



High rate of acute kidney injury in patients with chronic kidney disease and hepatitis C virus genotype 4 treated with direct-acting antiviral agents

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Abstract

Background Direct-acting antivirals (DAAs) have significantly improved the efficacy and safety of treating chronic hepatitis C (CHC), but their effectiveness and safety among patients with chronic kidney disease (CKD) remains poorly understood. Sofosbuvir/daclatasvir regimen is supposed to be used for patients with creatinine clearance more than 30 mL/min, while ombitasvir/paritaprevir/ritonavir regimen is used for patients with creatinine clearance less than 30 mL/min.

Aim The aim of the study was to assess the safety and efficacy of DAAs among patients with CKD.

Methods Eighteen CKD stage 2–3b patients received sofosbuvir for 3 months. In addition, 42 CKD stage-4 patients received ritonavir-boosted paritaprevir plus ombitasvir for 3 months. Finally, ribavirin was added for 30 of them.

Results The patients' age was 49.2 ± 12 years. Baseline serum creatinine was 3.76 ± 1.67 mg/dL. Fifty patients were HCV genotype 4. A 3-month sustained viral response was achieved in 56 patients and 49 patients achieved a 6-month viral response. There were 11 relapsers. Acute kidney injury (AKI) upon CKD (AKI/CKD) occurred in 28 patients, of which 20 needed hemodialysis. Fifteen/28 recovered from AKI, whereas 13 were maintained on hemodialysis. In multivariate analysis, there were only two independent risk factors for developing AKI/CKD, i.e., being cirrhotic as defined by baseline abdominal ultrasound findings [odds ratio 4.15 (1.33–12.97); $p=0.013$] and having had as DAA therapy OMV/PTV/RTV [odds ratio 7.35 (1.84–29.35); $p=0.001$].

Conclusion Treatment of HCV among stage 2, 3a, and 3b patients was achieved safely with a sofosbuvir-based regimen. We recommend that stage-4 patients wait until starting hemodialysis or transplantation.

Keywords Chronic kidney disease · HCV infection · Sofosbuvir · Daclatasvir · Acute renal failure · DAA therapy

Lionel Rostaing and Mohamed Adel Bakr contributed equally to this work.

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Introduction

Hepatitis C virus (HCV) infection is a recognized public health concern with global implications: it affects approximately 170 million individuals worldwide. Infection with HCV is associated with increased morbidity and mortality secondary to hepatic injury and associated complications [1]. The prevalence of hepatitis C virus (HCV) infection in Egypt is the highest in the world [2].

HCV infection is highly prevalent in chronic kidney disease (CKD) patients. HCV-infected patients have an increased risk for developing CKD and proteinuria. Furthermore, emerging data suggest that the rate of CKD progression to end-stage kidney disease (ESKD) is greater than for non-HCV-infected patients [3–5].

Sparse information exists on the treatment of patients with earlier stages of CKD where CKD progression could be slowed with HCV treatment and/or eradication. Although some guidelines propose universal treatment, others only still recommend this for high-priority groups [6].

The use of conventional alpha-interferon-based therapies in patients with advanced CKD has been associated with low efficacy and high toxicity [7].

In this context, HCV-infected patients with CKD stages 1 [glomerular filtration rate (GFR) > 90 mL/min per 1.73 m²], 2 (GFR 60–89 mL/min per 1.73 m²), and 3a (GFR 45–59 mL/min per 1.73 m²) should be considered to receive direct-acting antivirals (DAA), with the goal of slowing the progression of CKD. HCV-infected patients with CKD stages 3b (GFR 30–44 mL/min per 1.73 m²), 4 (GFR 15–29 mL/min per 1.73 m²), and 5 (GFR < 15 mL/min per 1.73 m²) require a more individualized approach. For stages 4 and 5 the timing of HCV treatment depends mostly on the renal-replacement therapy options being considered. The major decision point in this context is whether treatment should be recommended before or after kidney transplantation [8].

Patients with a living kidney donor should be treated to achieve a sustained viral response (SVR) prior to transplantation. For a patient who is going to receive a deceased-donor kidney, the options may include delaying antiviral treatment to receive a kidney from an anti-HCV-positive donor with the initiation of DAA treatment at post-transplantation [9]. Alternatively, patients could be treated at pre-transplant and then receive a transplant kidney from an anti-HCV-negative donor. Because not all centers currently accept kidneys from anti-HCV-positive donors, this option is not available for all patients. Initial reports have demonstrated that accepting a kidney from a positive donor is associated with a substantially shortened waiting time on the deceased donor waiting list in the USA [10, 11].

As sofosbuvir and its metabolites (GS-331007) are excreted by the kidney, available data do not support its use when GFRs are < 30 mL/min [12, 13]. Recently, the FDA has approved ombitasvir/paritaprevir/ritonavir plus dasabuvir (OBV/PTV/r + DSV) for the treatment of patients with severe renal disease, as the metabolism of these compounds is mediated predominantly by the liver [14].

Therapy with OBV/PTV/r + DSV ± ribavirin (RBV) is currently approved for the treatment of patients infected with HCV genotype (GT) 1, based on the results of several clinical trials in which the SVR at week 12 (SVR12) reached 95–100% [15, 16]. A regimen without dasabuvir (OBV/PTV/r) is indicated to treat HCV GT4, with a 91–100% sustained viral response within 12 weeks with RBV-free and RBV-containing combinations of treatment-naïve and treatment-experienced patients [17].

The aim of this prospective study was to assess in a real-life setting the safety and efficacy of two different DAA

regimens among Egyptian HCV patients with different stages of CKD.

Patients and methods

This was an observational, prospective, single-center pilot study. That study was approved by the Zagazig University IRB and registered on the following number: #2491-8-12-2015. As of January 2017, 3640 patients with CKD have been followed up in the Mansoura Urology and Nephrology Center outpatient clinics at Mansoura University, Egypt. Patients with unstable kidney function visit the OPC more frequently than stable patients. Exclusion criteria for this study were patients with stage-5 CKD, CKD patients with progressively increasing serum creatinine, patients aged < 18 years, patients with a malignancy, patients with cirrhosis (as defined by liver ultrasound) and patients with clinically decompensated liver disease. Thus, 2236 CKD patients were evaluated to be enrolled in this study. They were screened for HCV antibodies at the start of follow-up (1340) by using the immunoassay [ARCHITECT set (ABOTT; USA)].

A total of 532 of the 2236 (23.8%) CKD patients were HCV-antibody positive. Hepatitis C virus RNA PCR was performed using the HCV RNA TaqMan Real Time PCR test (Ampiprep/COBAS TaqMan 48 set; Roche). A value of < 15 IU/L was considered negative. HCV-positive PCR results were obtained from 412 of the 532 patients (77.4%); therefore, these patients were eligible to start receiving DAAs. Sixty patients were enrolled in this study as a pilot study.

Prior to treatment, laboratory investigations included assessing serum creatinine and 24-h urine creatinine clearance to determine CKD stage, liver function tests (aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transpeptidase), serum albumin, lipid profile, complete blood counts (hemoglobin level, platelet and white cell counts), antinuclear autoantibody (ANA), and alpha-fetoprotein for all patients. Also, pelvi-abdominal ultrasound and a liver and spleen ultrasound were performed.

The medications which were prescribed to the patients were checked for drug interaction with DAAs using Liverpool Hep-drug interaction site (<https://www.hep-druginteractions.org/>). 5 patients were receiving carbamazepine, 2 patients were on phenytoin, 2 patients were on apixaban, and 32 patients received calcium channel blockers for controlling hypertension. Therefore, these medications were stopped before initiating DAA therapy and were accordingly replaced by drugs that had no interaction with DAAs. Also, drugs known to cause AKI (angiotensin receptor blockers, angiotensin convertase enzyme inhibitors, non-steroidal anti-inflammatory drugs, proton pump inhibitors,

aminoglycosides, vancomycin, etc.) were suspended during DAAs treatment course. Hypertensive patients were controlled by atenolol and alpha-methyl dopa.

Treatment plan: CKD patients with measured creatinine clearance (crcl) > 30 mL/min/1.73 m² received a sofosbuvir-based regimen with or without ribavirin; patients with crcl of < 30 mL/min/1.73 m² received ritonavir-boosted paritaprevir/ombitasvir ± ribavirin (RTV/PTV/OMV). The type of treatment was chosen according to hepatology EASL guidelines, 2015. Ribavirin was added when baseline hemoglobin level was > 10 g/dL; the dose of ribavirin was adjusted according to crcl (patients with crcl > 50 mL/min received 1200 mg, those with crcl 20–49 mL/min received alternating dose: 200 and 400 mg every other day). During the HCV treatment period, ribavirin was stopped when hemoglobin level became < 8.5 g/dL, or when a white blood cell count was < 2500/mm³, or when a platelet count was < 100,000/mm³. DAA treatment duration was 3 months.

During and after treatment, kidney function was assessed at 2 weeks after starting treatment and then monthly. Liver function tests and a complete blood picture were monitored monthly. An HCV RNA PCR test was done prior to treatment, at 4 weeks after starting treatment and at 1, 3, 6, 12 months after completing treatment. A rise in serum creatinine of > 0.3 mg/dL within 48 h or 1.5 times the baseline within seven consecutive days in condition that baseline eGFR was < 60 mL/min/1.73 m² was indicative of acute kidney injury on top of CKD (A/CKD) [18]: it indicated suspension or cessation of treatment.

Statistical analysis

All data were tabulated in SPSS sheet V21. Descriptive analysis was used for demographic data and baseline characteristics. Chi-square test was used for comparing nominal and order data among both groups and Student's test was used for comparing continuous data. Repeated measures ANOVA test was used to compare laboratory investigations at different time points. Univariate (analysis of covariance) and multivariate (logistic regression) analyses were used to estimate odds ratio for risk factors. Different risk factors for relapse and acute kidney injury were evaluated using univariate analysis (crosstabs, square test) with calculation of odds ratio. Factors with odds ratio more than 1 were included in multivariate analysis using binary logistic regression test.

Results

Baseline data

Sixty patients with CKD were enrolled in this study. Table 1 illustrates the baseline characteristics of the included

Table 1 Demographics and baseline characteristics of the studied groups

Baseline characteristics	Chronic kidney disease patients No. (%)
Age (mean ± SD)	49.17 ± 12.067
Gender	
Male	41 (68.3)
Female	19 (31.7)
Body mass index (mean ± SD)	23.8 ± 1.07
Experienced treatment with interferon	8 (13.3)
Hypertension	31 (51.66)
Diabetes mellitus	19 (31.66)
Hepatitis B co-infection	1 (1.6)
Fibroscan	
F0	13 (21.67)
F1	23 (38.33)
F2	20 (35)
F3	4 (5)
CHILD score	
A	43 (71.67)
B	12 (20)
C	5 (8.33)
Liver ultrascan	
Normal	32 (53.33)
Enlarged	23 (38.33)
Cirrhotic	5 (8.33)
Spleen ultrascan	
Normal	23 (38.33)
Mild enlargement	32 (53.33)
Moderate enlargement	3 (5)
Marked enlargement	2 (3.33)
Hepatitis C genotype	
1	6 (10)
4	54 (90)
HCV RNA PCR (IU/L) (mean ± SD)	427655 ± 12,436
ALT (IU/L) (mean ± SD)	39.05 ± 19.3
Bilirubin (mg/dL) (mean ± SD)	0.5 ± 0.19
Albumin (g/dL) (mean ± SD)	3.53 ± 0.23
Hemoglobin (g/dL) (mean ± SD)	10.08 ± 1.5
Platelets (10 ³ /mm ³) (mean ± SD)	228.8 ± 106.3
Serum creatinine (mg/dL) (mean ± SD)	3.76 ± 1.67
Measured creatinine clearance (mL/min/1.73 m ²) (mean ± SD)	29.75 ± 14.06

PCR polymerized chain reaction, ALT alanine aminotransaminase, SD standard deviation

patients. One patient was co-infected with hepatitis B virus and he received lamivudine for 12 months and thereafter became HBV DNA negative. Mean baseline serum creatinine for all patients was 3.76 ± 1.67 mg/dL and measured creatinine clearance was 29.75 ± 14.06 mL/min (Table 1).

A sofosbuvir + daclatasvir (SOF/DAC) regimen was prescribed for 18 patients (mean serum creatinine: 3.7 ± 1.6 mg/dL) with a measured creatinine clearance of 47.83 ± 11.8 (> 30 mL/min/1.73 m²); in addition, 10 of them (55.5%) received ribavirin. An ombitasvir/paritaprevir/ritonavir (OMV/PTV/RTV) regimen was given to 42 patients (mean serum creatinine: 6.3 ± 2.8 mg/dL) with measured creatinine clearance of 22 ± 4.6 (< 30 mL/min/1.73 m²); in addition, 20 of them (47.6%) were given ribavirin. Ribavirin was only added when baseline hemoglobin level was > 10 g/dL.

Baseline characteristics of both groups were compared in Table 2 which showed no statistically significant difference regarding all variables. However, there was a significant difference regarding baseline renal function between the groups: in those that received OMV/PTV/RTV, measured creatinine clearance was 22 ± 4.7 mL/min/1.73 m², whereas measured creatinine clearance in those receiving SOF/DAC was 47.8 ± 11.7 mL/min/1.73 m² ($p = 0.0001$).

Efficacy

A rapid virological response (month one after starting DAA therapy) was achieved in all patients from both groups (see Table 3). An SVR at 12 weeks (SVR-12) was achieved in 56 patients, i.e., in 77.8% of patients who received SOF/DAC compared to 100% of patients who received OMV/

PTV/RTV ($p = 0.0063$) and at 24 weeks (SVR-24) for 49 patients, i.e., in 77.8% of patients who received SOF/DAC compared to 83.3% of patients who received OMV/PTV/RTV ($p = ns$) (see Table 3). However, the mean time on DAA therapy was 88.66 ± 1.03 days in SOF/DAC patients and 86.33 ± 1.27 days in OMV/PTV/RTV patients as treatment was suspended for some time due to rise in serum creatinine.

Eleven patients had a relapse: 4 within 3 months after treatment cessation and 7 beyond 3 months after the end of therapy. Out of them five needed hemodialysis while on DAA therapy and two were maintained on permanent hemodialysis after DAA therapy was finished, but as HCV PCR was negative for all patients until 1 month after completing the treatment course, the chance of being re-infected from the dialysis unit, i.e., nosocomial transmission was present in two patients only.

All relapsers were genotype 4. Seven were receiving the 3-month ritonavir-boosted regimen and four were receiving the 3-month sofosbuvir-based regimen. They all received full doses of the prescribed drugs. In addition, six patients received ribavirin for 4 weeks and stopped it thereafter due to hemoglobin drop from 9.94 ± 1.9 to 8.7 ± 0.54 g/dL ($p = 0.009$). Figure 1 illustrates the time of relapse. Two relapses occurred in patients who received previously IFN- α and showed relapse after a complete

Table 2 Demographics and baseline characteristics among the ombitasvir/paritaprevir/ritonavir (OMV/PTV/RTV) group and sofosbuvir/daclatasvir (SOF/DAC) group

	OMV/PTV/RTV group (42 patients) No. (%)	SOF/DAC group (18 patients) No. (%)	<i>p</i> value
Age (mean \pm SD)	48.047 \pm 11.8	51.78 \pm 12.6	0.276
Gender			
Male	19 (45.24)	12 (66.67)	0.83
Female	13 (30.95)	6 (33.33)	
Body mass index (mean \pm SD)	23.2 \pm 1.6	23.15 \pm 1.4	0.73
Experienced treatment with interferon	5 (11.9)	2 (11.11)	0.93
Hypertension	22 (53.38)	9 (50)	0.86
Diabetes mellitus	11 (26.19)	8 (44.44)	0.16
Hepatitis B co-infection	1 (2.38)	0	
HCV RNA PCR (IU/L) (mean \pm SD)	254,700 \pm 70,870	831,100 \pm 15,820	0.06
ALT (IU/L) (mean \pm SD)	36.60 \pm 22.62	44.78 \pm 16.41	0.17
Bilirubin (mg/dL) (mean \pm SD)	0.46 \pm 0.24	0.55 \pm 0.129	0.53
Albumin (g/dL) (mean \pm SD)	3.40 \pm 0.15	3.30 \pm 0.12	0.52
Hemoglobin (g/dL) (mean \pm SD)	10.04 \pm 1.36	10.19 \pm 1.87	0.72
Platelets (10 ³ /mm ³) (mean \pm SD)	224.82 \pm 147.4	239.75 \pm 47.7	0.84
Serum creatinine (mg/dL) (mean \pm SD)	4.64 \pm 1.18	1.73 \pm 0.28	0.0001
Measured creatinine clearance (mL/min/1.73 m ²) (mean \pm SD)	22 \pm 4.7	47.83 \pm 11.7	0.0001
Genotype			
1	6 (14.29)	0	0.165
4	36 (85.71)	18 (100)	

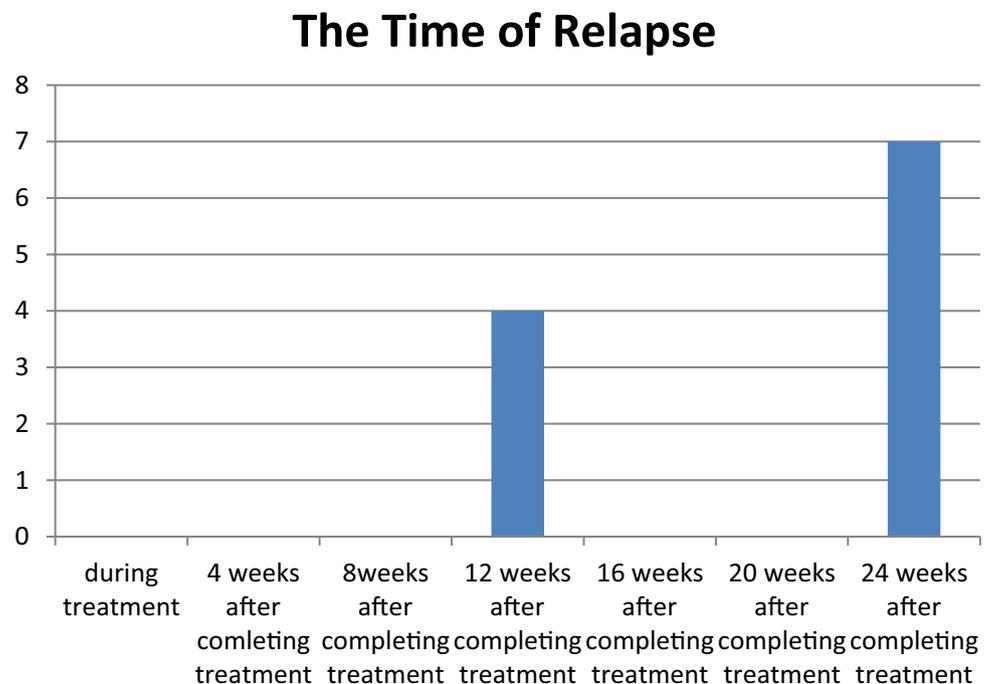
PCR polymerized chain reaction, ALT alanine transaminase, SD standard deviation

Table 3 Treatment outcome and side effects among the two DAA groups

	OMV/PTV/ RTV group No. (%)	SOF/DAC group No. (%)	<i>p</i> value
Ribavirin + any of the above regimen	20 (47.6)	10 (55.56)	ns
Rapid virological response (RVR)	42 (100)	18 (100)	ns
12-week sustained viral response	42 (100)	14 (77.8)	0.0063
24-week sustained viral response	35 (83.3)	14 (77.8)	ns
Rise of serum creatinine	20 (47.6)	8 (44.44)	0.82
A/CKD (recovered)	8 (19.05)	7 (38.89)	0.103
Accelerated progression of CKD, passed to ESRD	12 (28.57)	1 (5.56)	0.047
Need for hemodialysis	19 (45.24)	1 (5.56)	0.004
DAA therapy withholding	20 (47.6)	8 (44.44)	0.82
Anemia (yes)	20 (47.6)	11 (61.11)	0.45
Increase dose of erythropoietin-stimulating agents (yes)	20 (47.6)	11 (61.11)	0.45
Ribavirin withdrawal (yes)	20 (47.6)	10 (55.56)	0.57
Hepatic decompensation	4 (9.5)	3 (16.67)	0.42
Relapse	7 (16.67)	4 (22.22)	0.61
Dizziness	9 (21.4)	6 (33.33)	0.33
Fatigue	14 (33.33)	8 (44.44)	0.41
Gastrointestinal upsets	18 (24.85)	10 (55.55)	0.37

AKI/CKD acute kidney injury on top of chronic kidney disease, *CKD* chronic kidney disease, *ESRD* end-stage kidney disease, *DAA* direct-acting antivirals

Fig. 1 Time of relapse (number of relapsers increased from no relapser during treatment to 4 relapsers after 12 weeks from completing treatment and then 11 relapsers 12 weeks later)



course of IFN- α . Finally, among the relapsers, three patients had advanced fibrosis (F2, 3) and CHIL (B or C). Table 4 illustrates the risk factors for relapse. The risk factors for relapse were male gender, having hypertension,

being diabetic, having HCV genotype 1 and being placed on OMV/PTV/RTV regimen; however, none of these factors was statistically significant in the multivariate analysis.

Table 4 The risk factors for relapse among the two DAA groups

Risk factor	Odds ratio	95% confidence interval	<i>p</i> value	
Univariate analysis using crosstab test (Chi square) and odds ratio calculation				
Gender: male (vs. female)	1.29	0.3017–5.54	0.72	
Hypertensive (vs. non-hypertensive)	1.15	0.3101–4.279	0.83	
Diabetic (vs. non diabetic)	1.29	0.329–5.0998	0.71	
Hepatitis B co-infection (vs. no HBV infection)	1.2	0.04962–33.707	0.88	
Fibroscan: F2, or F3 (vs. F0, or F1)	0.104	0.01237–0.8771	0.037	
CHILD score B, or C (vs. A)	0.94	0.2167–4.0552	0.93	
Liver ultrasound: cirrhotic (vs. normal)	0.44	0.1177–1.6649	0.227	
Spleen ultrasound: enlarged (vs. normal)	0.24	0.0426–1.2467	0.089	
Genotype 4	3.4	0.1801–65.5971	0.4	
Genotype 1	0.29	0.0152–5.5537	0.32	
Sofosbuvir-based therapy (vs. other DAAs)	0.85	0.1975–9.6578	0.827	
Ritonavir + ombitasvir + paritaprevir (vs. other DAAs)	1.1765	0.2734–5.0628	0.827	
Risk factor	Regression estimate (B)	Odds ratio	95% confidence interval	<i>p</i> value
Multivariate analysis using binary logistic regression test including factors with odds ratio > 1 in univariate analysis				
Gender: male (vs. female)	0.2732	1.3	0.3018–5.5398	0.72
Hypertensive (vs. non-hypertensive)	0.1483	1.15	0.3101–4.2795	0.83
Diabetic (vs. non diabetic)	0.4563	1.58	0.3971–6.3058	0.52
Genotype 4	1.7456	5.7	0.9817–33.6789	0.059
Ritonavir + ombitasvir + paritaprevir (vs. other DAAs)	0.2581	1.29	0.3018–5.5398	0.72

DAA direct-acting antivirals

Renal function

With regard to renal function, before treatment, 3 patients were CKD stage 2, 7 patients were 3a, 8 were 3b, and 42 were stage 4. The major side effect was a rise in serum creatinine in 28 (46.7%) patients, i.e., acute kidney injury (AKI) on top of CKD (AKI/CKD) (see Table 5). Of these, 20 (71.4%) patients needed hemodialysis, either temporarily ($n=7$) or permanently ($n=13$), i.e., 15 patients recovered from AKI/CKD. Overall, mean serum creatinine for the 60 patients significantly increased between baseline and 1 month after starting treatment (3.77 ± 0.22 vs. 5.02 ± 0.41 mg/dL; $p=0.004$); this corresponds to a significant decrease in creatinine clearance (29.75 ± 1.8 vs. 25 ± 1.94 mL/min; $p=0.003$) (see Fig. 2). However, for the 28 patients who experienced AKI/CKD, mean serum creatinine at baseline was 4.33 ± 0.28 mg/dL and it increased to 5.88 ± 0.75 mg/dL at 4 weeks after starting treatment ($p=0.009$). For those who needed hemodialysis, mean serum creatinine at baseline was 5.7 ± 0.12 mg/dL, peaking to 9.3 ± 0.28 mg/dL when they required hemodialysis ($p<0.0001$). Eight patients subsequently died while on hemodialysis. They were all cured of HCV. Figure 3 details the patients' CKD stage trajectories according to baseline CKD stage.

Table 5 Side effects of DAA therapy

	Chronic kidney disease patients No. (%)
Rise of serum creatinine	28 (46.67)
A/CKD (recovered)	15(26.67)
Accelerated progression of CKD, evolved to ESKD	13 (21.67)
Need for hemodialysis	20 (33.33)
Ombitasvir/paritaprevir/ritonavir temporary suspension	20 (28.33)
Sofosbuvir/daclatasvir temporary suspension	8 (13.33)
Anemia	31 (51.6)
Increase dose of erythropoietin-stimulating agents	31 (51.6)
Ribavirin cessation	30 (50)
Hepatic decompensation	7 (11.67)
Dizziness	15 (25)
Fatigue	22 (36.67)
Gastrointestinal upsets	28 (46.67)

AKI/CKD acute kidney injury on top of chronic kidney disease, CKD chronic kidney disease, ESKD end-stage kidney disease, DAA direct-acting antivirals

Creatinine clearance progression (ml/min/1.73m²)

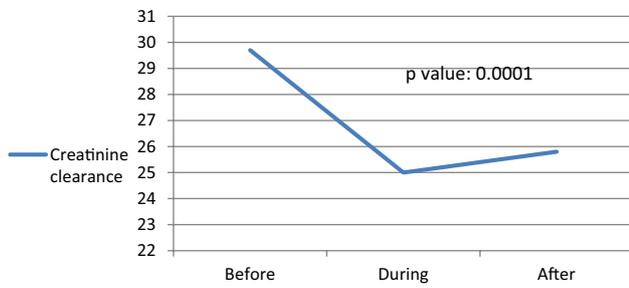


Fig. 2 Progression of creatinine clearance during the treatment course

For those patients who did not experience AKI, baseline serum creatinine was 3.02 ± 0.34 mg/dL. After 4 weeks, serum creatinine was 3.23 ± 0.4 mg/dL ($p = ns$). Figures 4 and 5 illustrate the changes in serum creatinine and measured creatinine clearance for each CKD stage. All CKD stages showed significant changes of serum creatinine before, during and after completing treatment (p value: 0.0001) except for stage 2 CKD patients. However, creatinine clearance was affected significantly only in stages 3a and 4 CKD patients.

There was no statistical difference regarding proteinuria before, after, or during treatment for all patients (3.9 ± 2.2 , 4 ± 2 , 4 ± 2.1 g/day respectively; p value 0.22).

AKI/CKD and type of DAA therapy: out of the 28 AKI/CKD patients, 20 patients received ombitasvir/paritaprevir/ritonavir therapy. Nineteen of them required hemodialysis therapy either temporarily (7 patients) or permanently (12 patients). A rise in serum creatinine was noticed at 2 weeks after starting that therapy in nine patients: thus, treatment was suspended temporarily for 2 weeks until recovery of signs of acute kidney injury, but one patient out of nine developed AKI/CKD again within the last 2 weeks of the treatment course and progressed to end-stage kidney disease (ESKD). The other 11 patients had an increase in serum creatinine during the last 3 weeks of DAA treatment; DAA

Median Serum creatinine

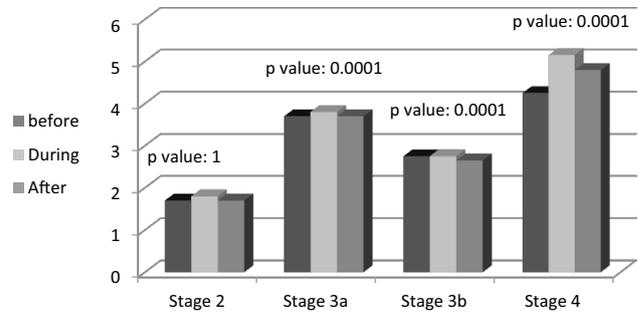


Fig. 4 Serum creatinine before, during and after treatment for different CKD stages shows statistically significant differences in each CKD stage except for stage 2 CKD patients

Median Creatinine clearance

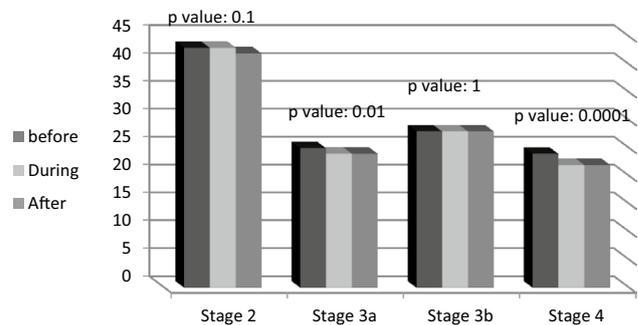


Fig. 5 Creatinine clearance before, during and after treatment for different CKD stages showed statistically significant differences among advanced CKD patients (stages 3a and 4)

treatment was not suspended; they all evolved to ESKD and were maintained therefore on chronic hemodialysis. Regarding sofosbuvir/daclatasvir-treated patients, eight developed AKI/CKD. Three of them had an increase in serum creatinine within 2 weeks of starting DAA therapy; treatment was interrupted temporarily for 10–18 days until recovery of AKI

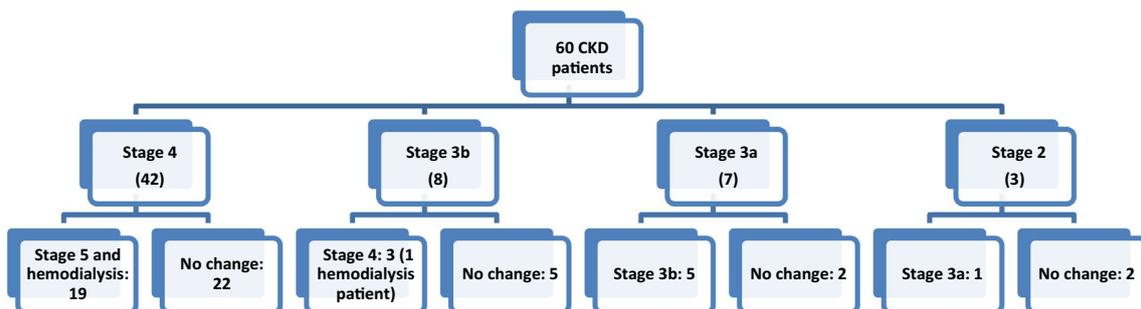


Fig. 3 Trajectories for CKD stages, i.e., after DAA therapy as compared to pre-DAA therapy ($n = 60$ patients)

and was then resumed. The five other patients had increased serum creatinine during the last 2 weeks of treatment and one out of them evolved to ESKD (Table 5). Overall, 14 AKI/CKD patients had advanced fibrosis by fibroscan (F2, or F3); moreover, 10 AKI/CKD patients had CHILD B or C.

Table 6 illustrates the risk factors for acute kidney injury on top of chronic kidney disease. In multivariate analysis, there were only two independent risk factors for developing AKI/CKD, i.e., being cirrhotic as defined by baseline abdominal ultrasound findings [odds ratio 4.15 (1.33–12.97); $p=0.013$], and having had as DAA therapy OMV/PTV/RTV [odds ratio 7.35 (1.84–29.35); $p=0.001$].

Anemia

The policy in our center is that any CKD patient with hemoglobin less than 11.5 g/dL is considered anemic regardless of the sex. In case of persistent anemia after correction of iron profile, the patient is placed on erythropoietin-stimulating agents (ESA). Worsening of anemia, i.e., when hemoglobin dropped > 1 g/dL over the first 4 weeks of treatment was reported in 31 patients; they subsequently received larger doses of erythropoietin. Their mean hemoglobin levels before and 1 month after starting DAA treatment

were 11.24 ± 1.22 and 8.1 ± 0.98 g/dL ($p < 0.00001$). Only one patient was not on ribavirin, i.e., the other 30 patients received ribavirin. We therefore stopped ribavirin in all patients at 28 days after starting it; subsequently, hemoglobin level improved significantly (9.66 ± 0.9 g/dL; $p < 0.00001$). Conversely, in patients who did not show worsening of anemia, their mean hemoglobin levels before and 1 month after starting DAA treatment were 8.92 ± 0.64 and 8.91 ± 0.63 g/dL ($p=0.14$).

All 60 patients were on ESA before treatment. Mean weekly dose of epoetin alfa before treatment was 9200 ± 788 IU, whereas it significantly increased to $14,600 \pm 872$ IU at 1 month after starting treatment ($p=0.0005$). Anemia was improved by the end of treatment and so erythropoietin doses were reduced to $10,300 \pm 644$ IU/week. Overall for the 60 patients, mean hemoglobin levels before, during, and after treatment were 8.9 ± 0.6 , 8.5 ± 0.8 , and 9.4 ± 0.98 g/dL, respectively: the difference was statistically significant ($p=0.0012$) (Table 3).

Hepatic decompensation

Hepatic decompensation (in the form of elevated liver enzymes, decreased albumin levels, and newly developed

Table 6 Risk factors for acute kidney injury on top of chronic kidney disease among the two DAA groups

Risk factor	Odds ratio	95% confidence interval	<i>p</i> value	
Univariate analysis using crosstab test (Chi square) and odds ratio calculation				
Gender: male (vs. female)	1.3	0.43–3.92	0.63	
Hypertensive (vs. non-hypertensive)	2.3	0.81–6.55	0.11	
Diabetic (vs. non diabetic)	1.1	0.36–3.28	0.86	
Hepatitis B co-infection (vs. no infection)	0.36	0.01–9.41	0.54	
Fibroscan: F2, F3 (vs. F0, F1)	2.22	0.76–6.30	0.14	
CHILD score: B, C (vs. A)	0.52	0.16–1.66	0.27	
Liver ultrasound: cirrhotic (vs. normal, enlarged)	4.28	0.11–4.80	0.013	
Spleen ultrasound: enlarged (vs. normal)	0.74	0.11–4.80	0.74	
Genotype 4	0.41	0.069–2.45	0.33	
Genotype 1	2.5	0.42–14.82	0.31	
Sofosbuvir-based therapy (vs. no sofosbuvir)	0.09	0.023–0.37	0.008	
Ritonavir + ombitasvir + paritaprevir therapy (vs. no)	10.71	2.67–42.86	0.008	
Risk factor	Regression estimate (B)	Odds ratio	95% confidence interval	<i>p</i> value
Multivariate analysis using binary logistic regression test including factors with odds ratio > 1 in univariate analysis				
Gender: male (vs. female)	0.2981	1.3	0.43–3.92	0.62
Hypertensive (vs. non-hypertensive)	−0.1326	0.88	0.31–2.43	0.80
Diabetic (vs. non-diabetic)	0.0423	1.04	0.35–3.09	0.94
Fibroscan: F2, F3 (vs. F0, F1)	0.4876	1.65	0.58–4.68	0.34
Liver ultrasound: cirrhotic (vs. normal, enlarged)	1.4673	4.15	1.33–12.97	0.013
Genotype 1	0.9325	2.5	0.42–14.82	0.29
Ritonavir + ombitasvir + paritaprevir therapy (vs. no)	2.0012	7.35	1.84–29.35	0.001

DAA direct-acting antivirals

lower-limb edema and ascites) was seen in seven patients within 12 weeks after completing treatment. Three were F0, one was F1 and three were F2 patients by fibroscan; six out of them were CHILD A and 1 was CHILD B patients at baseline. Of these, four were placed on ombitasvir/paritaprevir/ritonavir and three on sofosbuvir + daclatasvir. Patients complicated by hepatic decompensation at baseline showed slight improvement during treatment course, then decompensation recurred 2–3 months after treatment cessation.

Mean \pm standard deviation of alanine transaminase (ALT) among the seven patients who were decompensated before, during, and 3 months after completing treatment were 39.14 ± 11.9 , 33.57 ± 5.1 , and 56.14 ± 13.35 IU/L, respectively: the difference was statistically significant ($p=0.0006$). The values for serum albumin for the same group before, during, and 3 months after completing the treatment were 3.45 ± 0.29 , 3.48 ± 0.19 , and 2.8 ± 0.15 g/dL, respectively, and the differences were statistically significant ($p=0.0001$).

The incidence of adverse events, e.g., dizziness, fatigue, and gastrointestinal upsets (GIT) were 25%, 36.6% and 46.6%, respectively (Table 4).

Discussion

This study explored the efficacy and safety of DAAs among HCV patients with CKD in a real-life setting. To the best of our knowledge, this is the first study to include such a population from the Middle East that was predominantly HCV genotype 4.

We found that (i) ribavirin was poorly tolerated and was always withdrawn from therapy, (ii) acute renal failure upon chronic kidney disease frequently occurred (in 46.6% of patients and without recovery, i.e., end-stage kidney disease in 46.4% of cases), and (iii) relapsing after the end of DAA therapy was as high as 18.3%.

Our study included 60 patients, of which most were white, male, and had almost no portal fibrosis, i.e., most had a Child-A score, and most were genotype 4. Recently, there had been a few studies addressing DAA therapy in the setting of HCV patients having some degree of renal function impairment [19–22].

In our study, different CKD stages (from stages 2–4) were included: at baseline the mean serum creatinine was 3.76 ± 1.67 mg/dL and measured creatinine clearance was 29.75 ± 14.06 mL/min, i.e., we excluded (pre)dialysis patients. Pockros et al. [19] and Muñoz-Gómez et al. [20] included stages 4 and 5 only, and the median serum creatinine was 6.2 (2.2–10.8) mg/dL and eGFR was 18.1 (8.9–63.1) mL/min. Manoj et al. included 71 patients, of whom 86% were receiving hemodialysis. Finally, average

serum creatinine for the patients reported by Sise et al. was 1.3 mg/dL, i.e., an eGFR of 60 mL/min [23].

The most popular DAA-based regimen contains sofosbuvir; however, sofosbuvir is not indicated when eGFR is < 30 mL/min. In addition, it is estimated that 18% of sofosbuvir is removed following a 4-h hemodialysis session [24]. However, recent data have shown that there was no sofosbuvir accumulation in sofosbuvir-treated hemodialysis patients [25]. Conversely, renal impairment has no effect upon the pharmacokinetics of OMB, PTV, RTV [26], and daclatasvir [27]. Therefore, no OMB, PTV, and RTV dosage adjustment is required for patients with mild, moderate, or severe renal impairment [28].

Our DAA choices were similar to those recommended in the international guidelines for CKD patients with a GFR of > 30 mL/min, i.e., sofosbuvir-based therapy, the same as those suggested for the general population with HCV [29]. The RUBY-1 trial (paritaprevir/ritonavir, ombitasvir, and dasabuvir with or without RBV) reported high SVR rates (100% SVR4 in the 10/20 patients that reached post-treatment week 4) in HCV genotype 1-infected patients with stage 4–5 CKD [19]. Sise et al. used a sofosbuvir-based regimen to treat HCV stage 1–3 CKD patients. In contrast, Manoj et al. [23] used a sofosbuvir-based regimen for patients who were receiving hemodialysis and had low creatinine clearance. Similarly, Dumortier et al. [30] reported that SOF-based antiviral therapy, with a reduced dose of SOF, was safe and effective for the treatment of HCV patients with ESKD, including HD patients.

In our study, ribavirin was given to only 30 patients, but all needed to stop it because of anemia; however, they all achieved a sustained viral response at 12 weeks. This finding agrees with the RUBY-2 trial where the SVR rate without RBV was also high, even in genotype-1a patients. This approach seems a better option as it is RBV free [31]. Also, Bernstein et al. [22] suggested that those receiving an RBV-free regimen had less adverse effects, especially in patients with higher serum creatinine.

A rapid virological response (RVR) was achieved in 100% of the patients in our study. HCV load dropped to below the detection limits within 2–4 weeks from starting DAA treatment. The same results were obtained by Pockros et al. [19]: they found a sustained viral response at 12 and 24 weeks of 93.33% and 81.6%, respectively. Other studies reported 95.5% SVR [19, 20]. Kondo et al. [32] reported high rate on non-responders/relapsers (16.4%) that may be due to the use of a different drug combination (daclatasvir and asunaprevir). Finally, Sise et al. reported that 89% genotype 1b patients achieved an SVR compared to 83% of those with genotype-1a infection.

Other reports estimated SVR of 92–97% for genotype 4 HCV patients treated with SOF and simeprevir with or without RBV [33, 34]. Di Biagio et al. [35] recently

reviewed the efficacy of DAA therapies for HCV genotype 4 (GT4) patients. With regard to ombitasvir/paritaprevir/ritonavir, the PEARL-I study included 135 GT4 patients who were randomly assigned to receive once-daily OBV/PTV/r for 12 weeks with or without RBV. SVR was achieved by 100% of patients treated with the addition of RBV and by 91% of those treated without. In the AGATHE-II a phase 3, open label, 160 GT4 patients were treated with ombitasvir/paritaprevir/ritonavir for 12 weeks. SVR was achieved by 94% of patients without cirrhosis [35]. In our study, the relapse rate was high: 11 relapsers (18.33%) and 7 (11.6%) had received RTV/OMV/PTV, which are higher rates than that reported in the study by Pockros et al. [19], where there was 1 relapser out of 20 (5%). This could be explained by the large sample size in our series.

HCV infection has been linked to higher incidences of microalbuminuria and decreased eGFR, an increased risk of CKD progression and a higher risk of kidney-related mortality [36]; in our study, treatment of HCV among CKD patients with DAAs was associated with a rapid rise of serum creatinine (A/CKD) in 46.67% of our patients. This is similar to the rate reported by Saxena et al. [13], who showed that the use of SOF-based therapies given to patients with baseline renal function impairment (eGFR < 45 mL/min) was associated with a higher risk of worsening renal function and adverse events.

Manoj et al. [23] describe a decline in kidney function at 3 months after stopping treatment, but explained that this was because of a natural history for CKD. This was not the finding in the RUBY I study [19]. Two other studies using full-dose sofosbuvir in CKD patients (in combination with ribavirin, or ribavirin and peg-interferon, or daclatasvir, or daclatasvir and ribavirin, or simeprevir, or simeprevir and ribavirin) found that kidney function remained stable among patients not on dialysis [30, 37].

Also, Muñoz-Gómez et al. [20] reported not seeing cases of rapid increases in serum creatinine. In Sise et al.'s [21] study, patients experienced minor fluctuations in serum creatinine while on therapy; the majority (74%) had stable kidney function, and creatinine did not rise > 0.3 mg/dL from baseline at any time during treatment.

In our study, we found that the largest drop in creatinine clearance and rise of serum creatinine was among stage 3 and 4 CKD patients. The same findings were obtained by Bernstein et al. [22]. During the period of acute kidney injury, DAAs were suspended temporarily for 2–3 weeks until recovery. No DAAs were suspended in Pockros et al.'s [19] study, except for ribavirin, which was suspended due to anemia. As there was a moderately high relapse rate and a high rate of AKI/CKD, we compared the results of RTV/OMV/PTV to those from the sofosbuvir-based regimen. We found that the relapse and also the rise of serum creatinine

were greater among the RTV/OMV/PTV group. This may have been caused by the natural history of CKD.

Regarding safety, anemia was the most frequent adverse effect in our study; dizziness, fatigue, and gastrointestinal upsets were less common adverse events in our study. At baseline, our population was more anemic (hemoglobin was 10.1 ± 1.5 g/dL) than that of the population reported by Pockros et al. [19], where hemoglobin was 12.0 (9.5–16.6) g/dL. In addition we observed a decrease in hemoglobin level by -1.5 ± 0.3 g/dL between before treatment and at 4 weeks after treatment, and there was an increased need for ESA therapy (to 5400 ± 90 IU/week). Worsening anemia was associated with the use of ribavirin: anemia improved after cessation of ribavirin. It is well known that anemia is frequent in ribavirin-treated patients and the mechanisms are complex [38].

Our findings are similar to those observed by Pockros et al.: in their study anemia as a side effect occurred in 50% of cases and all had been receiving ribavirin. Ribavirin was suspended for 2 weeks, but then was re-added after a reduction in anemia [19]. Worsening anemia was not associated with ribavirin in the study by Muñoz-Gómez et al. [20], but the drop was greater among patients who received ribavirin. In clinical trials of OBV/PTV/r + dasabuvir given to patients with RBV and normal renal function, the incidence of anemia was less frequent: namely, 5.5% in the SAPHIRE I and II studies [39, 40]. The most common side effects reported by Muñoz-Gómez et al. [20] were asthenia and pruritis. In contrast our patients had lower serum creatinine and worse creatinine clearance.

DAA therapy might interfere with cyclosporine or tacrolimus pharmacokinetics. In healthy volunteers at steady-state concentrations of paritaprevir 150 mg daily coadministered with ritonavir 100 mg once daily, ombitasvir (25 mg once daily), and dasabuvir (400 mg twice daily) the pharmacokinetics, safety, and tolerability of a single dose of cyclosporine (30 mg) or tacrolimus (2 mg) were evaluated. Dose-normalized cyclosporine concentration at 24 h (C24) and area under the concentration–time curve from time 0 to infinity (AUC1) were 15.8-fold and 5.8-fold, respectively, and dose-normalized tacrolimus C24 and AUC1 were 17-fold and 57-fold, respectively, of either agent alone. In addition, cyclosporine and tacrolimus half-lives increased from 7–25 and 32–232 h, respectively [41]. Conversely, in tacrolimus-treated HCV (+)/RNA (+) solid organ transplant recipients receiving simeprevir plus sofosbuvir therapy, there was no statistically significant difference in immunosuppression dosages or levels during HCV treatment [42].

Our study has many advantages: it included a large number of CKD patients and did not include hemodialysis patients; thus, we could study the effect of DAAs on renal function better. Also, different CKD stages were included, and two different regimens were used. Lack of

randomization and an inability to include other regimens are limitations of this study.

Conclusions

We conclude that patients with CKD and creatinine clearance of > 30 mL/min/1.73 m² can be treated safely with a sofosbuvir-based regimen. Because treatment of patients with advanced CKD (stage 4) was associated with a higher incidence of A/CKD, hemodialysis, and relapse, we suggest postponing HCV treatment within this group until hemodialysis is started or until they receive a kidney transplantation. After transplantation, they could receive sofosbuvir-based regimen if creatinine clearance more than 30 mL/min or grazoprevir/elbasvir if creatinine clearance less than 30 mL/min. We also suggest that ribavirin should not be used with any of the above regimens.

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Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest.

References

- Bunchorntavakul C, Maneerattanaporn M, Chavalitdharmrong D (2015) Management of patients with hepatitis C infection and renal disease. *World J Hepatol* 7:213–225
- Polaris Observatory HCV Collaborators (2016) Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. *Lancet Gastroenterol Hepatol* 2:161–176
- Cacoub P, Desbois AC, Isnard-Bagnis C, Rocatello D, Ferri C (2016) Hepatitis C virus infection and chronic kidney disease: time for reappraisal. *J Hepatol* 65:S82–S94
- Fabrizi F, Dixit V, Martin P, Messa P (2012) The evidence-based epidemiology of HCV-associated kidney disease. *Int J Artif Organs* 35:621–628
- Park H, Adeyemi A, Henry L, Stepanova M, Younossi Z (2015) A meta-analytic assessment of the risk of chronic kidney disease in patients with chronic hepatitis C virus infection. *J Viral Hepat* 22:897–905
- Tsui JI, Vittinghoff E, Shlipak MG, Bertenthal D, Inadomi J, Rodriguez RA, O'Hare AM (2007) Association of hepatitis C seropositivity with increased risk for developing end-stage renal disease. *Arch Intern Med* 167:1271–1276
- Fabrizi F, Dixit V, Messa P, Martin P (2014) Antiviral therapy (pegylated interferon and ribavirin) of hepatitis C in dialysis patients: meta-analysis of clinical studies. *J Viral Hepat* 21:681–689
- Ladino M, Pedraza F, Roth D (2016) Hepatitis C virus infection in chronic kidney disease. *J Am Soc Nephrol* 27:2238–2246
- Reese PP, Abt PL, Blumberg EA, Goldberg DS (2015) Transplanting hepatitis C-positive kidneys. *N Engl J Med* 373:303–305
- Lubetzky M, Chun S, Joelson A, Coco M, Kamal L, Ajaimy M, Gaglio P, Akalin E, De Boccardo G (2017) Safety and efficacy of treatment of hepatitis C in kidney transplant recipients with directly acting antiviral agents. *Transplantation* 101:1704–1710
- Kamar N, Marion O, Rostaing L, Cointault O, Ribes D, Lavaysière L, Esposito L, Del Bello A, Métivier S, Barange K, Izopet J, Alric L (2016) Efficacy and safety of sofosbuvir-based antiviral therapy to treat hepatitis C virus infection after kidney transplantation. *Am J Transplant* 16:1474–1479
- Fabrizi F, Martin P, Messa P (2016) New treatment for hepatitis C in chronic kidney disease, dialysis, and transplant. *Kidney Int* 89:988–994
- Saxena V, Korashy FM, Sise ME, Lim JK, Schmidt M, Chung RT, Liapakis A, Nelson DR, Fried MW, Terrault NAHCV-TARGET (2016) Safety and efficacy of sofosbuvir-containing regimens in hepatitis C-infected patients with impaired renal function. *Liver Int* 36:807–816
- American Association for the study of Liver Disease/Infectious Disease Society of America/International Antiviral Society (2015) Recommendations for testing, managing, and treating hepatitis C virus. Updated 7 Aug 2015. <http://www.hcvguidelines.org>. Accessed 5 Jan 2016
- Andreone P, Colombo MG, Enejosa JV, Koksai I, Ferenci P, Maieron A, Müllhaupt B, Horsmans Y, Weiland O, Reesink HW, Rodrigues L Jr, Hu YB, Podsadecki T, Bernstein B (2014) ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. *Gastroenterology* 147(359–365):e1
- Kowdley KV, Lawitz E, Poordad F, Cohen DE, Nelson DR, Zeuzem S, Everson GT, Kwo P, Foster GR, Sulkowski MS, Xie W, Pilot-Matias T, Lioussis G, Larsen L, Khatri A, Podsadecki T, Bernstein B (2014) Phase 2b trial of interferon-free therapy for hepatitis C virus genotype 1. *N Engl J Med* 370:222–232
- Hézode C, Asselah T, Reddy KR, Hassanein T, Berenguer M, Fleischer-Stepniewska K, Marcellin P, Hall C, Schnell G, Pilot-Matias T, Mobashery N, Redman R, Vilchez RA, Pol S (2015) Ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in treatment-naïve and treatment-experienced patients with genotype 4 chronic hepatitis C virus infection (PEARL-1): a randomized, open-label trial. *Lancet* 385:2502–2509
- Jahangiri F, Hooman N (2015) Results and complications of children with ESRD undergoing peritoneal dialysis catheter placement 1997–2013 in Aliasghar Pediatric Hospital. *J Pediatr Nephrol Winter Suppl* 1:1
- Pockros PJ, Reddy KR, Mantry PS, Cohen E, Bennett M, Sulkowski MS, Bernstein D, Podsadecki T, Cohen D, Shulman NS, Wang D, Khatri A, Abunimeh M, Lawitz E (2015) Safety of ombitasvir/paritaprevir/ritonavir + dasabuvir for treating HCV GT1 infection in patients with severe renal impairment or end-stage renal disease: the RUBY-1 study. *EASL 2015. J Hepatol* 62:S257 (Abstract LO1)
- Muñoz-Gómez R, Rincón D, Ahumada A, Hernández E, Devesa MJ, Izquierdo S, Ortiz M, Hernández-Albujar A, Fernández-Rodríguez C, Calvo M, González R, Lozano M, Castellano G, Fernández-Vázquez I (2017) Therapy with ombitasvir/paritaprevir/

- ritonavir plus dasabuvir is effective and safe for the treatment of genotypes 1 and 4 hepatitis C virus (HCV) infection in patients with severe renal impairment: a multicentre experience. *J Viral Hepat* 24:464–467
21. Sise ME, Backman E, Ortiz GA, Hundemer GL, Ufere NN, Chute DF, Brancale J, Xu D, Wisocky J, Lin MV, Kim AY, Thadhani R, Chung RT (2017) Effect of sofosbuvir-based hepatitis C virus therapy on kidney function in patients with CKD. *Clin J Am Soc Nephrol* 12:1615–1623
 22. Bernstein DE, Tran A, Martin P, Kowdley KV, Bourliere M, Sulkowski MS, Pockros PJ, Renjifo B, Wang D, Shuster DL, Cohen DE, Jacobson IM (2018) Ombitasvir, paritaprevir, ritonavir, and dasabuvir with or without ribavirin in patients with kidney disease. *Kidney Int Rep* 4:245–256
 23. Manoj K, Nayak SL, Gupta E, Kataria A, Sarin SK (2018) Generic sofosbuvir-based direct-acting antivirals in hepatitis C virus-infected patients with chronic kidney disease. *Liver Int* 38:2137–2148
 24. Smolders EJ, de Kanter CT, van Hoek B, Arends JE, Drenth JP, Burger DM (2016) Pharmacokinetics, efficacy, and safety of hepatitis C virus drugs in patients with liver and/or renal impairment. *Drug Saf* 39:589–611
 25. Desnoyer A, Pospai D, Lê MP, Gervais A, Heurgué-Berlot A, Laradi A, Harent S, Pinto A, Salmon D, Hillaire S, Fontaine H, Zucman D, Simonpoli AM, Muret P, Larrouy L, Bernard Chabert B, Descamps D, Yazdanpanah Y, Peytavin G (2016) Pharmacokinetics, safety and efficacy of a full dose sofosbuvir-based regimen given daily in hemodialysis patients with chronic hepatitis C. *J Hepatol* 65:40–47
 26. Shuster DL, Menon RM, Ding B, Khatri A, Li H, Cohen E, Jewett M, Cohen DE, Zha J (2019) Effects of chronic kidney disease stage 4, end-stage renal disease, or dialysis on the plasma concentrations of ombitasvir, paritaprevir, ritonavir, and dasabuvir in patients with chronic HCV infection: pharmacokinetic analysis of the phase 3 RUBY-I and RUBY-II trials. *Eur J Clin Pharmacol* 75:207–216
 27. Gandhi Y, Eley T, Fura A, Li W, Bertz RJ, Garimella T (2018) Daclatasvir: a review of preclinical and clinical pharmacokinetics. *Clin Pharmacokinet* 57:911–928
 28. Sorbera MA, Friedman ML, Cope R (2017) New and emerging evidence on the use of second-generation direct acting antivirals for the treatment of hepatitis C virus in renal impairment. *J Pharm Pract* 30:359–365
 29. European Association for Study of Liver (2015) EASL Recommendations on treatment of hepatitis C 2015. *J Hepatol* 63:199–236. <https://doi.org/10.1016/j.jhep.2015.03.025>
 30. Dumortier J, Bailly F, Pageaux GP, Vallet-Pichard A, Radenne S, Habersetzer F, Gagnieu MC, Grangé JD, Minello A, Guillaud O, Kamar N, Alric L, Leroy V (2017) Sofosbuvir-based Antiviral therapy in hepatitis C virus patients with severe renal failure. *Nephrol Dial Transplant* 32:2065–2071
 31. Gane E, Sola R, Cohen E, Roberts SK, George J, Skoien R, Riordan S, Mobashery N, Abunimeh M, Cohen DE, Agarwal K (2016) RUBY-II: efficacy and safety of a ribavirin-free ombitasvir/paritaprevir/ritonavir ± dasabuvir regimen in patients with severe renal impairment or end-stage renal disease and HCV genotype 1a or 4 infection. *AASLD 2016. Hepatology* 64:361–601 (**Abstract 935**)
 32. Kondo C, Atsukawa M, Tsubota A, Shimada N, Abe H, Asano T, Yoshizawa K, Okubo T, Chuganji Y, Aizawa Y, Iio E, Tanaka Y, Iwakiri K (2017) Daclatasvir and asunaprevir for genotype 1b chronic hepatitis C patients with chronic kidney disease. *Hepatol Res* 47:1165–1173
 33. Willemse SB, Baak LC, Kuiken SD, van der Sluys Veer A, Lettinga KM, van der Meer JT, Depla AC, Tuynman H, van Nieuwkerk CD, Schinkel CJ, Kwa D, Reesink HW, van der Valk M (2016) Sofosbuvir plus simeprevir for the treatment of HCV genotype 4 patients with advanced fibrosis or compensated cirrhosis is highly efficacious in real life. *J Viral Hepat* 23:950–954
 34. Ahmed OA, Elsebaey MA, Fouad MHA, Elkadeem M, Badawi R, Khayyal A, Soliman S, Negm MS, Abd-Elsalam S (2018) Outcomes of treatment and predictors of response to sofosbuvir plus simeprevir in hepatitis c virus with genotype-4 infection. *Infect Disord Drug Targets*. <https://doi.org/10.2174/1871526519666181218104600>
 35. Di Biagio A, Taramasso L, Cenderello G (2018) Treatment of hepatitis C virus genotype 4 in the DAA era. *Virol J* 15:180
 36. Ridruejo E, Mendizabal M, Silva MO (2018) Rationale for treating hepatitis C virus infection in patients with mild to moderate chronic kidney disease. *Hemodial Int* 22:S97–S103
 37. Beinhart S, Al Zoairy R, Ferenci P, Kozbial K, Freissmuth C, Stern R, Stättermayer AF, Stauber R, Strasser M, Zoller H, Watschinger B, Schmidt A, Trauner M, Hofer H, Maieron A (2016) DAA-based antiviral treatment of patients with chronic hepatitis C in the pre-and postkidney transplantation setting. *Transpl Int* 29:999–1007
 38. Brochet E, Castelain S, Duverlie G, Capron D, Nguyen-Khac E, François C (2010) Ribavirin monitoring in chronic hepatitis C therapy: anaemia versus efficacy. *Antivir Ther* 15:687–695
 39. Feld JJ, Kowdley KV, Coakley E, Sigal S, Nelson DR, Crawford D, Weiland O, Aguilar H, Xiong J, Pilot-Matias T, DaSilva-Tillmann B, Larsen L, Podsadecki T, Bernstein B (2014) Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med* 370:1594–1603
 40. Zeuzem S, Jacobson IM, Baykal T, Marinho RT, Poordad F, Bourliere M, Sulkowski MS, Wedemeyer H, Tam E, Desmond P, Jensen DM, Di Bisceglie AM, Varunok P, Hassanein T, Xiong J, Pilot-Matias T, DaSilva-Tillmann B, Larsen L, Podsadecki T, Bernstein B (2014) Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med* 370:1604–1614
 41. Badri P, Dutta S, Coakley E, Cohen D, Ding B, Podsadecki T, Bernstein B, Awni W, Menon R (2015) Pharmacokinetics and dose recommendations for cyclosporine and tacrolimus when coadministered with ABT-450, ombitasvir, and dasabuvir. *Am J Transplant* 15(5):1313–1322. <https://doi.org/10.1111/ajt.13111> (**epub 2015 Feb 23**)
 42. Mansour M, Hill L, Kerr J (2018) Safety and effectiveness of direct acting antivirals for treatment of hepatitis C virus in patients with solid organ transplantation. *Transpl Infect Dis*. 20(6):e12972. <https://doi.org/10.1111/tid.12972> (**epub 2018 Aug 22**)

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