

COMBINATION THERAPY FOR CHRONIC HEPATITIS B

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THE RATIONALE FOR COMBINATION THERAPY

Among the approximately 350 million individuals with chronic hepatitis B infection in the world, up to 50 percent (175 million) may have chronic hepatitis B related symptoms or signs; in comparison, the number of people infected with HIV is estimated to be 40 millions. For nearly all clinical conditions that require treatment (chronic hepatitis progressing to cirrhosis; cirrhosis with active hepatitis at risk for variceal bleeding, ascites, and hepatocellular carcinoma; chronic hepatitis with high viremia at risk for transmitting HBV; chronic hepatitis B with extra hepatic complications), monotherapy with either a standard course of 16-26 weeks of interferon or 1 year of lamivudine is effective in only a minority of patients. So, current regimens are inadequate for 60-90 percent of patients with chronic hepatitis B in need of therapy. In view of the low efficacy in relation to costs the pressure to massively implement antiviral therapy in chronic hepatitis B has been restrained. To reduce the morbidity and mortality of chronic hepatitis B more effective therapy has to be developed.

For most patients an effective response is based upon profound suppression of HBVDNA followed by ALT normalization, whereas a sustained response requires an additional induction of host immunity. Interferon has only mild to moderate virus-suppressive activity but can induce an effective host immune response in susceptible patients; in contrast, lamivudine has marked virus-suppressive activity in the majority of patients but has not been shown convincingly to have clinically relevant immunomodulatory effects; in addition the virus-suppressive activity of lamivudine is limited in time by the progressive emergence of drug-resistant mutants.

It is therefore logical to explore the efficacy of combination therapy of lamivudine and interferon in the hope to increase the virus-suppressive activity, to prevent the emergence of lamivudine resistant mutants, and to induce host immunity in all treated patients. The goal of therapy is a sustained response: HBVDNA < 10e5 copies per ml and ALT normalization 6-12 months after stopping treatment.

In small but clearly defined subgroups of chronic hepatitis B interferon therapy is unlikely to be effective because of one or another form of immunodeficiency (dialysis, HIV, transplants); in others interferon therapy is contra-indicated because of the risk for toxicity (advanced cirrhosis, auto-immune disease, history of depression). For these patients combination therapy of lamivudine and a second drug active against lamivudine-resistant HBV (adefovir, entecavir) might lead to strong virus-suppression in nearly all patients and prevention of emergence of drug resistant HBV mutant. The goal of therapy is persistence of the response (HBVDNA < 10e5 copies per ml and ALT normal) by maintenance treatment.

Table 1. Limitations of current monotherapies addressed by combination therapies

| Treatment | Antiviral activity | Immune activation |
|-----------|--------------------|-------------------|
| IFN | + | ++ |
| LAM | ++ | -- |
| LAM + IFN | +++ | +++ |
| LAM + ADV | +++ | -- |

CURRENT RESULTS OF COMBINATION THERAPIES

Lamivudine – interferon combinations

Selection of studies for review. We aimed at including all published large randomized trials (24 or more patients per arm) in compensated, immunocompetent chronic hepatitis B patients comparing combination of lamivudine and interferon with standard lamivudine therapy (≥ 100 mg daily for 52 weeks), standard IFN therapy (10 MU tiw or 5 MU daily for 16-26 weeks) or placebo. In addition to four selected studies (1-4) cohort studies including 24 or more patients receiving lamivudine-interferon combination therapy were assessed (5).

Pre-treatment patient characteristics, especially virus level and type, levels of aminotransferases and previous interferon therapy, have a major impact on the treatment outcome. Therefore, different trials should only be compared after correction for baseline values.

HBeAg-positive hepatitis

Three large randomized controlled trials in HBeAg-positive chronic hepatitis B have been carried out. In the first international study (1) 226 previously untreated patients were randomized to receive either combination therapy of lamivudine 100 mg daily and alpha-interferon 10 million units three times weekly for 16 weeks after pretreatment with lamivudine for 8 weeks (n=75), alpha-interferon 10 million units three times weekly for 16 weeks (n=69), or lamivudine 100 mg daily for 52 weeks (n=82). The primary efficacy endpoint was the HBeAg seroconversion rate at week 52 (loss of HBeAg, development of antibody to HBeAg and undetectable HBV DNA).

The HBeAg seroconversion rate at week 52 was 29 percent for combination therapy, 19 percent for interferon-, and 18 percent for lamivudine monotherapy (p=0.10, and p=0.12, respectively, for comparison of combination therapy with interferon- or lamivudine monotherapy, intention-to-treat analysis). The difference in the HBeAg seroconversion rate at week 52 between combination therapy and lamivudine monotherapy was statistically significant in the per-protocol analysis comprising 180 patients (36% vs 19%, respectively; p=0.02).

The authors concluded that the potential benefit of combining lamivudine with interferon should be investigated further in studies with different regimens of combination therapy.

In the second published study Italian investigators (2) compared 24 weeks of interferon combination therapy with 52 weeks of lamivudine monotherapy in 151 patients with HBeAg positive chronic hepatitis B; 20 patients were non-responders to a previous course of interferon therapy. The study was completed by 94-96 % of the patients, indicating an excellent tolerance of combination therapy. HBeAg seroconversion with undetectable levels of serum HBVDNA by hybridization testing was observed in 35% at the end of treatment for the combination therapy versus 19% for lamivudine monotherapy. Relapse of detectable HBeAg and HBVDNA was observed in 7% for combination therapy and 21% for lamivudine therapy. The sustained HBeAg seroconversion rate of 33% for combination therapy was - on an intention to treat basis- significantly different from 15% for lamivudine monotherapy.

Strong elements in the trial design are the longer duration of combination therapy (24 weeks), the assessment at the end of therapy (24 or 52 weeks) and at the end of follow-up (48 weeks later). The result from this trial further supports the concept of combining lamivudine and interferon for increasing the sustained response rate in HBeAg positive chronic hepatitis B. However, the trial also reports findings which contrast with earlier observations. With lamivudine therapy the ALT normalization rate of 27% and the histological improvement in Knodell score also of 27% were remarkably low in view of the results in other large studies. In addition, the overall sustained response rate was 33% and therefore not importantly different from published results for interferon alone. For treatment-naïve patients further randomized controlled trials including interferon monotherapy are required before the clinical value of combination of lamivudine and interferon can be assessed with confidence. One such a trial comparing 52 weeks of combination therapy with 52 weeks of (pegylated) interferon has included 300 patients; its results will be available in 2003.

The third large randomized controlled trial (3) was performed in 238 chronic HBeAg-positive hepatitis B patients who had not responded to a previous course of interferon therapy. The HBeAg seroconversion rate (loss of HBeAg, development of antibody to HBeAg and undetectable HBV DNA by hybridization) at 12 months after start of therapy was similar for placebo (13%, n=56), lamivudine (18%, n=119) and combination therapy for 16 weeks after pretreatment with lamivudine for 8 weeks (12%, n=63) without a statistical significant difference (3). Unfortunately the study results presented in abstract form in 1998 are not fully published. In view of the potential important but unproven preliminary conclusions: combination therapy is of no value for this patient category, the sponsor should release the individual patient data for further analysis by scientific groups.

AntiHBe-positive hepatitis

The fourth randomized controlled trial on lamivudine-interferon combination therapy (4) comprised 50 patients with antiHBe-positive chronic hepatitis B that were treated for 12 months with lamivudine 100 mg daily (n=26) or with lamivudine 100 mg daily + interferon 5 MU t.i.w. At baseline, all patients were positive for HBVDNA by molecular hybridization and had elevated serum ALT levels. Twenty-one patients had previously been treated with interferon. All patients normalized ALT and became HBVDNA-negative by hybridization during treatment. When assessed by a quantitative PCR, HBVDNA levels declined more by lamivudine-interferon combination therapy than by lamivudine monotherapy. The rate of undetectable viremia was 54 and 27% at 2 months, and 83 and 62% at 6 months in lamivudine-interferon and lamivudine monotherapy, respectively. The response was maintained until the end of therapy in patients on lamivudine-interferon combination therapy; in contrast, 5/26 (20%) of patients on lamivudine alone had a virological and biochemical breakthrough due to selection of YMDD mutant HBV. After discontinuation of therapy, most patients relapsed; the sustained response at 18 months was 17% for lamivudine-interferon combination and 19% for lamivudine alone.

So, the combination regimen appears to prevent or delay the emergence of YMDD mutant HBV, but a 12-months course does not increase the sustained response rate observed for monotherapy in a clinically significant way.

A prospective pilot study in 29 consecutive antiHBe/HBVDNA positive patients by another Italian group (5) confirmed that 12 months of combination of lamivudine with interferon 6 MU t.i.w. is highly effective in inducing and maintaining virological and biochemical remission (93%). No YMDD mutant HBV was detected during combination therapy. However, the sustained response at 24 months was only 14%. Patients that were naïve to antiviral treatment (n=11) had a similar incidence of relapse as patients that had previously been treated with interferon (n=18).

Nucleoside-analogue combinations

Selection of studies for review. In view of absence of published randomized trials we looked for large studies (24 or more patients per arm) in chronic hepatitis B patients assessing combination of lamivudine and another nucleoside-analogue, published or published in abstract and presented at a major Hepatology meeting. No large study comparing combination of two nucleoside-analogues with monotherapy was found. Studies reviewed below report on the effects of adefovir add-on to lamivudine in patients with chronic hepatitis B and acquired resistance to lamivudine (6-8).

Lamivudine-resistant hepatitis

Addition of adefovir to lamivudine has been evaluated in lamivudine-resistant chronic hepatitis B and either HIV / HBV co-infection, decompensated cirrhosis or recurrence of HBV after liver transplantation.

In the study in HIV/HBV co-infection (6) 35 patients on lamivudine therapy (150 mg twice daily) as part of their antiretroviral regimen and a rebound in both serum HBVDNA and aminotransferases due to a documented HBV mutation in the YMDD motif received adefovir 10 mg once daily for 48 weeks. The existing anti-HIV therapy was maintained. Suppression of HBV replication was observed in all patients. Mean HBVDNA in serum fell from 10^8 (log 8) to 10^5 at week 24 and 10^4 at week 48. HBeAg-seroconversion was observed in 2/33 patients (6%). Adverse effects were mild. Concentrations of serum ALT increased from week 8 until week 20, and then declined until week 48; the degree of variability in serum ALT between patients at each time point was high. Increases in serum creatinine of greater than 44 $\mu\text{mol/L}$ above baseline were seen in two patients; serum creatinine returned to baseline after adjustment of either adefovir or antiretroviral medication.

In the study in advanced cirrhosis due to chronic hepatitis B (7) 39 patients on lamivudine therapy (100 mg daily) and a virologic breakthrough due to confirmed YMDD mutant HBV received add-on adefovir 10 mg once daily. Preliminary results at 24 weeks showed a fall in mean HBVDNA from 10^8 (log 8) to 10^5 . All patients had a 2 log drop in serum HBVDNA and 30% a 4 log drop; in 15% of patients serum HBVDNA became negative by a widely used commercial PCR method. HBeAg-seroconversion was observed in 5/29 patients (16%). In many patients the suppression in HBVDNA was associated with improvements of biochemistry and clinical status. The Child-Pugh score decreased from 6 (range 5-10) to 5 (range 5-10); the mean change from baseline was 0,8 and this result was statistically significant ($p < 0.001$). In addition to ALT normalization in about 50% of patients, significant improvements were observed in serum bilirubin and albumin (table 2). Adverse effects were infrequent. No increase in serum creatinine of 0.5 mg/dL was seen; there was a fatal exacerbation of hepatitis B at week 16 and one patient had a variceal bleeding.

In the third study (8) 131 patients post orthotopic liver transplantation with chronic hepatitis B and clinical lamivudine resistance (HBsAg, HBVDNA $> 10^6$ (log 6) and elevated serum ALT) received adefovir 10 mg once daily added to the background therapy; the treatment period was indefinite. The dose of adefovir was adjusted to changes in creatinine clearance and immunosuppressant related nephrotoxicity. Results at 24 and 48 weeks on serum HBVDNA, hepatitis activity and liver function (Table 2) were very similar to those described in the two earlier studies and confirmed the efficacy of additional adefovir in immunosuppressed patients with lamivudine-resistant chronic hepatitis B.

Table 2. Adefovir add-on therapy associated improvement in biochemical outcome measures

| Liver function parameters | Percentage abnormal tests | |
|---------------------------|---------------------------|---------|
| | Baseline | Week 24 |
| Bilirubin | 38 | 18 |
| Albumin | 51 | 26 |
| Prothrombin time | 51 | 41 |
| Aminotransferase ALT | 95 | 49 |

The beneficial effects were also observed in patients with significant co-morbidity like renal impairment, hepatic decompensation, inadequate hematologic function, or HDV, HCV, HIV co-infection. Adverse effects were mainly nephrotoxicity as 10-20% of patients showed a rise in serum creatinine of more than 0.5 mg/dL. The clinical improvement observed in these three studies has made the addition of adefovir to lamivudine instantaneously the combination of choice for patients with serious liver disease and failure to respond to lamivudine.

PERSPECTIVES

Selection of studies for review. From the Pub-Med file with key words Lamivudine, Interferon and Hepatitis pilot studies which pointed to potential novel developments were selected for assessment; to identify potential clinically important developments in nucleoside combination therapy we looked for pilot studies published in abstract and presented at a major Hepatology meeting.

Sequential lamivudine-interferon combination

In a French pilot study (9) in 14 HBVDNA-positive patients without a sustained response to interferon alone lamivudine monotherapy 100 mg once daily for 20 weeks was combined with interferon 5 MU t.i.w. for 4 weeks, and followed by interferon monotherapy for 24 weeks. Sustained serum HBVDNA clearance 6 months after the end of sequential treatment was observed in 8 of 14 patients (56%), HBeAg-to-antiHBe seroconversion in 5 of 11 patients (45%), and HBsAg-to antiHBs seroconversion in 3 of 14 patients (21%).

Since a similar Dutch study in 24 patients (vanNunen, unpublished observations) led to a sustained HBeAg response in only 2 of 20 patients that completed therapy (10%), further evaluation in clinical trials of adequate size should be undertaken.

Lamivudine plus intradermal vaccine with or without interleukin-2

To evaluate therapeutic immunostimulation 14 chronic hepatitis B patients with HBVDNA detectable by a hybridization method received daily lamivudine in combination with six monthly intradermal vaccinations with HBsAg; five patients received in addition interleukin-2 daily for 3 months (10). After therapy was stopped, seven of 9 lamivudine/vaccine recipients and two of 5 lamivudine/vaccine/il-2 recipients did not have detectable HBVDNA. Four patients (28%) cleared the virus and had normalized ALT levels during follow-up. Compared to 11 control patients receiving lamivudine alone patients receiving immunostimulation had a significant rise in HBcAg specific proliferative T helper cell response; however, the hepatitis B specific T helper cell induction failed to induce a sustained B cell response as detected by ELISPOT.

Combination of nucleoside-analogue with vaccine should be evaluated for the customary outcome measures at the end of treatment and end of 6-12 months of follow-up in controlled trials.

Lamivudine-Adefovir combination versus Adefovir alone

A randomized trial is ongoing comparing adefovir 10 mg daily, adefovir 10 mg daily + lamivudine 100 mg daily, and lamivudine 100 mg daily in patients with lamivudine-resistant chronic hepatitis B. In a preliminary report (11) on results at 16 weeks adefovir containing regimens show significant reductions in serum HBVDNA and serum ALT in contrast to no change in the lamivudine alone group. There appears also no difference in these outcome measures between adefovir alone and lamivudine-adevovir. This study points clearly to the need of further assessment of nucleoside-analogue combination therapy vs monotherapy in chronic hepatitis B.

SUMMARY AND RECOMMENDATIONS

The combination of lamivudine and interferon has now been proven to be significantly more effective than either treatment alone in naïve, HBeAg-positive, immunocompetent patients with compensated chronic hepatitis B. Combination therapy leads to a higher percentage of viral, biochemical and histological remission and to a lower percentage of lamivudine-resistance on treatment. Available evidence suggests

that the effects of combination therapy on virological, biochemical and histological outcomes on treatment are similar in other subgroups of chronic hepatitis B like antiHBe-positive chronic hepatitis B and in those not having responded to a previous course of antiviral therapy. However, the goal of combining a virus-suppressant with an activator of host immunity is to increase the rate of sustained remission significantly; at present there is insufficient evidence that this key goal has been reached. Therefore the combination of lamivudine with interferon cannot be recommended outside of clinical trials.

For both HBeAg-positive and antiHBe-positive chronic hepatitis B the results of ongoing large trials assessing combination therapy of lamivudine with pegylated interferon for 6-12 months will be forthcoming in 2003.

Further assessment of combination therapy of nucleoside-analogues with pegylated interferon is recommended. Drug regimens should aim for induction of HBVDNA negativity by PCR in serum by week 26 and continuation of combination therapy for another 6 months. Discovery of a drug that significantly reduces the relapse rate would bring about the long-awaited improvement in sustained response rates in immunocompetent patients with compensated chronic hepatitis B.

For lamivudine-resistant chronic hepatitis B addition of adefovir to lamivudine is effective in suppressing viral replication and in reducing hepatitis activity, both in immunodeficient and decompensated chronic hepatitis B. That the goal of therapy: persistence of the response (HBVDNA < 10e5 copies per ml and ALT normal) can be maintained long-term appears likely, since resistance to lamivudine-adefovur combination has a very low incidence according to current studies.

However, there is no proof that combination of lamivudine and adefovir is superior to adefovir alone. So, addition of adefovir to lamivudine is recommended for immunodeficient or decompensated chronic hepatitis B; for others, combination of two nucleoside-analogues cannot be recommended outside of clinical trials

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