last up to three decades. A 5-year follow-up study of individuals who remain in the immune-tolerant phase showed no or minimal disease progression [29]. In natural history studies of Asian HBsAg-positive children, the rate of spontaneous HBeAg seroconversion is low: <2% per year among children 3 years or younger and 4–5% per year in older children [30]. Approximately 90% of HBsAg carriers who acquire HBV in early life remain HBeAg positive at age 15–20 years, whereas HBeAg positivity decreases with increasing age and is <10% in patients older than 40 years [31].

The progressive decrease in HBeAg positivity starts in association with a transition to the immune clearance phase. The immune clearance phase is characterized by HBeAg seropositivity, fluctuating or high HBV-DNA and ALT levels, hepatitis flares, and increased inflammatory activity in the liver [32]. The clinical and histologic events that occur during this phase often influence the progression to liver disease. On the other hand, the immune clearance effort or events eventually lead to HBeAg seroconversion and transition to the inactive carrier phase [8]. HBeAg seroconversion is also associated with a sustained reduction in HBV-DNA levels [33].

Clinical remission of liver disease and a sustained inactive state are observed in the majority of patients (67–85%) who underwent HBeAg seroconversion, particularly among those in whom HBeAg seroconversion occurred before the age of 30 years and who maintain low or PCR-undetectable HBV-DNA levels [8, 9, 34]. Sustained disease remission after HBeAg seroconversion is associated with a regression of fibrosis upon liver biopsy. Hui and colleagues [34] evaluated the histology of liver samples from 128 HBeAg positive, treatment-naive Chinese patients who had undergone serial liver biopsies after HBeAg seroconversion. When disease remission was defined as HBeAg seroconversion and HBV-DNA level of $<10^4$ copies/ml (2×10^3 IU/ml), the regression of fibrosis was higher in patients with sustained disease remission (38.5%) than in those without remission (19.1%; $P < 0.00005$). Multivariate analysis revealed that sustained disease remission (relative risk [RR] = 3.00; 95% confidence interval [CI] = 1.29–7.01; $P = 0.01$) and 20–29 years of age at initial liver biopsy (RR = 2.94; 95% CI = 1.01–8.62; $P = 0.04$) were independently associated with the regression of fibrosis [34]. Furthermore, the rate of fibrosis progression was slower in patients with sustained disease remission than in patients who remained HBeAg positive (median = 0 fibrosis units/year; range = −2.00 to −0.70 fibrosis units/year versus median = 0.51 fibrosis units/year; range = 0 to +2.03 fibrosis units/year; $P = 0.02$). On the basis of these data, the authors concluded that HBeAg seroconversion was associated with a slower progression of disease and regression of fibrosis. Furthermore, among persons in such sustained inactive state, spontaneous HBsAg seroconversion to anti-HBs may occur at a rate of 1–2% per year [35]. HBsAg seroclearance confers excellent prognosis and is a state closest to a "cure" if there is no pre-existing cirrhosis or hepatitis C virus superinfection [36].

However, active hepatitis may relapse because of the reactivation of wild-type HBV associated with the reappearance of serum HBeAg (HBeAg seroreversion), or HBV with precore or basal core promoter mutations that abolish or downregulate the translation of HBeAg (HBeAg-negative hepatitis) [8, 9, 37]. In cohort studies involving adult CHB patients from Taiwan who had undergone spontaneous HBeAg seroconversion, the estimated annual incidence of hepatitis relapse was 2.2–3.3% [8, 9]. In one of these

studies involving 283 patients with CHB who were followed for a median period of 8.6 years after HBeAg seroconversion, 4.2% had HBeAg reversion and 24% developed HBeAg-negative hepatitis with detectable HBV-DNA; most patients relapsed during the first 10 years after HBeAg seroconversion. The cumulative probability of developing HBeAg-negative hepatitis following spontaneous HBeAg seroconversion was 14, 18, and 22% at 3, 5, and 10 years of follow-up, respectively [8].

A lower annual rate of CHB relapse was reported in a recent prospective long-term follow-up study involving 1,241 incidentally identified asymptomatic, adult, inactive HBsAg carriers, for whom the date of HBeAg seroconversion was unknown and they conceivably represent later phase after HBeAg seroconversion [38]. During a mean follow-up period of 12.3 years, the annual rate of hepatitis relapse was only 1.5% and was significantly lower in those younger than 30 years at entry. In this patient cohort, the cumulative risk of CHB relapse was also higher during the first 5- to 10-year follow-up period and decreased thereafter, becoming negligible after 20 years of follow-up. Overall, male gender, genotype C HBV infection, and delayed HBeAg seroconversion were found to be predictive factors for the reactivation of hepatitis B following HBeAg seroconversion [38]. Since the immune mechanism of HBeAg-negative hepatitis is similar to that of HBeAg-positive hepatitis, this phase with reactivation may be viewed as a variant of immune clearance phase [28].

HBeAg positivity and disease progression

The relationship between HBeAg seropositivity and the risk of developing HCC was evaluated in a long-term prospective study involving 11,893 Taiwanese men (age range = 30–65 years) without evidence of HCC [4]. During 92,359 person-years of follow-up, the incidence of HCC was higher for men who were positive for both HBsAg and HBeAg (1,169 cases per 100,000 person-years) than for men positive for HBsAg only (324 per 100,000 person-years). After adjustment for age, gender, hepatitis C serology, cigarette-smoking status, and alcohol use, the RR of HCC was more than sixfold higher in patients who were positive for both HBsAg and HBeAg (RR = 60.2; 95% CI = 35.5–102.1) than in those positive for HBsAg alone (RR = 9.6; 95% CI = 6.0–15.2) (Fig. 1) [4]. On the basis of these data, the authors concluded that HBeAg positivity is associated with an increased risk of developing HCC. These results have subsequently been confirmed in a long-term follow-up study involving 3,582 HBsAg-positive Taiwanese patients who were followed for a mean of 11 years. In this patient cohort, HBeAg seropositivity was associated with an increased risk for HCC (hazard ratio [HR] = 2.6; 95% CI = 1.6–4.2; $P > 0.001$) [7]. The cumulative HCC risk from age 30 to 70 years has been estimated to be 87% for those who were persistently seropositive for both HBsAg and HBeAg, 12% for those with persistent seropositivity for HBsAg only, and 1% for those who were seronegative for both HBsAg and HBeAg [39].

Patients who undergo HBeAg seroconversion are more likely to experience improved long-term outcomes, including disease remission, a lower incidence of cirrhosis and HCC, increased rates of survival, and the possibility of HBsAg loss or seroconversion [8, 14, 40]. For example, the beneficial effects of HBeAg seroconversion were investigated by Hsu and colleagues [8] in a study involving 283 patients with CHB who underwent spontaneous HBeAg

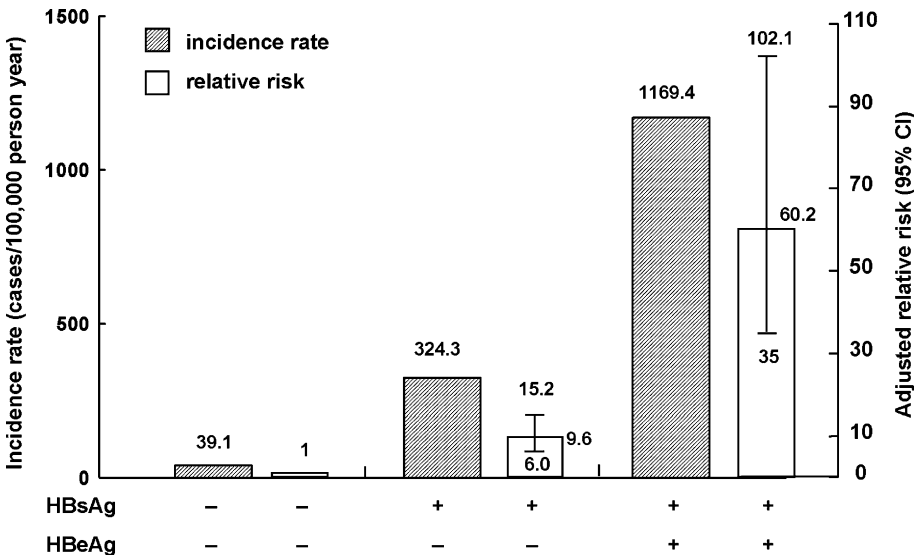

Fig. 1 Association of hepatitis B e antigen (HBeAg) seropositivity with an increased incidence and relative risk of developing hepatocellular carcinoma (HCC). HBsAg, hepatitis surface antigen. Adapted from Yang et al. [4] with permission

seroconversion. Of the 269 patients with no evidence of cirrhosis at the time of HBeAg seroconversion, only 21 (0.9%) developed cirrhosis during a median follow-up period of 9 years (range = 1.0–18.4 years). HBeAg reversion (odds ratio [OR] = 999; 95% CI = 0–999) and HBeAg-negative hepatitis (OR = 44; 95% CI = 5.55–348.82) were associated with a higher risk of developing cirrhosis than with sustained HBeAg seroconversion [8]. Similarly, in a prospective longitudinal study that assessed the natural history of HBeAg seroconversion and factors predictive of cirrhosis in 240 adult HBeAg-positive patients with normal ALT levels at entry, the persistence of HBeAg was associated with a higher likelihood of developing cirrhosis [9]. In this cohort, 85% of individuals underwent spontaneous HBeAg seroconversion between the age of 26 and 39 years, whereas only 10% underwent after the age of 40 years. Of note is that the age at HBeAg seropositivity was 10 years higher in patients who progressed to cirrhosis. The HR of progression to cirrhosis increased by 3.4 with each additional decade (95% CI = 1.4–8.2; $P = 0.006$) [9]. These data also suggest that the age at which HBeAg seroconversion occurs may be of clinical significance. Indeed, Yang and colleagues [41] compared liver biopsies from CHB patients older than 40 years ($n = 47$) and those younger than 39 years ($n = 93$). The rate of HBeAg positivity was not significantly different among those with milder and those with more severe histologic changes in the younger group. However, the prevalence of HBeAg positivity of patients older than 40 years was significantly higher among those with cirrhosis (50%) than in those without cirrhosis (16.2%; $P < 0.05$). A more recent long-term follow-up study also showed that patients with persistent HBeAg seropositivity had a much higher incidence of liver cirrhosis (Fig. 2) [14]. This is supported by evidence from studies of asymptomatic, HBeAg-positive HBV carriers that persistent HBeAg positivity or a prolonged immune clearance phase is associated with a higher risk of developing cirrhosis [10, 11]. On the basis of these results, it can be concluded that the persistence of HBeAg positivity in patients beyond the age of 40 years was associated with a poorer prognosis. Given that hepatitis flares occur frequently during the HBeAg-positive phase [32], patients with a longer HBeAg-positive phase could conceivably have more frequent or prolonged necroinflammatory liver damage, leading to a higher degree of hepatic fibrosis or cirrhosis development [42].

Treatment-induced HBeAg seroconversion and disease progression

Treatment-induced HBeAg seroconversion has also been shown to confer favorable outcomes and is a strong predictor of prolonged survival. Niederau and colleagues [12] conducted a follow-up study of 103 CHB patients treated with conventional interferon (IFN)-α and 53 untreated patients. After a median of 50 months after completing therapy, 53 of the 103 IFN-α-treated patients ultimately lost HBeAg (a cumulative rate of 56% at 5 years) and seroconverted to anti-HBe with HBV-DNA undetectability by hybridization assay. Of note is that HBsAg seroclearance occurred in 10 (19%) of the 53 patients who had undergone HBeAg seroconversion (with a calculated cumulative rate of 12% at 5 years) [12]. In contrast, only 7 of the 50 untreated individuals experienced spontaneous HBeAg conversion (cumulative rate of 28% at 5 years), and all remained positive for HBsAg. Of the 50 treated patients with persistent HBeAg positivity, 6 patients died of liver failure, 2 patients required liver transplantation, and 8

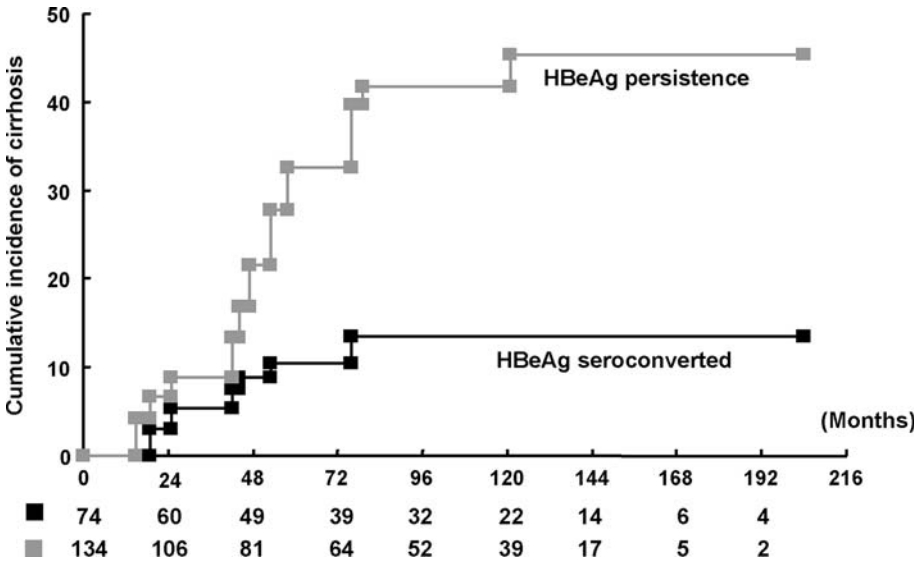

Fig. 2 Cumulative incidence of cirrhosis in untreated patients who have persistence of serum hepatitis B e antigen (HBeAg) and those who have undergone HBeAg seroconversion. Adapted from Lin et al. [14] with permission

patients developed cirrhosis during follow-up. Overall survival and survival without clinical complications were significantly longer in patients who experienced HBeAg seroconversion after therapy with IFN-α than in those who remained HBeAg positive ($P = 0.004$ and $P = 0.018$, respectively) [12]. In a regression analysis, the clearance of HBeAg was the strongest predictor of survival. Thirteen of the 50 untreated patients had severe complications, including 4 deaths and 1 need for liver transplantation; all 13 were persistently seropositive for HBeAg. Another study from Europe also showed a high HBsAg seroclearance rate in IFN-treated patients with HBeAg seroconversion [40].

These findings have been confirmed in a prospective randomized controlled study by Lin and colleagues [13], who examined the long-term effect of IFN therapy on survival and incidence of HCC in patients with CHB. This study involved 101 male CHB patients who were randomized to receive either IFN or placebo and were followed up for a median of 8.2 years (range = 1.1–11.5 years) after the end of therapy. Of the 101 patients, 34 patients received placebo (control) and 67 patients were treated with IFN (31 patients were treated with IFN alone and 36 patients were treated with IFN after prednisone priming). A higher proportion of IFN-treated patients than untreated patients seroconverted by the end of the trial (28 [42%] of the 67 patients in the IFN group versus 8 [24%] of the 34 patients in the placebo group) [13]. During follow-up, 22 (56%) of the 39 patients who did not seroconvert in the treated group and 5 (19%) of the 26 patients who did not seroconvert in the control group showed a delayed sustained response ($P < 0.005$). HCC was detected in 1 (1.5%) of the 67 treated patients and 4 (12%) of the 34 untreated patients ($P = 0.043$) [13]. The interval between study entry and HCC detection was 3.5–8.2 years. The cumulative incidence of HCC development was significantly higher in the control group than in the treated group ($P = 0.013$). In contrast, the cumulative survival rate was higher in the treated group than in the control group ($P = 0.018$). Multivariate analysis showed that IFN therapy, preexisting cirrhosis, and the patient's age at entry were significant independent factors for both the survival and development of HCC [13].

In a more recent study, Lin and colleagues [14] reported the long-term outcomes of IFN-α therapy involving 233 HBeAg seropositive patients and 233 well-matched untreated controls who were followed for 15 years. In this study, IFN-α-treated patients had a higher cumulative incidence of HBeAg seroconversion and a lower incidence of cirrhosis and HCC than for untreated controls at the end of 15 years of follow-up (median = 6.8 years; range = 1.1–16.5 years) (Table 1) [14]. Compared with untreated controls with persistent HBeAg, both untreated and IFN-α-treated patients who achieved HBeAg seroconversion showed significantly lower incidence rates of cirrhosis ($P = 0.031$ and $P = 0.023$, respectively), whereas IFN-α-treated patients who did not achieve HBeAg seroconversion had marginally significantly lower incidence rates of cirrhosis ($P = 0.065$, Fig. 3) [14]. It should be noted that a higher proportion of the IFN-α-treated patients than controls experienced HBsAg loss at the end of the follow-up period, although the rate was only 3% (vs. 0.4%; $P = 0.03$) [14]. Multivariate analysis showed that IFN therapy, HBeAg seroconversion, and genotype B HBV infection were independent factors associated with better long-term outcomes. A much higher rate of HBsAg seroclearance was reported in studies involving European patients who achieved HBeAg seroconversion during IFN therapy [12, 40].

Table 1 Effect of interferon (IFN)-α on long-term outcomes in Taiwanese patients with HBeAg positive chronic hepatitis B

*P vs. control	IFN alfa-treated patients ($N = 233$)	Matched untreated controls ($N = 233$)	P value*
Cirrhosis	18%	34%	0.041
HCC	3%	13%	0.011
HBeAg seroconversion	75%	52%	0.031
HBsAg clearance	3%	0.4%	0.03

* P vs. control; Follow-up: mean 11 years (median = 6.6 years; range = 1.1–16.5 years)

Adapted from Lin et al. [14]

PegIFN-α therapy results in HBeAg seroconversion rates of up to 32% and 48%, respectively, when assessed at weeks 24 and 48 post-treatment [43–46] and sustained after cessation of therapy in the majority (80–90%) of HBeAg-positive patients [47]. Baseline HBV and ALT levels are predictive factors for HBeAg seroconversion [47]. On treatment, HBeAg level of <10 Paul Ehrlich Institute Unit/ml at week 24 and HBsAg level of <1500 IU/ml at week 12 of PegIFN therapy are also reported to favor HBeAg seroconversion [48]. In contrast, HBeAg seroconversion rates reported with older oral nucleos(t)ide analogues (NAs; lamivudine and adefovir) have been considerably lower (12–16%), though the rate in patients with a baseline ALT of more than five times the upper limit of normal (ULN) was more than 50% [49]. Week 24 HBV-DNA level during NA therapy is also predictive of HBeAg seroconversion [22, 48]. In addition, a retrospective analysis of HBeAg seroconversion involving 98 HBeAg-positive patients with genotype C CHB who were treated with lamivudine, the cumulative relapse rates at 1 and 2 years post-treatment were 37.5 and 49.2%, respectively, and most relapses were accompanied by an elevation in ALT levels (94%) and reappearance of HBeAg (81%) [50]. More recently, higher rates of HBeAg seroconversion (20–25%) have been reported in clinical trials of newer oral

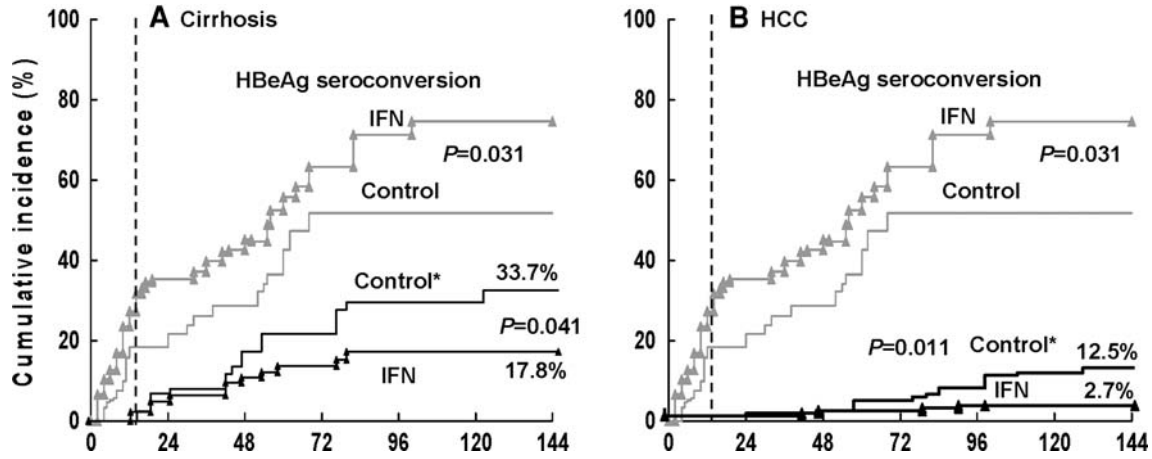

Fig. 3 Interferon (IFN) therapy significantly increased cumulative hepatitis B e antigen (HBeAg) seroconversion (*gray lines*) with corresponding decrease in cirrhosis and hepatocellular carcinoma (HCC) (*dark lines*). * Control group consisted of 1:1 age/sex/ALT/HBV-DNA-matched HBeAg-positive patients. Adapted from Lin et al. [14] with permission

NAs, including entecavir, telbivudine, and tenofovir [22, 51–54].

HBeAg seroconversion rates as high as 25% have been reported at 1 year of telbivudine treatment in Asian patients with HBeAg-positive CHB [52]. At 2 years of telbivudine and entecavir treatment, HBeAg seroconversion rates are comparable with those achieved at 24 weeks after a 48-week course of PegIFN in patients with HBeAg-positive CHB [21, 23, 55]. Most notable are the high rates of HBeAg seroconversion achieved after 2 years of telbivudine treatment in Asian patients with genotype C HBV (32%) and in patients with ALT levels of 2 or more times the ULN at baseline (36%) [55].

The off-treatment durability of HBeAg seroconversion was recently assessed in more than 1,000 HBeAg-positive patients who participated in two pivotal phase III studies comparing the safety and efficacy of telbivudine and lamivudine over a 2-year period in adult patients with CHB [53, 56]. The GLOBE study, conducted in 20 countries, compared these two antiviral agents in 1,367 patients (921 HBeAg positive) [22]. A similarly designed study was conducted in China and enrolled 332 patients (290 HBeAg positive) [52]. The HBeAg-positive patients were eligible for discontinuation of therapy if they had received antiviral treatment for more than 1 year and had HBV-DNA levels of <5 $\log_{10}$ copies/ml (2×4 $\log_{10}$ IU/ml), with HBeAg loss maintained on treatment for 24 weeks or more. A greater proportion of patients receiving telbivudine than those treated with lamivudine achieved HBeAg loss (Fig. 4a) and HBeAg seroconversion (Fig. 4b) at each study visit and thus met the criteria for treatment discontinuation [53]. The post-treatment durability of HBeAg seroconversion with telbivudine by Kaplan–Meier estimate during the follow-up period was

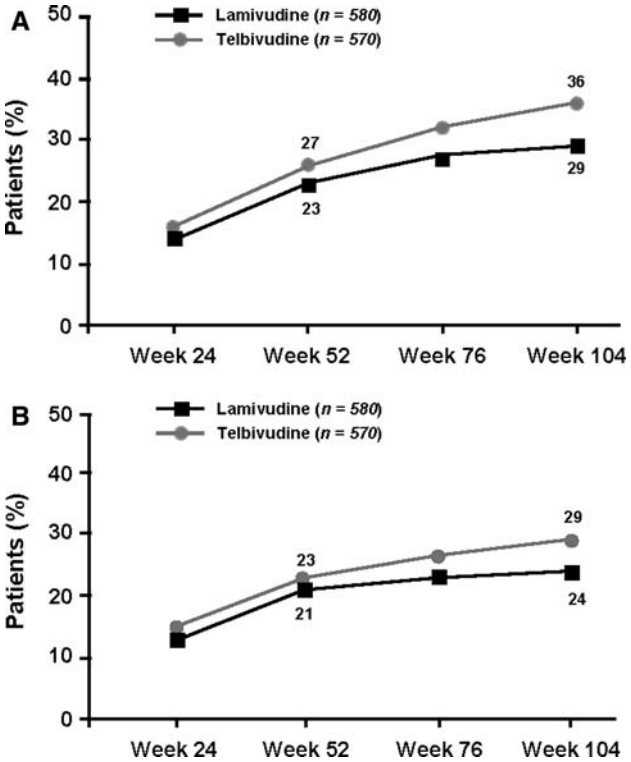

Fig. 4 The proportion of hepatitis B e antigen (HBeAg)-positive patients treated with telbivudine and lamivudine who achieved HBeAg loss (**a**) and HBeAg seroconversion (**b**) over a 2-year period in the intent-to-treat population. Adapted from Wang et al. [49] with permission

98, 94, and 86% after 12, 24, and 52 weeks, respectively [56]. In contrast, the off-treatment durability of HBeAg seroconversion for patients treated with entecavir at week 96 was only 77% [23].

As discussed previously, it is clear that the timing of HBeAg seroconversion has an important impact on disease progression, with delayed seroconversion associated with poorer outcomes [10]. It is now evident that HBeAg seroconversion in association with PCR-undetectable serum HBV-DNA levels is an achievable goal with oral NA treatment and can provide the possibility of improved outcomes with a finite course of therapy for individuals with HBeAg-positive CHB. Thus, a finite course of NA therapy may induce sustained HBeAg seroconversion and provide full immunologic control of disease in patients who would otherwise experience delayed seroconversion, high viral load, and increased risk for the progression of liver disease.

Socioeconomic impact of HBeAg seroconversion and the ability to discontinue therapy

Because of the high incidence of morbidity and mortality and the need for prolonged courses of treatment of patients with CHB, the direct and indirect costs of care are significant. In the United States, CHB is estimated to account for an average of $40,000 in costs over 2 years for healthcare services and medication. Furthermore, costs increase with disease severity, with estimated annual costs of $4,000 for a patient with compensated cirrhosis, $22,000 for a patient with decompensated cirrhosis, $19,000 for a patient with HCC, and $89,000 for a liver transplantation [57]. The economic burden of CHB on national healthcare systems is even more pronounced in countries with high endemicity [58]. For example, the estimated cost of medical treatment of chronic hepatitis, cirrhosis, and HCC in Taiwan was 5.6 billion new Taiwan yen (~US $170 million) in 2002 [59, 60]. Li and colleagues [61] reported that CHB accounted for about 4% of the national healthcare expenditure in Hong Kong, whereas Yang and colleagues [62] reported that the direct costs (prevention and disease related) of HBV disease comprised 3.2% of the South Korean national healthcare expenditure.

Emerging evidence from several studies indicates that the use of HBeAg seroconversion as an end point of therapy is a cost-effective strategy for disease management in patients with HBeAg-positive CHB [57, 63, 64]. Therapies that result in significant rates of HBeAg seroconversion may also produce overall healthcare cost savings despite the relatively high cost of initial therapy. For example, Takeda and colleagues [65] performed a systematic meta-analysis of the cost-effectiveness of lamivudine, adefovir, and PegIFN-α2a in the treatment of patients with CHB. They reported that the rates of HBeAg seroconversion were higher among patients receiving ongoing adefovir or PegIFN-α2a than with either placebo or ongoing lamivudine. Furthermore, their cost-effectiveness analysis demonstrated that incremental costs per quality-adjusted life-year for these therapies were between £5,994 and £16,569 and represented a cost-effective alternative to the use of lamivudine [65].

In another cost-effectiveness analysis of adefovir, entecavir, lamivudine, PegIFN, and telbivudine, conducted from a U.S. payer perspective, the authors found that the initiation of treatments that provide a high rate of HBeAg seroconversion in association with HBV-DNA suppression and favorable resistance profiles appear to offer the greatest clinical and economic values for HBeAg-positive CHB [64]. Similar findings were reported by Dan and colleagues [63] in an analysis of cost associated with treating CHB in Asia. When taken together, these data suggest that the achievement of durable HBeAg seroconversion and the potential to stop treatment after HBeAg seroconversion in patients with HBeAg-positive CHB represent a potentially important goal for cost-restrained patients and healthcare systems.

On the basis of findings from natural history and randomized clinical trials, recent treatment guidelines developed by the Asian-Pacific Association for the Study of the Liver and a panel of experts from the United States recommend that treatment be stopped when HBeAg seroconversion with undetectable HBV-DNA level has been documented on two separate occasions for six or more months apart [15, 16]. The importance of a 6- to 12-month period of consolidation therapy to reduce the risk of relapse after HBeAg seroconversion has been demonstrated in patients with HBeAg-positive CHB [66, 67]. In a study that examined determinants for sustained HBeAg responses to lamivudine therapy involving 82 HBeAg-positive CHB patients, an additional 8 months of lamivudine treatment (OR = 1.097; 95% CI = 1.028–1.171; $P = 0.005$), in addition to genotype B HBV (versus genotype C) and younger age, was an independent factor associated with sustained HBeAg response [66]. Similar findings were reported in a retrospective study that assessed factors predictive of posttreatment relapse after 12 months of lamivudine therapy in 461 Korean patients with CHB, mostly genotype C [67]. In this study, additional treatment for more than 12 months after HBeAg seroconversion was associated with a significantly lower relapse rate in patients 40 years and older ($P < 0.001$).

Conclusion

The use of HBV suppression as an end point in the treatment of CHB allows monitoring of early on-treatment responses and is associated with improved longer-term outcomes. However, HBeAg seroconversion is also an important independent therapeutic milestone in HBeAg-

positive patients. In addition, HBeAg seroconversion may lead to HBsAg seroclearance, which is the most desirable end point closest to a "cure." The ability of newer-generation oral NAs to induce higher rates of HBeAg seroconversion that are sustained after the cessation of therapy provides the possibility of a finite course of therapy for individuals with HBeAg-positive CHB. The ability of patients who achieve and maintain HBeAg seroconversion to stop treatment may lead to reduced treatment costs and improved quality of life. Thus, HBeAg seroconversion in association with PCR-undetectable serum HBV-DNA levels represents a meaningful treatment goal in the management of patients with HBeAg-positive CHB.

Acknowledgments The author thanks Kathleen Covino, PhD, for her editorial contributions and assistance in the preparation of the manuscript and Ms Su-Chiung Chu for her excellent secretarial assistance.

Conflict of interest statement The author has been involved in clinical trials and served as a global advisory board member of Roche, BMS, GSK, Novartis, and Gilead Sciences.

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