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Safety of peginterferon alfa-2a (40KD) treatment in patients with chronic hepatitis B infection: An observational, multicenter, open label, non-interventional study in Turkish patients

Nurdan TÖZÜN[1], Orhan SEZGİN[2], Murat GÜLŞEN[3], Sabite KACAR[4], Necati YENİCE[5], Şerif YILMAZ[6], Saadettin HÜLAGÜ[7], Bülent KANTARÇEKEN[8], Fahri YAKARYILMAZ[9], Alper YURCİ[10], Kemal Mustafa SEREZ[11], Halil BAHÇECİOĞLU[12], Sait BAĞCI[13]

Department of [1]Gastroenterology, Acıbadem University, Acıbadem Kozyatağı Hospital, İstanbul
Department of [2]Internal Medicine, Division of Gastroenterology, Mersin University School of Medicine, Mersin
Department of [3]Internal Medicine, Division of Gastroenterology, Gaziantep University School of Medicine, Gaziantep
Department of [4]Gastroenterology, Türkiye Yüksek İhtisas Research and Training Hospital, Ankara
Department of [5]Gastroenterology, Okmeydanı Research and Training Hospital, İstanbul
Department of [6]Gastroenterology, Dicle University School of Medicine, Diyarbakir
Department of [7]Gastroenterology, Kocaeli University School of Medicine, Kocaeli
Department of [8]Gastroenterology, Sütçü İmam University School of Medicine, Kahramanmaraş
Department of [9]Internal Medicine, Division of Gastroenterology, Kırıkkale University School of Medicine, Kırıkkale
Department of [10]Gastroenterology, Erciyes University School of Medicine, Kayseri
Department of [11]Gastroenterology, Haseki Research and Training Hospital, İstanbul
Department of [12]Gastroenterology, Fırat University School of Medicine, Elazığ
Department of [13]Internal Medicine, Division of Gastroenterology, Gülhane Military Medical Academy, Ankara

Background/aims: *Pegylated alfa interferon is the only immunomodulatory drug licensed for hepatitis B. We evaluated the safety and tolerability of peginterferon alfa-2a (40KD) in patients with chronic hepatitis B.* ***Materials and Methods:*** *A total of 113 chronic hepatitis B patients under peginterferon alfa-2a (40KD; 180 µg/week) treatment were included in this multicenter, open label, non-interventional study, and 66 patients completed the follow-up period. Vital signs, physical examination and laboratory findings, concomitant medications, and adverse events were recorded. A Quality of Life questionnaire (Short Form-36) was performed twice, at the beginning and at the end of the study.* ***Results:*** *There was no significant difference between initial and last visits in terms of physical examination findings and Short Form-36 scores. A total of 27 adverse events were reported in 15 patients (22.7%), with most of them being mild in intensity (70.4%). The rates of the adverse events were similar in the monotherapy and combination therapy groups (peginterferon alfa-2a + lamivudine, peginterferon alfa-2a + adefovir or peginterferon alfa-2a + entecavir therapy groups), at 23.7% and 14.3%, respectively. The dosage of peginterferon had to be reduced in 3 patients (4.5%) due to thrombocytopenia. Overall patient compliance to treatment was detected as 85.9%.* ***Conclusions:*** *Based on the lack of serious adverse events and absence of impairment in Quality of Life, peginterferon alfa-2a (40KD, 180 µg/week, subcutaneously) treatment for 48 weeks led to a high level of patient compliance and was associated with a high degree of safety and tolerability for the treatment of adult patients with chronic hepatitis B in real-life practice.*

Key words: Peginterferon alfa-2a, HBV infection, safety, patient compliance, tolerability, real-life practice

Address for correspondence: Nurdan TÖZÜN
Department of Gastroenterology, Acıbadem University, Acıbadem Kozyatağı Hospital, Kozyatağı, İstanbul, Turkey
Phone: + 90 216 571 44 44
E-mail: nurdan.tozun@acibadem.edu.tr

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Kronik hepatit B'li hastalarda peginterferon alfa-2a (40KD) tedavisinin güvenilirliği: Türk hastalarda yürütülen çok merkezli, açık etiketli, müdahalesiz, gözlemsel bir çalışma

Amaç: *Pegile interferon alfa hepatit B tedavisinde kullanımı onaylanmış tek immünmodülator ilaçtır. Biz, bu çalışmada kronik hepatit B'li hastalarda peginterferon alfa-2a (40KD) tedavisinin güvenilirliğini değerlendirdik.* ***Gereç ve Yöntem:*** *Bu çok merkezli, açık etiketli, müdahalesiz, gözlemsel çalışmaya dahil edilen peginterferon alfa-2a tedavisi (40KD; 180 µg/hafta) altındaki 113 kronik hepatit B hastasından 66'sı takip dönemini tamamladı. Vital bulgular, fizik muayane ve laboratuvar bulguları, eşlik eden ilaç kullanımı ve advers olaylar kaydedildi. Yaşam kalitesi anketi (kısa form-36) çalışmanın başında ve sonunda olmak üzere toplamda iki kez uygulandı.* ***Bulgular:*** *Başlangıç ve çalışma sonu vizitleri arasında fizik muayene bulguları ve kısa form-36 skorları açısından anlamlı bir faklılık gözlenmedi. Toplamda 15 hastada (%22.7) rapor edilen 27 adet advers olayın çoğunluğu (%70.4) hafif şiddette idi. Monoterapi ve kombinasyon tedavisi (peginterferon alfa-2a + lamivudin, peginterferon alfa-2a + adefovir veya peginterferon alfa-2a + entekavir tedavi grupları) gruplarında advers olay oranları sırasıyla %23.7% ve %14.3 olarak benzer şekilde bulundu. Peginterferona yönelik doz azaltımı trombositopeni nedeniyle toplamda 3 hastada (%4.5) gerçekleştirildi. Hastaların tedaviye uyum oranı %85.9 olarak belirlendi.* ***Sonuç:*** *Ciddi advers olaylara ve yaşam kalitesinde belirgin bir bozukluğa yol açmaması esas alındığında, 48 haftalık peginterferon alfa-2a (40KD, 180 µg/hafta, subkutan) tedavisi erişkin kronik hepatit B hastalarına yönelik klinik uygulamada; hasta uyumu, güvenlilik ve tolerabilite açısından olumlu sonuçlar vermiştir.*

Anahtar kelimeler: Peginterferon alfa-2a, HBV enfeksiyonu, güvenlilik, hasta uyumu, tolerabilite, klinik uygulama

INTRODUCTION

Hepatitis B virus (HBV) is one of the most serious and prevalent health problems, affecting more than 2 billion people worldwide. Although highly effective vaccines against HBV have been available since 1982, there are still more than 350 million chronic carriers. People with hepatitis B are at increased risk of developing hepatic decompensation, cirrhosis and hepatocellular carcinoma (HCC). The estimated worldwide mortality is 0.5 to 1.2 million deaths per year (1).

The goal of therapy for hepatitis B is to improve quality of life (QoL) and survival by preventing progression of the disease to cirrhosis, HCC and death. This goal can be achieved with sustained suppression of HBV replication. However, HBV infection cannot be completely eradicated due to the persistence of covalently closed circular DNA (cccDNA) in the nucleus of infected hepatocytes (2).

Peginterferon alfa-2a (40KD) has antiviral and immunomodulatory effects. The binding of interferon alfa to specific cell surface receptors initiates intracellular signaling resulting in the activation of gene transcription. This increased expression of intracellular genes results in increased breakdown of viral DNA and protects against viral injury. In addition, cell-mediated immune responses are also stimulated by interferon alfa. These immune responses target hepatocytes infected with HBV, reducing the number of cells containing the HBV cccDNA molecule that is responsible for the persistence of chronic HBV infection (3).

Treatment with interferon-based therapy may be associated with varying degrees of adverse events (AEs), such as fatigue, myalgia, flu-like symptoms, and alterations in mood, which may negatively affect the patient's Health-Related Quality of Life (HRQoL) by changing their vitality, social interaction and ability to function (4).

Despite considerable efforts to comprehend the efficacy, side effects and cost-effectiveness of new antiviral regimens for HBV, there is a significant paucity of HRQoL data for patients chronically infected with HBV (5). Since anti-HBV regimens have been designed for long-term viral suppression, it would be critical for the drugs to provide evidence that the side-effect profile of the HBV therapy does not negatively impact patients' HRQoL (5) in addition to its efficacy. Therefore, the present study was designed to assess the safety and tolerability of 48-week peginterferon alfa-2a therapy and to address all aspects of HRQoL in a cohort of Turkish CHB patients in order to provide national data on real-life practice of CHB management.

MATERIALS AND METHODS

A total of 113 patients meeting the inclusion criteria were included in this multicenter, open label, non-interventional study aiming to evaluate the safety and tolerability of peginterferon alfa-2a (Pegasys®; 40KD, 180 µg/week, subcutaneously)

in CHB patients treated in gastroenterology clinics across Turkey during a 12-month recruitment period between March 2006 and April 2007. CHB patients aged 18-65 years and on peginterferon alfa-2a (40KD) treatment with the diagnosis of CHB infection were included in the study upon receipt of their written informed consent. The main criteria for exclusion were pregnancy, lactation, any condition considered by the researcher to prevent participation of the patient in completing the study treatment period, presence of another liver disease, and known hypersensitivity to the study medication. The treatment duration was 48 weeks.

In line with the non-interventional, observational nature of the study, there was no limitation concerning concomitant medications, treatment regimens, procedures, or intervention to treatment or dose selection by the physician.

Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study, which was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the institutional ethics committee of the coordinator center.

Study Visits and Data Collection

Each center provided data obtained at each and every visit performed with respect to their routine clinical practice. Case Report Forms (CRFs) were prepared in accordance with visit number every 4 weeks for the first 20 weeks and every 8 weeks thereafter during the 48-week treatment period. Initial and last visits were obligatory according to the study protocol.

Patients were planned to be followed up for an additional 24 weeks after the treatment in order to evaluate drug safety. However, due to inability to reach the targeted number of the patient population, and of 21.2% (n=14) of patients being lost to follow-up during the additional post-treatment follow-up period, the data collected from 66 patients who had initial and end of treatment visit results were evaluated.

Patient demographics, previous history of hepatitis B infection and concomitant diseases as well as medical treatments were recorded at the initial visit. Vital signs, physical examination, laboratory findings, concomitant medications, and AEs were identified and recorded at visits performed during the 48-week treatment course. If available, liver biopsies were evaluated for histological activity, portal inflammation and/or bridging necrosis, intralobular degeneration and focal necrosis, and fibrosis scores. A QoL Questionnaire (Short Form [SF]-36) was applied twice, at the beginning and at the end (48 weeks) of the study. Loss of hepatitis B e antigen (HBeAg) and appearance of anti-HBe antibodies at the 48th week were assessed for initially HBeAg-positive patients. Incidence, severity and outcome of AEs as well as dose adjustments and compliance to treatment were evaluated to determine safety.

Health-Related Quality of Life Questionnaire (SF-36)

Health-related quality of life (HRQoL) was assessed twice, at the beginning and at the end (48 weeks) of the study, using the SF-36 questionnaire of the Medical Outcomes Study (6), which has also been validated in Turkish patients (7). Being a widely used and validated generic HRQoL questionnaire (8), the SF-36 includes 36 items divided into eight scales or indices, which can be aggregated into two summary scores: a mental component summary (MCS) and a physical component summary (PCS). These indices include Physical Functioning, Role Physical (role limitations as a result of physical health), Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional (role limitations as a result of mental problems) and Mental Health. SF-36 scores on the individual scales range between 0 and 100, while PCS scores range between 8 and 73, and MCS scores range between 10 and 74. Higher scores on each scale reflect a better QoL (5).

Statistical Analysis

Statistical analysis was done using the Statistical Package for the Social Sciences (SPSS) computer software (version 13.0, SPSS Inc. Chicago, IL, USA). Distribution of patients in terms of end points of the study and AEs were determined. Wilcoxon paired test and McNemar test were used to compare alterations in parameters at the initial and 48th week visits. Analysis of categorical data was performed by chi-square and Fisher's tests. Correlation analysis was performed to determine the association between end points and compliance to treatment. Data were expressed as mean ± standard deviation (SD), percent (%) and median (min-max) where appropriate. $p<0.05$ was considered statistically significant.

RESULTS

Patient Demographics and Medical History

The mean age of the 66 patients who completed the treatment period was 35.4±10.9 years. The majority (66.7%) were male. The educational status of the patient population was as follows: 1.7% uneducated, 33.9% primary school, 35.6% high school, and 28.8% university graduates. Mean body height and weight were 171.5±8.0 cm and 73.7±12.8 kg, respectively.

Mean duration of hepatitis B infection was determined to be approximately 3.5±4.7 years. Route of hepatitis transmission was intrafamilial in 16.1%, but unknown in the remaining. Regular alcohol consumption was rare (3.2%) among the study population. Previous history of hepatitis treatment was obtained from 83.3% of patients; peginterferon alfa-2a (180 µg/week, subcutaneously) was the drug used in 88.5%, lamivudine in 4.9% and standard interferon in 6.6%. There was no concomitant disease in 83.3% of the patients, with hypertension being the only disease reported in 2 patients. In 74.2% of the patients, no use of concomitant drug was reported. The major cause of concomitant drug use (lamivudine, entecavir, adefovir) was hepatitis B (30.8%).

Vital Signs, Physical Examination and Laboratory Findings

At the initial and 48th week visits, most of the patients were asymptomatic (71.5% and 69.7%, respectively), and there was no significant difference between the initial and last visits in terms of frequency of symptoms; fatigue was reported in 18.2% and 19.7% of the patients, respectively.

Hematological assessments at the 48th week revealed significant reduction in hemoglobin levels and leukocyte, platelet and neutrophil counts when compared to baseline values obtained at the initial visit ($p<0.001$ for each; Table 1); however, all values were considered within normal limits. Likewise, blood biochemistry revealed a significant decline in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels at the 48th week compared with the initial values ($p<0.001$ for each; Table 1).

Therapeutic Efficacy Parameters

Of the 21 patients with HBeAg positivity at baseline, HBeAg measurements could be recorded at the end of the treatment period in 14 patients, of whom HBeAg clearance was detected in 6 (42.9%). Both HBeAg and anti-HBeAg were negative in 2 of these 6 patients, but anti-HBeAg remained negative in the remaining 4 patients. Seroconversion was observed in 6 of 21 patients (28.6%) in the patient population.

Hepatitis Treatment during the Course of the Study

In the 4th week of the study, percentages of patients on peginterferon alfa-2a (40KD) vs. peginterferon alfa-2a combination therapy with lamivudine or adefovir treatment were 87.3%, 12.7% and 1.6%, respectively. No change in the treatment regimen was observed during the course of the study. At the end of the study, peginterferon alfa-2a (40KD) was found to be the preferred drug as monotherapy in 88.5% of patients, and in combination with lamivudine or adefovir in 9.8% and 1.6% of patients, respectively.

Safety Evaluation

A total of 26 AEs were reported in 15 patients (22.7%), the majority of which (70.4%) were mild events. Representing 22% of AEs in total, leukopenia was the diagnosis in 6 patients (9.1%), while thrombocytopenia (18.5% of AEs) was observed in 5 patients (7.6%). AEs were reported to resolve spontaneously in 59.3% of patients but to persist in 22.2% of the patients (Tables 2, 3).

It was denoted that 55.6% of the AEs were related with the study medication.

None of the patients evaluated in the study skipped a dose of the drug during the last 4 weeks of

Table 1. Comparison of initial and last visits in terms of laboratory test results

	Week 0		Week 48	
	n	Mean±SD	n	Mean±SD
Lab findings				
ALT (u/l)	61	135.8±117.8	55	47.7±40.5*
AST (u/l)	61	69.9±52.5	55	35.9±21.2*
Bilirubin (mg/dl)	56	0.8±0.4	44	0.6±0.3*

AST: Aspartate aminotransferase. ALT: Alanine aminotransaminase. * $p<0.001$; compared to initial visit performed in Week 0.

Table 2. Adverse events and patient compliance to treatment

	N	%
Number of patients compliant to the therapy	55	85.9
Number of patients with AEs	15	22.7
Adverse event severity by AE number		
Mild	19	70.4
Moderate	6	22.2
Severe	1	3.7
Not identified	1	3.7
Dose alteration due to adverse event		
None	25	92.6
Temporary discontinuation of the drug	1	3.7
Permanent discontinuation of the drug	1	3.7
SAE	0	0
Adverse event outcome		
Persisting	6	22.2
Resolved	16	59.3
Unknown	5	18.5
Total	27	100.0

SAE: Serious advers events

Table 3. Incidence and list of adverse events

	n	Overall Adverse Events* %	All Patients** %
Leukopenia	6	22.2	9.1
Thrombocytopenia	5	18.5	7.6
Anemia	1	3.7	1.5
Itchy scalp	1	3.7	1.5
Headache	1	3.7	1.5
Low back pain	1	3.7	1.5
Blurred vision	1	3.7	1.5
Palpitation	1	3.7	1.5
Depression	1	3.7	1.5
Flu-like syndrome	1	3.7	1.5
Hyperthyroidism	1	3.7	1.5
Hypertension	1	3.7	1.5
Tremor and headache after the first dose	1	3.7	1.5
Hair loss	1	3.7	1.5
Facial acne	1	3.7	1.5
Not identified	2	7.4	3.0
Total	26	100.0	

*percentage calculated over 26 adverse events in total ** percentage calculated over 66 patients

the treatment. Dosage of peginterferon alfa-2a (40KD; 180 mg/week) was reduced in 3 patients (4.5%) due to thrombocytopenia. Overall patient compliance to treatment was detected to be 85.9%.

Only 9 patients showed non-compliance due to a skip in the dose of the drug (n=6), dose modification (n=2), or for both reasons (n=1). Dose modification was performed in 2 patients in the 12th week and in 1 patient in the 44th week.

Health-Related Quality of Life Assessment

Concerning items of the SF-36 related to QoL, patients scored overall physical and mental component scores of the SF-36 questionnaire similarly at the initial and 48th week visits. Additionally, baseline and week 48 scores were obtained for items related to physical role, bodily pain, and general health items of the physical component as well as to energy-vitality, social functioning, emotional ro-

le, and mental health items of the mental component. Albeit not significant, there was a tendency for an impairment in mental health scores at the end of the 48th week (p>0.05; Figure 1).

DISCUSSION

Interferon alfa has been shown to be effective and well tolerated in the treatment of CHB. Approximately 30% of HBeAg-positive and 40% of HBeAg-negative cases have a sustained virological response six months after completion of a 48-week course of peginterferon alfa-2a. These responses remain durable up to the rate of 80-90% when evaluated several years later (9,10).

In early studies, HBeAg was cleared in one-third of patients treated with standard (non-pegylated) interferon alfa (11,12). On the other hand, at the end of the treatment period, HBeAg seroconversion was achieved in 27% of patients with HBeAg-positive disease who were treated with peginterferon alfa-2a for 48 weeks (13). HBeAg seroconversion rate has reached up to 42% at the one-year follow-up after the therapy (14). In the present study, HBeAg clearance rate was 42.9% (n=6/14) in patients who were initially HBeAg-positive, and HBeAg seroconversion rate was 28.6% at the end of the treatment, consistent with the earlier studies (13,15). Although HBV-DNA suppression and ALT normalization rates were not evaluated due to the lack of relevant data, significant loss of HBeAg with seroconversion is highly suggestive of therapeutic efficacy of 48-week long peginterferon alfa-2a (40KD; 180 mg/week) treatment in patients with HBeAg-positive disease.

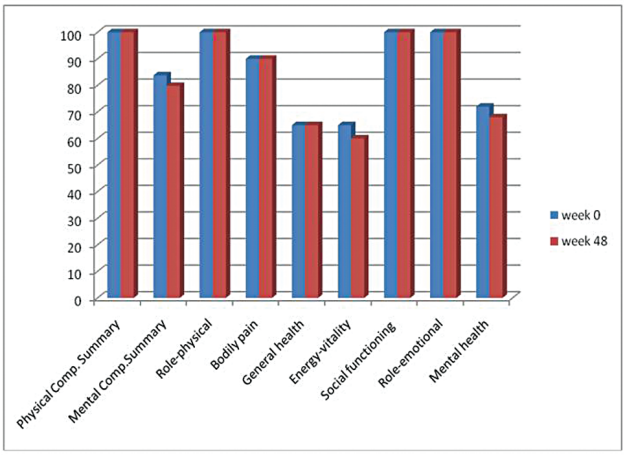

Figure 1. Comparison of initial and 48th week visits in terms of median scores obtained in the SF-36 Quality of Life Questionnaire.

Peginterferon has been documented to result in the highest rate of off-treatment sustained response amongst the currently available drugs for the treatment of CHB, as a strong predictor of disease resolution associated with excellent outcome. Long-term sustainability of the response cannot be evaluated in the present study due to significant amount of patients lost to follow-up after the 48th week of the study.

In relation to evaluation of a patient's functional health and well-being, HRQoL is a more integrated assessment than clinical parameters, particularly in chronic disease in which mortality is not an immediate concern. This is particularly important in CHB, in which the natural history is complex and comprises a number of phases (16).

Unfortunately, owing to the limited data on both the general aspects of HBV and HRQoL (the impact of having HBV on HRQoL) as well as the impact of new HBV treatment regimens on patients' HRQoL, this is a field that is poorly studied and not yet well characterized (17).

HRQoL was reported to be impaired in patients with CHB, albeit to a lesser extent than in those with CHC[18]. While hepatitis C patients have significantly reduced HRQoL, even those without advanced liver disease (18-21), gradual reduction in HRQoL occurs in CHB patients as liver disease advances further to decompensated cirrhosis and HCC (17). Virus-induced substantial and significant reduction in physical function has been cited for the reduction in the SF-36 scores that measured somatic symptoms (e.g., energy and fatigue and body pain) among CHC patients when compared to CHB patients (18). Implicated in low contribution rates for regular follow-up amongst CHB patients (22) who were aware of their illness, early changes related to the deterioration in HRQoL with progression of liver disease were reported to be in the dimensions of general and mental health, rather than physical symptoms (17).

In this regard, patients with chronic HBV infection were reported to have significant reductions in the SF-36 scores for the variables of mental health and general health perception, while minimal reduction was observed in the SF-36 scores that assess an individual's capacity for physical activities (physical and social functioning, role limitation, energy and fatigue, and body pain) in the literature (17,18). In line with this tendency towards the deterioration in mental health scores of HBV pati-

ents despite normal physical functions observed in our study population, chronic HBV patients were suggested to lack any significant impairment in their physical functions (18). Likewise, CHB patients were not able to classify the abnormality that they feel in overall health in any of the dimensions of SF-36, but were rather mentally affected by their more serious hepatitis B status (17). As indicated by lack of deterioration in the physical component summary scale, CHB patients do not feel symptomatic, but are concerned about prognosis and the need for therapy in relation to their abnormal laboratory and radiologic findings (17).

In agreement with better QoL identified among CHB patients, peginterferon alpha-2a treatment was reported to have a more benign impact on the HRQoL of patients with CHB compared with CHC patients based significantly on PCS scores (4). In this respect, a previous history of hepatitis B treatment in 83% of patients with peginterferon alpha-2a or standard interferon therapy seems to have a significant impact on better life quality among our patients in relation to acceptable patient tolerance to the treatment.

Interferon treatment was not associated with any negative influence on QoL in our population. Although our patients did not identify a significant improvement in their general well-being with respect to the last year at the 48th week of the treatment, certain physical limitations including climbing a few flights of stair and a few hundred meters walk, described at the initial visit, were reported to have improved at the end of the 48th week in our study. These findings are in line with the suggestion that peginterferon alfa-2a has no unfavorable influence on the QoL that complicates patient compliance to the treatment (23) both while on treatment and thereafter. It is crucial to maintain patient compliance with continued medication. Better patient compliance and HRQoL are expected to provide higher employment rates and better productivity in work, leisure and household activities.

In conclusion, peginterferon alfa-2a (Pegasys®; 40KD, 180 µg/week) treatment seems to offer an advantage in terms of efficacy and safety besides maintaining an acceptable HRQoL and leading to higher patient compliance. These factors should be considered in conjunction with safety and efficacy concerns in choosing optimal therapy for patients with CHB in real-life practice.

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