

THE TREATMENT OF E ANTIGEN POSITIVE CHRONIC HEPATITIS B WITH PEGYLATED-INTERFERON

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Introduction

Interferons were first used in the treatment of chronic hepatitis B two decades ago (Greenberg et al; Thomas et al; Wong et al) and eventually led to the registration of this drug in the treatment of chronic hepatitis B. The interferons act as immuno-modulators having a number of effects on the immune system and also act as an anti-viral agent by inducing oligoadenylate synthetase and other proteins which lead to cleavage of viral RNA. Although there was increasing efficacy with the dose of interferon - better results were achieved by using 9 mlU per square metre of body surface area three times a week - the significant side effects caused withdrawal in many patients. There were a variety of other dose regimens including a daily dose of half the amount. The dose recommended was 2.5 mlU or 5 mlU per square metre three times a week. This translated into 4.5/5 or 9/10 mlU three times a week. Furthermore, the side effects, often described as an influenza-like illness of myalgia, fever and headache occurred in most patients and there were a plethora of other side effects, including mood changes and even depression. The seroconversion rate in patients who had e antigen positive chronic hepatitis B ranged from 20 to 50 per cent of patients who had a six month course of treatment.

The introduction of Lamivudine (Lai et al; Dienstag et al), the first antiviral agent to be licensed, had a dramatic impact on the treatment of chronic hepatitis B as it seemed not to have side effects. Virtually all patients had viral inhibition and a reduction in HBV DNA levels in blood, and a slower decrease in transaminases. Unfortunately, the rate of seroconversion was only about 20% in a year so that cessation of the drug led to relapse of chronic hepatitis B. As a result, many patients continued on Lamivudine and seroconversion continued to occur but at a lower rate and possibly no greater than that seen spontaneously. Unfortunately the development of a Lamivudine resistant mutation in the YMDD domain of the polymerase gene at a rate of about 10 – 20 per cent per annum proved a major stumbling block in the management of this disease with antiviral agents (Liaw et al; Lau et al).

Protein pegylation

The use of polyethylene glycol attached to proteins has had a marked effect on their in vivo half-life. Proteins such as adenosine deaminase have been pegylated which allows a smaller amount to be used. Pegylation has also been used with the interferons (Xu et al). The pegylation process involves linking the polyethylene glycol polymer to the protein of interest at one or more of several sites. This may alter both its potency and also its pharmaco-kinetic and pharmaco-dynamic characteristics. The first pegylated interferon was a 5kD polymer bound to $\alpha 2a$ but its half-life was only a few days and benefits were insufficient.

In the last few years, there have been extensive trials carried out with two larger polymers, namely the 12kD PEG with linkage of interferon $\alpha 2b$ to the linear PEG and the 40kD branched PEG linked to interferon $\alpha 2a$. In addition, the binding sites differ and thus the stability of these molecules also differ both in vitro and in vivo. Furthermore, the different size of the two molecules leads to different volumes of distribution, the organs in which the drug is distributed and its sites of catabolism. In short, the 40kD interferon $\alpha 2a$ has a longer half-life (>100 hours) and its breakdown products are biologically active. It is largely catabolised within the liver. The 12kD $\alpha 2b$ interferon has a shorter half life and is somewhat more of a pro-drug acting as a depot of

interferon with release of free interferon that produce much of its efficacy and side effects.

The two pegylated-interferons have been used in a variety of trials in chronic hepatitis C (Heathcote et al; Zeuzem et al; Lindsay et al) and results show considerable improvement in efficacy over standard interferon and the use of pegylated-interferons in combination with Ribavirin enhances the effect even further, so that the majority of patients may now expect a sustained virological response in this disease. The side effect profile of the drug appears to be not dissimilar to that of standard interferon, although the duration of side effects is somewhat different as it relates to the blood level and is thus continuous rather than having peaks and troughs that occur with standard interferon given three times a week.

The challenge in chronic hepatitis B

Because of the improved results in chronic hepatitis C, the question naturally arose as to whether pegylated interferons would be of use in patients with chronic hepatitis B. The argument in favour of this approach is the evidence that higher doses of interferon are more effective. The recognition of the disadvantages of Lamivudine and the potential for hepatitis B virus treated with other antiviral agents to develop viral resistance (particularly if used in monotherapy), and the recognition that seroconversion of e antigen to anti e is the critical step in enabling cessation of treatment, meant that there was a strong possibility that pegylated interferons would be of value.

A trial was, therefore, carried out in that area of the world, namely the Asian-Pacific region, where the chronic hepatitis B prevalence is approximately 10% of the population and more than half of the patients with chronic hepatitis B in the world exist. It was decided to perform a four arm study using three different doses of PEG (40kD) interferon a2a compared with standard interferon over a period of six months and the results were presented at the American Association of the Study of Liver Diseases in Dallas in 2001 (Cooksley et al) and at the European Association for the Study of the Liver in Madrid in 2002 (Cooksley et al). A manuscript is currently in preparation, but the results indicate that more than twice as many patients receiving PEG (40kD) interferon a2a 180µg weekly for six months responded compared with patients receiving standard interferon. As a result of these encouraging results, two further phase 3 trials are under way using pegylated-interferon 180µg weekly in e antigen positive chronic hepatitis B and in e antigen negative chronic hepatitis B. Both of these are world wide studies and compare pegylated-interferon with Lamivudine and with a combination of Lamivudine with pegylated-interferon.

The rationale for the use of Lamivudine in combination with the pegylated-interferon has been cited elsewhere and the benefit is still disputed. In one study (Schiff et al) there was no improvement, but this may have been due to the fact that the patients were previous non-responders to standard interferon who received the combination of standard interferon and Lamivudine. In another study (Schalm et al) there were a number of logistical problems so that there was no significant difference in intention to treat analysis, whereas per protocol analysis had a p value of .02 when 36% of patients who received combination therapy seroconverted compared with only 22% of patients receiving Lamivudine alone or 19% with interferon alone. There are criticisms of the design of the study, whereby patients were being treated for different durations and furthermore, and there was the theoretical possibility that the use of Lamivudine for eight weeks before standard interferon was introduced may have inhibited replication to such an extent that there was no longer expression of viral proteins on the hepatocyte plasma membranes leading to failure of cytotoxic T cells to recognise and destroy the infected cells. Be that as it may, the current studies will clarify whether the combination of Lamivudine and Pegylated-Interferon 40kD a2a is better than monotherapy, with 40kD PEG-Interferon.

Tolerability

The number of patients with cirrhosis was not to exceed 20% and only 10-12 per cent of patients had cirrhosis in the study. The need to dose-reduce to avoid significant neutropenia or thrombocytopenia was similar to what has been shown before with pegylated-interferons and the patient tolerability to the side effects was very good. It is anticipated that the new studies will have similar outcomes.

The mechanisms of action

Although interferons are primarily immunomodulators, they also have an antiviral effect. It is unclear at this stage the relative importance of these two effects in patients treated with Pegylated-Interferon. In the abstract presented it was noted that at the end of six months treatment the decline in HBV DNA was similar to that seen in patients receiving Lamivudine, but much of this decline may have been due to the reduction in plasma HBV DNA subsequent to the seroconversion. The relative importance of these two effects will be important in determining whether Lamivudine in combination with Pegylated-Interferon will enhance the seroconversion rate.

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