Several agents currently are approved for the treatment of chronic hepatitis B: interferon (IFN) alfa-2b, pegylated interferon (PEG IFN) alfa-2a, lamivudine, adefovir, entecavir, and telbivudine [1–4]. Each agent has inherent limitations. IFN is effective in a minority of patients and has frequent side effects that limit its tolerability [5]. Large, randomized, controlled trials have demonstrated the efficacy of PEG IFN in the treatment of chronic hepatitis B [6–10]. The efficacy of lamivudine is limited by the emergence of drug-resistant hepatitis B virus (HBV) mutants, restricting its usefulness as a long-term therapy [11–13]. Adefovir is well tolerated and is associated with a low incidence of resistance, but its antiviral effect is not optimal [14–16]. Entecavir has a high antiviral effect and is well tolerated [17,18], but its long-term efficacy and resistance profile are not yet determined. Lamivudine, adefovir, and entecavir have the advantages of oral administration and excellent safety profiles, but they induce a sustained response after withdrawal of therapy in only a minority of patients; therefore in most patients treatment needs to be administered indefinitely.

IFNs have two mechanisms of action: a direct antiviral effect achieved inhibiting the synthesis of viral DNA and by activating antiviral enzymes, and a second mechanism that increases the cellular immune response against hepatocytes infected with HBV. PEG IFN, administered for 48 weeks,
achieves an overall sustained response rate of approximately 30%. Two large, randomized, controlled trials have investigated the use of PEG IFN alfa-2a in the treatment of chronic hepatitis B [8,9].

This article summarizes the results obtained with IFN and PEG IFN as monotherapy and in combination with lamivudine.

**Monotherapy treatment with interferon**

*Interferon alfa*

IFN has been used in the treatment of chronic hepatitis B for many years. IFN exerts an antiviral effect on HBV infection through two mechanisms [19]. First, IFN has a direct antiviral effect, inhibiting synthesis of viral DNA and activating antiviral enzymes. Second, IFN exaggerates the cellular immune response against hepatocytes infected with HBV by increasing the expression of class I histocompatibility antigens and by stimulating the activity of helper T lymphocytes and natural killer lymphocytes. Thus, IFN induces an early reduction of HBV replication (reflected by a reduction of HBV DNA in serum) and a late (about 2 months later) increase in serum alanine aminotransferase (ALT) levels. Many controlled studies of IFN in patients who have chronic hepatitis B have been reported. In these studies, using various regimens, mean virologic response rate was 37% versus 17%, the mean rate of HBeAg loss was 33% versus 12%, and the rate of hepatitis B surface antigen (HbsAg) loss was 8% versus 2% in the interferon-treated groups versus the placebo groups (Fig. 1) [5]. A dosage of 5 million units (MU) to 10 MU, three times per week for 4 to 6 months, combines good efficacy with satisfactory tolerance [4].

The discrepancies in the results of the different studies might be caused, in part, by the different therapeutic regimens but result mainly from the varying populations of patients included in these trials. A certain number of factors are predictive of poor response to IFN [20,21]. Low serum HBV DNA level and high serum ALT levels are predictors of nonresponse. Also, infection with HBV at birth or early in life (as often occurs in areas where HBV infection is hyperendemic, such as Southeast Asia) is a factor in poor response to IFN.

*Pegylated interferon*

More recently, the efficacy of IFN has improved by the replacement of standard interferon by IFN conjugated with polyethylene glycol, PEG IFN. This new form of IFN reduces the excretion of IFN by the kidneys, thus significantly increasing its half-life and resulting in more stable plasma concentrations of IFN. Improved pharmacokinetics have allowed the number of injections to be reduced from three to one per week, a regimen that obviously is more comfortable for the patient.
Two PEG IFNs, which differ in the quality and quantity of conjugated PEG to IFN, have been produced: 12-kD linear PEG for IFN 2b and 40-kD branched PEG for IFN 2a. In both cases, PEG IFN monotherapy was shown to be twice as effective overall as the corresponding nonpegylated IFN in chronic hepatitis C [22,23]. Therefore, the efficacy of PEG IFN was assessed recently in the treatment of chronic hepatitis B.

A randomized, controlled study of PEG IFN alfa-2a was performed in patients who had hepatitis B e antigen (HBeAg)-positive chronic hepatitis B [6]. Treatment duration and follow-up were each 24 weeks. At the end of follow-up, treatment response, defined as the loss of HBeAg with a serum HBV DNA level below 500,000 copies/mL and normal ALT levels, was observed in 19% to 28% of patients receiving PEG IFN alfa-2a (at doses of 90 μg, 180 μg, or 270 μg/wk) and in 12% of patients who received standard IFN-2a (Fig. 2). Side effects associated with PEG IFN were comparable to those observed with standard IFN. The safety profile of PEG IFN was comparable to that of conventional IFN, with the same frequency of adverse events or laboratory abnormalities.

This study does not prove the superiority of PEG IFN alfa-2a over standard IFN-2a, because the dose of IFN-2a used was relatively low (4.5 MU, three times per week), and the differences observed between each of the three PEG IFN alfa-2a treatment groups and the standard IFN-2a group were not significant. The overall rate of response in patients who received PEG IFN alfa-2a was higher than that observed in the IFN-2a group, however.

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**Fig. 1.** Meta-analysis of interferon-alpha trials in hepatitis B e antigen (HBeAg)-positive chronic hepatitis B. In this meta-analysis including 15 randomized, controlled trials (published between 1986 and 1992) comparing interferon versus placebo, including overall 837 patients with HBeAg-positive chronic hepatitis B, the superiority of interferon versus placebo was shown for the rates of undetectable serum HBV DNA (hybridization assays), HBeAg loss, and hepatitis B surface antigen (HbsAg) loss. (*Data from* Wong DKH, Cheung AM, O’Rourke K, et al. Effect of alpha-interferon treatment in patients with hepatitis B e antigen-positive chronic hepatitis B. Ann Intern Med 1993;119:312–23.)
A retrospective analysis showed that the rates of response were higher with PEG IFN than with standard IFN among the most difficult-to-treat patients (those who had high HBV DNA levels or low ALT levels). Therefore this study strongly suggests that PEG IFN alfa-2a is more effective than standard IFN-2a for the treatment of chronic hepatitis B.

Large, randomized, controlled trials have confirmed the efficacy of PEG IFN in HBeAg-positive and HBeAg-negative chronic hepatitis B. These studies, which compared PEG IFN monotherapies with the combination of PEG IFN plus lamivudine and lamivudine alone, are detailed in the next section.

**Combination of pegylated interferon plus lamivudine**

Previous studies of IFN plus lamivudine suggested that this combination could be more effective than lamivudine monotherapy [24]. The results of different studies were discordant, however, possibly because of differing, nonoptimal treatment regimens l.

**Hepatitis B e antigen–positive chronic hepatitis**

In a large, randomized, controlled study, 307 patients who had HBeAg-positive chronic hepatitis B were assigned randomly to receive either the combination of PEG IFN alfa-2b (100 µg/wk for 32 weeks, then 50 µg for 20 weeks) plus lamivudine (100 mg/d) or PEG IFN alfa-2b at the same dose plus placebo [7]. At the end of the 26-week posttreatment
follow-up, there was no difference in response rates between the two treatment groups. Serum HBV DNA was undetectable by polymerase chain reaction (PCR) (< 400 copies/mL) in 7% and 9%; HBeAg loss was observed in 36% and 35%; and normal ALT levels were achieved obtained in 32% and 35% in the PEG IFN monotherapy and the combination therapy groups, respectively. A relatively high rate of HBsAg loss (7%) was observed in both groups.

This study shows that, in patients who have HBeAg-positive chronic hepatitis B, the combination of PEG IFN alfa-2b plus lamivudine (administered simultaneously) is not superior to PEG IFN alfa 2b monotherapy 26 weeks after treatment.

In this study, response was defined by HBeAg loss. Main predictors of response were HBV genotype and pretreatment ALT level. Response was 34% in patients who had ALT levels lower than three times the upper limit of normal and 50% in patients who had ALT levels more than five times the upper limit of normal. Response rates were 60% for genotype A, 42% for genotype B, 32% for genotype C, and 28% for genotype D.

In another randomized, phase III trial, 814 patients who had HBeAg-positive chronic hepatitis B received either PEG IFN alfa-2a (180 µg once weekly) plus oral placebo, PEG IFN alfa-2a plus lamivudine (100 mg daily), or lamivudine alone (Fig. 3) [8]. The majority of patients in the study were Asian (87%). Most patients were infected with HBV genotype B or C. Patients were treated for 48 weeks and followed for an additional 24 weeks. After 24 weeks of follow-up, significantly more patients who received PEG IFN alfa-2a monotherapy or PEG IFN alfa-2a plus lamivudine than those who received lamivudine monotherapy had HBeAg seroconversion (32% versus 19% [P < .001] and 27% versus 19% [P = .02], respectively) or HBV DNA levels below 100,000 copies/mL (32% versus 22% [P = .01] and 34% versus 22% [P = .003], respectively). Rates of HBV DNA suppression to levels below 400 copies/mL at week 72 were 14% with both PEG IFN alfa-2a monotherapy and PEG IFN alfa-2a plus lamivudine and 5% with lamivudine alone (P < .001 for both comparisons with lamivudine monotherapy). Sixteen patients receiving PEG IFN alfa-2a (alone or in combination) had HBsAg seroconversion, as compared with none in the group receiving lamivudine alone (P = .001). The most common adverse events were those known to occur with therapies based on IFN alfa.

**Hepatitis B e antigen–negative chronic hepatitis**

A phase III, partially double-blinded study has evaluated the efficacy and the safety of PEG IFN alfa-2a alone or in combination with lamivudine versus lamivudine alone in patients who have HBeAg-negative chronic hepatitis B [9].

Patients were assigned randomly to one of the following treatments: PEG IFN alfa-2a (180 µg once weekly) plus oral placebo (once daily for 48
weeks), PEG IFN alfa-2a (180 µg once weekly) plus lamivudine (100 mg once daily) for 48 weeks, or lamivudine (100 mg once daily) for 48 weeks. In total, 552 patients were enrolled in the study. At the end of the 24-week posttreatment follow-up, the two PEG IFN treatment arms (with or without lamivudine) showed the same efficacy, which was superior to that observed in the lamivudine treatment arm: a biochemical response (normal ALT) was observed in 59%, 60%, and 44% of the patients, respectively, and a virologic response (serum HBV DNA < 20,000 copies/mL by quantitative PCR) was seen in 43%, 44%, and 29% of the patients, respectively (Fig. 4A and B).

Rates of suppression of HBV DNA to below 400 copies/mL at week 72 were 19% with PEG IFN alfa-2a monotherapy, 20% with PEG IFN alfa-2a plus lamivudine, and 7% with lamivudine alone (P < .001 for both comparisons with lamivudine alone). After 48 weeks, the extent of suppression of HBV DNA from baseline was greatest with PEG IFN alfa-2a plus lamivudine; the extent of HBV DNA suppression was similar with PEG IFN alfa-2a monotherapy and lamivudine monotherapy. The patterns of HBV DNA levels throughout the study are shown in Fig. 4B.

Although HBsAg loss is rarely observed in HBeAg-negative patients, a substantial rate of HBsAg loss was observed in this study in patients who received PEG IFN alfa-2a (4% and 3%, versus 0% in the lamivudine group).

Fig. 3. Pegylated interferon (PEG IFN) alfa 2-a in hepatitis B e antigen (HBeAg)-negative chronic hepatitis. In this randomized, controlled trial, the rates of response (normal serum alanine aminotransferase [ALT] level; HBeAg seroconversion; and serum HBV DNA < 100,000 copies/mL) 24 weeks after therapy were higher in the two groups that received PEG IFN alfa-2a (with or without lamivudine) than in the group that received lamivudine alone. There was no difference in response rates between the group that received PEG IFN alfa-2a alone and the group that received PEG IFN alfa-2a plus lamivudine. (Data from 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(26):2682–95.)
At the end of the 48-week treatment period, there was a higher incidence of lamivudine resistance in the lamivudine monotherapy group than in the PEG IFN alfa-2a plus lamivudine group. This finding confirms previous studies suggesting that IFN decreases the risk of lamivudine resistance\[25\].

The adverse events associated with PEG IFN alfa-2a therapy were similar to those observed in previous trials in patients who had chronic hepatitis C, but the frequency of the adverse events was lower than observed in patients who have chronic hepatitis C. In particular, the frequency of depression was
much lower: 3% to 4%, as compared with 16% to 20% in patients who have chronic hepatitis C.

This study shows that, in patients who have HBeAg-negative chronic hepatitis B, the efficacy of PEG IFN alfa-2a monotherapy, as assessed 24 weeks after treatment, is superior to that of lamivudine monotherapy and that the combination of PEG IFN alfa-2a administered simultaneously with lamivudine is not superior to PEG IFN alfa-2a used as monotherapy [9].

Recently, 3-year follow-up data were reported for a subgroup of patients in this trial (116/177 of those who received PEG IFN alfa-2a plus placebo and 114/179 of those who received the PEG IFN plus lamivudine combination) [26]. Biochemical and virologic response rates remained stable at 3 years after treatment with either PEG IFN alfa-2a monotherapy or with PEG IFN alfa-2a plus lamivudine. The biochemical response rates (normal ALT levels) were 31% for the PEG IFN alfa-2a arm and 31% for the PEG IFN alfa-2a plus lamivudine arm. The virologic response rates (defined by HBV DNA \( < 20,000 \) copies/mL) were 30% for the PEG IFN alfa-2a arm and 27% for the PEG IFN alfa-2a plus lamivudine arm. The virologic response rates (defined by HBV DNA \( < 400 \) copies/mL) were 18% for the PEG IFN alfa-2a arm and 13% for the PEG IFN alfa-2a plus lamivudine arm. Thus, sustained off-therapy responses were maintained in about 30% of the patients who had HBeAg-negative chronic hepatitis B 3 years after treatment with PEG IFN alfa-2a. In addition, loss of HBsAg increased with time and was 8% at 3 years after treatment [26].

**In practice: who and how to treat?**

The decision to treat or not to treat patients who have chronic hepatitis B is based mainly on the severity of the liver disease. It generally is recommended that patients who have chronic hepatitis B with elevated ALT levels and significant HBV replication be treated. The cut-off ALT and HBV DNA levels for therapy are not well determined, but there is some consensus that patients who have ALT levels higher than three times the upper limit of normal and HBV DNA levels higher than 100,000 copies/mL should be considered good candidates for therapy. Chronic hepatitis B, however, is a heterogeneous disease with fluctuations over time; therefore there are not good correlations between serum ALT levels or serum HBV DNA levels and the severity of liver lesions. Indeed a liver biopsy often is useful to determine the grade of necroinflammation and the stage of fibrosis as indications for treatment.

Treatment is not recommended in patients who have mild liver disease unless liver fibrosis deteriorates. The best way to reduce the number of patients who develop resistance to treatment is to select the right patients for treatment: patients who have active liver disease usually have relatively moderate levels of viral replication, have a good chance of responding
well to therapy, and have a low risk of developing resistance. For patients who have mild disease, the treatment can be delayed with regular follow-up.

PEG IFN monotherapy should be considered in patients who do not have contraindications, because this treatment is not associated with resistance and gives the best sustained response rate (about 33%) with a definite duration of therapy (48 weeks). About two thirds of patients who have chronic hepatitis B do not develop a sustained response and therefore need prolonged therapy with an analogue. During treatment with an analogue, the importance of good compliance and careful monitoring (measurement of HBV DNA levels at least every 3 months) should be emphasized. Indeed, patients who have HBV DNA levels higher than 1000 copies/mL after 6 months of therapy are at high risk for developing resistance. Early diagnosis of resistance allows therapy to be adjusted by introducing a drug to prevent a flare of hepatitis. At present no combination has been shown to have a better antiviral effect or a reduced risk of resistance, compared with monotherapy, but experimental studies and uncontrolled clinical data suggest that combinations may decrease the incidence of resistance. Therefore this strategy probably should be considered in patients who have cirrhosis to minimize the risk of liver failure, which may be associated with resistance.

**Summary**

In recent years, marked progress has been made in the treatment of chronic hepatitis B. The efficacy of lamivudine, the first nucleoside analogue available, is limited by the high incidence of resistance. Adefovir has better long-term efficacy because of a much lower frequency of resistance. Entecavir has a potent antiviral effect, a good safety profile, and a low rate of short-term resistance, but its long-term resistance profile is not yet known. Telbivudine also has a potent antiviral effect, but its long-term efficacy might be hampered by its resistance profile.

These drugs need to be administered indefinitely because withdrawal of therapy generally is associated with reactivation, and a sustained response is uncommon except in HBeAg-positive patients who develop HBeAg seroconversion. In case of HBeAg seroconversion, it generally is recommended that therapy be continued for at least 24 weeks before its withdrawal.

Large, randomized, controlled trials have demonstrated the efficacy of PEG IFN in the treatment of chronic hepatitis B. PEG IFN administered for 48 weeks gives an overall sustained response rate of approximately 30% in patients who have either HBeAg-positive or HBeAg-negative chronic hepatitis B. This sustained response rate was not higher with the combination of PEG IFN plus lamivudine. It is, however, noteworthy that the combination induced a more rapid and more marked antiviral effect than PEG IFN or lamivudine alone. In addition, the combination of PEG
IFN plus lamivudine was associated with a much lower rate of resistance than lamivudine alone. Therefore, the efficacy of combinations of PEG IFN with more potent analogues (such as entecavir, telbivudine, or tenofovir) and/or different schedules (e.g., sequential administration and/or longer duration of treatment) needs to be evaluated.

The ultimate objective of therapy of chronic hepatitis B is HBsAg loss (with or without HBsAg seroconversion), because HBsAg loss is associated with sustained remission of the disease and improved outcome. Therefore future studies should aim to increase the rate of HBsAg loss. The rates of HBsAg loss obtained with current treatments are around 3% to 8% 6 months to 3 years after PEG IFN therapy [7–9,26] and less than 1% per year with analogues.

The future of chronic hepatitis B therapy seems to be in the combination of different drugs. Ideally, the optimal combination of drugs would act on different sites of HBV DNA replication, have a potent antiviral effect, have an excellent safety profile, and induce a sustained response with a limited duration of therapy. Only the combination of PEG IFN alfa-2a plus lamivudine has shown an antiviral effect during therapy superior to that of monotherapy. The combination of PEG IFN alfa-2a with more potent analogues such as entecavir or tenofovir needs to be investigated further. Finding more effective combinations and understanding the mechanisms of resistance to therapy are important challenges to improve the efficacy of treatment and to decrease the global burden related to chronic hepatitis B.

References


