Efficacy of Peg interferon alfa-2a in patients with HBeAg-positive in chronic Hepatitis B patients in Kosovo

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Abstract

Aim: Approximately one third of the world's population has serological evidence of past or present infection with hepatitis B virus. Chronic hepatitis B infection is a dynamic process. Our aim was to assess the efficacy of Peg interferon alfa-2a in chronic hepatitis B patients with HBeAg-positive treated during the period 2010-2012 at the Infectious Disease Clinic of University Clinical Centre in Prishtina, Kosovo.
Methods: This study included 14 patients diagnosed with chronic hepatitis B, with detectable HBsAg for at least six months with positive HBeAg and negative Anti HBeAg. We analyzed the serological and laboratory aspects. We measured serum hepatitis B virus DNA level at the beginning of the therapy, at week 24 and at the end of the treatment. We assessed two main efficacy endpoints: HBeAg sero-conversion and viral suppression below 20.000 UI/ml (log 4,3 UI/ml).
Results: HBeAg sero-conversion was evident in one patient only, 24 weeks after the end of the therapy. The level of viral loud below 20.000 UI/ml (log 4,3 UI/ml) was evident in 4 (28.6%) of the cases at the end of the e treatment and in 3 (21.4%) patients at the end of the e follow-up period.
Conclusion: Our findings indicate that use of Peg interferon alfa-2a is safe and efficient in the treatment of HBeAg positive chronic hepatitis B patients.

Keywords: chronic hepatitis B, HbeAg, HBV-DNA, interferon alfa-2a.

Introduction

Between 350 and 400 million people worldwide are chronically infected with hepatitis B virus (HBV) (1). The two primary adverse outcomes of chronic infection are hepatocellular carcinoma (HCC) and cirrhosis, either of which can lead to a liver-related death (1-3). The goal of the therapy for chronic hepatitis B (CHB) is to improve the quality of life and survival by preventing progression of the disease to cirrhosis, decompensated cirrhosis, HCC and death. This goal can be achieved if HBV replication can be suppressed in a sustained manner. The long-term goals of treatment are virological clearance, delayed progression to cirrhosis or liver cancer and increased survival (1,4,5). The response to antiviral therapy could be classified in three categories: biochemical, virological and histological. In initially HBeAg positive-patients, effective treatment of chronic HBV is defined in terms of sustained clearance of circulating HBeAg with development of HBe antibodies and HBV-DNA decline to levels below 20.000 UI/mL. The improvement of liver disease could be assessed by documenting the normalization of serum alanine transaminase (ALT) levels (biochemical response), at least a two-point reduction of necro-inflammatory index and stable fibrosis score (no worsening) on liver biopsies (histological response). Furthermore, loss of HBsAg is associated with improved survival and reduced risk of HCC. Although the loss of HBsAg is clearly the ultimate goal of therapy in a HBV-related disease and it is therefore a useful surrogate endpoint, its relatively rare occurrence limits its utility for evaluation of new therapies (1,6). Currently, there are two different treatment strategies for both HBeAg-positive and HBeAg negative CHB patients: treatment for a limited duration with PEG-IFN, or a long-term treatment with NA(s). The main theoretical advantages of PEG-IFN are the absence of resistance and the potential for immune-mediated control of HBV infection with an opportunity to obtain a sustained virological response of treatment and a chance of HBsAg loss in patients who achieve and maintain undetectable HBV-DNA. Entecavir and tenofovir are potent HBV inhibitors with a high barrier to resistance (6-10). However, treatment duration is unpredictable prior to therapy as it depends on the timing of anti-HBe sero-conversion. Anti-HBe sero-conversion may not be durable after NAs discontinuation, at least with less potent agents, in a substantial proportion of these patients requiring close virologic monitoring after treatment cessation. An attempt for a limited NA treatment should use the most potent agents with the highest barrier to resistance to rapidly reduce levels of viremia to undetectable levels and avoid break-throughs due to HBV resistance. Once anti-HBe sero-conversion occurs during NA administration, treatment should be prolonged for an additional 12 months; a durable off-treatment response (persistence of anti-HBe sero-conversion) can be expected in 40%-80% of these patients (10-13). This study was designed to assess the efficacy of Peg interferon alfa-2a 48-week mono-therapy in HBeAg positive patients with chronic hepatitis B in Kosovo.

Methods

This study included 14 patients diagnosed with chronic hepatitis B, with detectable HBsAg for at least six months with positive HBeAg and negative Anti HBeAg. We analyzed the serological and laboratory aspects. We measured serum hepatitis B virus DNA level at the beginning of the therapy, at week 24 and at the end of the treatment. We assessed two main efficacy endpoints: HBeAg sero-conversion and viral suppression below 20.000 UI/ml (log 4,3 UI/ml). This was a 72-week study comprising 48 weeks of treatment and 24 weeks of follow-up. A dose of Peg interferon alfa-2a, 180 mcg was administered s.c. every week, for 48 weeks. The study was conducted in compliance with the Helsinki

Declaration and with the good clinical practice principles. All patients signed an informed consent form, before any procedure of the study was performed.

Patients

In total, 14 patients were enrolled. Age of patients was between 20 and 53 years; HBsAg positive for at least 6 months; HBsAb negative and HBeAg positive for at least 6 months; HBV DNA >20.000UI/mL (log 4,3 UI/ml) by PCR, a ALT level within the (range 1-37 U/ml).

Exclusion criteria included, co-infection with HAV, HCV, HDV, HIV infection, liver disease decompensation, retinopathy, hematological disease, malignity, and alcohol and drug abuse. Patients had not received any antiviral treatment for their chronic hepatitis B.

Main efficacy measures

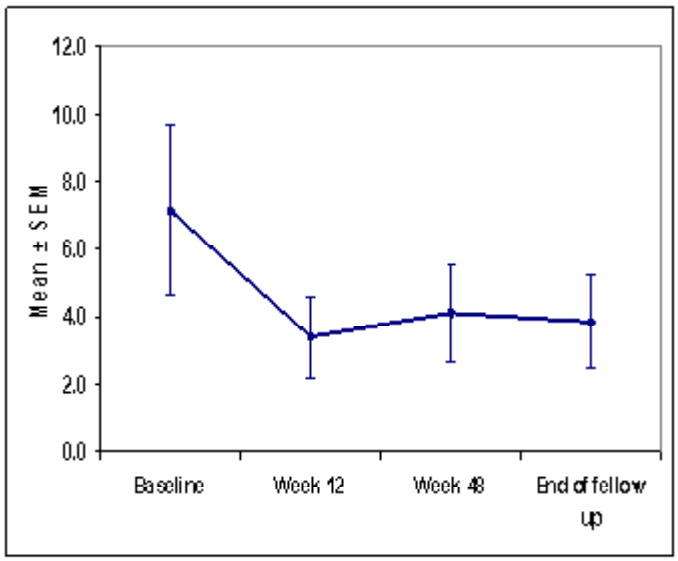
After 24 weeks of treatment, we measured the following parameters: HBe sero-conversion rates, suppression of viral replication (HBV DNA) to <20.000 UI /mL, and normalization of ALT levels.

Results

In our study, 12 (85.7%) patients were males. The mean age was 34.6 years old. In all the patients, it was administered for the first time a therapy with Peg interferon alfa-2a. At the end of the treatment period, there were 5 (35.7%) patients with HBV DNA <20.000UI/ml (log 4,3 UI/ml), whereas at the end of the follow-up period there were 7 (50%) patients.

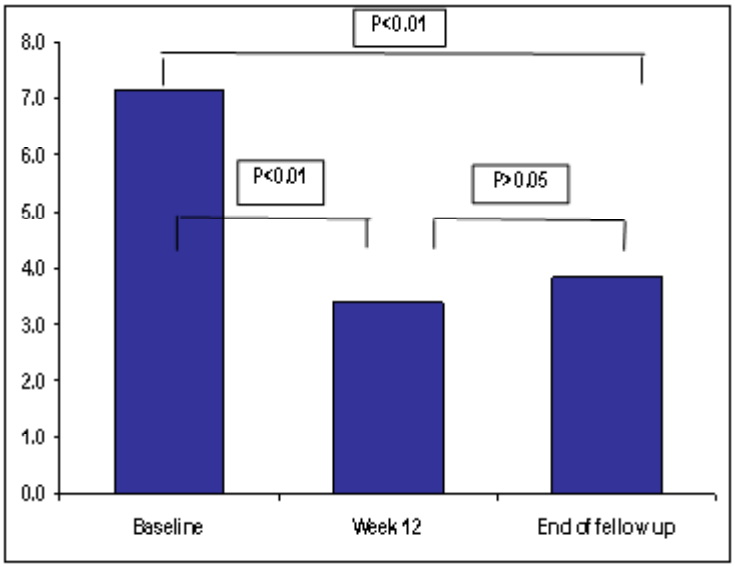
HBV DNA (log UI/ml) was in the baseline 7,72 Log UI/ml and in the end of therapy was 2,3 log UI/ml (Figure 1).

Figure 1. Dynamic of HBV-DNA (log UI/ml) level during and after peginterferon alfa-2a therapy in patients with HBeAg positive



We noticed a significant decrease of 5,4 log UI/ml at the end of the therapy. During the follow-up period, the mean HBV DNA was 3,31 log UI/ml (Figure 2).

Figure 2. The mean HBV DNA value



In this study, only one patient exhibited HBV DNA <100.000 UI/ml (log 5 UI/ml) with HBV DAN at the end of the therapy log 3.5 log UI/ml and at the end of the follow-up log 7.1 log UI/ml. There was only 1 (5.07%) patient with HBeAg sero-conversion at the end of the follow-up period. During the follow-up period, there were 3 (21.8%) patients with normalized ALT levels.

Mean ALT (U/L) decreased significantly between the baseline and the end of treatment (Figures 3-4).

Figure 3. Alanine aminotransferase levels over 72 weeks in patients with normalization of ALT at the end of the follow-up

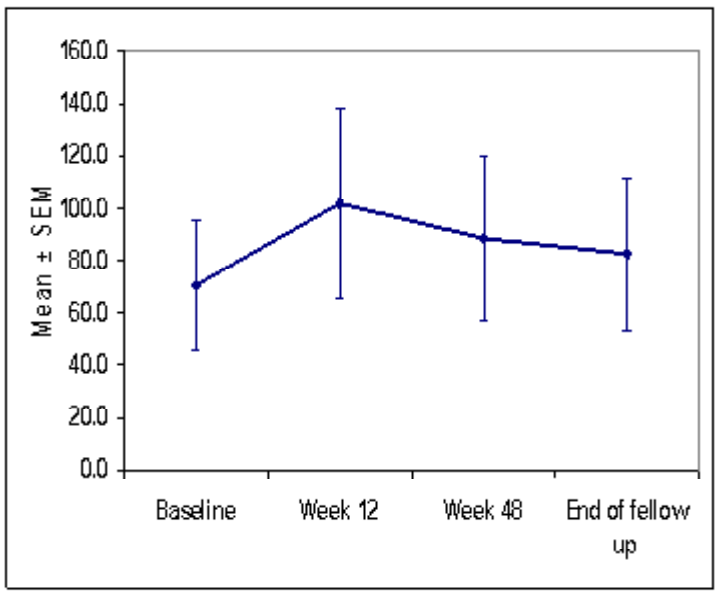
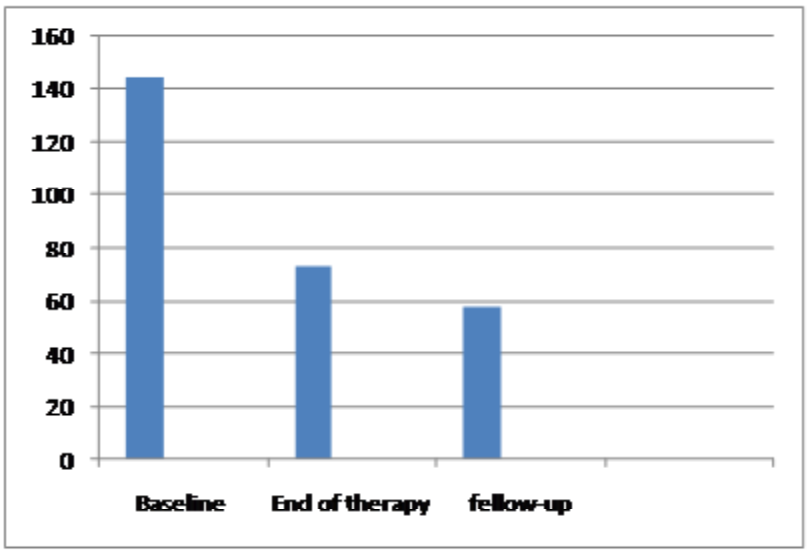


Figure 4. Mean serum alanine aminotransferase levels over 72 weeks in patients with normalization of ALT at the end of the follow-up



Discussion

The primary objective of antiviral treatment is stopping or delaying disease progression to decompensated cirrhosis, end-stage liver disease, HCC and death. There are a number of predictive factors for response to treatment; these factors should be evaluated at baseline, during the treatment and at the end of the therapy. Serological conversion of HBeAg and HBsAg is an important predictive factor of an effective therapy. The viral response is if the level of HBV DNA is les then 20000UI/ml or undetectable HBV-DNA (1-3,6). The number of patients included in this study was limited. Considering our findings, however, we obtained evidence that PEG-IFN alfa-2a is efficient and safe for the treatment of HBeAg-positive chronic hepatitis B. Suppression of viral replication at the lowest possible levels is crucial for future clinical disease evolution, ensuring achievement of therapeutic objectives, but also lowering the risk for hepatocellular carcinoma as proved by disease natural history studies (REVEAL study). In our study, the level of viral loud below of 20.000 UI/ml was observed in 3 (37.5%) patients at the end of the treatment. The follow-up of HBe Ag sero-conversion is the key objective and very important for patients with HBeAg positive in chronic hepatitis B therapy. We observed that patients with a biochemical response had a significantly lower mean HBV DNA (log). Also, there was a strong correlation between the decrease of HB-DNA and the ALT normalization. Hence, in all patients with HBV-DNA <20.000UI/mL (log 4,3 UI/ml) it was registered a normalization of alanine amino-transferase level at the end of the follow-up period. In conclusion, although this was a small study, it demonstrates that peg interferon Alfa-2a is safe and efficient in the treatment of HBeAg positive chronic hepatitis B.

Conflicts of interest: None declared.

References

1. European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B. J Hepatol 2009;50:227-42.

2. McMahon BJ. The natural history of chronic hepatitis B virus infection. Hepatology 2009;49:S45-S55.

3. Ganem D, Prince AM. Hepatitis B virus infection–natural history and clinical consequences. N Engl J Med 2004;350:1118-29.

4. Liaw YF, Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. N Engl J Med 2004;351:1521-31.

5. Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology 2001;34:1225-41.

6. Feld JJ, Wong DK, Heathcote EJ. Endpoints of therapy in chronic hepatitis B. Hepatology 2009;49:S96-S102.

7. Chang TT, Gish RG, de Man R, Gadano A, Sollano J, Chao YC, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. N Engl J Med 2006;354:1001-10.

8. Marcellin P, Heathcote EJ, Buti M, Gane E, de Man RA, Krastev Z, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. N Engl J Med 2008;359:2442-55.

9. Chang TT, Lai CL, Kew YS, Lee SS, Coelho HS, Carrilho FJ, et al. Entecavir treatment for up to 5 years in patients with hepatitis B e antigen-positive chronic hepatitis B. Hepatology 2010;51:422-30.

10. Reijnders JG, Perquin MJ, Zhang N, Hansen BE, Janssen HL. Nucleos(t)ide analogues only induce temporary hepatitis B e antigen seroconversion in most patients with chronic hepatitis B. Gastroenterology 2010;139:491-8.

11. van Nunen AB, Hansen BE, Suh DJ, Lohr HF, Chemello L, Fontaine H, et al. Durability of HBeAg seroconversion following antiviral therapy for chronic hepatitis B: relation to type of therapy and pre-treatment serum hepatitis B virus DNA and alanine aminotransferase. Gut 2003;52:420-4.

12. Lee HW, Lee HJ, Hwang JS, Sohn JH, Jang JY, Han KJ, et al. Lamivudine maintenance beyond one year after HBeAg seroconversion is a major factor for sustained virologic response in HBeAg-positive chronic hepatitis B. Hepatology 2010;51:415-21.

13. Zoulim F, Locarnini S. Hepatitis B virus resistance to nucleos(t)ide analogues. Gastroenterology 2009;137:1593-608.