Treatment of Hepatitis C Virus-Infected Patients with Renal Failure

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5.1 Hepatitis C Virus and the Kidney

The prevalence of hepatitis C virus (HCV) infection in patients with renal diseases is higher compared to the general population [1]. Anti-HCV antibody positivity is higher among hemodialysis patients suggesting that dialysis may be a risk factor in transmission of HCV infection [2]. On the other hand chronic HCV infection is independently associated with the development of chronic kidney disease. Fabrizi et al. in their meta-analysis demonstrated that chronic HCV infection was associated with a 43% increase in the incidence of chronic kidney disease [3]. The deposition of immune complexes (anti-HCV and HCV RNA) in the glomeruli appears to be responsible of the pathogenesis. The most common types are membranoproliferative glomerulonephritis usually associated with essential mixed cryoglobulinemia and less frequently membranous nephropathy [4, 5]. The risk of progression to end-stage renal disease (ESRD) in patients with chronic HCV and chronic kidney disease is also higher compared to general population [3]. According to the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines, patients having chronic HCV infection diagnosis should be screened for kidney disease and then followed up annually thereafter with urinalysis and serum creatinine level [3, 6].

Since HCV infection in ESRD patients may lead to increased risk of all-cause and liver-related mortality, HCV-infected patients with renal impairment should be considered for antiviral therapy [7].

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5.2 Patient Selection for Treatment

American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) guidelines recommend treatment for all patients with chronic HCV infection except those with short life expectancies (<1 year) due to underlying comorbidities [8]. Although AASLD no longer recommends prioritization of antiviral treatment in specific populations, treatment should be primarily considered in some specified groups such as patients with advanced fibrosis and persons at greater risk for rapidly progressive fibrosis and cirrhosis, persons who have undergone liver transplantation, patients with extrahepatic manifestations including significant HCV-related kidney disease (mixed cryoglobulinemic vasculitis and HCV-related glomerulonephritis), and HCV-infected persons at greatest risk for transmission. Treatment of chronic HCV infection may reverse proteinuria and nephrotic syndrome and may lead to resolution of cryoglobulinemia in most patients with extrahepatic manifestations. Therefore treatment of HCV-infected patients with especially mixed cryoglobulinemic vasculitis and HCV-related glomerulonephritis may be crucial in terms of resolution of renal involvement [8].

5.2.1 Treatment Options

The selection of the most appropriate regimen depends on genotype, presence or absence of cirrhosis, prior treatment history, and, in patients with renal failure, degree of renal impairment [8, 9].

Chronic kidney diseases (CKD) can be classified into five stages according to the estimated glomerular filtration rate (eGFR) level:

- *CKD stage 1* = normal (eGFR >90 mL/min per 1.73 m^2)
- *CKD stage 2* = mild CKD (eGFR 60–89 mL/min per 1.73 m^2)
- *CKD stage 3* = moderate CKD (eGFR 30–59 mL/min per 1.73 m^2)
- *CKD stage 4* = severe CKD (eGFR 15–29 mL/min per 1.73 m^2)
- *CKD stage 5* = end-stage CKD (eGFR <15 mL/min per 1.73 m^2)

CKD stages listed above determine the dose adjustment and the selection of appropriate treatment regimen [8–10].

– *Patients with mild-to-moderate renal impairment (eGFR ≥ 30 mL/min per 1.73 m^2)*: No dosage adjustments are necessary for directly acting antiviral (DAA) agents in patients with mild-to-moderate renal impairment. These group of patients should be treated according to the general recommendations [10].
– *Patients with severe renal impairment (eGFR <30 mL/min per 1.73 m^2) or on dialysis*: Antiviral treatment should be evaluated on a case-by-case basis since some drugs are not safe in patients with severe renal failure [10].

Combination therapy composed of pegylated interferon and ribavirin was previously the standard regimen for treatment of chronic HCV infection. Sustained virological response (SVR) rates were generally suboptimal (62–64%) in patients with renal disease or on dialysis and the toxicity rate was higher compared to the general population. Severe anemia rates (hemoglobin <8 g/dL) were significantly higher in the combination therapy group [11, 12]. With the advent of DAA agents having higher rate of SVR and lesser toxicity profile, interferon-based standard therapy has been replaced by new antiviral regimens. But still, pegylated interferon and ribavirin may be the only alternatives for treatment in some regions of the world until drug costs decline and access is provided [10].

5.3 Safety of Antiviral Drugs in Renal Impairment

Although sofosbuvir and ribavirin are mainly eliminated by the kidneys, principal elimination route of the remaining DAA agents is biliary and does not require dose adjustments in case of renal impairment [8, 9].

5.3.1 Sofosbuvir

In patients with severe renal impairment the exposure to nucleoside metabolite of sofosbuvir is increased [9, 13]. Whereas levels of the drug and its metabolite among patients with eGFR ≥30 mL/min per 1.73 m^2 are comparable to patients with normal renal function, drug levels are higher among patients with eGFR <30 mL/min per 1.73 m^2 or with ERDS. Due to high exposure to the metabolite and safety concern, sofosbuvir currently is not recommended in patients with severe renal impairment (eGFR <30 mL/min per 1.73 m^2) [8, 9].

5.3.2 Pegylated Interferon

Since half-life of the pegylated interferon increases in patients under hemodialysis this may lead to higher rate of adverse events [14, 15]. Pegylated interferon when used for treatment of chronic HCV infection in patients with renal impairment may lead to development or exacerbation of glomerulonephritis or vasculitis [16, 17]. Therefore dose reduction is required in case of renal failure and varies according to the formulation prescribed as stated below:

Pegylated interferon alfa-2a:

- If CrCl <30 mL/min: The dose should be reduced to 135 mcg once weekly, and the patient should be monitored for side effects.
- In case of ESRD requiring hemodialysis: The dose should be reduced to 135 mcg once weekly, and the patient should be monitored for side effects. If severe

adverse reactions or laboratory abnormalities develop, the dose should be reduced to 90 mcg once weekly until adverse reactions resolve [18].

Pegylated interferon alfa-2b:
- If CrCl <50 mL/min: Dual therapy of pegylated interferon alfa-2b and ribavirin is not recommended.
- If CrCl is 30–50 mL/min: Pegylated interferon alfa-2b is recommended as monotherapy and the dose should be reduced by 25%.
- If CrCl is 10–29 mL/min or the patient is on hemodialysis: The dose should be reduced by 50%.

If renal function declines during treatment, the drug should be discontinued [19].

5.3.3 Ribavirin

In case of renal insufficiency, accumulation of ribavirin may lead to severe anemia even at lower doses. Although it was contraindicated in ESRD due to the risk of anemia, low doses of ribavirin increase SVR rates. Therefore dose adjustment is required in patients with severe renal insufficiency or ESRD [7, 20]. But the dose reduction recommendations differ according to the manufacturer:

- The manufacturer of Rebetol contraindicated the use of ribavirin in patients with creatinine clearance of <50 mL/min. However the other manufacturer (Copegus) is approved in the United States for patients with ESRD and for those on hemodialysis as reduced doses [21, 22]. If the hemoglobin level decreases to <8.5 g/dL, ribavirin should be interrupted temporarily [7, 21, 22].

5.4 Efficacy of Antiviral Drugs in Renal Impairment

5.4.1 Pegylated Interferon and Ribavirin Combination Therapy

Pegylated interferon and ribavirin combination therapy was until recently the only treatment modality of chronic HCV infection but has been replaced currently by regimens including DAAs. But in resource-limited areas where DAAs are not available pegylated interferon and ribavirin may still be the only alternatives for treatment.

Fabrizi et al., in their meta-analysis of 24 prospective studies including 529 HCV-infected patients on hemodialysis, analyzed the efficacy of interferon-alpha monotherapy. SVR-48 rate was achieved in only 39% of cases [23]. However, studies evaluating the efficacy of pegylated interferon and reduced-dose ribavirin treatment in Asian population revealed that SVR-24 rate was approximately 60% [11, 12]. On the other hand, Rendina et al. in their study evaluating SVR-24 rate in 35

patients receiving pegylated interferon and ribavirin revealed that 97% of the patients achieved SVR at 24th week [24]. But it's noteworthy that 54% of the patients were infected with genotypes other than genotype 1 and this may be the reason of the very high SVR rate.

Furthermore, it is well known from the clinical studies that patients with HCV genotype 2 or 3 infection usually have higher SVR rates than those with genotype 1 or 4 infection [25].

Duration of treatment is 48 weeks for genotypes 1 and 4, and 24 weeks for genotypes 2 and 3 [24, 25].

5.4.1.1 Sofosbuvir-Based Regimens

In patients with mild-to-moderate renal impairment (eGFR ≥30 mL/min per 1.73 m^2) no dose adjustments are required for sofosbuvir-based regimens. But in case of severe renal failure (eGFR <30 mL/min per 1.73 m^2) data on the safety and efficacy of sofosbuvir-based regimens are limited [8, 9].

In an international prospective observational cohort study (TARGET), safety and efficacy of sofosbuvir-containing regimens in patients with mild-to-severe renal dysfunction (eGFRs <30, 31–45, 46–60, and >60 mL/min per 1.73 m^2) have been evaluated in real-world settings. A total of 1789 patients were enrolled in the study; 73 with eGFR ≤45 mL/min per 1.73 m^2 (18 with eGFR ≤30 mL/min per 1.73 m^2, 5 on dialysis) were compared to 1716 with eGFR >45 mL/min per 1.73 m^2. Antiviral regimens included in this study were sofosbuvir + pegylated interferon + ribavirin, sofosbuvir + simeprevir, sofosbuvir with or without ribavirin, or sofosbuvir + ribavirin. SVR rates were similar, ranging from 82 to 83% among all patients with different eGFR ranges. SVR was achieved in 83% of patients with renal impairment (eGFR ≤45 mL/min per 1.73 m^2) treated with sofosbuvir-containing regimens. The number of individuals with eGFR ≤30 mL/min was small, but worsening of renal function and renal adverse events was more frequently reported among these group of patients [8, 26].

Aggarval et al. in their study evaluated 14 patients with chronic HCV infection and ESRD who received sofosbuvir-based regimens retrospectively. Most patients were on chronic renal replacement therapy. All treatment regimens included sofosbuvir, and 4 out of 14 treatment courses included ribavirin. The first 7 out of 14 treatment courses used half-dose of sofosbuvir. Two patients were switched to full-dose sofosbuvir dosing at 4–6 weeks after initiation of the antiviral treatment. SVR-12 was reached in 13 out of 14 patients (92.8%). Patient who had relapsed was retreated for 24 weeks with full dose of sofosbuvir plus ledipasvir and SVR-12 was achieved. Minor adverse effects were headache in one, acid reflux in one, and fatigue in one patient. Two patients developed anemia and transfusion was required in one of them who was receiving ribavirin and developed sepsis [27].

Food and Drug Administration (FDA) approved this drug for patients with eGFR >30 mL/min per 1.73 m^2 [7]. Although some studies demonstrated that full-dose sofosbuvir may be safe, safe and effective doses of sofosbuvir have to be established in patients with eGFR <30 mL/min per 1.73 m^2 [28, 29]. If sofosbuvir-containing regimens have to be administered in patients with severe renal impairment it should only be prescribed by or in consultation with an expert in this field.

5.4.1.2 Daclatasvir-Based Regimens

Daclatasvir is primarily metabolized by the liver and renal elimination is minor. Although it is not among the recommended regimens according to the AASLD or European Association for the Study of the Liver (EASL) guidelines, in countries where daclatasvir plus asunaprevir is a recommended combination, this regimen is safe in patients with severe renal impairment, including HCV genotype 1 patients with hemodialysis [30].

5.4.2 Paritaprevir, Ritonavir, Ombitasvir, Dasabuvir (PrOD) with or Without Ribavirin

RUBY-1 clinical trial evaluated the efficacy of PrOD in 20 patients without cirrhosis infected with genotype 1 HCV, with stage 4 or stage 5 CKD (13 on dialysis). Enrolled patients were treated for 12 weeks with PrOD. Patients infected with genotype 1b were treated without ribavirin, whereas ribavirin (200 mg/day) was added to the treatment in 13 patients infected with genotype 1a. The SVR-12 rate was 95% (18/19) with only one patient relapsing and one patient died from a cause not attributed to the drug. Most adverse events were mild or moderate. Patients infected with genotype 1a had more frequent side effects related to ribavirin, including anemia, fatigue, and nausea, and ribavirin was interrupted in 69% of the patients. Erythropoietin treatment was required in four patients and only three patients restarted ribavirin [8, 9, 31]. Based on these findings, EASL guidelines recommend PrOD as an option for the treatment of HCV genotype 1 infection in patients with mild-to-moderate or severely compromised renal function and in ESRD whereas AASLD guidelines do not recommend as a first-line agent [8, 9].

5.4.2.1 Elbasvir-Grazoprevir

In a study (C-SURFER) evaluating the safety and efficacy of 12 weeks of elbasvir-grazoprevir therapy versus placebo, 122 HCV genotype 1-infected patients with CKD stages 4/5 were included. Seventy-five percent of the patients were on dialysis and only 6% had cirrhosis. The SVR-12 rates (intention-to-treat and modified intention-to-treat analysis) were 94% and 99%, respectively. The most common adverse events were headache, nausea, and fatigue, occurring at similar frequencies in patients receiving placebo. None of the patients discontinued therapy due to adverse effects, but one case of congestive heart failure was attributed to elbasvir-grazoprevir [32].

Based on these data, the fixed-dose combination elbasvir/grazoprevir is recommended for the treatment of HCV genotype 1 infection in patients with severely compromised renal function. Although genotype 4-infected persons were not evaluated in C-SURFER trial, results of the studies in with normal renal function can also be adapted to genotype 4-infected persons with CKD stage 4/5 [8].

Genotype 1a-infected patients harboring preexisting NS5A resistance-associated substitutions have a lower SVR12 rate with the 12-week regimen in studies

enrolling patients with normal renal function. Although extending the duration to 16 weeks and adding weight-based ribavirin may overcome this issue, these require further study [8–10].

5.4.2.2 Glecaprevir-Pibrentasvir

Approved in August 2017 by FDA, this pangenotypic drug is a fixed-dose combination of glecaprevir, an NS3/4A protease inhibitor, and pibrentasvir an NS5A inhibitor [33]. It is contraindicated in patients with decompensated cirrhosis (Child-Pugh class B or C). EXPEDITION-4 trial including 104 patients with genotype 1–6 infection and with stage 4 or 5 CKD, 82% of whom were on dialysis, revealed that treatment with glecaprevir-pibrentasvir for 12 weeks led to 98% SVR-12. Four percent of the participants discontinued the drug because of adverse events [34]. These results are promising in terms of treatment safety and efficacy.

5.4.3 Recommended Regimens

Patients with mild-to-moderate renal impairment (eGFR ≥30 mL/min per 1.73 m^2) can be treated according to the general recommendations since no dose adjustments for DAAs are necessary [8, 9].

According to AASLD guidelines, in patients with severe renal impairment (eGFR <30 mL/min per 1.73 m^2) daily fixed-dose combination of glecaprevir/pibrentasvir is the recommended regimen for all genotypes (genotypes 1–6) for 8–16 weeks. Fixed-dose combination of elbasvir/grazoprevir is recommended for genotypes 1a–b and genotype 4 for 12 weeks [8].

According to the EASL guidelines patients with severe renal impairment (eGFR <30 mL/min per 1.73 m^2) or with end-stage renal disease on hemodialysis infected with genotype 1a or genotype 4 should be treated with PrOD or with elbasvir/grazoprevir plus ribavirin (daily 200 mg) if Hgb level is >10 g/dL for 12 weeks. In patients infected with genotype 1b the treatment regimen is the same but ribavirin is not required. In case of urgent therapy, patients with severe renal impairment (eGFR <30 mL/min per 1.73 m^2) or with end-stage renal disease on hemodialysis infected with genotype 2 or genotype 3 should receive fixed-dose combination of sofosbuvir and velpatasvir, or combination of sofosbuvir and daclatasvir for 12 weeks. In genotype 3-infected patients if Hgb level is >10 g/dL, ribavirin (daily 200 mg) should be added; if not, the treatment duration should be prolonged to 24 weeks. Since renal function may worsen under these treatment regimens the patient should be closely monitored and interrupted if required [9].

In many countries, the access to new DAAs may be limited and the combination of pegylated interferon-alpha and ribavirin may still be the standard treatment modality in these group of patients. Recommended regimens according to different major guidelines are summarized in Table 5.1.

Table 5.1 Recommended regimens in patients with chronic kidney disease stage 4 or 5 or end-stage renal disease in treatment-naive and experienced kidney-transplant patients with or without compensated cirrhosis [8, 9]

AASLD				EASL		
	Genotype	Duration	Rating	Genotype	Duration	Rating
Daily fixed-dose combination of glecaprevir (300 mg)/ pibrentasvir (120 mg)	1–6	8 weeks[a] 12 weeks[b,c] 16 weeks[d]	I, B			
Daily fixed-dose combination of elbasvir (50 mg)/ grazoprevir (100 mg)	1a, 1b, 4	12 weeks	I, B	1a[e], 1b, 4[e]	12 weeks	B1, A1, B1
Paritaprevir (75 mg), ritonavir (50 mg), ombitasvir (12.5 mg), dasabuvir (250 mg)				1a[e], 1b, 4[e]	12 weeks	B1, A1, B1

[a]Without cirrhosis
[b]Compensated cirrhosis except genotypes 5 and 6
[c]NS3 or NS5A experienced
[d]Genotype 3 treatment experienced
[e]Plus ribavirin (daily 200 mg) if Hgb level is >10 g/dL for 12 weeks

5.5 Kidney-Transplant Patients

Since interferon is associated with an increased risk of acute rejection of the allograft interferon-based regimens are contraindicated in patients having had kidney transplantation [35]. Therefore interferon-free regimens are preferred in the setting of kidney transplantation.

Recommended antiviral regimens are the same as for the general population in kidney-transplant recipients with eGFR >30 mL/min per 1.73 m^2. But due to the limited experience, velpatasvir is not yet recommended for use in transplant patients. However, EASL guidelines recommend velpatasvir as an option in transplant recipients but warn against the possible drug interactions with immunosuppressive agents [9, 10].

In patients with eGFR <30 mL/min per 1.73 m^2 glecaprevir/pibrentasvir ranks among the recommended regimens. It is contraindicated in Child-Pugh class B and C cirrhosis, and it should be cautious against the possible drug interactions with immunosuppressive agents. For patients with genotype 1 or 4 infection, elbasvir/grazoprevir or PrOD may be alternative regimens, but the drug-drug interactions should be evaluated very carefully [10].

Various clinical trials have been designed to evaluate the efficacy of DAAs in transplanted patients:

The safety and efficacy of the combination of ledipasvir/sofosbuvir were evaluated in 114 kidney-transplant recipients in a phase 2 trial. Patients included in the study had been transplanted for longer than 6 months. Ninety-one percent of the patients had genotype 1 or 4. SVR-12 was achieved in all of the patients. In four patients with an eGFR >40 mL/min at screening eGFR decreased to <30 mL/min and increased to >30 mL/min in three of these patients during the treatment [36].

Table 5.2 Recommended and alternative regimens in treatment-naive and experienced kidney-transplant patients with or without compensated cirrhosis [8]

Recommended	Genotype	Duration	Rating
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)	1–6	12 weeks	I, A[a] IIa, C[b]
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	1, 4	12 weeks	I, A
Alternative			
Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) plus low initial dose of ribavirin (600 mg; increase as tolerated)	2, 3, 5, 6	12 weeks	II, A

[a]Genotypes 2, 3, and 6
[b]Genotype 5

In two other studies enrolling totally 45 kidney-transplanted patients efficacy of sofosbuvir-based regimens was evaluated. Ledipasvir, ribavirin, simeprevir, and daclatasvir were the antivirals combined with full-dose sofosbuvir. Sawinski et al. discussed treatment of patients with an eGFR <30 mL/min with their nephrologist whereas in the study of Kamar et al. all patients had eGFR of 30 mL/min or greater. Majority of the patients included in these studies had genotype 1 and advanced fibrosis. SVR-12 was achieved in all of the patients in both studies [37, 38].

Efficacy of the recently approved glecaprevir/pibrentasvir was evaluated in a phase 3 study (MAGELLAN-2) including 80 liver and 20 kidney-transplant patients. SVR-12 rate was 99% and the safety profile was very good [39].

Based on the above studies' data, recommended regimens in kidney-transplant patients according to AASLD/IDSA guidelines are summarized in Table 5.2.

In conclusion, with the advent of the directly acting antivirals SVR-12 rate is over 95% and near to 100% in HCV-infected patients with renal failure. Glecaprevir/pibrentasvir is recommended in all genotypes whereas elbasvir-grazoprevir is effective against genotypes 1a, 1b, and 4 in patients with renal impairment without dose adjustments. Paritaprevir, ritonavir, ombitasvir, and dasabuvir with or without ribavirin are other alternatives in patients infected with genotypes 1a, 1b, and 4 with SVR-12 rate of 95%. But in resource-limited areas where directly acting antivirals are not available pegylated interferon and reduced-dose ribavirin may still be the only alternatives for treatment.

References

1. Ladino M, Pedraza F, Roth D. Hepatitis C virus infection in chronic kidney diseases. J Am Soc Nephrol. 2016;27:2238–46.
2. Finelli L, Miller JT, Tokars JI, et al. National surveillance of dialysis-associated diseases in the United States, 2002. Semin Dial. 2005;18:52.
3. Fabrizi F, Verdesca S, Messa P, et al. Hepatitis C virus infection increases the risk of developing chronic kidney disease: a systematic review and meta-analysis. Dig Dis Sci. 2015;60(12):3801–13.
4. Johnson RJ, Gretch DR, Couser WG, et al. Hepatitis C virus-associated glomerulonephritis. Effect of alpha-interferon therapy. Kidney Int. 1994;46:1700.

5. McGuire BM, Julian BA, Bynon JS Jr, et al. Brief communication: glomerulonephritis in patients with hepatitis C cirrhosis undergoing liver transplantation. Ann Intern Med. 2006;144:735.
6. Levey AS, Atkins R, Coresh J, et al. Chronic kidney disease as a global public health problem: approaches and initiatives—a position statement from kidney disease improving global outcomes. Kidney Int. 2007;72:247.
7. Dumortier J, Bailly F, Pageaux GP, et al. Sofosbuvir-based antiviral therapy in hepatitis C virus patients with severe renal failure. Nephrol Dial Transplant. 2017;32:2065–71.
8. https://www.hcvguidelines.org/unique-populations.
9. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2018. J Hepatol. 2018;69(2):461–511.
10. Leise MD, Rostaing L. Treatment of chronic hepatitis C infection in adults with renal impairment. UpToDate Version 19.0.
11. Liu CH, Huang CF, Liu CJ, et al. Pegylated interferon-α2a with or without low-dose ribavirin for treatment-naive patients with hepatitis C virus genotype 1 receiving hemodialysis: a randomized trial. Ann Intern Med. 2013;159:729.
12. Tseng PL, Chen TC, Chien YS, et al. Efficacy and safety of pegylated interferon alfa-2b and ribavirin combination therapy versus pegylated interferon monotherapy in hemodialysis patients: a comparison of 2 sequentially treated cohorts. Am J Kidney Dis. 2013;62:789.
13. Gilead. Sofosbuvir for treatment of chronic hepatitis C infection. Briefing document prepared for the Antiviral Drugs Advisory Committee Meeting, 25 Oct 2013. http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/antiviraldrugsadvisorycommittee/ucm371877.pdf.
14. Rostaing L, Chatelut E, Payen JL, et al. Pharmacokinetics of alphaIFN-2b in chronic hepatitis C virus patients undergoing chronic hemodialysis or with normal renal function: clinical implications. J Am Soc Nephrol. 1998;9:2344.
15. Uchihara M, Izumi N, Sakai Y, et al. Interferon therapy for chronic hepatitis C in hemodialysis patients: increased serum levels of interferon. Nephron. 1998;80:51.
16. Beuthien W, Mellinghoff HU, Kempis JV. Vasculitic complications of interferon-alpha treatment for chronic hepatitis C virus infection: case report and review of the literature. Clin Rheumatol. 2005;24:507.
17. Ohta S, Yokoyama H, Wada T, et al. Exacerbation of glomerulonephritis in subjects with chronic hepatitis C virus infection after interferon therapy. Am J Kidney Dis. 1999;33:1040.
18. Pegylated interferon (peginterferon) alfa-2a: drug information. UpToDate Lexicomp.
19. Pegylated interferon (peginterferon) alfa-2b: drug information. UpToDate Lexicomp.
20. Kamar N, Boulestin A, Selves J, et al. Factors accelerating liver fibrosis progression in renal transplant patients receiving ribavirin monotherapy for chronic hepatitis C. J Med Virol. 2005;76:61.
21. Rebetol (ribavirin). US FDA approved product information. National Library of Medicine. http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=04d2b6f4-bd9b-4871-9527-92c81aa2d4d0.
22. Copegus (ribavirin). US FDA approved product information. National Library of Medicine. http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=d370635f-5530-4d42-a019-d76b61639787.
23. Fabrizi F, Dixit V, Messa P, et al. Interferon monotherapy of chronic hepatitis C in dialysis patients: meta-analysis of clinical trials. J Viral Hepat. 2008;15(2):79–88.
24. Rendina M, Schena A, Castellaneta NM, et al. The treatment of chronic hepatitis C with peginterferon alfa-2a (40 kDa) plus ribavirin in haemodialysed patients awaiting renal transplant. J Hepatol. 2007;46(5):768–74.
25. Liu CH, Kao JH. Treatment of hepatitis C virus infection in patients with end-stage renal disease. J Gastroenterol Hepatol. 2011;26(2):228–39.
26. Saxena V, Koraishy FM, Sise ME, et al. HCV-TARGET. Safety and efficacy of sofosbuvir-containing regimens in hepatitis C-infected patients with impaired renal function. Liver Int. 2016;36(6):807–16.
27. Aggarwal A, Yoo ER, Perumpail RB, et al. Sofosbuvir use in the setting of end-stage renal disease: a single center experience. J Clin Transl Hepatol. 2017;5:23–6.

28. Singh T, Guirguis J, Anthony S, et al. Sofosbuvir-based treatment is safe and effective in patients with chronic hepatitis C infection and end stage renal disease: a case series. Liver Int. 2016;36:802.
29. Desnoyer A, Pospai D, Lê MP, et al. Pharmacokinetics, safety and efficacy of a full dose sofosbuvir-based regimen given daily in hemodialysis patients with chronic hepatitis C. J Hepatol. 2016;65:40.
30. Omata M, Kanda T, Wei L, et al. APASL consensus statements and recommendation on treatment of hepatitis C. Hepatol Int. 2016;10(5):702–26.
31. Pockros PJ, Reddy KR, Mantry PS, et al. Efficacy of direct-acting antiviral combination for patients with hepatitis C virus genotype 1 infection and severe renal impairment or end-stage renal disease. Gastroenterology. 2016;150:1590.
32. Roth D, Nelson DR, Bruchfeld A, et al. Grazoprevir plus elbasvir in treatment-naive and treatment experienced patients with hepatitis C virus genotype 1 infection and stage 4-5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. Lancet. 2015;386(10003):1537–45.
33. https://www.accessdata.fda.gov/scripts/cder/daf/.
34. Gane E, Lawitz E, Pugatch D, et al. EXPEDITION-4: efficacy and safety of glecaprevir/pibrentasvir (ABT-493/ABT-530) in patients with renal impairment and chronic hepatitis C virus genotype 1-6 infection. In: Presented at the American Association for the Study of Liver Diseases Liver Meeting, Boston, MA, 11–15 Nov 2016.
35. 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;8:S1.
36. Colombo M, Aghemo A, Liu H, et al. Treatment with ledipasvir-sofosbuvir for 12 or 24 weeks in kidney transplant recipients with chronic hepatitis C virus genotype 1 or 4 infection: a randomized trial. Ann Intern Med. 2017;166(2):109–17.
37. 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 Transpl. 2016;16(5):1474–9.
38. 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.
39. Reau N, Kwo PY, Rhee S. MAGELLAN-2: safety and efficacy of glecaprevir/pibrentasvir in liver or renal transplant adults with chronic hepatitis C genotype 1–6 infection. In: EASL International Liver Meeting, Apr 2017.