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EFFICACY OF DIRECT-ACTING ANTIVIRAL THERAPY IN THE TREATMENT OF CHRONIC HEPATITIS C IN HEMODIALYSIS PATIENTS

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Chronic hepatitis C virus (HCV) infection is highly prevalent among patients on hemodialysis. It leads to the deterioration of renal function and progressive liver disease, significantly increasing overall mortality.

The aim of this study was to evaluate the efficacy and safety of direct-acting antiviral (DAA) therapy in hemodialysis patients who suffer from chronic hepatitis C.

This retrospective observational study enrolled 23 patients with chronic hepatitis C who were treated on an outpatient basis at the Clinic for Infectious Diseases, University Clinical Center of Niš, between June 2022 and April 2025, and have chronic kidney failure with necessity for hemodialysis. Therapeutic regimens were selected according to the European Association for the Study of the Liver (EASL) guidelines. Sustained virologic response (SVR12) was defined as undetectable serum HCV RNA 12 weeks after completion of treatment. The primary efficacy endpoint was the determination of SVR12. We also esimated changes in laboratory parameters and the occurrence of adverse reactions. Statistical analysis was performed using SPSS 29.0 software.

Of the total number of patients, 17 were male and 6 were female, with a mean age 57.83 ± 9.30. Genotype 1a was confirmed in 8 patients, 1b in 3, and genotype 3 in 5, while the genotype could not be determined in 7 patients. Two patients discontinued therapy on their own initiative due to nausea; the remaining 21 completed the full treatment cycle. The SVR12 rate was **100%** regardless of the therapeutic regimen used. No serious adverse reactions were recorded.

DAA therapy in hemodialysis patients with chronic HCV infection is highly effective and safe.

Keywords: chronic hepatitis C, direct-acting antiviral therapy, hemodialysis

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EFIKASNOST DIREKTNO DELUJUĆE ANTIVIRUSNE TERAPIJE U LEČENJU HRONIČNOG HEPATITISA C KOD PACIJENATA NA HEMODIJALIZI

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Hronična hepatitis C virusna infekcija je vrlo česta kod pacijenata na hemodijalizi i uzrokuje pogoršanje bubrežne funkcije i bolesti jetre povećavajući ukupnu smrtnost.

Cilj ovog istraživanja je procena efikasnosti i sigurnosti primene antivirusne terapije koja deluje direktno (engl. *direct-acting antiviral – (DAA) therapy*) kod pacijenata na hemodijalizi sa hroničnom hepatitis C virusnom infekcijom.

U ovom retrospektivnom opservacionom ispitivanju analizirana su 23 pacijenta sa hroničnim hepatitisom C koji su ambulantno lečeni na Klinici za infektologiju Unuverzitetskog kliničkog centra Niš, u periodu od juna 2022. do aprila 2025., koji imaju hronično bubrežno oštećenje i zahtevaju hemodijalizu. Odgovarajući

terapijski režimi su odabrani u skladu sa smernicama Evropskog udruženja za bolesti jetre. Stabilan virusološki odgovor je definisan kao nedetektabilna HCV RNK u serumu bolesnika 12 nedelja (SVR12) nakon završetka lečenja. Primarna krajnja tačka efikasnosti terapije bila je određivanje SVR12. Procenjene su i promene laboratorijskih parametara, kao i pojava neželjenih reakcija tokom lečenja. Za statističku analizu korišćen je softver SPSS 29.0 (SPSS, SAD).

Od ukpunog broja pacijenata bilo je 17 muškog i 9 ženskog pola, prosečne starosti 57.83 ± 9.30 godina. Dokazano je prisustvo genotipa 1a kod 8 pacijenata, 1b kod 3 pacijenta, genotipa 3 kod 5 pacijenata, dok kod njih 7 nije bilo moguće utvrditi genotip. Od svih ispitanika dva pacijenta su samoinicijativno prekinula terapiju zbog izražene mučnine, dok su preostala 21 ispitanika završila lečenje prema predviđenom planu.

Stopa SVR12 iznosila je 100% bez obzira na vrstu primenjenog terapijskog režima. Tokom lečenja nisu zabeležene ozbiljne neželjene reakcije.

Primena DAA terapije kod pacijenata na hemodijalizi sa hroničnom HCV infekcijom je visoko efikasna i bezbedna.

Ključne reči: hronični hepatitis C, antivirusna terapija koja deluje direktno, hemodijaliza

Introduction

Hepatitis C virus (HCV) infection is a significant global public health challenge, with an estimated prevalence of approximately 0.7% at the beginning of 2020 (1). Serbia is considered as an area of moderate prevalence (2). The consequences of HCV infection are numerous. Acute infection is asymptomatic in 80% of cases and in a large percentage, 50–90%, turns into a chronic form. Long-term evolution leads to liver cirrhosis and the development of hepatocellular carcinoma (3,4).

Patients with chronic kidney disease (CKD) are particularly susceptible to HCV infection due to treatment modalities such as hemodialysis (HD) and kidney transplantation (5). The prevalence of HCV in HD patients varies across regions, likely reflecting the level of medical care and local economic conditions. In 2004, the Dialysis Outcomes and Practice Patterns Study (DOPPS) indicated that 13.5% of HD cases were complicated by HCV (6). Specific risk factors include the duration of HD, younger age, diabetes mellitus, history of blood transfusions, and dialyzer reuse (7). In this population of patients, HCV increases the risk of transmission and worsens both renal and liver function, significantly raising mortality rates (8,9). Therefore, timely antiviral intervention is essential.

The usage of direct-acting antivirals (DAAs) and multidisciplinary collaboration between infectious disease specialists and nephrologists offers a path toward eradicating HCV within dialysis units (10). Therefore, this trial aims to evaluate the efficacy of DAA therapy in hemodialysis patients with chronic HCV infection.

Material and methods

Patients

The study enrolled 23 patients with chronic hepatitis C treated as outpatients at the Clinic for Infectious Diseases, University Clinical Center Niš, between June 2022 and April 2025., who were undergoing hemodialysis for end-stage kidney disease. The study followed the Declaration of Helsinki and was approved by the Ethics Committee of UKC Niš (No. 31217/2025). Chronic HCV infection was defined as anti-HCV antibody positivity and detectable serum HCV RNA (COBAS HCV test, detection limit 15 IU/ml) maintained for over 6 months (11). Exclusion criteria included decompensated cirrhosis (Child-Pugh B/C) and HBV or HIV co-infection.

Data collection

Demographic data, including gender and age, HCV RNA levels, genotype and comorbidities were collected from medical records. Baseline assessments included routine biochemistry, blood count, coagulation screening, alpha-fetoprotein level, abdominal ultrasound finding and the FIB-4 non-invasive fibrosis marker before initiating the therapy (12). Appropriate therapeutic regimens were selected according to genotype results, the presence or absence of cirrhosis, and the European Association for the Study of the Liver (EASL) guidelines (13).

Treatment outcome and statistical methods

Sustained virologic response (SVR12) was defined as undetectable serum HCV RNA 12 weeks after completion of treatment. The primary eficasy endpoint was SVR12. Safety was assessed by the proportion of patients discontinuing treatment due to adverse drug reactions; in addition, the safety of DAA therapy was assessed through the presence/absence of drug-related adverse reactions. Analysis was performed using SPSS 29.0. Quantitative variables were expressed as mean and standard deviation. Baseline and final data were summarized with descriptive statistics. The t-test for dependent samples was used to compare laboratory parameters before and after therapy, with significance set at $p < 0.05$.

Results

Baseline characteristics

Twentythree hemodialysis patients diagnosed with chronic HCV infection were analyzed. Of the 23 patients, 17 were male and 6 were female, with a mean age 57.83 ± 9.30. The presence of genotype 1a was confirmed in 8 patients, 1b in 3 patients, genotype 3 in 5 patients, while it was not possible to determine the genotype in 7 of them. The mean baseline viral load HCV RNA was 5.43 ± 1.16 (log10HCV RNA) (Table 1).

Table 1. Characteristics of the studied patients

Variables	Patients (n=23)
Gender	
Male	17 (73.9%)
Female	9 (39.1%)
Age	57.83 ± 9.30
Genotype	
1a	8 (34.78%)
1b	3 (13.04%)
3	5 (21.74%)
it is not possible to determine	7 (30.44%)
Average viral load PCR HCV RNA (log10 IU/ml)	5.43 ± 1.16
Previously treated HCV infection	3 (13.04%)
Kidney transplantation	4 (17.39%)
Cirrhosis	5 (21.74%)
Comorbidities (SAH, DM, CVD, COPD, SLE)	15 (65.22%)

Four patients with a history of kidney transplantation had failed kidney graft and required hemodialysis. 15 cases were simultaneously complicated by systemic arterial hypertension (SAH), diabetes mellitus (DM), cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD) and systemic lupus erythematosus (SLE). Three patients had previously failed interferon/ribavirin therapy in which treatment was discontinued due to significant adverse effects, with no HCV RNA negativity. The remaining 20 patients were not previously treated. Five patients had cirrhosis (Table 1).

Therapeutic regimens

Three patients (GT 1b) received elbasvir/grazoprevir 50/100mg, once daily for 12 weeks. The remaining twenty patients received glecaprevir/pibrentasvir 100/40mg, once daily, three tablets at the time, for 8 or 12 weeks depending on the genotype and the presence/absence of cirrhosis (15 patients for 8 weeks, 5 patients for 12 weeks).

Treatment outcomes

Among all patients, two patients stopped the therapy on their own initiative due to pronounced nausea that they associated with taking the therapy and were not motivated to continue the treatment. The remaining subjects, 21 of them, completed the treatment cycle according to the plan. The HCV RNA level was retested 12 weeks after the end of treatment and all patients had undetectable viremia, achieving a 100% SVR12 rate (Table 2).

Table 2. SVR in patients who completed treatment

Therapy	Number of patients	SVR rate
Elbasvir/grazoprevir	3	3 (100%)
Glecaprevir/pibrentasvir		
8 week	13	13 (100%)
12 week	5	5 (100%)
Total	**21**	**21 (100%)**

Changes in laboratory parameters

In order to evaluate the biochemical response to DAA therapy, laboratory parameters were analyzed before and after therapy in 21 patients who completed the therapy. The mean values of transaminases (aspartate aminotransferase (AST) and alanine aminotransferase (ALT)), hemoglobin (Hgb), platelet count (Plt) and total bilirubin before and after treatment are shown in Table 3.

Table 3. Comparison of laboratory parameters before and after treatment

Variables	Mean value ± SD		P < 0.05
	Pre	Posle	
AST (IU/ml)	33.28±26.62	19.90±4.89	0.028
ALT (IU/ml)	38.05±23.70	18.19±5.29	0.000
Hgb (g/L)	111.81±11.71	115.14±11.07	0.405
Plt (10^9/L)	158±54.45	193.28±94.49	0.065
Bulurubin (µmol/L)	12.22±5.92	8.45±2.05	0.031

Transaminase values were elevated at the beginning of treatment in 6 patients. After the end of treatment, improvement in liver enzymes was recorded in all patients. A statistically significant improvement in liver

function after usage of DAA therapy was recorded: **AST (**before: 34.24 ± 26.32 IU/L; after: 19.90 ± 4.89 IU/L; P = 0.028) and **ALT** (before: 40.71 ± 22.73 IU/L; after: 18.19 ± 5.29 IU/L; P = 0.000). A statistically significant decrease in total bilirubin was also found (before: 12.48 ± 7.33 µmol/L; after: 8.45 ± 2.05 µmol/L; P = 0.031), which further confirms the positive therapeutic response.

No significant changes were found for hemoglobin or platelets count (Hgb: P = 0.405; Plt: P = 0.065), although an increasing trend was observed for platelets after therapy. None of the patients experienced worsening of renal function after treatment.

Safety

Side effects were recorded from the beginning to the end of treatment and their possible conestion with DAA drugs was assessed. During the treatment 2 patients had nausea, 1 had itching of the skin of the hands, 1 patient complained of drowsiness and lack of concentration. Symptoms were mostly mild to moderate; the planned treatment was carried out in full. Only two patients discontinued treatment on their own due to severe nausea. During treatment, there were no serious adverse reactions, no need for hospitalization, drug-drug interactions with concomitant therapy that patients were taking due to existing comorbidities. Also there were no patient losses during follow-up or death (Table 4).

Table 4. Adverse effects during treatment with DAA therapy

Side effects	Patients, n(%) N=23
Discontinuation of therapy	2 (8.69)
Side effects	4 (17.39)
nausea	2 (8.69)
itching	1 (4.35)
drowsiness, lack of concentration	1 (4.35)
Serious adverse reactions	0
Drug-drug interaction	0
Hospitalization	0
Loss of tracking	0
Fatal outcome	0

Discussion

DAA therapy is a milestone in HCV management, both epidemiological and clinical. Its efficacy, short duration of treatment and minimal side effects have revolutionized outcomes, enabling high cure rates and reducing viral transmission within the population (14,15). Previous interferon-based regimens for the treatment of HCV infection, due to their toxicity and serious side effects, have limited their use in patients with end-stage renal disease (16). Low SVR rates of 33%–37% and discontinuation rates of 17%–30% further limited its applicability (17). Interferon therapy after kidney transplantation was contraindicated due to the risk of acute organ rejection (immune stimulation), which led nephrologists to delay or avoid HCV treatment. The modern approach, however, suggests the use of DAA therapeutic regimens, which are safe, while older methods (interferon+ribavirin) raised fears of relapse and graft dysfunction (18). Given the strong evidence showing worse outcomes in patients with CKD and HCV infection, and the high efficacy and tolerability of DAA therapy, HCV treatment should be a priority in these patients. DAA drugs effectively inhibit HCV replication by targeting NS3/4A protease, NS5B RNA polymerase, and NS5A protein. According to EASL guidelines, interferon-free oral regimens are the first-line therapy for patients with chronic hepatitis C and kidney damage. Treatment recommendations for patients with mild to moderate renal impairment, with an eGFR ≥30 mL/min/1.7 m2, do not differ from those for general population and do not require dose adjustments for any of the approved DAA regimens (13).

This paper presents our experience in the use of DAA therapy in patients with chronic hepatitis C and chronic renal failure undergoing hemodialysis. Our results indicate that the use of this therapy in hemodialysis patients with chronic HCV infection is highly effective and safe. Our findings confirm that these regimens are highly effective in the HD population, aligning with a prospective from 2023 showing high SVR12 even in patients with multiple comorbidities (19).

Most DAAs used in our study (elbasvir, grazoprevir, glecaprevir, pibrentasvir) are not renally excreted, eliminating the need for dose adjustment in HD patients (20). Suda et al. showed SVR rate for the elbasvir/grazoprevir regimen of 96.7% (22/23), (21) while the SVR12 in 3 patients treated with this regimen was 100% in our study. In the study conducted by Gane et al. the efficasy of the glecaprevir/pibrentasvir-based treatment, the SVR 12, was 98% (22).

Sofosbuvir (SOF) is the first in its class of NS5B polymerase inhibitors to be introduced and has revolutionized the treatment of HCV. In vivo, SOF undergoes intrahepatic metabolism to form a pharmacologically active metabolite, an analogue of uridine triphosphate, which is further dephosphorylated to form the final metabolite. SOF and its metabolites are mainly excreted by the kidneys, with 72% of elimination (23).

Initially the use of SOF was approached with caution in patients with CKD and it was thought to be associated with serious side effects, worsening renal function, and higher rates of anemia (24). The guidelines for the treatment of hepatitis C published by the European Association for the Study of Liver Diseases suggest that SOF should be used with a caution in patients with severe renal impairment and eGFR < 30 ml/min/1.7 m2, without a clear recommended dose (13). Despite early concerns about the accumulation of SOF and its active metabolite (25), numerous "real-world" data now suggest it is also safe and effective in hemodialysis patients (26), with sustained SVR ranging from 88% to 96% (27). Other analyses indicate remarkably low rates of renal injury in patients treated with SOF-based DAA therapy (28,29). According to a meta-analysis of observational studies (30 studies, n = 1537 patients) conducted by Fabrizi et al., the overall SVR12 rate was 99% and this meta-analysis demonstrated excellent efficacy of SOF-based therapy in patients with end-stage renal disease. The tolerance of SOF was also satisfactory in this population - serious adverse events and treatment discontinuations were rare (30).

The main limitation of our study is the small sample size, necessitating further research with larger cohorts. It is necessary to evaluate the efficacy and safety of DAA treatment protocols containing SOF. Also, the use of different liver function tests should be considered to further assess the toxicity of DAA therapy, which requires further research.

Conclusion

DAA therapy is well tolerated and highly effective in patients on hemodialysis. The results of our study showed that the use of DAA pangenotypic regimens glecaprevir/pibrentasvir and elbasvir/grazoprevir is safe and has excellent efficacy, with an SVR12 rate of as much as 100%. Strategies for eliminating HCV from dialysis units should consider DAA treatment as a preventive measure along with improving standard precautions to prevent nosocomial HCV infection. Integrating DAA treatment with standard infection control is a viable strategy for the micro-elimination of HCV within dialysis units, contributing to the global goal of eradicating HCV infection.

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