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Chapter 2

Hepatitis C Virus (HCV) Treatment in Croatia: Recent Advances and Ongoing Obstacles

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Additional information is available at the end of the chapter

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Abstract

The prevalence of hepatitis C virus (HCV) antibodies in Croatia is low in the general population (reported <1%), similar to the prevalence rates of many European countries, but is higher in the populations at risk, especially among intravenous drug users. With the development of new classes of direct-acting antiviral agents and interferon-free regimens, the landscape of HCV treatment has completely changed. Management of HCV infection in Croatia is in accordance with the European Association for the Study of the Liver (EASL) recommendations published in 2015, recently updated Croatian Guidelines (published in April 2016) and the recommendations of Croatian Health Insurance Fund (HZZO) which covers the costs of treatment. HZZO approved simeprevir at the beginning of 2015. By the end of the 2015 sofosbuvir, combination of sofosbuvir + ledipasvir and the combination of ombitasvir, paritaprevir and ritonavir ± dasabuvir became available. Although the drawback of these new highly effective treatments is their price, prioritization of patients on a national level offers equal opportunities to patients in need for treatment. Due to improvements in therapy and prevention, clinical care for patients with HCV in Croatia advanced significantly during the last two years.

Keywords: hepatitis C virus, Croatia, epidemiology, treatment, direct-acting antivirals (DAAs)

1. Introduction

The prevalence of hepatitis C virus (HCV) antibodies in Croatia is low in the general population (reported <1%). HCV seroprevalence in the Croatian adult general population is similar to the prevalence rates of many European countries (for example Spain, France, Belgium,

Poland, and Bulgaria) [1–5]. In comparison with other European countries, there have also been changes in the HCV epidemiology in Croatia over the past few decades. According to the published data, the estimated number of HCV-infected patients in Croatia is around 39,000, although the experts' opinion is that the real numbers are significantly smaller [6, 7]. There was no significant difference in the HCV seropositivity between males and females in the Croatian population, with the highest prevalence in the 30–39 age group (1.7%) [8]. Routine HCV screening of blood products was introduced in Croatia in 1992.

The prevalence of HCV infection in some population groups in Croatia is shown in **Table 1** [9–21]. Patients requiring multiple transfusions have a high prevalence of HCV infection, but with the implementation of mandatory anti-HCV and HCV RNA screening of blood/blood donations, the risk of transfusion-associated hepatitis C has virtually been eliminated. [22]. HCV seroprevalence in the Croatian pregnant women is comparable to data reported in Switzerland and Spain [23, 24]. In this population, injecting drug users (IDU), history of blood products transfusion before 1992 and hospitalization with surgical procedures were identified as most common risk factors [25]. Since blood donors represent a strictly controlled group, it is expected that the HCV prevalence is lower than in the general population [26]. There are no published data on the HCV prevalence in the Croatian healthcare workers who have sustained contaminated needle stick injuries (occupationally exposed groups) [27].

Population group	Prevalence of HCV infection in Croatia
General population	<1%
Injecting drug users (IDUs)	40%
Prison populations	8–44%
Human immunodeficiency virus-infected patients	15%
Persons with high-risk sexual behavior	4.6%
Alcohol abusers	2.4%
Pregnant women	0.5–1.5%
Pregnant IDUs	40–50%
Hemodialysis patients	2.3–3.2%
Children and adolescents	0.3%
First-time blood donors	0.1%
Healthcare workers (occupationally exposed groups)	No published data

Table 1. Prevalence of HCV infection in Croatia in different population groups.

Prevalence of HCV genotypes in Croatia varies by different population groups and regions. The prevalence of genotypes in Croatian population is shown in **Table 2**. In the general population, genotype 1 is the most widely distributed, while genotype 3 is predominant among IDUs. The most commonly detected subtype is 1b and it is predominant in hemodialysis patients. In prison population, genotype 1 and 3 are equally distributed and similar

genotype distribution is found in groups with high-risk sexual behavior [28–31]. Similar pattern of genotype distribution is found in other European countries, where genotypes 1 and 3 also account for the majority of HCV infections with the most frequent subtype 1b [32]. The prevalence of genotype 4 is rising in Europe (in countries such as France, Germany, Greece, Italy, Poland, Portugal, Spain, Sweden, and Switzerland) due to immigration in these areas [33].

HCV genotype	Prevalence
Genotype 1	60.4–79.8%
Genotype 1, subtype 1b	41.6%
Genotype 3	12.9–47.9%
Genotype 3 (IDUs)	60.5–83.9%

Table 2. Prevalence of HCV genotypes in Croatia.

2. Indications for treatment in Europe and Croatia

Following new trends in the management of viral hepatitis, an expert panel held the first Croatian Consensus Conferences on Viral Hepatitis in 2005, and later in 2009 and 2013. With the development of new classes of direct-acting antiviral agents (DAAs) and interferon-free regimens, the landscape of HCV treatment has significantly changed. The European Association for the Study of the Liver (EASL) published its recommendations in 2015, with the latest update in September 2016, and the World Health Organization in May 2016 adopted the first-ever Global Health Sector Strategy on viral hepatitis with the longer-term aim to reduce new viral hepatitis infection by 90% by 2030. Management of HCV infection in Croatia is in accordance with the EASL Guidelines published in 2015, Croatian Guidelines (published by the Croatian Referral Centre for the Diagnostics and Treatment of Viral Hepatitis at University Hospital for Infectious diseases 'Dr. Fran Mihaljević' and updated in April 2016), and the recommendations of the Croatian Health Insurance Fund (HZZO) which covers the costs of treatment for all patients in accordance with the recommended guidelines. These recommendations are based on currently licensed drugs and updated regularly, following approval of new drug regimens.

There are some differences comparing EASL and Croatian Guidelines, which are listed as following. According to EASL Guidelines from 2015 and Croatian Guidelines, treatment should be prioritized (considered without delay) in patients with significant fibrosis or cirrhosis (METAVIR Score F3 or F4), including decompensated (Child-Pugh B or C) cirrhosis, in patients with clinically significant extra-hepatic manifestations, in patients with HCV recurrence after liver transplantation, and in HBV/HIV-coinfected patients (not in latest EASL Guidelines in 2016). Compared with EASL Guidelines, in Croatia, treatment is also prioritized in patients

before or after solid organ transplantation and justified for individuals at risk of transmitting HCV (IDU, men who have sex with men with high-risk sexual practices, women of child bearing age who wish to get pregnant, hemodialysis patients, and incarcerated patients); in EASL Guidelines, they are in prioritized category. In Croatia, treatment is justified in patients with moderate cirrhosis (METAVIR F2) and in patients with long disease duration (>20 years), regardless of fibrosis (not in EASL recommendations; indication of moderate cirrhosis was in previous EASL recommendations from 2015.). Treatment can be deferred in Croatian patients (not in EASL Guidelines) with no or mild disease (METAVIR Score F0 and F1) and in patients with none of the clinically significant extra-hepatic manifestations. The latest EASL recommendations from 2016 (not in Croatian Guidelines) say that treatment should be considered without delay in patients with significant fibrosis or cirrhosis (METAVIR score F2, F3, or F4), including decompensated (Child-Pugh B or C) cirrhosis, in patients with clinically significant extra-hepatic manifestations (e.g., symptomatic vasculitis associated with HCV-related mixed cryoglobulinemia, HCV immune complex-related nephropathy, and non-Hodgkin B cell lymphoma), in patients with HCV recurrence after liver transplantation, and in individuals at risk of transmitting HCV (active injection drug users, men who have sex with men with high-risk sexual practices, women of child-bearing age who wish to get pregnant, hemodialysis patients, and incarcerated individuals). In all recommendations, treatment is not recommended in patients with limited life expectancy due to non-liver-related comorbidities [34–38].

3. Therapeutic protocol

The goal of therapy is to cure HCV infection to prevent hepatic cirrhosis, decompensation of cirrhosis, hepatocellular carcinoma, severe extrahepatic manifestations, and death. The endpoint of therapy is undetectable HCV RNA in blood by a sensitive assay 12 weeks (SVR12—sustained virologic response) and/or 24 weeks (SVR24) after the end of treatment [37].

For decision-making related to therapies/drug selection, various factors are important: age, duration of infection, stage of fibrosis/cirrhosis, response to previous antiviral therapy, extrahepatic manifestations, comorbidities (HBV/HIV coinfection, autoimmune disease), concomitant therapy, genotype (1, 2, 3, 4), subgenotype (1a, 1b), HCV RNA viral load, presence of mutations that confer resistance to certain antiviral drugs and IL-28B genotype (CC, CT, TT) if interferon-based therapies are being considered.

With the introduction of the first two protease inhibitors (PI) in 2011, the new era of HCV therapy began. Boceprevir and telaprevir as the first-generation of oral direct-acting antiviral agents (DAAs) became available in Croatia in 2013, for the treatment of genotype 1 HCV patients who failed PegIFN and ribavirin therapy.

Croatia is a member of the European Union and all drugs registered by European Medicines Agency are also approved for use in Croatia. Available drugs for the treatment of HCV in Croatia (with costs covered directly by Croatian Health Insurance Fund—HZZO) in 2016 are: PegIFN, ribavirin, simeprevir, sofosbuvir, combination of ombitasvir + ritonavir-boosted

paritaprevir ± dasabuvir, and sofosbuvir + ledipasvir. In the European Union, there are some drugs that are not yet available in Croatia: velpatasvir, daclatasvir, grazoprevir, and elbatasvir.

Croatian Guidelines for the treatment are based on EASL and AASLD recommendations, but are somewhat more restrictive. For the treatment of naive patients with genotype 1 in 2016, it was still recommended to use the combination therapy with PegIFN and ribavirin (24–48 weeks) for patients with mild fibrosis and favorable predictors of response. For those patients with unfavorable predictors, if they achieve rapid virologic response (RVR), standard PegIFN and ribavirin combination is also recommended, otherwise a protease inhibitor (PI)—simeprevir or sofosbuvir should be added. In those with advanced fibrosis (F3), simeprevir or sofosbuvir should be added to PegIFN + ribavirin. Patients with significant (F4) fibrosis, who have contraindications to IFN therapy, presence of extrahepatic manifestations, HIV-coinfection or in transplanted patients, IFN-free regimens should be used for 12 weeks (ombitasvir, ritonavir-boosted paritaprevir, dasabuvir ± ribavirin; sofosbuvir and ledipasvir ± ribavirin; sofosbuvir and simeprevir ± ribavirin). For patients with decompensated cirrhosis, the combination of sofosbuvir and ledipasvir with or without ribavirin should be used, which is the same as recommended by the EASL and AASLD Guidelines. The main difference to EASL Guidelines is that, according to EASL, naive patients with or without compensated cirrhosis are treated with fixed-dose combination of sofosbuvir and ledipasvir without ribavirin.

For the treatment of experienced patients with genotype 1, triple combination of PegIFN, ribavirin, and a PI (simeprevir or sofosbuvir) is recommended in those with previous relapse or partial response (F1-F3 fibrosis). For nonresponders to PegIFN-ribavirin treatment (regardless of fibrosis) and for patients with F4 fibrosis (regardless of type of response), as well as for patients with TT IL-28B genotype, contraindications to IFN therapy, presence of extrahepatic manifestations, HIV-coinfection and transplanted patients, IFN-free regimens are offered (previously mentioned for treatment of naive patients). For patients with decompensated cirrhosis, the only treatment option currently available is the combination of sofosbuvir and ledipasvir with ribavirin for 12 weeks or without ribavirin for 24 weeks. This is also the only available option for patients previously treated with the triple combination of PegIFN + ribavirin + first-generation PIs (boceprevir or telaprevir) (in Croatia, there are only a few patients that have not responded to treatment with new-generation DAAs, as they have recently become available). According to EASL, experienced, DAA-naive patients with genotype 1b with or without compensated cirrhosis should be treated with fixed-dose combination of sofosbuvir and ledipasvir without ribavirin, and with ribavirin in those patients with genotype 1a. In EASL Guidelines, for the treatment of naive and experienced patients with genotype 1, there are two more options (not available in Croatia): fixed-dose combination of sofosbuvir and velpatasvir without ribavirin, ritonavir-boosted paritaprevir, ombitasvir and dasabuvir with or without ribavirin, grazoprevir and elbasvir with or without ribavirin, and sofosbuvir and daclatasvir with or without ribavirin.

For the treatment of patients with genotype 4, the same recommendations as for genotype 1 apply, with the exception of fixed combination of ombitasvir, paritaprevir, and ritonavir, which is used without dasabuvir. In patients with cirrhosis, duration of treatment is 24 weeks.

In EASL Guidelines, for the treatment of these patients, there are few more options available: sofosbuvir and velpatasvir without ribavirin, grazoprevir and elbasvir with or without ribavirin, and sofosbuvir and daclatasvir with or without ribavirin.

For the treatment of naive patients with genotype 2, with F1-F3 fibrosis, the use of standard combination treatment with PegIFN and ribavirin for 24 weeks is still recommended. Naive patients with F4 fibrosis, nonresponders (regardless of fibrosis), patients with contraindications to IFN therapy, with presence of extrahepatic manifestations, HIV-coinfection and transplanted patients are treated with combination of sofosbuvir and ribavirin (12 weeks without cirrhosis and 16–20 weeks with cirrhosis). In EASL recommendations, for the treatment of these patients there are two options: sofosbuvir and velpatasvir without ribavirin and sofosbuvir and daclatasvir without ribavirin.

For the treatment of naive patients with genotype 3, with F1-F3 fibrosis, it is still recommended to use PegIFN and ribavirin for 24 weeks. Naive patients with F4 fibrosis and nonresponders to PegIFN + ribavirin therapy (regardless of fibrosis) are treated with combination of sofosbuvir, PegIFN, and ribavirin for 12 weeks. Patients with F1-F3 fibrosis and with contraindication to IFN therapy are treated with combination of sofosbuvir and ribavirin for 24 weeks. Those patients with F4 fibrosis and with contraindication to IFN therapy are treated with combination of sofosbuvir and daclatasvir for 12 weeks or combination of sofosbuvir, ledipasvir, and ribavirin for 24 weeks. In EASL Guidelines, for treatment of naive and experienced patients there are two options: sofosbuvir and velpatasvir with or without ribavirin and sofosbuvir and daclatasvir with or without ribavirin [37, 38].

4. Croatian Health Insurance Fund (HZZO)—reimbursement requirements

Croatian Health Insurance Fund (HZZO) is covering over 99% of the population. HCV treatments are funded from a separate budget for expensive medicines [39]. HZZO has listed conditions that patients have to fulfill in order for HCV treatment to be covered from the before-mentioned fund: age between 18 and 70 years, HCV RNA positive, with a specified genotype, histologic evidence of chronic inflammation (biopsy finding) or fibroscan result larger than 8 kPa, and abstinence of IDU and significant alcohol consumption for the past 12 months. In patients with normal alanine aminotransferase (ALT) level, treatment is indicated with fibrosis F ≥ 2 or fibroscan finding >8 kPa. Patients who are IDUs need to have evidence of abstinence from illegal substances for at least one year and documented psychiatrist's finding and results of toxicology testing every 3 months during medical treatment. Treatment reimbursement requirements in Croatia include: specialist recommendation for treatment, Hospital's drug committee approval, and request for treatment sent to Expert committee for the treatment of hepatitis C of HZZO for final approval of treatment modality and duration (respect priorities among patients). All other Croatian patients with chronic hepatitis C (not fulfilling the above-mentioned requirements) can also be treated based on the judgment of the treating physician, but with a more restricted reimbursement options.

5. Conclusion

Regarding improvements in therapy and prevention, clinical care for patients with HCV in Croatia has advanced significantly during the past two years. Comparing epidemiology, indications for the treatment, available drugs, and therapeutic protocols, it is clear that Croatia accompanies European trends in HCV treatment. In future, rapid changes in the treatment of chronic HCV infection with the innovation of new drugs will lead to more effective, shorter treatment courses and PegIFN-free modalities.

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