

## **Combination Therapy of HBV—Overview**

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### **Introduction**

The theoretical argument for combination rather than monotherapy in the treatment of chronic hepatitis B is enhanced antiviral efficacy and decreased likelihood of drug resistance. Although the short-term goals of antiviral therapy may differ according to the HBeAg status at the start of treatment, and the potential choices of combination therapies may be limited by liver disease status (compensated, decompensated, native or transplanted liver), the long-term goals are the same. That is, to clear virus, meaning to clear cccDNA from hepatocyte nuclei without unacceptable side effects, and in a cost-effective manner.

To date, published data on the outcome of combination therapies versus monotherapy have only been evaluated in the short term, i.e. 1 year. Thus, information on the durability of even short-term goals such as viral suppression, HBeAg seroconversion, HBs seroconversion, as well as drug-resistant rates is limited. Even more so, information on levels of cccDNA in liver tissue is lacking. At present, we have randomized control trial (RCT) data on 3 different combinations: Interferon-based therapy plus nucleoside analogue, a combination of 2 nucleoside analogues, or a nucleoside analogue and a nucleotide analogue. Sequential therapy of two antiviral agents, or of corticosteroid therapy followed by an antiviral agent, will not be discussed.

### **Effect on Viremia—Efficacy of Combination Therapy**

The mechanisms by which enhanced efficacy may be achieved using combination therapy vary according to the particular combination and the viral kinetics demonstrate these differences. Because the early studies which employed standard interferon  $\alpha$  plus a nucleoside analogue were performed using relatively insensitive methodology for the measurement of HBV DNA, only one such study will be discussed and most discussion around IFN  $\alpha$  will focus on the newer pegylated interferons and the data from these studies will be used to illustrate how the viral kinetic patterns differ according to treatment combination and how this may explain differences in efficacy and durability of response.

### **Pegylated Interferon $\alpha$ Plus Nucleoside Analogue**

The first study employing combination therapy was published by Janssen et al.<sup>1</sup> This report and a subsequent one on data obtained on portions of the same study by Flink et al.<sup>2</sup> describes the varied pattern of changes in viral titre, ALT, and HBeAg seroconversion during and after therapy. Janssen reported that the initial (first 4 week) fall in HBV DNA did not correlate with subsequent HBeAg seroconversion and likely represented the direct antiviral effect of the drug combination. Rather, it was the 4-week to 34-week fall in HBV DNA that predicted subsequent likelihood of HBeAg seroconversion, even in the face of a rise in ALT. These observations suggest that, when the combination of pegylated interferon  $\alpha$  (in this case pegylated interferon  $\alpha$  2b) plus lamivudine is given, it

is the combination of the antiviral and immunologic effect of this particular drug combination that may be responsible for its enhanced efficacy over monotherapy with the nucleoside analogue lamivudine. Flink et al<sup>2</sup> describe the different HBV DNA/ALT patterns as being “host” derived—when HBV DNA levels fall and ALT rises, or being “virally” mediated when both HBV DNA and ALT rise—thus illustrating how important it is when using a combination of Peg-interferon  $\alpha$  plus nucleoside to measure both simultaneously.

In both of the two combination studies employing pegylated interferon  $\alpha$  2a published by Marcellin et al<sup>3</sup> and Lau et al,<sup>4</sup> the combination of pegylated interferon  $\alpha$  2a plus lamivudine gave rise to the greatest fall in HBV DNA in both studies (compared to PEGIFN  $\alpha$ 2a monotherapy or lamivudine monotherapy). In the study of HBeAg-positive hepatitis by Lau et al,<sup>4</sup> this did not translate into a greater rate of HBeAg seroconversion, though the HBeAg seroconversion for both pegylated interferon  $\alpha$  2a  $\pm$  the addition of lamivudine was significantly greater than the HBeAg seroconversion rate with lamivudine alone at 72 weeks, i.e., 6 months after the cessation of all treatments. The durability of HBeAg antigen seroconversion was greater in those individuals who received PEGIFN  $\alpha$  2a  $\pm$  than those who received lamivudine alone. Similarly, in the paper by Marcellin et al,<sup>3</sup> the relapse rate following the initial benefit seen during 48 weeks on therapy was observed to be significantly greater in those who received lamivudine monotherapy compared to those who received PEGIFN  $\alpha$  2a monotherapy, or combined with lamivudine.

The results of a very recently published pilot study by D’Antiga et al,<sup>5</sup> which employed lamivudine 3 mg/kg daily for 8 weeks followed by the addition of standard interferon 5 mu/m<sup>2</sup> X3 weekly in combination for a further 10 months given to children who were HBeAg positive with near normal ALT values and liver histology, and HBV DNA levels greater than 1,000 pg/ml “immune tolerant,” support the suggestion by Janssen et al<sup>1</sup> that the combination of these two drugs with very different antiviral actions may explain why this combination is so much more effective than nucleoside analogues alone. Four of 23 (17%) of these children lost HBsAg during the 1 year of therapy; no drug resistance developed and no relapse was observed over 36-48 months of follow-up. This result is impressive! Although this is a pilot, nonrandomized study, all previous studies have shown that neither IFN nor lamivudine given as monotherapy afforded any benefit in immune-tolerant (albeit adult) individuals. The spontaneous loss of HBsAg in children who are hepatitis B carriers is no more than 0.9% per year. Although this is early pilot study data, the results of this particular combination of therapy are very encouraging.

### **Combination Nucleosides or Nucleoside Plus Nucleotide**

The effect of combinations of nucleoside(tide) analogues have been disappointing to date, as RCTs have observed no enhanced antiviral efficacy, either in treatment naive (telbivudine plus lamivudine)<sup>6</sup> or in patients with lamivudine resistance treated with additional adefovir dipivoxil.<sup>7</sup> Neither the initial fall in HBV DNA, nor the long term (1 year) effect on HBV DNA was any greater with combination therapy. However, in the study of HBeAg-positive hepatitis, a trial of telbivudine with or without the addition of lamivudine, showed the greater the fall in HBV DNA at 24 weeks into treatment, the

higher the rate of HBeAg seroconversion at 48 weeks, regardless of therapy. Unfortunately, neither of these two studies were continued beyond a year, so we do not know if there would be a benefit of combination therapy had it been given for longer. Neither study reported the relapse rate or the clinical effect of any relapse after cessation of therapy. We do, however, know from the study by Lau et al that relapse in HBeAg-positive patients treated with lamivudine monotherapy led to liver failure in two cases, whereas hepatic decompensation was not reported following cessation of PEGIFN  $\alpha$  2a monotherapy or when in combination with lamivudine.<sup>4</sup>

### **Drug Resistance—Safety of Combination Therapy**

All four large RCT of PEGIFN  $\alpha$ /lamivudine<sup>1,3,4,8</sup> combination showed that the lamivudine resistance rate at the end of 1 year on the combination was considerably less than in those who received monotherapy with lamivudine. In the only study of combination nucleoside therapy in naive HBeAg-positive hepatitis, namely the trial of telbivudine and lamivudine,<sup>6</sup> a higher resistance rate was seen in those on the combination than in those who received telbivudine monotherapy; the explanation for this is unclear. The study of combination lamivudine plus adefovir versus adefovir alone given to patients with lamivudine resistance did not report any adefovir resistance occurring within the first year of treatment, but subsequent reports (outside the context of a clinical trial) suggest that adefovir resistance may be observed within the first year of treatment of those with lamivudine resistance, even when dual therapy is employed.<sup>9,10</sup> The highest rate seen for adefovir resistance in this situation is in those who have undergone a liver transplant.<sup>9</sup> Ranges of adefovir resistance in those treated for lamivudine resistance ranged from 2-9% in the first year of dual therapy. In the study by Lampertico et al,<sup>11</sup> the results suggest that the sooner adefovir therapy is added to lamivudine, once genotypic resistance to lamivudine is detected, the faster the antiviral benefit observed; i.e. one should not wait for a rise in ALT level, only a rise in HBV DNA, to start dual therapy. In a follow-up to this study, these authors suggest that hepatic decompensation occurs only in those in whom the addition of adefovir in the presence of lamivudine resistance is delayed.<sup>12</sup> In the study by Peters et al,<sup>7</sup> there was a suggestion that fewer flare-ups as manifested by a rise in ALT > 5 ULN were seen in patients with lamivudine resistance who continued on lamivudine after the addition of adefovir than in the group who switched to adefovir monotherapy (these flares could not be correlated with a return to wild-type virus). For this and for the likely (but not proven) lower rate of adefovir resistance in the face of lamivudine resistance, dual therapy is advised in patients with, in this situation particularly those who have, underlying cirrhosis.

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