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Safety and Efficacy of Direct-acting Antiviral Therapies for Chronic HCV Infection in Hemodialysis Patients

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Abstract. *Background/Aim: The aim of this study was to determine the safety and efficacy of a direct-acting antiviral treatment, ombitasvir/paritaprevir/ritonavir and dasabuvir, without ribavirin, in a real-life setting. Patients and Methods: We performed a prospective observational study including 108 patients undergoing hemodialysis for end-stage kidney disease, referred to our clinic for antiviral therapy for chronic hepatitis C virus infection. Patients received treatment with ombitasvir/paritaprevir/ritonavir and dasabuvir, for 12 weeks. Sustained virologic response (SVR) was defined as undetectable viremia at 12 weeks after the end of therapy. For safety analysis, we monitored serum levels of hemoglobin, albumin, total bilirubin, alanine-aminotransferase and aspartate- aminotransferase at the beginning and end of therapy, as well as at SVR. Verbal Numeric Rating Scale was used to assess the presence of nausea, headaches and fatigue. Results: We noted a high prevalence of diabetic and hypertensive nephropathy as the underlying cause of chronic kidney disease. Most of the patients had F2 and F3 liver fibrosis (32.40% and 34.25%, respectively). The SVR rate was 96.2% (103/107 patients). We recorded an unrelated death after the completion of antiviral therapy. We found increased levels of nausea, headaches and fatigue at the end of therapy compared to at initiation, The presence and degree of symptoms did not correlate with the underlying cause of renal disease (p=0.72) nor with the degree of fibrosis (p=0.08). Minimal increases in transaminases and bilirubin were recorded at the end of treatment, with no statistical significance. Conclusion: Oral antiviral therapy with ombitasvir/paritaprevir/ritonavir and dasabuvir can be safely used in hemodialysis patients, with similar response rates compared to the general population.*

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Hepatitis C virus (HCV) infection is a major cause of mortality and morbidity both in the general population and in the population represented by patients in hemodialysis programs. The latter have an increased risk of developing many complications, and thus represent the main target for the eradication of HCV infection. Hemodialysis in supporting patients with end-stage renal disease unfortunately carries a risk for hepatitis C infection. The incidence of HCV infection among hemodialysis patients is higher compared to the general population in Europe, with variations between different regions of the continent; for example, in Romania both the incidence and the prevalence of the infection are still at an increased rate in chronic hemodialysis patients (1).

There is currently a wide range of therapeutic resources against HCV, represented by interferon-free, direct-acting antiviral (DAA) regimens including the daclatasvir plus asunaprevir dual regimen, ledipasvir/sofosbuvir combination, ombitasvir/paritaprevir/ritonavir combination, elbasvir plus grazoprevir dual regimen, and glecaprevir/pibrentasvir combination. Current European guidelines recommend the use of DAAs as early as possible in all patients with active HCV

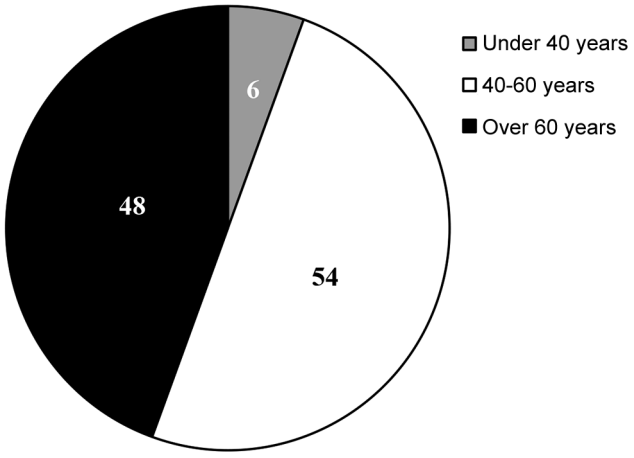

Figure 1. *Age distribution in the study group.*

Table I. *Baseline characteristics of the study group (N=108).*

Characteristic	Value
Sex, n (%)	
Male	60 (55.55%)
Female	48 (44.44%)
Age, years	
Mean±standard deviation	57.13±8.8
Underlying condition for chronic kidney disease, n (%)	
Diabetes mellitus	48 (44.44%)
Arterial hypertension	37 (34.25%)
Chronic pyelonephritis	12 (11.11%)
Nephrolithiasis	6 (5.55%)
Polycystic kidney	2 (1.85%)
Autoimmune disorders	3 (2.77%)
Duration of hemodialysis, years	
Mean±standard deviation	4.3±2.5
HCV-RNA, IU/ml	
Mean±standard deviation	223.361
Degree of liver fibrosis	
F0	9 (8.33%)
F1	22 (20.37%)
F2	35 (32.40%)
F3	37 (34.25%)
F4	5 (4.62%)

infection, regardless of the degree of liver fibrosis, either with genotype-specific or pan-genotypic regimens (2). DAA treatment in patients undergoing hemodialysis imposes specific problems, such as the use of nephrotoxic agents or antiviral clearance through dialysis (3). Recent studies have shown a lower complication rate in the use of DAA therapy compared to interferon therapy in patients enrolled in hemodialysis programs (4-6). However, ledipasvir–sofosbuvir therapy cannot be used in hemodialysis patients because sofosbuvir is contraindicated in patients with an estimated rate of glomerular filtration below 30 ml/min/1.73 m^2 (7). Current therapeutic regimens available for hemodialysis patients include grazoprevir–elbasvir, paritaprevir–ritonavir–ombitasvir with or without dasabuvir, simeprevir, and daclatasvir, as well as glecaprevir–pibrentasvir (8). A clinical trial reported sustained virological response rates of up to 99%, without significant clinical or hematological adverse reactions (9). The aim of our trial was to determine the safety and efficacy of a DAA, ombitasvir/paritaprevir/ritonavir and dasabuvir, without ribavirin, in a real-life setting.

Patients and Methods

We performed a prospective observational study including patients undergoing hemodialysis for end-stage kidney disease, referred to our clinic for antiviral therapy for chronic HCV infection. The study was performed during January 2017-January 2020. All patients were treated according to current national guidelines and signed informed consent forms regarding the use of their personal data for medical and scientific purposes under the condition of anonymization.

The inclusion criteria were: Active HCV infection (defined as detectable HCV-RNA in plasma), chronic hemodialysis performed for end-stage kidney disease, and willingness to sign informed consent. We excluded patients with hepatitis B virus or human immunodeficiency virus co-infection, decompensated cirrhosis, solid or hematological malignancies, acute kidney injury requiring hemodialysis, and those with severe comorbidities imposing a high mortality risk at 6 months. A total of 108 patients were included in the study.

Patients received treatment with ombitasvir, paritaprevir, ritonavir and dasabuvir for a duration of 12 weeks. The treatment was administered at normal dosages [12.5/75/50 mg (2 pills) per day in a single administration and 250 mg administered twice a day, respectively]. The patients were scheduled for dialysis as early in the day as possible, so that they could administer the antiviral medication after the procedure.

Data analyzed were age, sex, etiology of kidney disease, years of dialysis, degree of liver fibrosis [estimated by Fibroscan® (10)] and level of HCV viremia. Sustained virological response (SVR) was defined as undetectable viremia at 12 weeks after the end of therapy. For safety analysis, we monitored serum levels of hemoglobin, albumin, total bilirubin, alanine-aminotransferase and aspartate- aminotransferase at the beginning and end of therapy, as well as at SVR. Furthermore, the Verbal Numeric Rating Scale was used to assess the presence of nausea, headaches and fatigue, as the most common adverse reactions encountered during antiviral therapy. This scale uses numbers from 0 to 10 to describe the intensity of symptoms, where 0 means lack of symptoms and 10 means the highest intensity imaginable by the patient (11).

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA).

Results

The study group included 48 women (44.44%) and 60 men (55.55%), with a mean age and standard deviation of 57.13±8.8 years. We noted a preponderance of patients over 40 years old, as shown in Figure 1.

Table II. *Presence and levels of frequent symptoms from direct-acting antiviral (DAA) therapy in the study group.*

	At DAA initiation (N=108)		At end of DAA therapy (N=108)			At SVR (N=107)		
Symptom	Patients, n	Mean VNRS	Patients, n	Mean VNRS	*p*-Value	Patients, n	Mean VNRS	*p*-Value
Nausea	59	2.2	84	5.8	<0.01	42	2.1	0.03
Headache	37	2.4	62	3.5	0.02	41	2.6	0.04
Fatigue	72	3.3	102	5.9	0.01	69	3.4	0.04

SVR: Sustained virological response; VNRS: Verbal Numeric Rating Scale.

Table III. *Evolution of mean biological parameters from direct-acting antiviral (DAA) initiation to sustained virological response (SVR).*

Parameter	Normal level	Initiation of DAA therapy	End of DAA therapy	SVR
ALT, IU/ml	0-45	55.4	57.2	43.2
AST, IU/ml	0-35	31.2	37.1	29.5
Total bilirubin, mg/dl	0.2-1.2	0.75	1.13	0.87
Serum albumin, g/dl	3.5-5	3.76	3.28	3.45
Hemoglobin, g/dl	12-17	10.8	10.2	9.4

ALT: Alanine aminotransferase; AST: aspartate aminotransferase.

The baseline characteristics of the study group are presented in Table I. We noted a high prevalence of diabetic and hypertensive nephropathy as the underlying cause of chronic kidney disease. On the other hand, patients under 40 years old had a history of autoimmune disease or polycystic kidney disease; one patient had type 1 diabetes mellitus and also a history of renal transplant reject. Most of the patients had F2 and F3 liver fibrosis (32.40% and 34.25%, respectively), indicative of a prolonged liver disease.

Efficacy of DAA therapy. In order to evaluate the efficacy of DAA therapy, we determined HCV RNA at 12 weeks after the end of therapy. One patient died before reaching the scheduled determination and therefore he was excluded from this analysis. The SVR rate recorded was 96.2% (103/107 patients). The remaining four patients had detectable HCV viremia at SVR: two patients with higher levels than at initiation and two patients with lower levels. These patients were in the 50-59 years age group (one patient) and 60-69 years age group (three patients). All had advanced fibrosis (F3). The underlying renal disease was diabetic nephropathy in two patients, arterial hypertension in one and nephrolithiasis in one.

Safety of DAA therapy. The most frequent adverse events were nausea, headache and fatigue. As these are common in hemodialysis patients, we compared the levels indicated by the patients at initiation of therapy, at the end of therapy and at SVR. Patients' complaints were assessed by Verbal Numeric Rating Scale (11). The results, presented in Table II, show increased levels at the end of therapy compared to at initiation, levels which normalized at SVR. The presence and degree of symptoms did not correlate with the underlying cause of renal disease (p=0.72) nor with the degree of fibrosis (p=0.08).

We recorded one death between the end of treatment and SVR, in a 73-year-old male who developed an infection of the arteriovenous fistula, complicated with septicemia and septic shock.

We also evaluated the levels of alanine aminotransferase, aspartate aminotransferase, total bilirubin, albumin and hemoglobin at each time point. We found a minimal increase in levels of transaminases and bilirubin at the end of treatment, with no statistical significance. There was no difference in the serum levels of albumin or hemoglobin. At initiation, 80.55% of patients presented mild anemia, while 18.51% presented moderate anemia. At the end of treatment, 90.74% of patients presented mild anemia and 9.26% presented moderate anemia. Fourteen patients required blood transfusions for correction of hemoglobin level during therapy. Notably, all the patients maintained erythropoietin therapy during antiviral therapy. Table III depicts the evolution of the mean values of biological parameters during the time frame studied.

Discussion

Our study showed a high rate of SVR in hemodialysis patients undergoing DAA treatment with ombitasvir, paritaprevir, ritonavir and dasabuvir (96.2%; 103 out of 107 patients). In the RUBY II clinical trial developed for this

therapy in dialysis patients, the SVR rate was only 92% (12 out of 13 treated patients) (12). Our study included only patients with genotype 1b, as this is the prevalent genotype in Romania. Another trial evaluating glecaprevir and pibrentasvir in patients with end-stage renal disease found an SVR rate of 98%. This trial also reported an unrelated death shortly after treatment completion, so the virologicaI response could not be evaluated (13).

We found a higher prevalence of HCV in male patients undergoing hemodialysis compared to females. This is opposed to the prevalence in the general population (14). A possible explanation for this would appear to be the higher prevalence of end-stage kidney disease in male patients, due to the rapid deterioration of renal function (15).

The SVR rates reported in literature are similar for the general HCV population and dialysis patients. In the case of treatment with ombitasvir, paritaprevir, ritonavir and dasabuvir, SVR rates reported in clinical trials ranged from 91% to 100%, depending on the degree of fibrosis and HCV genotype (16-18). In a large, real-life trial in Spain, SVR rates in patients with chronic kidney disease were 86.7% in patients with stage IIIB, 95% in patients with stage IV and 93% in patient with stage V (19). There were 10 reported non-SVR, one of which was classified as virological failure.

Our trial found an increased number of patients complaining of nausea, fatigue and headache during therapy as compared to at baseline or 12 weeks after therapy. None of the patients discontinued therapy due to adverse reactions. These data are consistent with the pivot RUBY II trial for patients with chronic kidney disease, which reported mild and moderate adverse reactions (12). None of the patients in our study received ribavirin, therefore anemia was attributed to the presence of end-stage kidney disease. Unlike RUBY II, we report the requirement for blood transfusions in 14 patients during DAA therapy. A possible explanation for this may be the higher number of elderly patients, with cardiovascular comorbidities, in whom maintaining hemoglobin levels over 9 g/dl is indicated.

A common complication of DAA therapy is the temporary elevation of transaminases and bilirubin at the beginning of therapy, with later normalization (20). In our study, we report mild increases in transaminases as well as bilirubin, without statistical significance.

The importance of HCV cure in hemodialysis patients has two dimensions: Avoidance of progression of liver disease and its complications on the one hand, and ensuring optimal conditions for a potential kidney transplant on the other (8). A recent study evaluated the impact of HCV on liver inflammation by demonstrating increased alpha-fetoprotein levels in HCV-infected patients in the absence of hepatocellular carcinoma (21). Regarding alpha-fetoprotein in dialysis patients, it has been shown that levels do not increase with uremia but in fact decrease after dialysis sessions, thus raising questions of interpretation regarding its value as a tumor marker in patients with end-stage kidney disease (22).

In conclusion, our study shows that ombitasvir, paritaprevir and ritonavir combined with dasabuvir is a safe and efficient antiviral therapy in hemodialysis patients. The SVR rate in real life is consistent with those presented in literature (96.2%), and consistent with data from the general population. Dialysis patients are more prone to developing adverse reactions, most frequently nausea, headache and fatigue, but these are easily manageable and do not require treatment discontinuation.

Conflicts of Interest

None.

Authors' Contributions

All Authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by GD, MI, MD, TI, AT and ANS. The first draft of the article was written by LT, AZ, LI, LM and AMS and all Authors commented on previous versions of the article. All Authors read and approved the final article. The final editing was performed by LI, LM and MI.

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