ORIGINAL ARTICLE

Randomised study comparing 48 and 96 weeks peginterferon α-2a therapy in genotype D HBeAg-negative chronic hepatitis B

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ABSTRACT

Objective Treatment with peginterferon α-2a (PegIFN) for 48 weeks is the standard of care for selected HBeAg-negative patients chronically infected with hepatitis B virus (HBV), but with limited treatment efficacy. A study was undertaken to investigate whether treatment extension to 96 weeks improves the outcome in this patient population.

Methods 128 HBeAg-negative patients (120 genotype D) were randomised to weekly 180 μg PegIFN for 48 weeks (group A, n=51), 180 μg PegIFN for 48 weeks followed by 135 μg weekly for an additional 48 weeks (group B, n=52) or 180 μg PegIFN plus lamivudine (100 mg/day) for 48 weeks then 135 μg PegIFN for 48 weeks (group C, n=25). Endpoints were alanine aminotransferase normalisation plus HBV DNA <3400 IU/ml (primary), HBV DNA <2000 IU/ml and HBsAg clearance at 48 weeks after treatment.

Results Forty-eight weeks after treatment, six patients in group A and 13 in group B achieved alanine aminotransferase normalisation plus HBV DNA <3400 IU/ml (11.8% vs 25.0%, p=0.08), 6 vs 15 patients had HBV DNA <2000 IU/ml (11.8% vs 28.8%, p=0.03), 0 vs 3 achieved HBsAg clearance (0% vs 5.8%, p=0.24) and 0 vs 5 had HBsAg <10 IU/ml (0% vs 9.6%, p=0.06). While extended PegIFN treatment was the strongest independent predictor of response, the combination with lamivudine did not improve responses. Discontinuation rates were similar among the groups (19.6%, 23.1%, 32.0%, p=0.81) and were mostly due to PegIFN-related adverse events.

Conclusions In HBeAg-negative genotype D patients with chronic hepatitis B, PegIFN treatment for 96 weeks was well tolerated and the post-treatment virological response improved significantly compared with 48 weeks of treatment.

Trial registration number http://ClinicalTrials.gov registration number: NCT01095835.

Significance of this study

What is already known on this subject?

- HBeAg-negative chronic hepatitis B carries a significant risk of progression to cirrhosis, liver cancer and anticipated liver-related death. Long-term nucleos(t)ide therapy and, in selected patients, 48-week administration of pegylated-interferon (PegIFN) may attenuate progression of hepatitis B.
- Compared with nucleos(t)ide therapy, PegIFN α-2a causes higher rates of sustained virological response accompanied by HBsAg seroclearance in a subset of patients.
- HBeAg-negative patients with genotype D infection are more resistant to PegIFN than other genotypes due to the higher rates of hepatitis relapse in the first year of post-treatment follow-up. They have experienced higher rates of sustained responses to standard interferon administered for >48 weeks which reduced the rates of post-treatment hepatitis relapse.

What are the new findings?

- PegIFN 180 μg weekly for 48 weeks followed by 135 μg for an additional 48 weeks caused more virological responses (HBV DNA <2000 IU/ml: 28.8% vs 11.8%, p=0.03) and higher post-treatment rates of HBsAg <10 IU/ml (9.6% vs 0%, p=0.06) than weekly PegIFN 180 μg given for 48 weeks.
- Extended PegIFN treatment was well tolerated and discontinuation rates were similar to those with the 48-week standard of care.

How might it impact on clinical practice in the foreseeable future?

- HBeAg-negative genotype D patients with chronic hepatitis B may benefit in the long term from 96 weeks of PegIFN therapy.

INTRODUCTION

The hepatitis B virus (HBV) is a leading cause of morbidity and anticipated liver-related death, with approximately 400 million persons being chronically infected worldwide.[1–3] The lethal consequences of HBV are more common in patients with HBeAg-negative hepatitis, which represents the late phase of HBV infection, predominates in the Mediterranean basin and is expected to become

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the dominant HBV disease pattern worldwide in future years.[2–4] Since persistent suppression of the virus is the only therapeutic option available to stop progression of this infection towards end-stage liver disease and its lethal consequences,[2 3] direct antiviral agents like nucleos(t)ide analogues that act by causing permanent inhibition of HBV replication have gained popularity as a user-friendly, safe and effective treatment modality of HBV infection; however, they require life-long administration.[5–7] A limited course of interferon (IFN) may be a more interesting therapeutic option in selected HBeAg-negative patients since it may cause off-therapy HBsAg clearance and seroconversion which represent a proxy to a clinical cure of hepatitis B.[8]

Among HBeAg-negative patients, those infected with genotype D HBV are common in our regions and are more difficult to treat successfully with IFN than patients with other genotype-related hepatitis B, as demonstrated by the higher rates of hepatitis relapse in the year after treatment compared with genotype A or B infections.[9–11] An early study which demonstrated improved rates of durable responses in HBeAg-negative patients with genotype D following 24 months of treatment with standard IFN as a consequence of reduced rates of post-treatment hepatitis relapse[12 13] opened the way to a recent pilot study with peginterferon α-2a (PegIFN) administered for 60 weeks.[14] This study resulted in higher rates of sustained response compared with historical controls receiving the standard 48 weeks of treatment. Whether the combination of direct antiviral agents with extended IFN therapy has an added value in improving the therapeutic response of HBeAg-negative patients with chronic hepatitis B remains to be clarified.[8–15]

To assess whether 96-week treatment improves the outcome of PegIFN therapy in this difficult to cure population, we performed a randomised study which compared the efficacy and safety of 96-week versus 48-week treatment with PegIFN in patients predominantly infected with genotype D HBV. An additional exploratory group of patients treated for 96 weeks, in whom lamivudine was added to PegIFN during the first 48 weeks of treatment, was also included.

METHODS

Study design

This phase IIIB randomised open-label study was conducted in 22 centres in Italy between February 2005 and January 2010 (NCT01095835). At the end of the screening phase, eligible patients were randomised to one of three treatment groups. The randomisation list was generated centrally by an independent biostatistician using the Proc Plan of the SAS System V.8.2. Patients were assigned in a block randomised design of 25 in a 10:10:5 ratio to groups A, B and C, respectively. A total of 11 blocks were generated. Group A received PegIFN (Pegasys; F Hoffmann-La Roche, Basel, Switzerland) 180 μg weekly for 48 weeks, group B received PegIFN 180 μg weekly for 48 weeks followed by 135 μg weekly for 48 weeks (a total of 96 weeks of treatment) and group C received PegIFN 180 μg weekly plus lamivudine (Zeffix, GlaxoSmithKline, Brentford, UK) 100 mg daily for 48 weeks, then PegIFN 135 μg weekly for 48 weeks (a total of 96 weeks of treatment). The treatment period was followed by a 1-year (48-week) observation period. Evaluations were performed at treatment weeks 1, 2, 4, 6, 8, 12, 18, 24, 30, 36, 42 and 48 (all patients). Patients in groups B and C were also evaluated at treatment weeks 50, 54, 60, 66, 72, 78, 84, 90 and 96. Follow-up assessments were performed at weeks 2, 4, 8, 12, 18, 24 (6 months), 36 (9 months) and 48 (1 year) after treatment. The study was conducted according to the Declaration of Helsinki and the International Conference on Harmonisation Consolidated Guideline on Good Clinical Practice.

Patients

Adult patients (18–70 years) with HBeAg-negative chronic hepatitis B (hepatitis B surface antigen (HBsAg)-positive and anti-HBs-negative, HBeAg-negative and anti-HBe-positive) for at least 6 months, HBV DNA levels >17 200 IU/ml (>100 000 copies/ml) and alanine aminotransferase (ALT) levels ≥1 times upper limit of normal (ULN) but ≤10 times ULN during the screening visit were eligible for inclusion in the study. Patients were required to have a liver biopsy showing chronic hepatitis B and Ishak fibrosis score ≥1 performed within the 24 months preceding the screening. Patients with a histological diagnosis of cirrhosis (Ishak fibrosis score 5 or 6) and compensated liver disease could be included. Exclusion criteria included infection with hepatitis A virus, hepatitis C virus, hepatitis delta virus or HIV co-infection; previous treatment with interferon-based therapy, any anti-HBV nucleoside or nucleotide analogue, anti-neoplastic or immunomodulatory therapy within the 12 months preceding enrolment; Child–Pugh score >6 or history or other evidence of gastrointestinal bleeding or varices ≥grade 2; hepatocellular carcinoma; autoimmune liver disease; pre-existing severe depression or other psychiatric disease; significant cardiac or renal disease; seizure disorders; severe retinopathy or any other serious concomitant illnesses; alcohol or drug abuse.

Measurements

All the biochemical, virological, haematological and immunological assessments used to include or exclude patients and to monitor patients during and off therapy were performed in each centre according to locally validated procedures with the exclusion of HBV DNA, genotype of HBV and HBsAg levels. Routine baseline assessments of ALT levels were quantified at each centre with the centre's ULN used as reference. For analysis, these values were then standardised to the Roche reference range of 0–55 IU/l, with values ≤55 IU/l indicating normal ALT. Serum HBV DNA levels were measured centrally using the COBAS TaqMan HBV Test (Roche Molecular Diagnostics, Pleasanton, California, USA; limit of detection 6 IU/ml) at the Liver Center, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, University of Milan, Italy. HBV genotypes were determined by INNO-LiPA HBV genotyping (Innogenetics NV, Ghent, Belgium). HBsAg levels were quantified centrally (Abbott Laboratories, Wiesbaden, Germany) using the Abbott Architect HBsAg assay (Abbott Ireland Diagnostics Division, Sligo, Ireland; dynamic range 0.05–250.0 IU/ml) after a 1:150 dilution. Samples with HBsAg >250.0 IU/ml at this dilution were retested after a dilution of 1:500. Samples still displaying HBsAg levels of >250 IU/ml were retested with a final dilution of 1:1000. Samples with HBsAg levels <0.05 IU/ml at 1:150 dilution were retested undiluted.

Efficacy assessments

The efficacy analysis included all patients who received ≥1 dose of study medication (intention-to-treat population). The protocol-defined primary endpoint was a combined response (ALT normalisation and HBV DNA suppression to <3400 IU/ml (<20 000 copies/ml)) 48 weeks after treatment. Secondary and exploratory outcomes included biochemical, virological and serological efficacy parameters at the end of treatment and 24 weeks and 48 weeks after treatment. These included ALT normalisation; HBV DNA levels <3400 IU/ml, <2000 IU/ml or

below limit of detection (6 IU/ml); and HBsAg clearance (<0.05 IU/ml) or HBsAg ≤10 IU/ml. Patients with missing values to define the response were considered as non-responders. The occurrence of lamivudine resistance was determined in group C.

Safety assessments

Measures of safety included clinical adverse events (AEs), haematological measurements, clinical chemical measurements and vital signs. The analysis of on-treatment AEs included all AEs reported between the first study dose and the end of the first 8 weeks of the post-treatment follow-up period.

Statistical methods

The trial was designed as a superiority study to detect clinically meaningful differences in the rates of the combined response between groups A and B. Comparison with group C was exploratory only. The sample size of 95 patients per group was determined to have a statistical power of 80% of detecting a significant absolute difference of 18% in rates of the combined response between groups A (18%) and B (36%) when a two-sided test was employed at the 0.05 significance level. The sample size of group C was fixed at 50% of the sample size of groups A and B. This resulted in an overall total of 250 patients. Analyses of efficacy included data from all patients randomised and who received at least one dose of study medication. Continuous variables were summarised using descriptive statistics and discrete variables using number and percentage of patients. Differences in baseline characteristics between groups A and B were assessed using the Pearson χ^2 test for discrete variables and the two-sided t test or Wilcoxon test for continuous variables. The Pearson χ^2 test or Fisher exact test (in the case of cell frequencies <5) was also applied to verify the hypothesis of the primary and secondary endpoints. The 95% CI of the difference in response rates between groups was calculated. No adjustment for multiple testing was adopted.

Logistic regression analyses involving the effect of age, height, weight, gender, genotype, treatment regimen, baseline ALT level, baseline HBV DNA level, baseline HBsAg level and presence or absence of cirrhosis were undertaken to determine if any of these factors were predictive of the combined response and of the virological response 1 year after treatment. On-treatment HBV DNA and HBsAg levels were also tested as predictive factors. All reported p values were two-sided and the level of significance was set to 0.05.

RESULTS

Patient disposition

The enrolment target of 250 patients was not met and 131 patients were randomised. Of these, 128 received at least one dose of study treatment and formed the intention-to-treat population (figure 1), causing the study power to decline from the predefined 80% to 55%.

Baseline characteristics

The treatment groups were well balanced with regard to clinical and virological characteristics at baseline (table 1); 94% of the patients were infected with HBV genotype D. There were more men in group B than in groups A and C. A histological activity index score of 2 was the most frequently reported category in all groups (45.1% of patients in group A, 36.5% in group B and 40.0% in group C); only 16 patients (12.5%) had cirrhosis (Ishak score 5/6).

Patients treated with PegIFN (group A vs group B)

On-treatment response

In group A mean±SD (median) HBV DNA levels were 3.5±2.1 (2.9) $\log_{10}$ IU/ml at week 12, 2.6±2.0 (1.9) $\log_{10}$ IU/ml at week 24, 2.3±1.9 (1.8) $\log_{10}$ IU/ml at week 36 and 2.5±1.9 (1.9) $\log_{10}$ IU/ml at week 48 (figure 2). A similar decline was observed in group B (HBV DNA levels of 3.7±2.0 (3.5) $\log_{10}$ IU/ml, 2.8±2.2 (1.8) $\log_{10}$ IU/ml, 2.7±2.3 (1.9) $\log_{10}$ IU/ml and 2.4±2.2 (1.9)

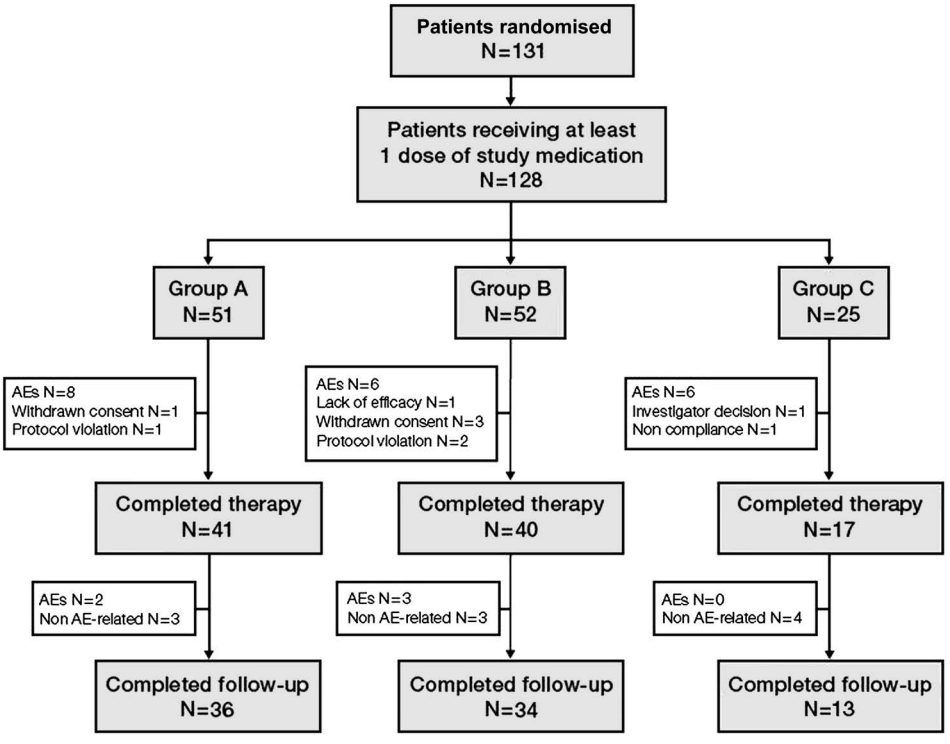

Figure 1 Patient disposition. Patients in group A received peginterferon α-2a 180 μg/week for 48 weeks, those in group B received peginterferon α-2a 180 μg/week for 48 weeks followed by peginterferon α-2a 135 μg/week for 48 weeks and patients in group C received peginterferon α-2a 180 μg/week plus lamivudine 100 mg/day for 48 weeks followed by peginterferon α-2a 135 μg/week for 48 weeks. AE, adverse event.

Table 1 Baseline characteristics of patients stratified according to treatment regime

	48-week PegIFN (group A, N=51)	96-week PegIFN (group B, N=52)	PegIFN + lamivudine (group C, N=25)	p Value* (A vs B)
Male sex, n (%)	33 (65)	45 (87)	18 (72)	0.0098†
Mean±SD age, years	45±10.2	44±10.4	46±8.6	0.6438‡
Mean±SD BMI, kg/m^2	26.6±4.7	25.6±3.7	26.4±2.9	0.1979‡
HBV genotype, n (%)				
D	48 (94.1)	48 (92.3)	24 (96.0)	0.7152†
Other	3 (5.9)	4 (7.7)	1 (4.0)	
Ishak score 5/6, n (%)	5 (9.8)	7 (13.5)	4 (16.0)	0.5629†
Median (range) standardised§ ALT (IU/l)	119 (34–897)	146 (51–897)	161 (34–897)	0.0634¶
Median (range) HBV DNA (log_{10} IU/ml)	6.1 (2.1–>8.0)	6.0 (2.6–>8.0)	6.2 (3.5–>8.0)	0.9135¶
Median (range) HBsAg (IU/ml)	5444 (300–142 744)	5271 (73–32 516)	6825 (669–37 031)	0.6452¶

*48-week vs 96-week PegIFN.
†Asymptotic Pearson χ^2 test.
‡Two-sided t test with unequal variances.
§Standardised ALT to 55 IU/l.
¶Two-sided Wilcoxon test with t approximation.
ALT, alanine aminotransferase; BMI, body mass index; HBV DNA, hepatitis B virus DNA; HBsAg, hepatitis B surface antigen; PegIFN, peginterferon α-2a.

log_{10} IU/ml, respectively). During the extended treatment period in group B (weeks 49–96), mean HBV DNA levels remained between 2.2 and 2.5 log_{10} IU/ml (figure 2). The results of the individual efficacy parameters at the end of treatment are shown in table 2.

Post-treatment response

Twenty-four weeks after treatment, 12 patients in group A and 15 in group B had HBV DNA <3400 IU/ml and normal ALT (23.5% vs 28.8%, p=0.54). Response rates for the composite endpoint (HBV DNA <3400 IU/ml and ALT normalisation 48 weeks post-treatment) were 11.8% (6/51) in group A and 25.0% (13/52) in group B (p=0.08; table 3), causing the study power to further decline from 55% to 39%.

There were no significant differences in the proportions of patients achieving ALT normalisation between groups A and B at either the 24-week (45.1% (23/51) and 46.2% (24/52), respectively; p=0.91) or 48-week post-treatment assessments (35.3% (18/51) and 34.6% (18/52), respectively; p=0.94; table 3). Seventeen patients (33%) in group A and 16 (31%) in group B had persistently normal ALT levels up to both 24 and 48 weeks post-treatment. Mean HBV DNA levels were significantly lower in group B than in group A patients at both time points (2.2 vs 3.4 log_{10} IU/ml at week 24, p=0.0082; 2.4 vs 3.6 log_{10} IU/ml at week 48, p=0.0103).

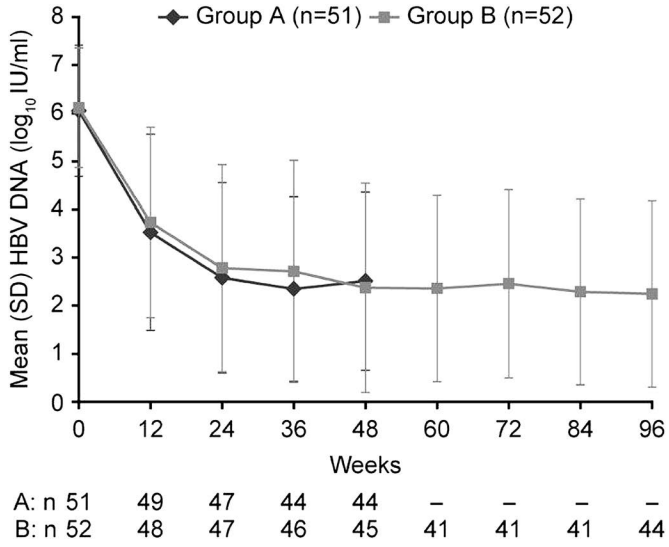

Figure 2 Changes in HBV DNA levels in patients treated for 48 (group A) or 96 (Group B) weeks with pegylated interferon α2a (intention-to-treat analysis).

Using the 3400 IU/ml cut-off, virological response rates between groups A and B were not significantly different at the 24-week post-treatment assessment (23.5% (12/51) and 30.8% (16/52), respectively; p=0.41). At the 48-week post-treatment assessment, the proportion of patients with HBV DNA <3400 IU/ml was significantly higher in group B than in group A (30.8% (16/52) and 11.8% (6/51), respectively, p=0.02; table 3). Similar patterns of response rates were seen using the 2000 IU/ml HBV DNA cut-off (for 48 weeks post-treatment 28.8% and 11.8%, respectively, p=0.03), as shown in figure 3; the corresponding features for genotype D-infected patients were 27% and 10%, respectively (p=0.0364). The statistically significant differences in virological responses between groups A and B at 48 weeks post-treatment but not at 24 weeks post-treatment reflected the decline in virological responses in group A (around 50% for HBV DNA <3400 IU/ml and 45% for HBV DNA <2000 IU/ml) but not in group B during post-treatment follow-up (figure 3). Indeed, the proportion of patients who maintained a virological response at both 24 and 48 weeks post-treatment was higher in the 96-week treatment group than in the 48-week treatment group (23% vs 8%, p=0.05).

HBV DNA was suppressed below 6 IU/ml in 7.7% of patients (4/52) in group B at both post-treatment assessments; in group A only one patient had HBV DNA below the limit of detection and this was only recorded at the 48-week assessment.

Of the patients who achieved HBV DNA <3400 IU/ml at the end of treatment, 16.1% (5/31) of group A and 42.9% (15/35) of group B had a sustained response 1 year post-treatment (p=0.02). For HBV DNA <2000 IU/ml, these figures were 16.7% (5/30) and 40.0% (14/35), respectively (p=0.04).

None of the group A patients achieved post-treatment HBsAg clearance or HBsAg levels <10 IU/ml while, in group B, five patients had HBsAg <10 IU/ml at the 48-week post-treatment time point (0% vs 9.6%, p=0.06) and three cleared HBsAg at the same time point (0% vs 5.8%, p=0.24; figure 4).

By univariate logistic regression analyses, baseline viraemia as log_{10} IU/ml (OR 0.634, 95% CI 0.436 to 0.924; p=0.0177) and a 96-week course of PegIFN (OR 3.041; 95% CI 1.073 to 8.618, p=0.0364) were associated with HBV DNA <2000 IU/ml at

Table 2 Intention-to-treat analysis of the response rates at end of treatment

Outcomes, n (%)	48-week PegIFN (group A, N=51)	96-week PegIFN (group B, N=52)	PegIFN+lamivudine (group C, N=25)	p Value* (A vs B)
HBV DNA <3400 IU/ml + ALT normalisation	15 (29.4)	20 (38.5)	8 (32.0)	0.3323†
HBV DNA <20 000 IU/ml + ALT normalisation	17 (33.3)	20 (38.5)	8 (32.0)	0.5876†
ALT normalisation	18 (35.3)	21 (40.4)	10 (40.0)	0.5944†
HBV DNA <20 000 IU/ml	36 (70.6)	36 (69.2)	19 (76.0)	0.8806†
HBV DNA <3400 IU/ml	31 (60.8)	35 (67.3)	19 (76.0)	0.4902†
HBV DNA <2000 IU/ml	30 (58.8)	35 (67.3)	18 (72.0)	0.3723†
HBV DNA <6 IU/ml§	9 (17.6)	16 (30.8)	6 (24.0)	0.1204†
HBsAg clearance	0 (0.0)	1 (1.9)	1 (4.0)	1.000‡

*48-week vs 96-week PegIFN.
†Asymptotic Pearson χ^2 test.
‡Fisher exact test.
§Limit of detection of the assay.
ALT, alanine aminotransferase; HBV DNA, hepatitis B viral DNA; HBsAg, hepatitis B surface antigen; PegIFN, peginterferon α-2a.

48 weeks post-treatment. Baseline viraemia as $\log_{10}$ IU/ml (OR 0.602, 95% CI 0.404 to 0.896; p=0.0124) and a 96-week course of PegIFN (OR 3.608; 95% CI 1.202 to 10.829, p=0.0221) predicted a sustained virological response also in a multivariate logistic regression analysis. The same two variables (baseline HBV DNA and a 96-week course of PegIFN) were associated with a sustained virological response defined as HBV DNA <3400 IU/ml. For the combined endpoint (ie, HBV DNA <3400 IU/ml and normal ALT levels), the multivariate logistic regression model included HBV DNA as $\log_{10}$ IU/ml (OR 0.702, 95% CI 0.474 to 1.041; p=0.078) and a 96-week course of PegIFN (OR 2.460, 95% CI 0.824 to 7.342; p=0.1067).

When on-treatment viraemia and serology were considered, HBV DNA levels as $\log_{10}$ IU/ml at week 12 (OR 0.739; 95% CI 0.555 to 0.983; p=0.0381) and at week 24 (OR 0.721; 95% CI 0.525 to 0.990; p=0.0429), HBsAg levels as $\log_{10}$ IU/ml at week 12 (OR 0.267; 95% CI 0.102 to 0.700; p=0.0073) and at week 24 (OR 0.251; 95% CI 0.107 to 0.588; p=0.0014) and HBsAg decline as $\log_{10}$ IU/ml drop at week 24 (OR 4.739; 95% CI 1.496 to 15.014; p=0.0082) predicted a sustained virological response at week 48 off treatment. By multivariate analysis, HBsAg levels at week 24 (OR 0.222; 95% CI 0.092 to 0.536; p=0.0008) and a 96-week course of PegIFN (OR 4.275, 95% CI 1.263 to 14.470; p=0.0195) were the only predictors of a response.

Patients treated with PegIFN plus lamivudine (group C)

In patients in group C the first 48 weeks of combination therapy resulted in mean±SD (median) HBV DNA levels of 1.7±1.0 (1.5) $\log_{10}$ IU/ml, 1.0±0.6 (0.7) $\log_{10}$ IU/ml, 0.7±0.2 (0.7) $\log_{10}$ IU/ml and 0.7±0.5 (0.7) IU/ml at weeks 12, 24, 36 and 48, respectively. During the subsequent 48 weeks of PegIFN monotherapy, HBV DNA levels increased, reaching 2.0±1.4 (2.1) $\log_{10}$ IU/ml at week 96, but remaining below baseline levels at all time points. At the end of treatment, 32.0% of patients (8/25) achieved a combined response (HBV DNA <3400 IU/ml and ALT normalisation). As far as the virological response is concerned, the end of therapy response rates were 76.0% (19/25) for HBV DNA <3400 IU/ml and 72.0% (18/25) for HBV DNA <2000 IU/ml (table 2). Forty-eight weeks post-treatment, five patients (20.0%) had HBV DNA <3400 IU/ml or HBV DNA <2000 IU/ml. However, only one (12.5%) of the eight patients with an end-of-treatment response sustained this at both post-treatment time points. One patient had HBsAg clearance at the end of treatment and at 24 weeks post-treatment but no patients had HBsAg clearance at 48 weeks post-treatment. None of the patients with detectable HBV DNA at week 24 (n=12) or at week 48 (n=19) of treatment tested positive for lamivudine resistance.

Safety and tolerability

Ten patients (19.6%) in group A, 12 (23.1%) in group B and 8 (32.0%) in group C withdrew from treatment for any reason (p=0.81 for the difference between groups A and B). AEs were the most common reason for early study discontinuation (table 4). Study medication dose was reduced in 15 patients in group A (29.4%), seven in group B (13.5%) and nine in group C (36.0%) (p=0.0573). The majority of dose reductions were required to manage AEs, mainly neutropenia (10 patients (20%) in group A, 4

Table 3 Intention-to-treat analysis of the response rates at the end of 48-week post-treatment follow-up

Outcomes, n (%)	48-week PegIFN (group A, N=51)	96-week PegIFN (group B, N=52)	PegIFN + lamivudine (group C, N=25)	p Value* (A vs B)
HBV DNA <3400 IU/ml + ALT normalisation	6 (11.8)	13 (25.0)	5 (20.0)	0.0834†
HBV DNA <20 000 IU/ml + ALT normalisation	10 (19.6)	15 (28.9)	6 (24.0)	0.2742†
ALT normalisation	18 (35.3)	18 (34.6)	9 (36.00)	0.9424†
HBV DNA <20 000 IU/ml	12 (23.5)	20 (38.5)	6 (24.0)	0.1016†
HBV DNA <3400 IU/ml	6 (11.8)	16 (30.8)	5 (20.0)	0.0186†
HBV DNA <2000 IU/ml	6 (11.8)	15 (28.8)	5 (20.0)	0.0314†
HBV DNA <6 IU/ml§	1 (2.0)	4 (7.7)	2 (8.0)	0.3627‡
HBsAg <10 IU/ml	0 (0.0)	5 (9.6%)	0 (0.0)	0.0565‡
HBsAg clearance	0 (0.0)	3 (5.8)	0 (0.0)	0.2427‡

*48-week vs 96-week PegIFN.
†Asymptotic Pearson χ^2 test.
‡Fisher exact test.
§Limit of detection of the assay.
ALT, alanine aminotransferase; HBV DNA, hepatitis B viral DNA; HBsAg, hepatitis B surface antigen; PegIFN, peginterferon α-2a.

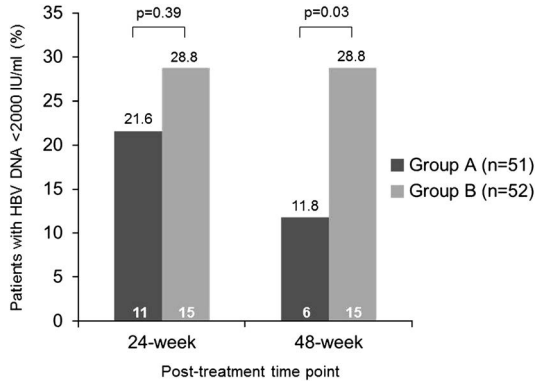

Figure 3 Virological response rates (HBV DNA <2000 IU/ml) after 24 or 48 weeks of post-treatment follow-up in patients treated for 48 (group A) or 96 (Group B) weeks with pegylated interferon α2a (intention-to-treat analysis).

(7.7%) in group B and 3 (12%) in group C) and/or thrombocytopenia (4 patients (8%) in group A, 1 patient (1.9%) in group B). The number of patients with at least one treatment-related AE was similar in all treatment groups (table 4; p=0.80 for comparison between groups A and B). There were no unexpected AEs; the most commonly reported were those known to be associated with IFN-based therapy including asthenia, fever, arthralgia/myalgia and headache (table 4). Mean neutrophil and platelet counts decreased during treatment in all groups but progressively returned to baseline levels during the follow-up period.

A total of 17 serious AEs (SAEs) were reported by 16 patients (p=0.10 for the comparison between groups A and B). SAEs were single cases in a variety of body systems and no individual SAE was reported by more than one patient. Overall, two SAEs in group A (interstitial lung disease and fever) and two in group C (Guillain-Barré syndrome and muscular weakness) were considered as possibly or probably related to study drug. Treatment was discontinued in all four cases; only the case of muscular weakness had not resolved by the end of the follow-up period. All other SAEs were considered to be unrelated to the study drug or of unknown relationship. One patient in group A died due to metastatic hepatocellular carcinoma during the post-treatment follow-up period, which was considered unrelated to the study treatment. The majority of the AEs (78%), treatment-related events (81%), SAEs (70%)

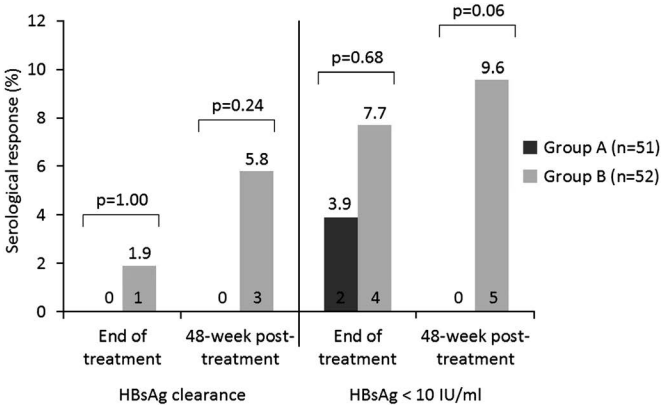

Figure 4 HBsAg response rates at the end of treatment and 48 weeks post-treatment in patients treated for 48 (group A) or 96 (Group B) weeks with pegylated interferon α2a (intention-to-treat analysis).

and premature discontinuations (58%) occurred during the first year of PegIFN administration.

DISCUSSION

This study is proof of the concept that, in HBeAg-negative patients with chronic hepatitis B, a 96-week course with PegIFN results in better clinical benefits than a 48-week course of similar treatment and that combined treatment with lamivudine has no added value. Indeed, more than twice as many patients receiving extended treatment with PegIFN achieved the endpoint of HBV DNA <3400 IU/ml plus ALT normalisation 48 weeks post-treatment, an outcome that was reinforced by the significantly higher proportion of patients achieving <3400 IU/ml HBV DNA (30.8% vs 11.8%) and <2000 IU/ml HBV DNA (28.8% vs 11.8%). Moreover, the few patients who had a serum HBsAg decline to <10 IU/ml or who achieved HBsAg clearance belonged to the extended treatment arm only.

The differences in treatment outcome between arms are the consequences of the fact that the response rates of the 96-week treatment arm remained stable during the follow-up period whereas those of the 48-week treatment declined between weeks 24 and 48 post-treatment as a consequence of a higher rate of hepatitis relapses (0% vs 45%). This is not a trivial point considering that, in the registration trial, a 48-week course of PegIFN in HBeAg-negative patients with other than genotype D yielded rates of sustained virological response of 40% at the 24-week post-treatment time point compared with 20% response rates in the difficult to cure genotype D subpopulation.[8 15] We also found low rates of virological response at 24-week follow-up, which further fell at week 48 of post-treatment follow-up (10%). Conversely, extended treatment with PegIFN led to an incremental benefit in these difficult to cure patients by causing a virological response rate of 29% at 48 weeks post-treatment, which was the consequence of a significant reduction in hepatitis relapse during follow-up.[16]

The clinical benefits of extended treatment with PegIFN did not translate into higher rates of suppressed HBV DNA only but included increased rates of off-therapy HBsAg clearance, from 2% at the end of treatment to 6% at 48 weeks post-treatment. An added value of extended therapy were the two additional patients who showed <10 IU/ml serum levels of HBsAg at 48 weeks post-treatment, a cut-off previously shown to predict HBsAg clearance in the post-treatment period.[17] Circumstantial evidence indicates that the 6% rate of HBsAg clearance observed 48 weeks after stopping a 96-week course of PegIFN is encouraging. In fact, the registration trial of PegIFN in HBeAg-negative patients had already reported a sixfold increase in the rate of HBsAg clearance throughout 5 years of post-treatment follow-up, particularly among responders with <2000 IU/ml HBV DNA at the end of therapy (28% clearance of HBsAg).[18] In our study, the 29% of patients who achieved <2000 IU/ml HBV DNA levels 48 weeks post-treatment following extended therapy with PegIFN might therefore experience additional benefits such as further clearance of serum HBsAg at any time point during post-treatment follow-up.

The clinical benefits of the extended treatment regimen are confirmed by the multivariate analysis where it appeared as an independent predictor of favourable outcome of HBV therapy. We acknowledge, however, that the clinical benefits of extended therapy with PegIFN need to be validated by both powered studies and field practice. The major caveat of our study was the smaller than planned patient population which was caused by the patient enrolment process being delayed by a strong competition with PegIFN that became commercially available in

Table 4 Numbers of patients reporting AEs and laboratory abnormalities

Outcomes, n (%)	48-week PegIFN (group A, N=51)	96-week PegIFN (group B, N=52)	PegIFN + lamivudine (group C, N=25)	p Value* (A vs B)
One or more treatment-related AE	42 (82.4)	41 (78.8)	20 (80.0)	0.8041
One or more SAE	8 (15.7)	3 (5.8)	6 (24.0)	0.1222
Deaths	1†	0	0	0.4951
Most common AEs‡				
Fever	19 (37.3)	19 (36.5)	8 (32.0)	1.000
Asthenia	17 (33.3)	19 (36.5)	11 (44.0)	0.6661
Flu-like symptoms	9 (17.6)	10 (19.2)	4 (16.0)	0.7997
Headache	13 (25.5)	8 (15.4)	7 (28.0)	0.3173
Myalgia	7 (13.7)	8 (15.4)	4 (16.0)	0.7830
Arthralgia	6 (11.8)	6 (11.5)	3 (12.0)	1.000
Back pain	3 (5.9)	6 (11.5)	2 (8.0)	0.3141
Muscular weakness	0	0	2 (8.0)	NA
Nausea	5 (9.8)	2 (3.8)	2 (8.0)	0.4336
Abdominal pain	4 (7.8)	4 (7.7)	3 (12.0)	1.000
Diarrhoea	1 (2.0)	3 (5.8)	2 (8.0)	0.3604
Dyspepsia	1 (2.0)	4 (7.7)	2 (8.0)	0.2024
Anxiety	4 (7.8)	5 (9.6)	2 (8.0)	0.7387
Insomnia	4 (7.8)	0	2 (8.0)	0.1164
Irritability	0	3 (5.8)	2 (8.0)	0.1164
Nervousness	0	3 (5.8)	1 (4.0)	0.1164
Pruritus	5 (9.8)	6 (11.5)	3 (12.0)	0.7574
Alopecia	3 (5.9)	3 (5.8)	1 (4.0)	1.000
Urticaria	1 (2.0)	1 (1.9)	2 (8.0)	1.000
Psoriasis	0	3 (5.8)	0	0.1164
Sciatica	1 (2.0)	3 (5.8)	0	0.3604
Pharyngitis	3 (5.9)	2 (3.8)	0	1.000
Urinary tract infection	3 (5.9)	1 (1.9)	0	0.6162
Tooth abscess	0	1 (1.9)	2 (8.0)	0.4943
Cough	3 (5.9)	6 (11.5)	0	0.3141
Anorexia	2 (3.9)	6 (11.5)	0	0.1567
Hypertension	1 (2.0)	4 (7.7)	0	0.2024
Vertigo	1 (2.0)	1 (1.9)	2 (8.0)	1.000
Laboratory abnormalities				
ALT increased	3 (5.9)	8 (15.4)	4 (16.0)	0.2008
Neutropenia	12 (23.5)	9 (17.3)	3 (12.0)	0.4719
Thrombocytopenia	6 (11.8)	6 (11.5)	1 (4.0)	1.000
Anaemia	5 (9.8)	4 (7.7)	1 (4.0)	0.7412
Dose modification	15 (29.4)	7 (13.5)	9 (36.0)	0.0573
Discontinuation				
Overall	10 (19.6)	12 (23.1)	8 (32.0)	0.8107
Due to AEs	8 (15.7)	6 (11.5)	6 (24.0)	0.2043

Patients may have more than one AE.
*Two-sided Fisher exact test, 48-week vs 96-week PegIFN.
†Metastatic hepatocellular carcinoma during follow-up.
‡Reported by at least 5% of patients in one of the treatment groups between first study dose up to 8 weeks after therapy.
AE, adverse event; ALT, alanine aminotransferase; PegIFN, peginterferon α-2a; SAE, serious adverse event.

Italy concurrently with the trial onset. When we designed the present study we thought interesting to explore whether a combination of PegIFN with the rapidly acting anti-HBV oral agent lamivudine had any added value on the assumption that combination therapy could improve the outcome of the anti-HBV therapy. On the other hand, pragmatic studies in the field are deemed necessary to assess treatment effectiveness as it results from patient adherence, compliance and response to therapy. The strict criteria of our study led to the enrolment of only a few patients with cirrhosis (16% with combined Ishak fibrosis score 5 and 6) or complications related to the metabolic syndrome, both of which are known to limit the access, adherence and response to IFN-based therapies.[8]

Notwithstanding differences with previous trials exploring the efficacy of combined PegIFN and lamivudine for 48 weeks,[8] we could not demonstrate any benefit with combination therapy in our patients who were given 135 μg PegIFN weekly for an additional 48 weeks after 48 weeks of combination therapy. Even though this exploratory group was not sufficiently powered with only 25 patients enrolled, combination-treated patients achieved comparable benefits in terms of end-of-treatment HBV DNA suppression to those treated for 96 weeks. We acknowledge, however, that the strategy of combination therapy in HBeAg-negative patients needs to be reassessed in light of the more potent third-generation nucleos(t)ide analogs that have become available in the last few years and new schemes of combination therapy.[5 6]

Additional endpoints of our study were tolerability and safety of extended treatment with PegIFN beyond 48 weeks, for which there are data in the hepatitis C population only.[19] Indeed, extended treatment with PegIFN was generally well tolerated, causing no increase in the withdrawal rates compared with the

48-week treatment course and no unexpected AEs. Overall, only 12% of patients treated for 96 weeks withdrew from therapy due to AEs, apparently fewer than the 25% reported in comparable patients receiving long-term treatment with standard IFN.[12 13] Two patients withdrew from treatment, one as a consequence of severe interstitial lung disease, a class-related AE that recently led to the interruption of the clinical development of IFN fused with human albumin, and the other due to muscle weakness previously reported in patients receiving PegIFN associated with telbivudine.[20] The patient with respiratory complications had fully recovered by the end of the follow-up period but the patient who experienced muscle weakness during combination therapy did not. We acknowledge that our choice of injecting a lower weekly dose of 135 μg for the extension period, which was dictated by the lack of available safety data on extending the 180 μg weekly dose of PegIFN beyond the canonical 48 weeks, could have favourably impacted on the safety of anti-HBV therapy.

In conclusion, this study suggests that extended treatment with PegIFN to 96 weeks safely improves sustained virological responses in HBeAg-negative genotype D patients compared with the current standard of care of 48 weeks.

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Contributors PL and MV had full access to all the data in the study and take responsibility for the integrity and accuracy of the data analysis. Study concept and design: MC and PL. Acquisition of data: PL, MV, GGDC, ES, MF, GGDM, SB, PF, SF, TG. Analysis and interpretation of data: PL, MC, LR, GGDM, ES. Drafting of the manuscript: MC, PL. Technical and administrative support: FF, BM. Role of the sponsor: representatives of Roche contributed to the design, conduct of the study and data collection.

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Competing interests MC has received grant and research support from MSD, Roche, BMS and Gilead Sciences; has served on Advisory Committees for MSD, Roche, Novartis, Bayer, BMS, Gilead Sciences, Tibotec and Vertex; and has received speaking and teaching fees from Tibotec, MSD, Roche, Novartis, Bayer, BMS, Gilead Sciences and Vertex. PL has served on the Advisory Board/Speaker Bureau for BMS, Roche, Gilead Sciences and GSK. LR and BM are employees of F Hoffmann-La Roche Ltd.

Patient consent Obtained.

Ethics approval The ethics committee of the coordinating centre obtained approval for the conduct of the trial and the study protocol was approved by the local independent ethics committee of each centre.

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APPENDIX 1

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Randomised study comparing 48 and 96 weeks peginterferon α-2a therapy in genotype D HBeAg-negative chronic hepatitis B

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