


Patients with Renal Impairment

Chronic hepatitis C is independently associated with the development of chronic kidney disease (CKD) ([Rogal, 2016](#)); ([Fabrizi, 2015](#)). A 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 CKD ([Fabrizi, 2015](#)). There is also a higher risk of progression to end-stage renal disease (ESRD) in persons with chronic HCV infection and CKD, and an increased risk of all-cause mortality in persons on dialysis ([Lee, 2014](#)); ([Fabrizi, 2012](#)).

Successful HCV antiviral treatment improves clinical outcomes. Antiviral therapy has been associated with a survival benefit in persons on dialysis in Swedish nationwide registry study ([Söderholm, 2018](#)). Among diabetic patients with ESRD receiving care at 4 US health systems, achieving a sustained virologic response (SVR) reduced the risk of developing extrahepatic manifestations of HCV disease, regardless of cirrhosis (sHR=0.46) compared to untreated patients ([Li, 2019](#)).

Recommendation for Patients With CKD Stage ^a	
RECOMMENDED	RATING 
No dose adjustment in direct-acting antivirals is required when using recommended regimens. ^b	I, A or IIa, B ^c
^a Chronic kidney disease (CKD) stages: 1 = normal (eGFR >90 mL/min); 2 = mild CKD (eGFR 60-89 mL/min); 3 = moderate CKD (eGFR 30-59 mL/min); 4 = severe CKD (eGFR 15-29 mL/min); 5 = end-stage CKD (eGFR <15 mL/min) ^b A ribavirin dose reduction may be required for patients with CKD stage 3, 4, or 5; see prescribing information for details. ^c The rating is I, A for patients with CKD stage 1, 2, or 3 and IIa, B for those with CKD stage 4 or 5.	

Elbasvir/Grazoprevir

The C-SURFER trial evaluated the safety and efficacy of 12 weeks of the daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) versus placebo among genotype 1 patients with CKD stage 4 or 5 (eGFR <30 mL/min). The initial study randomized eligible patients to immediate or deferred treatment with elbasvir/grazoprevir. The delayed treatment arm initially received placebo and was later treated with elbasvir/grazoprevir. Elbasvir and grazoprevir are primarily hepatically metabolized and undergo minimal renal elimination.

The data for the immediate treatment arm have been published ([Roth, 2015](#)). Seventy-five percent of the study participants were on hemodialysis, and 45% were African American. A small number of patients with compensated cirrhosis were included. Intention-to-treat (ITT) and modified intention-to-treat (mITT) SVR12 rates were 94% and 99%, respectively. There were no changes in erythropoietin use, hemoglobin, or other adverse events in the treatment groups compared to placebo. None of the genotype 1a patients with baseline NS5A resistance-associated substitutions (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 the moderately increased area under the curve (AUC) with grazoprevir and elbasvir observed in patients with stage 4/5 CKD ([Zepatier prescribing information, 2017](#)).

Based on these data, daily fixed-dose elbasvir/grazoprevir is recommended for the treatment of genotype 1 in patients with severely compromised renal function. While C-SURFER did not evaluate patients with genotype 4, 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 persons with genotype 4 and 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](#)).

Two real-world studies demonstrated the effectiveness of elbasvir/grazoprevir in persons with genotype 1 or 4 infection. In a retrospective cohort analysis from the TRIO network 99% (113/114) of patients with stage 4/5 CKD achieved SVR12 ([Flamm, 2018](#)). A nationwide retrospective observational cohort study of patients in the US Veterans Health Administration system demonstrated that 96.3% (392/407) of patients with stage 4/5 CKD achieved SVR ([Kramer, 2018](#)).

Glecaprevir/Pibrentasvir

The EXPEDITION-4 trial evaluated the safety and efficacy of 12 weeks of the pangenotypic NS3/NS4A protease inhibitor glecaprevir and the pangenotypic NS5A inhibitor pibrentasvir for genotype 1, 2, 3, 4, 5, or 6 infection ([Gane, 2017b](#)). This open-label study enrolled treatment-naïve and -experienced patients (previous interferon or peginterferon ± ribavirin, or sofosbuvir and ribavirin ± peginterferon) with CKD stage 4/5, including those with hemodialysis dependence. Baseline characteristics of the 104 patients enrolled in the study were 76% male; 25% black; 19% compensated cirrhosis; 40% treatment experienced; and 82% hemodialysis dependent. The genotype distribution was 22% genotype 1a; 28% genotype 1b; 16% genotype 2; 11% genotype 3; 19% genotype 4; 1% genotype 5; and 1% genotype 6. The daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120mg) was administered as three 100 mg/40 mg fixed-dose combination pills.

The study reported ITT and mITT SVR12 rates of 98% and 100%, respectively. There were no virologic failures. Two patients did not achieve SVR12; 1 patient discontinued the study due to diarrhea in the context of recent gastrointestinal bleeding and the other experienced a cerebral hemorrhage due to uncontrolled hypertension (had achieved SVR4). Adverse events included pruritus (20%), fatigue (14%), and nausea (12%). There were no serious adverse events related to the study drugs, and there were no grade 4 laboratory abnormalities reported.

The EXPEDITION-4 trial supports the efficacy and safety of glecaprevir/pibrentasvir in patients with CKD and ESRD. The recommended duration of therapy is the same as for patients without CKD.

An integrated analysis of the efficacy and safety of glecaprevir/pibrentasvir in persons with genotypes 1 through 6 and CKD stage 3b, 4, or 5 was performed from EXPEDITION-4 and EXPEDITION-5 clinical trials. This analysis included 205 patients with compensated liver disease (with and without cirrhosis) and an eGFR <30 mL/min (EXPEDITION-4) or <45 mL/min (EXPEDITION-5). The majority of patients were treatment naïve (69%), with genotype 1 (54%), and on dialysis (79%). In this integrated analysis, 100% SVR12 (mITT) was found with glecaprevir/pibrentasvir therapy in patients with chronic hepatitis C and severe renal impairment regardless of treatment duration ([Lawitz, 2018](#)).

Sofosbuvir-Based Regimens

Despite higher concentrations of the primary sofosbuvir metabolite GS-331007 in persons with renal impairment, several studies demonstrate the safety of sofosbuvir-based regimens in those with an eGFR <30 mL/min ([Desnoyer, 2016](#)); ([Nazario, 2016](#)); ([Saxena, 2016](#)). A phase 2, open-label study examined the safety and efficacy of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks in patients with genotype 1 or 4 with a creatinine clearance ≤30 mL/min (not undergoing dialysis). SVR was 100% in 18 patients with severe renal insufficiency. Treatment was well tolerated without any significant treatment-related cardiac adverse effects ([Lawitz, 2017b](#)).

A real-world case series of treatment-naïve and -experienced patients demonstrated that 12 weeks of sofosbuvir/velpatasvir administered in persons with any genotype and on dialysis resulted in a 95% (56/59) SVR12. There were no treatment-related discontinuations or serious adverse events. There were 2 virologic relapses; 1 was associated with nonadherence ([Borgia, 2019](#)).

In November 2019, the FDA amended the package inserts for sofosbuvir-containing regimens to allow use in patients with renal disease, including those with an eGFR ≤30 mL/min and those on dialysis.

Elbasvir, Grazoprevir, and Ledipasvir Metabolism

Elbasvir, grazoprevir, and ledipasvir 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—dose adjustments are not required in the setting of renal impairment.

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 treatment duration is unclear, expert consultation should be sought.

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