Persons 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).

The most frequent form of kidney involvement in chronic hepatitis C is membranoproliferative glomerulonephritis, usually caused by cryoglobulinemic vasculitis. In persons with immune complex glomerulonephritis, antiviral therapy should not be delayed while awaiting kidney biopsy (Awan, 2023). Remission of nephrotic range proteinuria (>3.5 g/d) can occur with antiviral treatment (Pérez de José , 2020). 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 (hazard ratio [HR] 0.70; 95% CI 0.55–0.88). Persons with HCV infection experienced a 2-fold and a 17-fold higher risk, respectively, 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 infection (Park, 2018).

Among persons with diabetes and 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 status (subdistribution HR 0.46; 95% CI 0.31–0.67) compared with untreated persons (Li, 2019). In a retrospective observational cohort study, predictors of estimated glomerular filtration rate (eGFR) improvement after antiviral therapy included baseline CKD (eGFR <60 mL/min/1.73 m^2) and not having diabetes (Sise, 2019). A prospective cohort study that evaluated outcomes among persons with eGFR >15 mL/min/1.73 m^2 demonstrated a lower risk of ESRD in persons who attain SVR12 (Liu, 2022).

A systematic review of 106 studies of specific direct acting antiviral (DAA) regimens conducted among persons with advanced kidney disease (CKD 4 or 5, persons on dialysis, kidney transplant recipients) concluded that DAAs are efficacious (SVR12 ≥93%) and safe in this population (Balk, 2023).

Recommendation for Persons With Chronic Kidney Disease[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/1.73 m^2); 2 = mild CKD (eGFR 60-89 mL/min/1.73 m^2); 3 = moderate CKD (eGFR 30-59 mL/min/1.73 m^2); 4 = severe CKD (eGFR 15-29 mL/min/1.73 m^2); 5 = end-stage CKD (eGFR <15 mL/min/1.73 m^2).
[b] A ribavirin dosage reduction may be required for persons with CKD stage 3, 4, or 5; see prescribing information for details.
[c] The rating is I, A for persons 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 daily fixed dose glecaprevir (300 mg)/pibrentasvir (120mg) for genotype 1, 2, 3, 4, 5, or 6 infection among persons with severe renal impairment, without cirrhosis or with compensated cirrhosis (Gane, 2017b). This open-label study enrolled treatment-naive and treatment-experienced adults (previous interferon or peginterferon ± ribavirin, or sofosbuvir and ribavirin ± peginterferon) with CKD stage 4/5, including those dependent on hemodialysis. Baseline characteristics of the 104 enrollees 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 study reported intention-to-treat (ITT) and modified intention-to-treat (mITT) SVR12 rates of 98% and 100%, respectively. There were no virologic failures. Two participants did not achieve SVR12; 1 person 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 attained 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 (Gane, 2017b). The EXPEDITION-4 trial supports the efficacy and safety of glecaprevir/pibrentasvir in persons with CKD including ESRD. The recommended duration of therapy is the same as for persons without CKD.

EXPEDITION-5 evaluated the efficacy and safety of daily 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 participants had genotype 1infection, 27% had genotype 2, 15% had genotype 3, and 4% had genotype 4; no participants had genotype 5 or 6 infection. Eighty-four participants were treated for 8 weeks, 13 participants for 12 weeks, and 4 participants for 16 weeks. The overall SVR12 rate 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 infection and CKD stage 3b, 4, or 5 was performed using data from the EXPEDITION-4 and EXPEDITION-5 clinical trials. This analysis included 205 adults with compensated liver disease (with and without cirrhosis) and an eGFR <30 mL/min/1.73 m^2 (EXPEDITION-4) or <45 mL/min/1.73 m^2 (EXPEDITION-5). The majority of participants were treatment naive (69%), with genotype 1 infection (54%), and on dialysis (79%). In this integrated analysis, a 100% SVR12 rate (mITT) was found with glecaprevir/pibrentasvir therapy in persons with chronic hepatitis C and severe renal impairment regardless of treatment duration (Lawitz, 2020).

Colchicine-induced rhabdomyolysis due to interaction with glecaprevir/pibrentasvir has been reported in a person while receiving treatment for gout. Despite a 50% dose reduction of colchicine before initiation of HCV therapy, the person experienced rhabdomyolysis (Patel, 2016). This potential interaction with colchicine has the potential for increased risk for muscle toxicity and should prompt consideration of discontinuation of colchicine during glecaprevir/pibrentasvir therapy, especially in persons with renal insufficiency (Harrison, 2020).

Sofosbuvir-Based Regimens

In November 2019, the US Food and Drug Administration (FDA) amended the prescribing information for sofosbuvir-containing regimens to allow use in persons with renal disease, including those with an eGFR ≤30 mL/min/1.73 m^2 and those on dialysis.

A retrospective evaluation of clinical trial participants from 76 clinical trials treated with sofosbuvir with an eGFR of 30 mL/min/1.73 m^2 to 89 mL/min/1.73 m^2 in a nationally representative administrative claims database

demonstrated that participants with CKD did not experience worsening eGFR during sofosbuvir-based treatment. Additionally, sofosbuvir was not associated with an increased risk of ESRD among people 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 daily ledipasvir (90 mg)/sofosbuvir (400mg) in adults with HCV infection and ESRD on dialysis demonstrated safety and effectiveness with: an 8-week course of therapy for treatment-naive participants with genotype 1 infection without cirrhosis; a 12-week course of therapy for treatment-experienced persons with genotype 1 infection, and for treatment-naive or treatment-experienced persons with non-genotype 1 infection without cirrhosis; and a 24-week course of therapy for those with genotypes 1, 2, or 4 infection with compensated cirrhosis. Ninety-four percent (89/95) of participants achieved SVR12. Six people died during treatment; no deaths were related to the study drugs (Huang, 2022).

A real-world case series of treatment-naive and treatment-experienced adults demonstrated that 12 weeks of daily fixed-dose sofosbuvir (400 mg)/velpatasvir (100 mg) administered to persons on hemodialysis with any HCV genotype infection resulted in an SVR12 rate of 95% (56/59). 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 adults on hemodialysis with any HCV genotype infection (68% genotype 1) demonstrated that 12 weeks of sofosbuvir/velpatasvir resulted in an SVR12 rate of 95% (30/31). There was a single virologic relapse among the 3 persons with cirrhosis (Gaur, 2020). A systematic review and meta-analysis across 21 studies involving 717 adults with CKD stage 4/5 (58.4% on dialysis) treated with sofosbuvir-based regimens demonstrated a pooled SVR rate of 97% (12/24) and a serious adverse event rate of 4.8%. Persons with and without cirrhosis attained comparable SVR12/24 rates (Li, 2019a).

Rare adverse advents have been reported among persons with CKD receiving DAAs. Colchicine-induced rhabdomyolysis has been reported in an individual 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 224 adults with genotype 1 infection and CKD stage 4/5 (eGFR <30 mL/min/1.73 m^2). The initial study randomized eligible participants 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 (168/224) of the study participants were on hemodialysis, and 45% were Black. A small number of participants with compensated cirrhosis were included. ITT and 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 with placebo. None of the participants with genotype 1a infection with baseline NS5A resistance-associated substitutions (RASs) experienced viral relapse. The only reported relapse occurred in a person with genotype 1b infection. 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 with grazoprevir and elbasvir observed in persons with stage 4/5 CKD (Zepatier prescribing information, 2019). Among participants assigned to deferred treatment 98% (97/99) achieved SVR12 (Bruchfeld, 2017). Among participants with genotype 1a infection, SVR12 rate was 85% (11/13) for persons with detectable baseline NS5A RASs and 100% (98/98) among those without baseline RASs. One serious adverse event (interstitial

nephritis) occurred during the deferred treatment that was considered study drug related. Overall, the efficacy of elbasvir/grazoprevir among participants assigned to deferred treatment paralleled the findings of the immediate treatment group. Overall efficacy remained high in all study population subgroups including cirrhosis, diabetes, and hemodialysis. These data support no modification of elbasvir/grazoprevir dosing for persons on hemodialysis. Of the 3 participants 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 elbasvir/grazoprevir (Bruchfeld, 2017).

Based on these data, daily fixed-dose elbasvir/grazoprevir is recommended for persons with genotype 1 infection and severely compromised renal function. While C-SURFER did not evaluate persons with genotype 4 infection, it is likely that the high efficacy of elbasvir/grazoprevir in genotype 1 and genotype 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 persons with stage 4/5 CKD attained SVR12 (Flamm, 2018). A nationwide retrospective observational cohort study of persons in the US Veterans Health Administration system identified 5961 adults (42.5% genotype 1a, 55.0% genotype 1b) who completed elbasvir/grazoprevir therapy, including 860 persons with stage 3 CKD, 740 persons with stage 4/5 CKD, and 4361 controls (eGFR ≥60 mL/min/1.73 m^2). The SVR rates were 97% overall, 96% for those with an eGFR ≥60 mL/min/1.73 m^2, 98% for those with stage 3 CKD, and 97% for those with stage 4/5 CKD. No statistically significant differences were found in the SVR rates based on dialysis status (utilized or not) among the persons with stage 4/5 CKD (adjusted odds ratio 0.91; 95% CI 0.56-1.47 and adjusted OR 1.74; 95% CI 0.63-4.81, respectively) compared with the controls (eGFR ≥60 mL/min/1.73 m^2) (Choi, 2020).

Rare adverse advents have been reported among persons with CKD receiving DAAs. 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, 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 the 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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