

Pegylated Interferons for the Treatment of Chronic Hepatitis B

Chun-Jen Liu¹ and Jia-Horng Kao^{*,1,2,3,4}

¹Division of Gastroenterology, Department of Internal Medicine, ²Graduate Institute of Clinical Medicine, ³Hepatitis Research Center, and ⁴Department of Medical Research, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan

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Abstract: Five drugs are approved for the treatment of chronic hepatitis B: conventional interferon (IFN) alfa, lamivudine, adefovir dipivoxil, pegylated interferon (peginterferon) alfa-2a and entecavir. Conventional IFN monotherapy has a narrow range of efficacy, should be administered subcutaneously and is commonly associated with adverse effects. Lamivudine is cheaper and well tolerated, but the virological response may not be durable and prolonged lamivudine treatment is commonly associated with the emergence of drug-resistant mutants. Adefovir dipivoxil is potent but with nephrotoxicity at higher doses. Entecavir is active against both lamivudine- and adefovir dipivoxil-naïve and -resistant HBV, however, its long-term efficacy remains to be evaluated. Peginterferon alfa-2a has recently been shown to be superior to conventional IFN and lamivudine in the treatment of both HBeAg-positive and -negative chronic hepatitis B. By using peginterferon alfa-2a monotherapy, the overall virological and serological responses are around 30%-44%. However, peginterferon alfa-2a in combination with lamivudine does not improve the results at the end of follow-up. Adverse effects are usually tolerable and comparable with conventional IFN. Similar efficacy of peginterferon alfa-2b has also been demonstrated in HBeAg-positive chronic hepatitis B. These observations suggest an important and even a primary role of peginterferon alfa in the treatment of chronic HBV infection.

Keywords: Chronic hepatitis, hepatitis B virus, treatment, pegylated interferon, interferon, lamivudine, adefovir, entecavir, genotype.

INTRODUCTION

Hepatitis B virus (HBV) infection causes a wide spectrum of liver diseases, such as fulminant or acute hepatitis, chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma [1,2]. The number of individuals infected with this virus has been estimated to be as high as 350 millions and the annual mortality associated with persistent HBV infection is about 1.2 million worldwide [3]. Due to this problem, in addition to implement universal vaccination against primary HBV infection, effective treatment of chronic hepatitis B to prevent progression into end-stage liver diseases and hepatocellular carcinoma (HCC) is also needed.

Currently, there are no effective antiviral agents to eradicate HBV in patients with chronic hepatitis B [4-6]. The short-term treatment goals are thus to permanently suppress HBV replication, reduce hepatitis activity, obtain hepatitis B e antigen (HBeAg) seroconversion, and improve fibrosis of the liver. Nowadays, 5 drugs have been approved for the treatment of chronic hepatitis B: conventional IFN (IFN) alfa, lamivudine (2',3'-dideoxy-3'-thiacytidine), adefovir dipivoxil (9-[2-(phosphonomethoxy)ethyl]adenine in the form of bis(pivaloyloxymethyl)ester), pegylated IFN (peginterferon) alfa-2a and recently entecavir (ETV; BMS-200475) [4-21]. The IFN was first used to treat patients with chronic HBV infection more than 2 decades ago. IFN alfa

was approved in the United States in 1992. Conventional IFN alfa monotherapy has a narrow range of efficacy [13-15]. Because of the side effects associated with interferon and the inconvenience of frequent subcutaneous injections, lamivudine soon became a popular drug around the world. Lamivudine, approved in the United States in 1998, is cheaper, better tolerated, and has been shown to be effective in patients with both HBeAg-positive and -negative chronic hepatitis B [4-6]. However, virological response to lamivudine is not as durable as that occurred spontaneously or induced by IFN treatment. In addition, prolonged lamivudine treatment is commonly associated with the emergence of lamivudine-resistant tyrosine-methionine-aspartate-aspartate (YMDD) HBV mutants accompanied by the development of breakthrough hepatitis. Adefovir dipivoxil is potent and has been approved for the treatment of chronic hepatitis B in many countries, but is nephrotoxic at doses higher than 10 mg per day [7,9]. Entecavir, a carbocyclic deoxyguanosine analog, which is active against both lamivudine- and adefovir dipivoxil-naïve and resistant HBV, is the most potent anti-HBV agent ever discovered [22,23], however, its long-term efficacy remains to be evaluated. Peginterferon alfa-2a has recently been shown to be superior to both conventional IFN alfa and lamivudine [10,16,17]. Overall, satisfactory sustained serologic response (HBeAg seroconversion) and virological response could be achieved in around 32% and 32%-36%, respectively, of HBeAg-positive patients at 6 months after the end of peginterferon alfa-2a monotherapy [16,17]. Likewise, satisfactory sustained virological response was achieved using peginterferon alfa-2a alone in around 43% of HBeAg-negative patients [10], however, peginterferon alfa-2a in

*Address correspondence to this author at the Director, Hepatitis Research Center, National Taiwan University Hospital, 1 Chang-Te St., Taipei 100, Taiwan; Tel: 886-2-23123456; Ext: 7307; Fax: 886-2-23825962; E-mail: kjh@ha.mc.ntu.edu.tw

combination with lamivudine does not improve the results at the end of follow-up. Adverse effects of peginterferons in all studies have been tolerable and are comparable with conventional IFN. A similar rate (29%) of sustained HBeAg seroconversion by using peginterferon alfa-2b has been demonstrated in HBeAg-positive chronic hepatitis B at 6 months after the end of treatment [8]. Thus, these observations suggest an important and even a primary role of peginterferon therapy in the treatment of both HBeAg-positive and -negative chronic hepatitis B. Of the two peginterferons, peginterferon alfa-2a has already been approved for the treatment of chronic hepatitis B in Taiwan, India, Hong Kong, New Zealand, Thailand, European Union, and the USA. The new version of APASL consensus report recommends that IFN, peginterferon alfa-2a, lamivudine and adefovir dipivoxil can be used as first-line therapies for chronic hepatitis B [11]. In this review article, the recent advances on the treatment of chronic hepatitis B by using peginterferons will be discussed.

OVERVIEW OF PHARMACOLOGICAL PROPERTIES

By inducing the release of intracellular enzymes such as 2'5'-oligoadenylate synthetase and double-stranded RNA dependent protein kinase, IFN alfa causes degradation of viral messenger RNA and inhibits protein synthesis [18]. Furthermore, it increases expression of major histocompatible complex antigens, increases natural killer and cytotoxic T cell activity, cytokine induction and production of endogenous interferon. Adverse effects frequently occur but are generally mild and reversible at current dosages. The pharmacokinetics of IFN alfa has been well described, and the decline in serum IFN concentrations is rapid after intravenous administration. The volume of distribution approximates 20%-60% of body weight. Terminal elimination half-lives range from 4-16 hrs. Subcutaneous administration of interferon alfa results in protracted but fairly good absorption (> 80%).

Pharmacodynamic Properties

Pegylation is the attachment of inert polyethylene glycol (PEG) polymer to a protein such as IFN [19,24]. This increases the size of the IFN molecule compared to the native protein. The absorption and half-life of the larger IFN molecule are longer than the native protein, and the rate of clearance is much lower. The amount of time IFN remains in the body appears to correlate directly with the size of the PEG strand attached to it. The size and branching of the PEG moiety also appear to affect tissue distribution, metabolic pathways, and routes of elimination of the parent molecule. In conclusion, the duration of biological activity is increased with the pegylated IFN. Pegylation may also reduce the immunogenicity of IFN, delay eventual immune system recognition and subsequent destruction of the IFN protein. Peginterferon alfa-2a is a covalent conjugate of recombinant interferon alfa-2a with a 40,000 daltons (40 kD) branched-chain PEG moiety. Peginterferon alfa-2b is a covalent conjugate of recombinant IFN alfa-2b with monomethoxy PEG in a 1:1 molar ratio. The molecular weight of the PEG portion of the molecule is 12,000 daltons (12 kD).

Pharmacokinetics

The peak concentration and area under the curve of peginterferon alfa-2a and peginterferon alfa-2b increase in a dose-related manner [19,25]. Pegylation results in a product with lower clearance than nonpegylated IFN alfa-2a and alfa-2b, and peginterferon alfa-2a has a 10-fold greater half-life than nonpegylated IFN alfa-2a. About 80% of the peak serum concentration is reached within 24 hours of administration of a single subcutaneous dose of peginterferon alfa-2a; however, peak serum concentration is not attained until 3-4 days following administration [26,27]. With once-weekly administration, steady-state serum concentrations are reached within 5-8 weeks [12]. At week 48, the peak to trough ratio is around 2, indicating that serum concentrations are sustained throughout the once-weekly dosing interval. Peginterferon alfa-2a has an absolute bioavailability of 84% and restricted biodistribution, with a steady-state volume of distribution of 6-14L following intravenous administration [12], and the elimination is unaffected by renal impairment. There was no significant alteration of peginterferon alfa-2a pharmacokinetic parameters in patients with various degrees of renal impairment. However, clearance of peginterferon alfa-2a is reduced by 25%-45% in patients with end-stage renal disease undergoing hemodialysis, and an initial dose of 135 microgram per week is recommended in these patients [26,27].

Peginterferon alfa-2b has a 5-fold greater half-life than nonpegylated IFN alfa-2b. The mean absorption half-life is 4.6 hours followed by a subcutaneous dose of peginterferon alfa-2b and 2.3 hours with interferon alfa-2b [19]. Peak serum concentrations occur from 15 to 44 hours after subcutaneous administration of peginterferon alfa-2b and are sustained for up to 48-72 hours. At therapeutic doses, peginterferon alfa-2b has approximately 10-fold greater peak levels and 50-fold greater area under the curve than interferon alfa-2b and also bioavailability is increased after multiple dosing. Week 48 mean trough concentrations are 3-fold greater than week 4 trough concentrations (320 pg/mL: range 0, 2960 vs. 94 pg/mL: range 0, 416). Renal elimination accounts for 30% of the clearance of peginterferon alfa-2b and in patients with impaired renal function (creatinine clearance <50 mL/minute), peginterferon alfa-2b clearance is reduced by half. No gender- or age-related differences in pharmacokinetics have been observed with peginterferon alfa-2b.

Tolerability

Peginterferon alfa-2a or alfa-2b are reasonably well tolerated in adult patients, with $\leq 7\%$ of monotherapy recipients discontinuing therapy because of adverse effects. Treatment-related adverse events and laboratory abnormalities are typical of those documented previously with conventional IFNs. The severity of adverse effects is dose dependent and at least one adverse event was reported in 80%-90% of peginterferon alfa recipients. Most patients treated have an influenza-like syndrome within 2-8 hrs of drug administration. Other effects such as fatigue, lethargy, and anorexia are also dose limiting. Neuropsychiatric reactions may also occur; on the other hand, available peginterferon alfa products confer enhanced therapeutic efficacy when

compared with their IFN alfa counterparts, and additional convenience of once weekly dosing without novel toxicities.

In summary, peginterferon alfa has a longer half-life, reduced immunogenicity, better pharmacokinetics, and enhanced biological activity when compared with standard IFN alfa. Better adherence rates are feasible because of the once weekly administration of peginterferon alfa. The adverse event profile is largely comparable and the improved pharmacokinetics of peginterferon alfa, compared with standard IFN alfa, has translated into greater efficacy with at least similar tolerability in patients with chronic hepatitis C or B. Although there are pharmacokinetic and pharmacodynamic differences between the two peginterferon alfas, it remains unclear whether these differences have any impact on the primary therapeutic endpoints.

THERAPEUTIC EFFICACY

A Review of Conventional IFN

A recent meta-analysis of 24 randomized controlled trials using IFN to treat chronic hepatitis B showed that the results for 4 endpoints favored IFN, namely, persistent normalization of serum ALT (by 25% of patients), clearance of HBeAg (by 25%), sustained loss of HBV DNA as measured by hybridization assays (by 23%), and clearance of HBsAg (by 6%) [13-15]. As to HBeAg-negative chronic hepatitis B, four randomized, controlled trials also revealed that combined normalization of serum ALT and persistent disappearance of HBV DNA by hybridization assays was achieved in 10%-47% of treated patients (mean, 24%) vs. 0% of untreated controls [14,28]. Nevertheless, 12 months of treatment produced better results than shorter treatment for patients with HBeAg-negative chronic hepatitis B, and a 12- to 24-month course of treatment with IFN is thus recommended [4-6].

HBeAg-Positive Chronic Hepatitis B

Peginterferon Alfa-2a

Phase II Proof-of-Concept Trial

Current therapies for chronic hepatitis B have a number of limitations. Peginterferon alfa has been shown to be superior to conventional IFN alfa in the treatment of chronic hepatitis C, and combination of peginterferon alfa and ribavirin is the current standard of care for chronic hepatitis C [29-37]. This proof-of-concept trial addressed whether peginterferon alfa-2a (40 kD) was also superior to conventional IFN alfa-2a in the treatment of chronic hepatitis B [16]. In this study, 194 IFN-naïve patients with chronic hepatitis B were randomized to receive weekly subcutaneous doses of peginterferon alfa-2a 90, 180 or 270 microgram, or conventional IFN alfa-2a 4.5 MIU three times weekly for 24 weeks, followed by 24 weeks of treatment-free observation (Table 1). At the end of follow-up, HBeAg was cleared in 37%, 35% and 29% of patients receiving peginterferon alfa-2a 90, 180 and 270 microgram, respectively, compared with 25% of patients on conventional IFN alfa-2a. The combined response (HBeAg loss, HBV DNA suppression, and ALT normalization) of all peginterferon alfa-2a doses combined was twice that achieved with conventional IFN alfa-2a (24% vs. 12%; $P = 0.036$). All treatment groups were similar with

respect to frequency and severity of adverse events. The results from this pilot study indicate that peginterferon alfa-2a tends to be superior in efficacy to conventional IFN alfa-2a in the treatment of HBeAg-positive chronic hepatitis B.

Recently, a phase III large multinational trial involving 814 HBeAg-positive patients with chronic hepatitis B and comparing 12 months of treatment with peginterferon alfa-2a monotherapy against lamivudine monotherapy and combination therapy (1:1:1) was reported (Table 1) [17]. After 24 weeks of follow-up, the proportion of patients achieving pre-defined co-primary endpoints (HBeAg seroconversion or HBV DNA $<100,000$ copies/mL) was significantly higher in peginterferon alfa-2a monotherapy or combination therapy than lamivudine monotherapy (32% vs. 27% vs. 19% and 32% vs. 34% vs. 22%, respectively). Furthermore, HBsAg seroconversion was evident in a small proportion of peginterferon alfa-2a recipients, but not in any lamivudine recipient. High serum ALT, low HBV DNA and low HBeAg levels at baseline were factors predictive of response in patients with HBeAg-positive chronic hepatitis B [38]. Notably, while the highest rates of HBeAg seroconversion were in patients with a baseline ALT level $>5X$ ULN (41% with peginterferon alfa-2a monotherapy, 37% with peginterferon alfa-2a plus lamivudine and 28% with lamivudine monotherapy), seroconversion also occurred in patients with baseline ALT levels $\leq 2X$ ULN (29%, 20% and 20% in the corresponding treatment groups). However, combination therapy did not confer additional benefit over peginterferon alfa-2a monotherapy with regard to the co-primary endpoints.

Peginterferon Alfa-2b

A recent randomized, controlled, open-label trial showed that the combination therapy with peginterferon alfa-2b (12 kD) and lamivudine was superior to lamivudine monotherapy (Table 2) [20]. Overall, 100 treatment-naïve Chinese patients with HBeAg-positive chronic hepatitis B and moderately elevated ALT levels were enrolled in a staggered regimen of combination therapy with peginterferon alfa-2b (1.5 microgram/kg of body weight per week; maximum, 100 microgram) given for 32 weeks plus lamivudine (100 mg daily) given for 52 weeks versus lamivudine (100 mg daily) monotherapy given for 52 weeks. The rate of sustained virological response was 36% for the combination treatment group and 14% for the lamivudine monotherapy group (95% CI, 6 to 38 percentage points). End-of-treatment outcomes showed that, compared with monotherapy, patients receiving combination therapy more often had virological response (60% vs. 28% [CI, 14 to 50 percentage points]); had more substantial reductions of HBV DNA (3.91 \log_{10} copies/mL vs. 2.83 \log_{10} copies/mL); and less often had lamivudine-resistant mutants (21% vs. 40%). The authors thus suggested that in patients with HBeAg-positive chronic hepatitis B, staggered combination treatment with peginterferon-alfa 2b and lamivudine may lead to a higher rate of virological response than lamivudine monotherapy.

Later on, the authors investigated the long-term post-treatment virological response to this combination treatment versus lamivudine therapy [21]. Forty-eight patients

Table 1. Efficacy of Peginterferon Alfa for the Treatment of HBeAg-Positive or -Negative Chronic Hepatitis B Assessed at 6 Months After the End of Treatment

Populations	No. of patients	Regimen	Efficacy (%)					
			HBV DNA suppression*	ALT normalization	HBeAg SC	HBeAg loss	HBsAg SC	HBsAg loss
HBeAg-positive								
Cooksley <i>et al.</i> [16]	143	PEG-IFN alfa-2a 90, 180, or 270µg qw x24w	36 ^{4,d}	36 ^d	32 ^d	34 ^d	NA	NA
	49	PEG-IFN alfa-2a 90µg qw x24w	43 ⁴	43	NA	37	NA	NA
	46	PEG-IFN alfa-2a 180µg qw x24w	39 ⁴	35	NA	35	NA	NA
	48	PEG-IFN alfa-2a 270µg qw x24w	27 ⁴	31	NA	29	NA	NA
	51	IFN alfa-2a 4.5MU tiw x24w	25 ^{4,d}	25 ^d	25 ^d	25 ^d	NA	NA
Lau <i>et al.</i> [17]	271	PEG-IFN alfa-2a 180µg qw + PL x48w	32 ^{2,a}	41 ^b	32 ^c	34 ^c	3 ^b	3 ^a
	271	PEG-IFN alfa-2a 180µg qw + LAM 100mg qd x48w	34 ^{2,b}	39 ^b	27 ^a	28 ^a	3 ^b	4 ^a
	272	LAM 100mg qd x48w	22 ^{2,a,b}	28 ^b	19 ^{a,c}	21 ^{a,c}	0 ^b	<1 ^a
Janssen <i>et al.</i> [8]	136	PEG-IFN alfa-2b 100µg qw x32w then 50µg qw x20w	27 ^{3,e}	32 ^e	29 ^e	36 ^e	5 ^e	7 ^e
	130	PEG-IFN alfa-2b 100µg qw x32w then 50µg qw x20w + LAM 100mg qd x52w	32 ^{3,e}	35 ^e	29 ^e	35 ^e	7 ^e	7 ^e
Chan <i>et al.</i> [20]	50	PEG-IFN alfa-2b 1.5µg/kg qw x32w + LAM 100mg qd x52w	NA ⁴	50	36	NA	NA	NA
	50	LAM 100mg qd x52w	NA	30	14	NA	NA	NA
HBeAg-negative								
Marcellin <i>et al.</i> [10]	177	PEG-IFN alfa-2a 180µg qw + PL x48w	43 ^{1,b}	59 ^b	NA	NA	3 ^a	4 ^b

(Table 1) Contd....

Populations	No. of patients	Regimen	Efficacy (%)					
	179	PEG-IFN alfa-2a 180µg qw + LAM 100mg qd x48w	44 ^{1,b}	60 ^b	NA	NA	2	3
	181	LAM 100mg qd x48w	29 ^{1,b}	44 ^b	NA	NA	0 ^a	0 ^b

PEG-IFN, pegylated interferon; LAM, lamivudine; PL, placebo; NA, not available; sc, seroconversion; qw, once weekly; w, week; qd, once daily; tiw, thrice weekly; MU, million units.

*Defined as a decrease in HBV DNA from baseline to ¹<20,000, ²<100,000, ³<200,000 and ⁴<500,000 copies/mL.

P ^a<0.05, ^b<0.01, ^c<0.001, when compared with lamivudine monotherapy; ^d>0.05 when compared with IFN monotherapy; ^e>0.05 when compared with peginterferon alfa-2b monotherapy.

Statistical analyses in each trial please refer to the cited references [8,10,16,17,20].

Table 2. Efficacy of Staggered Peginterferon alfa-2b Plus Lamivudine Versus Lamivudine Alone in the Treatment of HBeAg-Positive Chronic Hepatitis B

	Peginterferon alfa-2b/Lamivudine N=50	Lamivudine N=50	<i>P</i> value
End-of-treatment			
HBeAg seroconversion and HBV DNA <500,000 copies/mL	60%	28%	0.001
Median reduction in HBV DNA level, log ₁₀ copies/mL	3.89	2.74	NA
ALT normalization	90%	78%	NA
Drug-resistant YMDD mutants	21%	40%	NA
HBsAg loss	2%	0%	NA
24 weeks post-treatment			
HBeAg seroconversion and HBV DNA <500,000 copies/mL	36%	14%	0.011
ALT normalization	50%	30%	NA

NA, not available; YMDD, tyrosine-methionine-aspartic acid-aspartic acid motif of HBV DNA polymerase.

Staggered combination regimen: peginterferon alfa-2b 1.5 µg/kg per week for 32 weeks plus lamivudine 100mg daily for 52 weeks; peginterferon alfa-2b was administered 8 weeks before lamivudine was administered.

All statistical tests by using SPSS, version 11.0 (SPSS, Inc., Chicago, Illinois) [20]: Continuous variables by using the Mann-Whitney U test, categorical variables and proportions compared by using the Pearson chi-square test or Fisher exact test, as appropriate. The timing of HBeAg seroconversion compared by using Kaplan-Meier survival analysis. A *P* value < 0.05 considered statistically significant.

receiving combination treatment and 47 patients receiving lamivudine monotherapy were studied. The probabilities of sustained HBeAg loss and HBV DNA <100,000 copies/mL for combination treatment and lamivudine monotherapy were 33% and 13% at week 24, 31% and 11% at week 52, and 29% and 9% at week 76, respectively (log-rank test, *P* = 0.0015). These findings further supported that combination treatment of peginterferon and lamivudine has a higher sustained virological response than lamivudine. Nevertheless, these studies lacked a double-blind design and were conducted at one institution only. Furthermore, because of the staggered peginterferon-lamivudine regimen, patients

assigned to combination therapy received treatment for 8 weeks longer than those assigned to monotherapy, therefore, other well-designed studies are needed to confirm these findings.

Another recent study involved 266 patients randomized, who received peginterferon alfa-2b alone or in combination with lamivudine for 12 months. Asians represented 20% of the study population (Table 1) [8]. In this study, at the end of the 12 months of therapy, the patients receiving the combination therapy had achieved better results (loss of HBeAg, HBV DNA < 200,000 copies/mL, HBV DNA undetectable by PCR assay, or normalization of ALT). At

the end of the 6-month follow-up, however, the results were similar in both groups: HBeAg loss occurred in 36% of patients on combination therapy vs. 35% on monotherapy and normalization of serum ALT occurred in 32% and 35%, respectively. A total of 7 patients in each group lost HBsAg.

HBeAg-Negative Chronic Hepatitis B

Peginterferon Alfa-2a

The experience of using peginterferon alfa in the treatment of HBeAg-negative chronic hepatitis B is relatively limited. In a recent, large, phase III study of 537 patients with HBeAg-negative chronic HBV infection performed in Asia and in the Mediterranean region, 12 months of therapy with peginterferon alfa-2a (40 kD) alone or in combination with lamivudine against lamivudine alone were evaluated (Table 1) [10]. In this study, 37% of the study population was white and 61% was Asian. Cirrhosis or bridging fibrosis was present in 22%-41%, respectively, of the patients. The results showed that HBV DNA levels fell faster and to a lower level in the patients treated in combination with peginterferon alfa-2a and lamivudine (\log_{10} 7.35 to 1.2 copies/mL) than did the levels in those receiving peginterferon alfa-2a alone. However, six months after cessation of therapy, the proportions of patients in the two groups with normal serum ALT values were virtually identical (60% and 59%, respectively), as were the proportions with HBV DNA levels < 20,000 copies/mL (44% and 43%, respectively). The patients receiving lamivudine monotherapy had substantially inferior results: only 44% achieved normal serum ALT levels, and only 29% achieved HBV DNA levels < 20,000 copies/mL). Overall, 8 patients lost HBsAg, including 4 Asian patients and 4 white patients, however, the treatment was well tolerated. Although the long-term (5 years) follow-up data are not yet available, the evidence indicates that 12 months of peginterferon alfa-2a is superior to lamivudine in the treatment of HBeAg-negative chronic hepatitis B and that combination therapy with lamivudine has no role in the special clinical setting.

In summary, cumulating data suggest that for the treatment of HBeAg-positive chronic hepatitis B, peginterferon alfa-2a is superior to lamivudine, and tends to be superior to conventional IFN alfa-2a. The addition of lamivudine offers no benefit than using peginterferon alfa-2a or -2b alone, except that the risk of emergence of lamivudine-resistant HBV mutants is remarkably reduced. For patients with HBeAg-negative chronic hepatitis B, peginterferon alfa-2a is also superior to lamivudine and the addition of lamivudine offers no benefit than using peginterferon alfa-2a alone. Since the data regarding the effect of peginterferon alfa-2b monotherapy in patients with HBeAg-negative chronic hepatitis B is still lacking, this agent has not yet been approved for the treatment of chronic hepatitis B.

ROLE OF PEGINTERFERONS IN THE MANAGEMENT OF CHRONIC HEPATITIS B

At present, approved therapies for the treatment of chronic hepatitis B are conventional IFN alfa, lamivudine, adefovir dipivoxil, peginterferon alfa-2a and recently entecavir. However, most current treatment guidelines were

published prior to the approval of peginterferon alfa-2a and entecavir. The European Association for the Study of the Liver (EASL) guidelines recommend that patients with moderate or severe HBeAg-positive or -negative chronic hepatitis B without cirrhosis and who have serum ALT levels >2X ULN should receive IFN alfa, provided it is not contraindicated [4]. If IFN alfa is contraindicated, or the patients are non-responsive or intolerant of IFN, the nucleot(s)ide analogs such as lamivudine or adefovir dipivoxil should be considered [4]. Guidelines from the American Association for the Study of Liver Diseases (AASLD) recommend the use of IFN alfa, lamivudine and adefovir dipivoxil in patients with HBeAg-positive or -negative chronic hepatitis B who have serum ALT levels >2X ULN and compensated liver disease [5,6]. The recommended treatment duration in HBeAg-positive disease is 4-6 months for IFN alfa and ≥ 1 year for both lamivudine and adefovir dipivoxil. Recommended treatment duration in HBeAg-negative disease is 1 year for IFN alfa and > 1 year for both lamivudine and adefovir dipivoxil, although the optimal duration of nucleot(s)ide analog therapy is undetermined. Recently, the third version of APASL consensus report suggests that IFN, peginterferon alfa-2a, lamivudine and adefovir dipivoxil can be used as first-line therapies for chronic hepatitis B [11]. Again, the recommended treatment duration for IFN alfa is 4-6 months for HBeAg-positive patients and at least 1 year for HBeAg-negative patients. For peginterferon alfa-2a, the recommended duration is 6 months for HBeAg-positive patients and 12 months for HBeAg-negative patients. The recommended duration of lamivudine and adefovir dipivoxil therapy is a minimum of 1 year. In HBeAg-positive patients, treatment can be stopped when HBeAg seroconversion with undetectable HBV DNA has been documented on two separate occasions at least 6 months apart. In HBeAg-negative patients, treatment can be stopped if undetectable HBV DNA by polymerase chain reaction and normal serum ALT level has been documented on three occasions in a minimum of 6 months.

In contrast to nucleot(s)ide analogs, the advantages of conventional IFN alfa include a finite treatment duration and more durable response, with the added benefit of a lack of emergence of resistant mutants during the treatment course. Moreover, patients treated with conventional IFN alfa who undergo serum HBeAg seroconversion have an improved long-term clinical outcome (decreased risk of HCC development, liver transplantation and complications of cirrhosis as well as improved survival) compared with patients who do not achieve HBeAg seroconversion [15]. Furthermore, HBsAg loss associated with IFN alfa therapy has been reported in European studies, with the loss of HBsAg within 1 year of treatment in 5-10% of recipients. However, IFN alfa is not as well tolerated as the other approved treatment options, it requires parenteral administration and can be costly. HBsAg seroclearance has been uncommon in Asian populations. In addition, Asian patients with normal ALT levels respond poorly to IFN alfa therapy and finally, patients with HBeAg-negative hepatitis B, while initially responding to IFN alfa, often relapse after treatment is stopped.

Facing these facts demonstrating the benefit and disadvantages of IFN alfa, peginterferon alfa may play a more important role in the treatment of chronic hepatitis B. In general, peginterferon alfa is reasonably well tolerated, with the incidence and nature of adverse events typical of treatment with conventional IFNs. In clinical trials, rates of treatment withdrawal were low ($\leq 7\%$) and serious adverse events occurred infrequently. Furthermore, the tolerability profile of peginterferon alfa was not affected by the addition of lamivudine and like conventional IFNs, peginterferons have the advantage over lamivudine and adefovir dipivoxil of finite treatment duration. Compared with conventional IFN alfa-2a, peginterferon alfa-2a was associated with a higher combined response rate in patients with HBeAg-positive chronic hepatitis B. In addition, peginterferon alfa-2a is significantly more effective than lamivudine monotherapy at inducing sustained virological response and ALT normalization in both HBeAg-positive and -negative diseases. Whether peginterferons will supersede conventional IFNs and nucleot(s)ide analogs as the treatment choice for chronic hepatitis B deserves more comparative studies.

INDIVIDUALIZED MEDICINE

The responses to antiviral therapy are invariably influenced by both host and viral factors. Understanding of these factors is therefore important for practicing gastroenterologist/hepatologists and this may help design individualized medicine for the treatment of chronic hepatitis B.

Correlates with HBV Genotype

Recently, HBV genotypes have attracted increasing attention since they may affect the disease progression and outcomes of HBV-related chronic liver disease, as well as the response to antiviral therapies [8,16,17,38-53]. HBV has been designated 8 genotypes (A-H) based on genome sequence divergence. The epidemiology of HBV genotypes and their implications on the natural history and the responses to antiviral therapy have become increasingly recognized in both Asian and Western countries and each genotype has its distinct geographical and ethnic distribution. Genotypes A and D occur frequently in Africa, Europe and India, while genotypes B and C are prevalent in Asia. Genotype E is restricted to West Africa, and genotype F is found in Central and South America, however, the distribution of genotypes G and H is less clear [43].

Although clinical and pathogenic differences exist among HBV genotypes, the influence of HBV genotype on the response to current antiviral treatments is only partly clarified. Furthermore, due to the unique distribution of HBV genotypes in Asian and Western countries, the clinical significance of HBV genotype in some aspects could only be reliably compared between genotype B and C or genotype A and D.

Previous studies showed that the response rate, defined as normalization of serum ALT level, loss of HBeAg and HBV DNA 48 weeks post-treatment, was 41% and 15% in Taiwanese genotype B and C patients, respectively ($P = 0.045$) [39]. Particularly in those with higher baseline serum ALT levels, the response rate was 50% and 17%,

respectively ($P = 0.025$). In addition, younger age and genotype B infection may predict a better response to IFN-alfa and these data suggest that HBV genotype C, compared with genotype B, is associated with a lower response rate to IFN-alfa therapy. Wai *et al.* also compared the response to IFN therapy between genotype B and C in Chinese patients [40]. They similarly found the response was better in patients with genotype B than genotype C [12/31 (39%) vs. 7/42 (17%); $P = 0.034$].

A similar situation was observed between HBV genotype A and D patients. Hou *et al.* studied the relationship between HBV genotypes and IFN treatment response in a homogeneous group of 103 HBeAg positive patients with chronic hepatitis B recruited from 16 European centers [41]. Of these patients, 46 patients were infected with genotype A and 35 patients were infected with genotype D. These data showed that a response to IFN-alfa treatment occurred more often in genotype A patients than in genotype D patients (33% vs. 11%; $P = 0.03$). Erhardt *et al.* also revealed that of 144 subjects infected with genotype A or D, sustained response (six months after treatment) to standard IFN therapy was higher in HBV genotype A patients compared with genotype D patients (49% vs. 26%; $P < 0.005$) [42].

As to peginterferon alfa-2a, subgroup analysis in a phase II proof-of-concept trial revealed that HBV genotype was correlated with the response to peginterferon-based therapy [16]. Cooksley *et al.* showed that the response rate of using peginterferon alfa-2a or conventional IFN alfa-2a was higher in genotype B vs. C (33% vs. 21%; 25% vs. 6%; respectively) [16]. Regarding peginterferon alfa-2b, in another multi-center study, the overall response rate also differed according to HBV genotype: genotype A, 47%; genotype B, 44%; genotype C, 28%; and genotype D, 25% [8]. Nevertheless, conflicting data were found in another phase III clinical trial using peginterferon alfa-2a to treat HBeAg-positive chronic hepatitis B. Lau *et al.* demonstrated that there was no statistically significant difference in the treatment efficacy of HBeAg seroconversion at the end of 24-week post-treatment follow-up among HBV genotypes: genotype A, 52%; genotype B, 30%; genotype C, 31%; and genotype D, 22% [17]. Interestingly, subgroup analysis of the data collected from two phase III trials using peginterferon alfa-2a-based therapy demonstrated a higher rate of treatment response in genotype A compared to the other 3 genotypes in terms of HBsAg seroconversion, in both HBeAg-positive chronic hepatitis B (genotype A, 22%; genotype B, 0%; genotype C, 2%; and genotype D, 0%) and HBeAg-negative chronic hepatitis B (genotype A, 18%; genotype B, 2%; genotype C, 3%; and genotype D, 0%) [54]. Taken together, whether HBV genotypes correlate with the response to peginterferon-based therapy awaits further examinations.

In brief, existing evidence indicates a better sustained response to conventional IFN in genotype B patients than genotype C patients, and in genotype A patients than genotype D patients (Fig. 1), nevertheless, conflicting results exist regarding the response to peginterferon alfa (Fig. 2), and more studies are needed to clarify this issue.

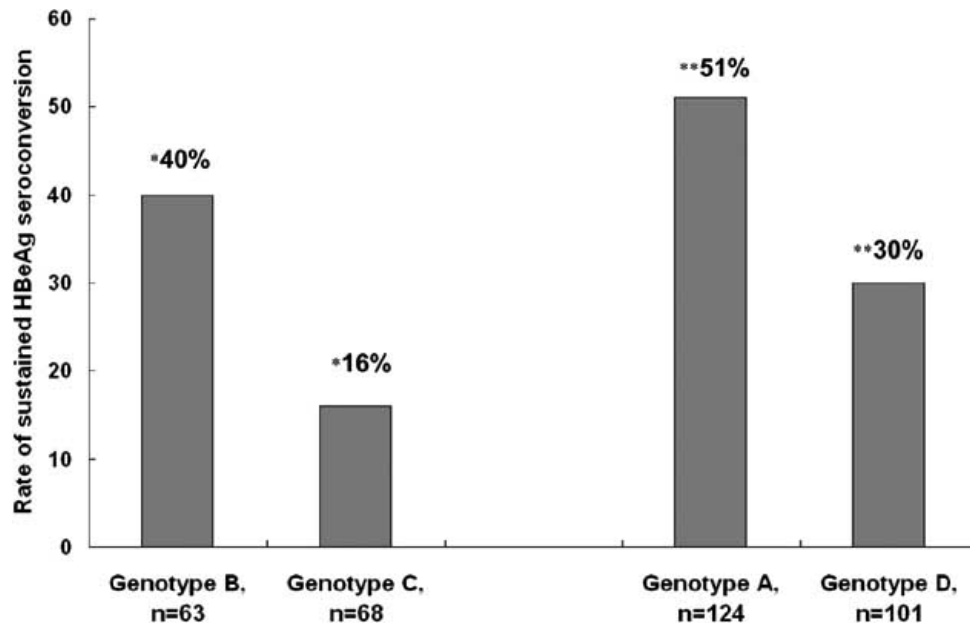


Fig. (1). HBV genotype and response to interferon therapy for 4-6 months. *Data pooled from Kao and Wai [39,40] and analyzed by chi-square test; $P < 0.05$ when compared between genotype B and C. **Data pooled from Hou and Erhardt [41,42] and analyzed by chi-square test; $P < 0.05$ when compared between genotype A and D.

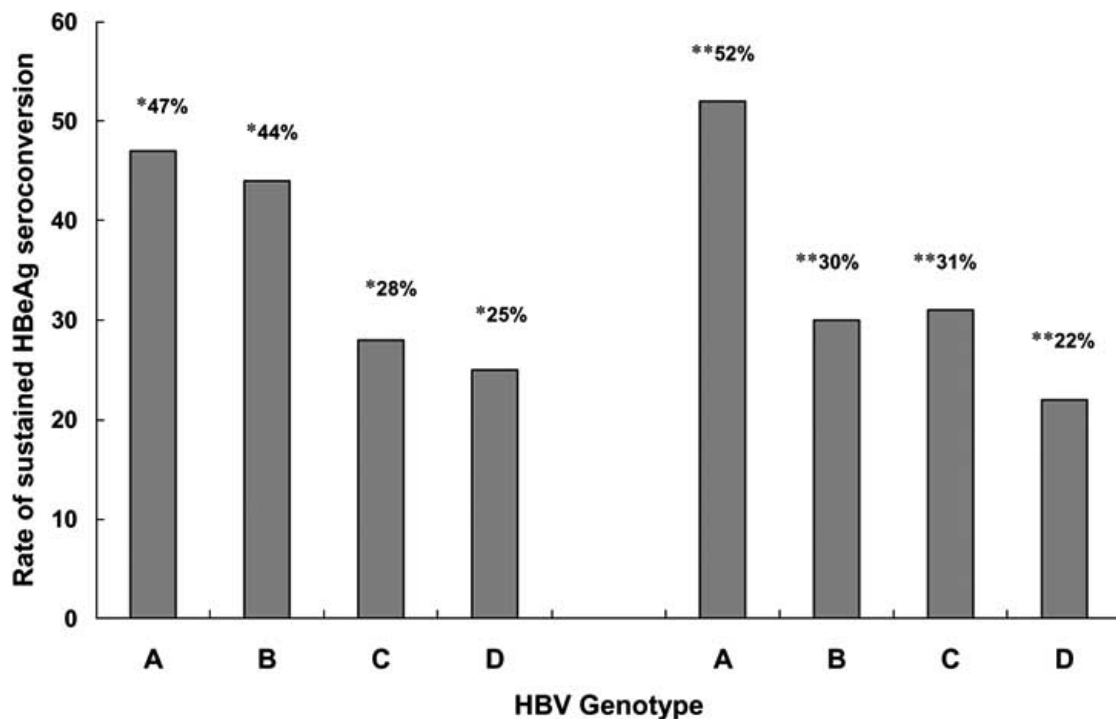


Fig. (2). HBV genotype and response to peginterferon therapy. Data obtained from *Janssen *et al.* [8] and **Lau *et al.* [17], respectively.

Correlates with Host and HBV Genetic Polymorphisms

Previous studies indicated only 20%-40% of patients with HBeAg-positive chronic hepatitis B respond well to IFN treatment [12]; however, as high as 40%-50% of those with HBV genotype A or B infection have a good response to IFN [39-41]. Thus, it is imperative to understand the molecular virological mechanisms contributing to the

differential responses among distinct HBV genotypes and within the same genotype as well. To address this issue, we prospectively compared the full-length HBV genomes in 18 genotype B patients who had received 24-week interferon 5 MU thrice weekly and were followed monthly for 12 months post-treatment, including 10 responders and 8 non-responders [55]. It was found that HBV nucleotide consensus sequence was identical between responders and

non-responders. The distribution of nucleotide variations along the whole HBV genomes was also not different between two groups of patients. The results suggest that IFN sensitivity-determining region might not exist within the genome of HBV genotype B. Whether this phenomenon can be generalized to other HBV genotypes needs to be confirmed.

Collectively, these data implicate that host factors and virus-host interactions may be more important than viral factors alone in determining the treatment outcomes with IFN. Of particular note, the previous study already demonstrated that certain host genetic background, such as single nucleotide polymorphisms (SNP) within eukaryotic translation initiation factor 2, subunit 1 and MxA promoter regions, are associated with the responsiveness to IFN treatment in patients with HBeAg-positive chronic hepatitis B [56,57]. The value of these host genetic polymorphisms in predicting responsiveness to peginterferon alfa-based therapy requires further examinations.

CURRENT AND FUTURE DEVELOPMENTS

Compared with conventional IFN alfa-2a and nucleot(s)ide analogs, peginterferon alfa-2a is associated with a higher response rate in patients with chronic hepatitis B. However, there are currently no published data evaluating health-related quality-of-life in head-to-head comparisons of approved therapy for patients with chronic hepatitis B. In addition, a recent cost-utility analysis by third-party payer revealed that IFN was most cost-effective in health care systems with tight budgetary constraints and a high prevalence of HBeAg-negative patients. Neither lamivudine nor adefovir dipivoxil monotherapy is cost-effective in chronic HBV infection. IFN therapy may still be preferred in health care systems with limited resources, especially in those serving populations with a high prevalence of HBeAg-negative HBV [58]. Similar pharmacoeconomic data are lacking and further studies should establish the cost effectiveness of peginterferons relative to other treatment options. Future studies should also focus on the optimal dose and duration of peginterferons in various clinical settings, and the long-term outcomes of patients receiving peginterferon-based therapy. A recent study provided evidence that in patients with HBeAg-negative chronic hepatitis B receiving peginterferon alfa-2a, rates of biochemical and virological response was sustained one year after the end of treatment [59]. Prolonged follow-up is needed to clarify this issue.

Searching for more potent antiviral and immunomodulatory agents with no resistance profile and durable responses should be kept for. Actually beyond PEG, other natural protein with long half-life and stability such as human serum albumin (HAS) has been linked to IFN to improve the antiviral efficacy of IFN-based therapy for chronic viral hepatitis [60,61]. Albuferon beta is a novel recombinant protein derived from a gene fusion of IFN-beta and HAS [60,61]. *In vitro*, Albuferon beta displays both antiviral and antiproliferative activities and triggers the IFN-stimulated response element signal transduction pathway. Albuferon beta demonstrated favorable pharmacokinetic properties. The enhanced *in vivo* pharmacological properties of IFN-beta when fused to serum albumin suggest a clinical

opportunity for improving IFN-beta therapy [61]. A recent phase II study demonstrated that Albuferon was safe, well tolerated and harbored robust antiviral activity after two doses in IFN-alfa-naïve patients infected with HCV genotype 1 [60]. Whether this agent can also enhance the antiviral activity for patients with chronic hepatitis B is interesting and needs more studies.

Although combination therapy with peginterferon alfa plus lamivudine in previous clinical trials was not shown to be advantageous, trials to investigate whether response rates could be improved with the use of similar combination therapy but in different regimen or with the use of peginterferon alfa in combination with other nucleot(s)ide analogs such as adefovir dipivoxil or entecavir are warranted [62].

Ideally, a treatment algorithm for chronic hepatitis B tailored to host (immune status and genetic polymorphisms), virus (HBV DNA level, HBeAg status, genotype, and precore/basal core promoter mutants) and liver disease (fibrosis stage) is eagerly awaited. These safe, easy to administer, and affordable ideal treatments may hopefully be available and widely distributed in the next one to two decades. Along with universal hepatitis B vaccination, the global eradication of HBV infection is therefore possible by the first half of 21st century [1].

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