JMSR
Journal of Medical and Surgical Research

Research Article

ISSN: 2351-8200

JMSR 2017; Vol. IV, n 1: 417- 421

RESPONSE TO PEGYLATED INTERFERON IN HEPATITIS B PATIENTS WITH HBE AG-NEGATIVE: LONG-TERM RESULTS AND PREDICTORS OF SUSTAINED-OFF VIROLOGICAL RESPONSE

Younes Cherradi, Mustapha Benazzouz, Hanaa Benbrahim, Abdellah Essaid, Rajaa Afifi
Department of Hepatogastroenterology "Médecine C", Ibn Sina University Hospital, Rabat, Morocco.
Medical School of Rabat, Mohammed the Vth University, Rabat, Morocco.

ABSTRACT:

Introduction: Chronic Hepatitis B (CHB) is a major public health problem in Morocco and worldwide. According to our real-life experience, genotype D and mutant phenotype are prominent in Moroccan population. In this study, we aimed to evaluate the place of PEG INF in HBe Ag Negative patients and to define good responders' profile.
Methods: It's a mono-centric study including all naive HBV-carriers treated by PEG INF since 2004. Patients with treatment failure and relapsers were not excluded. Patients with less than 24Wof regular follow-up after end of treatment and patients with HIV or HCV co-infection were excluded. Considered data were: age, gender, body mass index (BMI), initial ALT rates, initial viral loads, histological activity and fibrosis according to METAVIR score. The major endpoints of the study were Virological response (VR) and sustained off-treatment virological response (SVR) rates.
Results: From a total of 80 treated patients, 50 were considered for the study. Mean age was 41 years old and 74% of patients were male. HVB genotyping was performed in only 28 patients. Four patients were genotype A and 24 were genotype D. Ten patients were obese. Hepatic fibrosis was severe (F3- F4) in 6 patients. Treatment failure and relapse were reported in 9 patients (18%) and then only 41 patients achieved 48 weeks of treatment. They all achieved 72 weeks of regular follow-up. HBV DNA was undetectable by polymerase chain reaction in respectively 10% and 6% of patients at both 72W and 96W (respectively n=5/50 and n=3/50). Virological response was achieved by 34% of patients at 72W (n= 17/50) and SVR was obtained in 18% at 96W (n=9/50). No HBs seroconversion was reported. Gender, age< 50 years old, genotype and initial cytolysis were not significant predictors of SVR. Low initial DNA viral level (<4log) was the only significant factor associated to SVR (p= 0,002)
Conclusion: The advantage of PEG- INF is the short duration of treatment. In our population - where HBe antigen negative profile and genotype D are prominent-, DNA negativation rates were very low (only 6%) and SVR was achieved in 18%. A national randomized study will help to assess the efficacy of extended PEG-INF treatment duration in our HBe Ag negative CHB patients with genotype D.

Keywords: Ag Hbe negative, Chronic Hepatitis B (CHB), Morocco, Pegylated interferon (PEG-IFN), Sustained-off virological response (SVR).

Corresponding Author:
Dr. Y. Cherradi, MD.
Address: Department of Medicine, Mohammed Vth Hospital, Sefrou, Morocco.
Tel: + (212) 665659284
E-mail: cherradiyounes@hotmail.com

*****Published in June 2017.*

doi: 10.46327/msrjg.1.0000000000000-------
doi url: https://doi.org/10.46327/msrjg.1.0000000000000-------

INTRODUCTION

Chronic Hepatitis B (CHB) is a real global public health problem worldwide. It's an important risk factor of hepatocellular carcinoma (HCC) [1]. Patients with CHB can be divided into two major categories: Hepatitis B HBe Ag positive and HBe Ag negative (also called mutant phenotype). Hepatitis B carriers with HBe Ag negative usually present an aggressive course, with rapid evolution to cirrhosis and an increased risk of development of HCC and severe complications [2]. According to our real-life experience, Genotype D and mutant phenotype, which are bad predictors of response to interferon, are prominent in Moroccan patients.

Hepatitis B treatment can be conducted using nucleotis (t) ide analogues (NUCs) or pegylated interferon (PEG-INF). In our department, the therapeutic strategy was based on a first-line treatment by PEG-INF. EASL guidelines recommend PegINF as an initial treatment for patients with mild to moderate HBe Ag negative CHB [R]. This study aims to evaluate the place of PEG-INF in the management of patients with HBe Ag-negative and to define predictive factors of sustained off-treatment virological response.

JMSR
Journal of Medical and Surgical Research
Research Article
ISSN: 2351-8200
JMSR 2017; Vol. IV, n 1: 417- 421

PATIENTS & METHODS:

It's a monocentric and analytic study. It includes all naive CHB-carriers treated by 48 weeks of PEG-INF 180ug /week **since 2004**. Patients with treatment failure and relapsers were not excluded. Patients with less than 24 weeks of regular follow-up after end of treatment, patients with severe portal hypertension or complicated cirrhosis and patients with HIV or HCV co-infection were not considered for the study. Patients who stopped treatment because of intolerance and major side effects were also excluded. In the population retained for the study, we considered the following metadata: age, gender, body mass index (BMI), initial ALT rates, initial viral loads, histological activity (A) and fibrosis (F) according to METAVIR score. HBV serum DNA loads were regularly measured by Polymerase Chain Reaction (PCR). The major endpoints was the sustained off-treatment virological response (SVR) rates. Virological response (VR) was defined as serum HBV DNA levels < 2000 IU/ml at W72. SVR has been defined as serum HBV DNA levels < 2000 IU/ml for at least 12months after the end of therapy (W96).

RESULTS:

From 80 treated patients, 52 were considered for the study. Treatment was stopped in 02 patients because of severe side effects. On 50 patients, Mean age was 41 years old [22- 59]. Seventy for percent of patients were male (n= 37) with a sex-ratio at 1.9. Ten patients were obese (BMI> 30). HVB genotyping was performed in only 28 patients. Four patients were genotype A and 24 were genotype D. Moderate to severe necro-inflammatory activity (A2- A3) has been reported in 22 patients. Severe fibrosis (F3- F4) was reported in 6 cases at the onset of treatment. (**Table I**)

Table I: Patients General Features in our Series.

Total Treated Patients	80	
Patients Included in the study	50	
Age>40	21	
Gender	Male	33 (%)
	Female	17 (%)
Obesity	BMI<29.9	40 (%)
	BMI>30	10 (%)
Genotype	(A)	03 (%)
	(D)	23 (%)
Activity	A 0-1	26 (%)
	A 2-3	22 (%)
Fibrosis	F 1- 2	37 (%)
	F 3- 4	11 (%)
Initial DNA viral loads	<4 log	22 (%)
	> 4 log	28 (%)

Treatment failure and relapse were reported in 9 patients (18%) and then only 41 patients achieved 48 weeks of PEG-INF therapy. They all achieved at least 72 W of regular follow-up. HBV DNA was undetectable by PCR in respectively 10% and 6% of patients at 72W and 96W (respectively n=5/50 and n=3/50). VR was achieved in 34% of patients at 72W (n= 17/50) and SVR was obtained in 18% at 96W (n=9/50) (**Table II**).

Table II. Response to PEG-IFN at W48, W72 and W 96: EoT, VR and SVR Rates.

W	Patients (n)	ADN Negativation (A)	Viral loads <2000IU/ml (B)	Sustained-off Virological Response SVR (A+B)	Viral loads >2000IU/ml	Treatment Failure / Relapse
W24-36	50/ 50					
W48 (EoT*)	41/ 50	23 (46%)	12 (24%)		6 (12%)	n=9 /50 (18%)
W72	41/ 50	05 (10%)	12 (24%)	17 (34%)	24 (48%)	
W96	41/ 50	03 (6%)	06 (12%)	09 (18%)	32 (64%)	

*W= weeks; EoT= End of treatment; VR= Virological response; SVR= Sustained-off virological Response.

No HBs seroconversion was reported. Gender, age< 50 years old, genotype and initial cytolysis were not predictive factors of SVR. Low initial DNA viral level (<4log) was the only significant factor associated to SVR (**p= 0.002**) (**Table III**).

JMSR
Journal of Medical and Surgical Research
Research Article
ISSN: 2351-8200
JMSR 2017; Vol. IV, n 1: 417- 421

Table III. Predictive Factors of VR and SoVR.

		SoVR+ (96W)	SoVR- (96 W)	p
Age>50		4	3	ns
		6	4	
Gender	Male	6	6	ns
	Female	4	1	
Obesity	No	7	7	ns
	Yes	3	0	
Genotype	A	4	1	ns
	D	0	2	
A	A_{0-1}	2	3	ns
	A_{2-3}	8	4	
F	F_{1-2}	0	0	ns
	F_{3-4}	10	7	
DNA_0	< 4log	4	3	
	> 4log	6	4	0.002

DISCUSSION

Chronic Hepatitis B (CHB) is a major public health problem. Despite the improvement of HBV vaccination coverage, which reduces the proportion of children under 5 years of age with new infection from 4.7% to 1.3% [3], an estimated 257 million people (3.61% of the global population) were living with CHB in 2015 according to WHO Global Hepatitis Report [3, 4]. In Morocco, the prevalence of Hepatitis B infection (HBV) has been estimated at 1.79% [4, 5]. Like other Mediterranean countries, Genotype D is prominent in Moroccan chronic HBV carriers [4-8] and real-life experience showed that mutant phenotype is common in our patients.

In the last two decades, conventional and PEG-IFN, and NUCs have been approved for the treatment of CHB. Five NUCs has been shown to be efficient on suppression of HBV viral replication with a different resistance barrier profile: low for telbivudine, lamivudine and adevofir and high for both tenovofir (TNF) and entecavir (ETC). A new form of TNF, TNF alafenamide (TAF), has been reported as effective as TNF dipivoxil with fewer side effects on bone and kidney biomarkers [9]. New drugs, targeting specific steps of viral life cycle, DNAccc or improving the immune response of the host to the HVB [10- **11**], are considered now in research labs but won't be available soon. The current therapeutic strategies, including PEG-IFN and analogues with high resistant barriers (TNF, ETC and TAF), as first-line therapies seem to be still considered as the mainstay of treatment of hepatitis B in the few next years.

In this study, we were particularly interested in patients treated with PEG-INF. The specificity of Moroccan patients is a profile associating mainly HVB with both mutant phenotype and genotype D. Those two conditions are considered to be bad factors of response to PEG INF [12]. In the lack of co-morbidities and contra-indications to interferon, the choice of a first line PEG-INF therapy is based on many arguments: the goal of achieving long-term immunological control with short treatment duration, the desire to raise family in female patients and the high prevalence of HBs seroconversion compared to NUCs [**13, 14**]. The aim of this study was to evaluate the effectiveness of PEG-IFN in HBe Ag negative patients and the predictive factors of Sustained off-Treatment Virological Response in this population.

In patients with HBe Ag-Negative, The sustained virological response reported rates range from 44% at 6 months and 28% at 3 years after the end of treatment. Response rates have been reported to be less important in patients with genotype D or E with 20% [**12**]. Piratvisuth and all. showed a VR in 31% of patients with HBe Ag-negative CHB 1 year post-treatment with PEG-IFN alpha -2a. Among these, 88% maintained this response up to 5 years follow-up and, remarkably, 28% achieved HBs Ag clearance 5 years after treatment [**15***]. In our series with predominantly genotype D patients, virological response rates were estimated at 34% at 06 months after the end of treatment and the SVR was achieved in only 18% at 96 weeks.

Many studies were interested in predictive factors of response in HBe Ag negative patients treated by 48 weeks PEG-IFN. Genotype D has been reported as a bad predictor of response to PEG-IFN which is more effective in genotypes A or B than in genotypes C and D [**16**]. In another hand, an association of high HBs Ag levels [**17**]with < 2 log10 IU/ml decline of HVB DNA viral loads at 12 weeks of treatment has been retained as predictive factors of non-response to PEG-IFN and then, were assessed as treatment stopping rules in genotype D population. Since our study was conducted retrospectively from 2004, data concerning HBs Ag levels in treated patients were not collected unfortunately for all patients, and the predictive value of early decline of HBs Ag levels was not evaluated. However, we demonstrate that low initial DNA viral level (<4log) was the only significant factor associated to SVR (p= 0,002); SVR was achieved in 57% of patients with initial viral loads <4log. Gender, age< 50 years old, genotype and initial cytolysis were not predictive of good response.

In our patients with a prominent genotype D and mutant phenotype, the 48 weeks PEG-IFN treatment regimen seems not to be sufficient. The extended treatment duration with

JMSR
Journal of Medical and Surgical Research
Research Article
ISSN: 2351-8200
JMSR 2017; Vol. IV, n 1: 417- 421

PEG-INF should be considered as an optimal therapeutic strategy. Lampertico and al. investigate in a European randomized study, with predominance of genotype D, the efficacy of safety of extending the duration of PEG-IFN to 96 weeks in HBe Ag CHB negative patients [**13, 18**]. Fifty two patients were treated by 180 µg PEG-IFN for 48 weeks followed by 135 µg weekly for an additional 48 weeks. The SVR rates were significantly higher in the 96W compared to 48W population (respectively 12% vs. 29%) [**16**]. This trial assessed both safety and efficacy of extending treatment duration to 96 weeks. The safety of extended treatment duration was also assessed in a Chinese study which considered only 72 weeks of PEG-INF therapy in Ag-HBe negative patients compared to 48 weeks [**13**]. In this trial, patients were HBe Ag-negative, but HVB genotypes were not D (only B and C). Since the association of NUCs to PEG-INF didn't show any benefit [**18**, 19] in the management of CHB, The extension of treatment duration should be considered seriously in our patients. A national study should evaluate the impact of such as strategy on SVR especially in the high-risk group of patients with HBe Ag-negative, genotype D with high on-treatment DNA viral levels (> 4log).

An Italian multicenter study demonstrated in 128 HBe Ag-negative patients (mean age 45 years, 94% genotype D, 13% with cirrhosis) that extended treatment with Peg-IFN alpha-2a to 96 wk was well-tolerated and improved the rates of sustained virological response (29% vs. 12%, p = 0.03) in HBe Ag-negative genotype D patients when compared to the current standard of care of 48 wk [**18**].

There are several limitations in this study. Firstly, as a real-life retrospective study, the genotype of Hepatitis B was not available in all patients; as genotype D is certainly prominent, this may influences significantly the response to PEG-INF in our series. Secondly, HBs Ag levels were not available; A decline in hepatitis B virus HBs Ag has been demonstrated as a predictive factor of clearance [20- 22] and treatment efficacy.

CONCLUSION

Patients with CHB HBe Ag-HBe negative, genotype D and High on-treatment DNA viral loads are a group with high risk of non-response to 48 weeks PEG-IFN therapy. The optimization of treatment strategy should be considered in those patients; the extended duration of PEG-INF therapy to 96 weeks seems to be an interesting therapeutic option in the improvement of the outcome of CHB. A randomized study will help to assess the efficacy of this strategy in a national cohort of HBe Ag negative CHB patients with genotype D.

REFERENCES:

1- Y. Cherradi et al. Hepatocellular Carcinoma screening is indicated Even After Sustained Virological Response: -Moroccan University Hospital Experience- J. Med. Sur. Res.(JMSR) 2016; III, 2: 223-228
2- Saikia N., Talukdar R, Mazumder S, Khanna S and Tandon R. Management of patients with HBeAg-negative chronic hepatitis B Postgrad Med J. 2007 Jan; 83(975): 32–39.
3- WHO media center: http://www.who.int/mediacentre/factsheets/fs204/en/
4- Guo-Feng Chen, Cheng Wang,George Lau. Treatment of Chronic Hepatitis B infection Liver International Vol 37, Issue S1 January 2017, 59-66.
5- Bennani A, Baha W, Dersi N, Ennaji M, Lazaar F, El Malki A,1 and all. Hepatitis B & C epidemiology in Morocco. BMC Proc. 2011; 5(Suppl 1): P20.
6- Kitab B., Afifi R, Essaid A, Benazzouz M, Salih Alj H, Rebbani K and all. Genetic variability of Hepatitis B virus in Morocco. BMC Proc. 2011; 5(Suppl 1): P22.
7- Cherradi Y, Afifi R, Derdabi O, Essamri W, Benjelloun S, Razine R and all. Génotypes de l'hépatite virale B et réponse à l'interféron pégylé. JFHOD 2013, P 303. http://www.snfge.org/content/genotypes-de-lhepatite-virale-b-et-reponse-l
8- Kitab B, El Feydi AE, Afifi R, Derdabi O, Cherradi Y, Benazzouz M and all. Hepatitis B genotypes/subgenotypes and MHR variants among Moroccan chronic carriers. J. Infect. 2011 Jul; 63(1):66-75.
9- Wang H, Xi Lu, Xudong Yang and Nan Xu. The efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate in antiretroviral regimens for HIV-1 therapy. Medicine (Baltimore). 2016 Oct; 95(41): e5146.
10- Grimm D, Thimme R and Blum H.E. HBV life cycle and novel drug targets. Hepatol Int. 2011 Jun; 5(2): 644–653.
11- Testoni B, Durantel D, Zoulim F. Novel targets for hepatitis B virus therapy. Liver Int. 2017 Jan;37 Suppl 1:33-39.
12- EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection. Journal of Hepatology 2012; 57: 167-185
13- EASL Clinical Practice Guidelines on the management of hepatitis B virus infection. Journal of Hepatology 2017.
14- Lampertico P, Viganò M and Colombo M. Why do I treat HBeAg-negative chronic hepatitis B patients with pegylated interferon? Liver Int. 2013 Feb;33 Suppl 1:157-63.
15- Santantonio T A, Fasano M. Chronic hepatitis B: Advances in treatment. World J Hepatol 2014 May 27; 6(5): 284-292
16- WJG Hepatitis B virus genotypes: Global distribution and clinical importance https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4017058/pdf/WJG-20-5427.pdf
17- Moucari R, Mackiewicz V, Lada O, Ripault MP, Castelnau C, Martinot-Peignoux M and all. Early Serum HBsAg Drop: A Strong Predictor of Sustained Virological Response to Pegylated

ISSN: 2351-8200
JMSR 2017; Vol. IV, n 1: 417- 421

Interferon Alfa-2a in HBeAg-Negative Patients. Hepatology 2009, 49 (X).

18- Lampertico P, Viganò M, Di Costanzo GG, Sagnelli E, Fasano M, Di Marco Vand all. Randomised study comparing 48 and 96 weeks peginterferon α-2a therapy in genotype D HBeAg-negative chronic hepatitis B. Gut 2013; 62: 290-298

19- Eun Ju Cho, Jeong-Hoon Lee J-H, and Jung-Hwan Yoon. Combination of Pegylated Interferon and Nucleos(t)ide Therapy: Toward a Cure of Hepatitis B Virus Infection? Gut Liver. 2016 Jul; 10(4): 497–498.

20- Chih-Lin Lin1,2 and Jia-Horng Kao New perspectives of biomarkers for the management of chronic hepatitis B. Clin Mol Hepatol. 2016 Dec; 22(4): 423–431.

21- Marcellin P, F, Cihan Yurdaydin, Hadziyannis S, Moucari R, Kapprell H-P and all. Hepatitis B surface antigen levels: association with 5-year response to peginterferon alfa-2a in hepatitis B e-antigen-negative patients. Hepatol Int. 2013 Mar; 7(1): 88–97.

22- Wiegand J, Wedemeyer H, Finger A, Heidrich B, Rosenau J, Michel Gand all. A decline in hepatitis B virus surface antigen (hbsag) predicts clearance, but does not correlate with quantitative hbeag or HBV DNA levels. Antivir Ther. 2008;13(4):547-54.