MODERN TREATMENT OF DELTA INFECTION

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Annotatsiya: Hepatitis delta virus (HDV) is a satellite virus that infects about 5% of patients with chronic hepatitis B. It is believed that in the world there are about 15-20 million patients with chronic hepatitis D, which is one of the most severe liver diseases with high risk of developing cirrhosis and liver cancer. Pegylated interferon-a remains the only drug approved for the treatment of chronic hepatitis D, although it has low efficacy and a high incidence of adverse events. The study of the basic mechanisms of HDV replication has led to the creation of new classes of drugs that block the entry of the virus into the cell and the assembly of its virion. These drugs are currently being studied in phase II and III studies.

Kalit so'zlar: Hepatitis D virus, chronic hepatitis, treatment.

Hepatitis delta virus is a unique virus, the replication of which in the human body depends on the presence of a helper virus, the hepatitis B virus (HBV) [2]. The HDV viral particle consists of a nucleocapsid formed by a single self-protein of the virus, covered by an envelope consisting of HBV surface proteins (large, medium and small S proteins, or HBsAg). Inside the nucleocapsid is the HDV genomic RNA, only approximately 1700 nt long [36]. Chronic viral hepatitis D (HDV) is the most severe form of viral hepatitis in humans [17, 29]. According to the results of numerous clinical studies, HDV is characterized by a more severe course, accelerated the rate of development of liver cirrhosis, an increased risk of developing hepatocellular carcinoma (HCC) and the frequency of decompensation of liver cirrhosis in comparison with patients with HBV without a D-agent [17, 29]. The genetic diversity of the HD virus is related to the geographic origin of the isolates. Currently, based on differences in the genomic RNA sequence of more than 15–20%, 8 genotypes of the virus are identified, designated by numbers (HDV 1–8) [7–9]. HDV genotype 1 is ubiquitous, often isolated in the USA, Europe and the Middle East, and also found in Russia, Africa, Asia and Brazil [10]. HDV-2, formerly known as genotype IIA, is found in Japan, Taiwan and Russia [10, 11]. HDV-3 was isolated in South America (Peru, Colombia, Ecuador and Brazil). This genotype is associated with outbreaks of severe acute HD among the indigenous population of the Amazon. Apparently, HDV-3 is associated with a more aggressive course of infection [12, 13]. HDV-4 occurs in Taiwan and Japan, genotypes 5, 6, **7** and 8 – in Africe [10]. In general, African countries show the greatest genetic diversity in the distribution of HDV, and, presumably, this continent is the place of origin of this virus [14]. HDV infection can

occur simultaneously with HBV (co-infection) or as a superinfection against the background of a patient's pre-existing CHB. Concurrent infection with HBV and HDV can lead to moderate or severe illness or even fulminant hepatitis, but complete recovery usually occurs and chronic hepatitis B with delta infection (ICD-10) rarely develops (in less than 5% of cases of acute hepatitis) [15]. Like HBV, HDV is transmitted through contact with the blood or other body fluids of an infected person [15]. HDV superinfection in CHB typically accelerates the development of more severe liver damage to the point of advanced fibrosis at any age in 70–90% of people. Observations of patients infected with HDV have shown that in patients with active chronic hepatitis B with delta infection (CHB + D), liver cirrhosis develops faster (10 years earlier) than in patients with HBV monoinfection; Hepatocellular carcinoma (HCC) forms faster, despite the fact that the hepatitis D virus suppresses HBV replication [16]. Intrafamilial transmission of HDV is possible, which is a hidden form of household transmission of infection; it appears to be widespread in HDV-endemic regions, but it should be noted that vertical transmission from mother to child is extremely rare. As a rule, infection of children with HDV occurs at an early age in the form of superinfection against the background of perinatally acquired HBV infection [22].

According to the level of prevalence of HDV infection among patients with CHB, regions of the world can be conditionally classified into one of 4 zones:

- zones of high endemicity – the frequency of anti-HDV exceeds 60%;
- zones of average endemicity – the frequency of anti-HDV is 30–60%;
- low endemicity zones – the frequency of anti-HDV ranges from 10 to 30%;
- zones of very low endemicity – anti-HDV frequency <10% [25].

Areas of very low endemicity – anti-HDV frequency Federations based on the frequency of detection of anti-HDV among HBsAg-positive people are limited. The presented research results relate to determining the frequency of detection of anti-HDV among the general population and in patients with CHB only in some regions of the Russian Federation. It has been shown that the HD virus is relatively rare in the European part of the Russian Federation and is widespread in certain territories of the Asian part of the country - in Tyva, Yakutia, Chukotka, reaching 35% among CHB patients. According to W. Braga [25], infection with HDV genotype 3 is distinguished by a severe course of hepatitis, which is consistent with previously received reports on the characteristics of the course of HDV in those infected with this HDV genotype. HDV infection is also associated with a high risk of developing liver cirrhosis in HIV-infected patients [26, 27]. The pathogenesis of HDV is currently not well understood. Clinical observations support a predominantly immune-mediated mechanism of damage in HDV infection[18]. In a retrospective prospective study by A. Wranke et al. [32] anti-HDV IgM was detected in the majority of patients with chronic HDV infection (85%) and a statistically significant correlation was revealed between the

presence of anti-HDV IgM and the histological and biochemical activity of HDV. The development of long-term outcomes of chronic HDV infection in the form of decompensation, HCC, liver transplantation, and death was noted in 39% of anti-HDV IgM positive patients, and only in 9% of patients with no anti-HDV IgM. In a study by R. Romeo et al. [34], high levels of HDVRNA were associated with an increased risk of developing liver cirrhosis and HCC. Currently, there is no effective antiviral treatment for HD. For 30 years, the only drug used to treat viral HD was interferon-alpha (IFN-α), and since 2006, the use of pegylated interferon-alpha (peg-IFN-α) began [42]. However, as clinical data show studies, a sustained virological response after using the drug, both as monotherapy and in combination with nucleos(t)ide analogues, develops in no more than 23–47% of cases [47]. Interferon-α (IFN-α) is still the only an officially approved antiviral drug for the treatment of chronic HDV infection. However, the effectiveness of interferon therapy does not exceed 20-25%, and the frequency of relapses after completion of treatment, despite the lengthening of its duration, still remains high [7, 8]. Due to the low rate of virological response in patients with HDV, the ultimate goal of interferon therapy, indicating cure is considered to be clearance of HBsAg or seroconversion of HBsAg to HBsAb. Alternative treatment regimens using inhibitors of HBV entry into hepatocytes and prenylation inhibitors are currently at the stage of clinical trials [10-12]. The results of the second study (HIDIT II) have now been summed up, which showed that the use of peg-IFN-α in 24 months in combination with tenofovir did not improve virological response and did not exclude the development of late relapses [49]. It has been shown that the addition of entecavir to peg-IFN-α does not increase the rate of virological response after 24 weeks of treatment [50]. Unfortunately, phase II clinical studies of Mircludex B in combination with peg-IFN-α for 24 weeks showed sustained virological response response in only 1 out of 7 patients [53]. A representative of this group of drugs, lonafarnib, an inhibitor of farnesyltransferase (a cell enzyme that allows isoprenylated large D antigen to join the endoplasmic reticulum) underwent phase II clinical trials from December 2011 to June 2016. Patients (n=14) received lonafarnib 100 or 200 mg/day for 4 weeks. The reduction in viral load was 0.75 and 1.25 log IU/ml, depending on the dose of the drug. A significant side effect was severe dose-dependent gastrointestinal complications [56]. In phase III studies, the addition of ritonavir (a pharmacokinetic enhancer) increased the antiviral effect of lonafarnib and reduced the incidence of unwanted side effects [57]. Thus, modern antiviral drugs reduce the viral load, but practically do not lead to complete elimination of the virus and, as a consequence, cure from HD [58]. Soriano et al. [42] assessed the effectiveness of tenofovir therapy for an average duration of 58 weeks in a similar group of patients (HBV/HDV/HIV) receiving HAART therapy. At the end of treatment, HDV RNA clearance was observed in 53% of patients, but a decrease in HDV DNA levels was not associated with a decrease in HBsAg concentrations . In patients with a virological response, there was a 30%

decrease in liver density according to elastometry results, while in the absence of a virological response, this indicator did not improve. In this study, there was no significant decrease in HBsAg levels, however, 3 patients had clearance of HBsAg and HDV RNA [42] .A. Schieck et al. found that HBV hepatotropy is due to the specific binding of the myristoylated N-terminal pre-S1 domain of the HBV L protein to an unidentified specific receptor on the hepatocyte membrane [52]. The same domain is required for HDV entry into the hepatocyte [53]. P. Chen et al. [54] proposed a role for the above-mentioned sodium taurocholate contransporter peptide (NTCP) receptor based on the identification of a 10-amino acid region in the latter that directly interacts with pre-S1. The drug Myrcludex B (developed by Hepatera) is a lipopeptide extracted from the pre-S1 domain of the HBV virus envelope, which selectively blocks the corresponding receptor and, thereby, the penetration of HBV and HDV into the hepatocyte. It is believed that Myrcludex B prevents infection of hepatocytes, which should lead to a decrease in HDV replication with subsequent complete depletion. The effectiveness of Lonafarnib was studied in the LOWR HDV-1 study, the results of which were presented in April 2015 at EASL (European Society for the Study of Liver Diseases) [57, 58]. The purpose of LOWR HDV-1 was to determine the optimal dosing regimen of the drug, duration of therapy, the effectiveness of combination therapy of Lonafarnib in combination with ritonavir or pegylated IFN α-2a in comparison with Lonafarnib monotherapy, study the pharmacokinetics of the latter, tolerability and safety of therapy. In the absence of effective therapeutic options drugs that allow the elimination of the virus from the body, the only reliable means of controlling HDV infection is vaccination. Since the HDV viral particle, like HBV, contains HBsAg, the humoral immune response to the HBV vaccine fully protects against HDV infection [59]. Mass vaccination against hepatitis B leads to a decrease in the number of people infected with hepatitis B and, as a result, susceptible to HDV. In countries where mass immunization of newborns against HBV has long been introduced, cases of HDV infection among children and adolescents are practically not recorded, and most cases of infection are detected in older age groups [60]. The prevention of HDV infection in CHB patients also remains an unresolved issue. There is no specific vaccine against HDV, despite attempts to create peptide and DNA vaccines based on the HDV antigen. The humoral and T-cell responses to these vaccine preparations were insufficient to protect against HDV superinfection in the woodchuck model [61, 62]. Thus, there are currently no measures of specific protection against HD for patients with CHB. In conclusion, HD still remains an unsolved global health problem. After a long period of underestimating the significance of this infection, an understanding of its relevance has now come. This is due to the increase in population migration from endemic regions, the continued widespread prevalence of HBV in the world and the lack of specific protection against HDV superinfection, as well as limited treatment options for this severe liver disease. The presence of HDV in the world and in other regions indicates

the need to develop special programs for the diagnosis, prevention and treatment of this dangerous infection.

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