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Lack of Tissue Virological Response as a Predictor of Relapse in Chronic Hepatitis D after Completion Bulevirtide Therapy

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Aim: to evaluate the significance of a positive polymerase chain reaction result for hepatitis D virus RNA (HDV RNA) in liver biopsy specimens of patients with chronic hepatitis D (CHD) after completion of antiviral therapy (AVT) as a predictor of infection relapse.
Materials and methods. The study included 21 patients with CHD who received combined AVT with peginterferon alpha and bulevirtide for 48 weeks, followed by bulevirtide monotherapy for 48–96 weeks, making the total duration of antiviral therapy 96–144 weeks. In all patients HDV RNA became undetectable in serum 24–96 weeks from the start of treatment, with aviremia maintained for at least 48 weeks until the end of AVT. At the end of treatment, all patients underwent liver biopsy to detect HDV RNA in liver tissue.
Results. Out of 21 patients with sustained complete virological response (negative polymerase chain reaction result for HDV RNA in serum), 8 (38 %) had HDV RNA detected in liver tissue, indicating that a tissue virological response was not achieved. All 8 patients experienced a relapse of CHD within 24 weeks after discontinuing AVT.
Conclusions. In patients with chronic hepatitis D who have achieved a complete virological response in serum, the absence of a virological response in liver tissue (detection of HDV RNA in liver biopsy) is a predictor of relapse, providing a rationale for the continuation of antiviral therapy.
Keywords: chronic hepatitis D, antiviral therapy, bulevirtide, liver biopsy, complete virological response, tissue virological response
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Отсутствие тканевого вирусологического ответа как предиктор рецидива хронического гепатита D после завершения терапии булевиртидом

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Цель: оценить значение положительного результата полимеразной цепной реакции на РНК вируса гепатита D (HDV РНК) в биоптате печени больных хроническим гепатитом D (ХГD) после завершения противовирусной терапии (ПВТ) в качестве предиктора рецидива инфекции.
Материалы и методы. В исследование был включен 21 пациент с ХГD, которые получали комбинированную ПВТ пэгинтерфероном альфа и булевиртидом в течение 48 недель и продолжали монотерапию булевиртидом в течение 48–96 недель, то есть общая продолжительность противовирусной терапии составила 96–144 недели. У всех пациентов HDV РНК перестала определяться в сыворотке крови через 24–96 недель от начала лечения при сохранении авиремии не менее 48 недель до завершения противовирусной терапии. В конце лечения всем пациентам была выполнена биопсия печени с определением HDV РНК в ткани печени.
Результаты. Из 21 пациента с сохранением полного вирусологического ответа (негативный результат полимеразной цепной реакции на HDV РНК) в сыворотке у 8 (38 %) в ткани печени была обнаружена HDV РНК, то есть не достигнут тканевой вирусологический ответ. У всех 8 пациентов в течение 24 недель после прекращения ПВТ наблюдался рецидив ХГD.
Выводы. У пациентов с ХГD с полным сывороточным вирусологическим ответом отсутствие тканевого вирусологического ответа (обнаружение HDV РНК в биоптате печени) является предиктором рецидива, что служит основанием для продолжения ПВТ.
Ключевые слова: хронический гепатит D, противовирусная терапия, булевиртид, биопсия печени, полный вирусологический ответ, тканевой вирусологический ответ
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Introduction

Chronic hepatitis D (CHD) is the most aggressive infectious disease among all viral hepatitis types, characterized by rapid progression of fibrosis and a high rate of adverse liver outcomes. Approximately 18 % of patients with chronic hepatitis D have liver cirrhosis at the time of diagnosis, which, in turn, accounts for the high mortality from cirrhosis complications and hepatocellular carcinoma [1–6].

Despite the existing ICD-10 coding, CHD is considered not as a form of hepatitis B infection, but as a separate nosology, since the course of the diseases and treatment methods for these two conditions differ significantly.

Due to the lack of screening standards and the unavailability of HDV marker testing in HBV-infected patients, accurately determining the global prevalence of HDV infection is challenging. It is estimated that the number of HDV-infected individuals worldwide is approximately 12 million, with the virus detected in 5 % of HBV-infected patients [6].

On the other hand, the prevalence of HDV infection in patients with liver cirrhosis and hepatocellular carcinoma is much higher, with one study reporting rates of 18 and 20 %, respectively. This highlights the need for optimal antiviral therapy methods with high efficacy [7].

The lack of intrinsic enzyme systems, the complex life cycle of the virus, and the unavailability of sensitive test systems in some cases make it difficult to choose the optimal treatment tactic and duration. The effectiveness of treatment is assessed by quantifying HDV RNA in serum using PCR. A sustained virological response (SVR), analogous to chronic hepatitis C, is defined as the absence of HDV RNA 24 weeks after completing AVT.

Until recently, treatment for CHD had limited prospects due to the very low cure rates with pegylated interferon alpha therapy, which may have limited effectiveness because of its immunomodulatory action or direct antiviral action on the helper virus — HBV [8]. Initial clinical studies indicated that interferon therapy achieved an SVR in approximately 30 % of patients with hepatitis D [9]. However, subsequent studies failed to confirm the initial optimism. Using more sensitive diagnostic methods, it was found that even among patients who were thought to have achieved an SVR, HDV RNA persisted after the treatment course. Thus, the actual effectiveness of interferon therapy was found to be only 9–10 % [10].

The use of nucleos(t)ide analogs, employed for treating chronic hepatitis B, in chronic CHD also did not yield significant effects and did not enter clinical practice. However, they are prescribed according to indications for treating chronic hepatitis B: high viral load (HBV DNA > 2000 IU/mL) combined with elevated liver transaminase levels or the presence of liver cirrhosis [11, 12].

Studying the life cycle of the hepatitis D virus led to the creation of the drug bulevirtide — an entry inhibitor for hepatitis B and D viruses into hepatocytes, currently the only drug approved for treating HDV infection. During clinical trials,

bulevirtide demonstrated its effectiveness and safety, marking the beginning of a new era in the therapy of this disease.

Bulevirtide is a structural analog of the L-form of HBsAg; its mechanism of action is based on inhibiting the binding of the virion to the entry receptor for hepatitis B and D viruses in hepatocytes — the sodium taurocholate co-transporting polypeptide — through competitive interaction with the active site of the receptor [13, 14]. In 2019, the drug was registered in the Russian Federation, and in 2020, it received approval from the EMA (European Medicines Agency) for use in European Union countries for treating adult patients with CHD in the compensated stage of liver disease [15–17]. However, the optimal duration of therapy has not yet been determined, and existing methods for assessing virological response do not reliably predict the absence of infection relapse after completing etiological treatment. Therefore, there is a need for a method to predict hepatitis D relapse before the end of AVT. Including HDV RNA detection in hepatobiopsies as part of the management algorithm for patients in clinical studies could help establish guidelines for concluding AVT and improve treatment outcomes for those with CHD.

The aim of the study

To evaluate the significance of a positive polymerase chain reaction result for HDV RNA in liver biopsy (absence of a tissue virological response) in patients with chronic hepatitis D (CHD) after completing antiviral therapy (AVT) as a predictor of infection relapse.

Patients and methods

The study included 21 patients with CHD. Patients met the inclusion criteria, which were: signed informed consent for participation in the study, data collection, and use; age 18 years or older; initial combined therapy with bulevirtide and peginterferon alpha for at least 48 weeks, followed by bulevirtide monotherapy for 48 to 96 weeks; a negative qualitative PCR test for HDV RNA in peripheral blood for at least 48 weeks of antiviral therapy before study inclusion; absence of active liver inflammation; and availability of a liver biopsy performed as part of routine practice (not earlier than 3 weeks before inclusion) or planned before discontinuing bulevirtide.

Exclusion criteria were the following: presence of autoimmune hepatitis, drug or alcohol-induced liver injury, Wilson's disease, co-infection with hepatitis C virus, moderate or severe kidney/liver dysfunction; lack of informed consent. Additionally, patients receiving HBV and HDV therapy not in accordance with standard practice or with violations of the bulevirtide drug label instructions were not included in the study.

The study included patients aged 29 to 67 years, with a mean age of 49,1 years. Nearly half of the patients ($n = 10$; 48 %) were male. Twelve patients (57 %) had minimal liver fibrosis (F0-2 according to METAVIR), while nine patients (43 %) had advanced fibrosis or liver cirrhosis (F3-4 according to METAVIR) based on non-invasive liver stiffness measurement using transient elastography (FibroScan). The duration of therapy ranged from 96 to 144 weeks (Table 1).

Patients received combined antiviral therapy with peginterferon alpha at a dose of 1.5 μg/kg body weight per day administered subcutaneously and bulevirtide at a dose of 2 mg per day administered subcutaneously for 48 weeks, followed by continued monotherapy with bulevirtide for 48 to 96 weeks. All patients had their serum tested for HDV RNA monthly using PCR. After 24 to 96 weeks of AVT, HDV RNA was no longer detectable (achieving a complete virological response) in all patients. Achievement of virological clearance was accompanied by a biochemical response, evidenced by the normalization of alanine and aspartate transaminase levels (according to reference values provided in the laboratory report). Additionally, a reduction in liver fibrosis severity was observed in most patients, as indicated by liver elastography data (Table 2).

Upon achieving and maintaining a complete virological response for at least 48 weeks, all patients underwent a liver biopsy to assess the histological response and determine HDV RNA in liver tissue using PCR.

The obtained liver biopsy samples were divided for histological and virological studies. The liver tissue for morphological examination was fixed in 10 % neutral formalin, buffered with Lilly's buffer. Liver tissue samples, measuring 3–5 mm for virological testing, were placed in saline and transported to the PCR laboratory. The liver biopsy was transported at 18–25 °C within 2 hours, at 2–8 °C — for no more than one day, and at –18 to –60 °C — for up to 2 weeks.

Next 0.5 mL of lysis solution was added to the patient's liver biopsy sample, which was mixed by pipetting 3–4 times. The resulting sample was placed in a thermostat at 65 °C for 10 minutes. During the incubation, the sample was mixed by pipetting twice, then centrifuged for 1 minute at 13,000 rpm. The supernatant obtained from the sample was used for PCR analysis along with a reagent kit for qualitative detection of HDV RNA in serum.

Table 1. Initial characteristics of the patients (n = 21)
Таблица 1. Исходная характеристика пациентов (n = 21)

Parameter / *Параметр*	Mean value / *Средний показатель*
Age, years / *Возраст, лет*	49.1 (SD / *СО* — 10.6)
Men, *n* (%) / *Мужчины, n (%)*	10 (48 %)
ALT, U/L / *АЛТ, Ед./л*	79,4 (SD / *СО* — 63.5) 95% CI / *95% ДИ:* 53.6–105.6
Number of patients with F3–F4 (METAVIR), *n* (%) *Число пациентов с F3–F4 (METAVIR), n (%)*	9 (43 %)
Liver stiffness, kPa / *Плотность ткани печени, кПа*	10.5 (SD / *СО* — 4.7) 95% CI / *95% ДИ:* 8.7–12.7

Note: SD — standard deviation; CI — confidence interval.
Примечание: СО — стандартное отклонение; 95% ДИ — 95%-ный доверительный интервал.

Table 2. Dynamics of ALT and liver fibrosis in patients after therapy (n = 21)
Таблица 2. Динамика АЛТ и фиброза печени у пациентов после терапии (n = 21)

Parameter / *Параметр*	Baseline / *Исходно* (mean value / *средний показатель*)	After therapy / *После терапии* (mean value / *средний показатель*)
ALT, U/L / *АЛТ, Ед./л*	79.4 (SD / *СО* — 63.5) 95% CI / *95% ДИ:* 53.6–105.6	31.1 (SD / *СО* — 38.3) 95% CI / *95% ДИ:* 18.9–48.2
	p = 0,000001	
Liver stiffness, kPa *Плотность ткани печени, кПа*	10.5 (SD / *СО* — 4.7) 95% CI / *95% ДИ:* 8.7–12.7	9.4 (SD / *СО* — 4.3) 95% CI / *95% ДИ:* 7.7–11.3
	p = 0,1193	

Note: SD — standard deviation; CI — confidence interval.
Примечание: СО — стандартное отклонение; 95% ДИ — 95%-ный доверительный интервал.

RNA extraction from the liver biopsy and PCR amplification was performed using a reagent kit for the qualitative detection of HDV RNA in serum (the "RealBest Extraction 100" and "RealBest RNA HDV" test systems (AO Vector-Best, Russia). The analytical sensitivity of the method is 100 copies/mL of HDV RNA when extracting RNA from a 100 μL sample, and the specificity is 100 %.

Results

Among the 21 patients who achieved and maintained a complete virological response (aviremia during antiviral therapy), HDV RNA was detected in the liver tissue of 8 patients (38 %). All 8 patients experienced a relapse of CHD within 24 weeks after discontinuation of AVT, as evidenced by a positive PCR result for HDV RNA in the serum and increased transaminase levels.

Discussion

Traditional assessment of response to AVT in patients CHD is based on detecting and quantifying HDV RNA in the serum using PCR [16]. However, developing reliable methods for analyzing HDV RNA is challenging due to the virus's heterogeneity (at least 8 genotypes and several subgenotypes), rapid evolution of the pathogen, and the peculiarities of RNA secondary structure. Variability in extraction methods for HDV RNA, primer and probe design, and general issues with standardization contribute to significant variability in the performance characteristics of research and commercial tests. Many laboratories use a standard for HDV RNA from the World Health Organization, available for over 10 years, to determine the sensitivity limit of their tests, which facilitates comparison of RNA levels across different research centers [18–21].

Moreover, there is no evidence to suggest that achieving aviremia during AVT indicates cure of the infection or guarantees prevention of CHD relapse [1]. The rules for ending antiviral therapy are still debated, as aviremia at different points during AVT cannot reliably predict an SVR. Research focusing on detecting HDV markers in hepatocytes has shown a reduction in the number of HDV-infected hepatocytes after the end of therapy with bulevirtide [17].

In this study, we aimed to demonstrate that the presence of HDV RNA in liver tissue is a significant marker of active replication and, therefore,

an absolute predictor of relapse after therapy completion. Despite the prolonged period of aviremia during antiviral therapy (ranging from 48 to 96 weeks), all patients with tissue persistence of the virus experienced a relapse of CHD after discontinuation of treatment.

Thus, in patients with CHD who achieve aviremia, the absence of a tissue virological response, i. e., the detection of HDV RNA in the liver biopsy, serves as a reliable predictor of relapse, which justifies the continuation of AVT.

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