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Short Communication

Add-on peg-interferon leads to loss of HBsAg in patients with HBeAg-negative chronic hepatitis and HBV DNA fully suppressed by long-term nucleotide analogs

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ABSTRACT

Background and objective: The aim of this study was to prospectively evaluate whether the addition of peg-IFN to a stable NA regimen leads to loss of HBsAg in HBeAg-negative patients with chronic hepatitis and HBV DNA fully suppressed by long-term NA treatment.
Study design: We analyzed HBsAg levels in 10 HBsAg-positive, HBeAg-negative patients who received peg-IFN alpha-2a in addition to a NA regimen. Treatment lasted a maximum of 96 weeks, according to changes in the HBsAg titer. Before peg-IFN therapy, HBV DNA levels had been below the limit of detection for at least three years.
Results: HBsAg levels declined in nine patients. Among these nine, four became HBsAg-negative after 48 weeks of peg-IFN treatment; these patients received peg-IFN for only 48 weeks. NAs were stopped in these four patients, and these levels remained stable for at least 18 months (loss of HBsAg; HBV-DNA negative). HBs seroconversion was observed in two patients. The remaining five patients received 96 weeks of peg-IFN therapy. One patient became HBsAg-negative at the end of peg-IFN therapy; another became HBsAg-negative six months later. Three patients did not become HBsAg-negative. NAs were stopped in the two patients who became HBsAg-negative with no relapse during 12 months of follow up.
Conclusions: In HBsAg-positive, HBeAg-negative patients with HBV DNA were fully suppressed by long-term NA treatment, the addition of peg-INF for a maximum of 96 weeks based on HBsAg-titer monitoring led to a loss of HBsAg and cessation of NA therapy in six out of ten patients, with no relapse for 12–18 months of follow up. HBs seroconversion was observed in two patients.

1. Background

HBeAg-negative chronic hepatitis B (CHB) is currently the predominant type of CHB in Europe and the Mediterranean basin [1,2]. To date, two classes of drugs have been approved for the treatment of CHB: the immune-modulating drug pegylated interferon-alpha (peg-IFN) and inhibitors of viral replication, i.e., nucleotide analogs (NAs) [3,4]. Oral NAs are a potent therapeutic option for CHB but require long-term, indefinite therapy [5–7]. Ideally, treatment of CHB should aim at eliminating HBV, but this goal is not easily achievable with the currently available therapies [3,4].

Thus, it would be highly desirable to discover therapy that leads to the loss of HBsAg, allowing the patient to end treatment [4]. HBsAg reduction by NA is not as pronounced as by interferon treatment [8]. Recent trials combining peg-IFN and NA have shown the greatest decline in HBsAg [8–10], but the optimal schedule for combination therapy is unknown. Because HBsAg decline during therapy requires complete suppression of HBV DNA [11], it could be advantageous to add peg-IFN to long-term NA therapy in patients fully suppressed with NAs [12]. In this context, however, no study has tested the extension of peg-IFN treatment to 96 weeks based on HBsAg-titer monitoring.

Abbreviations: CHB, chronic hepatitis B; peg-IFN, pegylated interferon-alpha; NA, nucleotide analogs; BL, baseline; W48, week 48; W96, week 96; W120, week 120.

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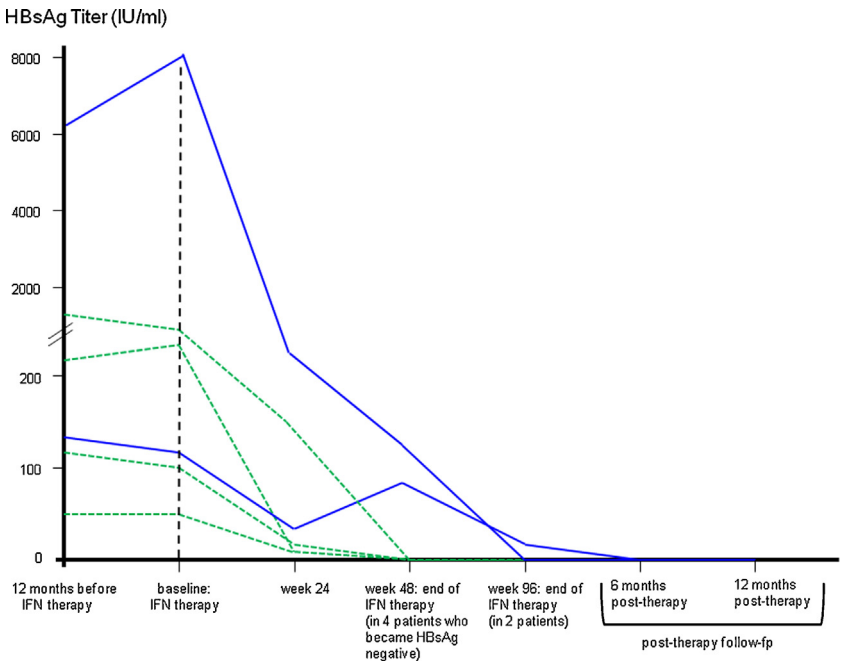

Fig. 1. HBsAg titers in the six patients who became HBsAg-seronegative. In these patients, the NA regimen was stopped when the patient became HBsAg-seronegative. The small dotted lines (green) represent the four patients who became HBsAg-seronegative at 48 weeks (peg-IFN and NA were stopped at W48); the solid lines (blue) represent the two patients in whom HBsAg levels decreased but did not become undetectable at W48 (peg-IFN lasted for 96 weeks). HBsAg levels were highly heterogeneous among patients. Thus, there is a break in the axis representing these values; the scale should be interpreted accordingly. (For interpretation of the references to color in the artwork, the reader is referred to the web version of the article.)

2. Objective

The aim of this study was to prospectively evaluate whether the addition of peg-IFN to a stable NA regimen leads to loss of HBsAg in HBeAg-negative patients with chronic hepatitis.

3. Study design

3.1. Patients

The inclusion criteria were HBsAg-positive, HBeAg-negative chronic hepatitis and long-term NA therapy with at least three years of fully suppressed viral load (limit of detection 20 IU/ml).

Ten consecutive patients were followed from September 2009 to March 2010 (median age 58 years old [min 41–max 76], all male). Peg-IFN alpha2a (Pegasys, Roche Pharma AG) was administered subcutaneously in a 180-μg dose once weekly for a maximum of 96 weeks. All patients had a viral load below the limit of detection for at least 36 months before interferon therapy was initiated. The patients' characteristics are shown in Table 1. Follow up was conducted 12–18 months after the end of peg-IFN therapy in all patients.

Patients were informed that their sample could be used for research purposes and were free to refuse. Samples were used anonymously, in accordance with principles of medical confidentiality.

3.2. HBsAg-titer quantification

Serum HBsAg-levels were quantified using the Quantitative Architect Abbott method (Abbott France, Rungis, France). HBV DNA was quantified using a Taqman assay (Roche Diagnostics) with a lower detection limit of 20 IU/ml. HBV genotyping was performed using the Trugene HBV-genotyping assay (Siemens, Germany) according to the manufacturer's instructions.

3.3. IL28B testing

The rs12979860 SNPs were analyzed in a Fret 5′ allelic-discrimination assay using the Roche LightCycler® FastStart DNA Master HybProbe with the LightCycler® 1.x/2.0/480 Instruments [13].

3.4. Data analysis

HBsAg levels one year before peg-IFN therapy, at baseline (BL), and during peg-IFN at week 24 (W24), week 48 (W48), and week 96 (W96) were compared pairwise to determine the decline in titer for each patient. HBV-DNA and HBsAg levels were also determined 12 months after interferon therapy in patients receiving 96 weeks of peg-IFN; these data were measured after 18 months in those receiving only 48 weeks of peg-IFN therapy.

4. Results

As expected, minimal changes in HBsAg levels were observed in patients treated with NAs alone within the year before the start of peg-IFN therapy; the median decline was 5 IU/ml [95%CI 0–360] (Figs. 1 and 2). During add-on peg-IFN therapy, HBsAg levels declined in nine out of ten patients; the median decline was 519 IU/ml [0–1997] (Figs. 1 and 2). In one patient, HBsAg levels remained high, and peg-IFN therapy was stopped at week 24 (Fig. 2). This patient remained HBsAg-positive. Among the nine remaining patients, four became HBsAg-negative at week 48 of peg-IFN therapy, so they received peg-IFN for only 48 weeks (Fig. 1). NAs were also stopped in these four patients, and these levels remained stable for at least 18 months after peg-IFN therapy (HBsAg-negative; HBV-DNA negative). HBs seroconversion was observed in two of these patients. The remaining five patients received 96 weeks of peg-IFN therapy. One patient became HBsAg-negative at the end of peg-IFN therapy, and one patient became HBsAg-negative six months later. Three patients did not become

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