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Nucleos(t)ide Analogue Treatment Cessation in Hepatitis B e Antigen-negative Chronic Hepatitis B Patients: A Retrospective Single-center Study

Hepatit B e Antijen Negatif Kronik Hepatit B Hastalarının Nükleoz(t)id Tedavisinin Kesildiği Retrospektif Tek Merkezli Bir Çalışma

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Abstract

Introduction: The optimal duration of nucleos(t)ide analogues (NAs) therapy is unknown for hepatitis B e antigen (HBeAg)-negative chronic hepatitis B (CHB) patients. The European Association for the Study of the Liver (EASL) recommends the cessation of NAs in selected non-cirrhotic HBeAg-negative patients achieving long-term (at least three years) virological suppression under treatment if close monitoring can be guaranteed after the cessation of NAs. This study aimed to test this "cut-off rule" in HBeAg-negative CHB patients treated with NAs.

Materials and Methods: Seventy-one non-cirrhotic patients were treated with NAs for an average of nine (3-14) years before treatment was discontinued, and patients' hepatitis B virus (HBV) DNAs were negative for an average of seven (3-13) years. After treatment cessation, serum HBV-DNA and alanine aminotransferase levels were monitored every four weeks for the first six months and every three months from six months to 12 months. The patients were followed-up for 48 weeks after treatment cessation.

Results: In 48 weeks after NA treatment cessation, 30 of 71 patients (42.3%) experienced relaps. Hepatitis B e antigen seroreversion in two consecutive visits was observed in one patient (3.4%), HBV-DNA >20,000 IU/ml twice was observed in 23 patients (76.6%), and both virological and biochemical relapses were observed in six patients (20%). Median retreatment time was 21.6 (4-48) weeks. There were no significant differences between relapsers and non-relapsers in terms of baseline features.

Conclusion: Although the viral suppression time in NA treatment of HBeAg-negative CHB patients was longer than the EASL recommendation, the relapse rate was found to be similar to that in other studies. Our study has shown that applying EASL recommendations in patients meeting the suitable criteria who can be closely followed up is appropriate.

Keywords: Chronic hepatitis B, hepatitis B e antigen, treatment cessation

Öz

Giriş: Hepatit B e antijeni (HBeAg) negatif kronik hepatit B (KHB) hastalarında, nükleoz(t)id analogları (NA) tedavisinin optimal süresi bilinmemektedir. European Association for the Study of the Liver (EASL), tedaviden sonra uzun süreli (en az üç yıl) virolojik baskılama sağlayan sirotik olmayan seçilmiş HBeAg negatif hastalarda NA'nın kesilmesini önerir. Bu çalışma, NA ile tedavi edilen HBeAg negatif KHB hastalarında "kesme kuralını" test etmeyi amaçlamıştır.

Gereç ve Yöntem: NA'ları ile ortalama dokuz (3-14) yıl tedavi edilen siroz olmayan 71 hasta çalışmaya alındı, bu hastaların hepatit B virüs HBV-DNA'ları ortalama yedi (3-13) yıl boyunca negatifti. Tedavi kesildikten sonra serum HBV-DNA ve alanin aminotransferaz seviyeleri, ilk altı ay boyunca her dört haftada bir ve altı aydan 12 aya kadar her üç ayda bir izlendi. Hastalar tedavileri kesildikten 48 hafta sonraya kadar takip edildi.

Bulgular: NA tedavisinin kesilmesinden sonraki 48 hafta içinde, 71 hastanın 30'unda (%42,3) nüks oldu. Hepatit B e antijeni seroreversiyonu, ardışık iki vizitte, bir hastada (%3,4), ardışık iki kez HBV-DNA >20,000 IU/ml, 23 hastada (%76,6), virolojik ve biyokimyasal relaps altı hastada (%20)

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saptandı. Medyan yeniden tedavi süresi 21,6 (4-48) hafta idi. Nüks olan ve nüks olmayan hastalar arasında başlangıç özellikleri açısından anlamlı bir fark yoktu.
Sonuç: Hepatit B e antijeni negatif KHB hastalarının NA tedavisinde viral süpresyon süresi EASL önerisinden daha uzun olmasına rağmen, nüks oranı diğer çalışmalardakine benzer bulunmuştur. Çalışmamız, EASL önerilerinin, yakın takip edilebilecek uygun kriterleri olan hastalarda uygulanabilir olacağını göstermiştir.
Anahtar Kelimeler: Kronik hepatit B, hepatit B e antijeni, tedavinin kesilmesi

Introduction

Chronic hepatitis B (CHB) infection is treated to prevent complications such as cirrhosis, hepatocellular carcinoma (HCC), and death from hepatitis B virus (HBV) infection[1,2]. These complications can be avoided if a decrease in HBV-DNA level is observed considering the close association between HBV-DNA levels and patient outcomes[1,2]. This is similarly true for alanine aminotransferase (ALT) normalization, hepatitis B e antigen (HBeAg) seroconversion, and liver histology improvement[1-3]. However, achieving any of these goals may require lifelong therapy in many patients, raising the need to carefully identify patients requiring therapy and to define optimal endpoints of therapy[1-3].

The American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL), and Turkish Liver Research Association have simplified their guidelines on the recommended first-line agents in the treatment of CHB[1-3]. The preferred nucleos(t)ide analogues (NAs) are entecavir (ETV) and tenofovir, formulated either as tenofovir alafenamide or tenofovir disoproxil fumarate (TDF)[1-4]. However, long-term NA treatment leads to noncompliance with treatment and drug-related side effects and increases health expenditures[5].

Determining the duration of HBV therapy is far more challenging than selecting appropriate agents because the optimal endpoints are still being defined. Most clinicians would accept hepatitis B surface antigen (HBsAg) loss and seroconversion as an endpoint; however, this is achieved at a very low rate with our currently available therapies[5,6]. Certainly, for HBeAg-negative patients and other patients-notably those with advanced fibrosis or cirrhosis-indefinite therapy is required. For these types of patients, treatment cessation is not recommended because a flare off-therapy can result in decompensation. Thus, the key clinical decision about when to stop therapy involves selecting the right patients to start therapy and educating them about the duration of therapy.

For HBeAg-negative CHB patients, the AASLD guideline recommends the following: If the patient is not diagnosed with cirrhosis, then the patient should be treated indefinitely or until HBsAg loss, unless another reason for treatment cessation is observed. If the patient is diagnosed with cirrhosis, then the patient should be treated indefinitely[2]. The EASL guideline recommends that patients may stop treatment after three years of virological suppression with close monitoring after treatment cessation if patients are not diagnosed with cirrhosis[1]. The Asian Pacific Association for the Study of the Liver guideline recommends that if patients are not diagnosed with cirrhosis, then they may stop treatment after at least two years of treatment with undetectable HBV-DNA at three separate visits that are six months apart[4].

All preferred oral agents reportedly achieve HBV-DNA suppression in above 90% of HBeAg-negative CHB patients. Most patients will not lose HBsAg. The rates of HBsAg loss with the oral agents (0% to 1%) are even lower for HBeAg-negative CHB than for HBeAg-positive CHB[1,2,5].

For patients with HBeAg-negative CHB, treatment cessation has a delay phase that can last up to 12 months when patients do not relapse immediately. Subsequently, these patients should be followed up regularly. During the reactivation phase, HBV-DNA levels could increase initially, followed by ALT levels. Not every patient may experience a significant ALT flare, and many patients will have decreased HBV-DNA level (e.g., <2000 IU/ml), and subsequently, ALT level decreases[6]. The aim is to convert the patient to an inactive carrier (or called HBeAg-negative CHB infection), and to follow-up this patient with three to six months intervals as recommended by the guidelines[1-4]. HBeAg-negative CHB infection is known to have no progression of hepatic diseases and a reduction in the carcinogenic rate[7,8] and the criteria are considered to be appropriate.

In general, retreatment is required in approximately 40% of patients in one year, which means that up to 60% of patients can remain off-treatment[1,3]. Approximately 10% to 20% of patients fall within an indeterminate status, where their HBV-DNA is >2000 IU/ml, but they do not meet the ALT requirements for treatment or vice versa[1,3]. Approximately 20% to 30% achieve a sustained virological response, defined as HBV-DNA <2000 IU/ml and normal ALT level for HBeAg-negative CHB patients. Some patients continue to achieve HBsAg loss up to 20% after three years of follow-up[8].

This study aims to test the treatment cessation of oral antiviral agents in Turkish HBeAg-negative CHB patients treated with NAs.

Materials and Methods

Study Design

This is a retrospective study conducted in an outpatient clinic at Antalya Training and Research Hospital in Turkey. Patients with advanced fibrosis and cirrhosis (Ishak score >4), those receiving immunosuppressive therapy, those infected with human immunodeficiency virus and hepatitis C or hepatitis D virus, and those with a history of HCC, malignancy, and liver decompensation were excluded. Hepatitis B surface antigen positivity, HBeAg negativity, and anti-hepatitis B e antibody (anti-HBe) positivity were observed at the beginning of the NA treatment of the patients. NA treatments were discontinued according to the stopping rule of the EASL guideline [i.e., HBV-DNA should be undetectable by polymerase chain reaction (PCR) for at least three years], and patients were followed-up for 48 weeks. A total of 71 patients were included in the study. Patients' exclusion criteria are shown in Figure 1.

Patients aged over 18 years were followed up for 48 weeks. The follow-up of the non-cirrhotic patients was performed every four weeks for the first six months and every three months from six months to 12 months after treatment cessation. NA treatment was restarted to patients who met at least one of the following three criteria: (1) confirmation of two consecutive laboratory results [ALT >10 x ULN (repeated at least 10 days apart)] with or without associated symptoms, regardless of HBV-DNA levels, (2) HBV-DNA level exceeding 20,000 IU/mL as a result of two laboratory tests (repeated at one month apart), and (3) ALT level between 5 x ULN and ≤10 x ULN for more than four weeks. When one or more of these criteria were observed in any of the patients, the treating physician was responsible in deciding whether oral antiviral therapy should be continued.

The study was approved by the Ethics Committee University of Health Sciences Turkey, Antalya Training and Research Hospital (decision no: 5/20, date: 12.03.2020). All patients provided informed consent prior to treatment cessation in accordance with the local ethics committee requirements.

Patients

Sex, age, initial liver fibrosis stage, previous treatment(s), type of NAs prescribed to the patient, use of pegylated interferon, initial serum HBV-DNA and ALT levels, treatment duration, and duration of HBV-DNA negativity (duration of consolidation) were compared between patients with clinical relapse (relapsers) and those with sustained response (non-relapsers).

Study Assessments

In follow-up and baseline evaluations of the study, serum HBV-DNA levels were measured using real-time PCR (Abbott TagMan 2000, Illinois-Des Plaines USA) (lower limit as quantification, 10 IU/ml) in addition to standard laboratory and clinical assessments. Hepatitis B surface antigen, HBeAg, anti-hepatitis B surface antibody (anti-HBs), and anti-HBe measurements were determined using chemiluminescence immunoassays (cobas e 601 analyzer, Roche Diagnostic, Mannheim, Germany). Hepatitis B virus serology, HBV-DNA measurement, and results of anti-HBs, ALT, and liver biopsy (scored according to Knodell's modified system) were used in standard follow-up[9].

Study Endpoints

The primary efficacy endpoint was the proportion of patients with HBV-DNA level below 2000 IU/ml at week 48. The proportion of patients who restarted NA treatment by weeks was evaluated.

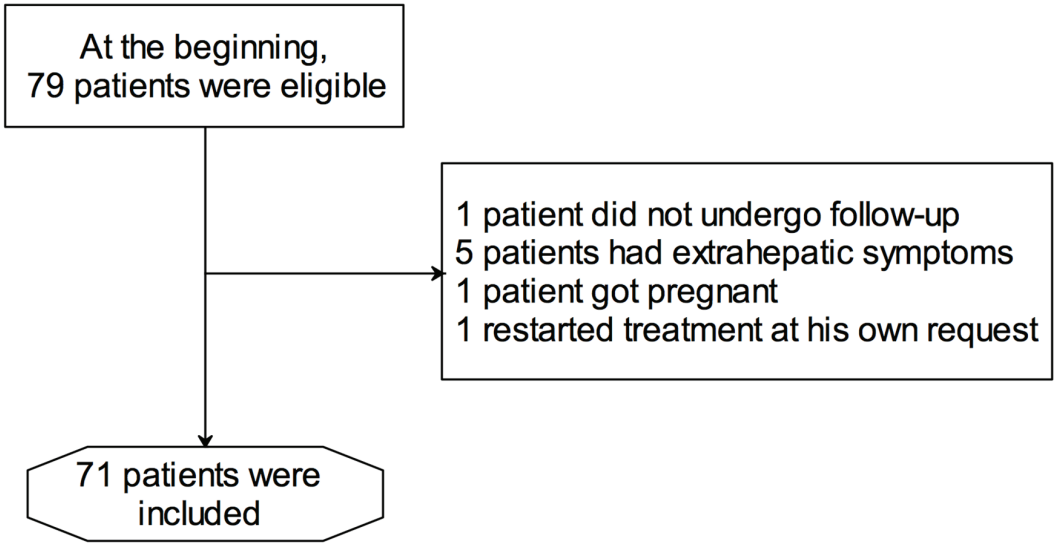

Figure 1. Patients' exclusion criteria flow

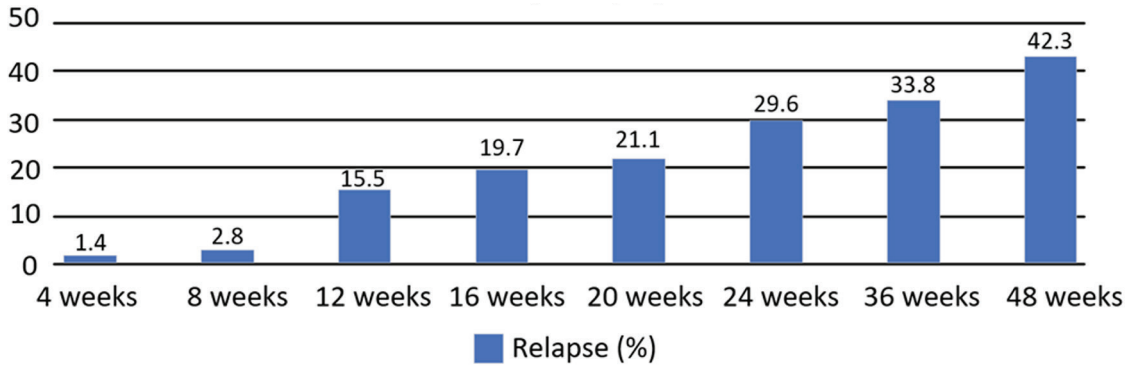

Figure 2. Cumulative relapse rates during the follow-up period

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 21.0 (SPSS, Chicago, IL, USA). Descriptive statistics were calculated for each variable. Data were expressed as medians and percentages. Distribution differences of clinical characteristics between groups were analyzed with Pearson chi-square test. All p values were 2-sided, and values were considered statistically significant if $p<0.05$.

Results

In our study, the treatment of 79 HBeAg-negative CHB patients treated with NAs was discontinued, and 71 patients met the inclusion criteria of this study. The patients' exclusion criteria are shown in Figure 1. Majority of the patients (54.9%) were males. The median age of the patients was 52 (26-73) years. Twenty-one of 71 patients (29.6%) experienced prior treatment with other NAs, and five (7.0%) patients experienced treatment with pegylated interferon. None of the patients lost hepatitis B surface antigen during treatment and the one-year off-therapy period.

Treatment characteristics of patients in baseline with or without clinical recurrence (relapsers versus nonrelapsers) are compared in Table 1. All initial characteristics were similar between relapsers and nonrelapsers. There was no significant difference between relapsers and nonrelapsers in terms of consolidation treatment period. The one-year relapse rate was 42.3% (30 of 71), and most of the relapses were observed at the 12th week (30%). Relapse rates by weeks are shown in Figure 2. In all patients with treatment cessation, HBV-DNA values were above the cut-off value of 10 IU/ml in the first 12 weeks of NA treatment cessation.

There were 41 (57.7%) patients with HBV-DNA level <2000 IU/ml at 48 weeks not receiving treatment. In comparison, relapse was observed in 30 (42.3%) patients: HBeAg seroreversion in two consecutive visits was observed in one (3.4%) patient, HBV-DNA >20,000 IU/ml twice was observed in 23 (76.6%) patients, and both virological and biochemical relapses were observed in six (20%) patients. No clinical symptoms were observed in patients who had high ALT values in two consecutive tests. Bilirubin level did not increase during ALT flare in those patients. The median (interquartile range) time to retreatment was 21.6 (4-48) weeks. Retreatment was initiated in all 30 patients who experienced relapse.

Safety

No serious clinical symptoms were observed in any patient during our study. Five patients had extrahepatic symptoms despite having HBV-DNA level below 20,000 IU/ml and normal biochemical test results, and these patients were excluded from the study (Figure 1). The symptoms observed were arthralgia, fatigue, and exanthema. When the treatment was restarted, all complaints were resolved.

Discussion

The relapse rate in our study was 42.3% (30/71) in patients who discontinued NA treatments. Hepatitis B guidelines do not define criteria that will determine when to stop the follow-up of patients whose NA treatment is discontinued and when to restart treatment[1,4]. The criteria when the treatment would be restarted in patients whose treatment had been discontinued were determined according to the criteria of the previous studies[10-12]. We evaluated ALT and HBV-DNA levels after NA treatment cessation. In 2012, Hadziyanmis et al.[12] presented one of the first studies of stopping adefovir therapy in HBeAg-negative CHB patients. In this study, 55% of patients had a sustained viral response (HBV-DNA <2,000 IU/ml and normal ALT levels), and 39% of patients who discontinued NA treatment experienced HBsAg loss at the 5th year of their follow-up. This high rate of seroconversion has become a reference for other similar studies.

Table 1. Comparisons of baseline features between relapsers and non-relapsers

	Total (n=71)	Non-relapser (n=41, 57.7%)	Relapser (n=30, 42.3%)	p value
Age, median (range) Mean±SD	52 (26-73) 49.1±11.9	53 (26-69) 49.3±11.8	46 (31-73) 48.8±12.4	0.520
Gender, n, (male, %)	39 (54.9%)	24 (58.5%)	15 (50%)	0.630
Baseline HBV-DNA (IU/ml), median (range)	1 x 10^6 (3870-4.22 x 10^9)	1 x 10^6 (3870-1.1 x 10^9)	1.1 x 10^6 (5 x 103-4.22 x 10^9)	0.317
Baseline ALT (U/l), median (range)	22 (7-173)	23 (7-173)	22 (8-54)	0.187
Fibrosis, median (range)	2 (0-4)	1 (0-4)	2 (0-4)	0.101
TDF, n (%)	33 (46.5%)	17 (41.5%)	16 (53.3%)	0.346
ETV, n (%)	26 (36.6%)	14 (34.1%)	12 (40%)	0.628
LAM, n (%)	5 (7.0%)	4 (9.8%)	1 (3.3%)	0.388
TBV, n (%)	7 (9.9%)	6 (14.6%)	1 (3.3%)	0.226
Prior use of other NA agents, n (%)†	21 (29.6%)	11 (26.8%)	10 (33.3%)	0.334
Prior use of PEG-IFN agents, n (%)	5 (7.0%)	3 (7.3%)	2 (6.7%)	0.647
Treatment duration (years), median (range)	9 (3-14)	9 (3-14)	9 (4-14)	0.434
Duration time of HBV-DNA negative (years), median (range)	7 (3-13)	7 (3-13)	7 (3-11)	0.648

†Other NA agents comprised adefovir dipivoxil, lamivudine, or telbivudine.
ALT: Alanine aminotransferase, ETV: Entecavir, LAM: Lamivudine, TBV: Telbivudine, TDF: Tenofovir disoproxil fumarate, SD: Standard deviation, HBV: Hepatitis B virus, NA: Nucleos(t)ide analogues, PEG-IFN: Pegile-interferon

Lifelong treatment raises some concerns such as reluctance, financial burden, drug resistance, and incompatibility for long-term NA treatment. For patients who are not regularly followed-up, severe reactivations that can lead to hepatic decompensation and even hepatic insufficiency may possibly be experienced[13,14]. Due to these disadvantages of lifelong therapy, recent studies have shown that the rate of HBsAg loss (up to 39% for up to five years) is greatly increased in patients discontinuing NA therapy based on appropriate criteria[15,16]. As a result, finitting NA treatment in appropriate patients will be significantly important.

The clinical effects of long-term treatment cessation of CHB were assessed in the FINITE study[17]. Non-cirrhotic patients with HBeAg-negative CHB who had been on TDF therapy for more than four years and had HBV-DNA suppression for more than 3.5 years were included in this study. Patients receiving TDF therapy were randomized to either discontinue or continue treatment. Within eight weeks after treatment was discontinued, most patients had an increase in HBV-DNA levels, and some had to restart therapy during the study period. However, 62% of the patients remained off-therapy, and 19% of the patients achieved HBsAg loss at week 144. Although relapse rates are similar to those in our study, the follow-up time after stopping treatment was longer than in our study, and the high rate of HBsAg loss could be due to this factor.

In Liem et al.'s[11] study, patients with HBeAg-negative CHB and virological suppression were randomized to stop or resume ETV or TDF after at least one year of treatment. If HBeAg was initially negative, the undetectable HBV-DNA had to continue for at least 36 months. The primary endpoint was achieving HBV-DNA <2000 IU/ml at week 48. Patients were retreated if their HBV-DNA level increased to >2000 IU/ml in conjunction with an ALT flare or if their HBV-DNA level exceeded 20,000 IU/ml on two consecutive visits. Virological relapse was common after treatment cessation, but in this study, approximately one-third of patients had a sustained response defined as HBV-DNA <2000 IU/ml with normal ALT levels. At week 72, 38% of patients needed retreatment, and the rate of HBsAg loss was only 2%. This was a variable patient population that included both those who had HBeAg seroconverted and those who were HBeAg-negative at the start of therapy. Nonetheless, even within this variable population, there was a subgroup who remained off-therapy. When investigators assessed the predictors of ALT flares off-therapy, they found that men were more likely to experience ALT flares than women, as were those who had higher HBV-DNA levels off-therapy. Although ALT flares can be observed at any time point, they were more likely to be observed in patients with HBV-DNA >10,000 IU/ml in the early period following treatment cessation (weeks four-six). In our study, 16 male and 14 female patients relapsed, which suggested that there was no statistical difference between sexes. The flares were mostly observed at 12th week in our study. The retreatment of relapsers

in our study was on average 21.6 (4-48) weeks because most of them did not want to undergo retreatment. As a result, we had to follow-up these patients closely and wait for their permission to undergo retreatment.

The most important differences of our study from other similar studies are that the duration of NA treatment [nine (3-14) years] and viral suppression time [seven (3-13)] were longer in our study than those in other studies. In fact, this is the unique aspect of our study because we found that the relapse rates of our study are similar to those of other studies, although we had longer treatment duration and longer duration of HBV-DNA suppression than other studies. We did not find lower relapse rates despite these differences. Additionally, the absence of HBsAg loss in one year in our study population is another difference. Conversely, higher HBsAg loss was observed in most other studies. This situation could be attributed to the fact that the most common type of HBV is genotype D in our country[18]. Genotype D is the genotype with the lowest virological response rate in treatment[19]. On the other hand, a review by Papatheodoridis et al.[20] mentioned that the average age of the study population, duration of consolidation, type of NA discontinued, and duration of NA treatment affected HBsAg loss. In a meta-analysis conducted by Kao and Berg[21] possible factors for predicting clinical recurrence after NA treatment cessation were host factors such as age, genetics, and immunity and viral factors such as HBV genotype, baseline serum HBV-DNA level, and HBsAg, hepatitis B core-related antigen (HBcrAg), and HBV RNA levels.

Long-term NA treatment cessation could result in frequent follow-up visits to physicians and patients for a certain period, uncertainty about long-term outcomes, and an increase in the number of necessary but costly laboratory tests. However, if there is no relapse, it can save the cost of treatment and provide psychological relief in patients. Although in the long term, sustained remission with cessation of NA therapy may result in HBsAg loss.

Our study had the following limitation: unavailability of biomarkers such as serum HBV RNA, HBcrAg, and quantitative HBsAg, which are the early precursors of reactivation[21]. These biomarkers were not included in routine laboratory applications in this study due to their high cost.

Conclusion

In conclusion, our study results could be promising for decision of NAs withdrawal in non-cirrhotic HBeAg-negative CHB patients. However, in countries with limited resources, since follow-up biomarkers cannot be used, more studies are required to develop appropriate strategies, including optimal duration of consolidation therapy, time to stop treatment, and restart treatment. Furthermore, additional studies to investigate potential predictive factors of achieving HBsAg loss after stopping therapy are also necessary.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee University of Health Sciences Turkey, Antalya Training and Research Hospital (decision no: 5/20, date: 12.03.2020).

Informed Consent: All patients provided informed consent prior to treatment cessation in accordance with local ethics committee requirements.

Peer review: Externally and internally peer reviewed.

Authors' Contributions

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

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

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