REVIEW ARTICLE

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Antiviral therapy in chronic hepatitis C virus infection

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Abstract

Background: Hepatitis C is a disease with significant global impact. According to the World Health Organization there are 71 million people chronically infected with the hepatitis C virus. About 399.000 people die each year, mostly from cirrhosis and hepatocarcinoma. GT 1 and 3 are the most common causes of infection. Chronic HCV infection is accompanied by extrahepatic manifestations reported in up to 75% of patients, rapid development of hepatic fibrosis and accelerated time to cirrhosis and increased risk for liver failure, HCC and liver-related mortality. HCV therapy is one of the interventions necessary to reduce global burden of disease. Because of their high virological efficacy, ease of use, safety and tolerability, IFN-free, ribavirin-free, DAA-based regimens must be used in HCV-infected patients without cirrhosis or with compensated cirrhosis, including: treatment-naive patients: never been treated for their HCV infection, treatment-experienced patients: previously treated with PEG-IFNa + RBV. From pangenotypic drugs or drug combinations for treatment HCV in Europe are recommended: sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir and glecaprevir/pibrentasvir. Genotype-specific drugs sofosbuvir/ledipasvir, ombitasvir/paritaprevir/ritonavir, or grazoprevir /elbasvir are recommended for (GT 1, 4, 5 and 6).
Conclusions: The new direct-acting antiviral treatment regimens can be given to most patients with chronic hepatitis C virus infection, including those with liver cirrhosis, they have shown high efficacy, achieving sustained virologic response in over 90% of patients. DAA are well tolerated and have minimal side effects that do not require treatment discontinuation.

Key words: viral hepatitis C, direct-acting antiviral combination therapies.

Introduction

Prior to the identification of HCV, only a small number of Non-A Non-B hepatitis patients have been successfully treated by long-term administration of interferon-alpha. However, the molecular features of hepatitis C virus made it possible to develop specific treatment and laboratory tests for the diagnosis and monitoring of HCV infection [1].

According to WHO data, around 70 million people with HCV infection were estimated by the end of 2017 viz. approximately 2-2.5% of the world's total population [2]. In the republic of Moldova, the incidence rate makes up 4.5% of people aged 30-49 and more prevalent in males than in females [3]. According to the National Public Health Agency data, the analysis of the dynamics of viral hepatitis morbidity over the last 10 years shows a continuous increase in cases of chronic hepatitis and liver cirrhosis in the Republic of Moldova. The prevalence of chronic HCV tends to increase from 189.4 in 2008 to 441.5 cases per 100.000 persons in 2017. This tendency of HCV morbidity growth is due to the lack of specific HCV preventive measures, as well as high level of viral hepatitis detection. It also should be noted that liver cirrhosis mortality, including hepatitis C virus has decreased from 88.3 to 100 thousand individuals in 2009 to 62.7 per 100 thousand population in 2017 as a result of the National Program for Combating Hepatitis B, C and Delta viruses [4, 5]. Chronic hepatitis C virus infection is one of the most common causes of chronic liver disease and liver transplantation all over Europe and the US. It is difficult to determine the number of new HCV infections since the most acute cases have not been clinically identified. Less than 25% of acute HCV cases are detected based on clinical manifestations [6].

Antiviral therapy: historical background, objectives and adverse reactions to treatment

Prior to of HCV identification, interferon-alpha was considered as a potential therapy in non-A, non-B viral hepatitis, which contributed to both normalization of transaminases and improvement of liver histology in some patients [1]. Since the identification of HCV by Choo in 1989, it has become possible to quantitatively determine the level of serum HCV RNA and evaluate the effectiveness of long-term viz. obtaining a sustained virologic response (SVR).

The first studies showed that Interferon-alpha-2b 3MU administered 3 times / week for 6 months has achieved SVR in 8% of cases, and increased to only 12% when therapy continued up to 12 months [7, 8].

Ribavirin alone was used in the treatment of chronic

HCV for the first time in 1991. Ten patients were administered Ribavirin 1000-1200 mg / day for 12 weeks. There was a considerable decrease in transaminases during treatment, however these returned to initial level after drug withdrawal. Hepatitis C virus has not been completely removed in any of the patients [9]. An increase in the effectiveness of antiviral treatment was observed in combined therapy viz. Ribavirin and IFN-alpha. Two major randomized trials were conducted in order to compare the efficacy of combined IFN-alpha-2b + Ribavirin and Interferon-alpha-2b alone administered to naive patients. The first results established a sustained virological response in 47-50% of cases following a combined therapy, whereas only 13% patients with Interferon alone and 0% in patients with Ribavirin monotherapy [10, 11]. The synthesis of pegylated interferon (PEG-IFN) that contains pegylated proteins and shows a much longer half-life, has improved the pharmacokinetics of IFN, thus reducing the dosing intervals. Two types of IFN-PEG are currently available: PEG-IFNα-2b (PEG-Intron, Merck) and PEG-IFNα-2α (PEGASYS, Roche). A large multicenter study in the US has not established any significant difference between the two PEG-IFN and RBV regarding SVR [12].

The combined therapy of PEG-IFN α-2a (180 μg / kg / week) and RBV at a dose of 1000 mg was found to be effective if the body weight <75 kg or 1200 mg if the body weight ≥75 kg in patients with GT1 HCV [13]. In case the hemoglobin level drops below 10 g / dl, the dose of ribavirin should be reduced by 200 mg and discontinued if the hemoglobin level is below 8.5 g / dl [14, 15]. Several studies were conducted on chronic HVC patients following a PEG-IFN + RBV treatment during the period of 2011-2013 years. SVR was reported in 42-52% of GT1 patients within 48 weeks and 76-84 % of GT2 and GT3 individuals within 24 weeks [16, 17]. Treatment regimens with PEG-IFN-α and Ribavirin are still valid for countries with limited access to DAA.

A good treatment adherence is an important factor in achieving optimal outcomes in the antiviral treatment of chronic hepatitis C virus infection. Adherence to interferon and ribavirin treatment was particularly difficult, since these have been the only option available over the past two decades. Almost all patients treated with interferon and ribavirin exhibited adverse reactions that significantly influenced the treatment adherence. The most common side effects were reported in patients treated with pegylated interferon and ribavirin showing symptoms of general intoxication and asthenia – 66%, headache – 50%, nausea – 43%, insomnia – 39%, pyrexia – 35%, anemia(10 g / dl) – 34%, myalgia – 27%, neutropenia (<1000 cells / μl) – 26%, depression – 26%, irritability – 25% and rash – 22%. According to Seyam et al. [18], 6-10% of patients who administered interferon therapy for 48 weeks lost weight. Weight regained quickly after therapy discontinuation.

The most frequent psychiatric adverse events induced by IFN α include fatigue – 40-80%, sleep disturbances – 20-45%, irritability – 20-45%, cognitive disorders affecting concentration and memory – 20-30 %, depressive episodes – 20-70%, delirium, psychosis, mania – 1-3%, suicidal thoughts – 3-10%, and suicide attempts – 0-0.02% of individuals [19, 20]. Interferon therapy is accompanied by a 30-50% decrease in the absolute number of WBCs within the first 4-8 weeks from the treatment onset and a rapid increase after its withdrawal. Anemia (<10 g/dl) was reported in up to 20% of patients [13]. The dose of ribavirin should have been reduced in severe cases of anemia. Thrombocytopenia occurs within the first 2 months after the onset of IFN therapy, reducing the platelet count by 30-40% compared to values before the treatment. As a rule, the platelet count returns to its normal values after 4 weeks from the antiviral therapy withdrawal [21]. Combination of Boceprevir and Telaprevir protease inhibitors in the treatment of chronic HCV increased the SVR rate up to 75% in HBV naïve patients [22, 23] and up to 29-88% in patients pretreated with antiviral drugs [24, 25]. However, both protease inhibitors required combination with PEG-IFN and Ribavirin, since the monotherapy may develop a rapid resistance and severe side effects such as anemia.

A French cohort study was conducted on patients with compensated liver cirrhosis who underwent telaprevir or boceprevir regimen. Severe adverse reactions (anemia in up to 50% of patients), including sepsis, hepatic decompensation and even death were reported [26, 27]. Renal failure was registered in patients following a triple therapy with telaprevir and bocepravir. Impaired renal function was reported in patients with pre-existing risk factors for renal disorders associated with a more marked decrease in hemoglobin level that was reversible in most cases after the treatment withdrawal [28, 29]. Due to a wide range of side effects of interferon, telaprevir and boceprevir-based triple therapy, their production was discontinued after approval of interferon-free treatment with DAA.

Sofosbuvir, the first polymerase inhibitor, has substantially improved the therapeutic efficacy in patients with chronic HCV. Treatment with PEG-IFN / RBV and SOF for a period of 12 weeks showed 89% SVR rate. When administered in combination with interferon and ribavirin, it exhibited minor adverse effects and a limited drug interaction [30, 31].

However, due to its renal excretion, Sofosbuvir should cautiously be administered in patients with advanced kidney disease and glomerular filtration rate <30 ml / min, as well as in end-stage renal diseases, unless an alternative treatment is available.

Interferon-free antiviral treatment: indications, contraindications, new treatment regimens with direct-acting antivirals

As new therapeutic opportunities have emerged, each patient with confirmed chronic hepatitis C should receive antiviral treatment. Patients who undergo a HCV infection treatment may experience a higher quality of life and a lower risk of developing liver cirrhosis, hepatocellular carcinoma and mortality associated with hepatic and extrahepatic

pathology [32, 33]. According to EASL 2018 recommendations, patients with chronic HCV should be preferably administered direct-acting antivirals with IFN-free and RBV-free regimens. The treatment should be initiated as soon as possible in patients with advanced fibrosis and an increased risk of liver complications. Moreover, a priority for immediate treatment of patients with hepatitis C virus is the severity of extrahepatic manifestations. Another reason for an early initiation of treatment in all individuals diseased with HCV infection is its further prevention and transmission to people at high risk (intravenous drug users, men who have sex with men, women in childbearing age, hemodialysis patients, inmates in prisons) [15].

Antiviral treatment is not recommended in patients with short-life expectancy due to non-HVC comorbidities [15].

The predictive factors for the selected treatment regimen should be considered prior to initiating the antiviral therapy in order to increase the SVR rate. Even though, HCV genotype, liver fibrosis and steatosis, initial viral load, insulin resistance, age, gender, BMI, ethnicity, and HIV co-infection are the SVR predictive factors suggesting the initiation of PEG-IFN / RBV therapy, then most of these factors are much less important for DAA therapy. The HCV genotypes 1a and 1b, antiviral resistance and in most countries the treatment cost are the other important parameters for IFN-free therapy. However, the severity of the disease at time of treatment initiation is still important to assess [34, 12]. Although there is a number of available antiviral regimens, not all of them show a pangenotypic effect, thus genotyping is mandatory when initiating an antiviral treatment in order to select the optimal regimen and treatment duration of chronic HCV [35].

If the HCV RNA level has been and remains the most important predictive factor of SVR in PEG-IFN + RBV treatment, at present, when new DAA regimens have been used, the HCV load does not appear to have a significant predictive value. Concomitantly, according to 2018 EASL recommendations, RNA-HCV concentration (<600.000-800.000 IU/ml) is a condition for reducing treatment duration in naive non-cirrhotic patients who initiate IFN-free treatment with sofosbuvir and ledipasvir [36, 37].

According to 2018 EASL guidelines, the viral load assessment is recommended only prior to treatment and at 12 or 24 weeks after the antiviral therapy ceases. Instead of HCV RNA, the HCV core antigen may be performed if HCV RNA tests are not available [15]. At the same time, quantitative HCV-RNA testing is recommended by the AASLD/IDSA guidance on week 4 of DAA therapy to monitor the patient compliance [48].

Interleukin IL28B plays an important role as a predictive factor for SVR in PEG-INF / RBV / IP treatment. IL28B has a much greater significance than the HCV load. IL28B-related data explain the SVR difference in PEG-INF / RBV treatment among different ethnic groups, such as reduced SVR in African and American patients, and a high SVR in Asian patients. Female gender, initial viremia of <6 log10 IU/ml and body mass <30 kg/m^2 are additional factors that may influence the SVR in SOF / LDV therapy. Patients with HCV GT1b respond better to some approved DAA therapies. The stages of liver damage and previous experience with PEG-IFN + RBV are important predictors in treatment response [38].

The emergence of DAA therapies has given rise to another major problem viz. developing drug-resistance. Patients receiving first-generation HCV-protease inhibitors boceprevir and telaprevir developed resistance within a few days. If resistance develops, it is not known yet how long it will persist and what are the significant consequences for future therapies. Some studies suggest that most IP-resistant variants revert to wild type within 1-2 years after the completion of treatment [39].

The combination of different DAA classes might solve out the problem of resistance. SOF has a very high resistance barrier [40]. Combined SOF and NS5A inhibitor (SOF / DCV or SOF / LDV or SOF / VEL) exhibit a SVR > 90%. However, according to the studies, NS5A-associated resistance may become a problem within the clinical practice.

Several studies on initial resistance prior to treatment initiation with NS5A inhibitors have been performed. The resistance made up approximately 16% in SOF / LDV group [39] and 20% in the GZR / EBR-treated patients [41]. The resistance levels have no impact on SVR in HCV GT1b patients, though it may be significant in GT1a and GT3 cases, particularly if other negative predictors (previous non-responder or advanced cirrhosis) are present. For these reasons, there is no point in assessing the resistance level prior to treatment initiation via first-line preparations; this should be done when selecting the optimal therapy unless the combined DAA therapy has failed.

Interferon-free direct-acting antiviral therapy has become available in many countries since 2014 and has substituted the standard interferon therapy. DAAs have shown a much better efficacy, a substantially improved tolerance and shorter treatment duration compared to interferon therapy [42, 15].

The DAA groups are as following NS3 / 4A protease inhibitors, NS5B polymerase inhibitors and NS5A replication complex inhibitors. The combination of at least two of these three major drug classes results in ≥95% of SVR in just 8-12 weeks of treatment [42]. Treatment options are different across the world, as not all countries have access to new treatment regimens, whereas the generic preparations [43] are available in few countries.

Since 2016, in the Republic of Moldova, the National Treatment Program of Viral Hepatitis has developed a program on antiviral treatment with DAAs of chronic HVC that has become available now. Two regimens were approved: sofosbuvir + ledipasvir and sofosbuvir + daclatasvir.

Sofosbuvir (SOF) is an all-genotype NS5B polymerase inhibitor with high resistance barrier that is combined with other antivirals. Sofosbuvir alone is not allowed. The combination of sofosbuvir with NS5A-daclatasvir (DCV) or ledipasvir (LDV) inhibitors has reached SVR in over 90% of cases [38, 44].

The SOF + LDV treatment regimen is available in a single tablet containing SOF (400 mg) and LDV (90 mg). This once-daily taken preparation is an advantage since it improves the treatment adherence. According to the EASL 2018 guide, SOF / LDV is recommended for patients infected with genotype 1, 4, 5 and 6 and is not recommended for patients with genotype 2 and 3. It should be used with caution in patients with chronic kidney disease where GFR <30 ml / min, unless other recommended therapeutic regimens are available and can be used without restrictions in patients with decompensated cirrhosis.

In patients GT1 chronic HCV-infected patients without cirrhosis, the treatment with SOF/LDV for 12 weeks reached a SVR of 96%, while treatment for 24 weeks – in 99% cases.

Most studies conducted in naive patients with HVC GT 2 and 3 [45] and treated with SOF/LDV experienced reduced SVR rates (64-68%), and those who received SOF/LDV regimen + RBV result in SVR of 97 – 100%. Based on these results, the SOF/LDV treatment regimen is not recommended in patients with HVC GT 2 and 3 because there are more optimal treatment options.

Based on study analysis of patients with GT4, 5 and 6 there is little data on IFN-free regimens. A study conducted on 41 naïve patients with GT5 and 25 with GT6 for 12 weeks with SOF / LDV, SVR resulted in 95-96% [45, 46].

HCV genotyping is required in order to select the best Direct-Acting Antiviral regimen. However, there are patients in whom genotyping was not possible to determine or mixed genotypes were recorded. In this case, AAD pangenotypic regimens are available. Combination of sofosbuvir and daclatasvir (DCV) is an example of such a regimen. Daclatasvir is an inhibitor of the NS5A replication complex and is given once daily at a standard dose of 60 mg [47].

The results of several studies confirmed that treatment with SOF / DCV and RBV-free for 12 weeks is recommended for naïve patients without cirrhosis. Treatment of cirrhotic patients should last up to 24 weeks. The treatment might be reduced up to 12 weeks in patients with cirrhosis, previously untreated and showing positive prognostic factors [38, 44].

A study was conducted on 41 patients with non-cirrhotic HVC GT1 who underwent PEG-IFN + RBV + IP and demonstrated a 100% SVR in both SOF + DCV therapy for 24 weeks and in SOF + DCV + RBV regimen for 24 weeks [44]. Since 2018, Daclatasvir has not longer been used in a series of countries, such as Germany, because it has to be combined with sofosbuvir, and this treatment regimen is more costly than any other pangenotypic AAD recommended in the 2018 EASL guide. However, the combination of sofosbuvir and daclatasvir is the basic treatment in countries where the generic drugs are used.

Among the pangenotypic combinations approved in 2017, the association of Glecaprevir – NS3 / 4A protease inhibitor and Pibrentasvir that is the second-generation selective inhibitor of the NS5A replication complex (GLE / PIB) is also possible. An integrated analysis of all Phase 2 and 3 studies in cirrhotic and non-cirrhotic patients showed very good results within a 12-week GLE / PID treatment, thus SVR was established in 99.8% of patients with GT1, 99% in patients with GT2, 95% in GT3, 99-100% in GT4-GT6 patients. There were no statistically significant differences in naive and pre-treated patients. The SVR rate was quite high within the group of patients treated for 8 weeks and ranged from 99% in GT1 and GT2 up to 92% in GT6 [48]. Based on these study results, an 8-week treatment with GLE / GDP is recommended for naive, non-cirrhotic patients and 12 weeks for naive patients with cirrhosis.

A 16-week GLE / PIB treatment [15, 49] is recommended in cirrhotic and non-cirrhotic patients treated with AADs. Another pangenotypic regimen includes sofosbuvir (SOF) and velpatasvir (VEL) that are available in a fixed dose of 400 / 100mg SOF / VEL in one tablet. According to the results of the Phase 3 trials, the standard treatment for 12 weeks in all chronic HCV patients, GT1, 2,4,5,6 and non-cirrhotic CT3 patients has recorded SVR in 97-100% and there was no obvious difference between experienced and naive patients [50, 51, 52]. A complete analysis of patients with advanced fibrosis and cirrhosis demonstrated SVR in 98% and 99%, respectively. Therefore, this therapeutic regimen may be recommended for all HCV patients, regardless of the stage of fibrosis, including those experienced, however not recommended for patients with chronic kidney disease (GFR <30 ml / min) [52, 53].

Nevertheless, the new DAA treatment regimens show very good results in the treatment of chronic HCV, there were subjects who did not achieve SVR. The combination of sofosbuvir, velpatasvir and voxilaprevir (VOX), approved in 2017, should be used as an alternative regimen for the treatment of patients who failed to respond to NS5A inhibitor therapy. This treatment has a pangenotypic effect and can be used as a first-line treatment regimen [54]. Two studies of Phase 3 investigated SOF / VEL / VOX treatment in both naïve and DAA patients.SVR recorded 96-100% of patients infected with all HCV genotypes, with or without cirrhosis [55]. Antiviral treatment exhibits some adverse effects, as well. Once the new DAA interferon-/ribavirin-free regimens have been introduced, the rate of adverse effects has decreased substantially, thus most patients complain of minor manifestations such as fatigue, headache, insomnia and nausea [56]. These side effects do not require discontinuation of treatment.

Patients treated with ribavirin, in addition to anemia, may experience pruritus, dry skin, coughing, and dyspnoea [57]. These side effects have already been described in combined ribavirin and interferon regimen but their incidence and severity are lower when ribavirin is combined with direct-acting antivirals. However, there have been a number of severe complications as bradycardia and cardiac arrest, including some lethal outcomes in patients taking antiarrhythmic drugs, particularly amiodarone, in combination with DAA including sofosbuvir [58].

Conclusions

1. Hepatitis C virus (HCV)-related morbidity is a major current issue both worldwide and in the Republic of Moldova. This disease predominantly affects persons aged 30-49 years, and tends to develop into hepatic cirrhosis and hepatocellular carcinoma.

2. Lack of specific HCV prophylaxis requires the identification of cases of HCV infection and the application of effective treatment regimens.

3. Over the last two decades, the only available treatment option for chronic HCV was PEG-IFN and RBV for 48 weeks, which recorded a 42-52% SVR in patients with GT1 and for 24 weeks – 76-84% in those with GT2 and GT3. However, the treatment was accompanied by a series of side effects in over 50% of patients, which reduced adherence to therapy.

4. The new direct-acting antiviral treatment regimens can be administered in most patients with HCV infection, including those with liver cirrhosis. These proved to be highly effective, resulting in a sustained virologic response in over 90% of patients.

5. DAAs are well tolerated and have minimal side effects that do not require treatment discontinuation.

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