

Reviews for APASL guidelines: immunomodulator therapy of chronic hepatitis B

Teerha Piratvisuth

Received: 12 November 2007 / Accepted: 16 January 2008 / Published online: 4 March 2008
© Asian Pacific Association for the Study of the Liver 2008

Abstract The primary aim of immunomodulator therapy is to help the natural human immune system to mount a defense against hepatitis B virus. IFN- α has been used for the treatment of HBeAg-positive and HBeAg-negative chronic hepatitis B for over two decades and has been shown to be effective in suppressing HBV replication and in inducing serological response leading to long-term clinical benefits. IFN- α has been used in patients with well-compensated cirrhosis with comparable or better response to that in non-cirrhotic patients. IFN- α therapy in patients with cirrhosis has a similar side effect profile as in those without cirrhosis. However, IFN- α is contraindicated in patients with overt or decompensated cirrhosis. Pegylated IFN- α has been shown to be effective in treatment of chronic hepatitis B with sustained response rate in about one-third of the treated patients. Peg IFN- α treatment in non-responders to lamivudine or adefovir dipivoxil showed similar response rate to that seen in naïve patients. Thymosin α_1 is effective in treatment of HBeAg-positive and HBeAg-negative chronic hepatitis B with a significantly increasing virological response over time after therapy.

Keywords Chronic hepatitis B · Immunomodulator · Interferon- α · Pegylated interferon- α · Thymosin α_1

Introduction

Approximately, 350–400 million people worldwide are chronically infected with the hepatitis B virus (HBV) [1], of which some 75% live in the Asia-Pacific region. Patients with chronic hepatitis B are at increased risk of disease progression to cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC) [2]. Effective therapy is necessary to reduce or prevent such disease progression. The treatment of chronic hepatitis B continues to be a challenge for physicians due to the high burden of the disease and the limited efficacy of available therapy. Currently, there are two HBV treatment strategies, immunomodulator therapies such as conventional Interferon, pegylated interferon, and thymosin α ; and oral antiviral therapy. The primary aim of immunomodulator therapy is to help the natural human immune system to mount a defense against HBV. IFN- α has been the mainstay of therapy for chronic hepatitis B, since the early 1980s.

The aim of this article is to review the available studies on immunomodulator therapy and to update the available evidence in order to propose an up-to-date guideline for immunomodulator therapy for chronic hepatitis B sufferers.

Conventional interferon

IFN has antiviral, immunomodulatory, and antiproliferative effects. IFN- α has been used for the treatment of chronic hepatitis B for over two decades and has been shown to be effective in suppressing HBV replication and in inducing remission of liver disease.

T. Piratvisuth (✉)
NKC Institute of Gastroenterology and Hepatology,
Songklanagarind Hospital, Prince of Songkla University,
Hat Yai 90110, Thailand
e-mail: teerha.p@psu.ac.th

IFN treatment in HBeAg-positive chronic hepatitis B (Table 1)

Meta-analyses of 15 randomized controlled trials found that treatment with IFN- α at a dose of 5 MU daily or 10 MU three times weekly for 4–6 months achieved higher HBeAg loss and HBV DNA suppression than untreated controls (33% vs. 12% for HBeAg loss and 37% vs. 17% for undetectable HBV DNA by hybridization assay, respectively) [3]. A lower dosage of IFN- α (5–6 MU three times weekly) has been used in Asian patients with similar efficacy [4, 5]. The extended treatment duration for longer than 6 months may improve the rate of HBeAg seroconversion in those who have HBeAg loss within 16 weeks of treatment [6]. Asian patients with elevated ALT responded to treatment at rates similar to Caucasians [7]. The efficacy of IFN- α in children with elevated ALT was similar to that in adults [8–11]. Retreatment of patients who failed to respond to previous IFN- α therapy with IFN- α achieved HBeAg loss in 20–40% of cases [12]. IFN- α -induced HBeAg seroconversion was sustained in 80–90% of cases and delayed HBeAg seroconversion (1–2 years post-treatment) could occur in 10–15% [13–15].

The long-term follow-up studies have shown increased clearance of HBsAg over time in patients with IFN- α -induced HBeAg loss (12–65% of patients within 5 years of HBeAg loss) [16–21], but loss of HBsAg over time has been shown to be rare in Asian patients [14, 22]. An 11-year follow-up study of 233 Taiwanese patients with HBeAg-positive chronic hepatitis treated with IFN- α found that treated patients had a lower incidence of cirrhosis (18% vs. 34% in matched untreated controls), a lower incidence of HCC (3% vs. 13%), and a higher survival rate (98% vs. 53%) [23]. A study in Caucasian patients also showed a lower incidence of HCC (1.9% vs. 3.2%) and a lower liver-related death incidence (4.9% vs. 8.7%) in 765 IFN- α -treated HBeAg-positive patients compared with 1,210 untreated controls [24]. However, a study of long-term follow-up of IFN treatment in 208 Chinese patients

with chronic hepatitis B did not show significant long-term clinical benefits when compared with 203 untreated patients [25] (The majority of the treated patients (64%) in this study had normal serum ALT and a median age of 27 years old which might be associated with poor response to IFN therapy, resulting in no significant improvement of long-term clinical outcomes, and the majority of untreated patients (72%) had normal serum ALT and a median age of 28 years old, which might be associated with a slow liver disease progression).

IFN- α treatment in HBeAg-negative chronic hepatitis B (Table 1)

IFN therapy resulted in end of treatment biochemical and virological response in 60–90% of HBeAg-negative, HBV-DNA-positive chronic hepatitis B cases [26–28]. However, over half of the responders relapsed post-therapy resulting in low sustained response: 10–15% with 4–6 months of treatment and 22% with 12 months of treatment [29–31]. A 6- to 10-month course of IFN therapy in Asian patients achieved sustained response at 6 months post-therapy of 30% [32]. A study of extended IFN- α treatment for 24 months induced sustained response in 30% and HBsAg clearance in 18% at 6 years post-therapy [33]. IFN- α retreatment in HBeAg-negative chronic hepatitis B achieved a response rate in 20–40% of treated patients [29]. IFN- α treatment improved survival and hepatic complication-free survival in patients with sustained biochemical response [30].

IFN- α treatment in chronic hepatitis B with cirrhosis

IFN- α has been used in patients with well-compensated cirrhosis with comparable response to that in non-cirrhotic patients [34–36]. IFN therapy in HBeAg-positive patients with compensated cirrhosis showed a sustained HBeAg loss in 30–63% of the patients. This sustained response rate was as good as (63% vs. 47%, $P = 0.08$) or better than in

Table 1 Conventional IFN- α therapy in patients with chronic hepatitis B

	Conventional IFN- α 5 MU qd or 10 MU TiW 12–24 weeks in HBeAg-positive [1]	Control	Conventional IFN- α 5 MU qd or 10 MU TiW 6–12 weeks in HBeAg-negative [26–3]	Control
Loss of serum HBV DNA ^a	37%	17%	60–90%	10–20%
Loss of HBeAg	33%	12%		
Loss of HBsAg	7.8%	1.8%		
Normalization of ALT	Difference of 23%		60–70%	10–20%
Durability of response	80–90%		10–22%	

TiW = 3 times per week

^a Hybridization or branched chain DNA assays (lower limit of detection 20,000–200,000 IU/ml or 5–6 log copies/ml)

those without cirrhosis (59% vs. 24%, $P = 0.01$, 50% vs. 29%, $P = 0.034$) [13–18, 36]. In HBeAg-negative patients, the sustained response rate to IFN- α therapy in cirrhotic patients was found to be similar to that in those without cirrhosis (26–28% vs. 18–27%) [30, 31]. IFN- α therapy in patients with cirrhosis has been shown to reduce the risk of decompensation, HCC, and prolong survival in responders [37]. IFN- α therapy in patients with well-compensated cirrhosis has a similar side effect profile as in those without cirrhosis [37]. However, IFN- α is contraindicated in patients with overt or decompensated cirrhosis because it may precipitate hepatic decompensation resulting in fatal complications [38, 39].

Pegylated interferon alfa (Peg IFN- α)

Peg IFN- α treatment in HBeAg-positive chronic hepatitis B

A study of a 24-week course of weekly Peg IFN- α -2a in Asian patients showed a higher combined response (HBeAg loss, HBV DNA <500,000 copies/ml, and ALT normalization rate; 28% vs. 12%, $P = 0.036$) and a higher HBeAg seroconversion rate than a 24-week course of conventional IFN- α -2a (33% vs. 25%, $P > 0.05$) [40]. The superior HBeAg loss over conventional IFN- α was confirmed by a study of Peg IFN- α -2b treatment for 24 weeks in 230 Chinese patients compared with conventional IFN- α -2b [41]. In a subsequent phase III trial involving 814 patients (>85% Asian), a 48-week course of Peg IFN- α -2a monotherapy 180 μ g once weekly achieved ALT normalization in 41%, HBeAg seroconversion in 32%, HBV DNA level <10⁵ copies/ml in 32%, HBV DNA <400 copies/ml in 14%, and HBsAg seroconversion in 3% of the patients assessed 24 weeks after treatment was stopped [42]. Recent analyses of only Asian patients in that phase III trial found a similar HBeAg seroconversion rate of 31% [43]. In a study of Peg IFN- α -2b involving mainly Caucasian patients (79%), a 52-week course (100 μ g once weekly for 32 weeks followed by 50 μ g weekly for 20 weeks) gave a 26-week sustained HBeAg seroconversion in 29% of patients and HBsAg clearance in 7% of patients [44]. The long-term follow-up post-Peg IFN- α -2a therapy showed delayed HBeAg seroconversion in 14% of the initial non-responders and durability of HBeAg seroconversion in 86% of initial responders at 1 year after the end of treatment [45]. Among Asian patients who achieved a sustained HBeAg seroconversion at 12 months post-treatment, 69% had HBV DNA levels <10,000 copies/ml and 38% had HBV DNA levels <400 copies/ml [43].

Peg IFN- α treatment in HBeAg-negative chronic hepatitis B

The treatment with Peg IFN- α -2a 180 μ g weekly for 48 weeks in HBeAg-negative chronic hepatitis B patients in a large phase III trial showed normal serum ALT in 59%, HBV DNA levels <20,000 copies/ml in 43%, HBV DNA <400 copies/ml in 14%, and HBsAg clearance in 3% of the patients at 6 months after the end of therapy [46]. In that phase III trial, 61% of the patients were Asian. The combined response, defined as ALT normalization and HBV DNA <20,000 copies/ml at 6 months after the end of 48 weeks Peg IFN- α -2a therapy, was 45% in Asian patients, which was similar to the 36% in overall patients [43]. Of the Asian patients with a normal ALT at 6 months post-treatment with Peg IFN- α -2a ($n = 58$) who participated in the long-term follow-up, 78% maintained a normal ALT at 12 months post-treatment [43]. Of a total of 46 Asian patients with HBV DNA levels <20,000 copies/ml at 6 months post-treatment, 61% and 26% of them had HBV DNA levels <20,000 copies/ml and HBV DNA <400 copies/ml at 12 months post-treatment, respectively [43].

Peg IFN- α treatment in chronic hepatitis B with cirrhosis

Approximately, 10–30% of the patients in the three Peg IFN- α trials had advanced fibrosis or cirrhosis [42, 46]. The side effect profiles of Peg IFN- α in patients with cirrhosis were similar to those without cirrhosis. The treatment with a 52-week course of Peg IFN- α -2b alone or in combination with lamivudine in 24 HBeAg-positive patients with cirrhosis showed higher sustained virological response, defined as HBeAg seroconversion and HBV DNA <10,000 copies/ml at 26 weeks after the end of therapy, than in those without cirrhosis (30% vs. 14%, $P = 0.02$) [47]. Improvement in liver fibrosis occurred more frequently in patients with advanced fibrosis than in those without advanced fibrosis (66% vs. 22%, $P < 0.001$) [47]. The side effects, including serious side effects, in patients with and without advanced fibrosis were comparable [47].

Combination therapy

Studies of combination therapy of IFN- α or Peg IFN- α and lamivudine compared with IFN- α or Peg IFN- α alone or lamivudine alone in HBeAg-positive and HBeAg-negative chronic hepatitis B patients have found that the combination therapy had greater on-treatment viral suppression and a higher rate of sustained response than lamivudine alone, but there was no difference in sustained off-treatment response when compared to IFN- α or Peg IFN- α alone [42–52].

A study of combination therapy with Peg IFN- α -2b 1.5 μ g/kg of body weight weekly, given for 32 weeks, plus lamivudine 100 mg daily, given for 52 weeks, compared with a 52-week course of lamivudine monotherapy in 100 Chinese patients with HBeAg-positive chronic hepatitis B, showed a better sustained virological response (HBeAg seroconversion and HBV DNA <500,000 copies/ml at 24 weeks after the end of therapy) in patients treated with combination therapy than in those treated with lamivudine monotherapy (36% vs. 14%) of the patients [48]. The combination therapy had a lower rate of lamivudine resistance than lamivudine monotherapy (21% vs. 40%) [48]. A study of Peg IFN- α -2b plus adefovir therapy for 48 weeks showed HBV DNA <100 copies/ml in 54%, HBeAg seroconversion in 33%, ALT normalization in 46%, and HBsAg seroconversion in 17% of cases at the end of treatment [53]. However, the number of patients in this study was too small to draw firm conclusions. A clinical trial of sequential therapy with lamivudine 100 mg daily for 4 weeks followed by Peg IFN- α -2b 1.0 μ g/kg per week for a further 24 weeks ($n = 36$ patients) compared with Peg IFN- α -2b monotherapy for 24 weeks ($n = 27$ patients) in HBeAg-positive chronic hepatitis B patients showed a significantly higher rate of HBV DNA undetectability (<4,700 copies/ml), 50% vs. 14.8%, and higher rates of HBeAg clearance, 38.9% vs. 14.8%, at 6 months post-therapy in patients with combination therapy than those with monotherapy [54]. To date, there has been no large clinical trial that confirms the benefits of Peg IFN- α plus lamivudine therapy over Peg IFN- α monotherapy.

Peg IFN- α in chronic hepatitis non-responders to lamivudine

The treatment with a 52-week course of Peg IFN- α -2b of HBeAg-positive non-responders to lamivudine showed HBeAg seroconversion in 29% and ALT normalization in 41% at 26 weeks after the end of treatment [55]. Patients with elevated serum ALT at the time of starting Peg IFN treatment had a better response rate [55]. A study of Peg IFN- α -2a in non-responders to lamivudine or adefovir dipivoxil presented at the APASL meeting in Manila, in 2006, also found that the response rates were similar to response rates seen in naïve chronic hepatitis B patients [56].

Predictors of response to conventional IFN and Peg IFN- α

The predictors of response to conventional IFN and Peg IFN- α therapy include a high baseline ALT, low baseline HBV DNA, and a high grade of necroinflammatory activity [7, 34, 48, 57, 58]. HBV genotypes A and B have been

reported as showing a better response than genotypes D and C, respectively [59–62]. However, a study involving a 48-week course of Peg IFN- α -2a treatment in Asians showed a similar response rate between genotypes B and C [43]. ALT flare followed by a decrease in HBV DNA, HBV DNA viral decline, and HBeAg levels during Peg IFN- α therapy were the predictors of response at the end of follow-up [63, 64]. Baseline ALT, baseline HBV DNA, and HBV genotype influenced the combined response at 24 weeks post-treatment in patients with HBeAg-negative chronic hepatitis B treatment with a 48-week course of Peg IFN- α -2a with or without lamivudine [58]. However, predictors of sustained response in HBeAg-negative patients are not consistent.

Side effects of IFN and Peg IFN- α

Standard IFN- α and Peg IFN- α have similar side effects. The most frequently reported side effects are flu-like symptoms, headache, fatigue, myalgia, alopecia, and local reaction at the injection site [43, 45, 48]. IFN- α and Peg IFN- α have myelosuppressive effects but neutropenia <1,000/mm³ and thrombocytopenia <50,000/mm³ are uncommon unless patients have cirrhosis or low cell counts prior to treatment. Neutropenia and thrombocytopenia induced by IFN or Peg IFN do not significantly increase the risk of infection and bleeding except in patients with cirrhosis or immunosuppression. Although IFN and Peg IFN have many side effects, they are well tolerated. Premature discontinuation due to patient's intolerance has been reported in 2–8% of patients treated with Peg IFN- α [43, 45, 48, 65].

Thymosin α_1 in chronic hepatitis B

A few studies have evaluated the efficacy of thymosin α_1 treatment in patients with chronic hepatitis B. Treatment with thymosin α_1 1.6 mg twice weekly for 6 and 12 months showed a complete response, defined as ALT normalization, undetectable HBV DNA by solution hybridization assay and HBeAg loss at 12 months after the end of therapy in 40–45% and 32% of treated HBeAg-positive patients [66, 67]. HBV genotype B responded to therapy better than genotype C (52% vs. 24%, $P = 0.036$) [67]. A study of 316 Japanese patients with HBeAg-positive chronic hepatitis B treated with either 0.8 or 1.6 mg of thymosin α_1 six times a week for the first 2 weeks and then twice a week for a further 22 weeks showed HBeAg seroconversion in 18.8% and 21.5% at 48 weeks after the end of treatment for the 0.8 and 1.6 mg doses, respectively [68]. In this study, 95% of the patients were genotype C

and an HBeAg seroconversion rate of 21.5% was similar to 24% in a study of Taiwanese patients infected with genotype C [67, 68]. A meta-analysis including 353 patients from five trials showed that the odds ratios for virological response to thymosin α_1 at the end of treatment and 6 and 12 months post-treatment were 0.56 (0.2–1.52), 1.67 (0.83–3.37), and 2.67 (1.25–5.68), respectively, with a significantly increasing virological response over time after thymosin therapy [69]. A randomized controlled trial of lymphoblastoid IFN 5 MU in combination with thymosin α_1 1.6 mg three times weekly compared with lymphoblastoid IFN 5 MU three times weekly was conducted in 96 patients with HBeAg-positive chronic hepatitis B [70]. The treatment duration was 24 weeks. The study found HBeAg loss in 45.8 and 28% of patients with combination therapy and with monotherapy, respectively, at 1 year after the end of treatment ($P = 0.067$) [70]. There was no difference in HBeAg seroconversion (43.8% vs. 28%, respectively, $P = 0.104$) and ALT normalization (56.3 vs. 56%, respectively, $P = 0.982$) at 1 year after the end of treatment between the combination and monotherapy groups [70]. A study of treatment with thymosin α_1 1.6 mg twice weekly for 6 months in Chinese patients with HBeAg-negative chronic hepatitis B showed a complete response, defined as ALT normalization and undetectable HBV DNA by PCR assay, in 11 of 26 patients (42.3%) at 6 months after the end of treatment [71]. The main advantages of thymosin α_1 are the fixed duration of treatment and minimal side effects.

Conclusions

A finite duration of conventional IFN- α treatment among patients with chronic hepatitis B results in increased sustained virological and biochemical response, improvement of liver histology, and prevention or reduction of disease progression. A long-term follow-up after IFN therapy shows a higher survival rate in treated patients. Peginterferon- α has a better pharmacokinetic profile requiring only a weekly dosing and slightly superior efficacy over conventional IFN. IFN or Peg IFN- α treatment in patients with well-compensated cirrhosis is as good as or slightly better than in those without cirrhosis with comparable side effects. Because of intolerability and fatal serious side effects, IFN is contraindicated in patients with decompensated cirrhosis. Peg IFN- α treatment in lamivudine non-responders has a sustained response as good as in naïve patients. Thymosin α_1 is effective in treatment of HBeAg-positive and HBeAg-negative chronic hepatitis B with a significantly increasing virological response over time after therapy. Because of a lack of studies on the benefits of individualized therapy according to HBV genotype, HBV genotyping before therapy is currently not recommended.

Recommendations for immunomodulator therapy in chronic hepatitis B

1. HBeAg-positive chronic hepatitis B:

Finite duration treatment with conventional IFN- α , peginterferon- α or Thymosin α_1 is recommended in patients with serum HBV DNA >20,000 IU/ml and serum ALT >2–10 \times ULN

Dose and treatment duration:

IFN- α 5 MU daily or 10 MU three times a week for 4–6 months. The lower dose of IFN- α 5 MU three times a week can be used in Asians.

Peg IFN- α -2a 180 μ g weekly or Peg IFN- α -2b 1.5 μ g/kg of body weight weekly for 6–12 months.

Thymosin α_1 1.6 mg twice a week for 6 months.

2. HBeAg-negative chronic hepatitis B:

Finite duration treatment with conventional IFN- α , peginterferon- α , or Thymosin α_1 is recommended in patients with serum HBV DNA >20,000 IU/ml and serum ALT >2–10 \times ULN or HBV DNA >2,000 IU/ml with a significant liver histology.

Dose and treatment duration:

IFN- α 5 MU daily or 10 MU three times a week for 12 months. The lower dose of IFN- α 5 MU three times a week can be used in Asians/Asian patients.

Peg IFN- α -2a 180 μ g weekly or Peg IFN- α -2b 1.5 μ g/kg of body weight weekly for 12 months.

Thymosin α_1 1.6 mg twice a week for 6–12 months.

3. Chronic hepatitis B with well-compensated cirrhosis can be treated with IFN- α or Peg IFN- α at the same dose used in those without cirrhosis.

4. Peg IFN- α can be considered for treating chronic hepatitis B non-responders to nucleos(t)ide analogues.

5. Although HBV genotype is a predictor of response, HBV genotyping before IFN- α or Peg IFN- α therapy is currently not recommended.

6. Future studies to identify the optimal combination therapy and to confirm its benefits are essential.

References

- Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. *J Viral Hepat.* 2004;11:97–107.
- Beasley RP. Hepatitis B virus. The major etiology of hepatocellular carcinoma. *Cancer.* 1988;61:1942–56.
- Wong DK, Cheung AM, O'Rourke K, et al. Effect of alpha-interferon treatment in patients with hepatitis B e antigen-positive chronic hepatitis B. A meta-analysis. *Ann Intern Med.* 1993;119:312–23.
- Guan R. Interferon monotherapy in chronic hepatitis B. *J Gastroenterol Hepatol.* 2000;15(Suppl.):E34–40.

5. Liaw YF, Lin SM, Chen TJ, et al. Beneficial effect of prednisolone withdrawal followed by human lymphoblastoid interferon on the treatment of chronic type B hepatitis in Asians: a randomized controlled trial. *J Hepatol.* 1994;20:175–80.
6. Janssen HL, Gerken G, Carreño V, et al. Interferon alfa for chronic hepatitis B infection: increased efficacy of prolonged treatment. The European Concerted Action on Viral Hepatitis (EUROHEP). *Hepatology.* 1999;30(1):238–43.
7. Lok AS, Wu PC, Lai CL, Lau JY, Leung EK, Wong LS, et al. A controlled trial of interferon with or without prednisone priming for chronic hepatitis B. *Gastroenterology.* 1992;102:2091–7.
8. Jara P, Bortolotti F. Interferon-alpha treatment of chronic hepatitis B in childhood: a consensus advice based on experience in European children. *J Pediatr Gastroenterol Nut.* 1999;29:163–70.
9. Gregorio GV, Jara P, Hierro L, et al. Lymphoblastoid interferon alfa with or without steroid pretreatment in children with chronic hepatitis B: a multicenter controlled trial. *Hepatology.* 1996;23:700–7.
10. Sokal EM, Conjeevaram HS, Roberts EA, et al. Interferon alfa therapy for chronic hepatitis B in children: a multinational randomized controlled trial. *Gastroenterology.* 1998;114:988–95.
11. Torre D, Tambini R. Interferon-alpha therapy for chronic hepatitis B in children: a meta-analysis. *Clin Infect Dis.* 1996;23:131–7.
12. Carreno V, Marcellin P, Hadziyannis S, et al. Retreatment of chronic hepatitis B e antigen-positive patients with recombinant interferon alfa-2a. The European Concerted Action on Viral Hepatitis (EUROHEP). *Hepatology.* 1999;30:277–82.
13. Niederau C, Heintges T, Lange S, et al. Long-term follow-up of HBeAg-positive patients treated with interferon alfa for chronic hepatitis B. *N Engl J Med.* 1996;334:1422–7.
14. Lin SM, Tai DI, Chien RN, et al. Comparison of long-term effects of lymphoblastoid interferon alpha and recombinant interferon alpha-2a therapy in patients with chronic hepatitis B. *J Viral Hepat.* 2004;11:349–57.
15. van Zonneveld M, Honkoop P, Hansen BE, et al. Long-term follow-up of alpha-interferon treatment of patients with chronic hepatitis B. *Hepatology.* 2004;39:804–10.
16. Niederau C, Heintges T, Lange S, et al. Long-term follow-up of HBeAg-positive patients treated with interferon alfa for chronic hepatitis B. *New Engl J Med.* 1996;334:1422–7.
17. Fattovich G, Giustina G, Realdi G, et al. Long-term outcome of hepatitis B e antigen-positive patients with compensated cirrhosis treated with interferon alfa. European Concerted Action on Viral Hepatitis (EUROHEP). *Hepatology.* 1997;26:1338–42.
18. Lau DT, Everhart J, Kleiner DE, et al. Long-term follow-up of patients with chronic hepatitis B treated with interferon alfa. *Gastroenterology.* 1997;113:1660–7.
19. Korenman J, Baker B, Waggoner J, et al. Long-term remission of chronic hepatitis B after alpha-interferon therapy. *Annl Internal Med.* 1991;114:629–34.
20. Krogsgaard K. The long-term effect of treatment with interferon-alpha 2a in chronic hepatitis B. The Long-Term Follow-up Investigator Group. The European Study Group on Viral Hepatitis (EUROHEP). Executive team on anti-viral treatment. *J Viral Hepat.* 1998;5:389–97.
21. Carreno V, Castillo I, Molina J, et al. Long-term follow-up of hepatitis B chronic carriers who responded to interferon therapy. *J Hepatol.* 1992;15:102–6.
22. Lok AS, Chung HT, Liu VW, Ma OC. Long-term follow-up of chronic hepatitis B patients treated with interferon alfa. *Gastroenterology.* 1993;105:1833–8.
23. Lin SM, Yu ML, Lee CM, et al. Interferon therapy in HBeAg positive chronic hepatitis reduces progression to cirrhosis and hepatocellular carcinoma. *J Hepatol.* 2007;46(1):45–52.
24. Craxi A, Di Bona D, Camma C. Interferon-alpha for HBeAg-positive chronic hepatitis B. *J Hepatol.* 2003;39(Suppl 1):S99–105.
25. Yuen MF, Hui CK, Cheng CC, et al. Long-term follow-up of interferon- α treatment in Chinese patients with chronic hepatitis B infection: the effect on hepatitis B e Antigen seroconversion and the development of cirrhosis-related complications. *Hepatology.* 2001;34:139–45.
26. Fattovich G, Farci P, Rugge M, et al. A randomized controlled trial of lymphoblastoid interferon-alpha in patients with chronic hepatitis B lacking HBeAg. *Hepatology.* 1992;15:584–9.
27. Hadziyannis S, Bramou T, Makris A, et al. Interferon alfa-2b treatment of HBeAg negative/serum HBV DNA positive chronic active hepatitis type B. *J Hepatol.* 1990;11(Suppl 1):S133–S6.
28. Pastore G, Santantonio T, Milella M, et al. Anti-HBe-positive chronic hepatitis B with HBV-DNA in the serum response to a 6-month course of lymphoblastoid interferon. *J Hepatol.* 1992;14:221–5.
29. Manesis EK, Hadziyannis SJ. Interferon alpha treatment and retreatment of hepatitis B e antigen negative chronic hepatitis B mutants. *Gastroenterology.* 2001;121:101–9.
30. Papatheododdis GV, Manesis E, Hadziyannis SJ. The long term outcome of interon-alpha treated and untreated patients with HBeAg-negative chronic hepatitis B. *J Hepatol.* 2001;34:306–13.
31. Brunetto MR, Oliveri F, Coco B, et al. The outcome of chronic anti-HBe positive chronic hepatitis B in alpha interferon treated and untreated patients: a long term cohort study. *J Hepatol.* 2002;36:263–70.
32. Lin CC, Wu JC, Chang TT, et al. Longterm evaluation of recombinant interferon alpha2b in the treatment of patients with hepatitis B e antigen-negative chronic hepatitis B in Taiwan. *J Viral Hepat.* 2001;8:438–46.
33. Lampertico P, Del Ninno E, Vigano M, et al. Long-term suppression of hepatitis B e antigen-negative chronic hepatitis B by 24-month interferon therapy. *Hepatology.* 2003;37:756–63.
34. Perrillo RP, Schiff ER, Davis GL, et al. A randomized, controlled trial of interferon alfa-2b alone and after prednisone withdrawal for the treatment of chronic hepatitis B. The Hepatitis Interventional Therapy Group. *New Engl J Med.* 1990;323:295–301.
35. Lok AS, WuPC, Lai CL, et al. A controlled trial of interferon with or without prednisone priming for chronic hepatitis B. *Gastroenterology.* 1992;102:2091–7.
36. Fattovich G, Giustina G, Sanchez-Tapias J, et al. Delayed clearance of serum HBsAg in compensated cirrhosis B: relation to interferon alpha therapy and disease prognosis. European Concerted Action on Viral Hepatitis (EUROHEP). *Am J Gastroenterol.* 1998;93:896–900.
37. Chu CM, Liaw YF. Hepatitis B virus-related cirrhosis: natural history and treatment. *Semin Liver Dis.* 2006;6(2):142–52.
38. Perrillo R, Tamburro C, Regenstein F, et al. Low-dose, titratable interferon alfa in decompensated liver disease caused by chronic infection with hepatitis B virus. *Gastroenterology.* 1995;109:908–16.
39. Hoofnagle JH, Di Bisceglie AM, Waggoner JG, Park Y. Interferon alfa for patients with clinically apparent cirrhosis due to chronic hepatitis B. *Gastroenterology.* 1993;104:1116–21.
40. Cooksley WGF, Piratvisuth T, Lee SD, et al. Peginterferon alpha-2a (40 kDa): an advance in the treatment of hepatitis Be antigen-positive chronic hepatitis B. *J Viral Hepatitis.* 2003;10:298–305.
41. Zhao H, Kurbanov F, Wan MB. Genotype B and younger patient age associated with better response to low-dose therapy: a trial with pegylated/nonpegylated interferon-alpha-2b for hepatitis B e antigen-positive patients with chronic hepatitis B in China. *Clin Infect Dis.* 2007 44(4):541–8.

42. Lau GK, Piratvisuth T, Luo KX, et al. Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. *N Engl J Med*. 2005;352:2682–95.
43. Piratvisuth T, Lau GKK, Chao YC, et al. Sustained Response to Peginterferon Alfa-2a (40 KD) with or without Lamivudine in Asian Patients with HBeAg-positive and HBeAg-negative Chronic Hepatitis B. *Hepatol Int*. 2008;2:102–10.
44. Janssen HLA, van Zonneveld M, Senturk H, et al. Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial. *Lancet*. 2005;365:123–9.
45. Lau GKK, Piratvisuth T, Luo KX, et al. Durability of response and occurrence of late response to peginterferon α -2a (40KD) [PEGASYS] one year post-treatment in patients with HBeAg-positive chronic hepatitis B. *J Hepatol*. 2006;44(Suppl 2):S1–S300.
46. Marcellin P, Lau GKK, Bonino F, et al. Peginterferon alfa-2a alone, lamivudine alone and the two in combination combination in patients with HBeAg negative chronic hepatitis B. *N Engl J Med*. 2004;351:1206–17.
47. Buster EH, Hansen BE, Buti M, et al. Peginterferon alpha-2b is safe and effective in HBeAg-positive chronic hepatitis B patients with advanced fibrosis. *Hepatology*. 2007;46(2):388–94.
48. Chan HL, Leung NW, Hui AY, et al. A randomized, controlled trial of combination therapy for chronic hepatitis B: comparing pegylated interferon-alpha2b and lamivudine with lamivudine alone. *Ann Intern Med*. 2005;142:240–50.
49. Schalm SW, Heathcote J, Cianciara J, et al. Lamivudine and alpha interferon combination treatment of patients with chronic hepatitis B infection: a randomised trial. *Gut*. 2000;46:562–8.
50. Ayaz C, Celen MK, Colak H, et al. Comparison of lamivudine and alpha-interferon combination with alpha-interferon alone in the treatment of HBeAg-positive chronic hepatitis B. *Indian J Gastroenterol*. 2006;25(2):71–3.
51. Karabay O, Tamer A, Tahtaci M, et al. Effectiveness of lamivudine and interferon-alpha combination therapy versus interferon-alpha monotherapy for the treatment of HBeAg-negative chronic hepatitis B patients: a randomized clinical trial. *J Microbiol Immunol Infect*. 2005;38(4):262–6.
52. Yurdaydin C, Bozkaya H, Cetinkaya H, et al. Lamivudine vs lamivudine and interferon combination treatment of HBeAg(-) chronic hepatitis B. *J Viral Hepat*. 2005;12(3):262–8.
53. Wursthorn K, Lutgehetmann M, Dandri M, et al. Peginterferon alpha-2b plus adefovir induce strong cccDNA decline and HBsAg reduction in patients with chronic hepatitis B. *Hepatology*. 2006;44(3):675–84.
54. Sarin SK, Sood A, Kumar M, et al. Effect of lowering HBV DNA levels by initial antiviral therapy before adding immunomodulator on treatment of chronic hepatitis B. *Am J Gastroenterol*. 2007;102(1):96–104.
55. Flink HJ, Hansen BE, Heathcote EJ, et al. Successful treatment with peginterferon alfa-2b of HBeAg-positive HBV non-responders to standard interferon or lamivudine. *Am J Gastroenterol*. 2006;101(11):2523–9.
56. Piratvisuth T, Boyer N, Tanwandee T, et al. Efficacy and safety of peginterferon α -2a (40 KD) (PEGASYS[®]) in patients with chronic hepatitis B who had received prior treatment with nucleos(t)ide analogue-the PEGaLAM cohort. *J Gastroenterol Hepatol*. 2006;21(Suppl 1):A32.
57. van der Eijk AA, Niesters HG, Hansen BE, et al. Quantitative HBV DNA levels as an early predictor of nonresponse in chronic HBe-antigen positive hepatitis B patients treated with interferon-alpha. *J Viral Hepat*. 2006;13(2):96–103.
58. Bonino F, Marcellin P, Lau GK, et al. Predicting response to peginterferon alpha-2a, lamivudine and the two combined for HBeAg-negative chronic hepatitis B. *Gut*. 2007;56(5):699–705.
59. Zhao H, Kurbanov F, Wan MB, et al. Genotype B and younger patient age associated with better response to low-dose therapy: a trial with pegylated/nonpegylated interferon-alpha-2b for hepatitis B e antigen-positive patients with chronic hepatitis B in China. *Clin Infect Dis*. 2007;44(4):541–8.
60. Flink HJ, van Zonneveld M, Hansen BE, et al. Treatment with Peg-interferon alpha-2b for HBeAg-positive chronic hepatitis B: HBsAg loss is associated with HBV genotype. *Am J Gastroenterol*. 2006;101(2):297–303.
61. Ma JC, Wang LW, Li XJ, et al. Relationship between HBV genotypes and anti-viral therapeutic efficacy of interferon-alpha. *Hepatobiliary Pancreat Dis Int*. 2007;6(2):166–71.
62. Hou J, Schilling R, Janssen HL, et al. Genetic characteristics of hepatitis B virus genotypes as a factor for interferon-induced HBeAg clearance. *J Med Virol*. 2007;79(8):1055–63.
63. Flink HJ, Sprengers D, Hansen BE, et al. Flares in chronic hepatitis B patients induced by the host or the virus? Relation to treatment response during Peg-interferon {alpha}-2b therapy. *Gut*. 2005;54(11):1604–9.
64. ter Borg MJ, van Zonneveld M, Zeuzem S, et al. Patterns of viral decline during PEG-interferon alpha-2b therapy in HBeAg-positive chronic hepatitis B: relation to treatment response. *Hepatology*. 2006;44(3):721–7.
65. van Zonneveld M, Flink HJ, Verhey E, et al. The safety of pegylated interferon alpha-2b in the treatment of chronic hepatitis B: predictive factors for dose reduction and treatment discontinuation. *Aliment Pharmacol Ther*. 2005;21(9):1163–71.
66. Chien RN, Liaw YF, Chen TC, et al. Efficacy of Thymosin alpha-1 in patients with chronic type B hepatitis: a randomized controlled trial. *Hepatology*. 1998;27:1383–7.
67. Chien RN, Lin CY, Yeh CT, et al. Hepatitis B virus genotype B is associated with better response to thymosin alpha-1 therapy than genotype C. *J Viral Hepat*. 2006;13(12):845–50.
68. Iino S, Toyota J, Kumada H, et al. The efficacy and safety of thymosin alpha-1 in Japanese patients with chronic hepatitis B; results from a randomized clinical trial. *J Viral Hepat*. 2005;12(3):300–6.
69. Chan HL, Tang JL, Tam W, et al. The efficacy of thymosin in the treatment of chronic hepatitis B virus infection: a meta-analysis. *Aliment Pharmacol Ther*. 2001;15:1899–905.
70. Lim SG, Wai CT, Lee YM, et al. A randomized, placebo-controlled trial of thymosin-alpha1 and lymphoblastoid interferon for HBeAg-positive chronic hepatitis B. *Antivir Ther*. 2006;11(2):245–53.
71. You J, Zhuang L, Cheng HY, et al. A randomized, controlled, clinical study of thymosin alpha-1 versus interferon-alpha in Chinese patients with chronic hepatitis B lacking hepatitis B envelope antigen. *J Chin Med Assoc*. 2005;68(2):65–72.