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Is combination therapy with lamivudine and interferon-alpha superior to monotherapy with either drug?

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Abstract

For the treatment of chronic hepatitis B (CHB) two drugs have been licensed world-wide: interferon-alpha (IFN) and lamivudine. Both drugs significantly increase the hepatitis B e-antigen (HBeAg) seroconversion rate, but a sustained treatment response occurs in less than 40% of patients. To explore whether there is an additional benefit of combining these two drugs, we reviewed the literature on lamivudine–IFN combination therapy in comparison to the two monotherapies in compensated, HBeAg-positive, CHB patients. We focussed on two clinically relevant outcome measures: HBeAg seroconversion, and change in liver histology. Candidates for lamivudine–IFN combination therapy were, previously untreated, patients with moderately elevated alanine aminotransferase (ALT). Such regimen should still be considered experimental. Viral kinetics may provide insight into how long therapy should be continued; prolongation of therapy to 52 weeks currently appears a reasonable approach. According to principles of anti-viral therapy today, simultaneously dosing of both drugs is to be preferred, since rapid maximal virus suppression is thought to be essential to prevent drug resistance and enhance seroconversion. From an immunological point of view, pre-treatment with lamivudine or IFN may alter the virus–host balance and set the stage for the other drug to enhance the effect of treatment. Further clinical research on lamivudine–IFN combination therapy appears warranted.

Keywords: Chronic hepatitis B; Interferon-alpha; Lamivudine; Combination therapy; Hepatitis B e-antigen seroconversion

1. Introduction

For the treatment of chronic hepatitis B (CHB) two drugs have been licensed world-wide: interferon-alpha (IFN) and lamivudine. Both drugs have been investigated extensively as monotherapy; they significantly increase the hepatitis B e-antigen (HBeAg) seroconversion rate, but a sustained treatment response occurs in less than 50% of patients. The question arises whether there is an additional benefit of combining these two drugs. In this paper, we review the literature on lamivudine–IFN combination therapy in comparison to the two monotherapies in compen-

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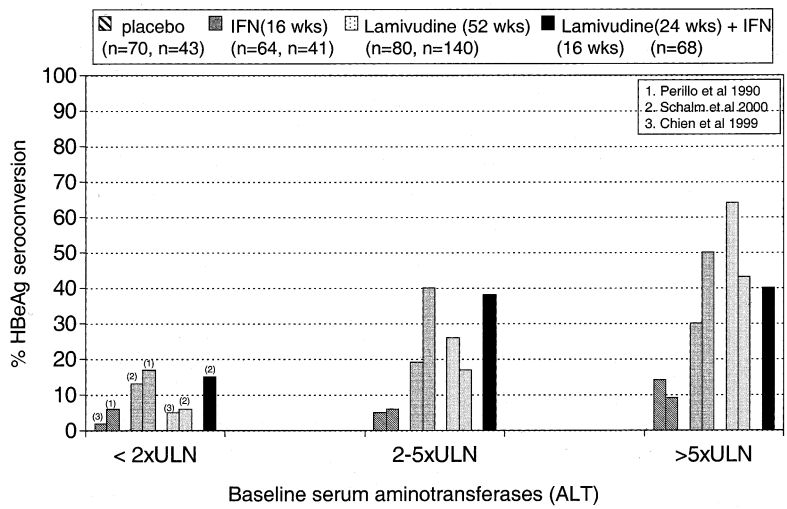

Fig. 1. Overview of treatment results in IFN naive, HBeAg-positive CHB patients, by treatment modality; relation between baseline ALT and response.

sated, HBeAg-positive, CHB patients. We focussed on two clinically relevant outcome measures: HBeAg seroconversion, and change in liver histology.

2. Selection of clinical studies for review

Pre-treatment patient characteristics, especially alanine aminotransferase (ALT) levels, have a major impact on the treatment outcome (Perrillo et al., 1990; Schalm et al., 2000; Chien et al., 1999). Therefore, different trials should only be compared after correction of baseline values. We aimed at including all published large[1] multicenter randomized trials in treatment-naive, HBeAg-positive, compensated, immunocompetent, CHB patients with standard lamivudine therapy ($\geqslant 100$ mg daily for 52 weeks), standard IFN (10 MU three times a week (t.i.w.) or 5 MU daily for 16–26 weeks) monotherapy and combination therapy of both drugs (Perrillo et al., 1990; Schalm et al., 2000; Chien et al., 1999; Lai et al., 1998; Dienstag et al., 1999a; Janssen et al., 1999). In addition to five eligible studies, we have included large international meta-analyses on IFN (Krogsgaard et al., 1994; Krogsgaard, 1998; Wong et al., 1993); meta-analyses on lamivudine or combination therapy are lacking. Furthermore, all other publications on lamivudine–IFN combination therapy were assessed.

[1] More than 40 patients in a treatment arm.

3. Hepatitis B e-antigen seroconversion

3.1. Standard therapy

The HBeAg response in relation to baseline ALT is illustrated in Fig. 1.

A large European Concerted Action on Viral Hepatitis meta-analysis of individual patient data, published by Krogsgaard et al. (1994), showed that the response to IFN therapy is dependent on baseline patient characteristics. Often, IFN therapy is said to be associated with loss of HBeAg in 30–40% of patients. However, IFN increases the spontaneous response rate, which varies between 5 and 10%, with a factor 2 resulting in response in 15–40% of patients (Perrillo et al., 1990; Schalm et al., 2000; Chien et al., 1999). Although the relative response is similar for all patients, those with elevated pre-treatment transaminases and low baseline hepatitis B virus (HBV) DNA levels have the largest absolute benefit from IFN ther-

apy (Lau et al., 1997; Krogsgaard et al., 1994; Wong et al., 1993; Brook et al., 1989a).

After 1 year of lamivudine monotherapy, HBeAg seroconversion occurs in maximal 20% of patients (Schalm et al., 2000; Lai et al., 1998; Dienstag et al., 1999a). Elevated baseline ALT is also the strongest predictor of lamivudine-induced HBeAg seroconversion: multivariate analysis showed that both ALT and histologic activity index (HAI) were highly significant correlated with HBeAg seroconversion, but the contribution of HBV DNA to the predicted response was negligible (Perrillo et al., 1999). Lamivudine increases the response rate with a factor less than 2 in case of ALT < 2 times the upper limit of normal (ULN), but this factor rises to 4 in case of ALT $> 5 \times$ ULN (Schalm et al., 2000; Chien et al., 1999).

The efficacy of lamivudine–IFN combination therapy given for 16 weeks after 8 weeks of lamivudine pre-treatment, was compared to standard IFN (10 MU t.i.w. for 16 weeks) and lamivudine (100 mg qd for 52 weeks) monotherapy in 230 treatment-naive HBeAg-positive patients. Combination therapy resulted in a HBeAg seroconversion rate of 29% in the intention-to-treat analysis. This outcome was not significantly higher than after IFN (19%) or lamivudine (18%) monotherapy. However, a per-protocol analysis, excluding all patients who did not meet the inclusion criteria at baseline or received the assigned treatment, revealed a significant higher seroconversion rate in the combination group. Thirty-six percent of patients receiving combination therapy responded versus 19 and 22% in the lamivudine and IFN monotherapy groups, respectively (Schalm et al., 2000).

In this study, a subgroup analysis based on pre-treatment ALT was performed, showing a 2–6-fold increase in the seroconversion rate in patients receiving combination therapy over that expected spontaneously. The absolute increase in the response was most pronounced in the group with moderately elevated ALT levels ($2–5 \times$ ULN). For patients with moderately elevated pre-treatment serum transaminases, combination therapy may have a benefit over monotherapy.

3.2. Prolongation of therapy

Prolongation of both IFN and lamivudine leads to increased HBeAg seroconversion rates. Prolongation of IFN therapy from the standard 16 to 32 weeks enhanced clearance of HBeAg and HBV DNA in patients with HBV DNA levels below 10 pg/ml (Abbott assay) at 16 weeks of therapy (Janssen et al., 1999).

Extension of lamivudine therapy from the standard 1 to 2 years was associated with a modest increase in response to 21–27% (Dienstag et al., 1999b; Buti et al., 2000; Liaw et al., 2000). In an Asian study, continuation for 4 years in 58 patients showed an increased HBeAg seroconversion rate of 47% (Chang et al., 2000). However, the definition of HBeAg seroconversion was altered in this study concentrating on HBeAg negativity independently of HBV DNA negativity. In nearly half of these responders a YMDD variant was detectable (Chang et al., 2000). The emergence of lamivudine-resistant strains is a major problem of long-term therapy; it has been reported in up to 60% of Caucasians at 2 years of therapy and 40–55% of Asian patients at 2–3 years (Buti et al., 2000; Liaw et al., 2000; Leung et al., 1999).

Prolonged combination therapy of IFN and lamivudine has not been investigated yet, with the exception of some cases. Fig. 2 illustrates a case of a young woman receiving lamivudine 150 mg daily for 1 year simultaneously with IFN 10 MU t.i.w. till week 32, followed by 5 MU t.i.w. up till 1 year. This patient seroconverted and lost hepatitis B surface antigen. The response was sustained after withdrawal of therapy during the follow-up of 1 year.

3.3. Durability of response

HBeAg seroconversion, either spontaneously or following IFN therapy, significantly reduces morbidity and mortality (Lau et al., 1997; Niederau et al., 1996; Liaw et al., 1988).

Several long-term follow-up studies have been performed to establish the durability of IFN-induced HBeAg seroconversion and the effect of the durability of the response on disease progression and survival (Krogsgaard, 1998; Lau et al., 1997;

Niederau et al., 1996; Carreño et al., 1992; Fattovich et al., 1997; Lin et al., 1999; Lok et al., 1993; Koorenman et al., 1991). Responders to IFN therapy have a significantly lower risk to develop cirrhosis (Lin et al., 1999). In addition, IFN has been identified as an independent factor related to a decreased risk for hepatocellular carcinoma development (Lin et al., 1999). Survival is found to be improved in five out of six studies assessing the impact of HBeAg seroconversion (Krogsgaard, 1998; Lau et al., 1997; Niederau et al., 1996; Carreño et al., 1992; Fattovich et al., 1997; Lin et al., 1999). In cirrhotic patients IFN-induced viral clearance improves survival, although Cox regression revealed ALT as the most important predictor of improved survival in these patients (Fattovich et al., 1997; Lin et al., 1999). IFN-induced HBeAg seroconversion is sustained in around 90% of patients (Fig. 3) (Krogsgaard, 1998; Lau et al., 1997; Niederau et al., 1996; Carreño et al., 1992; Lin et al., 1999; Lok et al., 1993; Koorenman et al., 1991).

Lamivudine-induced HBeAg seroconversion is suggested to be comparable to HBeAg seroconversion after IFN therapy (Dienstag et al., 1999b; Chang et al., 2000; Schiff et al., 2000). Forty-three lamivudine responders (defined as HBeAg-negative and detectable anti-HBe, or HBeAg and HBV DNA negative (bDNA) patients) were followed for a median of 21 months after cessation of therapy; only 19% (8/42) relapsed (Schiff et al., 2000). This encouraging report, however, needs confirmation, since the patient population was highly selected from several lamivudine trials, by including only patients who remained responders for at least 3 months of lamivudine or who had seroconversion maintained on at least two occasions of therapy over time. In contrast to these reports, single-center cohort studies show a relapse percentage that increases with time of follow-up (Song et al., 1999; Fontaine et al., 1999). One study comprising 34 responders (HBeAg-negative and anti-HBe-positive) to lamivudine ther-

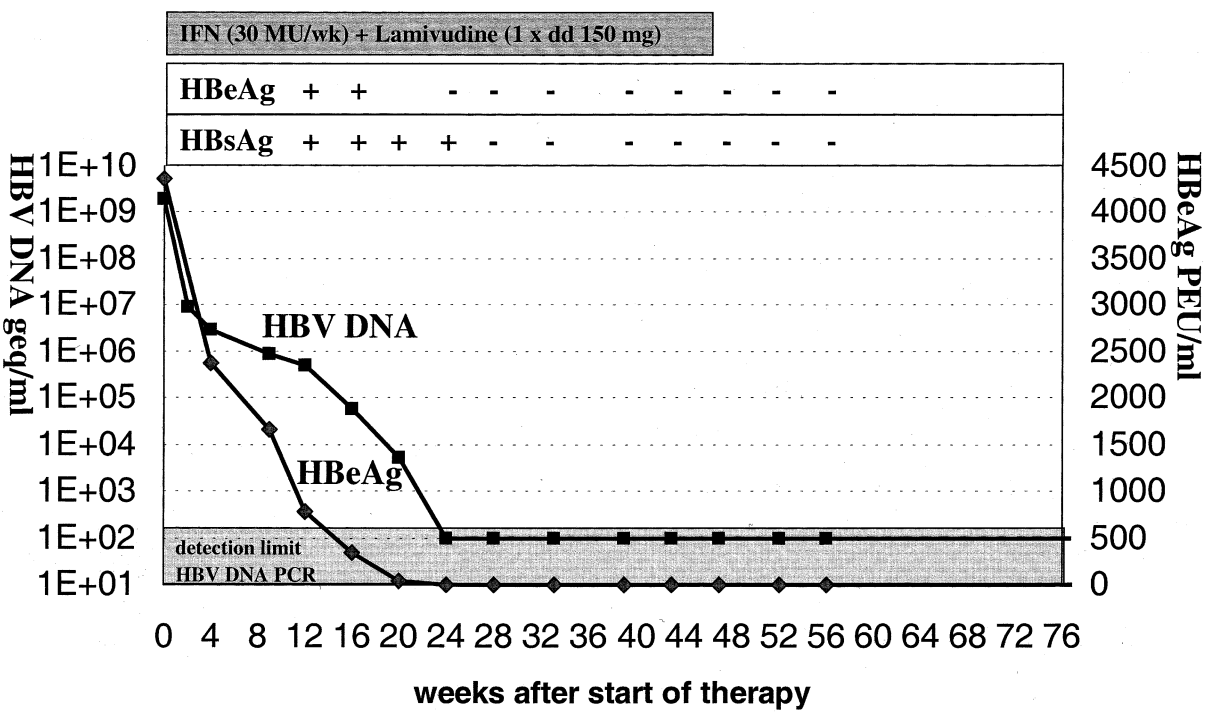

Fig. 2. Prolonged combination therapy of lamivudine and IFN for 52 weeks in an individual Caucasian woman of 23 years. Note the complete response occurring during therapy.

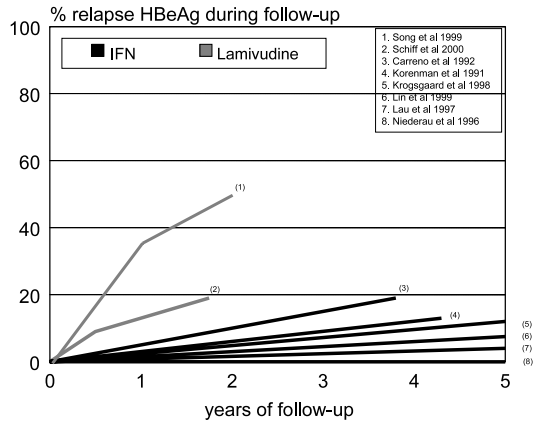

Fig. 3. Durability of HBeAg seroconversion after withdrawal of monotherapy with IFN or lamivudine during long-term follow-up. In case the follow-up after withdrawal of IFN therapy was beyond 5 years, the line was cut-off at 5 years.

apy reported a cumulative relapse percentage up to 49% at 2 years of follow-up (Song et al., 1999). Fig. 3 shows the durability of HBeAg seroconversion during long-term follow-up after withdrawal of lamivudine or IFN therapy.

No long-term follow-up data after combination therapy induced HBeAg seroconversion are available.

4. Improvement of liver histology

Fig. 4 illustrates effect of various therapies on the necro-inflammatory component of the Knodell scoring system (0–18 points). Histological improvement is defined as more than 2 points reduction of the necro-inflammatory score. An important factor, hampering the comparison of histological results of lamivudine with other therapies in several larger studies, is the fact that all biopsies were taken at the end of lamivudine monotherapy but 6 months after withdrawal of IFN or combination therapy.

Lamivudine significantly reduced the HAI score and prevented progression of fibrosis in HBeAg-positive patients at 1 year of therapy (Schalm et al., 2000; Lai et al., 1998; Dienstag et al., 1999a; Suzuki et al., 1999; Goodman et al., 1999). Results following withdrawal of lamivudine therapy are not available. Lamivudine shows histological benefit in about 50% of the patients, whereas IFN

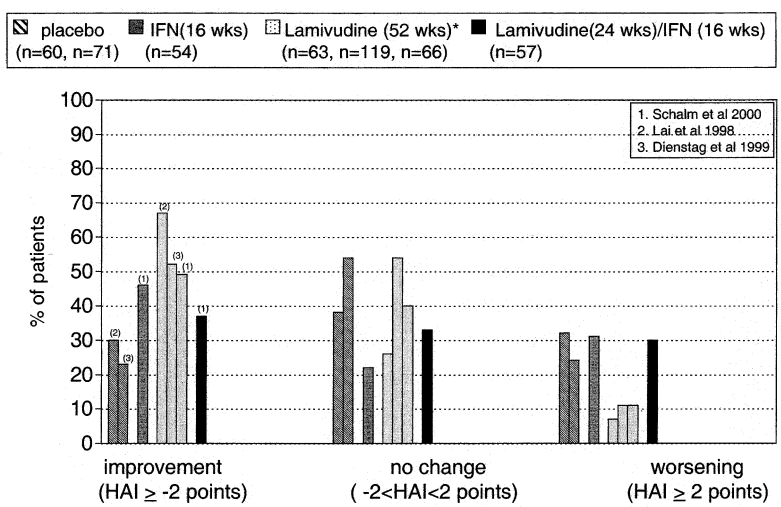

Fig. 4. Histologic changes after standard monotherapy with IFN (16 weeks) or lamivudine (12 months), or combination therapy with both drugs (lamivudine for 24 weeks combined with IFN for 16 weeks) evaluated by the Knodell necro-inflammatory scoring system excluding the fibrosis component (0–18 points). Improvement was defined as a reduction of at least 2 points, worsening as an increase of at least 2 points. Biopsies are taken at the end of lamivudine therapy in contrast to the end of follow-up for the other therapy groups. Improvement during lamivudine therapy is clearly illustrated; sustained improvement can only be assessed for IFN and lamivudine–IFN and appears small at 6 months after therapy.

therapy showed improvement in 45% and combination therapy in 38% of patients. The difference between active treatments appears more clear when disease progression is taken as the outcome measure: the number of patients with worsening of histology during lamivudine is minimal (7–11%), whereas IFN, combination therapy and placebo were associated with worsening of histology in about one-third of patients.

The differences between lamivudine and IFN can be partially explained by the fact that these are overall results, including responders as well as non-responders to therapy. In IFN and combination therapy, histological improvement is dependent on a virological response (Schalm et al., 2000; Lai et al., 1998; Brook et al., 1989b).

5. Safety

Combination therapy with IFN and lamivudine up to 26 weeks is generally well tolerated (Schalm et al., 2000; Alexopoulou et al., 1998; Mutimer et al., 1998; Schiff et al., in press). Combining both drugs does not change the safety profile; side effects are mainly IFN related (Schalm et al., 2000; Schiff et al., in press). IFN has a wide range of dose-depending side effects, which requires dose reduction in 20–40% of the patients and discontinuation in about 5% of the patients (Perrillo et al., 1990; Schalm et al., 2000; Krogsgaard, 1998; Wong et al., 1993). No pharmacokinetic interactions, that might affect the efficacy of both drugs, were observed during co-administration (Mutimer et al., 1998). Stopping lamivudine, also as part of combination therapy, is associated with a slightly increased risk of post-treatment flares in around 20% of patients (Schalm et al., 2000; Schiff et al., in press, Honkoop et al., 1995).

6. Other experiences with combination therapy in chronic hepatitis B

The enhanced seroconversion rate for combination therapy, as reported by Schalm et al. (2000), could not be confirmed in a study of 238 HBeAg-positive, previous IFN non-responders (Schiff et al., in press). Compared to the study in treatment-naive patients a similar trial design was used; only the arm with IFN monotherapy was replaced by placebo. At week 52, 12% of patients receiving combination therapy seroconverted for HBeAg, which was comparable to placebo (13%) but lower than lamivudine (18%) therapy.

The reason for the lack of response to lamivudine–IFN therapy most likely relates to patient characteristics. A subgroup analysis based on pre-treatment ALT is lacking, but median baseline ALT and HBV DNA levels were comparable in both studies. In general, host immunity was not overall low, in view of the response rate in the placebo and lamivudine groups. It is, however, conceivable that previous IFN non-responders have an immune status that makes it very difficult to respond to 16 weeks of IFN, even in the presence of lamivudine therapy.

Another study in 20 previous IFN non-responders, receiving combination therapy, showed a response in 20% of patients (Mutimer et al., 1998). This response was sustained in only one out of four patients. In a third study in previous non-responders, 6 months of lamivudine followed by 6 months of IFN led to a sustained response in 45% of patients, but this needs further investigation (Thabut et al., 2000). Finally, a study of 26 weeks of combination therapy in HBeAg-negative patients resulted in HBV DNA PCR negativity in 95%; however, withdrawal of combination therapy for this time period often led to a relapse of viral activity (Alexopoulou et al., 1998).

7. Conclusions and implications for future research

The relatively low sustained response rates with either IFN or lamivudine monotherapy, the possibility of relapse of viral activity after cessation of lamivudine monotherapy and the time-dependent emergence of viral resistance to lamivudine emphasize the need for combination therapy.

In previously untreated patients, those with moderately elevated ALT are candidates for lamivudine–IFN combination therapy. Such regimen should still be considered experimental.

Viral kinetics may provide insight into how long therapy should be continued; prolongation of therapy to 52 weeks currently appears a reasonable approach. According to principles of antiviral therapy today, simultaneously dosing of both drugs is to be preferred, since rapid maximal virus suppression is thought to be essential to prevent drug resistance and enhance seroconversion. From an immunological point of view, pretreatment with lamivudine or IFN may alter the virus–host balance and set the stage for the other drug to enhance the effect of treatment. Further clinical research on lamivudine–IFN combination therapy appears warranted.

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