MODERN PHARMACOTHERAPY OF CHRONIC HEPATITIS C DEPENDING ON THE GENOTYPE OF THE HEPATITIS C VIRUS

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Hepatitis C is an infectious disease of the liver caused by the hepatitis C virus (HCV), which affects the liver and causes inflammation. This virus can cause both acute and chronic course of hepatitis in (70-80% of patients), which can vary according to the severity of the disease.

The World Health Organization (WHO) estimates that about 71 million people worldwide suffer from chronic hepatitis C. According to the US Centers for Disease Control and Prevention (CDC), an annual increase in incidence is observed from 2010 to 2015. So in 2012, the registered cases of acute hepatitis C increased by 44.3% compared with 2011, and in 2013, the increase was 20.3%. In 2015, the growth rate decreased slightly and the increase was 11% [1]. In the European Region, the most affected endemias are the Eastern Mediterranean Region and At the same time, when evaluating the infection of the population in Egypt by serodiagnosis, 22% of seropositive citizens were identified, which is associated with violation of aseptic rules during the treatment against schistosomes [2]. Mortality among people infected with HCV, mainly among adults aged 55-64, and increased during 2006-2010 [3, 4]. According to WHO and estimates by national experts, Ukraine is among the countries with an average prevalence of hepatitis C. Every year, about 6,000 people are diagnosed with hepatitis C. There are 24,786 patients on the waiting list for treatment in Ukraine [5].

Injecting drug users (IDUs) are most at risk of contracting HCV. Older and former IDUs tend to have a much higher prevalence (approximately 70-90%) of chronic hepatitis C, which is associated with needle sharing in the 1970s and 80s. HCV can be sexually transmitted. The highest rate of HCV transmission is found in men who have sex with men. HCV can also be transmitted through tattoos, razors and acupuncture. Although it is difficult to differentiate the risk associated with injecting drug use and sex with partners infected with HCV [6]. Transmission of HCV from mother to fetus can be observed in about 4-5% of cases. Breastfeeding is safe [7, 8]. Transmission of HCV to health workers can occur as a result of injuries from needle pricking or other occupational exposures. Injection injuries in medical facilities lead to a 3% risk of HCV transmission HCV [9]. Nosocomial patient-to-patient transmission can occur through a contaminated colonoscope, during hemodialysis procedures, or during operations.

HCV is a spherical, enveloped, single-stranded RNA virus belonging to the Flaviviridae family. A genomic analysis of HCV led to the division of the hepatitis C virus into six genotypes. Subtype analysis was also righteous, which improved the genomic classification of HCV. Arabic numerals denote a genotype, and lower case letters denote subtypes for lesser homology within each genotype [10]. HCV subtypes pose a serious problem for immune-mediated control of HCV and can explain the diverse clinical course of the disease and the difficulties in vaccine development.

The main genotype of HCV worldwide is genotype 1, which accounts for 40-80% of all isolates. Genotype 1 may also be associated with more severe liver disease and an increased risk of developing hepatocellular carcinoma. Genotype 1a occurs in 50% - 60% of patients in the United States. Genotype 1b occurs in 15% -20% of patients in the United States. This genotype is most common in Europe, Turkey and Japan. Genotype 1c is found in less than 1% of patients in the United States. Genotypes 2a, 2b and 2c are found in 10-15% of patients in the United States. Genotypes 3a and 3b are found in 4% -6% of patients in the United States, India, Pakistan, Thailand, Australia and Scotland. Genotype 4 is found in less than 5% of patients in the United States, and is most prevalent in the Middle East and Africa. Genotype 5 is found in less than 5% of patients in the United States, and is most common in South Africa. Genotype 6 is found in less than 5% of patients in the United States, although it is actively represented in Southeast Asia, especially in Hong Kong and Macau. A specific genotype may also be associated with a particular mode of transmission, such as genotype 3, among individuals in Scotland who abuse injecting drugs [11, 12, 13].

For diagnostics, primary screening is carried out using a test for antibodies to HCV using enzyme immunoassay (Anti-HCV antibodies, antigens Core, NS3, NS4, NS5). In Ukraine, a rapid test is available for the detection of antibodies to the hepatitis C virus by immunochromatographic test - CITO TEST HCV. Testing for HCV RNA, quantitative testing of HCV RNA and the HCV genotype are performed using the polymerase chain reaction (PCR), which allows differentiation of genotypes HCV 1, 1a, 1b, 2, 3, 4 и 5.

The article analyses the recommendations of the American Society of Infectious Diseases (IDSA) and the American Association for the Study of Liver Diseases (AASLD), in collaboration with the US International Antiviral Society (IAS-USA) [14] on the pharmacotherapy of chronic viral hepatitis C.

Spontaneous cure for acute viral hepatitis C can occur in 15-50% of patients [15, 16]. Hepatitis C has become a treatable disease with the use of antiviral drugs (> 95%) [15, 17]. The pharmacotherapy of chronic HCV has two goals:

1. Achieving sustained HCV eradication or sustained virological response (SVR) - no serum HCV RNA 12 weeks after the completion of antiviral treatment.

2. Prevent the progression of cirrhosis, hepatocellular carcinoma, and decompensated liver disease requiring liver transplantation.

To date, pharmacotherapy of chronic viral hepatitis C uses a combination of pegylated interferon (PEG-IFN) with ribavirin and direct-acting antiviral

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drugs (DAD). At the same time, very recently, priorities have been removed from the AASLD/ISDA recommendations and today treatment is strongly recommended for all patients with chronic viral hepatitis C.

The addition of the oral nucleoside analogue of ribavirin to the PEG-IFN pharmacotherapy regimen marked a new era in the treatment of chronic HCV. The use of such a combination led to sustained eradication of HCV in 30-40% of cases. Pharmacotherapy with PEG-IFN alpha-2a and ribavirin can be individualized by genotype. Patients with HCV genotype 1 require treatment for 48 weeks and a standard dose of ribavirin. Patients with a genotype of 2 or 3 HCV genotypes adequately receive a low dose of ribavirin for 24 weeks [18].

Relatively recently, a number of DADs were developed for specific effects on various replication sites of the hepatitis C virus. These include: protease inhibitors NS3 / 4A (boceprevir, voxilaprevir, telaprevir, simeprevir, grazoprevir, glecaprevir); NS5B protease inhibitors (sofosbuvir, dasabuvir); protease inhibitors NS5A (ledipasvir, daclatasvir, ombitasvir, elbasvir, velpatasvir, pibrentasvir).

To date, according to the WHO recommendations [19], for the treatment of chronic viral hepatitis C, depending on the HCV genotype, in patients over 18 years old who have not received treatment, fixed combinations of DAD are used at the daily dosage.

Pharmacotherapy regimens recommended for chronic viral hepatitis C caused by the HCV genotype 1:

•Daily fixed dose of an elbasvir combination (50 mg) / grazoprevir (100 mg) for 12 weeks, if no base nonstructural substitutions related to protein NS5A resistance are found for elbasvir;

• Daily fixed dose combination glekaprevir (300 mg) / pibrentasvir (120 mg) for 8 weeks;

• Daily fixed dose combination of ledipasvir (90 mg) / sofosbuvir (400 mg) for 12 weeks and for 8 weeks for patients who do not have HIV infection and those with HCV RNA levels below 6 million IU/ml;

• Daily fixed dose of sofosbuvir combination (400 mg) / velpatasvir (100 mg) for 12 weeks.

Alternative schemes:

•Daily fixed dose of paritaprevir combination (150 mg) / ritonavir (100 mg) / ombitasvir (25 mg) with dasabuvir (600 mg) for 12 weeks as part of a sustained release regimen or plus two times a day dosed dasabuvir (250 mg) , with weight-based ribavirin;

• Daily intake of simeprevir (150 mg) plus sofosbuvir (400 mg) for 12 weeks;

• Daily intake of daclatasvir (60 mg) plus sofosbuvir (400 mg) for 12 weeks;

• Daily fixed dose of an elbasvir combination (50 mg) / grazoprevir (100 mg) with ribavirin on a basis of body weight for 16 weeks, if no replacements associated with protein resistance to elbasvir NS5A are found in patients. This scheme is recommended only for the eradication of HCV-genotype 1a.

Pharmacotherapy regimens recommended for chronic viral hepatitis C caused by the HCV genotype 2:

• Daily fixed dose combination of glekaprevir (300 mg) / pibrentasvir (120 mg) for 8 weeks;

• Daily fixed dose of sofosbuvir combination (400 mg) / velpatasvir (100 mg) for 12 weeks.

Alternative regimen is daily fixed dose of daclatasvir (60 mg) / sofosbuvir (400 mg) for 12 weeks.

Recommended pharmacotherapy regimens for chronic viral hepatitis C caused by the HCV genotype 3:

• Daily fixed dose combination of glekaprevir (300 mg) / pibrentasvir (120 mg) for 8 weeks;

• Daily fixed dose of sofosbuvir combination (400 mg) / velpatasvir (100 mg) for 12 weeks.

Alternative regimen is daily fixed dose of daclatasvir (60 mg) / sofosbuvir (400 mg) for 12 weeks.

Pharmacotherapy regimens recommended for chronic viral hepatitis C caused by the HCV genotype 4:

• Daily fixed dose combination of glekaprevir (300 mg) / pibrentasvir (120 mg) for 8 weeks;

• Daily fixed dose of sofosbuvir combination (400 mg) / velpatasvir (100 mg) for 12 weeks;

• Daily fixed dose combination of elbasvir (50 mg) / grazoprevir (100 mg) for 12 weeks;

• Daily fixed dose combination of ledipasvir (90 mg) / sofosbuvir (400 mg) for 12 weeks.

Alternative regimen is daily fixed dose combination of paritaprevir (150 mg) / ritonavir (100 mg) / ombitasvir (25 mg) and ribavirin (dose depends on body weight) for 12 weeks.

Pharmacotherapy regimens recommended for chronic viral hepatitis C caused by the HCV genotype 5, 6.

•Daily fixed dose of glycaprevir combination (300 mg) / pibrentasvir (120 mg) for 8 weeks in patients without cirrhosis of the liver or for 12 weeks in patients with cirrhosis of the liver;

• Daily fixed dose of the combination of sofosbuvir (400 mg) / velpatasvir (100 mg) for 12 weeks, regardless of the status of cirrhosis;

• Daily fixed dose combination of ledipasvir (90 mg) and Sofosbuvir (400 mg) for 12 weeks, regardless of the status of cirrhosis.

DAD for interrupting HCV replication in various places in different combinations showed 90-95% registered SVR compared to 50-70% in patients treated with PEG-IFN combined with ribavirin [20]. In Ukraine, on June 1, 2017, 369 patients with chronic viral hepatitis C received treatment with the most effective combination of DAD ledipasvir/sofosvir, 45 of which completed the treatment. The effectiveness of the treatment after the follow-up examination after 12 weeks of treatment was 94%, which indicates an extremely high efficacy of using DAD [21]. However, clinicians should be aware that amino acid substitutions in the viral protein, associated with resistance to inhibitors and leading to drug resistance, can worsen the response to treatment of DAD, in particular, the base NS5A resistance in patients with chronic viral hepatitis C.

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Study of Liver Diseases (AASLD), in collaboration with the US International Antiviral Society (IAS-USA) on the pharmacotherapy of chronic viral hepatitis C. The pharmacotherapy of chronic HCV has two goals: 1. Achieving sustained HCV eradication or sustained virological response (SVR) – no serum HCV RNA 12 weeks after the completion of antiviral treatment. 2. Prevent the progression of cirrhosis, hepatocellular carcinoma, and decompensated liver disease requiring liver transplantation. To date, pharmacotherapy of chronic viral hepatitis C uses a combination of pegylated interferon (PEG-IFN) with ribavirin and direct-acting antiviral drugs (DAD). At the same time, very recently, priorities have been removed from the AASLD/ISDA recommendations and today treatment is strongly recommended for all patients with chronic viral hepatitis C. The addition of the oral nucleoside analogue of ribavirin to the PEG-IFN pharmacotherapy regimen marked a new era in the treatment of chronic HCV. The use of such a combination led to sustained eradication of HCV in 30-40% of cases. Pharmacotherapy with PEG-IFN alpha-2a and ribavirin can be individualized by genotype. Patients with HCV genotype 1 require treatment for 48 weeks and a standard dose of ribavirin. Patients with a genotype of 2 or 3 HCV genotypes adequately receive a low dose of ribavirin for 24 weeks. Relatively recently, a number of DADs were developed for specific effects on various replication sites of the hepatitis C virus. These include: protease inhibitors NS3 / 4A (boceprevir, voxilaprevir, telaprevir, simeprevir, grazoprevir, glecaprevir); NS5B protease inhibitors (sofosbuvir, dasabuvir); protease inhibitors NS5A (ledipasvir, daclatasvir, ombitasvir, elbasvir, velpatasvir, pibrentasvir). To date, according to the WHO recommendations, for the treatment of chronic viral hepatitis C, depending on the HCV genotype, in patients over 18 years old who have not received treatment, fixed combinations of DAD are used at the daily dosage. DAD for interrupting HCV replication in various places in different combinations showed 90-95% registered SVR compared to 50-70% in patients treated with PEG-IFN combined with ribavirin. However, clinicians should be aware that amino acid substitutions in the viral protein, associated with resistance to inhibitors and leading to drug resistance, can worsen the response to treatment of DAD, in particular, the base NS5A resistance in patients with chronic viral hepatitis C.

Keywords. Hepatitis C, chronic, treatment, protocols, genotypic of virus dependence

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