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EFFICACY OF DIRECT-ACTING ANTIVIRAL THERAPY IN ACHIEVING SUSTAINED VIROLOGIC RESPONSE IN PATIENTS WITH CHRONIC HEPATITIS C

Aleksandar Ranković[1,2], Milica Ćosić-Petković[1,2], Maja Cvetanović[1,2], Jelena Spasić[1], Lidija Popović-Dragonjić[1,2], Nikola Milenković[1,2]

[1]University Clinical Center Niš, Clinic for Infectology, Niš, Serbia

[2]Faculty of Medicine, University of Niš, Niš, Serbia

Contact: Aleksandar Ranković

48 dr Zorana Djindjića Blvd. 18000, Niš, Serbia

E-mail: drarankovic@gmail.com

Chronic infection with the hepatitis C virus (HCV) represents a significant cause of chronic liver disease, with the potential for progression to cirrhosis and hepatocellular carcinoma. The introduction of direct-acting antiviral drugs (DAA) has enabled achieving high rates of virological cure, defined as a sustained virological response 12 weeks after the end of therapy (SVR12). The aim of this study was to assess the efficiency of DAA therapy in achieving SVR12 and its safety in patients with different clinical characteristics.

A retrospective analysis included 243 patients with confirmed chronic HCV infection who were treated at the Clinic for Infectious Diseases of the University Clinical Centre Niš from June 2022 to October 2025. Therapy was conducted with modern DAA regimens, with individual adjustments based on

patients' clinical and virological characteristics. Demographic, clinical, and laboratory parameters were analysed, with special emphasis on achieving SVR12 as the primary outcome.

A total of 243 patients were included (172 men, 71 women; mean age 51.7 ± 13.2 years). Genotype 3 was the most prevalent. Most patients had FIB-4 values between 1.45 and 3.25, while cirrhosis was present in 55 patients. SVR12 was assessed in 170 patients, with undetectable viremia achieved in 163 and persistent viremia in 7. In 69 patients, the follow-up period for SVR assessment has not yet elapsed, and 5 remain on treatment. No serious adverse events were observed.

DAA therapy showed high efficacy and a favourable safety profile in HCV infection, with high SVR rates.

Keywords: hepatitis C, DAA therapy, SVR12

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EFIKASNOST DIREKTNO DELUJUĆE ANTIVIRUSNE TERAPIJE U POSTIZANJU ODRŽIVOG VIROLOŠKOG ODGOVORA KOD PACIJENATA SA HRONIČNIM HEPATITISOM C

Aleksandar Ranković[1,2], Milica Ćosić-Petković[1,2], Maja Cvetanović[1,2], Jelena Spasić[1], Lidija Popović-Dragonjić[1,2], Nikola Milenković[1,2]

[1]Univerzitetski klinički centar Niš, Klinika za infektologiju, Niš, Srbija

[2]Univerztet u Nišu, Medicinski fakultet, Niš, Srbija

Kontakt: Aleksandar Ranković

Bulevar dr Zorana Đinđića 48, 18000 Niš, Srbija

E-mail: drarankovic@gmail.com

Hronična infekcija hepatitis C virusom (HCV) predstavlja značajan uzrok hronične bolesti jetre, sa potencijalom progresije ka cirozi i hepatocelularnom karcinomu. Uvođenje direktno delujućih antivirusnih lekova (DAA) omogućilo je postizanje visokih stopa virusološkog izlečenja, definisanog kao održivi viroloski odgovor 12 nedelja nakon završetka terapije (SVR12). Cilj ovog rada bio je da se proceni efikasnost DAA terapije u postizanju SVR12 i njena bezbednost kod pacijenata sa različitim kliničkim karakteristikama.

Retrospektivna analiza obuhvatila je 243 pacijenta sa potvrđenom hroničnom HCV infekcijom, lečenih na Klinici za infektologiju Univerzitetskog kliničkog centra Niš u periodu od juna 2022. do oktobra

2025. godine. Terapija je sprovođena primenom savremenih DAA režima, uz individualno prilagođavanje u skladu sa kliničkim i virusološkim karakteristikama pacijenata. Analizirani su demografski, klinički i laboratorijski parametri, sa posebnim osvrtom na postizanje SVR12 kao primarnog ishoda.

Od ukpunog broja pacijenata bilo je 172 muškarca i 71 žena, prosečne starosti 51,7±13,2 godine. U pogledu genotipske distribucije, genotip 3 bio je najčešći. Prema vrednostima FIB-4 skora, najveći broj pacijenata imalo je vrednost od 1,45–3,25, dok je ciroza jetre dijagnostikovana kod 55 pacijenata. Stabilan virusološki odgovor (SVR12) procenjen je kod 170 pacijenata. Negativan nalaz postignut je kod 163 pacijenta, dok je perzistentna viremija registrovana kod 7 ispitanika. Kod 69 pacijenata još uvek nije istekao predviđeni vremenski period za procenu SVR-a, dok je 5 pacijenata i dalje na terapiji. Tokom lečenja nisu zabeležene ozbiljne neželjene reakcije.

Primena DAA terapije pokazala je izuzetno visoku efikasnost i dobar bezbednosni profil u lečenju HCV infekcije, uz visoke stope SVR.

Ključne reči: hepatitis C, DAA terapija, SVR12

Introduction

Chronic hepatitis C virus (HCV) infection is one of the leading causes of chronic liver disease worldwide. The specificity of this infection is reflected in its often asymptomatic course, which is why many patients remain undiagnosed until advanced stages of the disease (1,2). Consequently, at the time of diagnosis, many patients already have structural liver changes that can affect therapeutic response.

Disease progression is the result of long-term viral replication and chronic inflammation, which leads to the development of fibrosis and then cirrhosis, with an increased risk of hepatocellular carcinoma (3,4). These changes directly affect the choice of therapy and the potential for achieving a sustained virological response, which is now considered the primary goal of treatment.

Earlier therapeutic approaches, based on interferon and ribavirin, were associated with limited success and significant side effects, which negatively affected overall treatment outcomes (5,6). The introduction of direct-acting antiviral drugs (DAAs) enabled targeted inhibition of viral replication and significantly improved therapy effectiveness (2,7).

In modern clinical practice, the success of therapy is defined as achieving a sustained virological response 12 weeks after the end of treatment (SVR12), a reliable indicator of permanent viral elimination and associated with reduced risk of disease progression and mortality (2,8,9). Precisely because of this, assessing the effectiveness of DAA therapy in achieving SVR12 is a central question in modern research on HCV infection.

Materials and methods

This study was a retrospective observational analysis aimed at evaluating the efficacy of direct-acting antiviral therapy in achieving sustained virologic response in patients with chronic HCV infection.

The research was carried out with the approval of the competent Ethical Committee of the UCC Niš (insert approval number) and in accordance with the principles of the Declaration of Helsinki. The data were processed anonymously, so respondents could not be identified.

The study included 243 patients with confirmed chronic HCV infection (positive HCV RNA), treated between June 2022 and October 2025. Inclusion criteria included DAA therapy and available treatment outcome data.

Before the start of the therapy, a diagnostic examination of the patients was carried out, which included standard biochemical analyses, complete blood count, coagulation screening, determination of the alpha-fetoprotein level, ultrasound examination of the abdomen, as well as assessment of the degree of liver fibrosis using a non-invasive marker (FIB-4) (10).

Virological evaluation included HCV RNA quantification by the PCR method and determination of virus genotype.

The demographic characteristics of the subjects, including gender and age, as well as the comorbidities present, were collected from medical records.

The selection of appropriate therapeutic regimens was made on the basis of genotyping results and the presence or absence of cirrhosis, in accordance with the guidelines of the European Association for Liver Diseases (EASL) (2).

Therapy was carried out using modern DAA regimens, including combinations of ofosbuvir/velpatasvir, glecaprevir/pibrentasvir and elbasvir/grazoprevir.

The primary outcome of the study was to achieve sustained virological response (SVR12), defined as the absence of detectable HCV RNA 12 weeks after the end of therapy. Secondary outcomes included assessment of therapy safety and analysis of changes in laboratory parameters.

Statistical software SPSS version 29.0 (SPSS, USA) was used for data processing. Quantitative variables are presented as means with standard deviation. Initial and final results were analysed using descriptive statistics.

The research was carried out in compliance with the legal regulations and the ethical standards, and was approved by the Ethics Board of the University Clinical Centre Nis, Republic of Serbia (No 16870/6).

Results

Characteristics of the examined patients

243 patients diagnosed with chronic HCV infection were analysed. Of the total number of patients, 172 men (70.8%) and 71 women (29.2%) had an average age of 51.7±13.2 years, with the predominant age group being 40–49 years (n=71; 29.5%) (Table 1).

Regarding genotypic distribution, genotype 3 was the most common, present in 83 patients (34.2%), followed by genotype 1a in 70 (28.8%), genotype 1b in 44 patients (18.1%), genotype 2 in 10 patients (4.1%) and genotype 4 in 7 patients (2.9%). The presence of two genotypes was determined in a smaller number of cases, including combinations 1b and 4 (n=10; 4.1%), 3 and 4 (n=1; 0.4%) and 1a and 1b (n=1; 0.4%), while in 17 patients (7.0%) the genotype was not determined (Table 1).

The FIB-4 index was calculated for all subjects, indicating different prevalences of fibrosis stages. According to FIB-4 score values, 78 patients (32.1%) had a value <1.45, 90 patients (37.0%) had a FIB-4 index of 1.45–3.25, while 75 patients (30.9%) had a FIB-4 >3.25. Of the total number of patients, 55 (22.6%) had liver cirrhosis (Table 1).

Examining the activity of the liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT), it was determined that the values were within the reference limits in 20.2% of patients. Elevated values, 2 to 10 times above reference values, were found in 79.4% of subjects, while in one patient (0.4%), markedly elevated enzyme activity was recorded (AST = 880 IU/L, ALT = 950 IU/L).

According to the comorbidity analysis, the most common patients with HCV infection also suffered from diabetes mellitus, followed by patients on hemodialysis and patients with hypothyroidism. Cardiovascular diseases were present in fewer patients, as was depression (Table 1).

Table 1. Characteristics of the examined patients

Variables	Patients (n=243)
Gender	
Male	172 (70.8%)
Female	71 (29.2%)
Age	51.7 ± 13.2
Genotype	
3	83 (34.2%)
1a	70 (28.8%)
1b	44 (18.1%)
2	10 (4.1%)
4	7 (2.9%)
1b i 4	10 (4.1%)
3 i 4	1 (0.4%)
1a i 1b	1 (0.4%)
Not p;ossible to establish	17 (7.0%)
FIB 4 score	
<1.45 1.45 - 3.25 >3.25	78 (32.1%)
<1.45 1.45 - 3.25 >3.25	90 (37.0%)
<1.45 1.45 - 3.25 >3.25	75 (30.9%)
Cirrhosis	55 (22.6%)

Antiviral therapeutic regimens

Patients were administered direct-acting antiviral (DAA) therapy in accordance with current guidelines. The largest number of patients were treated with the combination of glecaprevir/pibrentasvir 100 mg/40 mg, 3 tablets once daily, for 8 or 12 weeks, depending on genotype and the presence/absence of cirrhosis. The combination of sofosbuvir/velpatasvir 400 mg/100 mg once daily was administered to 85 patients, of whom 27 received ribavirin for 12 or 24 weeks. The remaining 33 patients were treated with elbasvir/grazoprevir 50 mg/100 mg once daily for 12 weeks (Table 2).

Table 2. Use of DAA therapeutic regimens and treatment duration

Therapy	Number of patients	Duration of therapy (weeks)
sofosbuvir/velpatasvir	77	12
sofosbuvir/velpatasvir	8	24
elbasvir/grazoprevir	33	12
glecaprevir/pibrentasvir	100	8
glecaprevir/pibrentasvir	24	12
glecaprevir/pibrentasvir	1	16

Treatment results

Stable virological response (SVR12) was assessed in 170 patients. A negative result was obtained in 163 (95.9%) patients, while persistent viremia was registered in 7 subjects (4.1%). All seven patients with persistent viremia did not have liver cirrhosis; three had genotype 3, three had genotype 1a, and one had genotype 1b. Regarding antiviral therapeutic regimens, persistent viremia was observed in three patients treated with sofosbuvir/velpatasvir, while four were treated with glecaprevir/pibrentasvir. Out of the total number of patients, 21 patients were on a hemodialysis program due to chronic renal failure. In 69 patients, the expected time period for SVR assessment has not yet expired, while 5 patients are still on therapy (Table 3).

Table 3. Results of treatment

Therapeutic regimens	Total number of patients	Negative HCV RNA	Positive HCV RNA
sofosbuvir/velpatasvir	51	48	3
elbasvir/grazoprevir	25	25	0
glecaprevir/pibrentasvir	94	90	4
SVR12	170	163 (95,9%)	7 (4,1%)

Note: For 69 patients, the waiting period for SVR assessment is still ongoing, while 5 patients were undergoing therapy at the time of analysis.

Adverse effects and safety evaluation of therapy

During antiviral therapy, a small number of adverse reactions were recorded. The most frequently reported symptoms were headache and fatigue, while a smaller number of patients reported nausea, vomiting, insomnia and dizziness. Observed adverse reactions were mild to moderate in intensity and transient in nature, and there was no need for hospitalisation or interruption of therapy in any patient. Also, there were no clinically significant interactions between drugs, as well as worsening of existing comorbidities during therapy. Based on the obtained results, the applied therapy showed a good safety profile and high tolerability.

Discussion

The results of our study on the effectiveness of DAA therapy in the treatment of HCV infection confirm significant progress in the therapeutic approach, achieved through the introduction of directly acting antiviral drugs, which have changed the previous therapeutic paradigm. In contrast to the earlier standard therapy based on interferon, which was accompanied by limited effectiveness, frequent side effects and long duration of treatment, the application of modern DAA therapeutic regimens enables a more effective therapeutic response, shorter duration of therapy and better tolerability, which represents a significant turning point in the treatment of HCV infection (11,12,13).

The high efficacy of DAA therapy was also confirmed by our study, with negative PCR for HCV RNA in 95.9% of patients and a good safety profile, consistent with available literature. Recent studies show that DAA therapy can achieve high sustained virological response (SVR12) rates, ranging from 90% to over 95%, and can be applied to patients at all stages of liver disease and with comorbidities, including the hemodialysis population (14, 15).

Statistically significantly higher HCV RNA positivity was observed in males compared with females after DAA therapy in the studied patients. The obtained results can be partly explained by the double representation of male subjects, which is related to their greater exposure to risk factors (16). In addition, biological differences between the sexes may partially explain this distribution, given that women are more likely to spontaneously clear the virus and less likely to develop chronic infection. Available literature data indicated that estrogen strengthens the antiviral immune response, with more pronounced T-lymphocyte activation in women, which can contribute to more effective control of viral replication and better treatment outcome in women, as demonstrated by our results (17,18).

The largest number of patients were infected with genotype 3, which could have contributed to the higher number of cases of persistent viremia after DAA therapy in this genotypic group. The epidemiological data from our study are consistent with the literature, showing a significant prevalence of genotype 3. According to Blach et al., HCV infection continues to represent an important global public health problem with significant prevalence of genotype 3 in Europe. Similar results were reported by Stameković et al., who found that the most represented genotypes, 1b and 3, in the Serbian population, and that there is a significant correlation between the distribution of genotype 3 and the age structure of the respondents (19.1). In addition to the highest epidemiological prevalence observed in our results, genotype 3 is also associated with a faster progression of fibrosis and the development of hepatic steatosis, which gives it clinical importance in the monitoring and treatment of patients (20,21).

At the moment of starting the therapy, an elevated activity of liver enzymes was observed in most patients, with the presence of a significant degree of fibrosis, which in some subjects was in the stage of liver cirrhosis. According to data from the World Health Organisation, most people with HCV infection remain undiagnosed, while due to the long-term asymptomatic course, the disease is often

detected in the later stages (22). In this context, the observed elevated ALT and AST levels in chronic hepatitis C can be explained by immune-mediated hepatocyte injury and persistent necroinflammatory activity in the liver parenchyma, leading to their release into the circulation (23). Our results showed that the effectiveness of DAA therapy and the occurrence of persistent HCV RNA were not correlated with initial laboratory parameters or the degree of liver damage, as confirmed by the absence of liver cirrhosis among patients with detectable HCV RNA.

On the other hand, the results of large cohort studies that included patients with advanced and decompensated liver disease treated for HCV infection indicate the existence of certain predictive factors of therapeutic response. In that population, the presence of ascites, hepatocellular carcinoma, lower albumin levels, and the use of proton pump inhibitors were identified as negative predictors of achieving SVR12 (24).

The literature indicates that DAA therapy failure may also be associated with viral resistance, with variants in the non-structural protein 5A (NS5A) playing a particularly significant role. Patients with genotype 3 are relatively more common among those with DAA therapy failure, and in selected cases, resistance testing can contribute to the optimisation of the therapeutic approach (21).

The best therapeutic response in our study was achieved with elbasvir/grazoprevir, as no patient with persistent viremia was observed in this group. This finding can be partially explained by the smaller number of patients treated with this therapy and by the selection of patients with HCV genotype 1b.

Persistent viremia was noted in patients who were treated with combinations of sofosbuvir/velpatasvir and glecaprevir/pibrentasvir, whereby the interpretation of these results must be taken with caution due to the possible lack of evidence of adherence and correct taking of therapy in individual patients, as well as a larger number of subjects in these therapeutic groups. Additionally, the reliability of the findings will be higher after completing the analysis of the remaining patients who still do not have sufficient time to assess SVR12.

The results of our study showed no statistically significant difference in treatment outcomes between patients with and without comorbidities. Such a result gives an advantage to modern DAA therapy, in

contrast to interferon therapy, which was limited by numerous contraindications, including decompensated cirrhosis, severe psychiatric, autoimmune diseases, and haematological disorders, which in the past further contributed to its limited clinical application in the treatment of HCV infection (7).

The most common comorbidities in the studied population were diabetes mellitus and hypothyroidism. This finding can be explained by the fact that chronic HCV infection, through its extrahepatic manifestations, can also affect the metabolic and endocrine systems, including the development of insulin resistance and thyroid dysfunction (25, 26). Namely, modern literature indicates that HCV is a systemic infection due to its ability to activate the immune system, disrupt metabolic processes, and induce autoimmune reactions, which contribute to the development of numerous extrahepatic manifestations. Zignego et al. additionally note that these mechanisms can be significant in the development of metabolic and endocrine disorders, which further explains the high frequency of these comorbidities in the studied population (27,28).

A significant improvement in the effectiveness of DAA therapy was also demonstrated in patients with HCV infection receiving hemodialysis (29). Hemodialysis is a known risk factor for HCV transmission, as consistently confirmed by numerous studies and clinical guidelines (30,31). In our trial, all hemodialysis patients achieved SVR, further indicating the high efficacy and favourable safety profile of contemporary DAA regimens, even in this high-risk population.

Thanks to the high efficacy of DAA therapy, a relatively small number of patients with positive HCV RNA results were identified. To better evaluate patients with persistent viremia after DAA therapy, additional studies with a larger sample are needed to yield more relevant conclusions.

Conclusion

DAA therapy has demonstrated extremely high efficacy and a favourable safety profile in the treatment of HCV infection, with high SVR rates. The therapy's success did not depend on initial laboratory parameters or the presence of comorbidities, including patients on hemodialysis. DAA therapy represents a turning point in the treatment of chronic HCV infection, showing high superiority

compared to previous therapeutic regimens. Therefore, evaluating its clinical effect remains an important area of future research.

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