

Interferon-free regimens in patients with hepatitis C infection and renal dysfunction or kidney transplantation

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Abstract

Treatment of patients with chronic kidney disease (CKD) and chronic hepatitis C (CHC) differs from that used in the general CHC population mostly when glomerular filtration rate (GFR) is below 30 mL/min, as sofosbuvir, the backbone of several current regimens, is officially contraindicated. Given that ribavirin free regimens are preferable in CKD, elbasvir/grazoprevir is offered in CHC patients with genotype 1 or 4 and ombitasvir/paritaprevir and dasabuvir in genotype 1b for 12 wk. Although regimens containing peginterferon with or without ribavirin are officially recommended for patients with CKD and genotype 2, 3, 5, 6, such regimens are rarely used because of their low efficacy and the poor safety and tolerance profile. In this setting, especially in the presence of advanced liver disease, sofosbuvir-based regimens are often used, despite sofosbuvir contraindication. It seems to have good overall safety with only 6% or 3.4% of CKD patients to discontinue therapy or develop serious adverse events without drug discontinuation. In addition, sustained virological response (SVR) rates with sofosbuvir based regimens in CKD patients appear to be comparable with SVR rates in patients with normal renal function. Treatment recommendations for kidney transplant recipients are the same with those for patients with CHC, taking into consideration potential drug-drug interactions and baseline GFR before treatment initiation. This review summarizes recent data on the current management

of CHC in CKD patients highlighting their strengths and weaknesses and determining their usefulness in clinical practice.

Key words: Chronic hepatitis C virus infection; Kidney; Renal; Kidney transplantation; Direct acting antiviral agents; Glomerular filtration rate; Hepatitis C

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Core tip: Recent evidence showed very good safety and efficacy of both interferon and ribavirin-free direct acting antivirals (DAAs) regimens in patients with severe kidney disease (CKD) or kidney transplantation. Nevertheless, sofosbuvir, the backbone of most antiviral schemes is officially contraindicated in patients with CKD (creatinine clearance < 30 mL/min). Accordingly, CKD patients with genotype 1 or 4 can be currently treated with available ribavirin free DAAs regimens without sofosbuvir, while those with non-1, non-4 genotype can officially be treated with peginterferon with or without ribavirin, but they are actually treated with sofosbuvir-based regimens mostly if they have advanced liver disease.

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INTRODUCTION

The prevalence of hepatitis C virus (HCV) infection among hemodialysis (HD) patients has been reported to range from 10% to 25%^[1]. Chronic hepatitis C (CHC) has been related with high morbidity and reduced survival in both patients with renal dysfunction and kidney transplant (KT) recipients^[2]. HCV treatment in patients with renal dysfunction has been a complex and challenging issue in the pre-direct acting antiviral (DAAs) era. Interferon-alpha (IFN) or pegylated IFN (PEG-IFN) with or without low doses of ribavirin (RBV) (200-400 mg three times weekly) was associated with low rates of sustained virological response (SVR) and several potentially dangerous side effects^[3] such as steroid resistant acute allograft rejection in KT recipients^[4].

In general, the introduction of first generation DAAs (*i.e.*, telaprevir and boceprevir) improved the SVR rates in CHC patients infected with genotype 1 but did not substantially improve the treatment of such patients with renal dysfunction or KT^[5]. Initially, both telaprevir and boceprevir had to be used in combination with PEG-IFN and RBV resulting in the potential appearance of limitations, worse tolerability and safety profile of both PEG-IFN and RBV. These could account for severe anemia with both drugs, rash and pruritus with telaprevir

and dysgeusia with boceprevir^[5]. Moreover, glomerular filtration rate (GFR) deterioration was reported to develop in about 5% of CHC patients who received telaprevir- or boceprevir-based therapy, particularly if they had additional risk factors for renal impairment (*e.g.*, arterial hypertension)^[6,7].

After 2014, newer DAAs have been licensed for the treatment of CHC by EMA and FDA. They include a nucleotide analogue NS5B polymerase inhibitor, sofosbuvir (tablet of 400 mg, Sovaldi[®], Gilead)^[8], the NS3/4 protease inhibitor, simeprevir (tablet of 150 mg, Olysio[®], Janssen)^[9], the NS5A inhibitor, daclatasvir (tablet of 60 mg, Dankliza[®], Bristol-Myers Squibb)^[10], the co-formulation of a NS5A inhibitor, ledipasvir, with sofosbuvir (tablet of 90/400 mg, Harvoni[®], Gilead)^[11], the co-formulation of a NS5A inhibitor, ombitasvir, with a NS3/4 protease inhibitor, paritaprevir, boosted by ritonavir (r) (tablet of 12.5/75 per 50 mg, Viekirax[®], Abbvie), with a non-nucleos(t)ide analogue NS5B polymerase inhibitor, dasabuvir (tablet of 250 mg, Exviera[®], Abbvie)^[12], the co-formulation of a NS5A inhibitor, elbasvir, with a NS3/4 protease inhibitor, grazoprevir (tablet of 50/100 mg, Zepatier[®], Merck)^[13] and the co-formulation of a NS5A inhibitor, velpatasvir, with sofosbuvir (tablet of 100/400 mg, Epclusa[®], Gilead)^[14] (Table 1). IFN-free and often RBV-free combinations of the newer DAAs given for 8-24 wk have been associated with very high (> 95%) SVR rates in most subgroups of CHC patients. Such combinations seem to represent the optimal choice against HCV infection in patients with chronic kidney diseases (CKD) or KT recipients, although its potential effects on renal function in all HCV patients and in HCV patients with renal impairment have just started to be evaluated. All newer DAAs are mainly eliminated through the liver, except for sofosbuvir which is eliminated through the kidney^[15]. According to licensed summaries of product characteristics, daclatasvir, dasabuvir, ombitasvir/paritaprevir/r and elbasvir/grazoprevir could be administered to patients with any severity of renal impairment. However, sofosbuvir and consequently its co-formulations, ledipasvir/sofosbuvir and velpatasvir/sofosbuvir, should not be used in patients with severe renal impairment [estimated GFR (eGFR) < 30 mL/min per 1.73 m²] and/or patients requiring HD. Furthermore, caution is required when simeprevir is offered in patients with severe renal impairment and/or on HD because the knowledge of how it affects kidney function is limited^[15].

The purpose of this review is to summarize the most recent data on the impact of the recent IFN-free anti-HCV regimes on kidney function in CHC patients as well as the safety and efficacy of these regimens in CHC patients with CKD and KT recipients.

IMPACT OF NEW DAAS ON RENAL FUNCTION

Non transplant setting

Given that sofosbuvir represents the back-bone of many current IFN-free regimens and at the same time it is the

Table 1 Main characteristics of the approved direct acting antivirals that are currently used for the treatment of hepatitis C

DAA (commercial name), dose	Category	Dose adjustment in renal impairment	Antiviral activity	CNIs co-administration
Sofosbuvir (Sovaldi®), tablet 400 mg, once daily	Nucleotide analogue NS5B polymerase inhibitor	Contraindicated in patients with GFR < 30 mL/min	Genotypes 1-6 High genetic barrier	No change
Simeprevir (Olysio®), tablet 150 mg, once daily with food	NS3/4A protease inhibitor	No change in renal impairment	Genotypes 1,4 Low genetic barrier	Contraindicated with cyclosporine
Daclatasvir (Daklinza®), tablet 60 mg, once daily	NS5A inhibitor	No change in renal impairment	Genotypes 1, 2, 3, 4 Low genetic barrier	No change
Ledipasvir/sofosbuvir (Harvoni®), tablet 90/400 mg, once daily	NS5A inhibitor + nucleotide analogue NS5B polymerase inhibitor	Contraindicated in patients with GFR < 30 mL/min	Genotypes 1, 4, 5, 6 High genetic barrier	No change
Ombitasvir/paritaprevir/ritonavir (Viekirax®), tablet 12.5/75/50 mg, two once daily with food	NS5A inhibitor + NS3/4A protease inhibitor boosted by ritonavir boosted	No change in renal dysfunction	Genotypes 1, 4 Genetic barrier depending on HCV genotype	Cyclosporine: 20% of pretreatment total daily dose; tacrolimus: 0.2 mg/72 h or 0.5 mg once weekly
Dasabuvir (Exviera®), tablet 250 mg, every 12 h	Non-nucleos(t)ide analogue NS5B polymerase inhibitor	No change in renal dysfunction	Genotype 1 Low genetic barrier	Co-administration increases tacrolimus concentrations
Elbasvir/Grazoprevir (Zepatier®), tablet 100/50 mg, once daily	NS5A inhibitor + NS3/4A inhibitor	No change in renal dysfunction	Genotypes 1,4	No change
Velpatasvir/sofosbuvir (Epclusa®), tablet 100/400 mg, once daily	NS5A inhibitor + nucleotide analogue NS5B polymerase inhibitor	Contraindicated in patients with GFR < 30 mL/min	Genotypes 1-6 High genetic barrier	No change

CNI: Calcineurin inhibitor; DAA: Direct acting antiviral; GFR: Glomerular filtration rate.

only agent with renal elimination, only sofosbuvir based regimens have been evaluated for potential effects on renal function. One study^[16] assessed the rate of renal impairment in patients treated with sofosbuvir-based regimens comparing it to that of telaprevir or boceprevir based regimens, which have been previously shown to cause renal impairment in 5%-7% of treated CHC patients^[7]. In total, 442 patients (50% with cirrhosis, > 95% with baseline GFR \geq 60 mL/min)^[16]. Renal impairment (defined as increase in serum creatinine \geq 50% from baseline) was observed at similar rates in all groups: 7% of 228 patients under boceprevir/telaprevir-based regimens, 5% of 76 patients under sofosbuvir plus PEG-IFN/RBV and 4% of 152 patients under IFN-free sofosbuvir-based regimens ($P = 0.40$), but the on-treatment median creatinine peak was lower in the boceprevir/telaprevir group compared to sofosbuvir containing groups (1.4 mg/dL vs 2.0 mg/dL, $P = 0.04$). In multivariable analysis, only ascites [odds ratio (OR) = 3.16] and preexisting proteinuria (OR = 5.74) were significantly associated with development of renal impairment and SVR did not differ between patients who did or did not develop renal impairment (88% vs 86%, $P = 0.90$). According to the authors, monitoring of renal function and standard nephroprotective measures may be useful when sofosbuvir-based regimens are applied, particularly in patients with ascites or pre-existing kidney disease. This finding was confirmed in a recent study^[17], in which 90 patients with HCV infection were treated with sofosbuvir plus ledipasvir: 17 patients had abnormal baseline renal function (GFR < 60 mL/min), while 42% had worsening GFR while on treatment. In multivariate analysis, baseline GFR < 60 mL/min was independently associated with worsening renal function on treatment (P

= 0.04).

On the other hand, HCV infection may have a negative impact on renal function, and thus, HCV eradication could be associated with improvement of GFR. This was shown in a recent study^[18] including 124 patients treated with DAAs (mean age 53.8 years, 67.7% treatment experienced, 83% had genotype 1 and 41% had cirrhosis). The achievement of SVR was associated with GFR improvement (baseline: 78.55 ± 8.96 vs SVR at week 12: 81.85 ± 12.87 mL/min, $P = 0.037$). Thus, renal function may be improved after effective treatment of HCV infection with DAAs-based regimens. However, caution is still advised if sofosbuvir is administered in patients with renal impairment, as renal function may get worse in addition to more adverse events particularly if RBV is also used in combination.

Another study assessed the potential effect of sofosbuvir-based regimens on renal function in patients with HCV decompensated cirrhosis, who represent a group at high risk for renal dysfunction^[19]. The on-treatment changes of serum cystatin C, as a marker of glomerular function, and of neutrophil gelatinase-associated lipocalin (NGAL), as a marker of tubular function, were evaluated in 52 patients with Child-Pugh score \geq 7 treated with sofosbuvir and a NS5A inhibitor (ledipasvir or daclatasvir) and RBV for 12 wk. Half of the patients had at least one renal risk factor (*e.g.*, hypertension, diabetes, therapy with diuretics), while 14% of the patients had eGFR < 60 mL/min. The eGFR did not change significantly during antiviral therapy, but cystatin C and NGAL levels increased from baseline to week 4 of therapy (cystatin C: 1.46 mg/L vs 1.55 mg/L, $P < 0.01$; NGAL: 28.1 ng/mL vs 32.8 ng/mL, $P < 0.01$) indicating transient renal dysfunction. Unfortunately, the evolution of these renal markers at

longer follow-up was not provided.

Transplant setting

The impact of sofosbuvir-based regimens on renal function was assessed in liver transplant (LT) recipients who are at high risk for renal dysfunction for several reasons including the long-term use of calcineurin inhibitors. A recent multicenter study^[20] evaluated 193 LT recipients with HCV recurrence treated with sofosbuvir-based regimens (mean age 58.7 ± 9.0 years, 30.6% cirrhotics). Renal dysfunction developed in 38% of patients. The presence of a preexisting renal disease (OR = 3.49), the baseline GFR (OR = 1.02) and tacrolimus-based immunosuppressive therapy (OR = 0.43) were all three predictive factors of renal dysfunction development. The same study group^[21] focused on 20 patients with combined liver-kidney transplantation (cirrhosis 25%, genotype 1 in 70%) who received sofosbuvir-based therapy for HCV recurrence. The authors reported that GFR decreased significantly from baseline value 50.9 mL/min to 41.8 mL/min at week 12 and to 42.7 mL/min at 12 wk after the end of antiviral therapy (*P* values always ≤ 0.0001).

Finally, 165 LT patients with HCV recurrence^[22] received sofosbuvir-based regimens. A decline in renal function was observed in 22% of patients, particularly in those with baseline eGFR < 30 mL/min (*P* = 0.01), cirrhosis (*P* = 0.01) and prior treatment failure (*P* = 0.03). Similarly to the non-LT setting^[18], renal function improvement after treatment was observed in 58% of patients and more commonly in those who achieved SVR, compared to those who did not (81% vs 19%, *P* < 0.05).

INTERFERON-FREE REGIMENS IN PATIENTS WITH CHC AND CKD

Interferon-free antiviral schemes approved for CHC and CKD

Ombitasvir/paritaprevir/dasabuvir based regimens: The combination of ombitasvir/paritaprevir/r and dasabuvir, which has been abbreviated as 3D regimen, is used with or without the addition of RBV for the treatment of genotype 1a or 1b CHC patients. Moreover, the combination of ombitasvir/paritaprevir/r (2D) with RBV is administered for the treatment of genotype 4 CHC patients. The potential effect of renal impairment on the pharmacokinetics of 3D combination was evaluated in more than 2000 patients from seven phase 2/3 studies^[23]. The severity of renal dysfunction was not found to affect the area under the plasma concentration curve (AUC) of 3D in 22 patients with GFR between 30 and 59 mL/min and therefore no dose-adjustments are required. However, no patients with end stage renal disease (GFR < 30 mL/min) were included in that initial evaluation. In a smaller study^[24], HCV patients with normal or mild renal impairment (*n* = 38), were compared to those with stage 4 or 5 CKD patients (with or without HD) (*n* = 19). During a 12-wk course with the

3D regimen, renal dysfunction did not affect significantly the pharmacokinetics of the 3D regimen. Ombitasvir and paritaprevir exposures were comparable (< 20% difference) in both groups and ritonavir and dasabuvir exposures were 33% and 37% lower, respectively. Thus, the authors concluded that no dose adjustment for the 3D regimen is required in HCV patients with severe renal impairment.

In the RUBY-I study^[25], the safety and efficacy of 3D given for 12 wk was evaluated in 20 genotype 1 treatment-naïve non-cirrhotics patients with CHC and CKD stage 4 or 5 (RBV was given at 200 mg/d in genotype 1a patients). Thirteen patients were under HD. The efficacy was high since SVR was achieved in 18 (90%) of 20 patients in the intention to treat analysis: One F3 genotype 1a patient relapsed 4 wk post-treatment, while a second patient died 14 d after the end of therapy due to left ventricular systolic dysfunction. Regarding safety profile, most adverse events were of mild to moderate severity. There were nine serious adverse events in 4 patients (including the patient who died), but none of them was considered to be related with antiviral therapy (including RBV). Four patients received erythropoietin for anemia but none required blood transfusion. No deterioration of liver or kidney function was observed during the study period.

More recently, real life data have been reported from two studies^[26,27] which evaluated the safety and effectiveness of 3D with or without RBV in 69 CHC patients with stage 4 or 5 CKD (*i.e.*, GFR < 30 mL/min) or under HD. Sixty-five (94.2%) patients had genotype 1 including 29 (44.6%) cases with genotype 1a. Twenty five (75.7%) of 33 patients were treatment naïve^[26] and 31 (45%) of 69 patients had cirrhosis^[26,27]. 3D was given for 12 wk in all 69 patients, combined with RBV in 32 (46.3%) of them^[26,27]. SVR rates at week 12 (SVR12) were 97% (65/67) [94.4% (17/18) for 3D and 94.4% (17/18) for 3D plus RBV, as provided by the study data]. In regards to safety profile, no patient discontinued 3D, two patients stopped RBV and five out of 69 patients (7.2%) developed serious adverse events requiring hospitalization (1 urinary tract infection, 2 heart failure, 1 arthritis and 1 atrial fibrillation) (Table 2).

Elbasvir/grazoprevir: Elbasvir/grazoprevir co-formulated in one tablet, with or without the addition of RBV, has been recently licensed by FDA and EMA for the treatment of HCV genotype 1 and 4^[13]. Given that these agents are cleared by the liver, they can be a good option for patients with CKD stages 4 and 5. In the C-SURFER phase III study^[28], 224 patients with eGFR < 30 mL/min were randomized to receive elbasvir/grazoprevir (*n* = 111) or placebo (*n* = 113) for 12 wk. At week 16, unmasking occurred and all patients in the placebo arm received elbasvir/grazoprevir as well. Almost half (52%) of the patients had genotype 1a, 83% were HCV treatment-naïve, 6% had cirrhosis, 19% had CKD stage 4 and 81% CKD stage 5 (76% of them under HD). In the intention to treat analysis, SVR was achieved in 94%

Table 2 Studies of interferon free regimens for treatment of hepatitis C virus patients with severe renal disease or under hemodialysis

Ref.	Patients, <i>n</i>	Patient characteristics	Regimen: Patients number (dose of sofosbuvir)	Sustained virological response at 12 wk, <i>n/N</i>	Adverse events, <i>n</i>
Pockros <i>et al</i> ^[25]	20	GT1: 20 patients (1a: 13)	3D ± RBV: 20	18/20 (EOT-VR: 20/20)	Death from drug unrelated cause (cardiac arrest at 14 d after the end of therapy): 1
Gomez <i>et al</i> ^[26]	33	GT1: 29 (1a: 6) Age: 57 yr	3D ± RBV: 33	31/31	Serious adverse events: 5 (all unrelated to study drugs)
Basu <i>et al</i> ^[27]	36	GT1: 36 (1a: 23)	3D ± RBV: 36	34/36	No serious adverse event
Roth <i>et al</i> ^[28]	122	GT1: 122 patients	Elbasvir/grazoprevir: 122	115/122	Serious adverse events: 16
Czul <i>et al</i> ^[29]	28	GT1: 26 (1a: 16) Age: 58 yr	SOF + SMV: 26 SOF + RBV: 2 (200 mg/eod-400 mg/d)	21/25	Encephalopathy: 1 Uncontrolled diarrhea: 1
Beinhardt <i>et al</i> ^[30]	15	GT1: 11 patients Age: 52 yr	SOF + DCV: 9 SOF + SMV: 5 SMV + DCV: 1 (400 mg/d)	1/1 (EOT-VR: 5/5)	Pancytopenia at week 7: 1 (change SOF from every 24 h to every 48 h)
Dumortier <i>et al</i> ^[31]	50	GT1: 28 patients Age: 60 yr	SOF + RBV: 7 SOF + RBV + PEG-IFN: 2 SOF + DCV ± RBV: 30 SOF + SMV ± RBV: 11	24/26 (EOT-VR: 50/50)	No serious adverse event
Gane <i>et al</i> ^[32]	10	GT1: 9 (1a: 7) Age: 62 yr	SOF + RBV: 10 (200 mg/d)	4/10	Serious adverse events: 2 (diabetic acidosis, angina)
Nazario <i>et al</i> ^[33]	40	GT1: 26 (1a: 26) Age: 57 yr	SOF + LDV: 9 SOF + DCV: 2 SOF + SMV: 29 (400 mg/d)	29/29	Drug discontinuation: 1 (unknown reason)
Baliellas <i>et al</i> ^[34]	21 (10 on hemodialysis)	GT1: 20 patients (1a: 2) Age: 57 yr	SMV + DCV: 12 SMV + DCV + RBV: 9	17/19	No serious adverse event
Moreno <i>et al</i> ^[35]	42	GT1: 25 (1a: 8) Age: 54 yr	SOF + RBV: 5 LDV/SOF: 8 SOF + DCV: 14 SOF + SMV: 3 SMV + DCV: 12	32/42	Drug discontinuation: 11
Saxena <i>et al</i> ^[36]	19	GT1: 16 (1a: 8)	SOF + SMV + RBV: 2 SOF + SMV: 11 SOF + RBV: 5 SOF + RBV + PEG-IFN: 1 (400 mg/d)	SOF + SMV + RBV: 2/2 SOF + SMV: 8/10 SOF + RBV: 4/4 SOF + RBV + PEG: 1/1	Therapy discontinuation: 1 Serious adverse events: 3
Martin <i>et al</i> ^[37]	10	GT1: 8 patients Age: 58 yr	SOF + RBV: 10 (400 mg/d)	6/10	Acute respiratory failure - drug discontinuation: 1, hematemesis: 1

DCV: Daclatasvir; EOT-VR: End of treatment virological response; GT: Genotype; RBV: Ribavirin; LDV: Ledipasvir; PEG-IFN: Pegylated interferon- α ; SMV: Simeprevir; SOF: Sofosbuvir; 3D: Ombitasvir/paritaprevir/ritonavir plus dasabuvir; eod: Every other day; HCV: Hepatitis C virus.

(115/122) of patients in the active arm: 1 noncirrhotic patient relapsed during the first 12 wk after the end of treatment, while 6 patients discontinued treatment for reasons unrelated to antiviral therapy. Serious adverse events occurred in 16 (14%) and 17 (15%) patients in the elbasvir/grazoprevir and placebo arms, respectively. None and 4% of the patients in the active and placebo groups, respectively, discontinued therapy due to an adverse event. The most common adverse events in the active arm were headache, nausea and fatigue (Table 2).

Interferon-free antiviral schemes not approved for CHC and CKD

In total, nine studies^[29-37] evaluated the safety and efficacy of various antiviral schemes in 235 patients with CHC and CKD. All patients had stage 4 or 5 CKD (*i.e.*, GFR < 30 mL/min) or were under HD. The mean age was provided in 7 studies and ranged between 52.4 and 62 years^[29-35]. Based on the available data,

169 (71.9%) of 235 patients had genotype 1 [67/122 (54.9%) genotype 1a]^[29,32-36]. One hundred (47.6%) of 210 patients were treatment naïve^[29,31,33-36] and 121 (51.4%) of 235 patients had cirrhosis^[29-37].

Sofosbuvir was given for 12-24 wk in combination with RBV in 42 (and PEG-IFN in 3)^[29,31,32,35-37], simeprevir in 87^[29-31,33,35,36] (and RBV in 2, unclarified in 11)^[31,36], daclatasvir in 55 patients^[30,31,33,35] and ledipasvir in 17^[33,35]. The dosage of sofosbuvir was 400 mg per day in 84^[29,30,33,36,37], 200 mg per day in 33^[29,32,36], 200 mg every other day in 2^[29] and unclarified in 82 patients. The dosage of PEG-IFN was not provided in the few studies including PEG-IFN containing regimens, while the dosage of RBV was 200 mg per day in 20^[32,37], variable (200 mg three times per week to 600 mg per day) in 35^[31] and unknown in the remaining patients receiving RBV. The daily dosage of simeprevir was 150 mg and of daclatasvir 60 mg in all patients. The dose of ledipasvir was dependent on the dose of sofosbuvir.

The efficacy of sofosbuvir-based antiviral therapy was provided in all studies. Based on the available data, the rates of end of treatment virological response and SVR at week 12 were 100% (91/91) and 87.1% (129/148), respectively [SVR: 55.2% (16/29) for sofosbuvir plus RBV, 92.1% (35/38) for sofosbuvir plus simeprevir (with or without RBV), 100% (14/14) for ledipasvir/sofosbuvir and 85.7% (12/14) for sofosbuvir plus daclatasvir]. The SVR rates were 80.6% (25/31) for simeprevir plus daclatasvir with or without RBV.

Regarding safety profile, only 14 (5.9%) of the 235 patients discontinued therapy due to adverse events (one under combination of sofosbuvir plus RBV due to acute respiratory failure and one under sofosbuvir plus simeprevir for unclarified cause, while no details were provided for 12 patients)^[33,35-37]. In addition, one patient developed pancytopenia at week 7 under therapy (no further data were given regarding antiviral therapy, but sofosbuvir was reduced from 400 mg/d to 400 mg every other day)^[30]. Finally, 8 (3.4%) of 235 patients developed serious adverse events requiring hospitalization without treatment discontinuation: Hematemesis^[37], new onset encephalopathy^[29], uncontrolled diarrhea^[29], diabetic ketoacidosis or angina^[32] (unclarified causes in 3 patients)^[36]. Renal safety was evaluated in two studies^[31,36] which reported no significant change of GFR from baseline to the end of treatment in non-haemodialysis patients under sofosbuvir-based regimens (Table 2).

Recently, the co-formulation of velpatasvir/sofosbuvir was approved for the treatment of all HCV genotypes. Its short-term safety and pharmacokinetics were evaluated in 10 subjects with eGFR < 30 mL/min^[38]. A single dose of 100 mg velpatasvir was followed by a 120-h intensive blood monitoring. Records were compared to control subjects with normal renal function (eGFR ≥ 90 mL/min) matched for age, sex and body mass index. Velpatasvir was well tolerated and all adverse events were of mild severity. Only an approximately 50% increase in the velpatasvir AUC was observed in the group of patients with renal dysfunction, while the maximum velpatasvir concentrations (C_{max}) were similar between the two groups. The authors concluded that velpatasvir could be administered without dose adjustment in patients with any GFR. However, since velpatasvir is available only in co-formulation with sofosbuvir, its use is driven by the limitations of sofosbuvir in patients with renal impairment.

INTERFERON-FREE REGIMENS IN KT RECIPIENTS WITH CHC

In total, 10 studies^[39-48] evaluated the safety and efficacy of current DAAs based regimens in 330 KT recipients with CHC for 12-24 wk. The mean age ranged from 53 to 65 years. Based on the available data, 247 out of 281 patients (87.9%) had genotype 1 CHC [54/143 (37.8%) genotype 1a]^[39-46]. One hundred and fifty one out of 238 patients (63.4%)^[40,42-44,46,47] were treatment naïve and 64 out of 252 patients (25.4%) had cirrhosis^[39,40,43,44,46,47].

Sofosbuvir was given in combination with RBV in 30 patients, simeprevir (± RBV) in 31, daclatasvir (± RBV) in 20 and ledipasvir (± RBV) in 230 for 12-24 wk. The 3D (or 2D) combination (± RBV) was given in 12^[46,48] and the combination of simeprevir and daclatasvir (± RBV) in 7 patients^[46]. The daily dosage of RBV was provided in only 2 studies^[42,43] ranging from 200 mg to 1200 mg per day.

Based on the available data, the week-12 SVR rates of sofosbuvir based regimens were 94.2% (193/205): 66.7% (10/15) for sofosbuvir plus RBV [100% (4/4) for genotype 2], 88% (22/25) for sofosbuvir plus simeprevir (with or without RBV), 75% (3/4) for sofosbuvir plus daclatasvir, 98% (158/161) for sofosbuvir plus ledipasvir (with or without RBV). In addition, in one study the week-12 SVR rates were 97.8% (45/46) for various antiviral schemes^[46]. No data have been available for the efficacy of 3D or simeprevir plus daclatasvir regimens^[46,48].

Regarding safety profile, 7 (2.1%) of 330 KT recipients discontinued therapy (4 under combination sofosbuvir and RBV due to pruritus, myalgia, anemia and unclarified reason; 1 under sofosbuvir plus daclatasvir due to virological failure; 2 under ledipasvir/sofosbuvir plus RBV for unclarified reasons)^[39,41,44,47], while one patient died 4 wk after the end of antiviral therapy due to bleeding from donor aorta graft^[40]. In addition, 15 KT recipients developed anemia requiring RBV dose reduction and/or erythropoietin injection or blood transfusion, one patient had an episode of bradycardia requiring pacemaker placement despite on regular amiodarone treatment, 2 patients presented worsening proteinuria (> 3 g/d), 4 patients developed rejection of kidney graft, and 12 patients developed unclarified serious adverse events^[47]. No dose adjustment of calcineurin inhibitors was required. Renal and liver function tests remained stable during antiviral treatment (Table 3).

DISCUSSION

Current DAAs against HCV have very good safety profiles. However, baseline GFR and potential drug-drug interactions should be always considered before treatment initiation. Since sofosbuvir is the only DAA with renal elimination, concerns for potential nephrotoxicity have been raised mainly for this agent. There have been reports suggesting that sofosbuvir might have a negative impact on renal function in patients at high renal risk (e.g., decompensated cirrhosis, LT, proteinuria), particularly if more sensitive renal function markers are used (e.g., cystatin C or serum or urine NGAL). However, renal function decline in such high renal risk patients does not necessarily reflect drug related toxicity, as shown in uncontrolled reports. In addition, improvement in renal function after treatment has also been reported in patients who achieved SVR despite the scarcity of long follow-up data after the end of therapy. Only nephrotoxicity related to sofosbuvir has been observed but seems to be minimal given the short duration of therapy. Therefore, no definite conclusion can be drawn,

Table 3 Studies of interferon-free regimens for treatment of hepatitis C virus positive kidney transplant recipients

Ref.	Patients, <i>n</i>	Patient characteristics	Regimen: Patients number	Sustained virological response at 12 wk, <i>n/N</i>	Adverse events, <i>n</i>
Huard <i>et al</i> ^[39]	17	GT1: 16 patients (1a: 5) Age: 65 yr	SOF + RBV: 17 (400 mg/d)	1/6	Therapy discontinuation: 4 (3 due to pruritus, myalgia, anemia, 1 unclarified) Anemia: 8
Lin <i>et al</i> ^[40]	15	GT1: 14 (1a: 10) Age: 55.8 yr	SOF + SMV ± RBV: 12 (SOF + SMV: 9)	13/15	No serious adverse events under therapy (1 died by massive hemorrhage 4 wk after therapy) Proteinuria: 2 Bradycardia under amiodarone (pacemaker placement): 1
Bhamidimarri <i>et al</i> ^[41]	14	GT1: 14 (1a: 12) Age: 54 yr	SOF + RBV: 2 SOF + LDV: 1 SOF + LDV: 13 (in 9 plus RBV) SOF + SMV: 1	13/14	No serious adverse events Therapy discontinuation: 1 Anemia: 7
Hussein <i>et al</i> ^[42]	3	GT4: 3	SOF + RBV (400 mg/d)	3/3	No serious adverse events
Sawinski <i>et al</i> ^[43]	20	GT1: 17 (1a: 7) Age: 57 yr	SOF + SMV: 9 SOF/LDV: 7 SOF + RBV: 3 SOF + DCV: 1 (400 mg/d)	20/20	No serious adverse events
Moreno <i>et al</i> ^[44]	12	GT1: 11 (1a: 4) Age: 53 yr	SOF + SMV: 1 SOF/LDV: 8 SOF + DCV: 3 (400 mg/d)	11/12	Therapy discontinuation: 1
El-Halawany <i>et al</i> ^[45]	11	GT1: 10 (1a: 10) Age: 57.6 yr	SOF + SMV: 2 SOF/LDV: 8 SOF + RBV: 1	10/11	No serious adverse events
Londono <i>et al</i> ^[46]	74	GT1: 61 (1a: 6) Age: 54 yr	SOF/LDV ± RBV: 37 SOF + DCV ± RBV: 15 SOF + SMV ± RBV: 6 SMV + DCV ± RBV: 7 SOF + RBV: 4 3 "D" or 2 "D": 5	45/46	Rejection episodes: 3
Colombo <i>et al</i> ^[47]	114	GT1: 104	SOF/LDV	112/114	Therapy discontinuation: 1 Serious adverse events: 12 Rejection episode: 1
Reddy <i>et al</i> ^[48]	50		SOF/LDV ± RBV: 42 SOF + DCV ± RBV: 1 3 "D": 7	10/10	

DCV: Daclatasvir; GT: Genotype; RBV: Ribavirin; LDV: Ledipasvir; PEG-IFN: Pegylated interferon-alfa; SMV: Simeprevir; SOF: Sofosbuvir; 3D: Ombitasvir/paritaprevir/ritonavir plus dasabuvir; 2 "D": Ombitasvir/paritaprevir/ritonavir.

while it seems reasonable to apply nephroprotective measures and careful renal monitoring during treatment with sofosbuvir-based regimens in patients at high renal risk. Anyway, eGFR monitoring is currently recommended at 4 wk of therapy and as clinically indicated for all patients receiving any regimen with DAAs^[49].

All current DAAs can be given in CHC patients with mild to moderate renal impairment (*i.e.*, eGFR ≥ 30 mL/min) without dose modification. Similarly, they could all be administered in severe renal impairment (*i.e.*, eGFR < 30 mL/min) or end-stage renal disease without dose modification as well, except for sofosbuvir. Of note, the currently recommended regimens for CHC patients with severe renal impairment or end-stage renal disease according to the AASLD and EASL are presented in Table 4^[49,50]. To date, HCV therapy is only recommended for patients with high urgency for treatment of the liver disease and without KT as an immediate option. Furthermore, antiviral therapy can be given after KT or even simultaneous liver and kidney transplantation,

when patients usually have eGFR > 30 mL/min and can receive any regimen. HCV therapy with an IFN free regimen is mandatory for CHC patients with cirrhosis and severe renal impairment usually due to hepatorenal syndrome, since HCV eradication may lead to liver function stabilization and such an improvement resulting in LT elimination. But more data are required in this subgroup before the optimal regimen can be decided. Regrettably, lack of adequate supporting evidence halts a widely disseminated recommendation.

The indication of elbasvir/grazoprevir as first line treatment for CHC patients with genotype 1 or 4 and severe renal impairment, always given without RBV for 12 wk, has been based on the results of the C-SURFER trial. In contrast to genotype 1a patients with eGFR > 30 mL/min who should be tested for NS5A resistance associated variants (RAVs) before therapy and require 16 instead of 12 wk treatment period - of elbasvir/grazoprevir combined with RBV in case of NS5A RAVs presence-, there is no recommendation for such pre-

Table 4 Recommended regimens from the American Association for the Study of Liver Diseases and European Association for the Study of the Liver for patients with chronic hepatitis C and severe renal impairment (glomerular filtration rate < 30 mL/min) who need urgent hepatitis C virus therapy and renal transplantation is not an immediate option

HCV genotype	AASLD recommended regimen	EASL recommended regimen ³
1	Elbasvir/grazoprevir for 12 wk (for 1a or 1b) or ombitasvir/paritaprevir/ritonavir plus dasabuvir ¹ (for 1b) for 12 wk	Elbasvir/grazoprevir or ombitasvir/paritaprevir plus dasabuvir (for 1a or 1b), for 12 wk (plus RBV 200 mg/d for 1a if the haemoglobin level is > 10 g/dL at baseline)
2, 3, 5 or 6	Pegylated interferon-alfa plus dose-adjusted ribavirin (200 mg daily) ²	Sofosbuvir/velpatasvir or sofosbuvir plus daclatasvir (plus ribavirin if the haemoglobin level is > 10 g/dL at baseline for genotype 3) for 12 wk (or for 24 wk without ribavirin for genotype 3) ⁴
4	Elbasvir/grazoprevir for 12 wk	Elbasvir/grazoprevir for 12 wk or ombitasvir/paritaprevir plus dasabuvir plus ribavirin (if the haemoglobin level is > 10 g/dL at baseline) for 12 wk

¹For HCV genotype 1a: Ombitasvir/paritaprevir/ritonavir plus Dasabuvir plus ribavirin at reduced doses (200 mg thrice weekly to daily) may be also used; ²Ribavirin should be discontinued when hemoglobin decreases by > 2 g/dL despite use of erythropoietin (or in case of severe anaemia (haemoglobin < 8.5 g/dL according to EASL guidelines); ³According to EASL guidelines: (1) antiviral therapy is indicated in those without an indication for kidney transplantation otherwise after kidney transplantation may be preferred; and (2) sofosbuvir should be used with caution (no dose recommendation can currently be given for these patients) and with careful monitoring of renal function; ⁴If treatment is urgently needed. HCV: Hepatitis C virus; AASLD: American Association for the Study of Liver Diseases; EASL: European Association for the Study of the Liver.

treatment testing in patients with genotype 1a and eGFR < 30 mL/min. The higher exposure to antiviral agents, the lower baseline HCV RNA levels in CHC patients and the severe renal impairment attribute for the previous difference. The 3D combination is considered an acceptable alternative for genotype 1 patients based on the results of the smaller RUBY I study and few real life data. The 3D combination is more attractive for patients with at least severe renal impairment and genotype 1b given for 12 wk without RBV. In contrast, the need for the addition of RBV makes it less attractive for such patients with genotype 1a. The safety and efficacy of the 2D regimen in patients with genotype 4 and CKD is currently under evaluation in the RUBY II trial.

The progress in HCV therapy seems to have been minimal for CHC patients with non-1, non-4 genotype and CKD, since current guidelines still recommend the PEG-IFN and RBV combination, which is associated with low efficacy, poor tolerance and potentially several adverse events. Therefore, several efforts have been focused on sofosbuvir based regimens despite its official contraindication in patients with stage 4 or 5 renal impairment (*i.e.*, with GFR < 30 mL/min or under HD)^[51]. The package labels record that up to 20-fold accumulation of the sofosbuvir metabolite GS-331007 is expected in patients with severe renal dysfunction, but the clinical significance of GS-331007 accumulation remains unknown. Moreover, a recent prospective observational study^[52] evaluated the pharmacokinetics of sofosbuvir in 2 dosing (400 mg per day or 3 times per week after HD), in HCV-infected patients under HD. No accumulation of sofosbuvir or GS-331007 was observed, while HD removed 53% of GS-331007.

Since sofosbuvir was chronologically the first licensed current DAA in most countries and is still required for the IFN-free treatment of patients with non-1, non-4 genotype, the safety and efficacy of sofosbuvir based regimens in patients with end stage renal disease (CKD stage 4 or 5) on or off HD have been reported in several

“real life” studies (Table 2). Its overall safety profile has been very good even in this setting with only 6% of patients (14/235) discontinuing therapy and 3.4% of patients (8/235) developing serious adverse events but without drug discontinuation. The SVR rates seem to be comparable with SVR rates in patients with normal renal function, although no definite conclusion can be drawn due to the suboptimal design of the studies, the suboptimal regimens used in some studies according to chronological availability, the small patient numbers and the variable sofosbuvir dosage. Provided that reduced sofosbuvir dosage reduces not only the plasma concentrations of GS-331007, but also the liver concentrations of the active sofosbuvir metabolite, GS-461203^[53] and no major safety issues have been raised with the use of any sofosbuvir dosage in patients with at least severe renal impairment, the standard dose of sofosbuvir (400 mg daily) seems to be optimal even for this setting but should be linked with close clinical, biological, cardiovascular, and therapeutic drug monitoring. Nevertheless, further studies including more patients are required to provide stronger answers to all unresolved issues with sofosbuvir use in patients with CKD. In addition, further studies are needed in children and adolescents with CHC. It is estimated that the prevalence of chronic HCV infection is low (*e.g.*, < 0.5 among European children)^[54] and currently no data on the efficacy and adverse effects of DAA are available in children with CHC.

For KT recipients, IFN-free, sofosbuvir based regimens are highly recommended providing that there is no severe underlying renal dysfunction because they are very effective with good tolerance, safety and minimal drug-drug interactions. Alternatively, the 3D or 2D regimens and the fixed elbasvir/grazoprevir combination could be the additional treatment options for patients with genotypes 1 and 4, but their safety and efficacy in the KT setting has not been evaluated yet. In general, the concurrent use of immunosuppressive agents has not been shown to affect the efficacy of any DAA

regimen and the main concern in transplant patients has been the potential drug interactions. Of the currently licensed DAAs, sofosbuvir, daclatasvir and ledipasvir have no interaction with the usual immunosuppressive agents and require no dosage modifications in transplant patients. On the other hand, simeprevir should not be given in patients receiving cyclosporine and initiation of 3D or 2D regimens should be given with reduced daily dose of cyclosporine (start with 20% of previous dose) or tacrolimus (start with 0.2 mg every 72 h or 0.5 mg once per week) in parallel with close level monitoring and dosage adjustment as required. Similarly, close monitoring of tacrolimus levels should be performed in patients undertaken elbasvir/grazoprevir because their co-administration results in increased tacrolimus plasma concentrations (Table 1).

In conclusion, IFN-free recent DAAs regimens offer for the first time the opportunity to treat effectively and safely most CHC special populations including those with severe renal dysfunction or KT. In particular, excellent IFN and RBV free options are already available for patients with genotypes 1 and 4 and severe renal impairment (eGFR < 30 mL/min) on or off HD such as elbasvir/grazoprevir for genotypes 1 and 4 and 3D for genotype 1b. To date, the patients with severe renal impairment and genotype 2, 3, 5 or 6 can be treated officially with PEG-IFN with or without RBV. Nevertheless, sofosbuvir-based regimens are actually applied if urgent treatment for the liver disease is required. Otherwise, such patients can wait for HCV treatment after KT or for future options with safer kidney profile, anticipated within the next few years.

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