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Pegylated interferons for chronic hepatitis B

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Abstract

Conventional interferon therapy has been used for the treatment of chronic hepatitis B (CHB) for many decades. However, the use of interferon has been limited by its short half-life and high incidence of dose-related side effects. A meta-analysis investigating the short- and long-term consequences of interferon therapy showed that, whilst interferon therapy was beneficial in the short term, resulting in normalization of alanine aminotransferase (ALT) levels, loss of HBeAg, 'e' seroconversion and suppression of hepatitis B virus (HBV) DNA, the long-term benefits were less substantial.

Pegylation of interferon (peginterferon alpha-2a [40 kDa]) led to improved pharmacokinetic and pharmacodynamic profiles, which translated to superior efficacy compared with conventional, nonpegylated interferon, in the treatment of chronic hepatitis C. A phase II study investigated the safety and efficacy of peginterferon alpha-2a (40 kDa) in the treatment of chronic hepatitis B. The results demonstrated a rapid and dramatic reduction in HBV DNA levels, HBeAg clearance and normalization of ALT with peginterferon alpha-2a (40 kDa) compared with conventional interferon. Furthermore, peginterferon alpha-2a (40 kDa) conferred a notably improved treatment response in patients with 'difficult-to-treat' hepatitis B infection.

In conclusion, peginterferon alpha-2a (40 kDa) is a promising emerging therapy for CHB.

Keywords: Peginterferon alpha-2a (40 kDa); Chronic hepatitis B; Interferon alpha

1. Introduction

Conventional interferon alphas (IFNα) have been used for the treatment of chronic hepatitis B (CHB) for many decades. They have a dual mode of action; antiviral via inhibition of viral replication, and immunomodulatory via enhancement of the immunological response of the host against the virus. Initially, a high-dose treatment regimen of 9 MIU/m^2 of body surface area was used three times a week; however, this regimen was associated with high treatment withdrawal rates due to significant side effects. Other dosing regimens of IFNα were recommended, such as 4.5/5 or 9/10 MIU per week. However, influenza-like side effects occurred in most patients and there were occasional side effects, including mood changes and depression.

A meta-analysis of all studies utilizing conventional IFNα for the treatment of CHB between 1987 and 1999 was recently performed to assess the efficacy and safety of conventional IFNα in the treatment of HBeAg-positive CHB (Craxi et al., 2003). Treatment endpoints were divided into short and long term. In the short term, normalization of alanine aminotransferase (ALT), clearance of HBeAg, loss of HBV DNA and clearance of HBsAg were analysed, whereas HBs seroconversion, disease decompensation and development of hepatocellular carcinoma (HCC) and liver-related mortality were long-term treatment endpoints.

Using the short-term parameters, the meta-analysis demonstrated that the probability of persistent ALT normalization, HBeAg clearance, sustained loss of hepatitis B virus (HBV) DNA and HBsAg clearance were all higher in the IFN treatment group compared with the no treatment group for both HBeAg-positive and HBeAg-negative patient subgroups.

The long-term outcome measures also favoured IFN treatment compared with no treatment, as a higher percentage of patients achieved HBs seroconversion with IFNα. Furthermore, fewer patients showed disease decompensation, development of HCC and liver-related mortality with IFN treatment compared with no treatment. However, the differences between the groups were not significant, indicating that, in HBeAg-positive CHB patients, the long-term benefits of conventional IFN treatment are less substantial (Craxi et al., 2003).

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2. Pegylation of interferon

The attachment of a polyethylene glycol (PEG) molecule to a therapeutic protein has a marked effect on the potency and pharmacodynamic-pharmacokinetic characteristics of that protein. Pegylation has been used in the development of pegylated IFNα.

The first pegylated IFNα to be developed was 5 kDa in size, but the overall clinical and laboratory benefits were limited. Since then, two other pegylated IFNs have been developed: a small linear 12 kDa PEG, linked to IFNα-2b [peginterferon alpha-2b (12 kDa)], and a large branched 40 kDa PEG, linked to IFNα-2a [peginterferon alpha-2a (40 kDa)]. Due to their differing size and structure, these molecules have different in-vitro and in-vivo characteristics. Whilst the peginterferon alpha-2a (40 kDa) has a longer half-life (∼80 h), it is mainly catabolized in the liver and has active breakdown products. The smaller peginterferon alpha-2b (12 kDa) has a shorter half-life (∼40 h) and may act as a pro-drug depot, slowly releasing IFN (Kozlowski et al., 2001; Wang et al., 2000).

Both of these pegylated IFNs have been investigated for the treatment of hepatitis C virus (HCV) infection and have been shown to be more efficacious compared with conventional IFNα (Heathcote et al., 2000; Zeuzem et al., 2001; Lindsay et al., 2001).

Due to this improved efficacy against hepatitis C, it was postulated that pegylated IFNs may also be effective for the treatment of CHB. The rationale behind this was based on the following:

(1) Pegylation allows for higher, more effective doses to be used, in contrast to conventional IFNα, which yields only intermittent drug exposure (high concentration peaks followed by rapid drug elimination),
(2) Pegylation allows for continuous drug exposure over the entire dosing interval, and
(3) Current treatments for CHB are limited by their long-term use and the possibility of development of viral resistance.

A phase II study was, therefore, performed to compare peginterferon alpha-2a (40 kDa) with conventional IFN for the treatment of CHB.

3. Clinical experience with peginterferon alpha-2a (40 kDa) (PEGASYS®)

An international, multicentre, parallel-group, open-label phase II study was performed to evaluate the safety and efficacy of three doses (90, 180 and 270 μg q.w.) of peginterferon alpha-2a (40 kDa) (PEGASYS®), compared with conventional IFNα-2a (4.5 MIU t.i.w.) for 24 weeks, followed by a 24-week follow-up period, in 194 patients with CHB (Cooksley et al., 2002).

HBeAg-positive CHB patients with HBV DNA >500,000 copies/ml and serum ALT levels between 2 and 10× upper limit of normal (ULN) were included in the study. Liver biopsy was used to confirm CHB status. Patients with decompensated liver disease, co-infection with HIV, HCV or HDV, or having received treatment with nucleoside analogues 6 months prior to study commencement, were excluded.

The primary response parameter was defined as the loss of HBeAg and the appearance of anti-HBe antibodies at the end of follow-up. The combined response was defined as ALT normalization, suppression of HBV DNA to <500,000 copies/ml and HBeAg loss.

All doses of peginterferon alpha-2a (40 kDa) produced a more rapid and dramatic reduction in HBeAg compared with conventional IFN. Likewise, suppression of HBV DNA was most notable for peginterferon alpha-2a (40 kDa) compared with conventional IFN (Cooksley et al., 2002). Importantly, the reduction in HBV DNA levels reported with peginterferon alpha-2a (40 kDa) was comparable with that seen with nucleoside/nucleotide analogues (Perrillo et al., 2001).

At the end of follow-up, a higher number of patients achieved combined response rates with peginterferon alpha-2a (40 kDa) than with conventional IFN. In fact, with peginterferon alpha-2a 180 μg q.w., 28% °F patients showed combined responses compared with 12% of patients on conventional IFN (Cooksley et al., 2002).

Patients with low baseline ALT levels, high pre-treatment HBV DNA levels and/or HBV genotype C show poor responses to antiviral therapy and are classically considered 'difficult-to-treat' (Wong et al., 1993; Niederau et al., 1996; Chien et al., 1999; Kao et al., 2000; Wai et al., 2002). In this phase II study, peginterferon alpha-2a (40 kDa) demonstrated greater response rates compared with conventional interferon α in these 'difficult-to-treat' patient populations, and also showed positive results in patients with cirrhosis (Cooksley et al., 2002).

Peginterferon alpha-2a (40 kDa) monotherapy was well tolerated at all three doses, with no serious safety concerns during the course of the study. Withdrawal rates and the need for dose modifications were similar in both the peginterferon alpha-2a (40 kDa) and the conventional IFN groups (Cooksley et al., 2002).

4. Conclusion

Conventional IFNα treatment is associated with an inconvenient, three-times weekly dosing regimen and frequent dose-related side effects. Other therapies for CHB, such as nucleoside/nucleotide analogues, are not ideal, as they result in a low rate of sustained response, have no defined treatment duration and thus require long-term maintenance therapy. In addition, nucleoside/nucleotide analogues are associated with a high incidence of viral rebound upon treatment termination (Song et al., 2000; Lee et al., 2002), and,

in the case of lamivudine, the emergence of drug-resistant mutants (Liaw et al., 1999; Lok et al., 2000). Better options for the treatment of CHB are therefore being sought.

At present there are many emerging therapies for CHB, of which peginterferon alpha-2a (40 kDa) (PEGASYS®) seems the most promising. The pharmacokinetic and pharmacodynamic properties conferred by the attachment of the 40 kDa PEG to IFN α-2a allows once-weekly dosing and results in improved treatment response in patients with CHB, including patients with 'difficult-to-treat' disease and cirrhosis. Based on these promising outcomes, phase III studies are currently underway to explore the use of 180 μg of peginterferon alpha-2a (40 kDa) once weekly, over a total treatment period of 48 weeks, in patients with HBeAg-positive and HBeAg-negative CHB.

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