Long term efficacy of pegylated ınterferone in the treatment of delta hepatitis: a single center experience

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Abstract

Background and aims: **Currently there is no satisfactory treatment of chronic HDV. We aimed to evaluate the long term efficacy of PEG-interferones.**

***Patients and Methods*: Patients who received PEG-interferone for chronic delta hepatitis during a 7-year period were retrospectively analysed. End of treatment response, virologic response at 6 months after treatment, and long term efficacy were evaluated. Predictors of treatment response were determined.**

Results: **The study group consisted of 31 patients. Twenty-three patients received either PEG-interferone alfa-2a (n=8) or PEG-interferone alfa-2b (n=15) for at least 48 weeks. Thirteen patients had an end of treatment virologic response (ITT:56.5%, PP:68.4%). HDV RNA negativity after 6 months off PEG-interferone treatment was achieved in 12 patients (ITT:52.1%, PP:63.1%). The patients were followed for a median duration of 36 months after PEG-interferone treatment (min-max:12-120 months). Four patients (33.3%) relapsed during the follow-up. Sustained virologic response (ITT) was 34.8% in the long term. Undetectable HDV RNA level at week 24 of treatment and biochemical response were independent predictors of end of treatment response and sustained virologic response in the long term, respectively.**

Conclusion: **PEG-interferones have an unsatisfactory efficacy on the treatment of HDV because of a considerable relapse in the long term.** (Acta gastroenterol. belg., **2016**, 79, **329-335**).

Keywords : hepatitis, delta, treatment, interferone

Introduction

Hepatitis D virus (HDV) is an incomplete RNA virus which requires the presence of hepatitis B surface antigen in order to enter hepatocytes. Patients co-infected with HDV have a more progressive course of hepatitis compared to those with chronic HBV, which is manifested by a rapid progression to cirrhosis and liver failure as well as an increased risk for hepatocellular carcinoma (1-3). HDV is estimated to infect about 15-20 million people worldwide (4). It is endemic in countries harboring populations of poor socioeconomic status. There is also a trend toward increasing prevalence of HDV in developed countries such as United States and some parts of Europe (5-7).

Although several drugs have been tried for the treatment of chronic HDV, there is no satisfactory treatment at the moment (8). Suppression of HBV by nucleos(t)ide analogs were expected to eradicate HDV, but famciclovir, adefovir, lamivudine, and entecavir were found to have no significant biochemical, virologic, and histologic effects on the course of HDV because of their inability to suppress HBsAg (9-12). Interferone-α is the only approved treatment of HDV with a suboptimal efficacy. Pegylated interferones are preferred to standart interferones because of their long half lifes. However, there are limited data about their efficacy, especially on the long term (10, 13-16). In this study, we retrospectively analysed our chronic HDV patients in order to evaluate the short and long term efficacy of PEG-interferones in the treatment of chronic HDV patients with various stages of liver fibrosis and to determine the predictors of treatment success.

Patients and methods

Patients

Patients who were treated at Türkiye Yüksek İhtisas Hospital, Department of Gastroenterology for chronic delta hepatitis between 2005 and 2012 were retrospectively analysed. The diagnosis of chronic delta hepatitis was based on Anti-HDV and HDV RNA positivity in the serum. Patients ≤18 years, those with decompansated cirrhosis, concomitant hepatitis C, hepatocellular carcinoma, and inability to use PEG-interferone treatment because of side effects were excluded from the study. Patients who were still on PEG

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Submission date : 13/11/2015
Acceptance date : 16/05/2016

treatment or had a follow-up period less than 12 months after PEG-interferone treatment were also excluded.

Virologic assays

Quantitative measurement of HDV RNA was assessed by using real time PCR with a lower limit of detection of 1500 copy/ml (Roche Diagnostics, Indianapolis, IN, USA). Quantitative measurement of HBV DNA was assessed by using either Cobas AmpliPrep/Cobas Taqman 48 or Cobas Taqman 48 (Roche Diagnostics, Indianapolis, IN, USA) with a lower limit of detection of 20IU/ml and 6IU/ml, respectively.

Liver biopsy

Liver biopsies were obtained before treatment and interpreted by experienced pathologists. Necroinflammation and fibrosis were graded according to HAI and Ishak modification of the HAI scoring system, respectively. Significant fibrosis was defined as a fibrosis score of ≥3.

Treatment of delta hepatitis

The study group included 31 patients who received PEG-interferone treatment. Three patients (9.7%) withdrew treatment because of side effects (deep thrombocytopenia in 1 patient and major depression in 2 patients). Five patients were lost to follow-up at various times during their PEG-interferone treatment. The remaining 23 patients received either PEG-interferone alfa-2a (180 μg/week) (n=8) or PEG-interferone alfa-2b (1.5 μg/kg weekly) (n=15) for at least 48 weeks. Four patients (2 with partial response and 2 relapsers) received an additional 48 weeks of PEG-interferone treatment. All of the patients were followed for possible complications of PEG-interferone during therapy. Complete blood count was followed every two weeks for the first two months and monthly thereafter until the end of treatment. Serum transaminases were followed monthly. Dose of PEG-interferones were adjusted according to the results of complete blood count. Four patients (14.3%, 2 with cirrhosis) had modifications in their PEG-interferone dose during treatment. HDV RNA was assessed before treatment, at the 24th week, end of treatment, 6 months after treatment, and at the last visit to the hospital.

Treatment of hepatitis B

Nine patients received either an oral nucleos(t)ide analogue or PEG-interferone treatment for hepatitis B (lamivudine in 2, entecavir in 2, tenofovir in 1, and PEG-interferone α-2a/b in 4 patients) and had a negative HBV DNA prior to delta hepatitis treatment. All of the 5 patients continued to take their oral nucleos(t)ide treatment during and after PEG-interferone treatment for delta hepatitis.

Definition of response

Biochemical response was defined as normalization of serum transaminases at the end of treatment. Partial virologic response was defined as a more than 2log decrease in HDV RNA levels at the end of treatment. End of treatment virologic response (EOTR) was defined as HDV RNA negativity at the end of PEG-interferone treatment. Sustained virologic response (SVR) was defined as HDV RNA negativity attained 6 months after PEG-interferone treatment and maintained at the last visit of the patient. Complete virologic response was defined as a combination of SVR and HBsAg seroconversion.

Statistical analysis

Statistical analysis was performed by using SPSS Version 16 (SPSS, Chicago, IL). Normality of the distribution for the data was tested with Kolmogorov-Smirnov test. The univariate analyses to identify predictive factors associated with EOTR and final SVR were investigated by using Kruskal-Wallis, One-Way ANOVA, Mann-Whitney U, Student t test, "Fisher exact test", Chi-square tests, where appropriate. Factors with a p value of less than 0.2 following univariate analyses were included in the multiple logistic regression analyses. A multiple linear regression model was used to identify independent predictors of SVR. Kaplan-Meier survival curve was built to compare cirrhosis free survivals between patients with and without sustained viral response. A value of $p<0.05$ was considered to be statistically significant.

Results

Baseline characteristics of the patients

Out of 23 patients who received at least 48 weeks of PEG-interferone treatment, 4 (17.4%) were female and 19 (82.6%) were male. The median age of the patients was 48 years (range:22-67). The median time elapsed between the diagnosis of delta hepatitis and hepatitis B was 2.0 years (range:0-14 years). Liver biopsies were obtained 5.1±1.3 months before the start of delta hepatitis treatment. Twenty-one patients (91.3%) had elevated serum ALT levels (14 (60.9%) >2xN) and 19 patients (82.6%) had elevated serum AST levels (8 (34.8%) >2xN). Liver biopsy was obtained in 21 patients (91.3%) and disclosed significant fibrosis in 11 (52.4%) patients. Two patients didn't undergo liver biopsy because a clinical diagnosis of cirrhosis was reached in the first patient based on his complete blood count, liver tests, and ultrasonography findings, and liver biopsy was contraindicated in the second patient due to an antiaggregant and anticoagulant use. Data of baseline demographic, biochemical, virologic, and liver biopsy are presented in Table 1.

Table 1. — **Baseline demographic, biochemical, virologic, and liver biopsy findings of the patients (n=23)**

Demographic data	
Age; Median (min-max)	48.0 (22.0-67.0)
Gender (Female)	4 (17.4)
Duration of hepatitis B infection (months) Median (min-max)	96 (24-312)
Duration of delta hepatitis (months); Median (min-max)	60 (24-216)
Biochemical findings	
ALT; Median (min-max)	90 (24-431)
AST; Median (min-max)	57 (24-306)
Platelet; Median (min-max)	190.000 (82.000-308.000)
Albumin; Median (min-max)	4.4 (3.4-5.4)
INR; Median (min-max)	1.1 (0.7-8.0)
Total bilirubin; Median (min-max)	0.7 (0.3-9.0)
Virologic findings	
HBeAg positivity; n (%)	5 (21.7)
HBV DNA (copy/ml); Median (min-max)	540 (0-4900000)
Liver biopsy findings	
HAI; Median (min-max)	10.5 (5-18)
Fibrosis stage; Median (min-max)	3.0 (0-3)
Significant fibrosis or cirrhosis; n (%)	12 (52.2)

*: 1 patient with partial response had no liver biopsy due to anticoagulant use

Table 2. — **Demographic, liver biopsy, virologic, and biochemical data of the patients according to their response at the end of treatment**

	EOTR (n=13)	Partial response (n=5)	No response (n=5)	p
Demographic data				
Age; Median (min-max)	44 (22-67)	49 (29-54)	57 (22-66)	0.5
Gender; Female (%)	1 (7.7)	1 (20.0)	2 (40.0)	0.2
Duration of Hepatitis B (months) Median (min- max)	96 (24-312)	132 (36-180)	60 (24-144)	0.2
Duration of Delta hepatitis (months) Median (min-max)	84 (24-216)	48 (24-96)	36 (24-132)	0.1
Liver biopsy findings				
HAI; Median (min-max)	10.5 (5-18)	10.5 (7-18)	10 (6-14)	0.8
Fibrosis; Median (min-max)	2.5 (0-3)	2.5 (2-3)	3.0 (1-3)	0.7
Significant fibrosis or cirrhosis; n (%)	7 (53.8)	3 (75.0)*	2 (40.0)	0.7
Virologic data (Baseline)				
HBeAg positivity; n (%)	2 (15.4)	3 (60.0)	-	0.09
HBV DNA(copy/ml); Median (min-max)	800 (82-4.900.000)	114 (0-9000)	250 (0-2240)	0.1
HDV RNA (copy/ml); Median (min-max)	356.000 (1000-12.000.000)	88.500 (1590-810.000)	200.000 (3110-1.000.000)	0.4
Detectable HDV RNA at treatment week 24	4 (30.8)	5 (100.0)	5 (100.0)	0.003
Biochemical data (Baseline)				
ALT; Median (min-max)	99 (34-431)	90 (24-167)	72 (41-294)	0.7
AST; Median (min-max)	57 (34-306)	84 ± 16	108 ± 26	0.4
Biochemical response; n (%)	7 (53.8%)	2 (40.0)	2 (40.0)	1.0
Platelet; Median (min-max)	190.000 (82.000-244.000)	220.000 (173.000-308.000)	167.000 (101.000-198.000)	0.2
Albumin; Median (min-max)	4.4 (3.7-4.9)	4.4 (4.1-5.4)	4.0 (3.4-4.8)	0.2
Total bilirubin; Median (min-max)	0.7 (0.6-7.0)	0.7 (0.5-2.4)	0.7 (0.3-9.0)	0.7
INR; Median (min-max)	1.1 (0.7-1.9)	1.0 (0.9-1.26)	1.1 (0.8-8.0)	0.7

Short-term treatment results

Among 23 patients who received 48 weeks of PEG-interferone treatment, 13 had an end of treatment virologic response (ITT:13/23,56.5%, PP:13/19,68.4%). Five (16.1%) patients had a partial response and 5 (16.1%) had no response to treatment. Two patients with a partial response received an additional 48 weeks of PEG-interferone treatment but both of them were lost to follow-up. Two relapsers received an additional 48 weeks of PEG-interferone treatment. Unfortunately the treatment was prematurely terminated due to deep leukopenia in one of them and the other patient was lost to follow-up. HDV RNA negativity after 6 months off PEG-interferone treatment, which was defined as SVR in previous studies, was achieved in 12 patients (ITT: 12/23,52.1%, PP:12/19,63.1%).

Biochemical response was attained in 43.5% of 23 patients, who received 48 weeks of PEG-interferone treatment. Complete virologic response could be achieved in none of them. Table 2 shows the baseline and on-treatment biochemical, virologic, and biopsy findings of the patients according to their response to treatment. There was no statistically significant difference between the EOTR rates of patients with significant (7/12,58.3%) and non-significant fibrosis (6/10,60%) (p=1.0). There was no statistically significant difference between the EOTR rates of patients receiving PEG-IFN α-2a (37.5%) and α-2b (66.7%) (p=0.2). Patients with EOTR had a higher biochemical response compared to those without EOTR (p=0.6). Undetectable HDV RNA at 24th week of treatment (p=0.001), baseline HBV DNA levels (p=0.04) and duration of delta hepatitis (p=0.04) were significantly higher in patients with EOTR (Table 2). A multiple linear regression analysis revealed undetectable HDV RNA level at week 24 of treatment (p=0.001) as the only independent predictor of EOTR (Table 3).

Table 3. — **Multiple linear regression analysis of predictive factors for EOTR**

	β-coefficient	SE β	p
Duration of Delta Hepatitis Infection	0.207	0.017	0.2
Detectable HDV RNA at week 24	-0.652	0.173	0.001
Baseline HBV DNA level	-0.027	0.001	0.8
HBeAg positivity	-0.136	0.192	0.4

Table 4. — **Comparison of demographic, biochemical, virologic, and histologic characteristics of patients according to their SVR status**

	SVR (+) (n=8)	SVR (-) (n=15)	p
Demographic findings			
Age; Median (min-max)	42 (22-54)	49 (22-67)	0.1
Gender; Female (%)	-	4 (26.7)	0.2
Duration of Hepatitis B infection; Median (min-max)	90 (24-312)	120 (24-252)	0.5
Duration of Delta hepatitis; Median (min-max)	78 (24-216)	60 (24-216)	0.6
Liver biopsy findings			
HAI; Median (min-max)	9 (5-17)	11 (6-18)	0.4
Fibrosis; Median (min-max)	2.5 (0-3)	3.0 (0-3)	0.5
Significant fibrosis or cirrhosis; n (%)	4 (50.0)	8 (57.1)	1.0
Virologic findings (Baseline)			
HBeAg positivity; n (%)	3 (37.5)	2 (13.3)	0.2
HBV DNA (copy/ml); Median (min-max)	2500 (0-1.000.000)	450 (0-4900000)	0.2
HDV RNA (copy/ml); Median (min-max)	450.000 (2780-12.000.000)	200.000(1000-1.400.000)	0.1
Detectable HDV RNA at week 24	3 (37.5)	11 (73.3)	0.08
Biochemical findings (Baseline)			
ALT; Median (min-max)	103.5 (24-431)	90 (34-294)	0.7
AST; Median (min-max)	57 (34-306)	63 (24-198)	0.7
Biochemical response; n (%)	6 (75.0%)	5 (33.3)	0.08
Platelet; Median (min-max)	192.000 (82.000-242.000)	190.000 (101.000-308.000)	0.9
Albumin; Median (min-max)	4.4 (3.7-4.9)	4.3 (3.4-5.4)	0.5
Total bilirubin; Median (min-max)	0.7 (0.5-7.0)	0.7 (0.3-9.0)	1.0
INR; Median (min-max)	1.1 (0.7-1.9)	1.0 (07-8.0)	0.8

Long-term treatment results

The patients were followed for a median duration of 36 months after PEG-interferone treatment (min-max:12-120 months). Out of 12 patients who had a negative HDV RNA 6 months after the end of 48 weeks of treatment, 4 (33.3%) relapsed during the follow-up (Figure 1). Therefore, ITT and PP SVR was 34.8% (8/23) and 42.1% (8/19) in the long term, respectively. None of the patients had a complete virologic response. HBeAg seroconversion was achieved in 3 of 5 patients.

There was no statistically significant difference between the baseline demographic, biochemical, virologic, and liver biopsy findings of the patients based on their long term SVR status (Table 4). There was no statistically significant difference between the SVR of patients with significant (4/12,36.4%) and non-significant (4/10,40%) fibrosis (p=1.0). A multiple linear regression analysis revealed biochemical response as an independent predictor of SVR (p=0.04) (Table 5). A Kaplan-Meier survival analysis showed that post-treatment cirrhosis free survival was significantly higher in patients who achieved SVR (p=0.017) (Figure 2).

Discussion

In this study we retrospectively analysed the data of chronic HDV patients who received PEG-IFN alfa treatment for 48 weeks and showed that PEG-IFNs had a virologic response of 52.1% at 6 months off-treatment which decreased to a SVR of 34.8% after a median further follow-up of 36 months. Undetectable HDV RNA level at week 24 of treatment and biochemical response were independent predictors of EOTR and SVR in the long term, respectively.

Interferone is the only currently approved treatment of chronic HDV. End of treatment virologic response rate varies between 31-71% after one year of standart interferone treatment. However virologic relapse is common after cessation of treatment and accordingly SVRs decrease to 18-50% after 6-12 months off-treatment (17-22). PEG-IFNs are preferred to standart interferone because of their long half lifes which allow to once weekly administration. Although there is no randomised trial comparing the efficacy of PEG-IFN and standart IFNs, they seem to have similar SVRs. Up to our knowledge there are 5 trials which reported heterogenous SVRs varying between 17-43% after 12-18 months of PEG-IFN treatment (10, 13-16). The great variability in the SVRs of these trials were probably due to their small sample sizes (n=12,14,16,29,48) and heterogenous baseline host and viral factors. Increasing the dose of PEG-interferone, prolonging the therapy to 24 months, and adding an antiviral effective against HBV were not found to significantly increase the SVR (23). Although there is no randomised trial comparing the efficacy of two PEG-interferones, reviews revealed no significant difference between them (24). Our results were comparable with the aforementioned trials and revealed a virologic response rate of 52% at 6 months

Table 5. — **Multiple linear regression analysis of predictive factors for SVR**

	β-coefficient	SE β	p
Age	-0.251	0.007	0.1
HDV RNA (Baseline)	0.400	0.001	0.06
Detectable HDV RNA at week 24	-0.110	0.196	0.5
Biochemical response	0.389	0.175	0.04

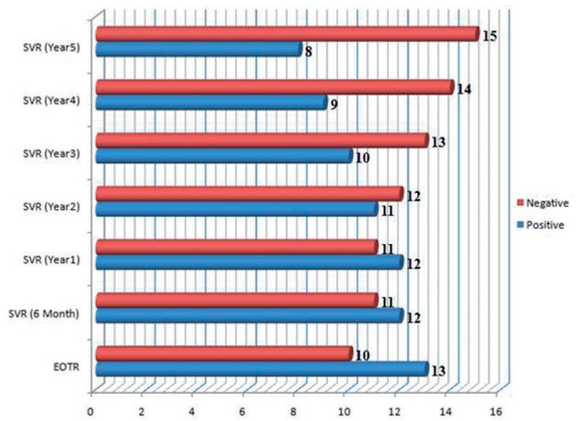

Fig. 1. — Sustained virologic response in the long term

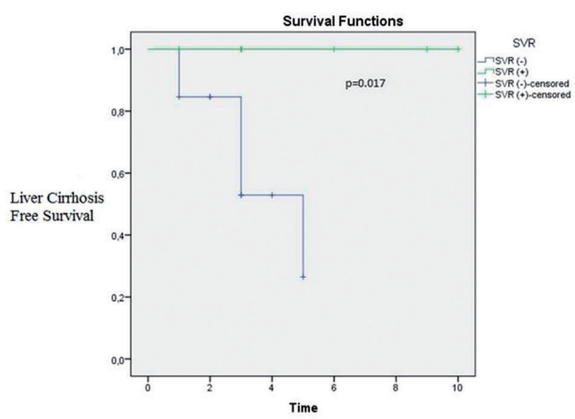

Fig. 2. — Kaplan-Meier survival analysis of the post-treatment cirrhosis free survival

off-treatment and no significant difference between the efficacy of two PEG-IFNs.

On the contrary to HCV, SVR determined after 6 months off treatment is not a reliable end point in the treatment of HDV. Residual very low amounts of HDV, which cannot be detected with the current most sensitive assays may relapse as long as HBsAg remains positive. In a recent Hep-Net-International Delta Hepatitis Trial (HIDIT)-1 trial, out of 16 patients tested HDV RNA negative 6 months after PEG-IFNa treatment, 9 had a late HDV RNA relapse after a median follow-up of 4.5 years (25).Only the patients who cleared HBsAg were cured of HDV. Our results also confirmed HIDIT-1 study and revealed a late HDV RNA relapse in 4 out of 12 patients (33.3%) after a median follow-up of 36 months. The only reliable end-point of therapy seemed to be the clearance of HBsAg. Therefore patients should be closely followed up for relapse in the long term. Prolonging IFN therapy can be considered in patients with a negative HDV RNA and a significant decrease in HBsAg levels in order to achieve HBsAg clearance (26,27).

Baseline and on-treatment predictors of PEG-IFN treatment success are not clearly established. A low baseline HBsAg, high ALT, and low HDV-RNA titers are the possible baseline predictors (28). A more than 3 log decrease in HDV RNA levels at the 24th week of treatment seems to predict a SVR (13,15). In our study we found that undetectable HDV RNA level at week 24 of treatment and biochemical response were independent predictors of EOTR and SVR in the long term, respectively.

A subanalysis of the Hep-Net-International Delta Hepatitis Trial (HIDIT) study revealed that the efficacy of PEG-IFN in 31 patients with advanced liver disease (fibrosis score ≥4) at the end of 24 weeks of treatment-free follow-up was (19%) similar to 27 patients with non-advanced liver disease (23%). But all of the clinically important side effects occured in patients with advanced liver disease (29). In our study we found no statistically significant difference between the SVR of patients with significant (36.4%) and non-significant (40%) fibrosis. (p=1.0).

One of the major limitations of our study was its retrospective design. Absence of HbsAg levels and HDV genotype limited the determination of basal treatment predictors of success. On the other hand, considerable number of patients and long term of follow-up were the main strengths of the study.

In conclusion, PEG-interferones have an unsatisfactory efficacy on the treatment of HDV because of a considerable relapse in the long term.

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