

СПОСОБЫ ЛЕЧЕНИЯ ВИРУСНОГО ГЕПАТИТА: ОБЗОР ЛИТЕРАТУРЫ

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Аннотация: В этой научной статье рассматриваются причины появления вирусной гепатита, классификация гепатитов, симптомы, диагностика заболевания, лечение и профилактика вирусного гепатита.

Ключевые слова: Хронический вирусный гепатит, синдром цитолиз, синдром альфа-интерферон.

MODERN METHODS OF TREATMENT OF VIRAL HEPATITIS

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Annotation: This scientific article discusses the causes of viral hepatitis, classification of hepatitis, symptoms, diagnosis of the disease, treatment and prevention of viral hepatitis.

Key words: Chronic viral hepatitis, cytolysis syndrome, alpha-interferon syndrome.

Introduction. Viral hepatitis B (HBV) is a viral anthroponotic infectious disease with a blood-borne transmission mechanism. The disease is characterized by cyclic hepatitis, accompanied in some cases by jaundice and possible chronicity.

Viral hepatitis causes more than one million deaths per year. The European Association for the Study of the Liver (EASL) is calling on various UN agencies to take action to combat viral hepatitis, a potentially fatal infection that infects 500 million people worldwide. Even more worrisome is the fact that most people do not know they are infected until the first signs of infection appear, which could be liver cancer or liver failure. The response to the appearance of virus antigens in the body is the development of specific total antibodies to HCV. The dynamics of the appearance of antibodies to

HCV in the blood of infected individuals is variable, the average interval from the onset of the disease to the appearance of antibodies is about 15 weeks. (4-32 weeks), antibodies against HCV in patients with chronic hepatitis are detected for a long time, more than 7 years.

Morphology and physico-chemical properties. The causative agent of HS is a small (30-38 nm in diameter) RNA-containing, enveloped virus. The floating density of HCV virions in the CsCl density gradient is 1.24 g/cm³, in the sucrose gradient it is 1.08-1.11 g/cm³; the sedimentation coefficient is 200 S. A lighter fraction is also found, equal to 1.04–1.06 g/cm³, which is probably due to the association of HCV with serum beta-lipoprotein. The heavier fraction (1.17 g/cm³) in the sucrose density gradient is most likely associated with non-infectious immune complexes of the virus and antibodies. The HCV nucleocapsid has a buoyant density in the sucrose gradient of 1.25 g/cm³ [20, 23]. for 2 min in an aqueous solution. In addition, the so-called “local” homologies (no more than 16 nt) with classical swine fever and bovine diarrhea viruses (Flaviviridae, Pestivirus) have been registered [31]. The homology of HCV RNA with the genomes of plant viruses suggested that in evolutionary terms, HCV occupies an intermediate position between animal and plant viruses. It was shown that HCV RNA contains a highly conserved 5'-untranslated region up to 340 bp, translation of the HCV genome. This RNA element binds the 40S ribosomal subunit in the absence of other translation initiation factors. The untranslated region at the 3' end is terminated by polyuridine ribonucleotides. They are followed by another highly conserved 98–100 bp sequence called the X-tail, which plays an important role in viral replication. The open reading frame encodes a polyprotein consisting of 3,010–3,033 aa. When this polyprotein is translated, at least 10 mature proteins are formed in the endoplasmic reticulum of an infected cell.

The function of the NS4b protein is unclear, and the NS5a protein modulates the effect of IFN on the virus. In the NS5a protein, a region has been identified that determines sensitivity to IFN. Mutations in this region significantly reduce the effectiveness of IFN treatment. It has also been shown that the NS5 protein is a potent inhibitor of IFN-induced protein kinase PKR, which belongs to antiviral factors. The NS5a protein has RNA-dependent RNA polymerase activity and plays an essential role in RNA synthesis and replication. The mechanism of initiation of RNA synthesis by viral RNA-dependent RNA polymerase has not been completely studied. persisting in the patient's body, the main feature was revealed - the high heterogeneity of certain parts of the genome [7, 10, 23]. Two hypervariable regions of HCV RNA are distinguished. , is located at the 5'-end of the E2 gene. The second hypervariable region (HVR2) with a length of 21 n.o. The adjacency of the hypervariable regions of the HCV genome provided the emergence of various HCV genovariants. Analysis of the RNA of numerous HCV variants circulating in different regions of the world revealed

the existence of major groups of the virus, designated by types or genotypes (with less than 72% nucleotide sequence homology between them) in total, six major HCV genotypes.

A comparative analysis of the homology of HCV RNA of different genotypes made it possible to establish the presence of more than 100 subtypes (the level of homology between different subtypes within the genotype is 72–86%). In addition, the presence of differences in sequences of 1–14% determines the existence of multiple variants of the virus or its quasi-species that appear as a result of long-term persistence of the virus in the human body. An HCV-infected patient may simultaneously harbor many millions of HCV quasi-species. Phylogenetic analysis of HCV RNA suggested that the division of HCV into genotypes could occur from 500 to 2000 years ago, and the division of genotype 1 into subtypes 1a and 1b more than 300 years ago [2]. The high variability of HCV RNA is associated with the appearance of point mutations, insertions, and deletions that occur during virus replication. Another mechanism that ensures the variability of the virus genome is recombination, which is characteristic of many RNA viruses: influenza virus, HIV, poliovirus, and dengue virus. The study of recombination between different HCV genotypes is at the initial stage [7]. HCV circulation has been found everywhere. According to WHO, the countries with the highest percentage of chronically infected patients are Egypt (2%), Pakistan (4.8%) and China (3.2%). The main mode of transmission of the virus in these countries is through the use of unprotected parenteral injection methods and contaminated equipment. They dominate Europe, North America, Asia and Oceania. In European countries, subtype 1b is 50-91% (Germany - 59%, Belgium - 65%, Hungary - 84%, Italy (Sicily) - 91%), and subtype 1a - no more than 40% (Germany - 32%, Denmark - 40%, France - 35%). In the USA, subtype 1a prevails, which even received the designation "American genotype". The incidence of subtypes 1a and 1b in the United States averages 37% and 30%, respectively.

All other genotyped HCV variants are represented in no more than 10%. In Japan, Taiwan, China (especially in the southern provinces), Singapore, Indonesia, South Korea, subtype 1b, the "Japanese genotype" is most often detected (with the exception of the Philippines, where the frequency of subtype 1b reaches 54.5%). Subtypes 2a and 2b have a more limited distribution in the world than subtypes 1a and 1b and a smaller proportion among the genotypes represented in a given area. The most common genotype 2 is represented in Asian countries. Genotype 3 is most common in Thailand (up to 50%), northern Europe (up to 25% in the UK) and Australia. In the countries of Central Asia, northern and central Africa, genotype 4 is widely represented. Thus, among donors of HCV carriers in Egypt, genotype 4 occurs in 30–40% of cases of HCV detection. Genotype 5 is often detected among patients with chronic hepatitis in South Africa, and genotype 6 was identified in the countries of

Southeast Asia, and CHC - 70. It should be noted that in 71 deceased, the etiology of chronic viral hepatitis was not deciphered [6].

According to D.K. Lvova et al., subtype 1b dominates in Russia [7, 8, 10, 12]. The share of subtype 1b is 64.7% in various regions of Northern Eurasia, 80–83% in the Far East, and 50–56% in the Central Black Earth and Volga-Vyatka regions of Russia. Subtype 1a was most often found in the Central, Northwestern, Volga-Vyatka regions - 11.2–21.9%, while in the territory of Eastern Siberia, the Central Black Earth region and the Urals it can be detected extremely rarely (up to 5%). Subtypes 2a and 2b among people with HCV in Russia are also classified as rarely detected (2a and 2b - 4.7–0.5%). Recently, the proportion of subtype 3a in the circulation of HCV in some regions of the Russian Federation has increased significantly and reaches 40% (long-term data from the D.I. Ivanovsky Research Institute of Virology in Moscow and the Moscow Region). HCV replication. Information on HCV replication is still extremely limited and in most cases contradictory. This situation can be explained by the absence, until recently, of an available experimental model of HCV. However, studies conducted in Russia [3, 4, 5, 6] and in other countries [9] have made it possible to develop experimental models of HCV in vitro and in vivo. Reproduction of HCV in primary cultures of brain cells of newborn white mice led to the selection of infectious cytopathogenic variants of HCV, characterized by a wide range of cell cultures sensitive to virus replication. This allowed the isolation of high-yielding HCV variants. Another model of HCV infection in vivo, created in Canada, is based on the implantation of the human hepatoma cell line Huh-7 in the liver of nude mice. After infection of Huh-7 cells with HCV, it was possible to find HCV RNA sequences in liver cells and blood sera of mice. Features of the clinical course of HS. The course of the disease varies from mild, lasting for several weeks, to severe chronic infection, lasting throughout life, leading to cirrhosis and liver cancer [6, 9, 13]. The incubation period for HCV is 2 weeks. up to 6 months. After the initial infection, about 80% of people are asymptomatic. The acute phase of HS is traditionally limited to 6 months. It can proceed both imperceptibly for a person (doctors call this stage subclinical or inapparent), and in the form of obvious external manifestations. In acute infections, patients have fever, weakness, loss of appetite, runny nose, nausea, abdominal pain, dark urine, gray face, joint pain, jaundice (yellowness of the skin and sclera of the eyes). Approximately 75-80% of newly infected people develop a chronic infection, and 60-70% of chronically infected people develop chronic hepatitis, which in 5-20% ends in cirrhosis of the liver, and 1-5% of chronically infected people with HCV die from cirrhosis or cancer liver. It is known that HCV is transmitted parenterally and, first of all, by syringe in risk groups (drug addicts, patients with hemophilia, patients in hemodialysis units and other categories of persons in contact with human blood or

its products). According to WHO, the most common way is the transmission of HCV by infection with infected blood [11].

Risk factors for intrauterine transmission of HCV were the presence of infection caused by HCV in both parents and the use of psychotropic drugs by the mother. Diagnosis of HS. Acute HCV infection is often not diagnosed because most infected people show no symptoms of the infection. Conventional antibody detection methods cannot differentiate between acute and chronic infection. The presence of antibodies against HCV indicates that a person is either infected with the virus or has been previously infected. Recombinant immunoblot assay (RIBA) and HCV RNA testing are used to confirm the diagnosis. Diagnosis of chronic infection is based on the detection of antibodies to HCV in the serum of people for more than 6 months. As with acute infection, the diagnosis of chronic infection is confirmed by additional tests. Special tests are often used to detect cirrhosis and liver cancer. Early diagnosis can prevent health problems that may result from infection and prevent transmission among family members and other close contacts. Some countries recommend screening of populations at risk of HCV infection, including: people who have received blood or blood product transfusions who have had organ transplants prior to screening; current or former drug addicts (including those who took drugs once, many years ago) persons on long-term hemodialysis; employees of medical institutions of persons infected with HIV; people with liver disease, or with poor results of tests reflecting liver function; newborns from infected mothers. Studies conducted in the field of HS diagnostics have shown that HCV RNA is detected with the highest frequency (up to 95%) by RT-PCR in human blood cells (lymphocytes, mononuclear cells) than in human blood serum (up to 76%). These data allow us to recommend the use of 99At present, a method has also been developed for the detection of antigenically active HCV proteins in mononuclear cells of the peripheral blood of patients with HS using monoclonal antibodies. The non-mutant HH genotype of the hemochromatosis gene (+63 H/D) was significantly more frequently detected in the group of patients with mild CHC and in the group of individuals characterized by a stable viral response to therapy. In the Russian population, such an association of IL-6 and HFE gene polymorphisms with the achievement of a stable viral response in the treatment of patients has been shown for the first time.

Based on the data obtained, it can be assumed that the likelihood of achieving a sustained viral response is minimal in patients infected with the subtype 1b virus and having allelic variants of the TT IL-6 gene and the DD variant of the HFE gene with the aim of creating experimental models of infection caused by HCV in vitro for screening antiviral compounds [4]. The data obtained made it possible to stably determine HCV RNA persisting in cell cultures. Data on a wide range of cell cultures sensitive to replication of isolated HCV strains, as well as the collected collection of

cytopathogenic HCV strains, make it possible to use them for screening antiviral drugs, since the problem of treating HCV remains highly relevant. . As a result of preclinical studies on the antiviral activity of the compounds on the in vitro model of HCV infection, data were obtained indicating the prospects for further study of the antiviral activity of many drugs, including birch bark extract - betulin and its derivatives, as well as extracts of birch fungus (chaga) *Inonotus obliquus* - Stimforte® [5,6]. Data were obtained on the high antiviral effect of these drugs against HCV infection in cell cultures. On May 13, 2011, the US Food and Drug Administration (USFDA) approved the use of a new protease inhibitor boceprevir (INN - boceprevir). The drug was developed by Schering-Plough Corp., and further, after the merger in 2009, research was continued by Merck & Co., Inc. [35]. On May 23, 2011, the USFDA approved the use of a new HCV protease inhibitor (INH, telaprevir). The drug was developed by Janssen in collaboration with Vertex and Mitsubishi Tanabe Pharma [4]. According to clinical studies, new HCV protease inhibitors are promising drugs. During phase III clinical trials, patients in the study group received telaprevir and peginterferon alfa2b/ribavirin for 12 weeks, then telaprevir was canceled and therapy continued with peginterferon alfa-2b/ribavirin, in some patients for another 12 weeks, and in another part for during 36 weeks. (12 + 36 = 48 weeks - standard duration of HCV therapy with peginterferon alfa-2b and ribavirin). In the telaprevir group, cure occurred in 60% within 24 weeks, i.e. twice as fast as conventional therapy.

Summary results of the efficacy of telaprevir obtained in phase III clinical trials: (sustained virological response, standard therapy (peginterferon alfa-2b / ribavirin) vs therapy in combination with telaprevir): in individuals receiving antiviral therapy for the first time : 46% vs 79% in previously treated patients: o in the group with relapse 22% vs 86%; o in the group of partial virologic response 15% vs 59%; o in the group that did not respond to previous treatment 5% vs 32% .It has been shown that telaprevir should not be combined with a number of other drugs, in order to avoid an increase in the risk of side effects and / or a drop in drug concentration and the risk of virological failure: atorvastatin, lovastatin, simvastatin, pimozide, rifampicin, alfusion, sildenafil, tadalafil, triazolam, St. John's wort and ergot preparations. The drugs have been shown to increase the risk of developing a number of side effects, such as skin lesions, rashes, neutropenia, anemia, disorders of the gastrointestinal tract. The prospect of developing a vaccine against HS. To date, there is no vaccine against HS [8]. At the same time, according to WHO recommendations, you can reduce the risk of infection if: try to avoid the use of unnecessary and unsafe injections; try to avoid the use of blood products suspected of HCV infection for medicinal purposes; collect and dispose of unsafe stabbing waste; prevent illegal drug use and the sharing of injecting equipment; avoid unprotected intercourse with infected HCV; prevent sharing of sharp objects that may be contaminated with infected blood; tattoos, piercings and acupuncture, etc.

Since the discovery of HCV, intensive research has begun to develop a vaccine against HS. Due to the fact that infectious strains of HCV have not been isolated from materials from patients, research is being carried out towards the development of genetically engineered, recombinant, subunit, peptide and DNA vaccines. Research conducted at the Research Institute of Virology

Conclusion. The problem of viral hepatitis B remains relevant due to the widespread prevalence of infection, the ease of implementation of transmission routes, and the possibility of developing chronic forms. The problem of viral hepatitis B is of particular relevance for primary health care physicians. Knowledge of the etiology, pathogenesis and features of the specific diagnosis of viral hepatitis B will allow family doctors to identify not only clinically pronounced, but also latent forms. Diagnosis of these forms of the disease will help reduce the prevalence of HBV infection

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