ORIGINAL ARTICLE

RESULTS OF PEGINTERFERON ALFA-2A TREATMENT IN PATIENTS WITH CHRONIC HEPATITIS B IN THE WESTERN PART OF ROMANIA

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ABSTRACT

Objective: Currently there are two major types of antiviral therapy in HBV chronic liver disease: PegInterferon alpha-2a and nucleoside/nucleotide agents. The aim of this study was to evaluate the response to PegInterferon alfa-2a treatment, in patients with chronic hepatitis B.
Material and Methods: We performed a retrospective study on a group of 277 patients with chronic hepatitis B. The indication for treatment was made according to national and international guidelines. Only patients treated for 48 weeks with PegInterferon alpha-2a and in whom a viral load at least 6 months after the end of treatment was available, were included in our study. We defined as complete sustained viral response (complete SVR) an undetectable viral load at least 6 months after the end of treatment and as a partial sustained viral response (partial SVR) a viral load less than 2000 IU/mL (10000 copies/ml) at 6 months or more after the end of treatment. **Results:** Of the 277 patients, 206 (74.4%) were HBeAg negative and the remaining 71 (25.6%) HBeAg positive. 17.4% (36/206) of HBeAg negative patients treated had SVR, while 11.3% (8/71) of the HBeAg positive patients had SVR (p=0.2612). Among HBeAg negative patients, 2.9% (6/206) had complete SVR and 14.5% (30/206) had partial SVR. In patients with positive HBeAg, complete SVR occurred in 1.4% (1/71) cases and partial SVR in 9.9% (7/71).
Conclusion: Our study showed a low rate of SVR in patients with HBV chronic liver disease following PegInterferon treatment, with no significant differences between those with HBeAg + or HBeAg-.
Key Words: Chronic hepatitis B, PegInterferon alpha 2a, Sustained Viral Response (SVR)

INTRODUCTION

Worldwide more than 350 million people are chronically infected with hepatitis B virus (HBV) [1]. HBV chronic infection is a very heterogeneous condition, starting with immune-tolerant carriers (usually with high viral loads, but with normal liver function tests), inactive carriers (patients with low viral loads - less than 2000 IU/ml, and with persistently normal aminotransferases) and ending with active carriers, or chronic B hepatitis patients, in which the viral load is higher than 2000 IU/ml (according to the EASL Guidelines) [2], with various levels of aminotransferases and with various severity of activity and fibrosis on liver biopsy.

Treatment of chronic B hepatitis patients depends on the intensity of viral replication, on the level of aminotransferases and on the severity of activity/fibrosis on liver biopsy. Despite the fact that there are some differences between the EASL [2] and AASLD Guidelines [3] regarding the moment when the treatment must be initiated, there is a consensus that therapy is needed in patients with active disease, demonstrated by clinical and/or histological evidence of progressive disease.

According to the EASL guidelines: "Patients should be considered for treatment when they have HBV DNA levels above 2000 IU/ml, serum ALT levels above the upper limit of normal (ULN) and severity of liver disease assessed by liver biopsy (or non-invasive markers once validated in HBV infected patients) showing moderate to severe active necroinflammation and/or at least moderate fibrosis using a standardized scoring system. In patients who fulfill the above criteria for HBV DNA and histological severity of liver disease, treatment may be initiated even if ALT levels are normal" [2].

Currently, there are several drugs licensed for the treatment of chronic B hepatitis: interferon (alpha-interferon, pegylated α-2a interferon), nucleosides (lamivudine, telbivudine, emtricitabine, entecavir) and nucleotides (adefovir and tenofovir) [2]. The decision to choose one drug or another depends on patients' age, on the disease's severity (interferon should not be administered in decompensated cirrhosis), on HBV genotype (genotype A is more responsive to interferon than genotype D) [4] and finally, considering the patients' preference. The advantages of interferon therapy are: a fixed duration of treatment (usually 48 weeks), no resistance after treatment, higher rates of HBeAg and HBsAg seroconversion. The advantages of analogues are: potent antiviral effect (for entecavir and tenofovir especially), the absence or very mild side effects, oral administration [2]. The disadvantages of interferon therapy are: moderate antiviral effect, inferior tolerability in comparison with analogues, risk of adverse events, subcutaneous injections. For analogues the disadvantages are: indefinite duration of therapy, risk of resistance (especially for low barrier drugs), unknown long-term safety [2].

The aim of this study was to evaluate the response to PegInterferon alfa-2a treatment in patients with HBV chronic hepatitis in the Western part of Romania.

MATERIAL AND METHODS

We performed a retrospective study on a group of 277 patients with chronic B hepatitis (HBsAg positive for at least 6 months, PCR DNA-HBV > 2000 IU/ml, with normal or increased aminotransferases and HAI > 4 on liver biopsy). In all patients we excluded other causes of chronic liver disease (HCV and/or HDV infection, hemochromatosis, Wilson's disease, cholestatic liver diseases, autoimmune hepatitis).

The indication for treatment was made according to national and international guidelines. We divided the patients in HBeAg positive and HBeAg negative patients, knowing that hepatic disease progression is different according to the HBeAg status (more aggressive in HBeAg positive patients). Only patients treated for 48 weeks with PegInterferon alpha-2a 180µg/week and in which a viral load at least 6 months after the end of treatment was available, were included in our study.

We defined a complete sustained viral response (complete SVR) as undetectable viral load evaluated at least 6 months after the end of treatment and as a partial sustained viral response (partial SVR) a viral load less than 2000 IU/ml (10000 copies/ml) 6 months or more after the end of treatment. The viral load before and post treatment was evaluated using Roche Taqman technique, with the inferior limit of detection 25 IU/ml. We did not perform HBV genotyping.

For a statistical study of quantitative variables, the mean and standard variation were calculated, and for the qualitative ones, the percentage was calculated. The percentages were compared by Fisher exact test. A p-value < 0.05 was considered to denote statistical significance. The statistical analysis was performed using Microsoft Excel and GraphPad Prism programs.

RESULTS

The main patients' characteristics are presented in Table 1.Of the 277 patients, 206 (74.4%) were HBeAg negative and the remaining 71 (25.6%) were HBeAg positive. In our cohort of patients, 17.4% (36/206) of HBeAg negative patients had SVR (partial or complete), while 11.3% (8/71) of the HBeAg positive patients had SVR (partial or complete) (p=0.2612) (Fig.1).

Among HBeAg negative patients, only 2.9% (6/206) had complete SVR and 14.5% (30/206) had partial SVR (Fig.1). In patients with positive HBeAg, complete SVR occurred in only 1.4% (1/71) cases and partial SVR in 9.9% (7/71) (Fig.1).

Parameter	
Total	n = 277
Age (years)	38.6 ± 14.3
Gender:	
- men	n = 145 (52.3%)
- women	n = 132 (47.7%)
HBe Ag:	
- negative	n = 206 (74.4%)
- positive	n = 71 (25.6%)
Severity of fibrosis (on biopsy):	
- F=0	n = 36 (13%)
- F=1	n = 168 (60.6%)
- F=2	n = 28 (10.1%)
- F=3	n = 45 (16.3%)
- F=4	n = 0 (0%)

Table 1: *Main patients' characteristics*

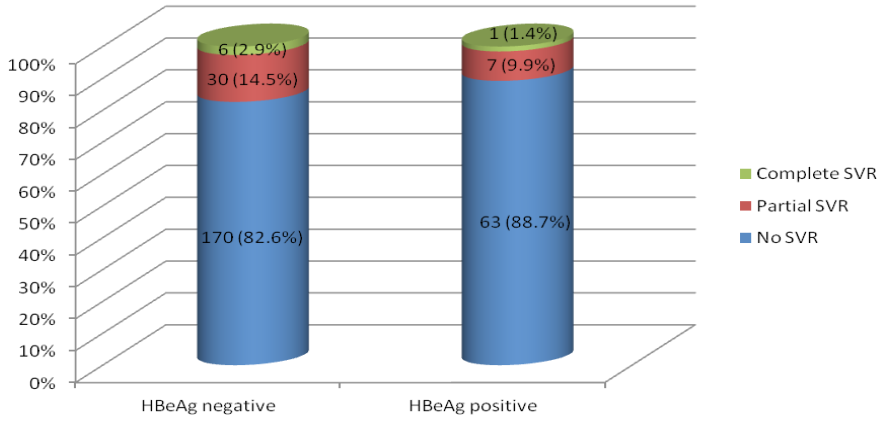

Fig.1: *Response rates in our cohort of patients.*

Among the 206 HBeAg negative patients, 105 (51%) were men and 101 (49%) were women. The rate of SVR didn't differ significantly among HBeAg negative men and women: 14.3% (15/105), vs. 20.8% (21/101), p=0.2715.

Among the 71 HBeAg positive patients, 40 (57.7%) were men and 31 (42.3%) were women. The rate of SVR didn't differ significantly between HBeAg positive men and women: 17.5% (7/40), vs. 3.2% (1/31), p=0.1262.

Among the 206 HBeAg negative patients, 114 (55.3%) were younger than 40 and 92 (44.7%) were older than 40 years. The rate of SVR didn't differ significantly between HBeAg negative patients younger or older than 40: 14.0% (16/114), vs. 21.7% (20/92), p=0.1961.

Among the 71 HBeAg positive patients, 49 (69.0%) were younger than 40 and 22 (31%) were older than 40. The rate of SVR was similar among HBeAg positive patients younger or older than 40: 10.2% (5/49), vs. 13.6% (3/22), p=0.6964.

DISCUSSIONS

Chronic hepatitis B (CHB) is a worldwide health problem due to the high risk of these patients to develop liver cirrhosis, hepatocellular carcinoma (HCC), and subsequent demise [5, 6]. The goal of therapy in CHB is to improve the quality of life and survival by preventing progression to cirrhosis, decompensated cirrhosis, end-stage liver disease, HCC and death. This goal can be achieved if HBV replication can be suppressed in a sustained manner [2].

The ideal treatment goal should be to cure HBV infection, thus to achieve HBsAg loss. Unfortunately, this goal is seldom obtained, due to the persistence of covalently closed circular DNA (cccDNA) in the nucleus of infected hepatocytes [7, 8] and also due to the integration of HBV DNA in the hepatocyte genome, which can be an important factor in carcinogenesis [9, 10].

Thus, a more realistic treatment goal, especially in HBeAg negative B chronic hepatitis, is to decrease the viral load, preferably to undetectable levels or to less than 2000 UI/ml, considered to be safe in preventing complications [2, 3]. In HBeAg positive patients, the main objective is seroconversion to anti-HBeAb positive and secondly to decrease the viral load [2, 3].

A pivotal study published in 2004, reported a SVR rate of 36% in HBeAg negative patients treated with PegInterferon alpha 2a, similar to that observed in patients treated with PegInterferon alpha 2a and Lamivudine, but much higher than in patients treated with Lamivudine alone [11].

Regarding response rates in HBeAg positive patients, loss of HBeAg and seroconversion to anti-HBeAb was reported in 32% of patients treated with PegInterferon alpha 2a [12], and in 29% of patients treated with PegInterferon alpha 2b [13]. However, HBV-DNA suppression to ≤ 400 copies/ml was achieved only in 14% (12) and 7% of cases [13], respectively.

In an older Romanian study on 43 HBeAg positive CHB patients, end-of treatment HBeAg seroconversion following PegInterferon treatment was observed in 4.65% patients. The seroconversion rate increased to 11.6 % during a six months follow-up [14]. Regarding the viral load, at the end of treatment 23.2% patients had a viral load < 100,000 copies/ml, during the follow-up period the percentage dropping to 16.3% [14].

In another Romanian study that included 57 patients, both HBeAg positive and HBeAg negative, the rate of SVR was 38.6% for both groups, and the rate of HBe seroconversion was 22% (4/18 patients) [15].

Our cohort of treated patients, in which 3/4 were HBeAg negative and 1/4 HBeAg positive, is a reflection of HBV epidemiology in our region [16]. On the other hand, this is a typical pattern for European population with high prevalence of HBeAg negative subjects.

The low rate of SVR in our cohort of patients treated with PegInterferon alpha 2a for 48 weeks can be partially explained by the genotype pattern of HBV in Romania. Previous studies [17, 18] showed that in our area approximately 70% of infected subjects are genotype D, and only 30% genotype A, more sensitive to interferon [4]. Some years ago a group of researchers suggested not to treat HBV genotype D with interferon, due to the low rate of SVR [4], but this recommendation is not mentioned in the current guidelines. On the other hand, the rate of seroconversion (especially to anti HBs) following analogs treatment is very low. Thus, the decision to chose one drug or another is difficult in many cases. Sometimes, in young patients we prefer interferon, well tolerated, with minor side effects in this category of patients and with finite duration of therapy. In older persons, with advanced disease, analogues are chosen in most cases.

Two treatment strategies are discussed at the moment to increase the response rates in CHB patients treated with PegInterferon: one is the strict monitoring of DNA level and HBsAg during PegInterferon treatment. If after the 12th injection the viral load doesn't decrease with 2 logs and the quantitative HBsAg with 1 log, the treatment should be stopped [19].

Another option is to combine PegInterferon with analogues. Published studies that assessed the efficacy of PegInterferon in combination with Lamivudine showed no long term benefit of combination therapy as compared with PegInterferon or Lamivudine alone, even if a more pronounced on-therapy virologic response was observed during combined therapy [4, 12]. High rates of HBsAg loss were reported following combined therapy with PegInterferon and Adefovir: 17% in HBeAg negative patients and 11% in HBeAg positive patients [20]. A study that evaluated the benefit of add-on therapy with PegInterferon in HBeAg positive patients

treated with Entecavir, showed an increased reduction in HBsAg, HBeAg and HBV-DNA levels, as well as more sustained responses after Entecavir discontinuation in the group receiving combined therapy as compared to the group receiving Entecavir alone [21]. A multicenter study presented at AASLD meeting in 2014 compared treatment results in 740 patients (58.4% AgHBe positive) randomized 1:1:1:1 to receive PegInterferon and Tenofovir for 48 weeks (arm A); vs. PegInterferon and Tenofovir for 16 weeks followed by Tenofovir for 32 weeks (Arm B); vs. continuous Tenofovir (Arm C); vs. PegInterferon for 48 weeks (Arm D). The best results were observed in Arm A (5.9% loss of HBsAg and 24.3% loss of HBeAg), while in arm B only 0.6% of patients presented HBsAg loss and only 20.2% lost HBeAg. Among those treated with just interferon (Arm D), 1.8% lost HBsAg and 12.5% lost HBeAg. None of the group treated with just tenofovir lost HBsAg and only 8.3% lost HBeAg [22].

Finally, another strategy is to decrease the viral load with analogues and then switch to PegInterferon. A study that included 192 patients showed that in subjects who achieve virologic suppression with entecavir, switching to a finite course of PegInterferon alfa-2a significantly increases rates of HBeAg seroconversion and HBsAg loss [23].

One limitation of our study is that it is a retrospective one. Another is that the HBV-DNA levels were evaluated at different times post therapy (but later than 6 months after end of therapy) and that the genotype was not recorded. Nevertheless, the purpose of this study was achieved: to evaluate the sustained virologic response following PegInterferon therapy in our population of hepatitis B patients.

Considering the small rate of SVR in our cohort of hepatitis B patients following PegInterferon treatment, strategies to increase the rate of response must be proposed. One option is to assess the HBV genotype and maybe decide the treatment accordingly; another is to evaluate viral kinetics during treatment and maybe switch to analogues in non or slow responders; thirdly, if future studies will confirm the benefit of combined therapy, to use this strategy (maybe in genotype D).

In conclusion: Our study showed a low rate of SVR in patients with chronic hepatitis B (17.4% of HBeAg negative patients and 11.3% of the HBeAg positive patients p=0.2612), following 48 weeks of PegInterferon treatment. Future therapeutic strategies are needed to improve the success rate of treatment in chronic hepatitis B patients.

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