Hepatitis C Treatment: A Review and Update

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Abstract

Hepatitis C virus infection (HCV) infects approximately 185 million individuals worldwide. It is a leading cause of chronic liver disease and the primary reason for liver transplantation. The main aim of antiviral treatment is to achieve a sustained virologic response, which means eradication of the virus. The combination of pegylated-interferon and ribavirin was the standard of care for over a decade, despite the long treatment duration and severe adverse effects. The introduction of direct-acting antivirals with pan-genomic properties and excellent tolerance increased rates of SVR and shortened the duration of the therapy. Furthermore, it allowed clinicians to customize HCV therapy according to important clinical parameters such as HCV-genotype and liver fibrosis stage.

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Introduction

Hepatitis C virus infection (HCV) represents a significant public health burden and infects approximately 185 million individuals worldwide. It is a leading cause of chronic liver disease, which can evolve to cirrhosis in 15% to 20% of those infected within 20 years, resulting in severe outcomes such as end-stage liver disease and hepatocellular carcinoma (1). It is the primary reason for liver transplantation in Europe and the United States (2). There are seven HCV genotypes with marked differences in global geographic distribution and susceptibility to antiviral therapy (3). Since the discovery of HCV in 1989, there have been numerous advances in medical therapies available for the treatment of HCV infection. The main aim of antiviral treatment is to eradicate the virus, defined as a sustained virologic response (SVR), which means undetectable levels of plasma HCV RNA for 12 to 24 weeks after completion of therapy (4). SVR is associated with decreases in all-cause mortality, liver-related death rates and complications, and hepatocellular cancer rates (5, 6). The first agents available for treatment of HCV were the alfa interferons which resulted in SVR rates of approximately 15% (7). The combination of interferon (IFN) and ribavirin (RBV) improved SVR rates to 41% for 48-week

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treatment regimens (8). With the introduction of pegylated-interferon (Peg-IFN), SVR rates increased to 50% (9). Besides its limited effectiveness, the combination of Peg-IFN and ribavirin was associated with long treatment duration and frequent and severe adverse effects, but remained the standard of care for over a decade. The introduction of direct-acting antivirals (DAAs) has revolutionized therapeutic options for HCV infection (10). The first two approved drugs were boceprevir and telaprevir, NS3/4A protease inhibitors, used in combination with traditional dual therapy (11, 12). This strategy managed to increase the rates of SVR to 70% (10-12), but with greater toxicity, an increased pill burden, drug-drug interactions, low barriers to resistance, and notable side effects (13-15). Since 2013, and the introduction of new, more effective DAAs with pan-genomic properties and excellent tolerance, the treatment of HCV has had a new scenario: increased rates of SVR (even up to 100%), shorter therapy duration and less toxicity (16).

Direct-acting antivirals

Currently available DAAs are classified into four categories based on their mechanism of action: non-structural 3/4A serine protease inhibitors, non-structural 5A inhibitors, nucleotide analogue inhibitors of the non-structural 5B polymerase and non-nucleoside inhibitors of the non-structural 5B polymerase (17, 18). These drugs target the replication, polyprotein processing, packaging in nucleocapsid, assembly, and release of HCV infectious particles (3). Mutations at different positions in the NS3 protease, NS5B5 polymerase and NS5A protein affect viral susceptibility and the outcome of DAA-based therapies. However, the high specificity of DAAs makes them sensitive to small changes in the viral sequence responsible for antiviral resistance (10). Different currently approved interferon-free combination therapies with DAAs provide synergistic antiviral potency and prevent the development of DAAs resistance (19).

First-generation NS3/4A protease inhibitors

The NS3/4A protease is involved in post-translational processing and releasing of the NS3, NS4A, NS4B, NS5A and NS5B from the HCV polyprotein (20), and it is critical for replication of the virus (21). In 2011, the first generation of NS3/4A inhibitors (boceprevir and telaprevir) was specific for the treatment of chronic hepatitis C, genotype 1, and was used in combination with PegINF and RBV. The mechanism of action is the forming of a reversible covalent bond with the NS3/4A active site. Limitations to the triple therapy for CHC included adverse effects such as gastrointestinal issues, skin reactions and bone marrow toxicity, and low barriers to resistance (22). Also, boceprevir and telaprevir are potent cytochrome p-150 inhibitors, resulting in significant drug-drug interaction (12).

Second-generation protease inhibitors

Second-wave protease inhibitors offer several advantages over the first generation: improved pharmacokinetics, which allows a once-a-day dosing schedule, more tolerable side-effects, and fewer drug-drug interactions (23).

NS5A inhibitors

Because of its critical involvement in viral replication and assembly (27), NS5A has been identified as a target for viral inhibition. Inhibition of NS5A at picomolar concentrations has been associated with significant reductions in HCV RNA levels in cell culture-based models (28, 29). NS5A inhibitors have pan-genotypic activity. Synergistic inhibition of viral production and an increased barrier to resistance (30) have been accomplished with the use of multiple DAAs, including an NS5A inhibitor, in cell culture. The exact mechanism of antiviral action of NS5A inhibitors is unknown, and its detailed function remains unclear. Available evidence suggests that they have multiple effects, interfering with several functions of NS5A in the HCV life cycle, and disrupt the establishment of replication sites (31). NS5A inhibitors are daclatasvir, ombitasvir, ledipasvir, elbasvir, and velpatasvir.

Table 1. *The list of currently available DAAs*

Medicine	Brand name	DAA class	Dosing	Genotypes
Sofosbuvir	Sovaldi	Nucleotide NS5B polymerase inhibitor	400 mg (one pill) per day	Genotypes 1, 2, 3, 4
Simeprevir	Olysio	NS3/4A protease inhibitor	150 mg (one capsule) per day	Genotype 1
Daclatasvir	Daklinza	NS5A protein inhibitor	60 mg (two pills) once a day	Genotypes 1, 3 and 4 [9]
Sofosbuvir + ledipasvir	Harvoni	NS5A inhibitor	Sofosbuvir (400 mg) plus ledipasvir (90 mg), in a single pill taken once per day	Genotype 1 [10]
Ombitasvir-Paritaprevir/ Ritonavir and dasabuvir	Viekira	NS5A inhibitor + NS3/4A protease inhibitor + CYP3A4 enzyme inhibitor + non-nucleoside NS5B polymeraseinhibitor	12.5-75-250-50 mg	Genotype 1
Daclatasvir in combination with sofosbuvir +/ RBV		NS5A inhibitor + nucleotide polymerase NS5B inhibitor	60 mg once daily + sofosbuvir 400 mg once daily ± weight-based ribavirin	Genotypes 1-4
Velpatasvir in combinationwith sofosbuvir	Epclusa	NS5A inhibitor + nucleotide NS5B polymerase inhibitor	400 mg of sofosbuvir and 100 mg of velpatasvir once daily	Genotypes 1-6

Polymerase NS5B inhibitors

NS5B is the RNA-dependent RNA polymerase, and it is next reasonable target for the treatment of HCV. NS5B inhibitors can be classified into non-nucleotide inhibitors (NNIs) and nucleotide inhibitors (NIs) (32), both of them binding to the NS5B polymerase to terminate replication of the virus. NS5B utilizes the HCV RNA genome as a template for RNA synthesis. Nucleoside analogue inhibitors incorporate into the HCV RNA chain leading to chain termination. Because of that, NS5B inhibitors commonly show pan-genotypic activity with a high barrier to resistance. They are commonly used in combination with other classes with higher barriers to resistance. The most used NS5B inhibitors are sofosbuvir, as a nucleoside analogue inhibitor (33), and dasabuvir, as an example of a non-nucleoside inhibitor.

Currently available DAAs and treatment strategies

A number of highly effective DAAs allow clinicians to customize HCV therapy according to HCV-genotype, liver fibrosis stage and previous treatment experience (34, 35). Commercialized DAAs approved by the United States Food and Drug Administration (FDA) (4) are listed in Table 1.

Several factors must be taken into account when selecting the suitable therapeutic regimen. Clinically, it is necessary to evaluate

Table 2. *Treatment strategies in Croatia*

Clinical parameters	**Treatment option**
Genotype 1 naive patients	
Mild fibrosis	Peg IFN +RBV for 24-48 weeks.
Advanced fibrosis	Simeprevir/sofosbuvir and PeglFN + ribavirin.
Significant fibrosis, contraindications to IFN therapy, presence of extrahepatic manifestations, HIV-Coinfection, transplanted patients	IFN-free regimens for 12 weeks: Ombitasvir, ritornavir-boosted paritaprevir, dasabuvir + ribavirin; Sofosbuvir and ledipasvir ± ribavirin; Sofosbuvir and simeprevir ± ribavirin.
Decompensated cirrhosis	Sofosbuvir and ledipasvir ± ribavirin for 24 weeks.
Genotype 1 experienced patients	
Relapse or partial responders with F1-F3	PegIFN-α+ RBV and simeprevir or sofosbuvir for 12 weeks.
Non-response (regardless of fibrosis); F4 fibrosis (regardless of type of response); TT IL-28B genotype; contraindications to IFN therapy; extrahepatic manifestations, HIV-coinfected and transplanted patients	IFN-free regimens for 12 weeks: Ombitasvir, paritaprevir and ritonavir, dasabuvir ± ribavirin; Sofosbuvir and ledipasvir ± ribavirin; Sofosbuvir and simeprevir ± ribavirin.
Decompensated cirrhosis	Sofosbuvir and ledipasvir with ribavirin for 12 weeks, or 24 weeks without ribavirin.
Previously treated with PegIFN-α RBV + PI	Sofosbuvir + ledipasvir ± ribavirin for 12 weeks.
Genotype 4	The same recommendations as for genotype 1, with the exception of fixed combination of ombitasvir, paritaprevir and ritonavir, which is used without dasabuvir.
Genotype 2	
Treatment naive with F1-F3 fibrosis	PegIFN-αand RBV for 24 weeks.
Treatment naive with F4 fibrosis, treatment experienced regardless of fibrosis stage, contraindications to IFN, extrahepatic manifestations or HIV coinfected patients, transplanted patients	Sofosbuvir and ribavirin for 12-20 weeks (depending on cirrhosis).
Genotype 3	
Treatment naive with F1-F3 fibrosis	Peg IFN and ribavirin for 24 weeks.
Treatment naive with F4 fibrosis, treatment experienced	PegIFN-αRBV and sofosbuvir for 12 weeks.
F1-F3 fibrosis, contraindication to IFN	Sofosbuvir and ribavirin.
F4 fibrosis, contraindication to IFN therapy	Sofosbuvir, ledipasvir and ribavirin for 24 weeks or sofosbuvir, daclatasvir and ribavirin for 24 weeks.

disease, the degree of hepatic fibrosis, the presence of decompensation in patients with cirrhosis, renal function, the presence of extrahepatic manifestations of HCV, and the other medications the patient is taking. Virologically, it is necessary to know the genotype and its subtype, as well as to monitor the viral load at 12 to 24 weeks after therapy is completed and, in some cases, to determine the IL28B polymorphism or Q80K mutation (36, 37).

The highest priority for treatment should be given to the patients with advanced fibrosis, compensated cirrhosis, severe extrahepatic hepatitis, as well as those on the active liver transplant waiting list, and liver transplant patients with recurrence of the infection. Patients with high priority for treatment are the non-responders to triple therapy or patients with extrahepatic manifestations of HCV. Independently of the disease status, treatment should also be considered for certain subgroups of HCV patients, such as patients at high risk of transmission or women of child-bearing age (34, 35).

HCV treatment in Croatia

The prevalence of HCV in Croatia in the general population is low, with the estimated number of HCV patients around 39,000 (38, 39) and higher prevalence rates in prison populations, HIV patients, individuals with high-risk sexual behavior and alcohol abusers. Management of HCV infection in Croatia is following the European Association for the Study of the Liver (EASL) guidelines, Croatian Guidelines, and the recommendations of the Croatian Health Insurance Fund (HZZO). According to the recommendations, the highest priority is given to the patients with significant fibrosis or cirrhosis, extrahepatic manifestations, in patients with HCV recurrence after liver transplantation and in HBV/HCV and HIV/HCV-coinfected patients. Priority is also given to individuals at risk of transmitting HCV (injection drug users, people with high-risk sexual practices, women of child-bearing age, haemodialysis patients). Treatment can be postponed in patients with no or mild liver fibrosis with no clinically significant extrahepatic manifestations. On the other hand, treatment is not recommended in patients with limited life expectancy (35-37, 40, 41). Available drugs covered directly by the Croatian Health Insurance Fund in 2016 are Peg IFN; ribavirin; simeprevir; sofosbuvir, ombitasvir + ritonavir-boosted paritaprevir +/- dasabuvir; and sofosbuvir + ledipasvir. Treatment strategies for patients with different clinical parameters are listed in Table 2.

Conclusion

The appearance of direct-acting antiviral drugs has brought significant advances in the treatment of hepatitis C – high tolerability and convenient dosing of an all-oral regimen, reduced progression to cirrhosis and lower incidence of complications. With continuous screening and education, as well as timely detection, diagnose and treatment of HCV, reducing the prevalence and final eradication of the disease appears to be promising.

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