Pegylated interferon alpha-2a (40 kDa) in the treatment of chronic hepatitis B

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Abstract: Chronic hepatitis B virus (HBV) is a serious and life-threatening disease afflicting 350 million of the world's population. So far, current monotherapy with conventional interferon-alpha, lamivudine, and adefovir dipivoxil remains unsatisfactory. In addition, the use of conventional interferon-alpha needs to be administered subcutaneously daily or thrice weekly and is associated with frequent adverse events. Although nucleoside–nucleotide analogs such as lamivudine and adefovir dipivoxil are well tolerated and can normalize serum alanine aminotransaminase rapidly, 1-year therapy with either lamivudine or adefovir dipivoxil results in low hepatitis B e antigen (HBeAg) seroconversion rates. In HBeAg negative patients, most of the patients would relapse after lamivudine has been discontinued. Pegylated interferon alpha-2a, an immunomodulatory agent, is a new drug that has just completed phase III clinical trials for the treatment of both HBeAg positive and HBeAg negative chronic HBV infection. The advantage of pegylated interferon alpha-2a in achieving sustained virological response over nucleoside–nucleotide analogs is particularly obvious in the HBeAg negative group. In both of these phase III studies, sustained off-treatment response is superior to the use of lamivudine. These recent data put pegylated interferon alpha-2a as the first choice of anti-HBV therapy, especially in young and motivated patients with chronic HBV infection.

Keywords: pegylated interferon alpha-2a, chronic hepatitis B, HBeAg seroconversion, sustained virological response

Introduction

Hepatitis B virus (HBV) infection is one of the most common viral infections in humans. Approximately 2 billion people have been infected with HBV and 350 million of them became chronically infected. Individuals with chronic hepatitis B infection are at an increased risk of developing liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC); 15%–40% of these individuals will develop these serious sequelae during their lifetime (Beasley 1988; McMahon 1997). Drugs that are currently approved by the Federal Drug Administration (FDA) for the treatment of chronic HBV consist of two groups: the immunomodulators such as conventional interferon alpha and pegylated interferon alpha-2a, and nucleoside–nucleotide analogs such as lamivudine, adefovir dipivoxil, and entecavir. However, not all patients with chronic hepatitis B infection respond to these treatments.

The currently approved antiviral regimens, especially the nucleoside–nucleotide analogs, have been shown to improve the short-term outcome of disease but lack the ability to provide cure or induce durable remission in most patients with chronic HBV (Lee 1997). Lamivudine, the first nucleoside–nucleotide analog to be approved for the treatment of chronic HBV, has a favorable safety profile but long-term therapy with this drug can lead to the selection of drug-resistant mutants (Wong et al 1993; Niederau et al 1996). The risk of mutation increases with the duration of treatment. At the end

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of the first, second, third, and fourth year of treatment, the incidences of resistance are: 15%–32%, 38%, 56%, and 67% respectively (Leung 2002). Adefovir dipivoxil is another oral nucleoside–nucleotide analog that requires long-term therapy. Initial reports show that adefovir dipivoxil selects resistant mutants in only a limited proportion of patients, but adefovir-resistant mutants do occur at cumulative rate of 18% by 192 weeks (Locarnini et al 2005).

A phase III study on entecavir showed that entecavir is superior to lamivudine in hepatitis B e antigen (HBeAg) positive and HBeAg negative nucleoside–nucleotide naïve patients (Chang et al 2004; Shouval et al 2004). Entecavir, with its profound suppression of serum HBV DNA, has less risk of resistance over time with no resistance at 96 weeks in HBeAg positive lamivudine-naïve patients (Gish et al 2005). Entecavir resistance in lamivudine-resistant patients is 7% genotypically and 1% phenotypically at 1 year. But follow-up studies to determine the resistance rate after 2–5 years of therapy are required, especially in lamivudine-resistant patients. Another major limit is the lack of knowledge on how long nucleoside–nucleotide therapy needs to be continued, especially in HBeAg negative patients. This group of patients has been shown to have persistent benefit with 144 weeks of adefovir dipivoxil therapy (Hadziyannis et al 2005). Furthermore, sustained response after withdrawal of entecavir has also been shown to be less than optimal in both HBeAg positive and HBeAg negative patients (Chang et al 2005; Lai et al 2005). Therefore, in view of the limitations of current therapies for chronic HBV, there is a need to develop new agents for the treatment of chronic HBV infection with improved efficacy.

Immunomodulators

Conventional interferon alpha

Conventional interferon alpha-2b is the first drug to be approved by the FDA for treatment of chronic HBV infection. However, the efficacy of conventional interferon alpha, defined as sustained loss of HBeAg and HBV DNA, is limited. In a meta-analysis of 15 randomized, controlled trials, loss of HBeAg and HBV DNA in HBeAg positive patients is seen in 33% and 37% on conventional interferon alpha-treated patients compared with 12% and 17% of untreated patients, respectively (Wong et al 1993). The studies reviewed in this meta-analysis employed direct spot hybridization for the detection of serum HBV DNA. In Caucasians, the long-term durability of HBeAg is as high as 90% (Niederau et al 1996), while around 20%–70% of patients with loss of HBeAg and hepatitis B e antibody (anti-HBe) seroconversion will eventually lose hepatitis B surface antigen (HBsAg) (Niederau et al 1996; Lau et al 1997). In those with detectable HBV DNA after HBeAg seroconversion, the HBV DNA will be undetectable in 60%–100% of those who lose HBsAg.

In HBeAg negative variants (precore mutants and others), prolonged interferon at a dose of 3–5 MU thrice weekly for at least 12 months results in a sustained biochemical remission in 15%–25% of patients (Manesis and Hadziyannis 2001; Papatheodoridis and Hadziyannis 2001). Factors that predict a favorable response to conventional interferon alpha include low pretreatment level of HBV DNA (<200 pg/ml), high levels of serum aminotransaminase (>100 U/L), and evidence of necroinflammatory activities in the liver (Brook et al 1989). In contrast, male sex, length of chronic state, Asian origin, precore mutants, and human immunodeficiency virus coinfection are factors associated with poor response to conventional interferon alpha (Schiff 1993). In a recent study from Taiwan, patients with genotype B were more likely to respond to conventional interferon alpha than those with genotype C (Kao et al 2000). A small study on the use of conventional interferon beta at 3 MU weekly for 24 weeks also showed a 50% HBeAg seroconversion rate similar to that achieved with conventional interferon alpha (Kagawa et al 1993). However, conventional interferon beta has never been recommended for use as a first-line agent for the treatment of chronic HBV due to a lack of large-scale randomized studies.

However, conventional interferon alpha is somewhat tedious and requires daily or 3 subcutaneous injections a week with a high occurrence of side-effects. Furthermore, the rate of achieving HBeAg seroconversion in Asian patients has been low (Conjeevaram and Lok 2003). This difference between Asian and Caucasian patients is thought to be related to the duration of the chronic state, the difference in genotype, and baseline characteristics such as serum alanine aminotransaminase (ALT) levels.

While Asians acquire HBV perinatally, Caucasians acquire HBV predominantly in their adolescence or adulthood. In perinatally acquired infection, infection is followed by a lengthy period of immune tolerance during which the HBV DNA is high while the serum ALT levels are normal or near normal and liver necroinflammation is minimal (Lai et al 1987; Lok et al 1989; Conjeevaram and Lok 2003). In the latter, there is more active host immune response directed towards clearance of the infection with raised ALT levels (Perillo 1989). These drawbacks with conventional interferon alpha therapy have led to the development of pegylated interferon alpha.

Pegylated interferon

Pegylation

Pegylated interferon alpha-2a (40 kDa) joins a number of therapeutic agents that are pegylated by the incorporation of a polyethylene moiety into the active product. Pegylation of the interferon alpha molecule is undertaken mostly to enhance the pharmacokinetic properties of unmodified interferon alpha, which will enable once a week dosing. Although a larger pegylation molecule can result in better stability and longer half-life, it will interfere with the active receptor binding (Youngster et al 2002).

Pegylation may occur at multiple sites of the interferon molecule, but pegylation at most of them does not retain the biochemical and therapeutic properties. Therefore it is very important to strike a balance between the pegylation site, size of the molecule, steric properties, and biochemical properties (Youngster et al 2002).

For example, the molecular weight of the pegylation chain must be greater than 4000 to avoid poisoning by ethylene glycol (Working et al 1997). The sites of attachment may be more than one single site, but multiple chains may lead to steric hindrance and prohibit the binding of the peglyated interferon to its effector (Harris et al 2001). The bonds must be strong and resistant to degradation (Wang et al 2000). The pegylation polymer is usually covalently attached, via an amide or urethane bond, to a lysine or histidine residue or the N-terminus of the protein. By controlling the reagents, condition, and the pH, pegylation of interferon at a specific site with a defined pegylated polymer can be achieved (Kozlowski et al 2001; Youngster et al 2002).

The first pegylated interferon alpha-2a to be developed was 5 kDa in size. However, this drug has limited overall clinical and laboratory benefits. Since then, pegylated interferon alpha-2a (40 kDa) and pegylated interferon alpha-2b (12 kDa) have been developed. As a result of their difference in size and structure, these two molecules have different in vivo and in vitro characteristics. Pegylated interferon alpha-2a (40 kDa) has a longer half-life and is mainly catabolized in the liver and has active breakdown products. Pegylated interferon alpha-2b (12 kDa) is a smaller molecule, has a shorter half-life, and acts as a pro-drug depot by slowly releasing interferon (Wang et al 2000; Kozlowski et al 2001).

Pegylated interferon alpha-2a (40 kDa)

The pegylation of interferon alpha-2a involves 2 chains of 20 kDa polyethylene glycol conjugated to the lysine residues (position 31, 121, 131, and 134) of the interferon alpha-2a molecule. The plasma level reaches its peak between 72 and 96 hours after administration and the volume of distribution is 8–12 L, suggesting it is highly compartmentalized in the intravascular space. The clearance half-life is 40–80 hours. The serum antiviral activity, as measured by the 2'-5' oligoadenylate synthetase activity, peaks at 24–48 hours after administration and it remains high for 1 week (Reddy 2004). Because of its highly intravascular compartmentalization, dose adjustment according to body weight is not necessary (Table 1).

Pegylated interferon alpha-2a (40 kDa) in HBeAg positive patients

When pegylated interferon alpha-2a was tested in a phase II study at 90, 180, and 270 μg/week for 24 weeks against conventional interferon alpha-2a, the HBeAg seroconversions were 37%, 35%, 29%, and 25% respectively (Cooksley et al 2003). The combined response (HBeAg loss, HBV DNA suppression < 500 000 copies/mL, ALT normalization) was higher in all pegylated interferon alpha-2a doses combined (24% vs 12%). The response was still higher among patients that were difficult to treat: 27% in patients with <2 times upper limit of normal (ULN) of baseline ALT vs 11% of interferon alpha-2a; 20% vs 0% in patients with HBV DNA >11.0 log copies/mL. The side-effects seemed to be dose-dependent and occurred more often in the 270-μg and 180-μg groups. However, no difference in side-effect could be observed when the 270-μg group was compared with the 180-μg group.

The beneficial effect of pegylated interferon alpha-2a

Table 1 Comparison between conventional interferon alpha-2a and pegylated interferon alpha-2a

	Conventional interferon alpha 2a	Pegylated interferon alpha-2a
Time to peak serum level (hours)	7.3–12	80
Absorption half-life (hour)	2.3	50
Volume of distribution (L)	31–73	8–12
Clearance (L/hour)	6.6–29.2	0.06–0.10
Elimination half-life (hours)	3–8	65

Table 2 Efficacy of pegylated interferon alpha-2a on hepatitis B e Antigen positive chronic hepatitis B virus patients

	Pegylated interferon alpha-2a plus placebo (n=271)	Pegylated interferon alpha-2a plus lamivudine (n=271)	Lamivudine (n=272)
Co-primary endpoints			
HBeAg seroconversion	32% (p<0.001)[a]	27% (p=0.023)	19%
HBV DNA < 100 000 copies/mL	32% (p=0.012)[a]	34% (p=0.003)[a]	22%
Secondary endpoints			
HBeAg loss	34% (p<0.001)[a]	28% (p=0.043)[a]	21%
ALT normalization	41% (p=0.002)[a]	39% (p=0.006)[a]	28%

Adapted from Lau, Piratvisuth, et al (2005).
[a] compared with lamivudine therapy.

was further substantiated in 2 multinational phase III studies (Marcellin et al 2004; Lau, Piratvisuth, et al 2005). In the phase III HBeAg positive study, 814 HBeAg positive chronic HBV-infected patients were randomized to receive either pegylated interferon alpha-2a 180 μg weekly monotherapy, pegylated interferon alpha-2a 180 μg weekly plus lamivudine 100 mg daily combination therapy, or lamivudine 100 mg daily for a total of 48 weeks and assessed at 24 weeks after the end of therapy (Lau, Piratvisuth, et al 2005). More than 85% of patients in this study were Asians, and the mean HBV DNA was 9.9–10.1 log copies/mL. About 15%–18% of patients had severe fibrosis or cirrhosis by liver biopsy at baseline, and 9%–15% had received lamivudine therapy and 2%–3% of patients had previously been treated with conventional interferon alpha-2a.

HBeAg seroconversion and suppression of HBV DNA to less than 100 000 copies/mL were significantly higher with pegylated interferon alpha-2a monotherapy and pegylated interferon alpha-2a plus lamivudine combination therapy when compared with lamivudine monotherapy (Table 2). More importantly, loss of HBsAg with development of hepatitis B surface antibody (anti-HBs) was achieved in 8 of the 271 patients (3.0%) on pegylated interferon alpha-2a monotherapy, 8 of the 271 patients (3.0%) on pegylated interferon alpha-2a plus lamivudine combination therapy, and none of the 272 patients (0%) on lamivudine monotherapy (p=0.004 for both comparisons) (Lau, Piratvisuth, et al 2005).

Pegylated interferon alpha-2a (40 kDa) in HBeAg negative patients

In another randomized, partially double-blind phase III controlled study, 537 HBeAg negative chronic HBV patients were randomized to receive either pegylated interferon alpha-2a 180 μg weekly, combination pegylated interferon alpha-2a 180 μg weekly plus lamivudine 100 mg daily, or lamivudine 100 mg daily monotherapy for 48 weeks and followed up for another 24 weeks after therapy (Marcellin et al 2004). Patients were included into this trial if they had been HBeAg negative and anti-HBe positive for at least 6 months, had an HBV DNA of more than 100 000 copies/mL, a serum ALT level greater than 1 but less than 10 times the upper limit of normal, and had findings on liver biopsy within the previous 24 months showing evidence of prominent necroinflammatory activity. The 2 primary end points assessed at 24 weeks after the completion of therapy of this study were normalization of serum ALT and suppression of HBV DNA below 20 000 copies/mL.

After 48 weeks of therapy, suppression of serum HBV DNA from baseline was the greatest with combination pegylated interferon alpha-2a plus lamivudine therapy. On the other hand, suppression of HBV DNA from the baseline was similar in patients on pegylated interferon alpha-2a monotherapy and lamivudine monotherapy.

At 24 weeks after therapy, normalization of serum ALT was higher in patients receiving pegylated interferon alpha-2a monotherapy (59%) and combination pegylated interferon alpha-2a plus lamivudine therapy (60%) when compared with those receiving lamivudine monotherapy (44%). Virologic response was also higher in patients receiving pegylated interferon alpha-2a monotherapy (43%) and combination pegylated interferon alpha-2a plus lamivudine (44%) than in patients receiving lamivudine monotherapy (29%). Suppression of HBV DNA to below 400 copies/mL at week 72 was also higher in those receiving pegylated interferon alpha-2a monotherapy (19%) and combination pegylated interferon alpha-2a plus lamivudine therapy (20%) when compared with those on lamivudine monotherapy alone (7%) (Marcellin et al 2004).

Most importantly, loss of HBsAg occurred in 7 patients receiving pegylated interferon alpha-2a monotherapy (5 Asians and 2 Caucasians) and in 5 patients receiving combination pegylated interferon alpha-2a plus lamivudine therapy (4 Asians and 1 Caucasian). This was significantly higher compared with lamivudine monotherapy alone (n = 0) (p = 0.007 and p = 0.030 respectively). HBsAg clearance with development of anti-HBs occurred in 8 patients on pegylated interferon alpha-2a (5 on pegylated interferon alpha-2a monotherapy and 3 on combination pegylated interferon alpha-2a plus lamivudine therapy) compared with none in patients receiving lamivudine monotherapy (p = 0.029) (Marcellin et al 2004).

Combination pegylated interferon alpha-2a (40 kDa) plus lamivudine therapy

Disappointingly, data generated from 2 studies do not support the use of combination therapy with pegylated interferon alpha-2a and lamivudine in terms of achieving a sustained off-treatment response (Marcellin et al 2004; Lau, Piratvisuth, et al 2005). In both phase III HBeAg positive and HBeAg negative studies, the degree of viral load suppression at the end of treatment was higher in those on a lamivudine-containing regimen than those on pegylated interferon alpha-2a alone (7.2 log vs 4.5 log respectively in the HBeAg positive study and 5.0 log vs 4.1 log respectively in the HBeAg negative study), but the rate of sustained disease remission was higher in the latter (Marcellin et al 2004; Lau, Piratvisuth, et al 2005). This finding suggests that the mechanism of viral load reduction, in addition to the degree of viral suppression, is an important factor affecting sustained disease remission. However, one benefit of combination pegylated interferon alpha-2a plus lamivudine therapy is a lower YMDD mutation (1%–4%) compared with lamivudine-only therapy (18%–27%) (Germanidis et al 2004).

Predictors of response

Patients infected with genotype A had the highest HBeAg seroconversion at 24 weeks after pegylated interferon alpha-2a (± lamivudine) therapy (52%) compared with patients infected with genotype B or C (30%–31%), but the rate of the gentotype C group was still better than with lamivudine-only therapy (Chow et al 2005).

Patients with a high baseline ALT level and low HBV DNA are also more likely to achieve sustained response with pegylated interferon alpha-2a therapy. High baseline ALT levels (> 5 times ULN) and low HBV DNA (< 9.1 log copies/mL) achieved HBeAg seroconversion rates of 41% and 53% respectively (Chow et al 2005). The authors also found that a more profound HBeAg suppression at week 12 of therapy (less than 10 IU/mL) was associated with a higher HBeAg seroconversion (53%).

A prior use of other antiviral therapies (lamivudine, or conventional interferon alpha) does not preclude patients from treatment with pegylated interferon alpha-2a, as the response rates were similar to those without such use before (Lau, Luo, et al 2005).

Durability of off-therapy sustained response

In a longer follow-up study on the durability of off-therapy response with pegylated interferon alpha-2a (Marcellin et al 2005), 177 HBeAg negative patients with biochemical and virological response at 6 months after the completion of 48 weeks of pegylated interferon alpha-2a were rolled over into a long-term observational study. The rates of biochemical and virologic response measured 12 months after the end of treatment with pegylated interferon alpha-2a monotherapy were similar to those reported 6 months after the end of treatment: 59% vs 59% for ALT normalization; 42% vs 43% for HBV DNA < 20 000 copies/mL; and 17% vs 19% for HBVDNA < 400 copies/mL. In a subanalysis of those patients who responded to pegylated interferon alpha-2a monotherapy at the end of treatment, more than half (75%) had HBV-DNA levels < 100 000 copies/mL for most of the 12 month follow-up; 30% had HBV-DNA levels < 20 000 copies/mL, and 15% had HBV-DNA levels permanently < 400 copies/mL.

Effect on liver histology

The effect of pegylated interferon alpha-2a on liver histology was analyzed by Lau et al and Cooksley et al (Cooksley et al 2005; Lau, Cooksley, et al 2005). Both studies found that pegylated interferon alpha-2a therapy can result in histological improvement (defined as drop of 2 points in the Modified Histologic Activity index) (Ishak et al 1995). Forty-nine percent of HBeAg positive and 59% of HBeAg negative patients treated with pegylated interferon alpha-2a had histological improvement on second liver biopsy at 24 weeks after the end of therapy (Cooksley et al 2005).

Histologic improvement is more pronounced in patients with virological response. Thus, HBeAg positive patients who had achieved ALT normalization, HBV DNA suppression,

and HBeAg seroconversion are more likely to have histologic improvement. Similarly, HBeAg negative patients with HBV DNA suppression or ALT normalization also showed improvement in liver histology. HBeAg negative patients achieving a combined response (normalization of serum ALT and suppression of HBV DNA) had a higher histological response (78% vs 49%) (Lau, Cooksley, et al 2005).

Adverse effects

The drop-out rates were low in both phase III studies (2%–7%). Most patients (about 80%) finished the prescribed dose (Lau, Luo, et al 2005). More patients given pegylated interferon alpha-2a suffered from at least 1 adverse effect (88%–89% vs 48%–56%). Most of them had fever, fatigue, headache, myalgia, alopecia, and injection site reaction. About 4%–6% of patients had serious adverse effects as a result of pegylated interferon alpha-2a monotherapy and pegylated interferon alpha-2a plus lamivudine combination therapy, and 2%–3% of lamivudine monotherapy had a serious adverse effect. Four deaths occurred in the combination therapy but 3 of them were not related to the treatment. The only death that was probably related was the development of thrombotic thrombocytopenia purpura. Two patients in the lamivudine monotherapy had liver failure resulting in 1 liver transplantation and 1 death.

Optimal duration of therapy with pegylated interferon alpha-2a (40 kDa)

Two studies have demonstrated the efficacy of 48 weeks of pegylated interferons alpha-2a either as monotherapy or in combination with lamivudine for the treatment of HBeAg positive and negative chronic HBV infection (Cooksley et al 2003; Marcellin et al 2004; Lau, Piravisuth, et al 2005), but it is uncertain if a shorter duration of treatment with pegylated interferons will affect the sustained virological response rate. This is because the current licensed duration of therapy with conventional interferon alpha is 16–24 weeks. At the moment, no direct comparison between 24 weeks and 48 weeks of pegylated interferon alpha for chronic HBV infection has been performed.

In a recent review of our experience in treating HBeAg positive Chinese patients in Hong Kong with either 48 weeks of pegylated interferon alpha-2a or 24 weeks of pegylated interferon alpha-2b, we found that those treated with 48 weeks of pegylated interferon alpha-2a had a higher sustained virological response, defined as HBeAg seroconversion with serum HBV DNA less than 10^5 copies/mL at week 72 (34% vs 8% respectively, $p = 0.04$) (Hui et al 2006). However, owing to the small sample size, the use of different pegylated interferon alphas and the retrospective nature of this study, the results should be interpreted with caution and show the need for a large-scale randomized prospective study comparing 24 with 48 weeks of pegylated interferon alpha in order to determine its optimal duration of therapy.

Conclusions

Pegylated interferon alpha-2a will have an important role in the treatment of chronic HBV infection. The choice of pegylated interferon alpha-2a as a first-line therapy for chronic HBV is based mostly on its efficacy in inducing off-therapy sustained disease remission (Marcellin et al 2004; Lau, Piratvisuth, et al 2005). Newer nucleoside–nucleotide analogs such as entecavir and telbivudine with a more pronounced and rapid suppression of HBV replication are expected to be approved later. Higher or more pronounced suppression of HBV DNA may be achievable with these drugs. However, their rates of HBeAg seroconversion after 48 weeks of therapy do not seem to be more pronounced than that achieved with lamivudine or adefovir dipivoxil. It is also uncertain if these new nucleoside–nucleotide analogs can lead to off-therapy sustained disease remission. A finite course of pegylated interferon alpha-2a with an increased rate of virologic and biochemical response coupled with its improved off-therapy response makes pegylated interferon alpha-2a a first-line therapy for chronic HBV.

In those who do not respond to pegylated interferon alpha-2a, long-term maintenance therapy with a nucleoside–nucleotide analog either as monotherapy or combination therapy may have to be considered. However, drug resistance and its avoidance is a major obstacle to maintenance therapy. New nucleoside–nucleotide analogs such as entecavir and telbivudine have a more pronounced viral suppression of HBV replication, but their rates of viral resistance during long-term therapy have yet to be evaluated and may be a frequent problem, making them unsuitable for effective long-term therapy (Hadziyannis 2003; Hadziyannis and Papatheodoridis 2003). Hence, control of chronic HBV may require long-term therapy consisting of combination therapy. The challenge is to find the correct combination (Shaw and Locarnini 2000).

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