Unique Patient Populations: Patients with Renal Impairment

HCV is independently associated with the development of chronic kidney disease (Rogal, 2016); (Fabrizi, 2015). A recent meta-analysis demonstrated that chronic HCV infection was associated with a 51% increase in the risk of proteinuria and a 43% increase in the incidence of chronic kidney disease (Fabrizi, 2015). There is also a higher risk of progression to ESRD in persons with chronic HCV and chronic kidney disease and an increased risk of all-cause mortality in persons on dialysis (Lee, 2014); (Fabrizi, 2012).

Recommended Dosage Adjustments for Patients with Mild to Moderate Renal Impairment

RECOMMENDED	RATING
For patients with mild to moderate renal impairment (eGFR 30 mL/min-80 mL/min), no dosage adjustment is required when using daclatasvir (60 mg*), fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg), fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg), or fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with (or without for HCV genotype 4 infection) twice-daily dosed dasabuvir (250 mg), simeprevir (150 mg), or sofosbuvir (400 mg) to treat or retreat HCV infection in patients with appropriate genotypes.	I, A

Recommended Regimens by evidence level and alphabetically for:

Patients with Severe Renal Impairment, Including Severe Renal Impairment (eGFR <30 mL/min) or End-Stage Renal Disease (ESRD)

RECOMMENDED	DURATION	RATING
For patients with genotype 1a, or 1b, or 4 infection and eGFR below 30 mL/min, for whom treatment has been elected, daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	I, B
For patients with genotype 1b infection and eGFR below 30 mL/min, for whom treatment has been elected, daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg)	12 weeks	IIb, B
For patients with HCV genotype 2, 3, 5, or 6 infection and eGFR below 30 mL/min, for whom the urgency to treat is high, PEG-IFN and dose-adjusted ribavirin** (200 mg daily)	-	IIb, B

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.
** Caution is recommended in this group, owing to the potential for hemolytic anemia due to impaired renal clearance in this population, and ribavirin should be restricted to those with a baseline hemoglobin concentration above 10 g/dL.

Alternative Regimen for Genotype 1a-infected Patients with eGFR Below 30 mL/min

ALTERNATIVE	DURATION	RATING
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and dose-adjusted ribavirin** (200 mg daily)	12 weeks	IIb, B

** Caution is recommended in this group, owing to the potential for hemolytic anemia due to impaired renal clearance in this population, and ribavirin should be restricted to those with a baseline hemoglobin concentration above 10 g/dL.

A recent study (C-SURFER) evaluated the safety and efficacy of 12 weeks of a second-generation NS3/NS4A protease inhibitor, grazoprevir (100 mg once daily) and an NS5A inhibitor, elbasvir (50 mg once daily) versus placebo for HCV genotype 1 patients with CKD stages 4/5. The original study was designed to randomize eligible patients to either immediate or deferred treatment with elbasvir and grazoprevir. The delayed treatment arm received placebo and was treated with elbasvir and grazoprevir later. The data for the immediate treatment arm have been published (Roth, 2015). The study participants were HCV genotype 1, CKD stages 4/5 (eGFR <30 mL/min), 75% on hemodialysis, 45% were African Americans. Small numbers of patients with compensated cirrhosis were allowed. The study reported an ITT and modified ITT of 94% and 99% for SVR12. There were no changes in hemoglobin or other adverse events or erythropoietin use in the treatment groups compared to placebo, while most patients in the treatment group normalized ALT and AST values compared to placebo. None of the genotype 1a patients with baseline NS5A RASs experienced viral relapse; the only reported relapse occurred in a patient with genotype 1b. The basis for the lack of impact of NS5A RASs on SVR rates in this population is unclear, but may relate to moderately increased AUCs of grazoprevir or elbasvir observed in stage 4/5 CKD (Elbasvir and Grazoprevir PI, 2016). Based on these data, the fixed-dose combination elbasvir (50 mg) and grazoprevir (100 mg) (hereafter, elbasvir/grazoprevir) is recommended for the treatment of HCV genotype 1 infection in patients with severely compromised renal function. No strong recommendation for NS5A RAS testing can be made in this population. While C-SURFER did not evaluate patients with genotype 4 infection, it is likely that the high efficacy of elbasvir/grazoprevir in genotype 1 and 4 infection in persons with normal renal function can be extrapolated to genotype 4-infected persons with CKD stage 4/5. Treatment with elbasvir/grazoprevir in persons with CKD has been shown to be cost effective in the United States (Elbasha, 2016).

Sofosbuvir and ribavirin are renally eliminated. Safe and effective doses of sofosbuvir in those with eGFR less than 30 mL/min have not been established. If urgency for treatment is high, there is accumulating evidence on use of sofosbuvir-based regimens in persons with eGFR <30 mL/min (Desnoyer, 2016).

Though recommendations exist for reducing ribavirin dose and/or dosing frequency in those with renal impairment, this drug is poorly tolerated in this population. Daclatasvir, elbasvir/grazoprevir, ledipasvir, PrOD, and simeprevir are primarily hepatically metabolized and undergo minimal renal elimination. While exposures to many of these agents are higher in severe renal impairment presumably due to effects of uremic toxins, parathyroid hormone, and/or cytokines on hepatic metabolism, they do not require dose adjustments in renal impairment. Refer to the table on drug dosing in renal impairment.

The HCV-TARGET study is an ongoing prospective observational cohort study that evaluates the use of direct-acting antiviral (DAA) agents across clinical practices in North America and Europe. The study reported the 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) (Saxena, 2016). The patients received different regimens that included sofosbuvir (PEG-IFN, ribavirin, and sofosbuvir; simeprevir and sofosbuvir with or without ribavirin; or sofosbuvir and ribavirin). Overall, the regimens were well tolerated with no increased discontinuation among patients with low eGFRs. The rates of sustained virologic response at 12 weeks (SVR12) were similar across the groups regardless of renal function. Notably, there was progressive deterioration of renal function and renal symptoms in the patients with eGFRs below 30 mL/min, suggesting the need for close monitoring of these patients. In summary, patients with low baseline renal function have a higher frequency of

anemia, worsening renal dysfunction, and more severe adverse events, but treatment responses remain high and comparable to those without renal impairment.

Data on patients treated with a regimen of simeprevir and low-dose sofosbuvir without ribavirin have been reported. In one study, 18 HCV-infected patients (11 requiring hemodialysis, 3 with a mean eGFR of 16 mL/min) underwent open-label treatment with simeprevir and sofosbuvir. All patients received full-dose simeprevir (150 mg) daily. Sofosbuvir dose was reduced to 200 mg daily in 15 patients and 400 mg every other day in 3 patients. The length of therapy was 12 weeks in 17 patients and 24 weeks in 1 patient with cirrhosis. One patient developed new onset hepatic encephalopathy and another developed uncontrolled diarrhea, both requiring hospitalizations during treatment. Minor adverse events were fatigue (28%), anemia (11%), rash or itching (11%), and nausea (5%), and were managed medically; there were no treatment discontinuations. Of the 16 patients who completed treatment, only 9 patients reached relevant milestones. Per the current per-protocol analysis, SVR4 was seen in 91% and SVR12 in 89%. One patient with cirrhosis (who had a prior HCV protease inhibitor-containing treatment failure) relapsed within 4 weeks after completion of treatment. In summary, the regimen of simeprevir and reduced-dose sofosbuvir is safe and well tolerated. In another study, 12 patients with eGFRs below 30 mL/min received sofosbuvir (400 mg) and simeprevir (150 mg). The regimen was well tolerated and resulted in viral suppression in all patients (Nazario, 2016).

Twenty patients with HCV genotype 1 infection and stage 4 or 5 (eGFR <30 mL/min) chronic kidney disease (CKD) without cirrhosis were treated with daily fixed-dose combination of paritaprevir (150 mg), ritonavir (100 mg), and ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) (PrOD) with or without ribavirin in a multicenter, open-label phase IIb study (Pockros, 2016). Notably, 70% of patients were black and 65% had CKD requiring hemodialysis. Ribavirin (in those with HCV genotype 1a only) was dosed 4 hours before hemodialysis and monitored with weekly hemoglobin assessments. Ribavirin doses were suspended for a 2 g/dL or more drop in hemoglobin level and resumed when the hemoglobin level normalized. All patients (10/10) achieved SVR4 (Pockros, 2016). Interestingly, the use of ribavirin was associated with more of a drop in hemoglobin level, and 8 of 13 patients required interruption of ribavirin dosing. Four of 8 patients also required erythropoietin treatment during the first 7 weeks of therapy. Mean drug concentrations (C_{trough}) of all drugs were measured and levels were within the range that was observed with previous pharmacokinetic studies in healthy volunteers. In summary, most patients with HCV genotype 1 with or without cirrhosis who were treated with PrOD with or without ribavirin achieved viral suppression. However, ribavirin-induced anemia can occur frequently, and close monitoring of all patients and judicious dose reductions of ribavirin are required. As described in other sections, PrOD should be used with caution in patients with Child Turcotte Pugh A cirrhosis and avoided in patients with CTP B or C cirrhosis.

For patients infected with HCV genotypes 2, 3, 5, or 6 with eGFR ≤30 mL/min for whom the urgency to treat is high, and for whom treatment has been elected before kidney transplantation, standard treatment remains PEG-IFN plus dose-adjusted ribavirin (200 mg daily). However, caution is recommended in this group, owing to the potential for hemolytic anemia due to impaired renal clearance in this population, and ribavirin should be restricted to those with a baseline hemoglobin concentration above 10 g/dL. Ribavirin should be discontinued if hemoglobin level declines by more than 2 g/dL despite the use of erythropoietin. Few data exist to guide treatment with current IFN-free regimens. Consideration may be given on an individualized basis to a sofosbuvir-based regimen, with careful attention paid to patient comorbidities and toxicities. However, additional pangenotypic options are anticipated in this population in mid-2017.

Unique Patient Populations Table: Dose Adjustments Needed for Patients with Renal Impairment

Renal Impairment	Mild	Moderate	Severe	ESRD with HD
eGFR (mL/min)	50-80	30-50	<30	
PEG-IFN	PEG-IFN (2a) 180 µg; PEG-IFN (2b) 1.5 µg/kg	PEG-IFN (2a) 180 µg; PEG-IFN (2b) 1 µg/kg (25% reduction)	PEG-IFN (2a) 135 µg; PEG-IFN (2b) 1 µg/kg (50% reduction)	PEG-IFN (2a) 135 µg/wk or PEG-IFN (2b) 1 µg/kg/wk or standard IFN 3 mU 3x/wk
Ribavirin	Standard	Alternating doses 200 mg and 400 mg every other day	200 mg/d	200 mg/d
Sofosbuvir	Standard	Standard	Limited data available	Limited data available
Ledipasvir	Standard	Standard	Data not available	Data not available
Daclatasvir	Standard	Standard	Limited data available	Limited data available
Ombitasvir	Standard	Standard	Limited data available	Limited data available
Dasabuvir	Standard	Standard	Limited data available	Limited data available
Paritaprevir	Standard	Standard	Limited data available	Limited data available
Simeprevir	Standard	Standard	Standard	Limited data available
Velpatasvir	Standard	Standard	Data not available	Data not available
Elbasvir	Standard	Standard	Standard	Standard
Grazoprevir	Standard	Standard	Standard	Standard
Abbreviations: eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HD, hemodialysis.				

DAA Therapy in Kidney Transplant Patients

A recent clinical trial described the safety and efficacy of ledipasvir/sofosbuvir in kidney transplant recipients (N=114) who were more than 6 months posttransplant (Colombo, 2016). The patients were mainly infected with genotype 1 or 4, with or without cirrhosis, and with or without prior treatment experience. Patients were randomized to receive ledipasvir/sofosbuvir for 12 or 24 weeks. Prior to treatment, median eGFR was 50 mL/min for those who were treated for 12 weeks and 60 mL/min for those who were treated 24 weeks. 96% achieved SVR12. Adverse events were common (64%) and 11% had a serious adverse event, but fewer than 1% discontinued treatment due to adverse effects (Colombo, 2016). In 3 patients, eGFR increased to greater than 30 mL/min at the last visit recorded; one patient who had interrupted study treatment had a final value of 14.4 mL/min. All but 1 of the 6 patients with cirrhosis whose eGFR decreased to below 40 mL/min continued study treatment without interruption; none permanently discontinued study treatment.

Several additional reports have described successful outcomes with DAA combination therapy in renal-transplant patients (Sawinski, 2016); (Kamar, 2016). Sawinski et al treated 20 HCV-infected kidney transplant recipients (88% genotype 1, half with advanced fibrosis, and 60% treatment-experienced) with sofosbuvir-based regimens and reported resulted 100%

SVR (Sawinski, 2016). Various sofosbuvir-based DAA combinations were used, including simeprevir plus sofosbuvir (n=9), ledipasvir/sofosbuvir (n=7), sofosbuvir plus ribavirin (n=3), and daclatasvir plus sofosbuvir (n=1). Two patients required dose reductions due to anemia (associated with ribavirin use), however no significant changes in serum creatinine, proteinuria, or graft rejection were seen before or after treatment. Forty-five percent of patients required dose reduction of immunosuppressive agents while on therapy (Sawinski, 2016).

A study of 25 kidney transplant recipients with chronic HCV infection that were treated with sofosbuvir-based regimens reported a 100% SVR (Kamar, 2016). Patients included were infected with genotype 1 (76%), had eGFR >30 mL/min (100%), and had advanced fibrosis (44%). Treatment regimens included ledipasvir/sofosbuvir (n=9), daclatasvir plus sofosbuvir (n=4), sofosbuvir plus ribavirin (n=3), ledipasvir/sofosbuvir plus ribavirin (n=1), simeprevir plus sofosbuvir plus ribavirin (n=1), simeprevir plus sofosbuvir (n=6), and sofosbuvir plus pegylated IFN/ribavirin (n=1). Treatment was well tolerated without any discontinuations, dose reductions, graft rejections, or changes in serum creatinine levels, and no drug interactions with calcineurin inhibitors were observed (Kamar, 2016).

Another study that treated three HCV genotype 4 kidney transplant patients with sofosbuvir (400 mg) plus ribavirin (1000 mg) for 24 weeks reported a 100% SVR (Hussein, 2016). Anemia was reported in two patients related to concomitant ribavirin use. No other adverse events were reported (Hussein, 2016).

Drug interactions are an important consideration with antiviral therapy in kidney transplant recipients. Please see the section titled, "Unique Patient Populations: Patients Who Develop Recurrent HCV Infection Post Liver Transplantation" for a table of drug interactions with DAAs and calcineurin inhibitors.

Mixed genotypes

Rarely, genotyping assays may indicate the presence of a mixed infection (eg, genotypes 1a and 2). Treatment data for mixed genotypes with direct-acting antivirals are sparse but utilization of a pangenotypic regimen should be considered. When the correct combination or duration is unclear, expert consultation should be sought.

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