



# Does Pegylated-Interferon Still Have High Efficacy Treatment Properties Against Chronic Hepatitis B?

Pegile-Interferon Kronik Hepatit B'de Hala Yüksek Etkili Tedavi Özelliklerine Sahip mi?

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## ABSTRACT

**Objectives:** Pegylated-interferon (Peg-IFN) alpha 2a/2b and nucleoside and/or nucleotide analogues (NAs) are currently the only two treatment approaches approved for the chronic hepatitis B (CHB). To date, few studies have compared Peg-IFN with NAs in the treatment of CHB. We aimed in this study to evaluate the effectiveness of Peg-IFN and potent NAs (entecavir and tenofovir disoproxil) and to compare cumulative virological and serological responses in Turkish CHB patients treated between 2006 and 2016.

**Materials and Methods:** In this observational retrospective study, we divided a total of 331 patients, who were diagnosed with CHB, into 3 groups: Peg-IFN treatment group (n=62), entecavir treatment group (n=131) and tenofovir disoproxil treatment group (n=138).

**Results:** Virologic response rate in the Peg-IFN treatment group (90%) at 12 months was higher than in the NAs treatment groups (80% for entecavir and 76% for tenofovir disoproxil) (p<0.05). Sustained virologic response (SVR) rate at 24 months was 61% in the Peg-IFN group (p<0.001). The rate of hepatitis B e antigen seroconversion was significantly higher in the Peg-IFN group (25%) than in the NAs groups (16% for entecavir, 13% for tenofovir disoproxil). Hepatitis B surface antigen (HBsAg) seroconversion rate was also higher in the Peg-IFN than in the NAs treatment groups (7.9% vs. 0.9% and 0%, respectively) (p<0.001). After HBsAg seroconversion, the titers of anti-HBs were retained for over six months.

**Conclusion:** Peg-IFN treatment was found to be effective with high SVR and hepatitis B e antigen and HBsAg seroconversion rates than NAs treatment in long-term follow-up of patients with CHB. Peg-IFN appears to be the first-choice treatment approach in patients with CHB until a new era in which hepatitis B is cured.

**Keywords:** Chronic hepatitis B, pegylated-interferon, nucleoside/nucleotide analogues, hepatitis B surface antigen, seroconversion

## ÖZ

**Amaç:** Pegile-interferon (Peg-IFN) alfa 2a/2b ve nükleozid ve nükleotid analogları (NA), şu anda kronik hepatit B (KHB) tedavisi için onaylanmış iki tedavi yaklaşımıdır. Bugüne kadar birkaç çalışma Peg-IFN ve NA'lar arasındaki tedavinin etkinliğini karşılaştırmıştır. Bu çalışmada, 2006-2016 yılları arasında Türk KHB hastalarında Peg-IFN ve potent NA'ların (entekavir ve tenofovir disoproksil) kümülatif virolojik ve serolojik yanıtlarını karşılaştırarak etkinliklerini değerlendirmeyi amaçladık.

**Gereç ve Yöntemler:** Retrospektif gözlemsel olan bu çalışmada KHB tanılı total 331 hasta (Peg-IFN tedavi grubu, n=62, entekavir tedavi grubu, n=131 ve tenofovir disoproksil tedavi grubu, n=138) değerlendirildi.

**Bulgular:** Virolojik yanıt oranı Peg-IFN tedavi grubunda 12. ayda (%90), NA tedavi grubundan (entekavir için %80, tenofovir disoproksil için %76) daha yüksekti (p<0,05). Peg-IFN'nin 24. ayda kalıcı viral yanıt (KVY) oranı %61 idi (p<0,001). Hepatit B e antijen serokonversiyonu Peg-IFN grubunda (%25) NA grubuna (entekavir için %16, tenofovir disoproksil için %13) göre belirgin yüksekti. Hepatit B yüzey antijeni (HBsAg) serokonversiyon oranı Peg-IFN grubunda NA tedavi grubuna göre daha yüksekti (%7,9 vs %0,9 ve %0) (p<0,001). HBsAg serokonversiyonundan sonra anti-HBs titreri altı aydan fazla korundu.

**Sonuç:** KHB hastalarının uzun süreli takibinde Peg-IFN tedavisi, NA'larına göre daha yüksek KVY ile daha yüksek HBsAg ve HBeAg serokonversiyon ile ilişkili bulundu. Peg-IFN hepatit B virüsün tedavisi edildiği yeni bir döneme kadar KHB hastalarında ilk seçenek tedavi yaklaşımı olarak görünmektedir.

**Anahtar Kelimeler:** Kronik hepatit B, pegile-interferon, nükleozid/nükleotid analog, hepatit B yüzey antijen, serokonversiyon

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## Introduction

Antiviral therapy is administered to prevent the progression of liver damage to cirrhosis, hepatocellular carcinoma (HCC) and death in patients with chronic hepatitis B (CHB). Currently, the available treatments for patients with CHB include pegylated-interferon (Peg-IFN) alpha 2a/2b and nucleoside/nucleotide analogues (NAs) (1,2). Peg-IFN is an immunomodulator with antiviral activity against hepatitis B virus (HBV) (3). NAs (i.e., lamivudine, telbivudine, entecavir, adefovir, tenofovir disoproxil and tenofovir alafenamide) inhibit reverse transcriptase activity of HBV polymerase (*pol*) (4). A therapy leading to hepatitis surface antigen (HBsAg) seroconversion would avoid requirement of additional treatments. The difficulty in eliminating HBV is due to the persistence of covalently closed circular DNA (cccDNA) that integrates into the host DNA (5).

Most guidelines recommend entecavir or tenofovir (disoproxil/alafenamide) and Peg-IFN, as monotherapy for the management of CHB (1,2,3,6). Deciding on the type of treatment depends on the patient's clinical status, HBV DNA load and the level of alanine aminotransferase (ALT) enzyme, hepatitis B e antigen (HBeAg) status, and liver histology (1,2,3). Entecavir is preferred in older patients due to the low risk for nephrotoxicity and acceleration of bone loss. Tenofovir disoproxil is very effective against NA-resistant and wild type HBV strains (7,8). Entecavir and tenofovir disoproxil, having similar high potency and genetic barriers, are used much more than Peg-IFN even in CHB patients with no contraindications to IFN (9). However, Peg-IFN is preferable in some circumstances, particularly in young patients eligible for shortened treatment duration. Peg-IFN has the advantages of absence of drug resistance, providing immune-mediated control of the HBV infection, the possibility of achieving a sustained virologic response (SVR), and the possibility of HBsAg loss in patients with an HBV DNA load of <2000 IU/mL. An additional advantage of Peg-IFN treatment is clearly established treatment duration of 48 weeks. On the contrary, the duration of NA therapy is yet to be clearly outlined (1,2,3).

A systematic review of 339 studies on the prevalence of CHB in Turkey revealed that the prevalence of HBsAg was 4.5% in the Turkish population. This rate may increase to 9.8% in the eastern part of Turkey (10,11). In our country, it is estimated that one out of every three people over 18 years of age has encountered HBV, in addition, more than 2 million adults have been reported to be HBsAg-positive (12). The rate of drug spending for CHB patients is 0.7% of the total and unfortunately, the rate for on treatment CHB patients is only 13.5-15% in Turkey (13). According to the data of the Intercontinental Market Services (IMS Health) in 2016, 61544 CHB patients in Turkey were receiving entecavir and tenofovir disoproxil treatment. The number of Peg-IFN-treated CHB patients has been reported to be 947 in 2016 in Turkey (14).

In this study, we aimed to evaluate the effectiveness of Peg-IFN and potent NAs. However, we compared cumulative virologic and serological responses in CHB patients over a given period of time.

## Materials and Methods

### Patients

In this retrospective observational study, we included 334 CHB patients treated with Peg-IFN (n=63), entecavir (n=131)

and tenofovir disoproxil (n=140) between 2006 and 2016 in the department of infectious disease at University of Health Sciences Antalya Training and Research Hospital.

According to the European Association for the Study of the Liver guideline, the diagnosis of CHB was made based on histological, virologic, serological and biochemical data (2). Grade and stage of the CHB were assessed using the Ishak (14) modified histological activity index (HAI) (15).

Patients with co-infection with HIV and other viral hepatitis viruses, immunodeficiency disorders, decompensated cirrhosis, HCC or any other malignancies, injecting and other drug users, solid organ recipients, those non-compliant with treatment and patients who received treatment less than 12 months, or less than 3 months due to adverse effect or intolerance, pregnant women, and any patient under the age of 18 years were excluded.

All the patients were followed up by hepatitis B serology, biochemistry, and virology at 1, 3 and 6 months. HBV DNA and serology parameters were recorded at 3-month intervals after 12 months of therapy with Peg-IFN and NAs.

During NAs treatment, their HBV DNA, evaluated using polymerase chain reaction (PCR), was negative, showing virologic response. The duration of Peg-IFN treatment was 48 weeks for all patients. Virologic response has been defined as a HBV DNA value of <2000 IU/mL (2). Both treatment groups were evaluated for virologic response at 6 months and at the end of the treatment. HBeAg seroconversion was defined as loss of HBeAg and development of anti-HBe on at least two consecutive follow-ups. HBsAg seroconversion was defined as absence of serum HBsAg and presence of anti-HBs after a 6-month period.

Compliance to therapy was accepted if patients took their pills once daily at the same time (0.5 or 1 mg entecavir and 245 mg tenofovir disoproxil per day) and were injected Peg-IFN (180 mcg for 2a, 1.5 mcg/kg for 2b) weekly and regularly, without interruption (except for their physician advices). After the treatment started, any symptom or abnormal laboratory and clinical findings were accepted as drug-related adverse effect.

### Laboratory Analysis

Serological markers of HBV were quantified by using chemiluminescence assay (Cobas platform, Roche Diagnostics, Mannheim, Germany), which has been the preferred test in the hospital since 1998. HBV DNA levels were quantified by sensitive real-time PCR (Abbott TagMan 2000, Illinois-Des Plaines USA) (lower limit as quantification, 10 IU/mL) and has been in use in the hospital since 2008.

Antiviral resistance analysis was made in Kocaeli University by the Sanger dideoxy sequencing method as follows; oligonucleotides (forward primer: 5' - TCG TGG TGG ACT TCT CTC AAT T - 3' / reverse primer: 5' - CGT TGA CAG ACT TTC CAA TCA AT - 3') were used for the HBV *pol* gene amplification. There are the PCR reactions: 95 °C - 10 min. for 35 cycles and then 95 °C - 45 s, 60 °C - 45 s, finally 72 °C - 45 s. The primers concentration was 0.3 mM. The amplicon size was 740 bp. A drug resistance tool that was Genafor/arevir (<http://coreceptor.bioinf.mpi-inf.mpg.de/>) used on the interpretation of HBV resistance mutations.

### Statistical Analysis

One-Way ANOVA was conducted to compare the continuous variables such as baseline demographic and laboratory characteristics (age, baseline HBV DNA load, HAI, patient follow-up

time, baseline ALT, fibrosis) between the subjects of Peg-IFN group and those of entecavir and tenofovir disoproxil group. Categorical variables (gender, HBeAg positivity, treatment status, and original type of therapeutic molecule) were compared using a chi-square test. The two-tailed t-test was conducted to compare the means of the HBV DNA monitoring between HBeAg-positive entecavir and tenofovir disoproxil treatment groups, Peg-IFN and HBeAg-negative entecavir patients as well as Peg-IFN and HBeAg-negative tenofovir disoproxil patients. Seroconversion rates were analysed using a chi-square test. A p value of  $\leq 0.05$  was considered statistically significant. SPSS v13 programme was used for statistical analyses.

## Results

There was no statistically significant difference in baseline age ( $p=0.5$ ), gender ( $p=0.5$ ), pretreatment mean ALT ( $p=0.5$ ), pretreatment HBV DNA ( $p=0.05$ ), and duration of follow-up ( $p=0.6$ ) between the groups. NAs were also similar in terms of being original and generic drugs ( $p=0.5$ ). Baseline demographic and clinical and laboratory characteristics of patients are shown in Table 1. Basal liver biopsy was done in all patients in Peg-IFN and in NAs treatment group. The fibrosis score was significantly lower in the Peg-IFN treatment group ( $p=0.001$ ).

Peg-IFN was injected in 63 patients (one patient was excluded due to signs of depression), entecavir was given to 131 patients, and tenofovir disoproxil was given to 140 patients, two of whom were receiving combination treatment with tenofovir disoproxil and entecavir as high HBV DNA levels were keeping on with entecavir monotherapy without any resistance and incompliance. These two patients were excluded from evaluation. Only two patients had entecavir resistance, in these patients the mutations were identified at the gene loci rtL180M, rtM204V and rtS202G. The treatment was therefore changed to tenofovir disoproxil.

Subsequently, in these two patients, renal toxicity developed because of tenofovir disoproxil treatment, in turn the patients were instead treated with entecavir.

Amongst the Peg-IFN group, there were only four HBeAg-positive patients; evaluation of virologic response was not conducted for this group. Amongst HBeAg-negative patients, the difference in the rate of HBV DNA suppression between the Peg-IFN and NAs groups were statistically significant for each month ( $p<0.001$  at 3, 6, 24, 36 and 48 months,  $p<0.05$  at 1 month and 12 month). Until 12 months of treatment, HBV DNA suppression was higher in the Peg-IFN group. By the second year of treatment (24 month), in the NAs group, the rates of HBV DNA suppression became higher ( $p<0.001$ ). In our study, the rate of virologic response was 90% at the end of the therapy and the SVR rate was 61% at 24 months amongst the Peg-IFN-treated patients. No statistically significant differences was found in HBV DNA suppression in NAs group between HBeAg-positive and negative patients ( $p>0.1$ ). In NAs, the suppression of HBV DNA was above 90% after 48 months of treatment. HBV DNA suppression rates are presented in Table 2.

The rates of HBeAg seroconversion was 25%, 16% and 13% in the Peg-IFN, entecavir and tenofovir disoproxil treatment groups, respectively. The difference between the treatment groups was statistically significant ( $p<0.001$ ). No statistically significant difference was found in HBeAg seroconversion rate between the two NAs ( $p>0.1$ ). HBsAg seroconversion rates were 7.9% and 0.9% in the Peg-IFN and entecavir treatment groups ( $p<0.001$ ). However, HBsAg seroconversion was detected in the tenofovir disoproxil treatment group. HBeAg and HBsAg seroconversion rates are presented in Table 3.

Some patients had anti-HBs titers after HBsAg seroconversion. HBsAg seroconversion was accepted based on the disappearance

**Table 1.** Baseline demographic and laboratory characteristics of the study patients

Characteristic	Pegylated-interferon	Nucleos(t)ide analogue	
		Entecavir	Tenofovir disoproxil
Patient, n	62	131	138
Gender (F), n (%)	27 (44)	48 (37)	59 (43)
Age, median years (range)	40 (21-55)	36 (20-68)	39 (22-73)
Baseline ALT, median U/L (range)	90 (12-330)	48 (15-300)	40 (10-300)
HBeAg positivity, n (%) <sup>a</sup>	4 (6)	34 (26)	43 (31)
Baseline HBV DNA load, median IU/mL (range)	2.4+E6 (2.5+E3-1.3+E9)	1.0+E8 (2.0+E4-1.7+E10)	1.2+E9 (1.0+E1-1.7+E10)
Biopsy status, median (range)			
HAI	6 (3-13)	7 (2-16)	7 (2-18)
Fibrosis <sup>b</sup>	1 (0-3)	2 (0-5)	2 (0-5)
Treatment status, n (%) <sup>a</sup>			
Naive	62 (100)	107 (82)	76 (56)
Experienced	-	24 (18)	62 (44)
Type of therapeutic molecule, n (%) <sup>a</sup>			
Original	62 (100)	70 (53)	67 (49)
Generic	-	61 (47)	71 (51)
Patient follow up time, median month (range)	30 (12-156)	36 (12-120)	36 (12-108)

F: Female, ALT: Alanine aminotransferase, HAI: Hepatic activity index, HBeAg: Hepatitis B e antigen, HBV: Hepatitis B virus  
<sup>a</sup>For the mean comparisons across groups;  $p<0.001$ , <sup>b</sup> $p<0.01$

of serum HBsAg and the presence of anti-HBs for more than 6 months. Anti-HBs titers occurred in five patients in the Peg-IFN treatment group and in one patient in the NAs treatment group. Anti-HBs occurred only in the entecavir treatment arm. However, in the second tests, there was an increase in anti-HBs antibodies and continued for a further six months. The period of anti-HBs occurrence and anti-HBs titers detected are presented in Table 4.

## Discussion

In the present study, the purpose was to compare the effectiveness of Peg-IFN and potent NAs treatments in CHB patients over an extended period (10 years). We used the standard parameters in both the serological and virologic responses. The rate of virologic response in the Peg-IFN group (90%) at 12 months was higher than in the NAs treatment group (80% for entecavir and 76% for tenofovir disoproxil). In addition, in our study, the SVR at 24 months was higher (61%) in the Peg-IFN group than in other studies. Information available regarding the treatment efficacy of Peg-IFN and NAs groups is limited. There is only one study from Turkey which compared the difference between Peg-IFN and adefovir treatment amongst a small CHB patient group (16). The rates for the virologic response at 48 weeks were similar to our study (90% for Peg-IFN, 80% for entecavir and 76% for tenofovir disoproxil). In a multicenter cohort study from Korea, after the end of Peg-IFN treatment, virologic response rate in HBeAg-negative patients was 30% in a period of one year (17). However, Yamazhan et al. (18) reported that the response rate of Peg-IFN treatment

was low at the end of treatment whereas one-year SVR in HBeAg-negative cases was 33%. In the current study, patients in all treatment groups displayed similar outcome in terms of baseline parameters; the fibrosis score however was significantly lower in patients treated with Peg-IFN. The lower SVR responses in other studies may depend on patients selected for Peg-IFN treatment.

High virologic and SVR rates may lead to long-term viral suppression that is known to reduce the degree of liver damage and the risk of end-stage liver disease (19,20). In the present study, HBV DNA suppression as a result of NAs treatment occurred in over 90% of cases after 48 months. It was long duration but long-lasting if the compliance to treatment provided perfect results could have been in the CHB patients treated with potent NAs. In a retrospective multicenter study conducted in Turkey, virologic response in patients treated with entecavir or tenofovir disoproxil therapy over a period of 4 years was similar to that in our NAs treatment group (21). On the other hand, there is a relationship between the concentration of HBV DNA and cirrhosis and HCC in patients with CHB (19). In our patients, who were on long-term follow-up, there were no HCC and cirrhosis in the two groups because Peg-IFN produced a high sustained off-treatment response, NAs evoked a high virologic response during uninterrupted therapy. Long-term NAs therapy has several disadvantages such as side effects, non compliance to therapy, reactivation and the risk of emergence of drug resistance by mutations (22). Although, the updated guidelines recommend discontinuation of NAs therapy (evidence level II-2, grade of recommendation 2) (23), patients

**Table 2.** Comparison of hepatitis B virus DNA suppression in the pegylated-interferon and nucleos(t)ide analogue treatments in the study patient groups

HBV DNA monitorization, (month)	HBV DNA suppression				
	Pegylated-interferona, n (%)	Nucleos(t)ide analogueb, n (%)			
		Entecavir		Tenofovir disoproxil	
		HBeAg (+)	HBeAg (-)	HBeAg (+)	HBeAg (-)
1	22 (35)	2 (6)	19 (20)	2 (5)	18 (19)
3	52 (84)	4 (12)	35 (36)	5 (12)	38 (40)
6	58 (94)	6 (18)	52 (54)	11 (26)	53 (56)
12	56 (90)	10 (29)	77 (78)	15 (35)	72 (76)
18	50 (80)	NA	-	NA	-
24 <sup>&amp;</sup>	38 (61)	17 (50)	82 (85)	24 (56)	85 (90)
36	41 (66)	22 (65)	88 (92)	37 (86)	90 (96)
48	27 (44)	33 (97)	96 (100)	42 (98)	92 (98)

The rule of HBV suppression; <sup>a</sup>In the Peg-IFN treatment; HBV DNA concentration should be less than 2000 IU/mL, <sup>b</sup>In the oral antiviral treatment; HBV DNA should be undetectable or less than 10 IU/mL by a sensitive PCR  
NA: Not available, <sup>&</sup>The 12<sup>th</sup> month virological response of Peg-IFN at the end of the treatment, HBeAg: Hepatitis B e antigen, HBV: Hepatitis B virus, Peg-IFN: Pegylated-interferon

**Table 3.** Hepatitis B e antigen and hepatitis B surface antigen seroconversion rate of the study patients

Seroconversion status	Chronic hepatitis B treatment		
	Pegylated-interferon	Entecavir	Tenofovir disoproxil
Before treatment HBeAg positive, n (%) <sup>a</sup>	4 (6)	34 (26)	43 (31)
HBeAg seroconversion, n (%) <sup>a,b</sup>	1 (25)	6 (16)	5 (13)
HBsAg seroconversion, n (%) <sup>a,b</sup>	5 (7.9)	1 (0.9)	ND

<sup>a</sup>For the mean comparisons across groups (pegylated-interferon and NAs) p<0.001, <sup>b</sup>For the mean comparisons across groups (entecavir and tenofovir disoproxil) p>0.1, HBeAg: Hepatitis B e antigen, HBsAg: Hepatitis B surface antigen

**Table 4.** Anti-hepatitis B surface level in pegylated-interferon and nucleos(t)ide analogue treated patients

Therapy	Patient	Time of seroconversion, years	Anti-HBs titer, IU/mL		
			First testing <sup>a</sup>	Second testing (6 <sup>th</sup> months)	Duration of titer (>6 <sup>th</sup> months)
Pegylated-interferon	1.	5 <sup>th</sup>	30	50	200
	2.	4 <sup>th</sup>	20	400	400
	3.	4 <sup>th</sup>	50	60	500
	4.	6 <sup>th</sup>	50	500	400
	5.	5 <sup>th</sup>	20	40	350
Entecavir	1.	5 <sup>th</sup>	80	90	100
Tenofovir	ND	ND	ND	ND	ND

Hepatitis B surface antigen seroconversion was the disappearance of serum hepatitis B surface antigen and presence of anti-hepatitis B surface for >6 months.  
<sup>a</sup>The time was that the anti-hepatitis B surface titres were detected for the first time  
 ND: Not determined, Anti-HBs: Anti-hepatitis B surface

in whom the therapy is discontinued, must be closely followed for reactivation (2,3,24). In low-income countries, the high cost of therapy limits the number of patients who receive treatment, which can ultimately influence the emergence of viral resistance on/off-treatment NAs in CHB patients (24).

As serological responses; HBeAg seroconversion rate was found to be significantly higher in the Peg-IFN group (25%) than in the NAs group (16% for entecavir and 13% for tenofovir disoproxil). Despite the long-term follow-up, HBeAg seroconversion rates were lower in the NAs group. This finding was also demonstrated by Xing et al. (24) that in long-term treatment with potent NAs, HBeAg seroconversion with the therapy was lower compared with spontaneous HBeAg seroconversion rate (25). The latest study conducted by Marcellin et al. (26) in 2017 showed remarkable results of Peg-IFN treatment in long-term follow-up of CHB patients (26). In HBeAg-positive patients, HBeAg seroconversion increased from 23% at the end of treatment to 38% after 3 years of therapy. ENUMERATE which is the largest "real-world" entecavir treatment study showed that five-year HBeAg seroconversion was 33.7% (27). A study with tenofovir disoproxil treatment also demonstrated a HBeAg seroconversion rate of 40% (28). In our real-world data, Peg-IFN showed durable e seroconversion but in the NAs treatment group, there was some seroreversion, and an additional 16% and 13% of the patients would achieve HBeAg seroconversion in HBeAg-positive CHB patients in the long-time period. Because of the immunomodulating effect of Peg-IFN that was sustained for a long time even after the end of therapy, no anti-HBe seroconversion in the Peg-IFN group was detected in the current study over the 10 years period.

In studies by Marcellin et al. (26), Ahn et al. (27), and Petersen et al. (28), HBsAg seroconversion rate was also clearly higher in Peg-IFN groups than in the NAs treatment groups (7.9%, 0.9% and 0%, respectively). The rate of HBsAg clearance 3 years after treatment was 2% in HBeAg-positive patients and 5% in HBeAg-negative patients treated with Peg-IFN; the rate of HBsAg loss was 4.6% for entecavir and the rate of HBsAg seroconversion was 0.8% for tenofovir disoproxil during long-term therapy (26,27,28). The production of HBsAg is associated with HBV replication and the amount of intrahepatic cccDNA. Higher HBsAg seroconversion rate in the long-term Peg-IFN treatment may be due to their good immunomodulating, weak antiviral activity and potential of immune-mediated control of HBV infection characteristics. The

possibility of treatment discontinuation in CHB patients was more likely in the Peg-IFN therapy group in our study.

We found that in the Peg-IFN group, anti-HBs titers of five patients were lasted longer than six months and one patient from the entecavir treatment group had the anti-HBs titer durability. Following the discontinued Peg-IFN therapy, SVR off-treatment in long-term treatment had a chance of HBsAg seroconversion and durable immunity when compared with NAs which also requires long-term administration (2). Actually, there is limited information regarding the level of anti-HBs titer and their duration related with the endpoint of CHB treatments and their long-term efficacy.

There are some limitations in our long-term based retrospective study: firstly, genotype D is known with the lowest rate of virologic response in Peg-IFN treatment (29). In Turkey, genotype D is predominant in CHB patients (30,31). It is worthwhile to note that the CHB patients distributed into the various treatment groups which displayed virologic and serological responses were infected with HBV genotypes other than genotype D. Secondly, quantitative HBsAg is not available in our hospital, therefore, the comparison, between the Peg-IFN and the NAs treatment groups could not be established. There may be more efficient parameters for the long-term surveillance of serological responses to the treatment.

## Conclusion

In conclusion, Peg-IFN treatment was found to be highly efficient based on SVR, HBeAg and HBsAg seroconversion rates when compared with NAs treatment during long-term follow-up in Turkish CHB patients. Therefore, Peg-IFN appears to be the first-choice treatment approach in particular patients with CHB until a new era in which HBV is cured.

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## Ethics

**Ethics Committee Approval:** This study was approved by the Clinical Research Ethics Committee of Antalya Hospital of Health Sciences University (decision no: 7/13-04.13.2017).

**Informed Consent:** All patients were given informed consent.

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

## Authorship Contributions

Concept: FS., Design: FS., Data Collection or Processing: FS., Ü.U., Analysis or Interpretation: FS., M.S., Literature Search: FS., M.S., Writing: FS., M.S.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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