Clinics and Research in Hepatology and Gastroenterology (2019) 43, 82—87

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

ORIGINAL ARTICLE

Efficacy of ombitasvir/paritaprevir/ritonavir/ribavirin in management of HCV genotype 4 and end-stage kidney disease

Mohamed A. Mekky[a,*], Mohamed O. Abdel-Malek[a], Heba A. Osman[b], Essam M. Abdel-Aziz[c], Abdel-Kader A. Hashim[d], Helal F. Hetta[e], Khairy H. Morsy[f]

[a] *Tropical Medicine and Gastroenterology Department, Hepatology Division, Faculty of Medicine, Assiut university, 71515 Assiut, Egypt*
[b] *Tropical Medicine and Gastroenterology Department, Hepatology Division, Faculty of Medicine, South Valley university, Qena, Egypt*
[c] *Department of Internal Medicine, Nephrology Division, Faculty of Medicine, Assiut university, Assiut, Egypt*
[d] *Department of Internal Medicine, Nephrology Division, Faculty of Medicine, South Valley university, Qena, Egypt*
[e] *Medical Microbiology and Immunology Department, Faculty of Medicine, Assiut university, Assiut, Egypt*
[f] *Tropical Medicine and Gastroenterology Department, Hepatology Division, Faculty of Medicine, Sohag university, Sohag, Egypt*

Available online 27 August 2018

KEYWORDS
HCV;
End-stage kidney disease;
DAAs

Abstract
Background: Till now, pooled data about the safety and efficacy of different direct-acting antiviral (DAAs) regimens in different renal situations are still under evaluation.
Aim: To evaluate a real-life experience of the efficacy and safety of ombitasvir/paritaprevir/ritonavir plus ribavirin (OBV/PTV/r plus RIB) in patients with end-stage kidney disease (ESKD).
Patients and methods: Between January 2017 and January 2018, an open-label multicenter prospective study was designed to enroll all consecutive patients with proven CHC genotype 4 infections and concomitant ESKD based on estimated glomerular filtration rate (eGFR) with (HD group) or without hemodialysis (non-HD group). Patients were given a co-formula of OBV/PTV/r (25/150/100 mg) once-daily plus RIB was given for 12 weeks. Sustained virologic response (SVR 12) was the primary endpoint.

Abbreviation: HD, hemodialysis.

* Corresponding author.
E-mail address: mmekky75@yahoo.com (M.A. Mekky).

https://doi.org/10.1016/j.clinre.2018.08.003

Results: A total of 110 patients were enrolled. An overall SVR 12 was reported in 104 (94.5%) patients, and treatment failure were reported in 6 patients [2 patients (1.8%) were relapsed, and 4 patients (3.6%) patients were non-responders]. SVR12 was 96% in HD and 91.4% in non-HD patients ($P = 0.286$).

There were no reported serious adverse events. Anemia was reported in 66.6% ($n = 50$) in HD group and in 31.4% ($n = 11$) in non-HD group.

Conclusion: Although it is still challenging, achievement of SVR12 in patients with chronic HCV and concomitant end-stage kidney disease in the era of DAAs became possible with a 12 weeks course of a co-formula of ombitasvir/paritaprevir /ritonavir plus ribavirin.

ClinicalTrials.gov ID: NCT03341988.

Introduction

Management of patients with hepatitis C virus (HCV) related liver disease with concomitant co-morbidity was challenging, especially in the period before the era of new direct-acting antiviral (DAA) agents. With the introduction of DAAs protocols, the therapeutic options were expanded to endorse many patients that were previously assigned as difficult-to-treat population [1]. Different situations were encountered with co-infection with HCV such as chronic kidney disease (CKD) with its spectrum from mild forms to the end-stage kidney disease (ESKD), patients on hemodialysis (HD), and in post-renal transplant settings [2,3]. Till now, pooled data about the safety and efficacy of different DAAs regimens in different renal situations are still under evaluation [4], especially in Egypt, where HCV genotype 4 the most dominating genotype [5]. In Egypt, there were two adopted protocols for patients with HCV and CKD; the sofosbuvir-based combinations and the ombitasvir, paritaprevir, and ritonavir plus ribavirin-based combination [5,6]. Sofosbuvir was proved to be contraindicated in patients with end-stage renal diseases as its elimination based mainly on renal route that may affect its bioavailability [7]. On the other hand, ombitasvir, paritaprevir, and ritonavir plus ribavirin regimen was proved to be a well-tolerated protocol in non-cirrhotic patients with CKD [6,8].

Therefore, we herein, tried to evaluate a real-life practice of ombitasvir, paritaprevir, and ritonavir plus ribavirin regimen in patients with ESKD, with or without hemodialysis in Egyptian based multicenter cohort.

Patients and methods

Patients' recruitments

Between January 2017 and January 2018, a prospective multicenter cohort study was designed to enroll all consecutive patients presented at the Viral Hepatitis Management Outpatient Clinics at three dedicated centers (Assiut University Hospital, South Valley University Hospital, and Sohag University Hospital) in Egypt.

Patients with proven CHC genotype 4 and concomitant ESKD with or without hemodialysis were selected. Enrolled patients were 18-years-old or more, naive to prior HCV treatment, genotype 4, had compensated liver disease were enrolled.

Patients with combined HCV/HBV co-infection, HIV co-infection, hepatocellular carcinoma (HCC), decompensated liver cirrhosis (Child—Pugh Score above 6), and non-genotype 4 were excluded.

Study definitions

ESKD was based on estimated glomerular filtration rate (eGFR) that calculated by the Cockroft—Gault equation [9,10]. Two sets of patients were enrolled: the first group was ESKD patients without hemodialysis (non-HD group); patients with eGFR between 59—30 mL/min and the second group was ESKD patients and on regular hemodialysis (HD group); patients with eGFR less than 30 mL/min and on hemodialysis.

HCV treatment response: sustained virologic response was defined as HCV-RNA under the detection limit at week 12 after the end of treatment (SVR12), non-responder was defined as a detectable viremia at week 12, and relapse was defined as re-appearance of HCV viremia during follow-up after being undetectable at week 12 [11].

Study methods and assays

Liver disease-status was assessed before therapy by Child—Turcotte Pugh (CTP) Score [12] and liver stiffness Score measurements by Fibroscan® (EchoSens, Paris, France) in kilopascals (kPa) according to the manufacturer's instructions (score less than 7.4 kPa equal to F0—F2, 9.5—12.4 kPa equal to F3, and 14.5 kPa or greater equal to F4 on METAVIR pathologic scoring system) [13,14].

HCV genotype assessment by direct sequencing of the 50 untranslated region (50UTR), using RT-PCR-based assay (AmpliSens HCV genotype-FRT PCR kit).

HCV viremia was measured using the real time PCR (Roche COBAS Taq Man HCV assay version 2.0 with a lower limit of detection 15 IU/mL).

HCV medications and protocols (Fig. 1)

Non-HD groups (patients with eGFR between 59—30 mL/min and without hemodialysis): a co-formula of ombitasvir (OBV; 25 mg)/paritaprevir (PTV; 150 mg)/ritonavir (r; 100 mg) (OBV/PTV/r) once-daily plus ribavirin (RIB) at alternating dosing of 200 mg and 400 mg daily was given for 12 weeks.

HD group (patients on hemodialysis): a co-formula of OBV/PTV/r (25/150/100 mg) once-daily plus RIB 200 mg 3 times/week, only in the days that they have their hemodialysis settings, 4 hours before the hemodialysis setting for 12 weeks.

Follow-up

In all patients, hematologic (hemoglobin level), liver (CTP score parameters), renal (eGFR), virologic (HCV-RNA viremia), and the co-medications were evaluated at baseline (week 0), and serially at weeks 4, 12 during therapy, and at week 24 after treatment.

Study outcome measures and endpoints

The primary endpoint was the achievement of SVR at week 12 (SVR12) post-treatment. The potential adverse events were evaluated in each visit for the development of adverse events or any significant interactions.

Statistical analysis and ethical considerations

Frequencies, percentages, and means were used, as appropriate, for descriptive analysis. Chi^2 test was used to compare parametric qualitative data, while Mann—Whitney test was used to compare non-parametric quantitative. Statistical analysis was conducted by SPSS (V.19, SPSS Inc.; Chicago, IL, USA). A P-value < 0.05 was considered significant.

All authors declare that all procedures followed in the current study were in accordance with the STROBE statement [15] and the ethical standards of our institutional review board (IRB) [IRB17100240] and with the Helsinki Declaration of 1975, as revised in 2008.

Results

Patients' characteristics (details in Table 1)

A total of 110 patients (male = 78 (70.9%) and the mean age 48.8 ± 15.3 years) were recruited. Most of patients were on hemodialysis (n = 75, 68.2%).

Efficacy results (details in Fig. 1, Table 1)

Of the 110 patients, SVR was reported in 104 (94.5%) patients, and treatment failure were reported in the remaining 6 patients [2 patients (1.8%) were relapsed, and 4 patients (3.6%) patients were non-responders]. The SVR12 in HD group was 96% (one relapse and two were non-responders) and 91.4% in non-HD patients (one relapse and two were non-responders) without statistical significance (P = 0.286).

Table 1 CKD category and the virologic response.

	Virologic response		Total
	SVR	Non-SVR	
CKD category			
Non-HD	32	3	35
	91.4%	8.6%	100%
HD	72	3	75
	96%	4%	100%
Total	104	6	110
	94.5%	5.5%	100%

CKD: chronic kidney disease; SVR: sustained virologic response; HD: hemodialysis.
P = 0.286 (Chi^2 test).

Adverse event (AE) and safety evaluation

During the period of the study, there were no reported serious AEs that necessitated stoppage of treatment or leaded to severe illness or co-morbidities. There were no drop-outs during the study period.

Anemia was reported in 66.6% (n = 50) in HD group and in 31.4% (n = 11) in non-HD group and was managed either with reduction of ribavirin dose, iron supplementation, erythropoietin injection or rarely with blood transfusion. Other AE were shown in Tables 2 and 3.

Ribavirin dose

Ribavirin dose was re-adjusted due to anemia (detected between the 4th week to the 8th week) in seven patients in HD group from 600 mg/week to 400 mg/week and SVR was achieved in 6 of them (one patient was relapsed). Stoppage of ribavirin was mandated in another five patients in HD group (4 of them achieved SVR and one was non-responder) and in one patient in non-HD group that showed relapse.

Discussion

The interaction between chronic HCV infection and different forms of renal dysfunction was reported since the discovery of HCV either as a part of extra-hepatic manifestations of HCV or as a disease sequelae [16,17]. In patients with severe forms of ESKD or on hemodialysis, their morbidity and mortality was noted to be higher than the general population when co-infection with HCV was found and, moreover, HCV infection was considered as an independent risk of death in those high-risk patients [18,19]. Since the early trials of HCV management protocols, even with the new era of DAAs, a great burden was found in managing this unique population [20] and the still challenging by the paucity of researches and the heterogeneity of the available data.

The AASLD-ISDA guidelines in 2015 state that for patients infected with hepatitis C and eGFR < 30 mL/min, a combination therapy of ritonavir-boosted paritaprevir, dasabuvir,

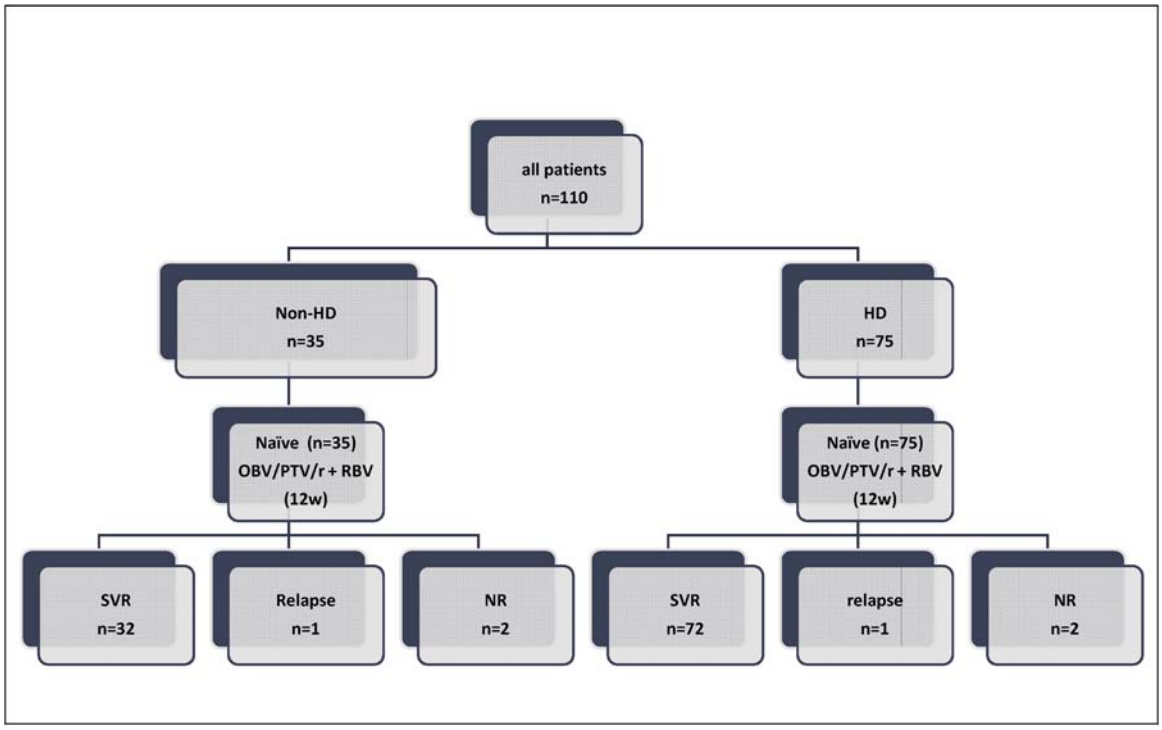

Fig. 1 Algorithm of treatment protocol and results.

Table 2 Descriptive characteristics of enrolled patients ($n = 110$).

Characteristic	Results		*P*-value
	HD group ($n = 75$)	Non-HD group ($n = 35$)	
Age (years) mean rank	80.57	43.80	0.001[a]
Sex (M:F)	52 (69.3%):32 (30.7%)	26 (74.3%):9 (25.7%)	0.384[b]
Fibroscan			0.02[b]
F0	14 (87.5%)	2 (12.5%)	
F1	31 (77.5%)	9 (22.5%)	
F2	12 (70.6%)	5 (29.4%)	
F3	10 (47.6%)	11 (52.4%)	
F4	8 (50.0%)	8 (50.0%)	
Adverse events[c]	62 (82.6%)	23 (65.7%)	0.001[b]
Mean time of dialysis (months ± SD)	36 ± 11	0	—
Presence of co-morbid disease(s)			
Diabetes mellitus	20 (26.6%)	13 (37.1%)	0.4[b]
Hypertension	43 (57.3%)	22 (62.8%)	0.01[b]
Cardiac disease (ischemic and/or cardiomyopathy)	9 (12%)	3 (8.5%)	0.001[b]

[a] Mann—Whitney test.
[b] Chi^2 test.
[c] Details are described in Table 3.

and ombitasvir, with or without ribavirin can be used [21]. In our study we investigated a rather fixed nation-wide protocol in a real-life cohort that was implemented by our national viral hepatitis committee [22—24]. The co-formula of ombitasvir/r/paritaprevir/ribavirin was implemented in genotype 4 in concordance to the results of PEARL-I study and AGATE-I study [25,26] and in and in Egyptian protocol this combination was devoted to patients with HCV and concomitant renal disorders.

It worth noted that, the recent updated AASLD-ISDA guideline in 2017, recommended the use of daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) or daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) in genotype 4 patients [27].

In this series, we demonstrated an overall efficacy (SVR24 rate was 94.5%) and a good safety profile. However, we reported relatively high percentages of adverse events, in

Table 3 Adverse events details among different patients groups.

	Non-HD group ($n = 35$)	HD group ($n = 75$)	Total ($n = 110$)
Anemia (< 10 g/dL)	11 (31.4%)	50 (66.6%)	61 (55.4%)
Headache	23 (65.7%)	62 (82.6%)	85 (77.2%)
Epigastric pain (post-DAAs intake)	13 (37.1%)	60 (80%)	73 (66.3%)
Fatigue/myalgia	20 (57.1%)	50 (66.6%)	70 (63.6%)
Pruritus	3 (8.5%)	0	3 (2.7%)
Worsening eGFR	0	0	0
Raised ALT	0	1 (1.3%)	1 (0.9%)

CKD: chronic kidney disease; HD: hemodialysis; RTx: renal transplant; SVR: sustained virologic response; NR: non-responder; ESKD: end-stage kidney disease; DAAs: direct-acting antivirals; eGFR: estimated glomerular rate.

spite of being minor, and this may be a plausible finding; as all of our patients had a different profile of renal impairment, dialysis, co-medications, and co-morbidities that may be associated with such acceptable adverse events.

In patients with ESKD, sofosbuvir is not the best recommended regimen, especially in eGFR < 30 mL/min [28].Our regimen of ombitasvir/r/paritaprevir/ribavirin yielded a good SVR rate of 91.4%. However, the adverse events were more in this group (general complains in most of patients and anemia in about half of them). There is an emerging evidence of the promising results in using a half dose of sofosbuvir such as the study of Goel et al. as they tried a fixed daily doses of daclatasvir 60 mg and sofosbuvir 200 mg for12 weeks in ESKD patients with eGFR < 30 mL/min and they reported 90.2% SVR rate [29].

In hemodialysis (HD) group, we reported a relatively high SVR rate (about 96%) and only 4% of them showed treatment failure with OBV/PTV/r plus RIB.

The use ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin in patients with ESKD was described in many trials and most of these results showed high SVR rates more than 95% [30—32].

Herein, and according to our nation-wide protocol, we did not use dasabuvir in our regimen and instead we use only add-on ribavirin and our SVR rate (about 95%) was relatively comparable to those previously reported figures.

Our study revealed relatively well-tolerated drugs in all study groups without discontinuation of therapy due to an adverse event and most of side effects were observed to be related to ribavirin. Some adverse events such as epigastric pain post receiving the medications are very common in patients on ribavirin was reported in many studies [33]. On the other hand, complaints such as myalgia and headache may be explained by the primary disease of the kidney rather than treatment related events, however, it was difficult to judge as most patients reported these events post-treatment with DAAs.

To the best of our knowledge, there is no published study tackle the use of ombitasvir, paritaprevir, and ritonavir plus ribavirin regimen in patients with ESKD, either with or without hemodialysis in Egyptian cohort infected with HCV genotype 4. However, it lack of randomization and blindness that was difficult to apply because the fixed regimen adopted by our nation-wide protocol.

Conclusion

Achievement of SVR12 in patients with chronic HCV and concomitant end-stage kidney disease with ombitasvir, paritaprevir, and ritonavir plus ribavirin regimen is possible with relatively well-tolerated adverse events.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Ferenci P. Treatment of hepatitis C in difficult-to-treat patients. Nat Rev Gastroenterol Hepatol 2015;12:284.
[2] Jadoul M, Martin P. Hepatitis C treatment in chronic kidney disease patients: the kidney disease improving global outcomes perspective. Blood Purif 2017;43(1—3):206—9.
[3] Sawinski D, Kaur N, Ajeti A, et al. Successful treatment of hepatitis C in renal transplant recipients with direct-acting antiviral agents. Am J Transplant 2016;16(5):1588—95.
[4] Kamar N, Marion O, Rostaing L, et al. Efficacy and safety of sofosbuvir-based antiviral therapy to treat hepatitis C virus infection after kidney transplantation. Am J Transplant 2016;16(5):1474—9.
[5] Gomaa A, Allam N, Elsharkawy A, El Kassas M, Waked I. Hepatitis C infection in Egypt: prevalence, impact and management strategies. Hepat Med 2017;15(9):17—25.
[6] Waked I, Shiha G, Qaqish RB, et al. Ombitasvir, paritaprevir, and ritonavir plus ribavirin for chronic hepatitis C virus genotype 4 infection in Egyptian patients with or without compensated cirrhosis (AGATE-II): a multicentre, phase 3, partly randomised open-label trial. Lancet Gastroenterol Hepatol 2016;1(1):36—44.
[7] Saxena V, Koraishy FM, Sise ME, et al. Safety and efficacy of sofosbuvir-containing regimens in hepatitis C-infected patients with impaired renal function. Liver Int 2016;36(6):807—16.
[8] Cheng EY, Saab S, Holt CD, Busuttil RW. Paritaprevir/ritonavir/ombitasvir and dasabuvir for the treatment of chronic hepatitis C virus infection. Expert Opin Pharmacother 2015;16(18):2835—48.
[9] Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31—41.
[10] Kidney Disease: Improving Global Outcomes. KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. Kidney Int 2008;73(Suppl. 109):S1—99.

[11] Ghany MG, Strader DB, Thomas DL, et al. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009;49(4):1335—74.
[12] Christensen E. Prognostic models including the child-Pugh, Meld and Mayo risk scores — where are we and where should we go? J Hepatol 2004;41:344—50.
[13] Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The metavir cooperative study group. Hepatology 1996;24:289—93.
[14] Ziol M, Handra-Luca A, Kettaneh A, et al. Non-invasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. Hepatology 2005;41(1):48—54.
[15] Elm Von, Altman D, Egger M, Pocock S, Gotzsche P, Vanderbroucke J, for the STROBE initiative. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Int J Surg 2014;12:1495—9.
[16] Fabrizi F, Takkouche B, Lunghi G, Dixit V, Messa P, Martin P. The impact of hepatitis C virus infection on survival in dialysis patients: meta-analysis of observational studies. J Viral Hepat 2007;14:697—703.
[17] Morsy KH, Mekky MA, Abdel Malek MO, Abbas WA. Incidence, causes, and outcomes of renal failure among cirrhotic patients. Turk J Gastroenterol 2015;26(6):517—21, http://dx.doi.org/10.5152/tjg.2015.15169.
[18] Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. Kidney Int Suppl 2008;109:S1—99.
[19] Stehman-Breen CO, Emerson S, Gretch D, Johnson RJ. Risk of death among chronic dialysis patients infected with hepatitis C virus. Am J Kidney Dis 1998;32:629—34.
[20] Terrault NA, Adey DB. The kidney transplant recipient with hepatitis C infection: pre- and post-transplantation treatment. Clin J Am Soc Nephrol 2007;2(3):563—75.
[21] Panel AIHG, AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology 2015;62:932—54.
[22] Khattab MA, Ferenci P, Hadziyannis SJ, et al. Management of hepatitis C virus genotype 4: recommendations of an international expert panel. J Hepatol 2011;54(6):1250—62.
[23] Shiha G, Metwally AM, Soliman S, Elbasiony AM, Mikhail NNH, Easterbrook P. An educate, test, and treat programme towards elimination of hepatitis C infection in Egypt: a community-based demonstration project. Lancet Gastroenterol Hepatol 2018:262—7, http://dx.doi.org/10.1016/S2468-1253(18)30139-0 [pii: S2468-1253(18)30139-0 (Epub ahead of print)].
[24] El-Akel W, El-Sayed MH, El Kassas M, et al. National treatment programme of hepatitis C in Egypt: hepatitis C virus model of care. J Viral Hepat 2017;24(4):262—7.
[25] Hézode C, Asselah T, Reddy KR, et al. Ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in treatment-naive and treatment-experienced patients with genotype 4 chronic hepatitis C virus infection (PEARL-I): a randomised, open-label trial. Lancet 2015;385(9986):2502—9.
[26] Asselah T, Hézode C, Qaqish RB, et al. Ombitasvir, paritaprevir, and ritonavir plus ribavirin in adults with hepatitis C virus genotype 4 infection and cirrhosis (AGATE-I): a multicentre, phase 3, randomised open-label trial. Lancet Gastroenterol Hepatol 2016;1(1):25—35.
[27] Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology 2015;62(3):932—54, http://dx.doi.org/10.1002/hep.27950 [Epub 2015 Aug 4].
[28] Sisse ME, Backman E, Ortiz GA, et al. Effect of sofosbuvir-based hepatitis C virus therapy on kidney function in patients with CKD. Clin J Am Soc Nephrol 2017;12(10):1615—23.
[29] Goel A, Bhadauria DS, Kaul A, et al. Daclatasvir and reduced-dose sofosbuvir: an effective and pangenotypic treatment for hepatitis C in patients with eGFR < 30 mL/min. Nephrology (Carlton) 2018, http://dx.doi.org/10.1111/nep.13222 [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/29327401.
[30] Welzel TM, Hinrichsen H, Sarrazin C, Buggisch P, et al. Real-world experience with the all-oral, interferon-free regimen of ombitasvir/paritaprevir/ritonavir and dasabuvir for the treatment of chronic hepatitis C virus infection in the German hepatitis C registry. J Viral Hepat 2017;24(10):840—9.
[31] Abad S, Vega A, Hernández E, et al. Universal sustained viral response to the combination of ombitasvir/paritaprevir/ritonavir and dasabuvir with/without ribavirin in patients on hemodialysis infected with hepatitis C virus genotypes 1 and 4. Am J Nephrol 2017;45:267—72.
[32] Polepally AR, Badri PS, Eckert D, Mensing S, Menon RM. Effects of mild and moderate renal impairment on ombitasvir, paritaprevir, ritonavir, dasabuvir, and ribavirin pharmacokinetics in patients with chronic HCV infection. Eur J Drug Metab Pharmacokinet 2017;42(2):333—9.
[33] Querenghi F, Yu Q, Billaud G, Maertens G, Trépo C, Zoulim F. Evolution of hepatitis C virus genome in chronically infected patients receiving ribavirin monotherapy. J Viral Hepat 2001;8(2):120—31.