Antimicrobial Original Research Paper

Pegylated interferon in HBeAg-positive and -negative chronic hepatitis B patients: post-treatment 1-year results of three Turkish centres

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In this study, we aimed to evaluate the 1-year post-treatment follow-up results of 112 patients who received pegylated interferon (PEG-IFN) for 52 weeks. HBeAg negativity/seroconversion and/or negative HBV-DNA at the end of the treatment were considered as response. Patients who had response at the end of treatment but had HBV-DNA breakthrough during 1-year follow-up were considered as relapse. The study group comprised 112 cases (34 HBeAg-positive, 78 HBeAg-negative). In HBeAg-positive and -negative cases, end-of-treatment response rates were 2.9% and 60.2%, whereas 1-year sustained virological response rates were 0 and 33.3%, respectively. When we compared relapse cases versus cases with response at the end of 1-year follow-up, being female and having low viral load were the two parameters associated with higher response rates (Chi-square, $P = 0.028$; Mann–Whitney U test, $P = 0.023$). Overall non-response rates to PEG-IFN were high (57.1%). Results in HBeAg-positive cases were disappointing.

Keywords: Chronic hepatitis B, Genotype, Pegylated interferons, Primary non-responders, Secondary non-responders, Treatment response

Introduction

After about 20 years in the treatment age of chronic hepatitis B (CHB), evaluation of the long-term outcomes in any kind of treatment is still of prime importance.[1] Recombinant and the more recent pegylated interferons (PEG-IFNs) are the drugs with the longest clinical experience. When compared to antiviral agents, the main advantages of PEG-IFNs are standard treatment duration and higher rates of HBeAg and HBsAg loss[2] However, the current clinical practice guidelines indicate the appropriate selection of patients due to high relapse rates and treatment continuation decision relies on the HBeAg and/or HBsAg titers during the treatment.[3–5] The aim of this study was to evaluate retrospectively the 1-year post-treatment follow-up results of patients who received PEG-IFN for 52 weeks between 2008 and 2010.

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Methods

This study was conducted retrospectively in three centres in two provinces of Turkey. Two centres are located in İzmir, western Turkey, while one is located in Adana, southern Turkey.

All patients who received PEG-IFN for 1 year between 2008 and 2010 were included in the study, except anti-HDV-positive cases.

All cases were evaluated once every 3 months in terms of their HBsAg loss and/or seroconversion, HBeAg loss and/or seroconversion, ALT and HBV-DNA [COBAS AmpliPrep COBAS TaqMan 48 (CAP-CTM; Roche, Branchburg, NJ, USA)] levels during the treatment, at the end of the treatment and at 1 year post-treatment.

End-of-treatment (EOT) response for HBeAg-positive patients was defined as HBeAg loss/seroconversion or undetectable HBV-DNA at the end of treatment as well as at 1 year post-treatment, and undetectable HBV-DNA among anti-HBeAg-positive patients. Patients who did not have 1 log decrease on the twelfth week of treatment were considered as primary non-responders.[6] Secondary non-responders (viral breakthrough) were defined as

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Table 1 Patients' baseline characteristics in study group

	Gender (male/female)	Age	Compensated cirrhosis	Pre-treatment ALT	Pre-treatment HBV-DNA (IU/l)	Modified Knodell (grade)	Modified Knodell (stage)
HBeAg-positive ($n = 34$)	23/11	29.0±9.4	2/34	116.7±78.4 (31–433)	9.3×10^7	6.5±2.6 (3–12)	1.4±0.8 (0–3)
HBeAg-negative ($n = 78$)	54/24	39.2±10.2	/78	106.5±74.7 (22–448)	1.5×10^7	7.1±2.9 (3–14)	1.4±1.0 (0–3)
Total ($n = 112$)	77/35	36.1±11.0	6/112	109.6±75.6	3.9×10^7	6.9±2.8	1.4±0.9
P		< 0.001	0.870	0.513	0.022	0.298	0.936

cases who had primary response or had undetectable HBV-DNA levels, but developed detectable HBV-DNA during treatment. Patients who had response at the end of treatment, but had HBV-DNA breakthrough [> 2000 IU/ml COBAS AmpliPrep COBAS TaqMan 48 (CAP-CTM; Roche)] during the 1-year follow-up were considered as relapse. Result analysis was performed in terms of intention to treat analysis (ITT). Chi-square, Student's *t*-test, and Mann–Whitney *U* test were used for statistical analysis.

Results

The study group comprised 112 cases (34 HBeAg-positive, 78 HBeAg-negative, 77 male, 35 female, age 36.19 ± 11.01 years). Sixty-eight patients were treated with PEG-IFN-alpha-2a (180 μg/ml) and 44 patients received PEG-IFN-alpha-2b (1.5 μg/kg) once a week for 1 year. Age, gender, pre-treatment ALT and HBV-DNA levels, clinical status, and liver biopsy scores as modified Knodell grade and stage are shown in Table 1. In HBeAg-positive and -negative cases, EOT response rates were 2.9% (1/34) and 60.2% (47/78), whereas 1-year sustained virological response (SVR) rates were 0 and 33.3% (26/78), respectively (Table 2). One HBeAg-positive case had anti-HBe seroconversion, but seroreverted at 1 year post-treatment. HBsAg loss did not occur in any of the cases.

In terms of side effects, 32 (28%) had flu-like symptoms in the first 4 weeks of the therapy, 13 (11.6%) had both moderate anaemia (haemoglobin: 10–8.5% mg/dl) and moderate leukopenia (5000–3500/mm^3), and one had local skin infection among the study group. Moreover, none of these side effects necessitated dose modification or drug cessation.

When we compared the 22 cases with relapse (21 HBeAg-negative, 1 HBeAg-positive) at the end of the 1-year follow-up with the 26 cases (all HBeAg-negative) with sustained response in terms of gender, age, ALT, and HBV-DNA levels at the beginning of treatment, we found that being female and having low viral load (HBV-DNA $< 10^7$ IU/ml) were the two parameters associated with sustained response (Chi-square, $P = 0.028$; Mann–Whitney *U* test, $P = 0.023$).

Discussion

Although the treatment of CHB has started in the 1990s, a dynamic process is experienced in this field including release of new medications, new techniques in detecting HBV-DNA, and updates in treatment response definitions in the guidelines. When this cohort was being followed up, non-response to interferon treatment was defined as less than 1 log decrease in HBV-DNA level on the third month of the treatment, according to the EASL 2009 treatment guideline.[6] In the presented series, primary non-responders among HBeAg-positive and HBeAg-negative patients were 31% and 19%, respectively. This rate is considerably high especially for HBeAg-positive patients. However, the initial HBV-DNA level of this group was higher than the anti-HBe-positive group, which might explain the difficulty in attaining 1 log decrease at the third month of treatment. This is the reason why long-term evaluation of interferon treatment were considered more rational and the definition of primary non-responders was removed in the EASL 2012 treatment guideline.[5] Similarly, four patients, who were defined as secondary non-responders in the anti-HBe-positive group previously according to 2009 guideline (because of having positive HBV-DNA at the end of treatment), were categorized as a satisfactory virological endpoint for IFN-based treatment according to 2012 EASL guideline. One year after treatment, two of these four cases had continuous virological response, whereas two had relapsed.

In our study, response rates at the end of treatment were 2.9% and 60.2%, whereas 1-year post-PEG-IFN treatment response rates were 0% and 33.3%, among

Table 2 Results of the study in terms of ITT analysis

	Primary non-responders, *n* (%)	Secondary non-responders, *n* (%)	End-of-treatment response, *n* (%)	One-year sustained virological response, *n* (%)
HBeAg-positive ($n = 34$)	31 (91.2)	2 (5.9)	1 (2.9)	0 (0)
HBeAg-negative ($n = 78$)	19 (24.4)	12 (15.4)	47(60.2)	26 (33.3)
Total ($n = 112$)	50 (44.6)	14 (12.5)	48 (42.9)	26 (23.2)
P	< 0.001	0.221	< 0.001	NA

HBeAg-positive and -negative cases, respectively. Both EOT response and SVR rates were low especially in HBeAg-positive cases. Two previous studies have reported relatively high HBeAg seroconversion rates among HBeAg-positive patients after 1-year PEG-IFN treatment (32% and 29%, respectively), while their rate of negative HBV-DNA rates (HBV DNA < 60–80 IU/ml) were low (14% and 7%, respectively).[7,8] Although PEG-IFNs are known to have good immunomodulating and weak antiviral activity, published studies in Turkey do not achieve the HBeAg and HBsAg loss and seroconversion rates achieved in other countries. In a study by Yapalı *et al.* on 2794 chronic hepatitis B patients with a mean follow-up of 184 weeks, overall 1-year HBsAg loss rate was 0.26%. This rate was 4.35% among patients with response to IFN treatment and 0.09% among patients with failure.[9] The low HBsAg loss rates in Turkey as compared to studies from other countries may be related to much younger infection acquisition age in Turkey as compared to Europe.[10]

When we compared HBeAg-negative patients with HBeAg-positive ones, HBeAg-positive cases have lower response to PEG-IFN. Karabay *et al.* have reported a 6-month post-treatment response rate of 17% among 155 HBeAg-negative patients treated with PEG-IFN.[11] This rate is comparable to 33.3% SVR rate in our HBeAg-negative cohort.

Treatment of chronic HBV infection requires initiation of appropriate treatment options, i.e. interferon or antiviral to appropriate cases. In HBeAg-positive CHB, predictors of anti-HBe seroconversion after treatment with PEG-IFN are (1) low viral load (HBV-DNA < 2×10^8 IU/ml); (2) high serum ALT levels (> 2–5 times ULN); (3) high activity scores on liver biopsy (at least A2); and (4) HBV genotypes A and B which are associated with higher rates of anti-HBe seroconversion and HBsAg loss when compared with genotypes D and C.[12–15] In the presented series, when compared to relapsing patients, patients responding to treatment were significantly more likely to be female and had significantly lower basal HBV-DNA levels. These two criteria are the predictors of good response before the initiation of treatment. However, there are reports indicating that HBV genotype is another important criterion predicting treatment outcome and it would be beneficial to determine the HBV genotype before initiating interferon treatment.[12] Among genotype D patients, independent of ALT and HBV-DNA levels, response rates to interferon treatments is generally low.[13] Buster *et al.* reported sustained response rates among genotype A, B, and C patients as 37%, 25%, and 20%, respectively. However, it was only 8% in genotype D patients.[13] In another study by Şentürk *et al.*, evaluating the long-term outcomes of interferon treatment among HBeAg-positive patients, seroconversion had occurred in 39% of the 71 CHB patients at the end of treatment. After a 152-week follow-up of the same group of patients, 84% of the seroconverting patients were reported to have HBeAg seroreversion or HBV-DNA elevation (over 2000 IU/ml).[15] Similar to their findings, the response rate of our HBeAg-negative cohort dropped from 60% at the end of treatment to 33% at 1-year post-treatment. We can speculate that the low post-treatment 1-year response rates of our patients might be due to genotype D which is widespread in our country.[16]

In conclusion, our response rates to PEG-IFN treatment are low. Results in HBeAg-positive cases are disappointing. In HBeAg-negative cases, end of treatment response rates were relatively good, but 1-year follow-up results suggest that more than half of the responders had relapsed.

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