

Preliminary report on safety and response rate of pegylated interferon- alpha 2a (pegasys) in genotype D chronic hepatitis B patients in Iran

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ABSTRACT

Aim: The aim of study was to determine the preliminary result of treatment with pegasys in Iranian chronic hepatitis B patients (with genotype D) referred to Tehran Hepatitis center (THC).

Background: The genotype of HBV and ethnicity of the patients can affect the response rate to pegasys.

Patients and methods: During 2006-2008, 12 Patients with naïve chronic hepatitis B (genotype D) that referred to THC and candidate for treatment were consequently enrolled in this cross sectional study. All of the patients signed the written consent to enter the study. They were treated weekly with 180 microgram of pegylated interferon- alpha 2a (pegasys) subcutaneously. They were visited monthly during their treatment and follow up course in THC. The safety of treatment, the end of treatment response, the relapse rate and the sustained virologic response were measured in these patients.

Results: The end of treatment response rate was 83.3% in total. In patients who had end treatment response, the relapse rate was 50% (4/8) among HBeAg negative patients and 75% (3/4) among HBeAg positive patients. The sustained virologic response rate in this study was 41.6%.

Conclusion: Our study showed that after treatment with pegasys, the genotype D chronic hepatitis B patients had an acceptable sustained virologic response rate (More than 30%). But the influence of HBV genotype on treatment response with pegasys needs to be reevaluated in these patients in future studies. In addition other patient-specific characteristics like genetic aspects should be taken into consideration.

Keywords: *Hepatitis B, Therapy, Pegasys.*

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INTRODUCTION

Hepatitis B virus (HBV) infection is the main cause of chronic liver diseases and hepatocellular carcinoma(HCC) in the world (1). It is estimated that around 400 million people are chronically

infected with this virus (1-3). In Iran, there are an estimated around two million hepatitis B carriers (4). Carriers of HBV infection are at increased risk of developing cirrhosis, hepatic decompensation, and HCC (5) and the level of HBV viremia has a positive relationship with HBV -related complications (6).

The goal of therapy in CHB patients is sustained suppression of HBV viremia and

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decrease progression of liver disease to cirrhosis and HCC, with the ultimate goal of improving survival. This can be pursued by maintaining constant inhibition of viral replication through a long term treatment with nucleos(t)ide analogs or by inducing, through the combined antiviral and immunomodulatory effects of interferon, a sustained immune response (7, 8). Standard interferon alpha (IFN- α) has been used for the treatment of chronic HBV infection since the 1980s and has been a mainstay in the treatment of chronic HBV infection since it was licensed for this indication in the early 1990s (9). Alpha interferon acts by inducing an antiviral state in cells, through engagement of cell surface receptors and subsequent activation of pathways that lead to increased expression of intracellular genes that cause an increase in breakdown in viral RNAs and protection against viral injury. Alpha interferon also stimulates cell-mediated immune responses which target infected hepatocytes leading to a decrease in cells that harbor the intrahepatic; HBV covalently closed circular DNA (cccDNA) molecules responsible for persistence of HBV infection. Limited response rate to interferon and high side effects made the researchers discover other antiviral drugs. Treatment of chronic HBV infection has improved over the last decade, with seven antiviral drugs being available currently (10). In comparison to interferon, oral agents used in the treatment of chronic hepatitis B were better tolerated by the patients but there are three problems facing their usage, the end of duration of the treatment has been not determined yet, suppression of HBV DNA occurs only during therapy, and there is a high potential risk for emerging resistant HBV mutants during therapy (11-16).

The addition of a PEG molecule to IFN significantly prolongs its half-life, resulting in more sustained IFN activity and a more convenient once-weekly dosing. There has been a resurgence of interest in interferon therapy for

chronic hepatitis B patients over the past 5 years, largely based on results of large clinical trials demonstrating that peg-interferon has more potent antiviral activity than standard alpha interferon and, in contrast to nucleoside analogs, does not result in antiviral resistance and can be given for a finite period rather than indefinitely. PEG-IFN α -2a has been licensed for the treatment of both HBeAg-positive and HBeAg-negative chronic HBV as a 48-week course, given by subcutaneous injection once weekly in a dosage of 180 mg. PEG-IFN α 2b has as yet been licensed for the treatment of chronic HBV in specific Asian countries (17).

Current guidelines, however, do not provide specific recommendations as to which chronic hepatitis B patients should be treated with peg-interferon (11). There is not enough data about treatment with PEG-IFN α -2a in Iranian chronic hepatitis B patients with predominant genotype D. Because the genotype of HBV and ethnicity of the patients can affect the response rate to pegasys (18), the goal of present study was to determine the preliminary result of treatment with pegasys In Iranian chronic hepatitis B patients (with genotype D) referred to our center.

PATIENTS and METHODS

The naïve chronic hepatitis B genotype D patients were consequently enrolled in this cross sectional study in our center. Entry criteria included an HBV DNA level of $>100\ 000$ copies/ml and an ALT level >1 times but <10 times the upper limit of normal (ULN; 40 IU/l in this study). All included patients had CHB status confirmed by liver biopsy within the 6 months prior to treatment. Exclusion criteria included decompensated liver disease, antiviral therapy prior to study, viral co-infections (hepatitis C virus, hepatitis delta virus or human immunodeficiency virus), or pre-existent neutropenia or thrombocytopenia. The study was

Table 1- Patients' baseline characteristics

	Age	Sex	BMI	ALT	HBV DNA PCR (Copies/ml)	Necro-Inflammation (Grade)	Fibrosis (stage)	Sonography Finding	HBeAg
1	40	M	24	80	641810	6	3	FL, Grade II	N
2	40	M	21	62	1925000	8	2	—	N
3	18	M	22	51	251954000	5	1	—	P
4	44	F	24	115	1130000	12	4	—	N
5	18	F	20	61	1610000000	3	0	—	P
6	15	M	18	70	140000000	3	0	—	P
7	25	M	19	70	100000	3	1	—	N
8	24	M	25	46	110000	5	1	FL, GradeII	N
9	60	M	19	50	1630000	7	3	—	N
10	38	M	21	48	3797500	5	2	—	p
11	23	M	22	95	568000	3	1	—	N
12	33	F	18	87	11887600	5	1	—	N

N: Neg; P: Positive; M: Male; F: Female; FL: Fatty liver

approved in the ethics committee of the Baqiyatallah research center for gastroenterology and liver diseases. The patients were informed concerning the pros and cons of the various treatments available for chronic hepatitis B and if they accepted the treatment with pegasys, they signed a written consent for participation in the study. There was not any grant to the patients for usage the pegasys during the treatment course. The patients were treated weekly with 180 microgram pegylated interferon- alpha 2a (pegasys) subcutaneously. During the treatment course and after that in post-treatment follow up (for at least 6 months) the patients were monitored every month by routine physical examination, as well as biochemical and hematological assessments. At specific times (before treatment, three, six and twelve months post treatment, and six months after discontinuation of treatment), the blood samples of the patients for measurement of HBV DNA viral load were submitted into a referral virology laboratory in Tehran without reporting the type of treatment. Serum HBV DNA was measured using the COBAS AMPLICOR HBV MONITOR. The treatment in these patients

was continued beyond the three months if they showed a decline more than 2 log of HBV DNA viral load in comparison with their pre-treatment HBV DNA viral load. The baseline variables (Table 1) and outcome variables (Table 2) were registered in questionnaire of the patients in each related visit. The end of treatment response after 24 weeks post-treatment ,among HBeAg negative cases was defined as normalization of ALT and undetectable HBVDNA and among HBeAg positive cases was defined as HBeAg loss and low HBVDNA viral load less than 2000 copies/ml. A sustained virological response was defined as an HBV DNA level of <20 000 copies/ml at the end of treatment and at 18 weeks post-treatment. Post-treatment virological relapse was defined as HBV DNA level of <20 000 copies/ml at the end of treatment and >20 000 copies/ml at 18 weeks post-treatment.

RESULTS

Among Twelve patients were enrolled in the study 25% (3/12) of the patients were female. The mean for the age of the patients was 31.5 (min 15,

Table 2- Overview of response rate in HBeAg-positive and HBeAg-negative patients

Change in Drug Dosage During Treatment	HBeAg positive		HBeAg negative	
	End of therapy (Months*)	Follow-up (Months) [†]	End of therapy (Months*)	Follow-up (Months) [†]
1 No			Undetectable(6)	SS [‡] (9)
2 No			2log ↓ (12)	Nonrelapse(6)
3 No	yes (12)	Nonrelapse(6)		
4 No			persist (6)	SS [‡] (2)
5 No	No(6)	SS [‡] (3)		
6 No	No(6)	SS [‡] (12)		
7 No			Undetectable(12)	Nonrelapse(6)
8 No			Undetectable(6)	Nonrelapse(6)
9 No			Undetectable(12)	SS [‡] (24)
10 No	yes(12)	SS [‡] (6)		
11 No			Undetectable(6)	SS [‡] (6)
12 No			Undetectable(12)	HBsAg Neg.

* Duration of treatment course in month; [†] Months after discontinuation of treatment; [‡] SS=Switch shift to oral nucleos(t)ide

max 60) and 33.3 % (4/12) of the patients were HBeAg positive. The Mean baseline of HBV DNA viral load was 10^6 copies/ml (Min: 10^5 , Max: 10^8). The mean baseline of ALT was 69 IU/ml (Min 46, Max 115). The rate of withdrawal from therapy due to appearance of adverse events was zero in the study.

Fifty percent (6/12) of the patients completed their full course of treatment (48 weeks). Among the remaining 6 cases who could not complete their treatment course the mean duration of the treatment was 24 weeks. Among HBe Ag negative patients the end of treatment response rate was 75% (6/8). Among HBeAg positive patients the end of treatment response rate was 50% (2/4). The end treatment response rate was 83.3% in total. Among patients with end treatment response, the relapse rate was 50% (4/8) among HBeAg negative patients and 75% (3/4) among HBeAg positive patients. The sustained virologic response rate in this study was 41.6%.

DISCUSSION

According to our knowledge this is the first preliminary report regarding the treatment of naïve chronic hepatitis B patients with PEG-IFN α -2a (pegasys) in Iran. Worldwide many studies in this domain showed that HBV genotype D is associated with low response to IFN-based therapy with the highest response rates in patients infected with genotype A (19). Most of these studies showed that chronic hepatitis B patients with sustained response of at least 30% to be good candidates for PEG-IFN therapy and up to this result, genotype D patients with less than this limit response rate were introduced as not good candidate for treatment with pegasys (20). Based on this preliminary study, usage of PEGINF-alfa 2a (pegasys) in Iranian genotype D chronic hepatitis B patients was safe and the end of the treatment response rate was 83.3 % (10 of 12 patients). On the other hand, in our study the sustained virologic response rate was 41.6% that is still more than 30% which is accepted to be a good

level for sustained response rate in these patients. In spite of the above information it is still not known whether these responses rates can be sustained in the long-term or not. The licensing of PEG-IFN and an additional four nucleos(t)ide analogues for the treatment of chronic hepatitis B available in the last few years, choice of antiviral therapy has become more important and more complex at the same time. Both treatment with IFN-based therapy and nucleos(t)ide analogues have proven effective and can improve long-term outcome. In order to decide which drug should be used as first-line therapy in specific patients, the pros and cons of the available drugs as well as patient specific characteristics should be taken into consideration. All of the major practice guidelines have advocated IFN-based therapy as potential first-line therapy for both HBeAg-positive and HBeAg-negative patients (21) particularly because sustained response and HBsAg loss seem to occur more often with IFN and PEG-IFN than with the direct antiviral agents (22). PEG-IFN seems to yield the highest rate of off-treatment sustained response after 1 year course of therapy among currently available drugs for the treatment of chronic hepatitis B (20, 23). It is also associated with favorable long-term clinical outcomes, including incidence of cirrhosis and HCC (24). However, worldwide the use of PEG-IFN currently accounts for no more than 10% of all prescriptions for the treatment of chronic hepatitis B (25). PEG-IFN-induced response is sustained in about 85% and 40% of HBeAg-positive and HBeAg-negative patients, respectively (26). In HBeAg-negative patients sustainability of PEG-IFN-induced response is thus lower than in HBeAg-positive patients but higher than with nucleos(t)ide analogues. Due to the low sustained response rate in HBeAg-negative patients, PEG-IFN is relatively less often given to HBeAg-negative as compared to HBeAg positive patients. In our study, on the other hand, the end treatment response rate was at least similar between HBeAg

negative and the HBeAg positive patients. However the number of cases in our study was not enough that the results could be interpreted statistically. Also in our study one case (who was HBeAg negative) seroconvert the HBsAg and the Anti HBs was appeared in her serum after the course of the treatment. HBsAg seroconversion can be achieved after interferon-based therapy by peg-interferon alfa-2a in patients with HBeAg-negative. Disease characterized successful immunological response to HBV infection and the closest outcome to clinical cure (15). In our study among HBeAg negative patients in 75 percents and among HBeAg positive patients in 50% of the patients, the HBV DNA viral load was undetectable at the end of treatment. After the discontinuation of pegasys in our study, the relapse rate among the former was 50% and among the later was 75%. This implies that the duration course of treatment may need to be more prolonged in these patients especially in HBeAg positive patients that showed a higher relapse in the study. Recently performed studies with one year of PEG-IFN in HBeAg-positive patients identified high baseline alanine aminotransferase (ALT), low baseline HBV DNA, sex and age as predictors of response (27, 28). In our study presence the same criteria were more associated with positive end treatment response. A drawback of PEG-IFN therapy, however, is the frequent occurrence of side effects such as flu-like symptoms, myelo-suppression, and depression (29). In our study the minor side effects of pegasys (like myalgia and bone pain) were very well tolerated by the patients and the major side effects (like profound neutropenia, severe thrombocytopenia and severe depression) that might have made us change the dose or discontinue the treatment did not occurred. In our study in patients who relapse after discontinuation of pegasys, when the treatment switched to nucleoside analogue (like adefovir or lamivudine) the viral load dramatically decreased after one

month of switch shift treatment. In fact nucleos(t)ide analogues directly target the HBV polymerase, and treatment with these drugs usually results in a rapid decline in serum HBV DNA levels. At the same time, the combination of peg-interferon α -2a and lamivudine seems to be beneficial to patients with genotype D. Genotype D patients receiving combination therapy had substantially higher rates of combined response than genotype D patients receiving peginterferon α -2a monotherapy. This apparent benefit of the combination regimen versus peg-interferon α -2a monotherapy was not seen in patients infected with the other genotypes (28). However, this observation agrees with those of a recently published study by Colombatto et al. (30) where bio-mathematical modeling revealed a greater reduction in HBV-infected cells at the end of therapy among patients with genotype D who were receiving combination therapy.

Since the evidence for the influence of HBV genotype on choice of antiviral therapy in chronic hepatitis B is increasing, determination of HBV genotype is essential in patients whose sustained off-treatment response is pursued. Our study showed that the genotype D chronic hepatitis B patients had acceptable sustained virologic response rate (More than 30%). In our study, the number of the cases was not enough to fulfill statistical evaluation. Thus, the influence of HBV genotype on treatment response with pegasys needs to be re-evaluated in chronic hepatitis genotype D patients in future studies. There might be other patient-specific characteristics including genetic aspects should be taken into consideration for prediction of sustained response rate in genotype D patients who are candidate for treatment with pegasys.

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