DOI: 10.20514/2226-6704-2024-14-2-124-131
УДК 616.36-002.2-085.281.8
EDN: PYHQXH

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ЭФФЕКТИВНОСТЬ ПРОТИВОВИРУСНОЙ ТЕРАПИИ АНАЛОГАМИ НУКЛЕОЗ(Т)ИДОВ И ЕЕ ПРЕДИКТОРЫ У ПАЦИЕНТОВ С ХРОНИЧЕСКИМ ГЕПАТИТОМ В

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Efficacy and its Predictors of Antiviral Therapy with Nucleos(T)Ide Analogs in Patients with Chronic Hepatitis B

Резюме

Актуальность. Противовирусная терапия аналогами нуклеоз(т)идов хронического гепатита В направлена на предотвращение прогрессирования заболевания и развития осложнений. Однако существующая терапия не позволяет ликвидировать вирус гепатита В, и для сохранения клинического эффекта у большинства пациентов требуется длительное лечение. В связи с этим изучение факторов, ассоциированных с эффективностью аналогов нуклеоз(т)идов, является актуальным. **Цель** — оценка эффективности и выявление предикторов ответа на противовирусную терапию аналогами нуклеоз(т)идов у пациентов с хроническим гепатитом В. **Материалы и методы.** Ретроспективно-проспективное обсервационное исследование включало 71 пациента с хроническим гепатитом В, получавших аналоги нуклеоз(т)идов в Центре диагностики и лечения хронических вирусных гепатитов в период с 2008 г. по 2023 г. Эффективность терапии аналогами нуклеоз(т)идов оценивалась через 24, 48 и 96 недель приема препаратов. Были изучены прогностические факторы, ассоциированные с получением вирусологического ответа через год противовирусной терапии и с достижением выраженного снижения плотности печени при транзиентной эластометрии. **Результаты.** Частота вирусологического и биохимического ответа увеличивалась по мере продолжения противовирусной терапии, а через 96 недель приема аналогов нуклеоз(т)идов составила 92,6 %. Исходный уровень вирусной нагрузки представляет собой независимый прогностический фактор достижения авиремии через 48 недель терапии (p=0,022). Клиренс HBsAg наблюдался у 2 (2,8 %) пациентов, клиренс HBeAg — у 5 HBeAg-позитивных пациентов. На фоне приема аналогов нуклеоз(т)идов было отмечено значимое снижение фиброза печени по данным транзиентной эластометрии, при этом ее высокий уровень в начале противовирусной терапии является фактором, связанным с выраженным снижением плотности печени (на 25 % и более) (p=0,022). **Заключение.** Противовирусная терапия аналогами нуклеоз(т)идов продемонстрировала высокую эффективность при подавлении репликации вируса гепатита В, нормализации активности аминотрансфераз и уменьшении фиброза печени. Исходные уровни вирусной нагрузки и транзиентной эластометрии являются наиболее важными прогностическими факторами, ассоциированными с эффективностью противовирусной терапии аналогами нуклеоз(т)идов.

Ключевые слова: *противовирусная терапия, аналоги нуклеоз(т)идов, эффективность, фиброз печени*

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Конфликт интересов
Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования
Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 02.02.2024 г.
Принята к публикации 14.03.2024 г.

Для цитирования: Нгуен Т.Х., Ильченко Л.Ю., Мельникова Л.И. и др. ЭФФЕКТИВНОСТЬ ПРОТИВОВИРУСНОЙ ТЕРАПИИ АНАЛОГАМИ НУКЛЕОЗ(Т)ИДОВ И ЕЕ ПРЕДИКТОРЫ У ПАЦИЕНТОВ С ХРОНИЧЕСКИМ ГЕПАТИТОМ В. Архивъ внутренней медицины. 2024; 14(2): 124-131. DOI: 10.20514/2226-6704-2024-14-2-124-131. EDN: PYHQXH

Abstract

Background: Antiviral therapy with nucleos(t)ide analogs for chronic hepatitis B is aimed at preventing disease progression and the development of complications. However, current therapies do not allow elimination of hepatitis B virus, and long-term treatment is required to maintain clinical effect in most patients. In this regard, the study of associated factors with the efficacy of antiviral therapy of nucleos(t)ide analogs is actual. **Aim:** To evaluate efficacy and identify predictors of response to antiviral therapy with nucleos(t)ide analogs in patients with chronic hepatitis B. **Materials and methods:** This retrospective-prospective observational study included 71 patients with chronic hepatitis B who received nucleos(t)ide analogs at the Center for Diagnosis and Treatment of Chronic Viral Hepatitis from 2008 to 2023. The efficacy of antiviral therapy with nucleos(t)ide analogs was evaluated after 24, 48, and 96 weeks of drug intake. The prognostic factors associated with obtaining a virologic response after one year of antiviral therapy and with achieving a significant decrease in liver density by transient elastometry were examined. **Results:** The virologic and biochemical response rate increased as antiviral therapy continued, and after 96 weeks of taking nucleos(t)ide analogs was 92.6 %. Baseline viral load level was an independent prognostic factor for achieving aviremia after 48 weeks of antiviral therapy (p=0.022). HBsAg clearance was observed in 2 (2.8 %) patients, HBeAg clearance — in 5 HBeAg-positive patients. On nucleos(t)ide analogs treatment there was a significant decrease of liver fibrosis measured by transient elastometry, and a high level of transient elastometry at the beginning of antiviral therapy is a factor associated with a significant decrease in liver density (by 25 % or more) (p=0.022). **Conclusion:** Antiviral therapy with nucleos(t)ide analogs has demonstrated high efficacy in suppressing hepatitis B virus replication, normalizing aminotransferase activity, and reducing liver fibrosis. Baseline viral load and transient elastometry levels are the most important prognostic factors associated with the efficacy of antiviral therapy with nucleos(t)ide analogs.

Key words: *Antiviral therapy, nucleoside and nucleotide analogs, efficacy, liver fibrosis*

Conflict of interests
The authors declare no conflict of interests

Sources of funding
The authors declare no funding for this study

Article received on 02.02.2024
Accepted for publication on 14.03.2024

For citation: Nguyen T.H., Ilchenko L.Yu., Melnikova L.I. et al. Efficacy and its Predictors of Antiviral Therapy with Nucleos(T)Ide Analogs in Patients with Chronic Hepatitis B. The Russian Archives of Internal Medicine. 2024; 14(2): 124-131. DOI: 10.20514/2226-6704-2024-14-2-124-131. EDN: PYHQXH

ALT — alanine aminotransferase, NA — nucleoside analogues, AST — aspartate aminotransferase, HBV — hepatitis B virus, VR — virological response, MLDR — marked liver density reduction, DNA — deoxyribonucleic acid, LAM — lamivudine, AVT — antiviral therapy, TBV — telbivudine, TDF — tenofovir disoproxil fumarate, TE — transient elastometry, HF — hepatic fibrosis, CHB — chronic hepatitis B, ETV — entecavir

Introduction

Despite the availability of an efficient hepatitis B virus (HBV) vaccine, chronic hepatitis B (CHB) remains a serious global healthcare concern. According to the World Health Organisation, approximately 300 million people suffer from CHB all over the globe and are at risk of severe hepatic complications [1]. Every year, almost 1 million people all over the world die of hepatic cirrhosis and hepatocellular carcinoma [2]. According to an analysis presented by the Russian Agency for Health and Consumer Rights in 2022, the incidence of CHB in the Russian Federation was 6.37 cases per 100,000 people (9,297 cases), i.e. the rate has increased by 42.5 % vs 2021 [3].

Currently, complete recovery from HBV infections is still impossible because the virus DNA integrates with the host genome, and products which can block or destroy covalently closed circular HBV DNA are at preclinical or early clinical development stage. The key objective of the therapy in patients with CHB is extension of their life expectancy and improvement of the quality of life by preventing disease progression [4].

According to clinical guidelines, nucleoside analogues (NA) are the first-line drugs for antiviral therapy (AVT) in patients with CHB due to their high antiviral activity and safety [4-6]. However, with the use of NAs, the rate of aviremia achievement and fibrosis severity vary. Incomplete virological response (VR), which depends on blood HBV DNA after 12 months of therapy, is observed in 10–30 % of patients who underwent NA therapy [4, 7]. This problem can cause poor compliance among patients.

Therefore, **the objective** of this study is to assess the efficacy of antiviral therapy with NAs and to identify predictors of therapy response in patients with CHB.

Materials and Methods

A retrospective-prospective, observational study included 71 patients with CHB, who were treated with NAs at the Centre for Diagnostics and Therapy of Chronic Viral Hepatitis in 2008–2023.

Inclusion criteria:

1. Patients with CHB
2. Over 18 years of age, both males and females
3. Antiviral therapy with NAs.

Exclusion criteria:

1. Patients with markers of HIV, hepatitis C, hepatitis D
2. Pregnancy and breastfeeding.

Patients were treated with the following NA products: 50 (70.4 %) — entecavir (ETV), 13 (18.3 %) — telbivudine (TBV), 5 (7.0 %) — tenofovir disoproxil fumarate (TDF), 3 (4.2 %) — lamivudine (LAM). The therapy lasted for 6 to 192 months, mean value: 15.0 [12.0–31.0] months.

The efficacy of NA AVT was assessed on the basis of the following:

- Virological response (HBV DNA < 50 IU/mL)
- Biochemical response (alanine aminotransferase (ALT) level of ≤ 40 U/L)
- Serological response (HBsAg clearance/seroconversion, HBeAg clearance/seroconversion in HBeAg-positive patients)
- Reduction in fibrosis severity.

Changes in hepatic fibrosis (HF) during AVT were assessed by transient elastometry (TE) using Fibroscan® (model 502 Touch Echosens, France) in accordance with the standard operating procedures. Marked liver density reduction (MLDR) means reduction in TE value by at least 25 % from the baseline.

Statistical processing was performed using SPSS software (version 25.0; SPSS Inc., USA). Categorial clinical data between independent groups were compared using chi-square and Fischer's exact test, while numerical information was compared with the help of Mann-Whitney test. Changes in numerical data during the therapy were evaluated with Wilcoxon test; McNemar chi-test was used for categorial data. Event probability (taking into account independent variable values) was calculated using binary logistic regression. Reliability operating characteristics (ROC) were analysed in order to assess the factor efficacy for therapy response forecasting and to calculate sensitivity, specificity, area under ROC curve (AUROC), and optimal threshold value. $p < 0.05$ was statistically significant.

The study was approved by the Local Ethics Committee at the N. I. Pirogov Russian National Research Medical University at the Ministry of Health of Russia (Minutes No. 213 dated 13 December 2021).

Results

The test group included 36 male and 35 female patients. The mean age at baseline was 47.0 [30.0–57.0] years old. The majority of patients (81.7 %) were HBeAg-negative. Baseline characteristics of HBeAg-negative and HBeAg-positive patients are presented in Table 1.

HBeAg-positive patients were younger and had high activity of ALT, aspartate aminotransferase (AST) and HBV DNA, as compared to HBeAg-negative patients.

Table 1. *Comparative baseline characteristics of HBeAg-negative and HBeAg-positive patients treated with nucleos(t)ide analogs*

Parameter	HBeAg-negative n=58	HBeAg-positive n=13	p
Age, years	48,0 [33,0-58,0]	30,0 [27,0-43,0]	**<0,05**
Male, n (%)	28 (48,3)	8 (61,5)	>0,05
Platelets, 10^9/l	227 [183-267]	219 [200-250]	>0,05
HBV DNA, $\log_{10}$ IU/mL	4,0 [3,5-4,8]	7,9 [4,3-8,0]	**<0,05**
Alanine aminotransferase, IU/L	33,5 [18,5-60,0]	60,6 [45,0-90,0]	**<0,05**
Aspartataminotransferase, IU/L	27,4 [20,1-46,5]	53,8 [34,2-70,0]	**<0,05**
Transient elastometry, kPa	6,8 [5,4-10,4]	6,1 [5,4-11,8]	
Fibrosis stage F0-1, n (%)	23 (50,0)	6 (60,0)	
Fibrosis stage F2, n (%)	9 (19,6)	1 (10,0)	>0,05
Fibrosis stage F3, n (%)	8 (17,4)	1 (10,0)	
Fibrosis stage F4, n (%)	6 (13,0)	2 (20,0)	

Notes: data are presented as median [25th-75th percentiles] or number (%); p — significance level (statistically significant differences in bold)

Virological response

After 24, 48, 96 weeks of AVT, the rate of virological response (VR) was 69.0 % (47/71), 87.6 % (57/65) and 92.6 % (25/27), respectively (Fig. 1).

On week 24 of AVT, VR was achieved in 77.6 % (45/78) of HBeAg-negative and 30.8 % (4/13) of HBeAg-positive cases, including after the therapy with ETV, TBV, TDF and LAM — 36/50, 10/13, 0/5 and 3/3 cases, respectively.

After 48 weeks of therapy, aviremia was recorded in 92.7 % (50/54) of HBeAg-negative and 63.6 % (7/11) of HBeAg-positive patients. VR was observed as follows: ETV — 42/46, TBV — 10/12, TDF — 2/4, and LAM — 3/3 patients.

The rate of aviremia on week 96 of AVT was 95.2 % (20/21) of HBeAg-negative patients and 83.3 % (5/6) of HBeAg-positive patients.

It has been shown that the rate of VR after 24 and 48 weeks of NA AVT in HBeAg-positive patients was lower than in HBeAg-negative patients ($p < 0.05$). However, after 96 weeks of therapy, no differences were observed ($p > 0.05$) (Fig. 1).

A linear logistic regression model, which included sex, age, platelet count, baseline HBeAg status, baseline HBV DNA, ALT, AST, TE values, demonstrated that initial HBeAg status ($p = 0.016$, 95 % confidence interval (CI) 0.028–0.690), HBV DNA level ($p = 0.001$, 95 % CI 0.259–0.711) and ALT value ($p = 0.048$, 95 % CI 0.876–1.000) were associated with aviremia on week 48 of AVT. According to multivariance analysis results, only baseline HBV DNA level (odds ratio (OR) = 0.534; 95 % CI 0.312–0.914; $p = 0.022$) is an independent prognostic factor of VR.

An analysis of the ROC curve showed that the baseline HBV DNA at the threshold value of ≤ 5.1 $\log 1_{10}$ (≤ 10^5) IU/mL was a good VR predictor at week 48 of therapy (AUROC = 0.894; 95 % CI 0.804–0.984; $p < 0.001$), with sensitivity of 87.5 % and specificity of 82.5 % (Fig. 2).

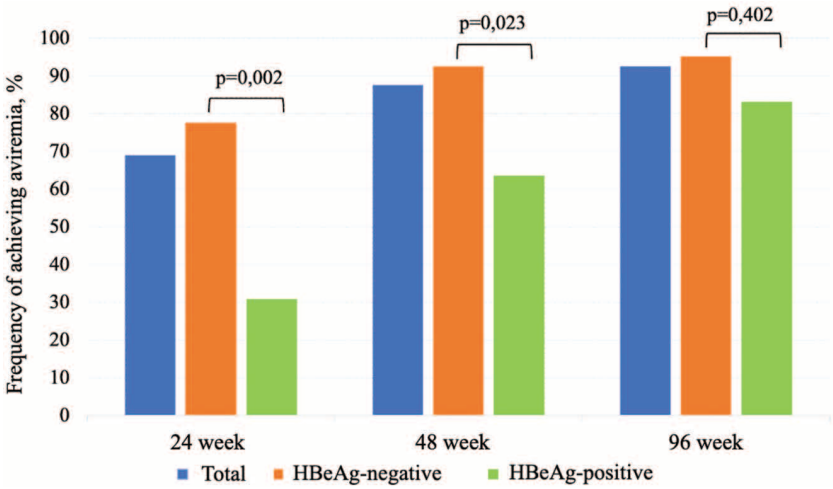

Figure 1. *Frequency of virologic response in HBeAg-negative and HBeAg-positive patients after 24, 48 and 96 weeks of therapy*

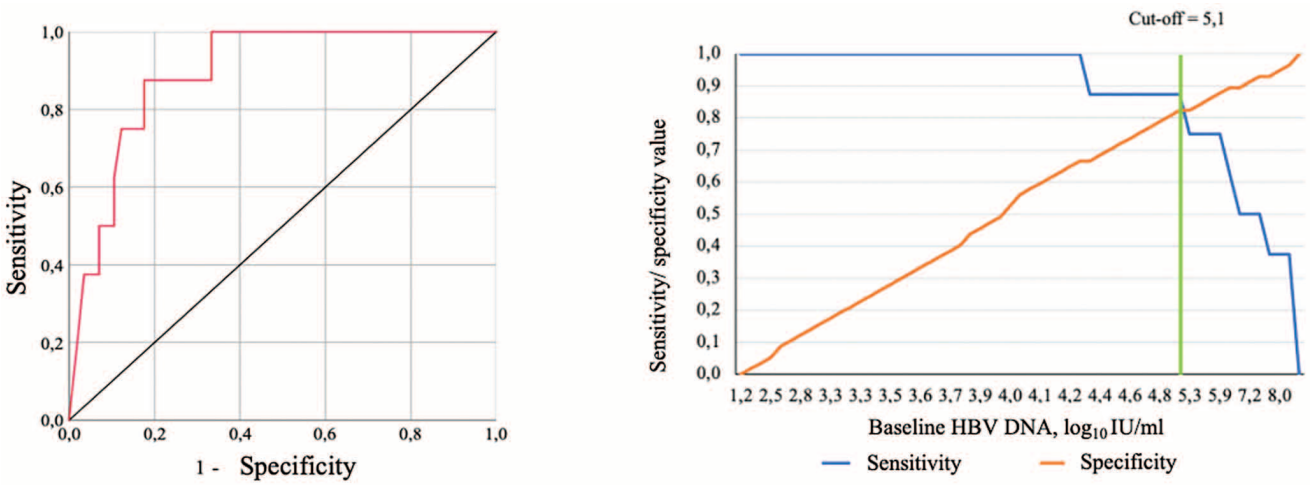

Figure 2. *Baseline HBV DNA level as a predictor of virologic response at week 48 of therapy*

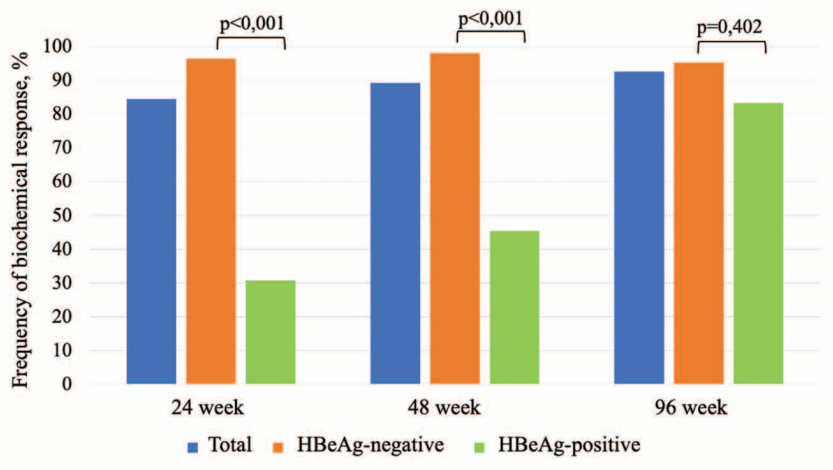

Figure 3. *Frequency of biochemical response in HBeAg-negative and HBeAg-positive patients after 24, 48 and 96 weeks of therapy*

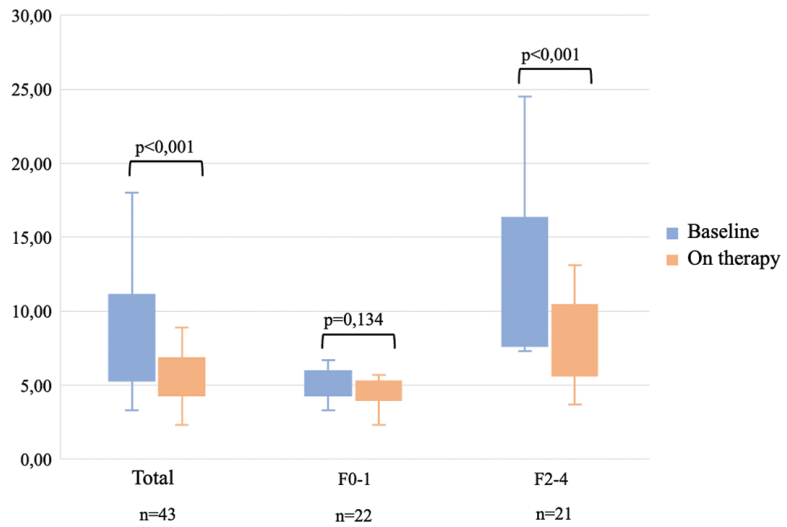

Figure 4. *Dynamics of liver fibrosis during therapy with nucleos(t)ide analogs according to transient elastometry data*

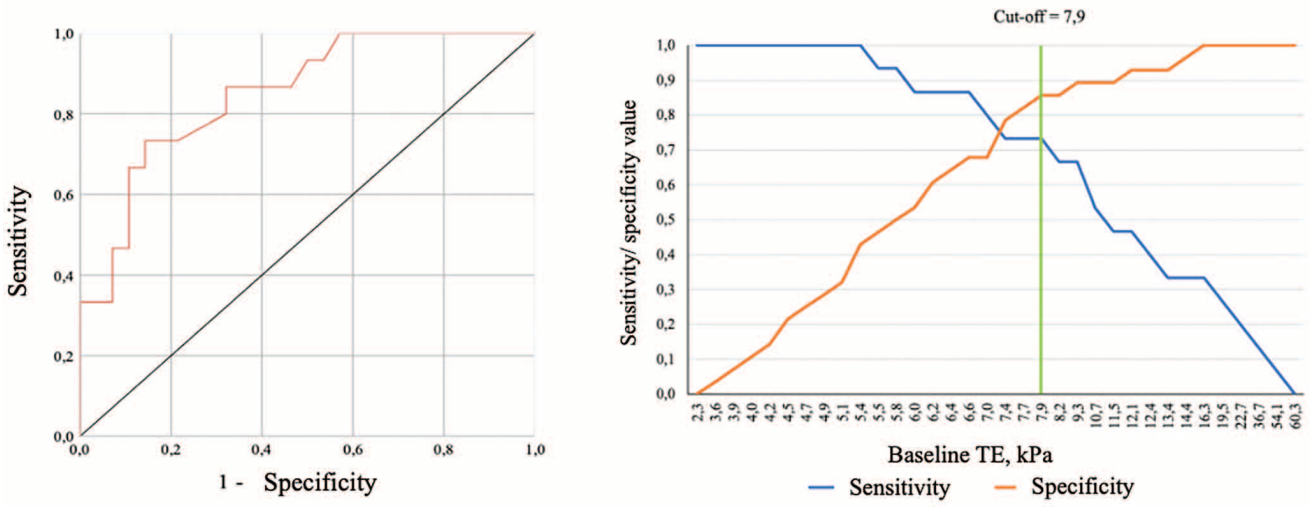

Figure 5. *Baseline level of transient elastometry index as a predictor of achieving a significant decrease in liver density during therapy*

Biochemical response

After24, 48, 96 weeks of AVT, biochemical response was observed in 84.5 % (60/71), 89.2 % (58/65) and 92.6 % (25/27) of cases, respectively (Fig. 3).

On week 24 of therapy, ALT activity normalised in 96.5 % (56/58) of HBeAg-negative and 30.8 % (4/13) of HBeAg-positive patients; on week 48 — in 98.1 % (53/54) and 45.5 % (5/11), respectively; on week 96 — in 95.2 % (20/21) and 83.3 % (5/6), respectively.

It has been demonstrated that, after 24 and 48 weeks of NA AVT, the rate of biochemical response in HBeAg-positive patients was significantly lower than in HBeAg-negative patients ($p < 0.05$); however, after 96 weeks of treatment, no differences were observed ($p > 0.05$) (Fig. 3).

Serological response

Two (2.8 %) patients on ETV had HBsAg claerance. HBsAg seroconversion (anti-HBsAg) was observed in one patient, 27 months after completion of ETV therapy. HBsAg clearance was recorded only in HBeAg-positive patients (2/13).

HBeAg clearance was observed in 5/13 (38.5 %) HBeAg-positive patients, including four patients with HBeAg seroconversion. HBeAg clearance was achieved in three cases of ETV therapy, 1 case of TBV therapy, and one case of TDF therapy.

Changes in hepatic fibrosis

Changes in HF were assessed using TE in 43 cases, with the mean interval between first and repeated procedure of 21.0 [12.0–30.0] months.

According to the METAVIR scale, TE data were used to diagnose stage F0-1 at the beginning of AVT in 22 (51.2 %) patients, F2 — in 8 (18.6 %) patients, F3 — in 6 (14.0 %) patients, and F4 — in 7 (16.3 %) patients.

The therapy resulted in TE value reduction from 6.7 [5.3–11.1] kPa to 5.3 [4.3–6.8] kPa ($p < 0.001$), and in patients with F2-4 this reduction was statistically significant (from 11.1 [7.8–14.6] kPa to 6.8 [6.0–8.9] kPa ($p < 0.001$)) (Fig. 4).

HF regression by at least 1 point was observed in 55.8 % of cases. After AVT, a share of patients with HF stage F0-1 increased from 51.2 % to 76.7 %. The majority (72.1 %) of patients demonstrated reduction in TE values by at least 10 %, and MLDR (by at least 25 %) was achieved in 15 (34.9 %) cases.

According to linear logistic regression results, MLDR-associated factors were age ($p = 0.027$, 95 % CI 1.006–1.102), sex ($p = 0.048$, 95 % CI 1.028–13.515) and TE at the beginning of AVT ($p = 0.008$, 95 % CI 1.086–1.710). A multivariance analysis demonstrated that the baseline TE level (OR = 1.345; 95 % CI 1.044–1.732; $p = 0.022$) should be treated as an independent prognostic factor of MLDR achievement.

ROC curve analysis showed the TE value at the beginning of AVT with the threshold value of ≥ 7.9 kPa as a predictor of MLDR (AUROC = 0.851; $p < 0.001$), where sensitivity is 73.3 % and specificity is 85.7 % (Fig. 5).

Discussion

Currently, NAs are recommended as a first-line therapy for patients with chronic HBV infection due to its high efficacy in inhibition of virus replication and prevention of disease progression [4-6].

This study has demonstrated higher rates of achieving non-detectable HBV DNA levels and ALT activity normalisation with continued NA AVT. In their work, J.-Y. Cho et al. reported anaemia in 80.0 %, 95.6 % and 99.4 % of patients during year 1, 3 and 5 of ETV therapy, respectively [8]. F. Suzuki et al. observed virological response in 81 %, 89 % and 91 % of patients undergoing ETV therapy after 1, 2 and 3 years, respectively [9].

Our data demonstrated that the rate of virological and biochemical response after 24, 48 weeks of treatment was significantly lower in HBeAg-positive patients as compared with HBeAg-negative patients. However, after 96 weeks of therapy, there were no statistically significant differences. This result can be explained by higher levels of HBV DNA and transaminases at the beginning of AVT in HBeAg-positive patients vs. HBeAg-negative patients. Rapid achievement of aviremia and ALT activity normalisation in HBeAg-negative patients was also described in a paper by Ibragimov EK et al. [10] and in a paper by Jacobson IM et al. [11].

In this study, HBV DNA at the beginning of AVT of > 10^5 IU/mL was an independent predictor of delayed virological response during the first year of therapy. Similar data on delayed aviremia in patients with a high baseline HBV DNA level were obtained by H. Zhou et al. [12].

Earlier studies demonstrated that reduction in TE values correlates with less severe HF [13, 14]. W. Xu et al. showed that reduction in TE values by 25 % and more is optimal for forecasting HP regression based on liver biopsy results [14].

AVT resulted in reduction in HF severity (according to TE), and a significant drop in the TE value was observed in patients with F2-F4. The share of patients with stage F0/F1 increased from 51.2 % to 76.7 %.

MLDR (reduction in TE by ≥ 25 %) was observed in 34.9 % of patients receiving NAs. ROC curve analysis demonstrated that the baseline TE at the threshold value of ≥ 7.9 kPa is a good predictor of MLDR, with sensitivity of 73.3 % and specificity of 85.7 %. The obtained results allowed seeing that the efficacy of NA AVT was higher in patients with marked fibrosis in comparison to minor fibrosis, thus pointing out

to the significance of AVT in hepatic cirrhosis and marked fibrosis [15].

Conclusions

NAs are efficient in inhibiting virus replication; they normalise functional status of the liver and reduce HF severity. Low HBV DNA levels at the beginning of AVT are an independent prognostic factor of aviremia achievement during the first year of the therapy. The use of TE in clinical practice makes it possible to efficiently monitor changes in HF during the treatment with NA AVT in patients with CHB.

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Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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