



## Effect of Hepatitis B Virus Genotypes and Viral Load on the Response of Patients Treated with Peginterferon- $\alpha$ -2a

Hepatit B Virüsü Genotiplerinin ve Viral Yükün Peginterferon- $\alpha$ -2a ile Tedavi Edilen Hastaların Yanıtı Üzerindeki Etkisi

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### ABSTRACT

**Objectives:** Present study was aimed to find out the influence of genotype and hepatitis B virus (HBV)-DNA on the treatment response of the patients with chronic HBV.

**Materials and Methods:** It was a cross-sectional, retrospective study carried out on patients undergoing treatment of chronic HBV. A total of 54 patients with chronic HBV, who were under treatment with peginterferon- $\alpha$ -2a, were included. Effects of genotypes and other factors on virologic response, combined response and hepatitis B surface antigen (HBsAg) clearance were analyzed with logistic regression and chi square test.

**Results:** Baseline viral load and HBV genotype were found to have significant influence on the patients' response. Patients with genotype A were found to respond more to the treatment than patients with mix genotype infection (A + D). However, this difference was only significant for virologic response. Patients with low (<20,000 IU/mL) baseline viral load showed higher rate of virologic response, combined response and HBsAg clearance than those with high (>20,000 IU/mL) viral load at baseline.

**Conclusion:** Peginterferon- $\alpha$ -2a therapy is more efficacious in mono-infected HBV patients either with genotype A or D than patients with mix genotypes (A + D). Moreover, patients with low viral load at baseline have a higher response rate than the patients with high viral load at baseline.

**Keywords:** Hepatitis B virus, HBV genotypes, peginterferon, viral load, treatment response

### ÖZ

**Amaç:** Bu çalışmada, kronik hepatit B virüslü (HBV) hastaların tedavi yanıtı üzerine genotip ve HBV-DNA'nın etkisini ortaya çıkarmak amaçlanmıştır.

**Gereç ve Yöntemler:** Kronik HBV tedavisi gören hastalar üzerinde yürütülen kesitsel, retrospektif bir çalışmadır. Peginterferon- $\alpha$ -2a ile tedavi gören toplam 54 kronik HBV'li hasta incelendi. Genotiplerin ve diğer faktörlerin virolojik yanıt, kombine yanıt ve hepatit B yüzey antijen (HBsAg) klirensi üzerindeki etkileri lojistik regresyon ve ki-kare testi ile analiz edildi.

**Bulgular:** Başlangıçtaki viral yük ve HBV genotipinin hastaların tedavi yanıtı üzerinde önemli etkiye sahip olduğu bulundu. Genotip A'ya sahip hastaların, miks genotip enfeksiyonu (A + D) olan hastalardan daha fazla yanıt verdiği bulundu. Bununla birlikte, bu fark sadece virolojik yanıt için anlamlıydı. Düşük (<20.000 IU/mL) başlangıç viral yükü olan hastalar, başlangıçta yüksek (>20.000 IU/mL) viral yüke sahip olanlara göre daha yüksek oranda virolojik yanıt, birleşik yanıt ve HBsAg klirensi göstermiştir.

**Sonuç:** Peginterferon- $\alpha$ -2a tedavisi, genotip A veya D olan mono-enfekte HBV hastalarında karma genotipli (A + D) hastalara göre daha etkilidir. Ayrıca, başlangıçta düşük viral yüke sahip hastalar, başlangıçta yüksek viral yüke sahip hastalardan daha yüksek bir yanıt oranına sahiptir.

**Anahtar Kelimeler:** Hepatit B virüsü, HBV genotipleri, peginterferon, viral yük, tedavi yanıtı

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## Introduction

Chronic Hepatitis B virus (HBV) infection is a leading health problem worldwide. About 400 million people are chronically infected with HBV in world and there are about 9 million HBV carriers in Pakistan (1,2,3). Chronic infection with HBV is also one of the major causes of many liver disease complications like cirrhosis, hepatocellular carcinoma and complete liver failure, which may lead to death (4).

Treatment of chronic HBV infection has generally low response rate and it is also associated with drug resistance and relapse (5). Peginterferon- $\alpha$ -2a, having antiviral activity as well as immunomodulatory function, was reported to have relatively higher response rates as compared to oral agents and conventional interferon in chronic HBV infections (4,5,6).

HBV genotype is established as a strong factor influencing treatment response in chronic HBV infection and contribute in treatment response of patients (5,7,8,9). Comparing genotypes A and D, it is reported that the patients infected with HBV genotype A has higher response rate to interferon  $\alpha$  than the patients with genotype D (9). Similarly when the response rates to interferon- $\alpha$  treatment were studied for genotypes B and C, it was found that genotype B infected patients were more sensitive for the treatment than genotype C infected chronic HBV patients (8). Genotype B was reported to have higher rate of hepatitis B surface antigen (HBsAg) clearance than genotype C while infection with genotype A was associated with better rate of HBsAg clearance when compared to the genotypes B, C, D and F infections (10,11).

Most of the previous studies available on the topic have focused genotypes B and C while only a few studies are published who compared genotypes A and D or their combination. The studies involving mix genotyping infections like A + D are needed to know about the dynamics of treatment response in patients with two or more than two genotypes at a time. In Pakistan, where genotype D, A and a mixture of both is prevalent, research has not been performed on this topic. The objective of the present study was to assess the response of peginterferon- $\alpha$ -2a in HBV patients infected with mono-genotypes A, D versus mix genotype infection and to compare hepatitis B e antigen (HBeAg) positive and negative infection for the same treatment.

## Materials and Methods

### Patients Selection and Outcome Definition

A total of 54 patients received treatment of peginterferon-2a (180  $\mu$ g weekly) for 6 months at Pakistan Atomic Energy Commission General Hospital, Islamabad, Pakistan. Virologic

response, combined response (virological + biochemical) and HBsAg clearance were determined after 24 weeks. Virologic response was considered as undetectable HBV-DNA in serum, combined response as undetectable level of HBV-DNA and normal alanine aminotransferase (ALT) in serum while HBsAg clearance was defined as undetectable level of HBsAg in serum.

### Laboratory Tests

HBV-DNA was extracted and quantified using commercially available extraction kits (AJ Roboscreen, GmbH, Germany) following the manufacturer's protocol. Genotypes of HBV were determined following genotype specific PCR method (12). Quantities of ALT were determined by local laboratory methods and protocols.

### Statistical Analysis

Regression analysis and Pearson's chi-square test were used to assess the influence of different viral, biochemical and patient factors including genotype, baseline HBV-DNA, baseline ALT, HBeAg, gender and age on different types of patients' response. Odds ratio (OR) along with confidence interval (CI) was calculated for each factor. The factors found significant in logistic regression analysis were then subjected to Pearson chi-square test to compare the patients' response rates. SPSS, version-16.0 was used for analyses.

### Ethical Approval and Patient's Consent

The study was approved by the Ethics Committee of University of the Poonch Rawalakot, Azad Jammu and Kashmir (approval number: UPR/HAEC/2020/M3/C07). All the patients signed a written informed consent.

## Results

### General Characteristics of Patients

A total of 54 patients completed 6 months of peginterferon- $\alpha$ -2a therapy which included 37 male and 17 female patients with mean age of  $33.1 \pm 12.6$  years. Out of the total 54 patients, 8 were infected with genotype A, 22 with genotype D while 24 of the patients were infected with a combination of both genotypes A and D (mix). Thirty-eight (70.4%) of the patients were HBeAg positive while remaining 16 (29.6%) were negative for HBeAg (Table 1).

### Baseline Factors

Out of the 6 factors analyzed in binary logistic regression, only genotype and baseline HBV-DNA were found to be significantly influencing the patients response. All the other factors, i.e. baseline ALT, HBeAg, gender and age had no significant effect on patients response (Table 2).

**Table 1.** Baseline characteristics of the patients in three genotype groups

Characteristic	Genotype A (n=8)	Genotype D (n=22)	Genotype A + D (n=24)	Overall
HBV-DNA IU/mL (median)	3,153.651	211,400	31,342.846	6,571.235
ALT, U/L (mean $\pm$ SD)	90.25 $\pm$ 25.2	62.9 $\pm$ 24.4	112.6 $\pm$ 67.5	93.5 $\pm$ 47.5
Age years (mean $\pm$ SD)	32.25 $\pm$ 14.4	37.4 $\pm$ 12.1	29.4 $\pm$ 11.6	33.1 $\pm$ 12.6
HBeAg positive (n%)	87.5%	63.6%	70.8%	70.4%
Male gender (n%)	62.5%	91%	50%	68.5%

HBV: Hepatitis B virus, ALT: Alanine aminotransferase, SD: Standard deviation, HBeAg: Hepatitis B e antigen

### HBV Genotype and Patient's Response

In logistic regression analyses, genotype was found to be significantly influencing the virological response. When patients having single genotype infection were compared with the patients having mix genotype infection, the patients with single genotype infection were found to be significantly more responders ( $p=0.022$ ) as compared to the patients having mix genotype infection with OR of 3.92 (Table 2). However, combined response and HBsAg clearance were not significantly different between both the patient groups.

In genotype comparisons, genotype A infected patients had a significantly ( $p=0.020$ ) higher virologic response than the mix infection patients with OR of 3.30 (Table 2). HBsAg clearance and combined response were not different significantly. No difference in any type of response was recorded between either genotype A and D or between genotype D and the mix (A + D) genotype infection (Table 2).

When analyzed with chi-square test, significantly higher rate ( $p=0.030$ ) of virological response was noted for genotype A infected patients as compared to the patients with mix (A + D) genotype as 75% of the patients with genotype A showed virologic response as compared to 25% of the patients with mix genotype infection (Table 3). There was no difference between both the groups in combined response and HBsAg clearance. Neither genotype A nor the mix genotype showed a significant difference with genotype D infected patients in any type of response rate (Table 3).

### Baseline Viral Load and Patient's Response

A total of 10 patients in the cohort had lower than 20,000 IU/mL of HBV-DNA before treatment (baseline) while the remaining 44 had higher than 20,000 IU/mL of baseline viral load. In logistic regression analysis, baseline HBV-DNA (viral load) was found to be significantly affecting patient's virologic response. Low baseline HBV-DNA (<20,000 IU/mL) was found as a strong predictor of both virologic and combine response, as patients with low HBV-DNA had a significantly greater trend of both virological response (OR: 7.15,  $p=0.044$ ) and combined response (OR: 16.30,  $p=0.007$ ) as compared to the patients with high (>20,000 IU/mL) baseline HBV-

DNA. However, HBsAg clearance was not significantly ( $p=0.055$ ) higher for low baseline HBV-DNA as compared to high baseline HBV-DNA though an OR of 8.52 (95% CI: 0.95-76.35) was observed (Table 2).

When compared with chi-square test, it was observed that HBV-DNA level at baseline was significantly associated with all three types of patients' responses (Table 4). The patients with low viral load at baseline had significantly higher rates of virologic response ( $p=0.012$ ), combined response ( $p=0.005$ ) and HBsAg clearance ( $p=0.008$ ) as compared to the patients having high viral load at baseline (Table 4).

### Discussion

This study reports a higher rate of all types of response rates for genotype A than mix genotype infection (A + D), but it also reports that the response rates between genotype A and genotype D infected patients is not significantly different. The study also compared the single genotype infection and dual genotype infection. Dual genotype infection (A + D) was found to be significantly less responsive as compared to mono-genotype infection specially with genotype A. The results of the current study are in part consistent and in part not consistent with some of the previous reports (9,13,14,15). These studies found a higher response rate of patients with genotype A compared to genotype D patients. We also noted that genotype A is the most sensitive genotype but its response rate is not significantly higher than genotype D, yet it is significantly higher than mix genotype infection. These results indicate that genotype play a role in response of patients to peginterferon- $\alpha$ -2a therapy and are partially supporting the results of another study (5) who reported that the patients with different genotypes have different response rates.

In the current study, single genotype infection was found to be more sensitive as compared to the mix genotype infections. This result is not supported by some of the previously published literature because of the fact that the mix infection with these genotypes (A and D) is less commonly found in the world and less studied. However, it is present in a considerable number of patients

**Table 2.** Logistic regression analysis for effect of baseline factors on virologic response, combined response and HBsAg clearance

Factor	Comparison	Virologic response		Combined response		HBsAg clearance	
		OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Genotype	Mono v Mix	3.92 (1.21-12.67)	<b>0.022</b>	3.00 (0.71-12.66)	0.135	4.60 (0.50-42.37)	0.178
	A v D	3.30 (0.54-20.27)	0.197	0.83 (0.13-5.35)	0.848	3.17 (0.36-27.57)	0.297
	A v Mix	3.00 (1.19-7.56)	<b>0.020</b>	1.52 (0.56-4.16)	0.408	2.77 (0.77-9.97)	0.119
	D v Mix	3.00 (0.86-10.42)	0.084	3.27 (0.72-14.73)	0.123	3.63 (0.35-37.83)	0.281
Age	Young v Old	2.93 (0.72-11.89)	0.132	3.91 (0.68-22.54)	0.127	1.02 (0.12-8.59)	0.982
Gender	Male v Female	0.25 (0.05-1.15)	0.075	0.86 (0.15-4.87)	0.862	1.41 (0.09-21.24)	0.800
ALT	Low v High	2.92 (0.69-12.48)	0.060	2.05 (0.44-9.75)	0.364	3.11 (0.38-25.46)	0.290
HBV-DNA	Low v High	7.14 (1.05-48.52)	<b>0.044</b>	16.30 (2.12-125.18)	<b>0.007</b>	8.52 (0.95-76.35)	<b>0.055</b>
HBeAg	Neg v Pos	1.21 (0.29-5.10)	0.787	0.57 (0.09-3.43)	0.540	1.53 (0.16-14.84)	0.714

v: Versus, Low HBV-DNA: <20,000 IU/mL, High HBV-DNA:  $\geq$ 20,000 IU/mL, Low ALT: Elevated up to 2xULN, high ALT: >2xULN, Neg: Negative, Pos: Positive, Young: <40 years, Old:  $\geq$ 40 years, Mix: A + D, mono: Genotype A or D only, OR: Odds ratio, CI: Confidence interval, HBsAg: Hepatitis B surface antigen

**Table 3.** Effect of genotype on rate of virologic response, combined response and HBsAg clearance

Response	Genotype A (n=8)	Genotype D (n=22)	Genotype A + D (n=24)
<b>Virologic response</b>			
n, (%)	6 (75)	11 (50)	6 (25)
p-value	<b>0.030*</b>	0.126	-
<b>Combined response</b>			
n, (%)	2 (25)	7 (32)	3(12)
p-value	0.578	0.159	-
<b>HBsAg Clearance</b>			
n, (%)	2 (25)	3 (14)	1 (4)
p-value	0.147	0.336	-

\*Pearson chi-square test (Fisher's exact test, 2 sided), genotype A versus A + D, HBsAg: Hepatitis B surface antigen

**Table 4.** Effect of baseline HBV-DNA on rate of virologic, combine and HBsAg response of the patients

Response	Low HBV-DNA (n=10)	High HBV-DNA (n=44)
<b>Virologic response</b>		
n, (%)	8 (80)	15 (28)
p-value		<b>0.012*</b>
<b>Combined response</b>		
n, (%)	6 (60)	6 (14)
p-value		<b>0.005*</b>
<b>HBsAg clearance</b>		
n, (%)	4 (40)	2 (4.5)
p-value		<b>0.008*</b>

\*Pearson chi-square test (Fisher's exact test, 2 sided), HBV: Hepatitis B virus, HBsAg: Hepatitis B surface antigen

in Pakistan. This is the first report involving the influence of mix infection with genotypes A and D on treatment response of chronic HBV patients. Further studies may highlight the case more clearly.

Besides genotype, baseline viral load was also recognized as an important factor in virologic response, combine response and HBsAg clearance of the patients in our study. Patients with low baseline viral load showed a significantly higher rate of all three types of responses. This study supports the previous studies in regard of the finding that patients with low HBV-DNA are more likely to respond to therapy than the patients having high baseline HBV-DNA as a lot of previous studies also reported almost similar findings (14,16,17). Similarly, low baseline HBV-DNA was found to be a predictor to peginterferon- $\alpha$ -2a therapy by a study in HBeAg negative patients (5).

Low HBV-DNA at baseline was also found to have association with better response in other therapies like adefovir, lamivudine and telbivudine in many studies (5,18,19,20,21). Our study also confirm the role of baseline HBV-DNA in treatment response from Pakistan which was not known previously. However, for confirmation, the role of genotype in treatment of chronic HBV patients suggested by this study as well as by some previous studies described above may be investigated further with larger data size and all types of antiviral therapies being used.

## Conclusion

Genotype A infection and low viral load (HBV-DNA) at baseline are strong predictors of patients' response to peginterferon- $\alpha$ -2a therapy. The study concludes that genotype A infected patients have a better chance of virological response to peginterferon- $\alpha$ -2a therapy than the patients having mix infection with genotypes A and D simultaneously. Patients with <20,000 IU/mL of HBV-DNA at baseline have better rate of virological response, combine response and HBsAg clearance than the patients having >20,000 IU/mL of HBV-DNA at baseline.

## Ethics

**Ethics Committee Approval:** The study was approved by the Ethics Committee of University of the Poonch Rawalakot, Azad Jammu and Kashmir (approval number: UPR/HAEC/2020/M3/C07).

**Informed Consent:** All the patients signed a written informed consent.

**Peer-review:** Externally peer-reviewed.

## Authorship Contributions

Concept: M.M., M.A.A., Design: M.M. Data Collection or Processing: M.M., M.A.A., M.N.H., Z.A., Analysis or Interpretation: M.M. Literature Search: M.M., M.N.H. Writing: M.M., Z.A.

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