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Direct-acting antivirals: a new strategy in the treatment of hepatitis C virus infection in patients with cirrhosis

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Abstract

Background: Hepatitis C virus (HCV) infection has a significant worldwide impact. Patients with hepatic cirrhosis with HCV have an annual risk of decompensation of 3-5%, a risk of developing hepatocellular carcinoma between 1.4-6.9% and a risk of mortality of 2% / year. Therefore, the treatment of chronic HCV infection is a priority for patients with severe hepatic fibrosis and cirrhosis. The emergence and approval of direct-acting antivirals (DAA) in recent years have revolutionized antiviral therapy, especially for patients with liver cirrhosis. Following numerous studies it has been found that, this treatment is well tolerated by these patients. The combination of DAA from different groups has a potent enhancing effect, and the sustained viral response (SVR) rate reaches up to 85-98% in patients with liver cirrhosis. In general, the chance of performing SVR with DAA in patients with compensated cirrhosis (Child-Pugh A) is comparable to non-cirrhotic patients. However, there is a risk for decompensation and acute liver failure during and after treatment. Patients with decompensated liver cirrhosis and advanced liver fibrosis may have greater benefit from antiviral therapy after liver transplantation.

Conclusions: The data obtained from the analyzed studies suggest that DAA antiviral therapy prevents the progressive evolution of the disease towards hepatocellular carcinoma or decompensation. At the same time, a correct therapeutic approach and a permanent monitoring of these patients can improve the quality of life, significantly prolonging the years of life.

Key words: direct-acting antivirals, cirrhosis, hepatocellular carcinoma, hepatitis C virus.

Introduction

Hepatitis C virus (HCV) infection is a disease with a significant global impact. According to the World Health Organization (WHO) data, 71 million people worldwide are infected with HCV [1]. About 700,000 people die annually from HCV complications, including cirrhosis, hepatocellular carcinoma (HCC), liver failure. In Western European countries, approximately 5 million people are infected with HCV, 40% of whom are in the stage of liver cirrhosis and 30% are candidates for liver transplant [1, 2].

In the Republic of Moldova the prevalence of HCV infection in the general population was estimated at 4.5-5.0%, with the prevalence of genotype (GT) 1b – 98% [3-5]. According to the cumulative data, at the end of 2016 in the Republic of Moldova, there were 15.400 people infected with HCV [6, 7]. At the same time, in the last years, there is an increase in the prevalence of cirrhosis through HCV from 21.4 (2005) to 52.8 (2014) cases / 100.000 inhabitants [5].

Due to the fact that most cases (about 80%) are asymptomatic, the actual incidence of HCV infection is much higher.

After HCV infection, the rate of chronicization is 55-85%, and the rate of development of cirrhosis after 20 years after infection is 15-30% for infected persons after the age of 40 [2, 8]. The evolution of the disease is not linear; the progression of fibrosis is accelerated after the age of 50, regardless of the infection [9, 10]. Patients with cirrhosis and HCV have an annual risk of decompensation of 3-5%, a risk of developing HCC between 1.4-6.9% and a risk of mortality of 2% / year [11-13].

In the context of the exposed data and the fact that the majority of patients take non-clinical forms, we can conclude that, from an epidemiological point of view, HCV is a problem, which has a negative impact on public health. Thus, the objectives proposed by WHO, included in the strategy for Global Health 2015-2030, are to increase the percentage of people tested for hepatitis C from 20% to 90% and those treated from 7% to 80% [1].

Direct-acting antiviral (DAA) treatment

Until hepatitis C was identified as an agent of non-A non-B hepatitis, Interferon (IFN) – alpha contributed to the normalization of transaminases and to the improvement of liver histology in some patients. Over time, the sustained virus response rate (VRR) increased from 5-20% in interferon monotherapy, to 40-50% in the combination of IFN and ribavirin (RBV) [14].

Due to the limited efficacy and secondary extensive side effects of standard pegylated alpha – IFN (PEG) and RBV antiviral combination therapy, new antiviral drugs were needed.

The opportunity to administer direct-acting antiviral drugs (DAAs) is a substantial advantage in the treatment of chronic HCV infection, having the possibility of oral administration, short duration of treatment, high sustained viral response (SVR), decreased liver stiffness, improved liver function, and minimal side effects [15, 16]. The combi-

nation of DAA from different groups has an enhanced potentiation effect, and the SVR rate reaches up to 85-98% in patients with cirrhosis [17, 18, 19].

The data obtained from the analyzed studies suggest that such treatments can extend the life span of the cirrhotic patients, preventing the progressive evolution of the disease towards HCC or decompensation. Thus, patients with an advanced degree of fibrosis and an increased risk of liver complications, as well as those with severe extrahepatic manifestations will have priority over immediate treatment, using the most advantageous therapeutic options.

A correct therapeutic approach and a permanent monitoring of these patients can improve the quality of life, significantly prolonging the life years.

Although there are still barriers that prevent the complete eradication of HCV infection, mutual international efforts to overcome them determine optimism regarding the future of treatment for this disease.

Treatment with DAA in cirrhosis with HCV infection: objectives, response to treatment, monitoring, adverse events

Liver cirrhosis represents the final evolutionary stage of any liver disease, being the consequence of destroying liver cells and reducing the ability of liver tissue to regenerate. The rate of chronicization and progression to cirrhosis is correlated with the age of infection (greater than 40-50 years), male sex, presence of HBV / HIV coinfection, alcohol consumption, severity of liver fibrosis, presence of steatosis [20-22]. For people with chronic infection, the risk of cirrhosis is between 15 and 30% for a period of 20 years [9].

At the same time, a diagnosis of compensated cirrhosis is associated with a 4.7 times higher risk of death compared to the general population, and decompensated cirrhosis is associated with a 9.7 times higher risk [22, 23].

The emergence and approval of DAA in recent years have revolutionized antiviral therapy, especially for patients with cirrhosis. Following numerous studies, it has been found that this treatment is well tolerated by patients with advanced liver disease [24, 25]. The current therapeutic possibilities have the advantage of being highly effective, and the main purpose of DAA therapy is to eradicate the infection as early as possible and to prevent the evolution of the disease in order not to reach the advanced stages of the disease.

Before making the decision in favor of a particular treatment regimen with DAA, several factors that may influence this therapy should be considered. First, the HCV genotype must be determined. Most DAA regimes are available and active against GT1. Second, previous antiviral therapies should be considered. Patients with relapse or unresponsiveness after treatment with PEG-INT and RBV still have high chances of viral eradication. However, previous treatments followed by DAA may be associated with resistance, which may influence the outcome of therapy with other DAA regimens [24, 25]. Here, resistance analysis is recommended to select an effective DAA combination. Also, the interaction between the drugs administered in the associated diseases and those of the antiviral therapy with DAA should be checked.

Advantages of DAA administration in patients with liver cirrhosis:

- Possibility of oral administration.
- Short duration of treatment.
- High SVR and minimal adverse reactions [18, 26, 27, 28].
- Decreased hepatic stiffness (fibrosis) in patients with SVR [15, 29].
- Improvement of liver function [30, 31].

Before initiating antiviral therapy, patients with liver cirrhosis should be examined in order to assess: presence / absence of esophageal varices, HCC and signs of hepatic decompensation (hepatic encephalopathy, ascites, etc.). In general, the chance of performing SVR with DAA in patients with compensated cirrhosis (Child-Pugh A) is comparable to non-cirrhotic patients. However, there is a risk of decompensation and acute liver failure during and after treatment [25]. Therefore, patients with advanced and decompensated cirrhosis should be treated and monitored in experienced centers, and the possibility of liver transplantation should be evaluated.

Patients with decompensated liver cirrhosis and advanced liver fibrosis may have greater benefit from antiviral therapy after liver transplantation [19, 32].

The combination of sofosbuvir (SOF) / daclatasvir (DCV) with / without RBV and SOF / ledipasvir (LDV) with / without RBV clearly influences hepatocytolysis syndrome in patients with hepatic cirrhosis, the transaminase profile being significantly improved at the end of treatment (88-95% of patients had normal values), recording the biochemical response [27, 33]. On the other hand, the combination of 2 DAA and RBV in patients with compensated liver cirrhosis showed a higher efficacy (SVR 96%), compared to the schemes without RBV (SVR 88%)[33, 34].

RVS rates are decreased (82-87%) in patients with decompensated cirrhosis, especially in those with platelets <75000 [17, 27]. Studies have shown that the effectiveness of DAA therapy decreases with the degree of decompensation of cirrhosis. Thus, the SOLAR-2 study evaluated the use of SOF / LDV and RBV in 329 patients with decompensated cirrhosis for 12 and 24 weeks. RVS rates at 12 weeks ranged from 87% to 96% for Child Pugh B patients and 72-85% for Child Pugh C patients (genotype 1) [30]. Similar data were obtained in the ALLY-I study, patients being treated with SOF / DCV and RBV: the 12-week RVS rate was 96% in Child Pugh B patients and 56% in Child Pugh C patients [32, 35].

FDA (Food and Drug Administration) recommends 12 weeks of RBV treatment in naive patients with compensated / subcompensated cirrhosis [36]. The European Association for the Study of Liver Disease (EASL) recommends 24 weeks without RBV in patients with decompensated cirrhosis or those with pre / post liver transplant and 12 weeks with RBV in patients with compensated cirrhosis [37].

Afdhal N. et al. reported in a batch of 50 patients with

cirrhosis and HCV genotype 1 and 4 (60% Child Pugh B stage) in treatment with SOF and RBV, in 89% of patients a rapid viral response (RVR) was obtained) at week 4 of treatment and 97% at week 8 [18]. Out of a total of 108 patients with cirrhosis Child Pugh B genotype 1 and 4 treated with SOF / LDV and RBV, SVR was achieved in 89% of those who received 12 weeks of treatment [38]. It is remarkable that these rates of SVR are comparable to those for compensated cirrhosis or even non-cirrhotic patients. DAA treatment in patients with cirrhosis improves liver function by about 40% [2, 8, 31].

The combination paritaprevir (PTV) / ritonavir (RTV) / ombitasvir (OBV) plus dasabuvir (DVR) (3D regimen) was approved by the FDA in December 2014 for the treatment of HCV GT1 infection. The use of a 12-week PTV / OBV regimen stimulated with RTV with RBV (without DVR) in the treatment of HCV GT4 infection is studied in studies PEARL-1, AGATE-1 and AGATE-2. PEARL-1 is a study of 91 naïve patients with cirrhosis, where all patients had SVR [39]. The AGATE-1 and AGATE-2 studies added the results of the PEARL-1 study by including patients with cirrhosis. All participants in the AGATE-1 study had cirrhosis, where 97% SVR rates were reported (59/61) [40]. The AGATE-2 study investigated patients with and without cirrhosis. In these cohorts, SVR rates of 97% (30/31) and 94% (94/100) were obtained. Extending treatment duration to 24 weeks did not increase SVR rate in patients with cirrhosis [41].

The OPTIMIST-2100 Phase III study had patients with HCV GT1 cirrhosis who were treated with SOF / simeprevir (SMV) for 12 weeks. RVS rates made up 83% (86/103) [26].

In June 2016, the FDA approved the first pangenotypic regimen – SOF / velpatasvir (VEL), which introduced a new era of DAA therapy. This combination simplifies the management of HCV infection treatment, because the need to determine the genotype before initiating antiviral therapy disappears. ASTRAL-1-5 studies have confirmed the pangenotypic efficacy of SOF / VEL, as well as the efficacy of this regimen in HIV co-infection and in decompensated liver disease [42-44]. SOF / VEL with / without RBV has been shown to be an effective pangenotypic therapeutic option including in cirrhosis with HCV.

The American Association for the Study of Liver Diseases (AASLD) and EASL recommend the administration of DAA regimens containing SOF with one of the following preparations: LDV, VEL, DCV in combination with RBV in patients with decompensated cirrhosis [2, 45].

The EASL recommends monitoring with abdominal ultrasound and alpha-fetoprotein (AFP) every 6 months, for early detection of HCC, for all patients with FibroScan> 9.5 kPa (Metavir ≥ F3) [2]. The EACS (European AIDS Clinical Society) recommends surveillance only for cirrhotic patients, and FibroScan> 12.5 kPa is considered to indicate cirrhosis [46]. The occurrence of esophageal varices after SVR is rare, if varicose veins were not present at pre-treatment endoscopy. Endoscopic control for varicose veins is recommended every 2 years after SVR in all patients with cirrhosis [26]. According to the Baveno VI statement, patients with compensated cirrhosis can avoid endoscopy provided they have platelets> 150,000 and FibroScan <20 kPa [47].

Invasive assessment of hepatic gradients of venous pressure before and after antiviral treatment showed a partial regression and normalization in most patients with portal hypertension who had SVR [48].

Although, it has been shown that an SVR for antiviral treatment with DAA induces regression of liver cirrhosis and reduces the risk of mortality in cirrhotic patients, however, a significant risk for HCC development, cholangiocarcinoma and hepatic decompensation is still present, and long-term surveillance is mandatory. The results of the studies showed that, in these patients, the risk is significantly reduced compared to those who failed the treatment [49-52].

Adverse events of DAA therapy

There are few studies describing the adverse events (AE) associated with DAA therapy in patients with liver cirrhosis. A study aimed at AE research included 102 patients (74% cirrhosis) with chronic HCV infection who underwent DAA therapy for 12 or 24 weeks. All patients received SVR. About 90% of patients reported at least one AE associated with current treatment. The most common AEs reported were: fatigue (43%), headache (42%), neuropsychiatric symptoms (30%) and nausea (26%). Neuropsychiatric symptoms were more frequent in patients with previous antiviral treatment experience compared to naive patients [28].

Current guideline recommendations support the use of SOF-based DAA regimens in combination with LDV, VEL or DCV, with or without RBV, for the treatment of HCV infection in patients with cirrhosis. NS3 / 4 protease inhibitors (Telaprevir, Boceprevir and Simeprevir) are not recommended in cirrhosis because of their potential to aggravate liver disease. Apart from SOF that is mainly excreted by the kidneys, most DAAs are metabolized by the liver with bile excretion as a major pathway. Therefore, in patients with severe renal impairment (glomerular filtration rate <30 ml / min), the administration of SOF is contraindicated and treatment of HCV infection should be postponed until after transplantation. At the same time, data from some studies suggest that SOF therapy can be used safely and effectively in those with chronic kidney disease in stages 4 and 5, although patients with compensated liver disease were included in the studies [53, 54].

Most EAs are related to the administration of RBV, so dose adjustment is needed. RBV-induced anemia may be moderate / severe, requiring dose adjustment or withdrawal of therapy with this preparation. In patients with decompensated cirrhosis, it is suggested to administer RBV with an initial dose of 600 mg / day and increased depending on the tolerability of the patients.

It has been noted that, most commonly, adverse reactions to RBV manifest in patients with a higher degree of cirrhosis [16, 33, 55]. Studies in such patients have shown that RBV cancellation or dose reduction during treatment does not significantly influence the virological response to treatment [30, 33, 56]. However, patients with hepatic cirrhosis

require hospitalization at the initiation of antiviral therapy, mainly due to complications caused by the disease.

The effectiveness of the PTV / RTV / OBV plus DVR combination is similar compared to LDV / SOF. However, the 3D regimen has two main disadvantages: the greater number of pills administered per day and the potential drug interactions [45]. The most common adverse events encountered during approval studies were: sleep disorders, nausea and pruritus. Increases of bilirubin to more than three times the upper limit of normal value were more frequently seen in patients with cirrhosis (9.7%). Relevant increases of ALAT were also noted. An Israel multicenter cohort study reported 7 patients who received PTV / RTV / OBV plus DVR and developed decompensation within 1 to 8 weeks of starting therapy, and one patient died [57]. Due to these possible hepatotoxic effects and worsening of liver function in patients with advanced disease, this treatment cannot be recommended for patients with decompensated cirrhosis[58]. Patients with compensated cirrhosis who receive this regimen should monitor the clinical picture and symptoms of hepatic decompensation, being subjected to hepatic laboratory tests at the beginning and at least every 4 weeks during therapy [45].

Hepatic fibrosis

Hepatic fibrosis, following chronic infection, is the most important factor related to HCV morbidity and mortality.

Hepatic fibrosis is a prognostic marker for the evolution of HCV infection. Thus, three types of fibrosis progression can be identified: the rapid progressive type (develops cirrhosis in less than 20 years), the intermediate type (develops cirrhosis between 20-50 years), the slow progressive type (without evolution towards cirrhosis or very slow evolution in more than 50 years) [59].

The researchers identified several factors that influence the regression or evolution of fibrosis. There were no significant associations with the patient's sex, age, race / ethnicity, other medical conditions or complications of cirrhosis [60, 61]. However, diabetes and esophageal varicose veins have been associated with a lower likelihood of fibrosis improvement [29].

A meta-analysis of 111 studies revealed that fibrosis progression was nonlinear, with an estimated risk of cirrhosis of 16% and 41% after 20 and 30 years of infection respectively [61]. Other studies have also shown nonlinear development, with major acceleration of fibrosis progression after age 50 [62].

When advanced fibrosis develops (stage F3 after the METAVIR scale), the risk of progression to cirrhosis is approximately 10% per year.

Studies were conducted with monitoring of the fibrosis degree in cirrhosis with HCV after treatment with DAA obtained SVR. Thus, in a study in which 65 people with cirrhosis were evaluated after DAA treatment, 55% showed improvement and 45% of the fibrosis remained unchanged. It was found that the average time to improvement was 2.5-3.0 years from the time of initiation of therapy, indicating that those with less severe hepatic injury have a faster improvement [15].

HCV infection has increased the interest for the study of the cellular and molecular mechanism of hepatic fibrosis, with a view to identifying effective therapeutic, etiological, pathogenic and antifibrotic means.

Hepatocellular carcinoma

Patients who develop liver cirrhosis prior to initiation of antiviral therapy should be maintained in the HCC surveillance program because the risk of malignant development is high, even if elimination of SVR infection is achieved.

The appearance in the liver cirrhosis of regenerative nodules or hyperplastic nodules is the main alarm signal, because following genetic changes that occur during repetitive cell proliferation, these nodules change into dysplastic nodules, a process that leads to liver damage [63].

Numerous studies have been carried out over the years, targeting patients who have developed CHC following antiviral therapies [28, 37-39].

In the study that included 103 patients with a history of HCC in a previously treated (surgical) history with a complete response (absence of characteristic nodules), they received DAA treatment. Patients pretreated with IFN in the background were not included in the study. After a monitoring of approximately 6 months, 18 patients had recurrence of HCC with the development of the characteristic intrahepatic tumor nodules [64].

On the other hand, another study conducted on 819 patients evaluated the risk of developing HCC after DAA treatment compared to patients treated with IFN. It was found that rates of HCC development did not differ between patients treated with DAA and those receiving IFN. At the same time, all patients who developed HCC were in the stage of liver cirrhosis [65].

Data from some studies have shown that patients with cirrhosis and HCC have SVR rates (74%) lower than patients with cirrhosis, but without HCC (91%) [66, 67].

There was also a correlation between HCC and high levels of alpha-fetoprotein, platelet count ≤110 x109 / l, advanced fibrosis (F4), adverse effects on more common antiviral therapy, RVS rate in comparison with lower DAA with those who do not develop HCC (87.3 vs 95.5%) [68].

Until recently, the category of patients with HCC associated with viral hepatitis C had a lower survival rate than those with HCC of other etiology, due to the lack of effective treatment for the underlying hepatitis C virus infection, but the new interferon-free therapies significantly improved these figures.

Treatment with DAA in patients with chronic HCV hepatitis does not increase the risk of developing HCC, so this treatment is considered a method of preventing the progression of the disease to cirrhosis and HCC.

Conclusions

1. Interferon-free treatment simplified therapeutic behavior and exponentially reduced adverse effects.

2. New generations of drugs (DAAs), which provide high SVR, are the best and reasonable option including for patients with advanced liver cirrhosis.

3. Based on the results presented in different clinical studies, it is recommended to initiate DAA therapy earlier in order to ensure a faster decrease in liver stiffness after treatment.

4. The choice of antiviral treatment regimen and its duration is individualized according to the degree of fibrosis, genotype, concomitant diseases and adverse effects that may occur.

5. In patients with hepatic cirrhosis, DAA therapy has been shown to be the most effective prevention for the development of hepatocellular carcinoma.

6. After obtaining SVR, patients with liver cirrhosis, however, present a significant risk for developing hepatic decompensation, so long-term surveillance is mandatory.

7. The risk of HCC and mortality is significantly reduced, but not completely eliminated in cirrhotic patients who have obtained SVR, as opposed to untreated patients and patients who do not get SVR, especially in the presence of other causes of hepatic impairment: metabolic syndrome, consumption of alcohol and co-infection with HBV / HIV.

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