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Original Article

Direct Acting Antiviral Treatment for Patients with End-Stage Kidney Disease with Acute HCV Infection

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Abstract. Background: Hepatitis C virus (HCV) infection is a public health problem. Such an infection is prevalent and aggressive in patients with end-stage kidney disease (ESKD). The efficacy and the safety of direct-acting antivirus (DAA) in patients with acute HCV and ESKD are under investigation. The aim of this study was to assess the safety and efficacy of sofosbuvir-containing regimens in this difficult-to-treat population.
Methods: A prospective and observational study was conducted to evaluate the efficacy and the safety of sofosbuvir containing regimen in patients with ESKD who were undergoing haemodialysis and were acutely infected with HCV. Subjects either received sofosbuvir 200 mg and daclatasvir 60 mg daily or sofosbuvir 400mg/ledipasvir 60mg daily for 12 weeks.
Results: 19 Patients were recruited in this study who were infected with HCV genotype 1a. All subjects achieved a sustained virologic response (SVR) twelve weeks after finishing the treatment course. No significant adverse effects were reported, and the treatment course was well tolerated.
Conclusions: sofosbuvir-containing regimens were effective and safe for the treatment of acute HCV in patients with ESKD who were on haemodialysis.

Keywords: Acute HCV, ESKD, ESRD, DAA, Sofosbuvir.

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Introduction. Infection with HCV is a major public health issue with more than 70 million infected people around the world.[1] The death toll for such a disease is more than 350,000 annually mainly due to the complications of infection such as liver cirrhosis, hepatic failure and hepatocellular carcinoma.[1]

The carcinogenesis of HCV is not fully understood.[2] Although it is well known that HCV increases the risk of cancer through a complex molecular pathway that involves an inflammatory process, it is controversial that HCV plays a direct role in the development of liver cancer.[2] Additionally, specific HCV genotypes are associated with a higher risk of hepatocellular carcinoma. In a study conducted in the USA, HCV genotype 3 was shown to be associated with a higher risk of cancer.[3] In addition, a study conducted in Italy showed a significantly higher rate of HCV 1b infection in patients with hepatocellular carcinoma.[4,5]

Risk factors for HCV infections vary from a country to another. Unsafe healthcare practice was the main cause of the spreading of this disease in 2000.[1] The next mode of the transmission in the low and middle-income countries is blood and blood products transfusion due to the lack of blood donor screening.[1] Additionally, the venous injection in drug abusers is a leading cause of the spread of the virus in both developing and developed countries. Patients with ESKD are at higher risk of HCV infection.[1,6] Although the spread of the virus in hemodialysis units is declining, the prevalence of HCV in such patients is

still high.[7] Previous studies showed that the prevalence of anti-HCV antibody positivity among subjects with ESKD and on regular hemodialysis ranged from 5% to 60%.[7] In a study conducted in Iraq, 5% of patients who were on dialysis were HCV positive.[8] Acute HCV infection is defined as the occurrence of its manifestation within six months of exposure.[9] It can be defined as the presence of a positive HCV RNA with a concurrent negative anti-HCV antibody level or a positive anti-HCV antibody level after a prior negative anti-HCV antibody within the previous six months,[9,10] With the availability of DAA medications, the mainstream approach of treatment has shifted obtaining a high sustained virologic response.[11] Previously, interferon was used for the treatment of acute HCV in some circumstances with significant side effects.[12] Otherwise, the treatment with DAA is associated with minor side effects and higher cure rates.[11] Studies investigating the effectiveness of DAA in acute HCV are limited and with small sample size. In one study, 20 patients were recruited, and the sustained viral response (SVR) was achieved in all patients.[9] One study was conducted to investigate the effectiveness of DAA in patients with acute HCV and ESKD. Thirty-three patients, who were infected with HCV genotype 1b and 2a were enrolled and were given treatment for 24 weeks.[13] SVR was achieved in all patients without significant side effects.[13] This study aimed to investigate the safety and efficacy of 12 weeks sofosbuvir-containing regimens in patients with ESKD who were infected with acute HCV genotype 1a.

Methods. *Patients and treatment*. In December 2017, an outbreak of HCV occurred in the dialysis unit in Zakho city. In this dialysis unit, 40 ESKD patients were receiving regular hemodialysis. Once the outbreak was established, the unit was closed, and all patients were closely monitored for six months by HCV-antibodies testing plus HCV real-time PCR (RT-PCR). Patients diagnosed with HCV were directed to the infectious disease unit in Azadi teaching hospital. Acute HCV infection was defined as a positive HCV RT-PCR test in the setting of a concurrent negative HCV-antibodies results or a positive HCV-antibodies result after a prior negative result of HCV-antibodies within the past six months. We recruited patients with the following criteria: patients with ESKD requiring hemodialysis, positive for HCV RNA for less than six months and older than 18 years old. Patients with acute renal failure were excluded.

ELISA and Biochemical tests. The HCV-antibody, hepatitis B surface antigen (HBsAg) and hepatitis B core IgG (HBcAb) and HIV Ab&Ag were investigated by ELISA kit (DIA.PRO diagnostic Bioprobes, Italy) following the manufacturer's instruction. The detection of HCV and HIV was with a sensitivity (100%) and specificity (100%), while the sensitivity and specificity of the test for HBsAg were respectively 100% and 97.5%, according to the manufacturer.

ALT, AST and serum albumin were measured by Cobas chemistry analyzer (Roche). INR was estimated by START4 semiautomated system (STAGO).

Table 1. Patients' characteristics, biochemical test, ultrasound results, and treatment course used for treatment

Patients	Gender	Age	S. Creatinine mg/dl	INR	S Albumin g/dl	ALT IU/L	AST IU/L	Genotype	U/S of liver	City	Treatment Course
Patient 1	F	58	6	1.2	4.2	130	80	1a	Normal	Zakho	Sofo400/Ledipasvir90
Patient 2	M	66	8	1.3	4.26	14	29	1a	Normal	Zakho	Sofo200/Daclas 60
Patient 3	F	45	9.9	1.01	4.3	240	103	1a	Normal	Zakho	Sofo200/Daclas 60
Patient 4	F	60	5	1.37	3.25	83	103	1a	Normal	Zakho	Sofo200/Daclas 60
Patient 5	M	27	9	1.37	3.04	45	33	1a	Normal	Zakho	Sofo200/Daclas 60
Patient 6	F	50	8	1.39	3.54	97	128	1a	Normal	Zakho	Sofo200/Daclas 60
Patient 7	M	61	6	1.16	3.8	202	249	1a	Normal	Zakho	Sofo200/Daclas 60
Patient 8	M	60	5	0.79	3.9	70	77	1a	Normal	Zakho	Sofo200/Daclas 60
Patient 9	M	38	8	1.33	3.55	184	169	1a	Normal	Zakho	Sofo200/Daclas 60
Patient 10	F	63	10.4	1.03	3.1	441	156	1a	Normal	Zakho	Sofo200/Daclas 60
Patient 11	F	47	6	1.06	4.4	33	41	1a	Normal	Duhok	Sofo200/Daclas 60
Patient 12	F	68	11	1.1	4.36	29	14	1a	Normal	Zakho	Sofo200/Daclas 60
Patient 13	M	75	6	1.17	3.7	103	65	1a	Normal	Zakho	Sofo400/Ledipasvir90
Patient 14	F	60	7	1.17	3.7	34	52	1a	Normal	Zakho	Sofo200/Daclas 60
Patient 15	F	37	8	1.1	4.8	35	17	1a	Normal	Zakho	Sofo200/Daclas 60
Patient 16	M	38	8	1	3.7	480	400	1a	Normal	Zakho	Sofo200/Daclas 60
Patient 17	M	70	2.8	1.1	3.18	28	19	1a	Normal	Zakho	Sofo200/Daclas 60
Patient 18	M	68	5	1	3.88	76	64	1a	Normal	Zakho	Sofo200/Daclas 60
Patient 19	M	50	11	1	4.13	6	12	1a	Normal	Zakho	Sofo200/Daclas 60

HCV quantification and genotyping. In this study, the quantification of HCV was performed using Xpert HCV quantification assay (Cepheid, Sunnyvale, California, the USA). Fresh samples were kept at 4°C and tested within seventy-two hours after the collection. One ml was added to a test cartridge, which was loaded into a GeneXpert instrument. The linear range of the Xpert HCV assay is 10 IU/ml to 10^8 IU/ml. Results were reported as follows: HCV present (with the associated quantitation reported in IU per milliliter), or HCV was absent. All positive samples were genotyped by reverse hybridization (NLM, Milan, Italy).

Results. *Patients*. During the period between December 2017 and March 2018, 19 patients were involved in the outbreak and were referred to our unit. Amongst those, 12 were male and the average age of the patients was 54.8±13.6 years (**Table 1**). All patients involved in the outbreak were infected with HCV genotype 1a. Additionally, all patients were negative for HIV and HBsAg. All patients recruited in this study were treatment naive. The investigation of the outbreak in the center showed that the mode of transmission was an inappropriate medical procedure.

Treatment efficacy. The primary end-point of this project was to investigate the proportion of subjects who achieved SVR, which was defined as negative HCV RT-PCR at twelve weeks after treatment. In our study, 17 patients received a half dose of sofosbuvir (200 mg daily) after dialysis and a full dose of daclatasvir (60 mg daily) for 12 weeks. Two patients received sofosbuvir 400mg/ledipasvir 90mg fixed dose. The duration of treatment was for 12 weeks. The viral load became undetected in 16/19 (84.2%) patients after four weeks of treatment (**Table 2**). Sustained virologic response was achieved in all patients.

Safety outcomes. All subjects completed treatment the 12 weeks course and were followed up for the following 12 weeks. The treatment course of acute HCV in ESKD was well tolerated. During the study period, the most frequently reported adverse effects were fatigue, anorexia, headache and dizziness.

Discussion. International guidelines do not provide an insight on how to choose the regimen, timing, and duration of therapy for acute HCV. Additionally, no useful guidance is provided for specific cases such as patients with ESKD. Substantial uncertainty exists regarding the optimal treatment regimen and duration of DDA in acute hepatitis. The 2016 American Association for the Study of Liver Diseases (AASLD)–Infectious Diseases Society of America (IDSA) guidelines suggested "the same regimens for acute HCV as recommended for chronic HCV infection … owing to high efficacy and safety", whereas the 2016 European Association for the Study of the Liver (EASL) guidelines recommended sofosbuvir–ledipasvir, sofosbuvir–velpatasvir or sofosbuvir plus daclatasvir for 8 weeks in acute HCV infection, with a

Table 2. Virological response to antiviral treatment

Patients	Viral Load (RTPCR) IU/mL			
	Before Treatment	4 weeks after treatment	End of treatment	12 weeks after stopping treatment
Patient 1	7870 IU/mL	undetected	undetected	undetected
Patient 2	165000 IU/mL	undetected	undetected	undetected
Patient 3	606 IU/mL	undetected	undetected	undetected
Patient 4	757000 IU/mL	less than 10 IU/mL	undetected	undetected
Patient 5	30300 IU/mL	less than 10 IU/mL	undetected	undetected
Patient 6	25600 IU/mL	less than 10 IU/mL	undetected	undetected
Patient 7	2820000 IU/mL	undetected	undetected	undetected
Patient 8	4450000 IU/mL	undetected	undetected	undetected
Patient 9	2990000 IU/mL	undetected	undetected	undetected
Patient 10	244000 IU/mL	undetected	undetected	undetected
Patient 11	527439 IU/mL	undetected	undetected	undetected
Patient 12	540 IU/mL	undetected	undetected	undetected
Patient 13	7160000 IU/mL	undetected	undetected	undetected
Patient 14	2200000 IU/mL	undetected	undetected	undetected
Patient 15	7980 IU/mL	undetected	undetected	undetected
Patient 16	4450000 IU/mL	undetected	undetected	undetected
Patient 17	13000000 IU/mL	undetected	undetected	undetected
Patient 18	21400 IU/mL	undetected	undetected	undetected
Patient 19	490000 IU/mL	undetected	undetected	undetected

longer duration of 12 weeks recommended for those infected with HIV and/or baseline HCV RNA levels >1,000,000 IU/ml.[15] So, current international recommendations for the treatment of acute HCV infection are controversial, and the treatment of acute HCV infection could elaborate according the circumstances, taking into account the baseline HCV RNA titres, the HCV co-infections and the pre and on-treatment viral kinetics.[15] The available studies of the treatment of acute HCV infection support the use of sofosbuvir plus ledipasvir for eight to twelve weeks. Infection with HCV and its related complications are associated with a significant rate of morbidity and mortality in patients with ESKD, due to extrahepatic manifestations and especially to a glomerular involvement.[16] One of the renal complications related to HCV infection is membranoproliferative glomerulonephritis with or without cryoglobulinemia.[16] Additionally, previous studies showed an association between HCV infection and membranous nephropathy, focal segmental glomerulosclerosis, fibrillary or immunotactoid glomerulopathies, and thrombotic microangiopathy.[16] Early treatment of HCV may prevent such complications and play a significant role in a long-term comprehensive plan to eliminate the infection by preventing the transmission in high risk groups such as patients on regular dialysis.

DAA medications have revolutionized the treatment of HCV infection. However, no data are available on their effectiveness and safety in treating ESKD patients with acute HCV. Our findings showed that a 12 weeks treatment course with an interferon-free DAA resulted in a sustained virologic response 12 weeks after treatment in all patients with acute HCV genotype 1a plus ESKD patients. The treatment course was not associated with serious side effects related to the medications. The treatment course was associated with rapid decline in the HCV-RNA levels in our patients. In our study, cephid Xpert was used for HCV-RNA detection. In three patients, the level of RNA was detectable but not quantifiable. This was not associated with prior RNA levels. In a previous study recruiting patients with acute HCV and EDKD recruiting patients with HCV genotypes 1b and 2, all patients achieved SVR after receiving a course of treatment for 24 weeks.[13] This is the first study about the treatment of acute HCV in ESKD patients using 12 weeks course. Our findings are important for treatment plan as indicate economic advantage by using half the dose of expensive sofosbuvir, shorter period (12 weeks) and are important for public health as HCV infection can be treated successfully and hence prevent further spread of such an infection. The small sample size must not negate the importance of the study as it showed promising results for the treatment of infection and the prevention of further cases. The main challenge in treating acute HCV is the diagnosis of such cases as the vast majority of cases pass unnoticed. Our study has limitations. We acknowledge that our study was not randomized and the analysis was based upon the per-protocol population. However, we believe that randomized project was considered to be extremely difficult when dealing with such a public health problem.

Conclusions. In conclusion, DAA containing sofosbuvir were suitable for the treatment of acute HCV infection in patient with ESKD without major adverse events.

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