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 was associated with a survival benefit among persons on dialysis in a nationwide Swedish registry study (Söderholm, 2018). In a retrospective cohort analysis utilizing the Truven Health MarketScan Database (2008-2015), HCV treatment was associated with a 30% decreased risk of developing CKD (HR, 0.70; 95% CI, 0.55-0.88). Persons with HCV infection experienced a twofold and a 17-fold higher risk of membranoproliferative glomerulonephritis (HR, 2.23; 95% CI, 1.84-2.71) and cryoglobulinemia (HR, 16.91; 95% CI, 12.00-23.81), compared with persons without HCV (Park, 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). In a retrospective observational cohort study, predictors of eGFR improvement after antiviral therapy included baseline CKD (eGFR <60 mL/min) and not having diabetes (Sise, 2019). A prospective cohort study that evaluated estimated glomerular filtration rate in patients with eGFR >15 mL/min demonstrated a lower risk of ESRD in patients who achieve SVR12 (Liu, 2022).

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.

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-naive 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, including ESRD. The recommended duration of therapy is the same as for patients without CKD.

EXPEDITION-5 evaluated the efficacy and safety of fixed-dose glecaprevir/pibrentasvir for chronic HCV infection in adults without cirrhosis or with compensated cirrhosis and stage 3b, 4, or 5 CKD. Among the 101 study participants, 76% (n=77) were on dialysis and 24% (n=24) had predialysis CKD. Fifty-five percent of patients had genotype 1, 27% had genotype 2, 15% had genotype 3, and 4% had genotype 4; no patients had genotype 5 or 6 infection. Eighty-four patients were treated for 8 weeks, 13 patients for 12 weeks, and 4 patients for 16 weeks. The overall SVR12 was 97% (98/101) with no reported virologic failures (Lawitz, 2020).

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 based on the 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 naive (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).

Colchicine-induced rhabdomyolysis due to interaction with glecaprevir/pibrentasvir has been reported in while receiving treatment of gout. Despite a 50% dose reduction of colchicine before initiation of HCV therapy, the patient experienced rhabdomyolysis. This potential interaction with colchicine has the potential for increased risk for muscle toxicity and should prompt consideration of discontinuation of colchicine during therapy, especially in patients with renal insufficiency (Harrison, 2020).

Sofosbuvir-Based Regimens

In November 2019, the US 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.

A retrospective evaluation of clinical trial participants in 76 clinical trials treated with sofosbuvir with an estimated glomerular filtration rate (eGFR) of 30-89 mL/min/1.73 m^2 in nationally-representative administrative claims database demonstrated that participants with CKD did not experience worsening eGFR during sofosbuvir-based treatment, and sofosbuvir was not associated with an increased risk of ESRD in patients with CKD (Sulkowski, 2022). In a Taiwan real-world HCV registry program of 12,995 persons with a prospective evaluation of serial eGFR levels during and following treatment, sofosbuvir was not associated with eGFR change (Huang, 2022).

A prospective multicenter, open-label evaluation of ledipasvir/sofosbuvir (90mg/400mg) daily in patients with HCV with end-stage kidney disease on dialysis demonstrated safety and effectiveness at 8 wks (genotype 1 naïve without cirrhosis), 12 weeks (treatment-experienced genotype 1 treatment-naive or experienced nongenotype 1 without cirrhosis) and 24 weeks (genotypes 1, 2, 4 with compensated cirrhosis). Ninety-four percent (89/95) achieved sustained virologic response 12 weeks after treatment. Six patients died during treatment, however no deaths were related to treatment (Huang, 2022).

A real-world case series of treatment-naive and -experienced patients demonstrated that 12 weeks of sofosbuvir/velpatasvir administered in persons with any genotype and on dialysis resulted in 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). A retrospective analysis of 31 treatment-naive patients on hemodialysis demonstrated that 12 weeks of sofosbuvir/velpatasvir administered in persons with any genotype (68% with genotype 1) resulted in a 95% (30/31) SVR12. There was a single virologic relapse among the 3 persons with cirrhosis (Gaur, 2020). A systematic

review and meta-analysis of 717 patients with CKD stage 4/5 (58.4% on dialysis) treated with sofosbuvir regimens across 21 studies demonstrated a pooled SVR 12/24 of 97% and a serious adverse event rate of 4.8%. Cirrhotic and noncirrhotic patients achieved comparable SVR rates (Li, 2019a).

Rare adverse advents have been reported among patients with CKD receiving DAAs. Colchicine-induced rhabdomyolysis has been reported in a patient with renal dysfunction being treated with ledipasvir/sofosbuvir while continuing atorvastatin (Patel, 2016). Acute interstitial nephritis following DAA treatment has been described in association with sofosbuvir/ledipasvir (n=5), elbasvir/grazoprevir (n=2), and sofosbuvir/simeprevir (n=1) (Duque, 2021).

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 metabolized in the liver 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, 2019). Among 99 patients assigned to deferred treatment 97 (98%) achieved SVR (Bruchfeld, 2017). In patients with genotype 1a, SVR12 was 85% (11/13) among patients with detectable baseline NS5A RASs and 100% (98/98) among those patients without RASs. One serious adverse event occurred during the deferred treatment (interstitial nephritis) that was considered study drug related. Overall, the efficacy of this regimen among patients assigned to deferred treatment reflected the findings of the immediate treatment group, and the overall efficacy remained high in all subgroups including cirrhosis, diabetes, and hemodialysis. These data support no modification of elbasvir plus grazoprevir dosing for patients on hemodialysis. Of the 3 patients who relapsed in both the immediate and deferred treatment groups, 2 had genotype 1a infection with baseline NS5AA RASs, underscoring the importance of baseline NS5A RASs affecting treatment outcome with this regimen (Bruchfeld, 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).

Several 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 identified 5961 patients (42.5% genotype 1a, 55.0% genotype 1b) who completed elbasvir/grazoprevir therapy, including 860 patients with stage 3 CKD, 740 patients with stage 4/5 CKD, and 4361 controls (eGFR ≥60 mL/min). The SVR rates were 97% overall, 96% for those with an eGFR ≥60 mL/min, 98% for patients with stage 3 CKD, and 97% for participants with stage 4/5 CKD. No statistically significant differences were found in the SVR rates in persons with or without dialysis among the stage 4/5 CKD patients (adjusted OR 0.91; 95% CI 0.56-1.47 and OR 1.74; 95% CI 0.63-4.81) compared with those with an eGFR ≥60 mL/min (Choi, 2020).

Elbasvir, Grazoprevir, and Ledipasvir Metabolism

Elbasvir, grazoprevir, and ledipasvir are primarily metabolized in the liver 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.

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