Lamivudine and alpha interferon combination treatment of patients with chronic hepatitis B infection: a randomised trial

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Abstract

Background, aim, and methods—Alpha interferon is the generally approved therapy for HBe antigen positive patients with chronic hepatitis B, but its efficacy is limited. Lamivudine is a new oral nucleoside analogue which potently inhibits hepatitis B virus (HBV) DNA replication. To investigate the possibility of an additive effect of interferon-lamivudine combination therapy compared with interferon or lamivudine monotherapy, we conducted a randomised controlled trial in 230 predominantly Caucasian patients with hepatitis B e antigen (HBeAg) and HBV DNA positive chronic hepatitis B. Previously untreated patients were randomised to receive: combination therapy of lamivudine and interferon, lamivudine monotherapy, interferon monotherapy, or placebo. The primary efficacy end point was the HBeAg seroconversion rate at week 52 (loss of HBeAg, development of antibodies to HBeAg and undetectable HBV DNA).

Results—The HBeAg seroconversion rate at week 52 was 29% for the combination therapy, 19% for interferon monotherapy, and 15% for lamivudine monotherapy (p=0.12 and p=0.10, respectively, for comparison of the combination therapy with interferon or lamivudine monotherapy). The HBeAg seroconversion rates at week 52 for the combination therapy and lamivudine monotherapy were significantly different in the per protocol analysis (36% (20/56) v 19% (13/70), respectively; p=0.02). The effect of combining lamivudine and interferon appeared to be most useful in patients with moderately elevated alanine aminotransferase levels at baseline. Adverse events with the combination therapy were similar to interferon monotherapy; patients receiving lamivudine monotherapy had significantly fewer adverse events.

Conclusions—HBeAg seroconversion rates at one year were similar for lamivudine monotherapy (52 weeks) and standard alpha interferon therapy (16 weeks). The combination of lamivudine and interferon appeared to increase the HBeAg seroconversion rate, particularly in patients with moderately elevated baseline aminotransferase levels. The potential benefit of combining lamivudine and interferon should be investigated further in studies with different regimens of combination therapy.

Keywords: chronic hepatitis B; hepatitis B virus; nucleoside analogue; lamivudine; alpha interferon; combination therapy; HBeAg seroconversion

Until recently, the only generally approved treatment for chronic hepatitis B was alpha interferon, which is a natural antiviral agent but acts primarily by immunomodulation. The efficacy of interferon is variable, with rates of hepatitis B e antigen (HBeAg) loss ranging from 15 to 37%. Virological response rates are higher in patients with elevated serum aminotransferases which presumably reflects the immune activity to the virus. Interferon treatment is associated with considerable but tolerable side effects in approximately 90% of patients.

Lamivudine is an oral nucleoside analogue that inhibits hepatitis B virus (HBV) DNA synthesis by chain termination. Previous clinical trials have shown that lamivudine treatment rapidly suppresses HBV replication, enhances aminotransferase normalisation, improves histological outcome, and has an excellent safety profile. HBeAg seroconversion, the surrogate marker with predictive value for improved survival, was observed in 16% of Asian patients after one year of lamivudine therapy.

Since the two drugs have different mechanisms of action, we conducted a study to determine if combination treatment with both lamivudine and interferon had an additive effect against HBV and would lead to higher HBeAg seroconversion rates than either monotherapy.

Materials and methods

Patients

Eligible patients included males and females, 16–70 years of age, with detectable hepatitis B surface antigen (HBsAg) and HBeAg in serum at the time of screening and for at least six and three months, respectively, before study entry; serum HBV DNA levels of at least 5 pg/ml at baseline.

Abbreviations used in this paper: HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; ALT, alanine aminotransferase; ULN, upper limit of normal.
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approved by the ethics committees at partici-
gave written informed consent. The study was
and its subsequent amendments. All patients
the guidelines of the Declaration of Helsinki
specified for interferon.

medical history or by raised alanine
prothrombin time prolonged more than three
evidence of liver disease of other aetiology
toxic, immune); or any contraindications

II studies
treatment arms. However, emerging results from phase

†An initial eight week pretreatment period with
lamivudine was included in the combination arm
treatment and thereafter every 4–8 weeks.
Serum was analysed for HBV DNA, HBeAg,
and anti-HBe at various times between base-
line and the end of study, with key points at
weeks 24, 52, and 64. Serum was analysed for
the presence of YMDD variant HBV at week
52 and week 64. Biochemistry and haematol-
ogy laboratory evaluations and adverse events
were assessed at each clinic visit. Patients were
requested to have had a liver biopsy within 12
months of the study baseline, and at week 52.

STUDY DESIGN
Patients eligible at screening returned for a
baseline assessment within four weeks. At
baseline (day 1), patients were randomised to
receive one of the following three treatment
regimens: (i) combination treatment: eight
weeks of oral lamivudine 100 mg once daily
followed by 16 weeks of lamivudine 100 mg
once daily and alpha interferon (Intron A,
Schering Plough, Kenilworth, USA) 10 million
units three times weekly subcutaneously†; (ii)
interferon monotherapy: eight weeks of oral
placebo once daily followed by 16 weeks of
placebo once daily and interferon 10 million
units three times weekly; and (iii) lamivudine
monotherapy: lamivudine 100 mg once daily
for 52 weeks‡. Treatment was allocated in
blocks of six per investigational centre (ratio of
random assignment to the three treatment
regimens: 2:2:2); the randomisation code was
computer generated.

All treatment arms were blinded up to week
8. At week 8, investigators opened sealed enve-
lopes corresponding to patients’ treatment
numbers which contained instructions on
whether or not to dispense interferon. On
opening the envelopes, the lamivudine mono-
therapy arm effectively became unblinded
although the interferon and combination arms
remained blinded. Results of HBV serology
were kept blinded during treatment and follow
up. Patients were followed up after treatment
cessation to week 64 (end of the study): 12
weeks of follow up for lamivudine patients and
40 weeks of follow up for patients who received
interferon or the combination treatment.

The primary outcome measure was HBeAg
seroconversion at week 52 (loss of HBeAg,
development of antibodies to HBeAg (anti-
HBe), and undetectable HBV DNA). Second-
ary efficacy variables included histological
response (reduction in Knodell score by at least
2 points in the biopsy at week 52), HBV DNA
loss, and ALT normalisation at week 52.

MONITORING
Patients returned for assessments every four
weeks after the baseline visit until the end of the
treatment and thereafter every 4–8 weeks.
Serum was analysed for HBV DNA, HBeAg,
and anti-HBe at various times between base-
line and the end of study, with key points at
weeks 24, 52, and 64. Serum was analysed for
the presence of YMDD variant HBV at week
52 and week 64. Biochemistry and haematol-
ogy laboratory evaluations and adverse events
were assessed at each clinic visit. Patients were
requested to have had a liver biopsy within 12
months of the study baseline, and at week 52.

LABORATORY METHODOLOGY
Viral markers were assayed at a single reference
laboratory (Covance, Harrogate, UK). Serum
HBV DNA was quantified by a solution-
hybridisation assay (Abbott, Chicago, USA)
with a lower limit of quantitation of 3.0 pg/ml
of serum (approximately 8×10^6 copies of HBV
DNA, Eurohep standard). HBeAg, anti-HBe,
and HBsAg were assessed by qualitative micro-
particle enzyme immunoassay (Abbott). The
incidence of YMDD variant HBV DNA was
assessed by a restriction fragment length poly-
merase chain reaction assay, as described by Lai
and colleagues. The assay performed at Glaxo
Wellcome, Triangle Park, USA, had a lower
limit of detection of approximately 500 copies
of HBV DNA/ml of serum.

Liver biopsy specimens were randomly
assigned a predetermined computer generated
code at Glaxo Wellcome and sent for histologi-
cal assessment to a single independent his-
topathologist who was blinded with respect to
patient identity, treatment assignment, date,
and sequence of biopsy specimen. The biopsy
specimens were scored according to the
Knodell histological activity index.

STATISTICAL ANALYSES
Based on an estimated rate of HBeAg serocon-
version at 52 weeks of 40% for interferon and
lamivudine monotherapy and 65% for the
combination therapy, a sample size of 210
patients was calculated to provide 80% power
to detect a significant difference in HBeAg
seroconversion rates between the combination
treatment and interferon, and the combination
and lamivudine monotherapy. The study was
not powered to establish whether the HBeAg seroconversion rates were equivalent between lamivudine and interferon monotherapies.

The primary population for the efficacy analyses was the intent to treat population (ITT). The ITT population was defined as patients with confirmed chronic hepatitis B (i.e. patients who were HBsAg positive for at least six months at screening and had evidence of ALT elevation (>ULN) and/or histological evidence of inflammation by a Knodell HAI score $\geq 2$ points) who were randomised to treatment.

A secondary analysis, for the primary end point only, was performed on a subpopulation of the ITT population referred to as the per protocol population. This population was redefined retrospectively due to the unexpected variability in hepatitis B virus markers between screening and baseline. The criteria for patient inclusion in the per protocol population were positivity for HBeAg and HBV DNA at baseline, use of trial medication according to the randomisation and protocol, and non-use of prohibited medications.

Safety data were analysed by treatment received for all patients who were given at least one dose of study medication (“as treated population”).

Missing data for HBeAg, anti-HBe, and HBsAg parameters were assigned values based on the method of last observation carried forward. In the analysis of HBeAg seroconversion, a patient was considered to have seroconverted if it occurred prior to withdrawal or a missing HBV DNA value. In the analysis of ALT and HBV DNA, missing data were considered as failures (HBV DNA detectable or ALT above the normal reference range).

The Cochran-Mantel-Haenzsel test adjusted for centre, or Fisher’s exact test was used to compare differences in proportions between treatment groups. A supplementary analysis of HBeAg seroconversion at week 52 for the ITT population was performed using generalised estimating equation analysis to address the issue of small centres; the results were similar to those using Cochran-Mantel-Haenzsel. All $p$ values are two sided.

**Results**

**STUDY POPULATION**

Fifty one centres from 15 countries participated in recruitment between July 1994 and June 1996. A total of 310 patients were screened, of which 230 patients were randomised to treatment. Patients who failed the screening were mainly those who did not demonstrate persistent HBV DNA positivity or those with ALT values $<1.3\times$ULN.

Of the 230 patients randomised to treatment, 226 fulfilled the entry criteria of HBsAg positivity for longer than six months and evidence of disease activity at screening (ITT population). The numbers of patients in the ITT population randomised to the combination treatment, interferon monotherapy and lamivudine monotherapy were 75, 69, and 82, respectively (fig 1). The per protocol population comprised 180 patients: 15 patients had HBV serological ineligibility at baseline, 28 patients were non-compliant with the study medication, one patient received prohibited medications and eight patients were incorrectly dispensed medication (some patients appeared in more than one violation category).

All treatment arms were well matched with regard to baseline characteristics (table 1).

**PRIMARY EFFICACY MEASURE (FIG 2)**

**HBeAg seroconversion**

At week 52, the rate of HBeAg seroconversion was $29\%$ (20/68) for the combination group, $19\%$ (12/64) for interferon, and $18\%$ (14/80) for lamivudine monotherapy (combination group $v$ interferon: odds ratio 1.9 (confidence interval (95\% CI) 0.8–4.4), $p=0.12$; combination

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**Figure 1** Progress of patients through the various stages of the trial.
groups of lamivudine: odds ratio 2.0 (95% CI 0.9–4.7), p=0.10, ITT analysis). Of the 14 lamivudine-treated patients who had seroconverted by week 52, 81% (9/11 of those followed up) were maintained on therapy through to week 64 (fig 2).

In the per protocol population analysis, the HBeAg seroconversion rate at week 52 was 36% (20/56) in the lamivudine-interferon combination group, 22% (12/54) in the interferon group and 19% (13/70) in the lamivudine group. The HBeAg seroconversion rate in the combination group was significantly higher than that for lamivudine monotherapy (odds ratio 3.3 (95% CI 1.2–8.8), p=0.02) but failed to reach significance compared with interferon monotherapy (odds ratio 2.3 (95% CI 0.9–5.5), p=0.07).

In a subgroup analysis, the HBeAg seroconversion rate was determined for three categories of baseline ALT. The HBeAg seroconversion rate in the total study population was different for the three categories, with the lowest rate for patients with serum ALT <2×ULN (11%, 9/82) and the highest rate for patients with serum ALT levels ≥5×ULN (38%, 13/34). The combination therapy appeared to increase the HBeAg seroconversion rate predominantly in those with baseline serum ALT >2× and <5×ULN (fig 2).

SECONDARY EFFICACY MEASURES

Histological findings

Paired liver biopsy slides, at pretreatment and at week 52, were available for 77% (174/226) of patients. The histological response (reduction in HAI score by >2 points) was 37% (21/57) for patients receiving the combination treatment, 46% ((25/54) for interferon, and 49% (31/63) for lamivudine. Evidence of histological progression (worsening) of liver disease (increase in HAI score by ≥2 points) was 30% (17/57) for the combination group, 31% (17/64) for interferon, and 11% (7/63) for lamivudine. No differences between the combination therapy and interferon monotherapy were observed.

ALT normalisation and loss of HBV DNA

Data for ALT normalisation and loss of HBV DNA are given in table 2. Data are presented as point prevalence at weeks 24, 52, and 64.

Table 1 Patient characteristics at entry to the study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lam/interferon (n=75)</th>
<th>Interferon (n=69)</th>
<th>Lamivudine (n=82)</th>
<th>Total (n=226)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (median (range))</td>
<td>31 (15–60)</td>
<td>32 (16–70)</td>
<td>30 (16–69)</td>
<td>31 (15–70)</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>71 (%)</td>
<td>81 (%)</td>
<td>71 (%)</td>
<td>74 (%)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72.0 (42–115)</td>
<td>71.0 (45–115)</td>
<td>68.5 (45–118)</td>
<td>70.4 (42–118)</td>
</tr>
<tr>
<td>Ethnicity (%)</td>
<td>Caucasian</td>
<td>Asian-Oriental</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT (&lt;ULN) (median (range))</td>
<td>2.2 (0.8–26.1)</td>
<td>2.4 (0.8–10.1)</td>
<td>2.6 (0.8–12.9)</td>
<td>2.4 (0.8–26.1)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>3.2 (3.4)</td>
<td>3.1 (2.1)</td>
<td>3.3 (2.8)</td>
<td>3.2 (2.8)</td>
</tr>
<tr>
<td>HBV DNA (pg/ml)</td>
<td>94.0 (1.5–786)</td>
<td>109.0 (1.5–1322)</td>
<td>136.0 (1.5–2264)</td>
<td>113.5 (1.5–2264)</td>
</tr>
<tr>
<td>Mean log10 (SD)</td>
<td>1.74 (0.75)</td>
<td>1.78 (0.77)</td>
<td>2.04 (0.66)</td>
<td>1.86 (0.73)</td>
</tr>
<tr>
<td>&lt;3 pg/ml (%)</td>
<td>4 (5)</td>
<td>3 (4)</td>
<td>4 (5)</td>
<td>11 (5)</td>
</tr>
<tr>
<td>Positive for HBsAg (%)</td>
<td>72 (96)</td>
<td>68 (99)</td>
<td>81 (99)</td>
<td>221 (98)</td>
</tr>
<tr>
<td>Positive for HBV DNA and HbeAg (%)</td>
<td>68 (91)</td>
<td>64 (93)</td>
<td>80 (98)</td>
<td>212 (94)</td>
</tr>
<tr>
<td>Knodell HAI score</td>
<td>4 (0–14)</td>
<td>4 (0–13)</td>
<td>4 (0–12)</td>
<td>4 (0–14)</td>
</tr>
<tr>
<td>&lt;2</td>
<td>8 (11)</td>
<td>6 (9)</td>
<td>11 (5)</td>
<td>18 (8)</td>
</tr>
<tr>
<td>Evidence of cirrhosis (%)</td>
<td>3 (4)</td>
<td>8 (12)</td>
<td>5 (6)</td>
<td>16 (7)</td>
</tr>
</tbody>
</table>

Evidence of cirrhosis is indicated by a score of 4 on the fibrosis component of Knodell histological activity index score. HBV DNA values below 3 pg/ml (lower limit of detection) have been set to 1.5 pg/ml in the calculation of summary statistics.

Figure 2 Percentage HBeAg seroconversion for the three treatment arms (lamivudine-interferon, interferon, and lamivudine) by various times (left) and by baseline ALT levels at week 52 (right). The number of patients in each category is given above the bar.
HBeAg loss is defined as undetectable (ASV values below the cut off) in any treatment group.

### Table 2 Secondary efficacy measures: point prevalence in percentages (intention to treat population eligible for response at baseline)

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Time (week)</th>
<th>Lam/interferon (n=68)</th>
<th>Interferon (n=64)</th>
<th>Lamivudine (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg loss</td>
<td>24</td>
<td>19 (62)</td>
<td>11 (57)</td>
<td>14 (70)</td>
</tr>
<tr>
<td></td>
<td>52</td>
<td>35 (55)</td>
<td>23 (56)</td>
<td>23 (60)</td>
</tr>
<tr>
<td></td>
<td>64</td>
<td>33 (55)</td>
<td>29 (48)</td>
<td>21 (62)</td>
</tr>
<tr>
<td>HBV DNA loss</td>
<td>24</td>
<td>84 (62)</td>
<td>30 (57)</td>
<td>64 (70)</td>
</tr>
<tr>
<td></td>
<td>52</td>
<td>36 (55)</td>
<td>29 (55)</td>
<td>60 (60)</td>
</tr>
<tr>
<td></td>
<td>64</td>
<td>31 (55)</td>
<td>29 (49)</td>
<td>32 (63)</td>
</tr>
<tr>
<td>ALT normalisation</td>
<td>24</td>
<td>34 (62)</td>
<td>21 (58)</td>
<td>51 (72)</td>
</tr>
<tr>
<td></td>
<td>52</td>
<td>38 (55)</td>
<td>29 (55)</td>
<td>57 (78)</td>
</tr>
<tr>
<td></td>
<td>64</td>
<td>36 (50)</td>
<td>32 (50)</td>
<td>21 (63)</td>
</tr>
</tbody>
</table>

HBeAg loss is defined as undetectable (ASV=YM, Abbott); HBV DNA loss is defined as HBV DNA values below the cut off (3 pg/ml, Abbott HBV DNA test); ALT normalisation is defined as ≤1.0×ULN. Number of patients is indicated in parentheses.

### Table 3 Most common adverse events during treatment (number of patients)

<table>
<thead>
<tr>
<th></th>
<th>Lam/interferon (n=76)</th>
<th>Interferon (n=70)</th>
<th>Lamivudine (n=84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral respiratory infections</td>
<td>32 (4.3×ULN)</td>
<td>37 (5.1×ULN)</td>
<td>25 (4.3×ULN)</td>
</tr>
<tr>
<td>Headache</td>
<td>71* (9.3×ULN)</td>
<td>47 (6.7×ULN)</td>
<td>27† (6.4×ULN)</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>36 (4.7×ULN)</td>
<td>40 (5.7×ULN)</td>
<td>11† (2.6×ULN)</td>
</tr>
<tr>
<td>Abdominal discomfort and pain</td>
<td>11 (1.4×ULN)</td>
<td>23 (3.3×ULN)</td>
<td>13 (1.6×ULN)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>14 (1.9×ULN)</td>
<td>16 (2.3×ULN)</td>
<td>13 (1.9×ULN)</td>
</tr>
<tr>
<td>Malaise and fatigue</td>
<td>66 (8.7×ULN)</td>
<td>70 (9.9×ULN)</td>
<td>35† (8.4×ULN)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>9 (1.2×ULN)</td>
<td>23 (3.3×ULN)</td>
<td>4† (0.5×ULN)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>30 (4.0×ULN)</td>
<td>33 (4.7×ULN)</td>
<td>4† (0.5×ULN)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9 (1.2×ULN)</td>
<td>10 (1.4×ULN)</td>
<td>8† (1.0×ULN)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>33 (4.4×ULN)</td>
<td>34 (4.9×ULN)</td>
<td>19 (2.3×ULN)</td>
</tr>
<tr>
<td>Fever/chills</td>
<td>46 (6.1×ULN)</td>
<td>45 (6.4×ULN)</td>
<td>6† (0.7×ULN)</td>
</tr>
<tr>
<td>Hair loss and alopecia</td>
<td>30 (4.0×ULN)</td>
<td>21 (2.9×ULN)</td>
<td>8† (1.0×ULN)</td>
</tr>
</tbody>
</table>

Most common adverse events defined as those occurring during treatment in ≥15% of patients in any treatment group.

* p value: lam/interferon v interferon: 0.004 (borderline significant in view of multiple testing); † p value lam/interferon v lamivudine: <0.002 (significant after correction for multiple testing).

#### Incidence of YMDD variant HBV

The incidence of YMDD variant HBV was evaluated in all patients where serum samples were available at weeks 52 or 64, or both. YMDD variant HBV variants were not detected in any serum sample from interferon or combination treated patients.

At week 52, 21% (13/61) of patients who were treated with lamivudine were HBV DNA PCR negative, 31% (19/61) had a YMDD variant HBV, and 48% (29/61) had wild type HBV. At week 64, 21% (12/57) had YMDD variant HBV, indicating the re-emergence of the wild type virus after stopping lamivudine treatment.

### SAFETY

The percentage of patients completing treatment was 92 (70/76) for the combination treatment, 91 (64/70) for interferon at 24 weeks and 83 (70/84) for lamivudine at 52 weeks. Withdrawals by week 52 are summarised in fig 1. Five patients withdrew before completing treatment because of adverse events; the reason for withdrawal in the lamivudine group was asymptomatic raised serum transaminases two weeks after the start of therapy (one patient) and asymptomatic elevated CPK levels (two patients); in the combination group, one patient withdrew because of fever, chills, and insomnia, and another patient because of fatigue, headache, and mental disturbance. There were no withdrawals caused by adverse events in patients treated with interferon only.

Other reasons for discontinuation included pregnancy, emigration, non-compliance or the patient’s request to withdraw for non-specific reasons.

The most common adverse events are summarised in table 3. There was a high incidence of headache in the combination group (71%, 54/76) but other adverse events were similar in the combination and interferon groups. The incidence of adverse events for the interferon regimens was much higher than that observed for lamivudine therapy, despite the longer treatment duration; the difference was significant (p<0.002) for headache, muscle pain, anorexia, malaise and fatigue, fever/chills, and hair loss.

In approximately 20% of patients in the interferon and combination groups, the interferon dose was adjusted during the study.

Hepatitis flares (ALT levels ≥500 IU/l and >2-baseline) were observed during and after treatment. During treatment, flares occurred in 12% (10/82) of patients who received lamivudine, in 11% (8/70) of interferon recipients, and in 0% (0/75) of those given the combination therapy.

Post-treatment, the incidence of hepatitis flares was 13% (10/78) in the lamivudine group, 9% (6/68) in the interferon group, and 7% (5/74) in the combination group. Three of the hepatitis flares (two lamivudine, one interferon) were associated with elevation of serum bilirubin (>2×ULN); all events resolved spontaneously.

#### Discussion

In this study of HBeAg positive chronic hepatitis B patients of predominantly Caucasian origin, HBeAg seroconversion rates were similar after 52 weeks of lamivudine monotherapy (18%) and 16 weeks of interferon therapy (19%). However, a combination of 24 weeks of lamivudine and 16 weeks of interferon produced a higher HBeAg seroconversion rate (29%).

The rate of HBeAg seroconversion of 19% for the interferon monotherapy group appears low compared with the generally quoted rate of 33% for loss of HBeAg. The low rate of HBeAg seroconversion in our study partly reflects the use of the most stringent definition of response (HBeAg seroconversion v loss of HBeAg). Also, our study population had lower mean baseline ALT values (3.2×ULN) compared with patients studied by Perillo and colleagues (4.3×ULN) and a HBeAg loss rate of 37%. The rate of HBeAg loss for interferon in this study was 23% compared with 29% in a recently published European study; in patients with a low mean baseline ALT, loss of HBeAg even fell to 15%. These data reinforce the conclusion of a European meta-analysis based on individual patient data that the effect of alpha interferon is relative to baseline ALT levels and that the absolute benefit seems greatest in patients with high serum ALT levels.

The HBeAg seroconversion rate after 52 weeks of lamivudine monotherapy (18%) observed in our trial was similar to the HBeAg seroconversion rate of 16% reported by Lai.
and colleagues\textsuperscript{12} after one year of lamivudine treatment in Asian patients.

Clearance of HBeAg after interferon treatment is reported to be sustained in approximately 90% of patients and associated with an improved clinical outcome in long term follow up studies.\textsuperscript{14} All lamivudine treated patients who HBeAg seroconverted are currently being followed up long term; HBeAg seroconversion is reported to be approximately 90% at six months post-treatment.\textsuperscript{14} Thus our data suggest that lamivudine for 52 weeks has the potential to induce prolonged HBeAg seroconversion in patients with chronic hepatitis B at a similar rate to that of a 16 week course of interferon treatment.

The combination of lamivudine with interferon appeared to be associated with a higher HBeAg seroconversion rate compared with either form of monotherapy. In this study, the efficacy of the combination therapy was most pronounced in patients with moderately elevated baseline ALT (2–5×ULN). In patients with high ALT levels (>5×ULN), no additional effect of combining interferon and lamivudine on the HBeAg seroconversion rate was observed. Seroconversion based on baseline ALT categories (<2×ULN, 2–5×ULN, >5×ULN) in the present study are consistent with the results of Liaw (data on file at Glaxo Wellcome) in Asian patients and underlines the importance of this baseline feature for the prediction of HBeAg seroconversion. These exploratory findings require confirmation in a prospective study.

Patients who received lamivudine monotherapy derived histological benefit, irrespective of their HBeAg seroconversion status,\textsuperscript{12} whereas the histological response after interferon treatment is usually observed only in patients who have demonstrated a serological response.\textsuperscript{19} Results from this study agree with a previous report\textsuperscript{12} indicating improvement in histological inflammation in patients after one year's lamivudine treatment.

The incidence of YMDD variant HBV DNA after one year of lamivudine therapy was 31% in this study; this is higher than that previously reported in Asian patients (14%)\textsuperscript{15} but similar to that in a recent series of Caucasian patients.\textsuperscript{20} The reason for this discrepancy is uncertain but is probably related to differences in study populations. When lamivudine treatment was stopped at week 52 in patients with YMDD variant HBV, there was re-emergence of YMDD variant HBV DNA in Asian patients receiving lamivudine or placebo.\textsuperscript{12}

In conclusion, HBeAg seroconversion rates at one year were similar for lamivudine monotherapy and a standard course of interferon. Combination therapy may be more effective than either monotherapy. Studies with other regimens regarding duration of lamivudine and interferon therapy are needed to identify subgroups of patients in whom combination therapy may be the best treatment option.

Solko Schalm advised on the original protocol design, was a centre coordinator, performed data collection, and advised on statistical analysis, and prepared the manuscript. Jenny Heathcote, Geoffrey Farrell, Janusz Cianciara, Morris Sherman, and Bernard Willems were centre coordinators, performed data collection, and advised on the manuscript. Amar Dhillion was the central study histopathologist. Judy Barber was the statistician and analysed the study data. Alison Moorse was the overall study coordinator, advised on data analysis, and contributed to the writing of the manuscript. Fraser Grey advised on data analysis and manuscript preparation.

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