Original article

A randomized controlled trial of sequential pegylated interferon-α and telbivudine or *vice versa* for 48 weeks in hepatitis B e antigen-negative chronic hepatitis B

Paola Piccolo[1,2], Ilaria Lenci[1], Daniele di Paolo[1], Luigi Demelia[3], Orazio Sorbello[3], Lorenzo Nosotti[4], Mario Angelico[1]*

[1]Hepatology Unit, Tor Vergata University, Rome, Italy
[2]Medicine Unit, Fatebenefratelli Hospital Isola Tiberina, Rome, Italy
[3]Gastroenterology Department, Cagliari University Hospital, Cagliari, Italy
[4]Hepatology Unit, National Institute for Health, Migration and Poverty, Rome, Italy

*Corresponding author e-mail: paola.piccolo@uniroma2.it

Background: Short-term treatment for hepatitis B e antigen (HBeAg)-negative chronic hepatitis B remains unsatisfactory. The aim of our study was to compare the efficacy and safety of two sequential regimens of pegylated interferon (PEG-IFN)-α and telbivudine (LdT).
Methods: Adult patients with biopsy-proven HBeAg-negative chronic hepatitis B, elevated alanine aminotransferase (ALT) and serum HBV DNA≥2,000 IU/ml were randomized 1:1 at baseline to receive PEG-IFN 180 μg/week for 24 weeks followed by LdT 600 mg/day for 24 weeks (PEG-IFN first), or *vice versa* (LdT first), plus 24-week follow-up; individuals with HCV, HDV or HIV coinfections and lamivudine resistance were excluded. Primary end points were serum HBV DNA<2,000 IU/ml and normal ALT at week 72.
Results: A total of 30 patients (86% male, median age 48 years) were enrolled: mean ±SD baseline serum HBV DNA was 5.56 ±1.4 log IU/ml and ALT was 2.9 ±2.5× upper limit of normal. At end of follow-up (week 72), HBV DNA<2,000 IU/ml was achieved in 13.3% of participants in the PEG-IFN first group versus 46.7% of those in the LdT first group (*P*=0.046). Mean ±SD ALT levels were significantly lower in the LdT first group (1.3 ±0.9 versus 3.2 ±2.7× upper limit of normal; *P*=0.03). PEG-IFN dose was reduced in 2 (7%) patients and 1 (7%) patient dropped out due to myalgia.
Conclusions: Sequential treatment with 24 weeks PEG-IFN followed or preceded by 24 weeks of LdT is safe. Virological response rate at week 72 was significantly higher in patients treated with LdT followed by PEG-IFN than *vice versa*. A sequential antiviral regimen of LdT followed by PEG-IFN, if confirmed in larger series, could improve response rates compared with standard PEG-IFN monotherapy.

Introduction

Although a safe and effective vaccine has been available for many years [1,2], HBV still chronically infects >350 million people worldwide [3–5]. Chronic hepatitis B causes significant morbidity and mortality, and remains a frequent indication for liver transplantation due to progression to liver cirrhosis and hepatocellular carcinoma [6,7]. In Southern Europe, >90% of chronic infections are sustained by hepatitis B e antigen (HBeAg)-negative virus [8,9], which has high rates of progression to cirrhosis, as well as lower response rates to antiviral therapy [10]. Furthermore, in Mediterranean countries the most common viral genotype is D, which is also associated with lower response rates to interferon-based antiviral therapy [11,12].

Antiviral treatment for HBV relies on two types of pharmacotherapy: immune-modulators (standard interferon and pegylated interferon [PEG-IFN]-α), and HBV polymerase inhibitors. The latter include the nucleoside (lamivudine, entecavir and telbivudine [LdT]) and the nucleotide (adefovir dipivoxil and tenofovir disoproxil fumarate) analogues. Advantages of interferon-based therapy are short-term duration (1–2 years) and sustained suppression of viral replication after treatment suspension, which is associated

with a favourable outcome [13,14]; however, the rates of response to a standard regimen of PEG-IFN-α for 48 weeks are approximately 20% in large clinical trials [15–17]. Nucleoside/nucleotide analogues are very effective in suppressing viral replication, but are burdened by the need for long-term (indefinite) treatment, which carries the risk of drug-induced viral resistance [18–22]. The possibility of combining PEG-IFN-α and nucleoside/nucleotide analogues to improve response rates has been explored in several studies [23,24]; however, no benefit has been demonstrated to date. The use of a sequential regimen to improve treatment outcome and possibly to reduce pharmaceutical costs is an appealing alternative. However, the use of a nucleoside/nucleotide analogues to lower HBV viral load before initiating interferon-based therapy has given encouraging results [25–27].

In compensated chronic HBeAg-negative hepatitis B patients, previous studies have shown that LdT treatment results in undetectable serum HBV DNA levels in approximately 90% after 6 months of treatment [28]. Similarly, during effective PEG-IFN monotherapy, nadir HBV DNA levels are obtained within the first 24 weeks of treatment [29]. We therefore hypothesized that by adopting a sequential antiviral regimen, treatment duration with each drug could be reduced to 24 weeks, thereby reducing costs compared with a standard 48-week course of PEG-IFN, without compromising efficacy.

The aim of this randomized controlled trial was to investigate the safety and efficacy of novel combination treatment strategies using two sequential regimens: PEG-IFN-α for 24 weeks followed by LdT for 24 weeks or *vice versa*, for the treatment of patients with compensated chronic HBeAg-negative hepatitis B.

Methods

Study design

This was an investigator-initiated randomized multicentre trial designed in early 2008, conducted in four out-patient hepatology/infectious disease clinics in central Italy. The protocol was approved by the Ethical Committees of all participating centres and registered in the National Observatory for Clinical Investigations (OsSC-AIFA; EudraCT number 2008-001768-35). Eligible patients were centrally randomized at baseline in a 1:1 ratio to receive either PEG-IFN-α2a (Pegasys; Roche, Monza, Italy) 180 μg/week subcutaneously for 24 weeks followed by LdT (Sebivo; Novartis, Milan, Italy) 600 mg/day orally for 24 weeks (PEG-IFN first) or LdT 600 mg/day orally for 24 weeks followed by PEG-IFN-α2a 180 μg/week for 24 weeks (LdT first). Both groups were followed for 24 weeks after treatment completion. Allocation to treatment groups was sent via web-based case report form to the investigators after computer-generated randomization by the central monitor. Treatment was self-administered and compliance was self-reported. All patients gave written informed consent and the study was conducted according to the guidelines of the Declaration of Helsinki and the principles of Good Clinical Practice.

Patients

To be eligible for the study patients needed to be ≥18 years of age with biopsy-proven chronic hepatitis B defined as: hepatitis B surface antigen (HBsAg)-positive for ≥6 months, HBeAg-negative, with elevated alanine aminotransferase (ALT) levels (greater than the upper limit of normal [ULN] and <10× ULN on ≥2 occasions in the preceding 6 months), quantitative serum HBV DNA>2,000 IU/ml (COBAS TaqMan HBV Test version 2.0; Roche Diagnostics (Milan, Italy), lower limit of detection 12 IU/ml, lower limit of quantification 20 IU/ml), and a histological diagnosis of chronic hepatitis B within the preceding 24 months. Liver biopsies were assessed by local pathologists and scored by the Ishak [30] method for grading and staging. HBV genotype was assessed through direct sequencing of HBV polymerase.

Exclusion criteria were the presence of clinical signs of cirrhosis, coinfection with HCV, HDV or HIV, chronic liver disease of other aetiology, pregnancy or lactation, creatinine levels >1.5×ULN, neutrophil count <1,500 cells/mm^3, platelet count <90,000 cells/mm^3, history of severe psychiatric disease, substance abuse (including alcohol) or dependence, methadone maintenance, severe comorbidity, and any antiviral treatment for chronic hepatitis B in the 3 months preceding study enrolment. Patients with lamivudine-resistance at HBV polymerase genome sequencing were also excluded.

Efficacy measures

All patients randomized who received ≥1 dose of study medication were included in the analysis. Serum HBV DNA levels were measured at weeks 4, 12 and every 12 weeks thereafter during PEG-IFN treatment, at weeks 4, 8 and every 8 weeks thereafter during LdT treatment, and every 8 weeks during post-treatment follow-up.

The primary outcome measure was a reduction of serum HBV DNA to <2,000 IU/ml (3.3 log IU/ml) at the end of 24 weeks of post-treatment follow-up (week 72). Secondary outcome measures were normal ALT levels (biochemical response), combined HBV DNA suppression and biochemical response, undetectable serum HBV DNA, and HBsAg loss or seroconversion at end of follow-up.

End-of-treatment virological and biochemical response were defined as undetectable HBV DNA and normal ALT at week 48, respectively.

Table 1. Baseline characteristics of all patients and in the two treatment arms

Characteristic	Overall	PEG-IFN first	LdT first	*P*-value
Patients, *n*	30	15	15	–
Male, *n* (%)	26 (87)	13 (87)	13 (87)	1.00
Mean age, years ±SD	48 ±11.2	46.1 ±12.4	49.9 ±9.9	0.37
Mean BMI ±SD	25.3 ±3.1	24.7 ±3.6	26 ±2.6	0.25
Mean ALT, ×ULN ±SD	2.9 ±2.5	2.7 ±1.9	3.2 ±3.0	0.61
Median ALT, ×ULN (range)	2.0 (1.1–13)	2.1 (1.1–7.7)	2.0 (1.2–13.1)	0.69
Mean HBV DNA log IU/ml ±SD	5.6 ±1.4	5.7 ±1.2	5.4 ±1.6	0.61
Median HBV DNA, log IU/ml (range)	5.6 (3.6–8.1)	5.8 (3.7–8.0)	5.1 (3.6–8.1)	0.50
Genotype D, *n* (%)	26 (87)	14 (93.3)	12 (80)	0.28
Mean HBsAg, log IU/ml ±SD	3.9 ±0.4	3.9 ±0.4	3.3 ±1.0	0.17
Mean histological grading ±SD[a]	4.4 ±2.0	4.5 ±2.3	4.2 ±1.7	0.72
Mean histological staging ±SD[a]	1.7 ±1.4	1.7 ±1.0	1.8 ±1.8	0.74
Advanced fibrosis, *n* (%)[b]	2 (6.7)	0	2 (13.3)	0.14

[a]Using the Ishak score. [b]Ishak staging ≥5/6. ALT, alanine aminotransferase; BMI, body mass index; HBsAg, hepatitis B surface antigen; LdT, telbivudine; PEG-IFN, pegylated interferon; ULN, upper limit of normal.

ALT flare was defined on treatment as any increase >2× the previous serum ALT level and during follow-up as any increase >2×ULN in a patient who had normal ALT at end of treatment.

Patients with undetectable serum HBV DNA at the end of treatment who did not maintain a sustained HBV DNA suppression were defined as virological relapsers. Patients with detectable serum HBV DNA at end of treatment who did not achieve a sustained HBV DNA suppression were considered non-responders.

Quantitative serum HBsAg (Architect; Abbott Diagnostics) was measured at baseline and every 24 weeks during treatment. The concentration of HBsAg in specimens was determined using a previously generated Architect HBsAg calibration curve (range 0.05–250 IU/ml). Samples were diluted 1:20 and 1:500 with the Architect HBsAg diluent to expand the upper limit of the dynamic range from 250 to 125,000 IU/ml.

Safety

Patients were evaluated for clinical and laboratory adverse events including measurement of serum creatine kinase levels at all study visits: during PEG-IFN treatment at baseline, week 2, week 4 and every 4 weeks thereafter, and during LdT treatment at baseline, week 4 and every 8 weeks thereafter. All patients were evaluated every 8 weeks during follow-up. Adverse events were graded as mild, moderate or severe by the individual investigators. Severe adverse events were classified into life-threatening, requiring hospitalization, significantly disabling or incapacitating, or medically significant. All patients randomized who received ≥1 dose of study medication were included in the analysis.

Statistical analysis

Data were analysed using the NCSS 2007 statistical software package for Windows (Number Cruncher Statistical System, Kaysville, UT, USA) according to the intention-to-treat principle. Data were mainly expressed as mean or median values with standard deviation and/or ranges. For quantitative variables, univariate analysis was conducted using the Student's *t*-test. Statistics on categorical variables was performed with the Fisher's exact test.

A sample size of 15 patients per treatment group was calculated to provide a statistical power of 80% at the 0.05 level of significance and to detect a difference in response rates of 30% between the two treatment arms, with a non-inferiority limit of 10%.

Results

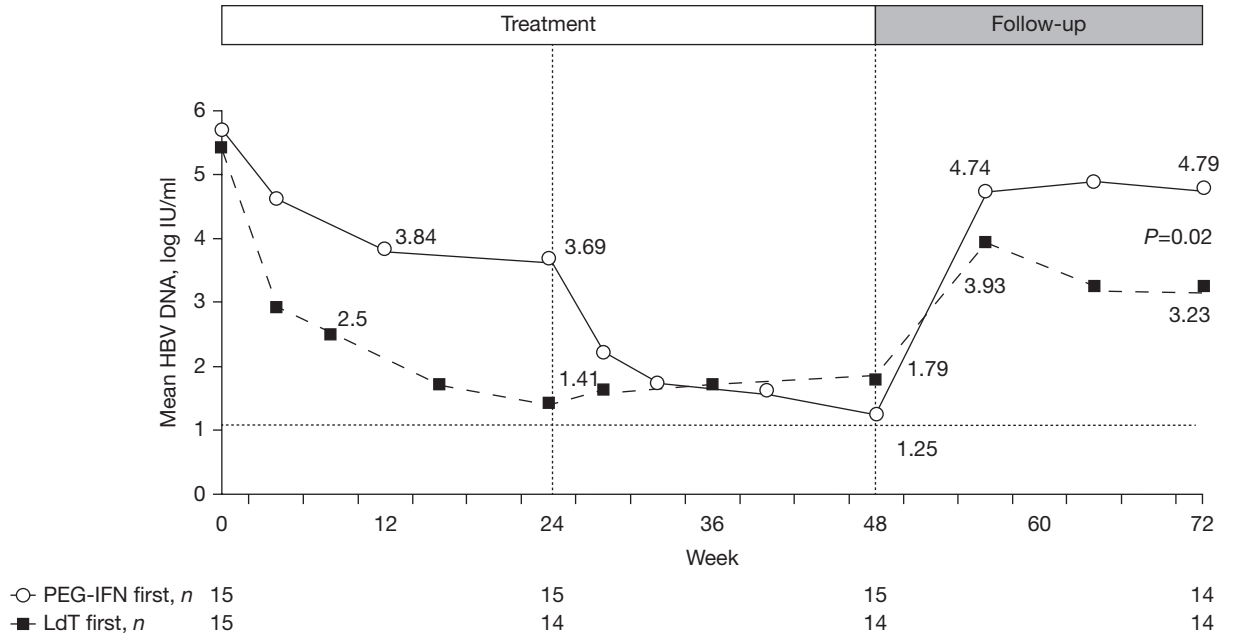
Between October 2008 and March 2010, 31 patients were screened; 1 patient was excluded due to leukopenia; 30 met eligibility criteria (87% male, mean ±SD age 48 ±11.2 years) and were randomized at baseline, and all received ≥1 dose of study medication. All patients were included in the intention-to-treat analysis. The two treatment groups were matched for all baseline variables. Baseline characteristics of the patients in the two treatment groups are listed in Table 1.

Overall, 2 (6.7%) patients had advanced fibrosis at baseline liver biopsy (Ishak staging 5/6) and 6 (20%) patients had received antiviral treatment for HBV in the past (4 standard interferon, 1 lamivudine and 1 adefovir dipivoxil).

Virological response

After 24 weeks of treatment, a reduction of ≥2 log IU/ml in serum HBV DNA was obtained in 8/15 (53.3%)

Figure 1. Variation in mean serum HBV DNA levels during 48 weeks of treatment and 24 weeks of follow-up in the two treatment arms



Patients receiving pegylated interferon (PEG-IFN)-α first had significantly lower viraemia at week 48; however, patients who received telbivudine (LdT) first had lower HBV DNA levels at end of follow-up (week 72).

patients in the PEG-IFN first group versus 14/15 (93.3%) in the LdT first group (P=0.013).

Undetectable serum HBV DNA at week 24 was obtained in 3/15 (20%) patients in the PEG-IFN first group versus 10/15 (66.7%) in the LdT first group (P=0.009).

At the end of treatment (week 48), serum HBV DNA was undetectable in 12/15 (80%) patients in the PEG-IFN first group versus 7/15 (46.7%) in the LdT first group (P=0.058).

Virological relapse in patients who had undetectable HBV DNA at end of treatment was observed in 10/11 in the PEG-IFN first group (90.9%) versus 2/7 in the LdT first group (28.6%; P<0.01).

At the end of follow-up (week 72) sustained HBV DNA suppression to <2,000 IU/ml was obtained in 2/15 (13.3%) patients in the PEG-IFN first group versus 7/15 (46.7%) in the LdT first group (P=0.046). HBV DNA was undetectable at the end of follow-up in 0 and 2/15 (13.3%), respectively (P=0.14).

Mean ±SD HBV DNA levels at week 72 were 4.79 ±1.65 log IU/ml in the PEG-IFN first group versus 3.23 ±1.70 log IU/ml in the LdT first group (P=0.02). The variation in mean serum HBV DNA levels during treatment and follow-up are shown in Figure 1.

Virological breakthrough

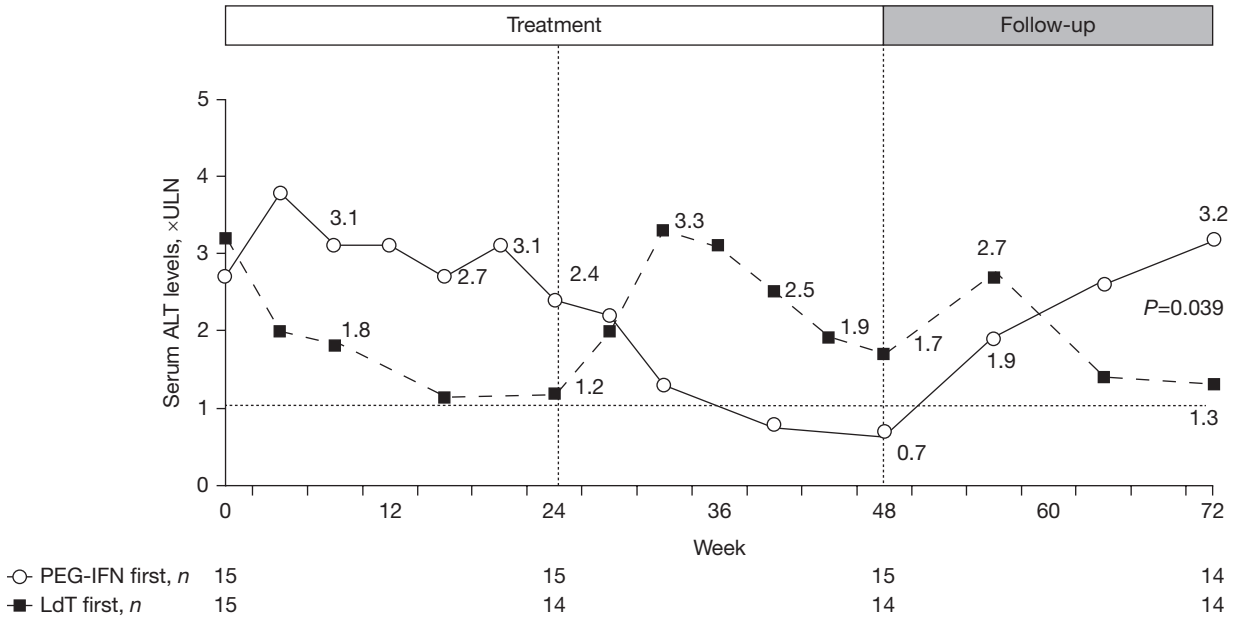
Virological breakthrough was defined as any increase >1 log IU/ml in serum HBV DNA from previous nadir on treatment. During the first 24 weeks of treatment no virological breakthrough was observed.

During weeks 24–48 of treatment, 1/15 (6.7%) patients in the PEG-IFN first group (who was therefore receiving LdT at time of breakthrough) presented with a >1 log IU/ml increase in serum HBV DNA compared with 3/14 (21.4%) patients in the LdT first group (P=0.24). Direct sequencing of HBV polymerase was performed in the one patient receiving LdT who developed an increase in viral load, and no mutations causing resistance to LdT were identified.

Biochemical response

After 24 weeks of antiviral treatment, ALT normalization was achieved in 1/15 (6.7%) patients in the PEG-IFN first group versus 11/15 (73.3%) patients in the LdT first group (P<0.001). At the end of treatment (week 48), ALT normalization was achieved in 14/15 (93.3%) patients in the PEG-IFN first group versus 5/15 (33.3%) patients in the LdT first group (P<0.001). At the end of follow-up (week 72) sustained biochemical response was obtained in 5/15 (33.3%) patients in

Figure 2. Variation in mean serum alanine aminotransferase levels during 48 weeks of treatment and 24 weeks of follow-up in the two treatment arms



ALT, alanine aminotransferase; LdT, telbivudine; PEG-IFN, pegylated interferon; ULN, upper limit of normal.

the PEG-IFN first group versus 7/15 (46.7%) patients in the LdT first group (P=0.45). Mean ±SD serum ALT levels at week 72 were 3.12 ±2.60×ULN in the PEG-IFN first group versus 2.16 ±2.7×ULN in the LdT first group (P=0.18). The variation in mean ALT levels during treatment and follow-up are shown in Figure 2.

Combined virological and biochemical response was obtained in 2/15 (13.3%) and 7/15 (46.7%) patients in the two groups, respectively (P=0.046). A summary of virological and biochemical response rates is shown in Figure 3.

Quantitative HBsAg/seroconversion

Mean ±SD baseline quantitative HBsAg levels were 3.9 ±0.4 log IU/ml in the PEG-IFN first group and 3.3 ±1 log IU/ml in the LdT first group. There were no significant differences between the two treatment groups in quantitative HBsAg levels at 24 and 48 weeks of treatment. Mean variation in quantitative HBsAg levels at week 48 was -0.1 ±0.4 log IU/ml among virological responders versus -0.2 ±0.1 log IU/ml among virological relapsers/non-responders (P=0.25). No patients lost HBsAg during treatment or follow-up.

Safety

Treatment was well-tolerated overall. One patient in the LdT first group discontinued treatment prematurely due a clinical adverse event (myalgia with elevated creatine kinase levels), and one patient in each group dropped out after treatment completion due to non-compliance with scheduled follow-up visits.

Dose reductions in PEG-IFN were required in 2/30 (6.7%) patients due to neutropaenia and myalgia. The most common clinical adverse events were fever and fatigue. No dose modifications of LdT were needed.

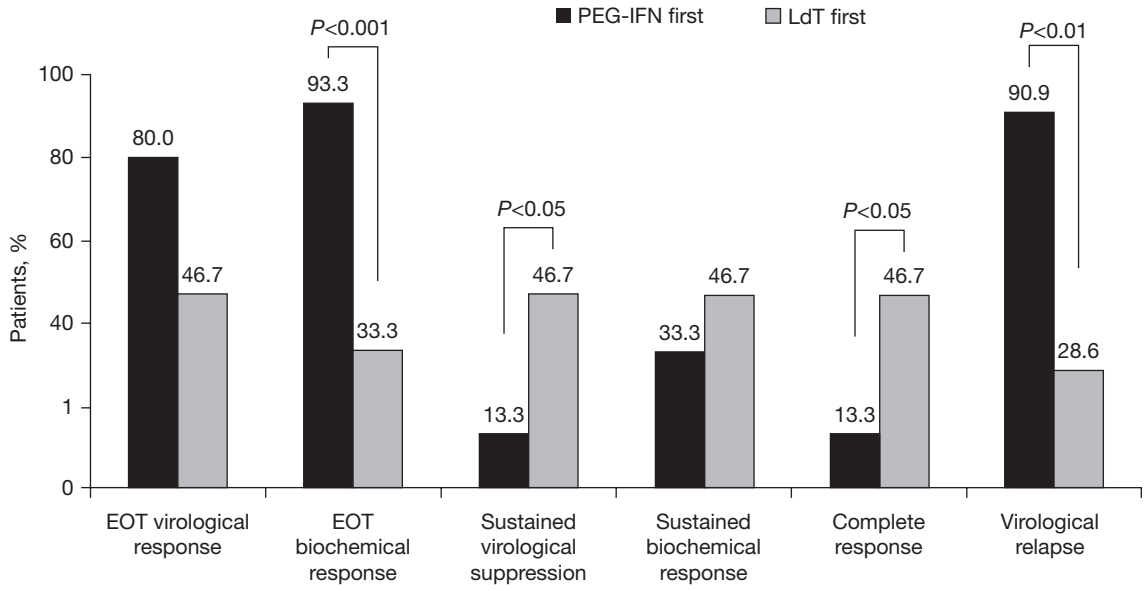
One serious adverse event (myalgia of the lower extremities with elevated creatine kinase levels) was reported in the LdT first group after 8 weeks of treatment, requiring premature discontinuation, with no reported sequelae.

A total of 4 (13.7%) patients had asymptomatic serum creatine kinase elevations ≥2×ULN (range 2.2–5×ULN).

Discussion

PEG-IFN-α is a potentially curative first-line therapy for compensated chronic hepatitis due to both wild-type (HBeAg-positive) and HBeAg-negative HBV infection in patients with significant viral replication, disease activity (as indicated by persistently abnormal ALT levels) and progressing hepatic fibrosis [15–17]. International guidelines based on large registration trials report rates of sustained viral suppression after 48 weeks of PEG-IFN treatment of 20%, depending

Figure 3. Comparison of study end points between the two treatment groups



End points were as follows: end of treatment (EOT; week 48) virological response (HBV DNA<12 IU/ml), EOT biochemical response (normal alanine aminotransferase [ALT]), sustained virological suppression (end of follow-up week 72; HBV DNA<2,000 UI/ml), sustained biochemical response (normal ALT; week 72), complete response (normal ALT and HBV DNA<2,000 IU/ml; week 72), and virological relapse (HBV DNA>2,000 IU/ml at week 72 in patients with undetectable HBV DNA at week 48). LdT, telbivudine; PEG-IFN, pegylated interferon.

on viral genotype. In HBeAg-negative chronic hepatitis B, use of nucleoside/nucleotide analogues as first-line monotherapy is limited by need of indefinite treatment duration and the consequent time-dependent risk of selecting drug-resistant HBV mutations. This issue is particularly relevant in Southern Europe, where >70% of patients are infected by genotype D and 90% are HBeAg-negative [8,9]. In this setting, the search for a treatment strategy combining the advantages of PEG-IFN-α and nucleoside/nucleotide analogues to allow treatment courses of definite duration has been recognized as a major unmet clinical need [15]. However, the optimal regimen of PEG-IFN-α with nucleoside/nucleotide analogues has not been identified, and published studies of dual therapy have not proven any benefit in terms of long-term outcome and/or cost savings. Randomized controlled trials of PEG-IFN monotherapy versus combination of PEG-IFN-α with antivirals have been performed with lamivudine [23] and adefovir dipivoxil [24], although neither demonstrated a benefit of combination therapy.

Using a short course of nucleoside/nucleotide analogue therapy to reduce viral load before starting PEG-IFN has also been explored [25–27]. In the study by Sarin *et al.* [25], 63 HBeAg-positive patients received either placebo or lamivudine for 4 weeks, then PEG-IFN for 24 weeks; patients who had received lamivudine before PEG-IFN showed a significantly higher rate of HBeAg loss, undetectable HBV DNA and anti-HBe seroconversion at the end of 24 weeks of follow-up. In the study by Moucari *et al.* [27], 20 consecutive HBeAg-negative patients received adefovir dipivoxil for 20 weeks, then added PEG-IFN for 4 weeks of combination treatment, then continued only PEG-IFN for 44 weeks. There was no control group in this study; however, 50% of patients maintained a virological response (defined as HBV DNA<10,000 copies/ml, equivalent to 2,000 IU/ml) 6 months post-treatment.

Despite these encouraging results, at present it is unknown whether reducing viral load with a nucleoside/nucleotide analogue before PEG-IFN therapy is more effective than starting a nucleoside/nucleotide analogue after PEG-IFN treatment has already exerted its immunomodulatory effects.

In the present clinical trial, we investigated the efficacy of two sequential nucleoside/nucleotide analogue and PEG-IFN regimens in achieving sustained HBV DNA suppression in a cohort of patients with compensated chronic HBeAg-negative hepatitis B. The majority of patients were infected with HBV genotype D, and mean baseline HBV DNA was 5.5 log IU/ml, as expected in our geographical region.

The benefit of a sequential treatment regimen in which each drug is administered for 24 weeks is a reduction

in treatment-related adverse events as well as treatment cost. Indeed only 1 (3.3%) patient did not complete treatment due to adverse events, and dose reduction in PEG-IFN was required in 2 (6.7%) patients overall.

By the end of 48 weeks of therapy, patients who had received PEG-IFN followed by LdT had a higher rate of undetectable HBV DNA (80% versus 46.7%; *P*=0.05) and a lower level of mean serum HBV DNA (1.25 log IU/ml versus 1.79 log IU/ml; *P*=0.03) compared with patients who received LdT followed by PEG-IFN.

This stronger inhibition of viral replication on-treatment, however, did not translate in a maintained viral suppression during follow-up. In fact, patients who received PEG-IFN followed by LdT showed a greater 'rebound' effect after LdT suspension, with a greater increase in serum HBV DNA between weeks 48 and 56 (3.5 log IU/ml versus 2.1 log IU/ml, respectively; *P*=0.03), and a lower rate of sustained viral suppression at end of follow-up (HBV DNA<2,000 IU/ml in 13.3% versus 46.7%). The long-term durability of the virological response in the LdT first arm will be observed as follow-up continues beyond the 'standard' 24 weeks.

It is well-known that suspension of nucleoside/nucleotide analogue- or interferon-based antiviral treatment can cause a flare in viral replication and necroinflammation, which requires careful monitoring of ALT levels and liver function tests. Interestingly, the most significant ALT flares occurred on treatment in the LdT first group, after LdT had been withdrawn and PEG-IFN had been administered for 8–12 weeks (week 24 mean ±SD ALT 1.2 ±0.8×ULN and week 32 mean ALT 3.3 ±3.6×ULN). Conversely, after treatment suspension, patients in the LdT first group showed a less intense ALT flare (end of treatment week 48 mean ALT 1.7 ±1.2×ULN and follow-up week 8 mean ALT 2.7 ±3.4×ULN; Figure 2).

Among patients who received PEG-IFN first, although >90% had normal ALT levels at the end of treatment, only 33% maintained normal ALT during follow-up. Withdrawal of LdT after PEG-IFN treatment was associated with a steady increase in mean ALT levels during follow-up, as depicted in Figure 2.

Early viral clearance appears to be crucial for maintaining a sustained response [28]: in our study the 80% of patients who obtained the primary outcome measure had achieved viral clearance after 4 weeks of therapy. However, the interplay between viral replication and host response cannot be predicted in terms of HBV DNA levels only. In fact, there were no significant differences in HBV DNA levels and rate of undetectable HBV DNA at the end of treatment among virological responders and relapsers/non-responders.

The possibility of a synergistic effect of LdT on a PEG-IFN-induced specific immune response in HBV infection is plausible. In a recent study in 50 Asian patients treated with LdT for 52 weeks, major changes of T-lymphocyte subgroups were observed in the peripheral blood. Furthermore, with a quantitative reduction in viral replication, the frequency of $CD4^+$ T-cells and the $CD4^+/CD8^+$ ratio increased during therapy [31]. In HBeAg-positive patients, LdT has been associated with an encouraging 6% rate of HBsAg loss [32], although comparisons with other analogues are hampered by the lack of head-to-head studies.

We did not detect significant differences in quantitative HBsAg level decline during treatment among patients who achieved a virological response, compared with those who did not; this could be explained by the relatively small number of patients and the wide range of baseline HBsAg levels.

In conclusion, sequential treatment regimens with PEG-IFN-α2a for 24 weeks followed or preceded by LdT for 24 weeks in HBeAg-negative chronic hepatitis B are well-tolerated and safe. The average drug costs of these regimens is 25% less compared with PEG-IFN monotherapy for 48 weeks (7,440 EUR versus 9,840 EUR), and the excellent tolerability profile reduces the need for medications for side-effect management (for example, anti-depressants, hypnotics and anxiolytics).

Regarding efficacy, beginning antiviral treatment with PEG-IFN and switching to LdT after 24 weeks resulted in greater serum HBV DNA suppression and ALT normalization on treatment, compared with the regimen with LdT followed by PEG-IFN. However, after 24 weeks of follow-up, patients who had received LdT followed by PEG-IFN exhibited greater HBV DNA suppression and less intense ALT flares, with a significantly higher proportion of patients with HBV DNA remaining below the threshold of significant replication. Therefore, this trial confirms the beneficial effect of nucleoside/nucleotide pretreatment before a finite course of PEG-IFN.

Larger trials exploring multiple sequential treatment steps with PEG-IFN-α and oral antivirals could be the next step towards a new treatment paradigm for chronic hepatitis B.

Acknowledgements

Partial funding was provided by Roche Pharmaceuticals (Milan, Italy).

Disclosure statement

MA is a consultant for Roche Pharmaceuticals. All other authors declare no competing interests.

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Accepted 6 June 2012; published online 7 August 2012