CLINICAL AND VIROLOGICAL CHARACTERISTICS OF CHRONIC HEPATITIS B AND RESPONSE TO ANTIVIRAL THERAPY

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Chronic hepatitis B (CHB) is a common infectious disease that represents one of the main causes of liver cirrhosis (LC) and hepatocellular carcinoma (HCC). CHB is still difficult to treat due to the lack of drugs that completely eliminate hepatitis B virus (HBV) from hepatocytes. The study was aimed to describe the CHB clinical and laboratory features, assess the efficiency of antiviral therapy and identify the factors associated with the response to antiviral therapy. The results of clinical and laboratory assessment, instrumental examination, serological and molecular testing of the patients (n = 201) followed up between 2007–2021 in the Viral Hepatitis Diagnosis and Treatment Center at the Clinical Hospital No. 85 of FMBA of Russia were assessed based on primary sources. Most of the patients in the group were males (56.7%); the HBeAg-negative patients predominated (93%). LC was diagnosed in nine patients (4.5%), among them one patient had HCC. The HBV D genotype was determined in 95.4% of cases, A genotype in 3.1% of cases, and C genotype in 1.5% of cases. After a year of treatment with the nucleos(t)ide analogues (entecavir or tenofovir) 88% of patients showed no viremia and their biochemical parameters were back to normal (88%). The overall seroconversion rate was 41.7% for HBeAg and 3% for HBsAg. Thus, high rates of virological response and enzyme activity normalization were obtained. Low baseline viremia level is an independent prognostic factor of achieving a virological response. The HBsAg level in the end of therapy makes it possible to predict relapse after the treatment cessation.

Keywords: chronic hepatitis B, antiviral therapy, prognostic factors

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КЛИНИКО-ВИРУСОЛОГИЧЕСКАЯ ХАРАКТЕРИСТИКА ХРОНИЧЕСКОГО ГЕПАТИТА В И ОТВЕТ НА ПРОТИВОВИРУСНУЮ ТЕРАПИЮ

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Хронический гепатит В (ХГВ) — широко распространенное инфекционное заболевание, одна из основных причин цирроза печени (ЦП) и гепатоцеллюлярной карциномы (ГЦК). Лечение ХГВ до сих пор затруднено из-за отсутствия препаратов, полностью элиминирующих вирус гепатита В (HBV) из гепатоцита. Целью работы было описать клинико-лабораторные особенности ХГВ, оценить эффективность противовирусной терапии и выявить факторы, ассоциированные с ответом на нее. На основании первичной документации проведена оценка результатов клинико-лабораторного и инструментального обследования, а также данных серологических и молекулярно-биологических методов исследований пациентов (n = 201), наблюдавшихся в период 2007–2021 гг. в Центре диагностики и лечения хронических вирусных гепатитов КБ № 85 ФМБА России. Большинство пациентов в группе — мужчины (56,7%); преобладали HBeAg-негативные больные (93%). У девяти (4,5%) пациентов диагностирован ЦП, у одного из них — ГЦК. Генотип D HBV установлен в 95,4% случаев, А — в 3,1% и С — в 1,5%. После года терапии аналогами нуклеоз(т)идов (энтекавир или тенофовир) у 88% пациентов отсутствовала виремия, нормализовались биохимические показатели (88%). Общий уровень сероконверсии по HBeAg составил 41,7% и по HBsAg — 3%. Таким образом, получены высокая частота достижения вирусологического ответа и нормализация активности ферментов. Низкий исходный уровень виремии является независимым прогностическим фактором для достижения вирусологического ответа. Уровень HBsAg в конце терапии позволяет прогнозировать рецидив после окончания лечения.

Ключевые слова: хронический гепатит В, противовирусная терапия, прогностические факторы

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Chronic hepatitis B (CHB) which is widespread throughout the world represents a serious global public health issue. According to the World Health Organization, there are 296 million people with CHB all over the world, up to 1.5 million new cases of infection are reported annually. In 2019, a total of 820,000 died, mostly from such complications, as liver cirrhosis (LC) and hepatocellular carcinoma (HCC) [1].

In the Russian Federation (RF) the CHB incidence rate stabilized at around 14.0–16.0 per 100,000 population in 2000–2009. There had been a decreasing trend of CHB incidence since 2010. In 2020, the incidence rate was 4.4 per 100,000 population, which was three times lower than in 2010 (13.3 per 100,000 population). This was probably due to active immunization of the population. However, the incidence of CHB in some regions of the RF remains high. Thus, in 2019, the CHB incidence in St. Petersburg was 44.0 per 100,000 population, while it was 54.3 per 100,000 population in the Republic of Tuva, 25.0 per 100,000 population in the Sakha Republic (Yakutia), and 13.0 per 100,000 population in Moscow. The prevalence of CHB in some regions is close to 1000 per 100,000 population, i.e. it constitutes about 1% of the total population [2–4].

The chronic infection caused by hepatitis B virus (HBV) is a dynamic process that reflects interaction between HBV replication and the patient's immune response. Five phases are conventionally distinguished in the natural course of chronic HBV infection based on the presence of HBeAg, HBV DNA levels, alanine aminotransferase (ALT) levels, and the absence or presence of the hepatic inflammation components [5]. Despite the variability in the course of chronic HBV infection, one third of patients eventually develop LC and 5–10% of patients develop HCC [6].

Antiviral therapy (AVT) slows down the disease progression, thereby reducing morbidity and mortality. However, regardless of the advances in therapy, recovery from CHB remains a challenging task, since antiviral drugs that are currently used in actual practice make it possible to achieve clinical remission, but do not eliminate HBV. Improving the survival rate by preventing the disease progression, LC decompensation, and HCC development is a final goal of the CHB treatment.

The study was aimed to describe the CHB clinical and laboratory features, assess the efficiency of AVT and identify the factors associated with the response to AVT.

METHODS

Primary sources (medical records) were analyzed in the Viral Hepatitis Diagnosis and Treatment Center. Among 989 medical records a total of 224 records of all patients infected with HBV who had been followed up between January 2007 and December 2021 were selected to provide the basis for the database.

The results of clinical and laboratory assessment, serological and molecular testing, and instrumental examination were analyzed based on the primary sources.

Inclusion criteria for the retrospective observational study: male and female HBsAg-positive patients; age 18–75 years; availability of the informed consent.

Exclusion criteria: patients having incomplete records; patients with human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis D virus (HDV) co-infection; no informed consent available.

A total of 23 patients were excluded due to non-compliance with the inclusion criteria; the clinical group included 201 people. The follow-up period was 1–15 years. The vast majority of patients (75.1%) were followed up during the first three years, a quarter of patients (23.4%) were followed up for 3–10 years, and three patients (1.5%) were followed up for more than 10 years.

All the patients attached to the medical institutions of FMBA of Russia underwent a comprehensive examination that included analysis of complaints and the disease history along with physical examination when contacting the Center. The following data were recorded when performing examination: gender, age (at the time of the first visit), the date when HBsAg were first detected, and duration of HBV infection. Laboratory and instrumental tests were performed in accordance with the clinical guidelines [2, 7]. The complete blood count (red blood cells, hemoglobin, platelets, white blood cells), biochemical profile (total protein, albumin, cholesterol, ALT, aspartate aminotransferase (AST), total bilirubin (TB), direct bilirubin, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT)), coagulation profile (partial thromboplastin time (PTT), international normalized ratio (INR), fibrinogen, prothrombin index (PTI), prothrombin time) tests were performed with the analyzers used in the laboratory of the Clinical Hospital № 85 of FMBA of Russia.

Serological markers of HBV infection (HBsAg), antibodies against HBsAg (anti-HBs), antibodies of the immunoglobulin G and M classes against the hepatitis B core antigen (anti-HBcore IgG, anti-HBcore IgM), HBeAg, antibodies against HBeAg (anti-HBe) were defined. The levels of HBsAg and anti-HBs were estimated by ensyme immunoassay (EIA). The HBV DNA was detected by polymerase chain reaction (PCR; sensitivity of the method was at least 50 IU/mL). The HBV genotypes were determined by the PCR amplification and sequencing of the viral genome fragment encoding the small surface protein (HBsAg).

All patients underwent hepatobiliary and spleen ultrasonography (AIXPLORER; France) and esophagogastoduodenoscopy (EGD) according to the indications (OLYMPUS GIF-E3; Japan). The liver stiffness was measured using the Fibroscan 502 Touch system (Echosens; France) according to the standard procedure. The fibrosis stage was determined in accordance with the METAVIR scoring system [8].

The virological response (VR) during treatment with the nucleos(t)ide analogues (NAs) was defined as achieving undetectable viremia (HBV DNA < 50 IU/mL), while VR during treatment with pegylated interferon — (PEG-IFN-α) for 12 months was defined as HBV DNA level < 2000 IU/mL; sustained virological response (SVR) was defined as the serum HBV DNA level < 2000 IU/mL 12 months after the end of therapy. Biochemical response (BR) was characterized by normal ALT activity (< 40 U/L).

The following was diagnosed based on the asessment performed during the first visit: four (2%) patients had HBeAg(+) chronic HBV infection, 10 (5%) – HBeAg(+) CHB, 37 (18.4%) – HBeAg(-) CHB, and 150 (74.6%) – HBeAg(-) chronic HBV infection (inactive HBsAg carriers).

Progression of infection was detected in 31 patients during the follow-up in the Center (within 1–10 years after the first visit): HBeAg(+) CHB in three cases and HBeAg(–) CHB in 19 cases. Furthermore, nine HBeAg(–) patients (4.5%) developed LC, among them one patient developed HCC. Probably, this was due to no AVT.

Statistical analysis

Statistical processing was performed using the SPSS 25.0 software package (SPSS: An IBM Company; USA).

Table 1. Comparative characteristics of HBeAg(+) and HBeAg(–) patients

Parameters	HBeAg(–), *n* = 187	HBeAg(+), *n* = 14	*p**
Gender Males Females	 103 (55.1%) 84 (44.9%)	 11 (78.6%) 3 (21.4%)	0.152
Age, years	50.0 [36.0–58.0]	28.5 [20.5–45.5]	0.001
Red blood cells, 10^{12}/L	4.7 [4.3–5.0]	4.8 [4.5–5.1]	0.488
Hemoglobin, g/L	144.0 [135.0–152.0]	147.5 [138.0–155.0]	0.268
White blood cells, 10^9/L	5.9 [4.9–6.8]	5.7 [4.3–6.3]	0.329
Platelets, 10^9/L	222.0 [194.0–256.0]	224.0 [201.0–267.0]	0.683
Total cholesterol, mmol/L	4.98 [4.3–5.8]	4.78 [4.1–5.2]	0.149
Total bilirubin, μmol/L	14.0 [10.25–18.9]	12.7 [9.1–18.0]	0.39
GGT, U/L	22.2 [15.9–35.1]	24.3 [18.6–43.0]	0.307
ALT, U/L > 40.0 U/L	24.0 [18.0–36.0] 37 (19.8%)	57.6 [34.9–78.0] 10 (71.4%)	0.001 <0.001"
AST, U/L > 40.0 U/L	23.8 [19.9–34.0] 32 (17.1%)	35.3 [30.3–46.0] 6 (42.9%)	0.020 0.029
Fibrosis, kPa	5.4 [4.5–7.2]	5.7 [5.4–6.9]	0.427
HBV DNA, $\log_{10}$ IU/mL	3.4 [1.0–4.1]	7.5 [3.2–7.8]	0.001
HBsAg, $\log_{10}$ IU/mL	3.4 [2.2–3.7]	4.1 [2.1–4.6]	0.259
Disease duration, years	5.0 [1.0–11.0]	5.0 [1.0–7.0]	0.726

Note: the data are presented as ME [25th and 75th percentiles] or *n*/*N* (%); **p* — significance level.

Quantitative indicators were presented as median (ME) [25th and 75th percentiles], and the qualitative data were presented as percentage. The chi-squared test and the Fisher's exact test were used to compare qualitative clinical data between groups, while the numerical data were compared using the Mann–Whitney *U* test. Logistic regression was used to assess the factors related to undetectable HBV DNA levels. The cumulative rates of virologic relapse were estimated by the Kaplan–Meier method and compared using the log-rank test. The Cox regression analysis was used to assess the relationship between the risk factors and the virologic relapse. Log transformation was applied to the HBV DNA and HBsAg levels. A *p*-value lower than 0.05 was considered statistically significant.

RESULTS

Characteristics of patients

A total of 201 patients were enrolled (114 males and 87 females, the male-to-female ratio was 1.3 : 1.0). The patients' median age at the time of the first visit was 50.0 [33.5–58.0] years and the median disease duration was 5.0 [1.0–11.0] years. The majority of patients had minimal clinical manifestations: fatique and the right upper quadrant pain. The patients were divided into two groups in accordance with their baseline HBeAg status: HBeAg positive (HBeAg(+)) and HBeAg negative (HBeAg(–)). The HBeAg(–) patients predominated (187/201; 93%). The patients' demographic and clinical characteristics are provided in Table 1.

The median age of the HBeAg(–) patients was higher than that of the HBeAg(+) patients: 50.0 [36.0–58.0] years and 28.5 [20.5–45.5] years, respectively; $p = 0.001$. The HBeAg(+) patients showed higher median ALT activity than the HBeAg(–) patients (57.6 U/L and 24.0 U/L, respectively; $p = 0.001$). Furthermore, elevated ALT was reported in 19.8% of the HBeAg(–) patients and 71.4% of the HBeAg(+) patients ($p < 0.001$).

Among 37 HBeAg(–) patients (19.8%), ALT activity was three times higher than the upper limit of normal (ULN) in 28 cases, 3–5 times higher than the ULN in four cases, up to 5–10 times higher than the ULN in four cases, and more than 10 times higher than the ULN in one patient. A total of 10 HBeAg(+) patients (71.4%) with elevated ALT were reported (ALT was three times higher than the ULN in eight of them and five times higher than the ULN in in two of them).

Likewise, the median AST level was higher in the HBeAg(+) patients than in the HBeAg(–) patients (35.3 U/L and 23.8 U/L, respectively; $p = 0.020$). The rate of the HBeAg(+) patients with elevated AST was 42.9% compared to the HBeAg(–) patients (17.1%) at $p = 0.029$.

Assessment of liver fibrosis by transient elastography was performed in 151/201 patients (75.1%). The body mass index did not exceed 25 kg/m^2. The following fibrosis stages were determined at the time of the first visit: F0/F1/F2 in 133/151 cases (88.1%), F3/F4 in 18/151 cases (11.9%). The HBV DNA levels were defined in 194 patients: these were 7.5 [3.2–7.8] log IU/mL in the group of HBeAg(+) patients and 3.4 [1.0–4,1] log IU/mL in the group of HBeAg(–) patients ($p = 0.001$).

The HBV genotype was studied in 65/201 patients (32.3%). Predominance of D genotype (62/65 (95.4%)) over the A (2/65 (3.1%)) and C (1/65 (1.5%)) genotypes was noted. HBV genotyping was performed in two HBeAg(+) patients, the HBV A and C genotypes were determined.

Table 2. Antiviral drugs used for treatment of CHB (n = 66)

Drugs	HBeAg(–) patients	HBeAg(+) patients
ETV	37	6
TDF	1	3
TBV*	10	2
LAM*	2	0
PEG-IFN-α-2a	0	1
ETV, TDF	3	0
TBV**, ETV	1	0

Note: ETV — entecavir; TBV — telbivudine; TDF — tenofovir disoproxil fumarate; LAM — lamivudine; PEG-IFN-α-2a — pegylated interferon α-2a; * — AVT in 2009–2011; ** — TBV for 12 months in 2009–2010, then ETV.

Efficacy of AVT for CHB

Currently, AVT for CHB approved in the RF involves the use of the nucleos(t)ide analogues (NAs) and pegylated interferons — (PEG-IFN-α). The NAs that are registered in Russia and are preferred for treatment of CHB include the drugs showing high antiviral activity: entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF). Since the patients followed up in the Center in 2007–2021 were enrolled, some patients received lamivudine (LAM) or telbivudine (TBV) during the first years of follow-up.

A total of 66 patients (32.8%) in the studied group who bought the drugs themselves received AVT. ETV was most often used by both HBeAg(–) and HBeAg(+) patients: 43/66 (65.2%) received this drug only, while the others (23) received other antiviral medications (Table 2).

A total of 65 patients were prescribed NAs. Among them 61 patients received only one drug, the treatment regimen was changed in four HBeAg(–) patients (antiviral drug was replaced by another one), that is why the total number of observations was 69 (58 HBeAg(–) and 11 HBeAg(+) patients). Three patients received ETV for 21–36 months, then switched to TDF, one patient received TBV for 12 months, then switched to ETV (Table 3).

The HBeAg(+) patients were younger and had higher ALT, AST, and viremia compared to the HBeAg(–) patients (Table 3). The median duration of therapy was 12.0 [11.0–30.0] months. The results of AVT with NAs (ETV, TDF, TBV, LAM) are provided in Table 4.

AVT efficiency in the HBeAg(+) patients

No viremia after 24, 48, 96 weeks of taking ETV was reported in 3/6, 4/5, and 1/1 patients, respectively. In patients who received TDF, VR was achieved after 24, 48, 96 weeks in 0/3, 1/3, and 1/3 patients, respectively. Two patients had been taking TBV for about two years; no viremia was detected in one of them after 24 and 48 weeks.

SVR after discontinuation of treatment was achieved in 3/3 patients. Among them one patient received TBV and the others received ETV.

The HBeAg seroconversion was reported in 4/11 patients (36.4%): it was associated with ETV therapy (two cases) or with TDF and TBV therapy (single cases).

When taking NAs, 2/11 HBeAg(+) patients (18.2%) who received ETV showed the HBsAg clearance, anti-HBs were found in 1/11 patient (9.1%). The HBsAg seroconversion was reported in this patient 27 months after the ETV discontinuation.

ALT activity back to normal after 24, 48, 96 weeks of taking ETV was reported in 1/6, 3/5, and 1/1 patients, respectively. As for patients who received TDF, no BR was observed after 24 and 48 weeks of therapy; one patient out of three showed BR after 96 weeks. ALT activity back to normal was observed in one patient treated with TBV out of two after 24 weeks, such ALT activity persisted at week 48 of therapy.

Only one HBeAg(+) patient had been taking PEG-IFN-α-2a in a dose of 180 mg/week for 48 weeks; HBsAg and HBeAg seroconversion together with undetectable HBV DNA were reported in the end of therapy.

AVT efficiency in the HBeAg(–) patients

After 24, 48, 96 weeks of taking ETV no HBV DNA was reported in 78%, 92.1%, and 94.1% of patients, respectively. In patients who received TDF, VR was achieved after 24, 48, 96 weeks in 3/4, 4/4, and 4/4 cases, respectively. A total of 11 patients had been taking TBV for about two years; VR was reported after 24

Table 3. Comparative characteristics of HBeAg(+) and HBeAg(–) patients who received NAs

Parameters	HBeAg(–) patients, n = 58	HBeAg(+) patients, n = 11	p*
Gender Males Females	 28/58 (48.3%) 30/58 (51.7%)	 8/11 (72.7%) 3/11 (27.3%)	0.137
Age, years	48.0 [32.0–57.0]	30.0 [25.0–52.0]	0.028
ALT, U/L > 40.0 U/L	27.7 [18.1–48.4] 20/58 (34.5%)	60.6 [43.3–90.4] 9/11 (81.8%)	0.006 0.006
AST, U/L > 40.0 U/L	25.3 [19.1–43.4] 15/58 (25.9%)	44.8 [28.2–70.0] 6/11 (54.5%)	0.016 0.078
Platelets, 10^9/L > 180 × 10^9/L	227.5 [179.0–269.0] 43/58 (74.1%)	228.0 [201.0–255.0] 11/11 (100.0%)	0.670 0.105
Fibrosis, kPa	6.6 [5.3–10.4]	6.1 [5.4–7.6]	0.649
HBV DNA, $\log_{10}$ IU/mL	4.0 [3.3–4.8]	7.0 [3.6–8.0]	0.016
HBsAg, $\log_{10}$ IU/mL	3.3 [3.0–3.8]	4.3 [3.8–4.5]	0.105

Note: the data are presented as ME [25th and 75th percentiles] or n/N (%); *p — significance level.

Table 4. Comparative efficiency of antiviral therapy with NAs

Virological response	ETV		TDF		TBV		LAM
	HBeAg(–) patients	HBeAg(+) patients	HBeAg(–) patients	HBeAg(+) patients	HBeAg(–) patients	HBeAg(+) patients	HBeAg(–) patients
Virological response							
24 weeks	32/41 (78.0%)	3/6 (50.0%)	3/4 (75.0%)	0/3 (0.0%)	9/11 (81.8%)	1/2 (50.0%)	2/2 (100.0%)
48 weeks	35/38 (92.1%)	4/5 (80.0%)	4/4 (100.0%)	1/3 (33.3%)	9/10 (90.0%)	1/2 (50.0%)	2/2 (100.0%)
96 weeks	16/17 (94.1%)	1/1 (100.0%)	4/4 (100.0%)	1/3 (33.3%)			
Biochemical response							
24 weeks	39/41 (95.1%)	1/6 (16.7%)	3/4 (75.0%)	0/3 (0.0%)	11/11 (100.0%	1/2 (50.0%)	2/2 (100.0%)
48 weeks	37/38 (97.4%)	3/5 (60.0%)	4/4 (100.0%)	0/3 (0.0%)	10/10 (100.0%)	1/2 (50.0%)	2/2 (100.0%)
96 weeks	16/17 (94.1%)	1/1 (100.0%)	4/4 (100.0%)	1/3 (33.3%)			

Note: the data are presented as *n/N* (%).

and 48 weeks in 9/11 and 9/10 patients. VR was achieved after 24 and 48 weeks of taking LAM in 2/2 patients.

SVR was achieved in 11/24 patients (45.8%). Among them three patients received TBV and eight patients received ETV. Virological relapse was reported in 13/24 patients (54.2%) after discontinuation of treatment with NAs, the median time was 6.0 [6.0–11.0] months.

No HBsAg clearance was reported in any of the HBeAg(–) patients who had been taking NAs.

ALT activity back to normal after 24, 48, 96 weeks of taking ETV was reported in 95.1%, 97.4%, and 94.1% of patients, respectively. As for patients who received TDF, BR was achieved after 24, 48, 96 weeks in 3/4, 4/4, and 4/4 patients, respectively, while in patients treated with TBV and LAM it was achieved after 24 and 48 weeks.

Thus, in patients who received NAs with a high barrier to drug resistance (ETV and TDF), VR was achieved after 24 and 48 weeks of treatment in 70.4 and 88.0%, while BR was achieved in 79.6 and 88.0%, respectively. It was shown that the rate of achieving VR and BR after 24 and 48 weeks of treatment with NAs was higher in the HBeAg(–) patients than in the HBeAg(+) patients, however, no differences were observed after 96 weeks of taking NAs (Table 5). After discontinuation of treatment with NAs, SVR was achieved in 14/27 patients (51.9%). When comparing the rates of achieving SVR, no significant differences were revealed between the HBeAg(+) and HBeAg(–) patients ($p = 0.222$). The HBeAg seroconversion was achieved in five cases (41.7%): after treatment with PEG-IFN-α (one case), ETV (two cases), TDF (one case), and TBV (one case). The HBsAg clearance was observed in three patients (4.5%): the patient who received PEG-IFN-α and two patients who received ETV. The HBsAg seroconversion was reported in two cases (3.0%) of treatment with PEG-IFN-α and ETV.

Factors affecting the ARV efficiency

Factors predictive of virological response

The univariate and multivariate logistic regression models were used to analyze the factors associated with VR at week 48 of the NA therapy. The univariate regression analysis identified the following factors associated with undetectable HBV DNA levels after 48 weeks of therapy: HBeAg status ($p = 0.011$); HBV DNA ($p = 0.001$) and ALT ($p = 0.042$) levels. The multivariate regression analysis showed that the baseline HBV DNA level (relative risk (RR) 0.411; 95% confidence interval (CI) 0.211–0.800; $p = 0.009$) was an independent prognostic factor of aviremia (Table 6).

HBsAg as a predictor of SVR after discontinuation of NA therapy

After discontinuation of NA therapy in 27 patients who had achieved VR, virological relapse was reported in 13/27 individuals (48.1%). The cumulative rate of virological relapse 6, 12, 24, and 36 months after discontinuation of NAs reached 25.9%, 40.7%, 44.4%, and 48.1%, respectively. Most cases of virological relapse were detected during the first 12 months of follow-up (11/13; 84.6%). The Cox regression analysis taking into account gender, age, HBV DNA levels before treatment, HBeAg status, and the HBsAg levels in the end of therapy showed that higher HBsAg levels in the end of therapy were

Table 5. Comparative efficiency of antiviral therapy with NAs in the HBeAg(+) and HBeAg(–) patients

Virological response	HBeAg(–) patients	HBeAg(+) patients	*p**
24 weeks	46/58 (79.3%)	4/11 (36.4%)	0.007
48 weeks	50/54 (92.6%)	6/10 (60.0%)	0.016
96 weeks	20/21 (95.2%)	2/4 (50.0%)	0.057
24 weeks	55/58 (94.8%)	2/11 (18.2%)	< 0.001
48 weeks	53/54 (98.1%)	4/10 (40.0%)	< 0.001
96 weeks	20/21 (95.2%)	2/4 (50.0%)	0.057
SVR	3/3 (100.0%)	11/24 (45.8%)	0.222

Note: the data are presented as *n/N* (%); **p* — significance level.

Table 6. Univariate and multivariate analysis of the raw factors associated with VR after 48 weeks of therapy with the nucleos(t)ide analogues

Indicators	Univariate analysis			Multivariate analysis		
	OP	95% CI	*p**	OP	95% CI	*p**
Gender (female)	0.931	0.212–4.097	0.925			
Age (increment 1 year)	1	0.954–1.049	0.988			
HBeAg(+) status	0.12	0.024–0.609	0.011	0.248	0.027–2.249	0.215
HBV DNA (increment 1 $\log_{10}$ IU/mL)	0.336	0.180–0.627	0.001	0.411	0.211–0.800	0.009
ALT (increment 1 U/L)	0.993	0.986–1.000	0.042	0.996	0.986–1.005	0.392
AST (increment 1 U/L)	0.991	0.980–1.001	0.083			
Platelets (less than 180 × 10^9/L)	0.818	0.146–4.582	0.819			
Liver fibrosis (F3/F4)	0.485	0.072–3.290	0.459			

Note: **p* — significance level.

predictive of virological relapse after discontinuation of NAs (RR: 3.909; 95% CI: 1.729–8.835; $p = 0.001$).

The patients with SVR had lower HBsAg levels in the end of therapy than the patients with virological relapse (1.9 [1.4–2.6] and 3.5 [3.3–4.0] log10 IU/mL, respectively; $p < 0.001$).

The patients were divided into three groups based on the HBsAg levels in the end of therapy:

Group 1: HBsAg < 100 IU/mL ($n = 8$);

Group 2: HBsAg — 100–1000 IU/mL ($n = 6$);

Group 3: HBsAg > 1000 IU/mL ($n = 13$).

No virological relapse was observed in patients of group 1, however, it was observed in 33.3% of group 2 (2/6) and 84.6% of group 3 (11/13). Significant intergroup differences in the virological relapse rate were revealed (log rank X2 = 12,280; $p = 0.02$). The HBsAg level < 100 IU/mL in the end of therapy was a significant predictor of SVR after discontinuation of NAs.

DISCUSSION

The clinical presentation of chronic HBV infection is characterized by the long term mildly symptomatic or asymptomatic disease with rare exacerbations or no exacerbations at all. However, the main danger related to this infection is the high risk of LC and HCC that reaches 8–20% within 5 years after the diagnosis in individuals with chronic HBV infection [2]. Our study explains the CHB course in patients who have been followed up in the Center for 1–15 years. The majority of patients had minimal clinical manifestations: fatique and the right upper quadrant pain predominated. However, among them LC was diagnosed in nine patients (4.5%), one of these patients developed HCC.

Currently, the HBeAg(–) form of this infection predominates in many countries of the world, including the RF. According to the reference center of surveillance for viral hepatitis of the Central Research Institute of Epidemiology of Rospotrebnadzor, in 2015 the share of HBeAg(–) patients was 90%. Our study yielded the same result: the HBeAg(–) patients constututed 93%. Predominance of the HBV D genotype (95.4%) was detected that was in line with the data of other studies focused on the HBV genotype distribution in Russia [7, 9].

The group of the HBeAg(+) patients is represented by younger individuals with the higher viremia and higher rate of hyperenzymemia compared to the HBeAg(–) patients.

Suppression of virus replication is an important goal of AVT and the basic premise of the CHB progression prevention. Currently, NAs are used for treatment of CHB in the world, including the RF, due to their high antiviral activity, low rate of side effects and the ease of use (1 tablet per day). Furthermore, NAs with a high barrier to drug resistance (ETV and TDF) are the top-priority drugs to be used for AVT.

The data obtained confirm high efficiency of the ETV and TDF therapy in patients with CHB. Aviremia after 48 weeks of treatment with ETV or TDF was achieved in 88% of cases. This, some papers report aviremia in 89.4% [10] and 88% [11] of patients who received ETV for a year. The other authors also observed aviremia in 86.2% of patients after a year of treatment with TDF [12].

Our findings showed the differences in achieving aviremia between the HBeAg(–) and HBeAg(+) patients. The patients with the HBeAg(–) CHB had a higher rate of VR after 24 and 48 weeks of treatment with NAs than the HBeAg(+) patients. Earlier it was shown that no HBV DNA was detected within the year of treatment in 75% of the HBeAg(+) patients and 99% of the HBeAg(–) patients who received ETV [10]. However, no differences in VR between patients of the Center were observed when performing treatment with NAs for 96 weeks.

Achieving BR defined as ALT activity back to normal can be considered as the desired therapy outcome. In the analyzed group of patients, BR was reported in 88% of cases after 48 weeks of treatment with ETV or TDF. The other researchers also demonstrate high rate of the ALT activity normalization during treatment with ETV and TDF [13–15]. Furthermore, we have shown the differences in the BR rate between the HBeAg(–) and HBeAg(+) patients after 24 and 48 weeks of treatment with NAs, which is consistent with the data provided by other authors [12, 16, 17]. It has been shown that the presence of HBeAg before treatment can be predictive of the ALT normalization failure [18].

The HBsAg clearance with or without seroconversion is considered an optimal treatment outcome and recovery from CHB. In the analyzed group, the HBsAg clearance was observed only in three HBeAg(+) patients (4.5%): in one patient who received PEG-IFN-α and two patients who received ETV. The HBsAg seroconversion was reported in two cases (3%).

The literature data suggest the higher rate of HBsAg clearance in patients with the HBeAg(+) hepatitis B. Thus, when performing treatment with TDF for 48 weeks, the HBsAg clearance after seven years was observed in 3.2% and 11.8% of patients with HBeAg(+) CHB and in 0% and 0.3% of patients with HBeAg(–) CHB, respectively [12, 19]. In general, very few (about 1%) of HBeAg(–) patients achieved the HBsAg clearance, even in case of the long term NA therapy (> 5 years) [11, 20]. The HBsAg clearance and seroconversion are more often reported in the HBeAg(+) CHB patients: 5–10% of the long term treatment cases [21, 22].

As for patients of the Center, the lower baseline HBV DNA level was an independent factor associated with aviremia after 48 weeks of treatment with NAs, which was consistent with the data reported by other authors [10]. They showed that the baseline HBV DNA level ≤7.6 $\log_{10}$ copies/mL was an independent prognostic factor of developing VR by year three of treatment. Similar results were obtained in a number of studies [23–25].

The virological relapse after the NA therapy discontinuation was observed in 13/27 patients of the Center (48.1%), while the higher HBsAg level in the end of therapy was predictive of virological relapse after the NA discontinuation. It has been shown that high baseline HBV DNA level and high HBsAg level in the end of treatment are the independent predictors of virological relapse [26]. In the analyzed group, no virological relapse was observed in patients with the HBsAg level in the end of therapy of less than 100 IU/mL, in contrast to patients with the levels of 100–1000 IU/mL (33.3%) and more than 1000 IU/mL (86,4%), respectively.

The recent systematic review that includes 11 studies involving 1716 patients suggests that the HBsAg levels in the end of therapy of less than 100 IU/mL are optimal for discontinuation of NAs and reduce the risk of virological relapse 12 months after the therapy cessation or later [27].

CONCLUSIONS

Chronic infection caused by HBV is a slowly progressive disease with the typical asimptomatic or mildly symptomatic course, however, the risk of developing LC and HCC is relatively high. The timely AVT is the only way to prevent these complications. AVT with NAs ensure high rates of virus replication suppression and ALT normalization. Low baseline level of viral load is an independent prognostic factor of achieving VR. The HBsAg level in the end of therapy is useful for predicting the HBV infection relapse after the treatment cessation.

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