Sustained response to peginterferon alfa-2a (40 kD) with or without lamivudine in Asian patients with HBeAg-positive and HBeAg-negative chronic hepatitis B

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Abstract

Purpose The 2 reported trials investigated the effectiveness of treatment with peginterferon alfa-2a in Asian patients with chronic hepatitis B (CHB).

Methods Patients with HBeAg-positive ($n = 708$) or HBeAg-negative ($n = 332$) CHB were enrolled in 2 randomized, double blind, placebo-controlled studies.

Patients received peginterferon alfa-2a 180 μg once weekly, peginterferon plus lamivudine 100 mg per day, or lamivudine alone for 48 weeks. Patients were followed up at 6 and 12 months posttreatment.

Results Peginterferon alfa-2a provided significantly higher rates of HBeAg seroconversion (31%) in HBeAg-positive patients than did lamivudine (19%, $P = 0.005$) 6 months posttreatment, irrespective of genotype. Of these, 83% achieving seroconversion during treatment or early posttreatment sustained their response at 12 months posttreatment. In patients who seroconverted, 69% maintained HBV DNA suppression at $<10,000$ copies/ml and alanine aminotransferase (ALT) normalization. In HBeAg-negative patients, peginterferon produced a significantly higher combined response of HBV DNA at $<20,000$ copies/ml and ALT normalization (45%) than lamivudine (31%, $P = 0.032$), irrespective of genotype. Almost 80% of these patients sustained their response at 12 months posttreatment.

Conclusions In conclusion, a finite course of peginterferon alfa-2a provides significant and sustained treatment benefit in Asian CHB patients, who have traditionally been regarded as difficult to treat.

Keywords HBeAg seroconversion · Combined response · Peginterferon alfa-2a · CHB · Asian patients

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Introduction

Approximately 50 million new cases of hepatitis B virus (HBV) infection are diagnosed annually, 75% of which occur in Asian countries, where HBV is endemic and a leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma [1]. Protracted low-level viremia

appears to cause insidious and continued liver damage, associated with ALT levels $0.5\text{--}2 \times$ upper limit of normal (ULN), and this seems to be the most likely cause of complications of CHB in Asian patients [2]. Therefore, chronic hepatitis B (CHB) is a major health burden in the Asia-Pacific region, with significant morbidity and mortality [3]. Probably, as a result of perinatal infection with predominantly genotype C, Asian patients have traditionally been considered to have difficult-to-treat CHB, as overall experience in clinical trials suggest that a non-Asian ethnic origin is predictive of a favorable response [4]. Although Asian patients were found to have a response similar to that of non-Asians, where levels of hepatitis B deoxyribonucleic acid (HBV DNA) and alanine aminotransferase (ALT) were comparable [5], predominantly they tend to have higher levels of viral DNA and lower levels of ALT than non-Asians [6]. The genotype of HBV also appears to affect the outcome of therapy with interferon, with higher response rates noted for genotypes A and B than for genotypes D and C [7, 8].

Current treatment options for CHB include treatment with the nucleos(t)ide analogues lamivudine, adefovir, entecavir, and more recently telbivudine, as well as conventional interferon alfa [9–11]. One of the problems with using these agents is that seroconversion of hepatitis B e antigen (HBeAg), which is associated with improved long-term clinical outcomes [12, 13], is generally low [14–16], and protracted use of nucleos(t)ide analogues is associated with increasing drug resistance [17, 18]. HBeAg-negative CHB responds well to current therapies during treatment, but relapse rates off-treatment are high, resulting in poorly sustained responses [19–22]. Consequently, treatments with nucleos(t)ide analogues may often be continued for an indefinite period, with the accompanying risk of drug resistance developing, as well as unknown implications for long-term safety. Although rates of HBeAg seroconversion appear to be somewhat higher with conventional interferon alfa than lamivudine or adefovir [10], the former has suboptimal pharmacokinetics, resulting in an inconvenient dosing schedule and unpredictable exposure to drug [23]. A high relapse rate and less durable response have been suggested for patients of Asian origin compared with Caucasians [24, 25].

Two trials of pegylated interferon alfa-2b (40 kD) (with and without additional lamivudine) in the treatment of HBeAg-positive CHB patients have been reported [26, 27]—one composed of predominantly Caucasian patients [26] of whom approximately three-quarters were infected with HBV genotypes A or D, while the second was composed of Asian patients infected with genotypes B or C [27]. Combination of pegylated interferon alfa-2b plus lamivudine provided significantly better virological and biochemical responses than lamivudine at the end of

treatment, and of follow-up, in Asian patients [27]. This combination was found to be most effective in predominantly Caucasian patients with genotype A infection (compared with those infected with genotype D), where a 7% loss of hepatitis B surface antigen (HBsAg) was also recorded [26].

Pegylated interferon alfa-2a (40 kD) (Peg-IFN- α -2a) has superior pharmacokinetics compared to conventional IFN, permitting once-weekly dosing and maintenance of effective serum concentrations throughout the dosage interval [28, 29], and has elicited improved clinical outcomes in patients with HBeAg-positive CHB compared with conventional interferon alfa [6]. Two studies involving patients with HBeAg-negative and HBeAg-positive CHB, treated for 48 weeks with either peginterferon alfa-2a or lamivudine, or a combination of the two, established that patients treated with peginterferon alfa-2a had significantly higher response rates than lamivudine alone, and that this was sustained for 24 weeks after treatment had ceased [30, 31]. The combination of peginterferon alfa-2a and lamivudine did not enhance posttreatment response rates. This report examines the efficacy, tolerability, and durability of treatment with peginterferon alfa-2a in exclusively Asian patients who participated in these 2 trials [30, 31]. In addition, this analysis seeks to confirm that an HBsAg response is feasible in Asian patients following a finite treatment with peginterferon alfa-2a—an outcome not observed with lamivudine and considered extremely rare.

Patients and methods

Asian patients with HBeAg-positive ($n = 708$) or HBeAg-negative ($n = 332$) CHB were enrolled in 2 clinical trials [30, 31]. Patients were randomized (1:1:1) to receive peginterferon 180 μg once-weekly plus oral placebo, peginterferon plus lamivudine 100 mg per day, or lamivudine alone. Treatment lasted for 48 weeks with a 24-week posttreatment follow-up period. A long-term follow-up at 1 year posttreatment was also performed for Asian patients who had received peginterferon alfa-2a monotherapy.

HBeAg was measured using frozen sera from patients. A microparticle enzyme immunoassay (AXSYM HBe 2.0, Abbott Laboratories, Abbott Park, IL, USA) was used to determine HBeAg concentrations, which was validated in-house using reference standards obtained from the Paul Ehrlich Institute (PEIU/ml). The assay range was 0.15–200 PEIU/ml, and samples with concentrations outside this range were diluted to an appropriate amount with fetal calf serum (FCS) to ensure linearity.

The HBV DNA measurements employed in vitro nucleic acid amplification with the COBAS AMPLICOR

HBV Monitor (Roche Diagnostics, Branchburg, NJ, USA). The assay had a working range from 4.0×10^2 to 4.0×10^7 copies/ml. The assay performance has been validated in a routine diagnostic laboratory [32].

Two measures of efficacy were used at 24 weeks posttreatment for HBeAg-positive patients: HBeAg seroconversion, that is, the disappearance of HBeAg and appearance of anti-HBe antibodies, and viral response, defined as suppression of HBV DNA to below 100,000 copies/ml. In HBeAg-negative patients, a combined response was also calculated for ALT normalization and HBV DNA suppression.

The effect of viral and host factors on the HBeAg seroconversion rate (HBeAg-positive) and combined response rate (HBeAg-negative) were also calculated. Response rates were examined for patients infected with HBV genotype B and C by baseline HBV DNA levels of, respectively, ≤ 9.81 and $> 9.81 \log_{10}$ copies/ml for HBeAg-positive patients, and ≤ 6.88 and $> 6.99 \log_{10}$ copies/ml for HBeAg-negative patients, since baseline HBV DNA in HBeAg-positive disease is higher than in HBeAg-negative disease, and these levels were considered to be statistically relevant. In addition, response rates in these 2 genotype groups were examined by baseline ALT levels (≤ 2 , > 2 to ≤ 5 , and $> 5 \times \text{ULN}$).

In addition, measurements were made of the seroconversion of HBsAg, which leads to the appearance of antibodies to this antigen (anti-HBs). This process usually indicates that hepatitis has effectively resolved in patients infected with HBV [33].

Data were also collected at 12 months posttreatment in the long-term follow-up phase of the studies for patients treated with peginterferon alfa-2a monotherapy. The efficacy end points for HBeAg-positive patients were maintenance of HBeAg seroconversion at 12 months posttreatment, and also a “late response,” defined as no HBeAg seroconversion at 6 months posttreatment but one that developed seroconversion at 6–12 months posttreatment. HBV DNA levels were monitored over the 12-month follow-up period, and results were stratified as $> 100,000$, 10,001–100,000, 401–10,000, and ≤ 400 copies/ml. ALT and HBV DNA levels were also monitored throughout the 12-month follow-up period.

ALT and HBV DNA levels were also monitored throughout the 12-month follow-up period in patients with HBeAg-negative CHB. The efficacy end points used for HBeAg-negative patients in the long-term follow-up phase were ALT normalization ($< 1 \times \text{ULN}$ and 1 to $\leq 1.5 \times \text{ULN}$) and HBV DNA suppression ($< 20,000$ copies/ml) at 6 months posttreatment, and HBV DNA peak levels at 6–12 months posttreatment ($> 20,000$ to $\leq 100,000$, > 400 to $\leq 20,000$, and ≤ 400 copies/ml).

Statistical evaluations

Response rates were calculated for all Asian patients who received at least one dose of study treatment, according to the intention-to-treat (ITT) principle. Patients with missing values at 24 weeks posttreatment were classified as having no response. The Cochran–Mantel–Haenszel test was used to compare differences in response rates between the treatment groups. If the overall test of treatment effect was significant, then pairwise comparisons were performed. Fisher exact test was used where appropriate. For each treatment group, response rates were calculated with corresponding 95% confidence intervals (CI).

Results

Patients

Out of the HBeAg-positive patients participating in the original study, 708/814 (87%) were Asian, as were 332/537 (61%) of HBeAg-negative patients (Table 1). The majority of HBeAg-positive (66%) and HBeAg-negative (57%) Asian patients were infected with genotype C; the percentages with genotype B were 33% and 40%, respectively.

Response to peginterferon alfa (40 kD) treatment in patients with HBeAg-positive CHB

Six months posttreatment

HBeAg seroconversion: At 24 weeks posttreatment, 31% of HBeAg-positive patients given peginterferon exhibited seroconversion, as did 29% of patients given the peginterferon/lamivudine combination ($P = \text{NS}$) and 19% of patients given lamivudine monotherapy ($P = 0.005$ and 0.02, respectively), as shown in Fig. 1. The seroconversion rate in Asian patients given peginterferon was similar to

Table 1 Patient characteristics at baseline (ITT population)

Characteristic	Patients with HBeAg-positive CHB	Patients with HBeAg-negative CHB
Total patients, <i>N</i>	814	537
Total Asian patients, <i>n</i> (% of <i>N</i>)	708 (87)	332 (61)
<i>Genotype (% of Asian patients)</i>		
B	33	40
C	66	57

Fig. 1 Patients with HBeAg-positive CHB: HBeAg seroconversion 24 weeks posttreatment in Asian patients (intention-to-treat population). Similar percentages of Asian patients given peginterferon and peginterferon/lamivudine had HBeAg seroconversion at 24 weeks posttreatment. This was significantly greater than the seroconversion rate noted for patients given lamivudine monotherapy

that observed for the trial population as a whole (32%) [31].

Effect of viral and host factors on HBeAg seroconversion: The effects of HBV genotype, baseline HBV DNA (≤ 9.81 and > 9.81 copies/ml), and baseline ALT ($\leq 2 \times$, > 2 to $\leq 5 \times$ and $> 5 \times$ ULN) are shown in Fig. 2 for peginterferon alfa-2a monotherapy. Similar percentages of patients with HBV genotype B (30%) and C (32%) exhibited HBeAg seroconversion at 24 weeks posttreatment ($P = 0.8807$). More patients (35%) with lower baseline HBV DNA levels (≤ 9.81 log₁₀ copies/ml) seroconverted than did patients with higher baseline HBV DNA

Fig. 2 Patients with HBeAg-positive CHB: Effect of viral and host factors on HBeAg seroconversion in Asian patients (intention-to-treat population) peginterferon alfa-2a (Peg-IFN-α-2a) monotherapy. HBeAg seroconversion rates at 24 weeks post treatment with Peg-IFN-α-2a monotherapy were similar for genotypes B and C. More patients with baseline HBV DNA ≤ 9.81 log₁₀ copies/ml had HBeAg seroconversion than > 9.81 log₁₀ copies/ml. Notably more patients with baseline ALT $> 5 \times$ ULN had HBeAg seroconversion than with lower levels of ALT

levels (> 9.81 log₁₀ copies/ml, 25%), although this difference was not statistically significant ($P = 0.1217$).

More patients with baseline ALT $> 5 \times$ ULN (39%) seroconverted than did patients with lower baseline levels (27% with $\leq 2 \times$ ULN and 29% with > 2 to $\leq 5 \times$ ULN), but there was no statistically significant difference among the patients' responses in this and the 2 other subgroups ($P = 0.1801$ and $P = 0.2864$, respectively).

HBsAg seroconversion: A total of 8 patients out of 476 (2%) treated with peginterferon alfa-2a with or without lamivudine achieved HBsAg seroconversion. In contrast, no patient treated with lamivudine monotherapy achieved HBsAg seroconversion.

Twelve months posttreatment

Overall, 60% of the total study population participated in the long-term study. In an analysis of 150 Asian HBeAg-positive CHB patients who participated in the long-term follow-up, 58 (39%) achieved HBeAg seroconversion 6 months posttreatment, which was sustained at 12 months posttreatment in 83% of these patients (48/58). Among 92 patients who lacked an HBeAg response at 6 months posttreatment, 15% (14 patients) developed HBeAg seroconversion 6–12 months posttreatment. Therefore, 41% of patients (62/150) overall who participated in the long-term follow-up achieved HBeAg seroconversion by 12 months posttreatment.

Among those patients who achieved a sustained seroconversion at 12 months posttreatment, 69% had HBV DNA levels $< 10,000$ copies/ml, 79% had HBV DNA levels $< 100,000$ copies/ml, and 38% had HBV DNA levels ≤ 400 copies/ml, (Fig. 3). Of those who had a late HBeAg response, 46% had HBV DNA levels $< 10,000$ copies/ml, and 77% had HBV DNA levels $< 100,000$ copies/ml. In contrast, 99% of patients who did not achieve seroconversion at any time during the long-term follow-up had HBV DNA levels $> 100,000$ copies/ml.

An HBeAg response in the long-term study was also associated with suppressed ALT levels (Fig. 4). Patients who achieved HBeAg seroconversion by 6 months posttreatment and sustained this response over the 12-month follow-up had median ALT levels within the normal range by 3 months posttreatment, which were maintained within this range at 12 months posttreatment. Patients with a late response during the long-term study had median ALT levels that declined to within the normal range by 6 months posttreatment. Patients without seroconversion had median ALT levels that remained above the normal range throughout the study and the long-term follow-up. A decline in ALT levels was noted during treatment, but ALT

Fig. 3 Patients with HBeAg-positive CHB: HBV DNA levels at 12 months posttreatment according to type of response. HBeAg seroconversion in the long-term follow-up study was associated with HBV DNA levels; 69% of patients with sustained HBeAg seroconversion had HBV DNA levels of <10,000 copies/ml

levels rose to a plateau from 3 months posttreatment to 12 months posttreatment.

Response to peginterferon alfa (40 kD) treatment in patients with HBeAg-negative CHB

Six months posttreatment

Combined response (ALT normalization, HBV DNA <20,000 copies/ml): The combined response of ALT normalization and HBV DNA suppression to <20,000 copies/ml is shown in Fig. 5. A significantly higher ($P = 0.032$)

Fig. 4 Median ALT levels over time in Asian patients with HBeAg-positive CHB who participated in the long-term study according to type of response. Patients who achieved seroconversion by 24 weeks posttreatment and sustained this response during the long-term follow-up had a continual decline in median ALT levels, which were within the normal range by 3 months posttreatment. Patients without seroconversion had median ALT levels >ULN throughout the treatment phase and 12-month follow-up, with a rebound following treatment cessation

Fig. 5 Asian patients with HBeAg-negative CHB: Combined response at 24 weeks posttreatment (intention-to-treat population). A significantly higher percentage of patients administered peginterferon alfa-2a experienced a combined response of ALT normalization and HBV DNA <20,000 copies/ml than did patients given lamivudine

percentage of patients treated with peginterferon alfa-2a experienced a combined response (45%) compared with patients given lamivudine monotherapy (31%). This response rate was higher than that achieved in the population as a whole (36%) [30]. The combined response in patients given peginterferon alfa-2a plus lamivudine (41%) was not significantly different from the response in patients given peginterferon alfa-2a monotherapy. The proportion of patients attaining HBV DNA levels <10,000 copies/ml (Table 2) was similar for those receiving peginterferon monotherapy (50%, 54/108) and the combination treatment (42%, 47/112), and was notably higher than those given lamivudine (27%, 30/112), with significantly different response rates between the three treatment groups ($P = 0.0015$).

Effect of viral and host factors on the combined response rate: The combined response was similar for patients infected with genotype C (49%) and those infected with genotype B (43%) (Fig. 6). The combined response

Table 2 Patients with HBeAg-negative disease achieving HBV DNA <10,000 cp/ml at 6 months and 12 months post-treatment

	Treatment	Response rate (<10,000 cp/ml)
6 months post-treatment	Peg-IFN α -2a	54/108 (50%)
	Peg-IFN α -2a + Lamivudine	47/112 (42%)
	Lamivudine	30/112 (27%)
12 months post-treatment	Peg-IFN α -2a	31/78 (40%)
	Peg-IFN α -2a + Lamivudine	30/73 (41%)
	Lamivudine	16/48 (33%)

Fig. 6 Asian patients with HBeAg-negative CHB: Effect of viral and host factors on combined response (intention-to-treat population) to peginterferon alfa-2a (Peg-IFN- α -2a) monotherapy. The combined response (ALT normalization and HBV DNA <20,000 copies/ml) rate at 24 weeks posttreatment with Peg-IFN- α -2a was slightly higher for genotype C than genotype B. Baseline HBV DNA levels had no influence on combined response. However, the combined response was markedly higher in patients with baseline ALT >5 $\times$ ULN than lower levels of baseline ALT

rate was 47% in patients with baseline HBV DNA (≤ 6.99 log₁₀ copies/ml) and 44% with baseline HBV DNA (> 6.99 log₁₀ copies/ml) ($P = 0.8467$). Although the combined response appeared markedly higher in subjects with baseline ALT $> 5 \times$ ULN (71%) than at lower levels, 43% and 40% for > 2 to $\leq 5 \times$ ULN and $\leq 2 \times$ ULN, respectively, it was not statistically significantly different ($P = 0.1253$ and $P = 0.0656$, respectively).

HBsAg seroconversion: A total of five patients out of 220 (2%) treated with peginterferon alfa-2a with or without lamivudine achieved HBsAg seroconversion. In contrast, no patient treated with lamivudine monotherapy achieved HBsAg seroconversion.

Twelve months posttreatment

Of the Asian patients with a normal ALT at 6 months posttreatment ($n = 58$) who participated in the long-term follow-up, 78% maintained a biochemical response during the 1-year posttreatment period (as measured at 6, 9, and 12 months), 63% had normal ALT levels throughout, while 16% had normal ALT levels with occasional elevation that never exceeded $\leq 1.5 \times$ ULN. The ALT levels among patients with a biochemical response 6 months posttreatment were observed to decline continually over the treatment period; an effect that was maintained at 12 months posttreatment (results not shown).

A total of 46 HBeAg-negative Asian patients had HBV DNA <20,000 copies/ml at 6 months posttreatment. Most of these (36 patients, 78%) maintained suppression of HBV DNA levels to below 100,000 copies/ml at 6–12 months posttreatment. Levels of HBV DNA were ≤ 400 copies/ml in 26% (12/46) of these patients, and $\leq 20,000$ copies/ml in

61% (28/46) at 6–12 months posttreatment. In those patients with a virological response of 6 months posttreatment, HBV DNA levels were found to decline considerably during the treatment period, and then rose slowly during the immediate follow-up period, although HBV DNA levels posttreatment were reduced by more than 3.0 log₁₀ copies/ml compared to baseline values, with median HBV levels oscillating between 2.8 and 3.0 log₁₀ copies/ml (results not shown). The proportions of patients who achieved <10,000 copies/ml HBV DNA in all three treatment arms 12 months posttreatment is shown in Table 2.

Discussion

In the Asian patients studied in the 2 clinical trials, peginterferon alfa-2a provided significantly higher rates of sustained response at 24 weeks posttreatment in both HBeAg-positive and HBeAg-negative patients than did lamivudine. It has been suggested that an Asian ethnic origin was predictive of non-response to interferon in CHB [34], but this is not borne out by our results. The comparatively low rate of response that was observed in Asian patients given lamivudine was similar to that reported for Asian patients in a previous trial [8]. Response rates among HBeAg-positive Asian patients (31%) were similar to those in the trial population, as a whole (32%). The combined response rates in HBeAg-negative Asian patients (45%) were at least as good as or higher than in the overall population (36%).

Better rates of HBeAg seroconversion in genotype B infected patients compared with genotype C have been demonstrated in studies of conventional interferon, peginterferon alfa-2b, and 24 weeks' peginterferon alfa-2a. In our study, patients infected with genotype C achieved HBeAg seroconversion just as well as those infected with genotype B (32% vs. 30%, respectively). This is in contrast to CHB patients treated with lamivudine, where a higher sustained response has been previously noted in patients infected with genotype B (61%) than genotype C (25%, $P = 0.009$) [35]. This has particular importance for treating Asian patients, since genotype C was reported to have a high prevalence in studies of Korean patients and was associated with a lack of durability of HBeAg seroconversion [36, 37]. Such lack of differentiation between genotypes in response to treatment in our study may be due to the more prolonged period of therapy with peginterferon alfa-2a and its superior efficacy, which has already been noted in comparison to conventional interferon in Asian patients [6]. In addition, a recently reported study comparing peginterferon alfa-2b with conventional interferon in Chinese patients also showed that the pegylated form

provided significantly higher rates of HBeAg seroconversion, with significantly more genotype C patients attaining a sustained response in this treatment group compared with those given conventional interferon [38]. A study of peginterferon alfa-2b treatment for 52 weeks has shown better HBeAg loss in genotype B infected patients compared with genotype C, but the dose of peginterferon alfa-2b was reduced from 100 to 50 µg weekly after week 32 [26]. Thus, the similar response rates observed in our study in genotype B and C infected patients to peginterferon alfa-2a need to be confirmed by additional trials.

In patients with HBeAg-positive CHB, seroconversion of HBeAg was associated with lower baseline HBV DNA levels ($\leq 9.81 \log_{10}$ copies/ml) and elevated baseline ALT levels ($\geq 2 \times \text{ULN}$), although further stratification by baseline ALT was not significantly associated with a serological response. Previous studies of interferon or lamivudine treatment of CHB had suggested that patients who had achieved HBeAg seroconversion had lower baseline serum HBV DNA levels and higher baseline serum ALT levels compared with those patients who did not seroconvert [15, 39]. The results for peginterferon alfa-2a in these 2 clinical trials support the findings of an earlier study which reported that low viral load (odds ratio 1.6 [1.3–1.8], $P = 0.009$) and high baseline ALT levels (odds ratio 1.1 [1.0–1.2], $P = 0.02$) were also predictive of seroconversion in HBeAg-positive patients treated with peginterferon alfa-2b alone or in combination with lamivudine [26]. Patients with HBeAg-positive CHB are considered candidates for treatment, although the likelihood of a response to therapy increases with higher ALT levels and treatment is recommended in patients with ALT $\geq 2 \times \text{ULN}$ [10, 40–42]. Other patients should be closely monitored before treatment is initiated.

The combined response of ALT normalization and HBV DNA $< 20,000$ copies/ml in HBeAg-negative patients was higher response rate (71% vs. 40–43%) in patients with high baseline ALT levels ($> 5 \times \text{ULN}$). In contrast to patients with HBeAg-positive CHB, where loss of HBeAg, seroconversion to anti-Hbe, and reduced viral load have been considered markers for successful therapy, there has been little information for HBeAg-negative patients about the markers that best predict response [43]. In the 2 studies reported here, baseline ALT levels of $\geq 2 \times \text{ULN}$ were predictive of a combined response to treatment in HBeAg-negative individuals. Thus, it may be reasonable to suggest that all patients with HBeAg-negative CHB and elevated ALT should be considered for treatment, as lack of treatment can lead to cirrhosis, portal hypertension, and hepatic decompensation [44]. However, therapy may often be unsatisfactory and patients with mild histologically confirmed hepatic disease may have very slow disease

progression, and initiation of therapy is perhaps not to be recommended [40–42].

HBsAg seroconversion occurred in 8 of 476 (2%) HBeAg-positive Asian patients and 5 of 222 (2%) HBeAg-negative Asian patients treated with peginterferon alfa-2a. In contrast, no patients treated with lamivudine alone achieved HBsAg seroconversion within 1 year posttreatment. Loss of HBsAg and disappearance of viremia is considered to reflect an effective “cure” of the HBV infection [45]. This may not be entirely true, though, as there is evidence that complete eradication of HBV is not accomplished with currently available agents in either HBeAg-positive or HBeAg-negative CHB patients [41]. Indeed, residual amounts of HBV undergoing replication can be detected even in patients who have lost HBsAg and developed anti-HBs antibodies [46–48].

Even though complete clearance of HBV cannot be attained, HBeAg loss in HBeAg-positive CHB patients and seroconversion to anti-HBe are linked with reduction in HBV DNA serum levels, biochemical remission, the loss of HBsAg in some patients and improved long-term outcome [12, 48]. However, for HBeAg-negative CHB patients, biochemical remission, low levels of residual viremia, and loss of HBsAg in some patients also improve survival [49].

Good virological and biochemical responses to treatment have been observed at the end of lamivudine treatment in Asian patients, but high relapse rates are often observed, with only 11–20% of patients maintaining their response 2 years after treatment has ceased [21, 50, 51]. Interferon alfa has been found to be effective in HBeAg-positive CHB, but less so in HBeAg-negative CHB, where the majority of patients relapse [20, 52–54]. In this study of HBeAg-positive Asian patients, 83% of those with HBeAg seroconversion at 6 months posttreatment maintained their response at 12 months posttreatment. HBeAg seroconversion was associated with long-term HBV DNA suppression, with 79% of patients who seroconverted having HBV DNA $< 100,000$ copies/ml, and 69% with HBV DNA $< 10,000$ copies/ml at 12 months posttreatment. Among HBeAg-negative Asian patients, 78% of patients with a response at 6 months posttreatment sustained their response at 12 months posttreatment to ALT $\leq 1.5 \times \text{ULN}$ and HBV DNA $\leq 100,000$ copies/ml. Importantly, a considerable proportion of the patients involved in the 2 studies achieved sustained suppression of HBV DNA to below 10,000–20,000 copies/ml, a level recently shown to be associated with a markedly reduced risk of disease progression and HBV-associated hepatocellular carcinoma [55, 56]. Therefore, peginterferon alfa-2a provides significant treatment benefit in both HBeAg-positive and HBeAg-negative Asian patients, who have traditionally been regarded as difficult to treat.

In conclusion, in Asian patients with HBeAg-positive and HBeAg-negative CHB, a 48-week course of peginterferon alfa-2a produced good rates of virological and biochemical responses that were sustained 1 year after the end of treatment. The response was equally good in Asian patients with HBV genotype B or C with a 48-week course of peginterferon alfa-2a, but this result needs to be confirmed with additional future studies. Peginterferon alfa-2a was able to induce HBsAg seroconversion after this finite treatment period, an observation not made in any Asian patients treated with less than 2 years' lamivudine treatment.

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