Kidney Transplant Patients

Post Kidney Transplantation: Genotype 1-6

Recommended and alternative regimens listed by pangenotypic, evidence level and alphabetically for:

Treatment-Naive and Non-DAA-Experienced Kidney Transplant Patients With Genotype 1-6 Infection, With or Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	12 weeks	I, A[c] IIa, C[d]
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	IIa, C
Genotype 1, 4, 5, or 6 only: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Genotype 1 or 4 only: Daily fixed-dose combination of elbasvir (50 mg)/ grazoprevir (100 mg) for patients without baseline NS5A RASs[e] for elbasvir	12 weeks	I, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.
[c] Based on evidence for patients without cirrhosis.
[d] Based on evidence for patients with compensated cirrhosis.
[e] Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance.

Recommended regimen for:

DAA-Experienced Kidney Transplant Patients With Genotype 1-6 Infection, With or Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg), with or without ribavirin[b]	12 weeks	IIa, C

[a] Excludes CTP class B and class C patients. For decompensated cirrhosis, please refer to the appropriate section.
[b] For patients with cirrhosis and multiple negative baseline characteristic, consideration should be given to adding ribavirin. If renal dysfunction is present, a lower starting dose is recommended. Maximum ribavirin dose is 1000 mg/d for patients who weigh <75 kg and 1200 mg/d for those who weigh ≥75 kg.

For additional information on treatment of DAA failures post transplant, treatment of decompensated cirrhosis following transplantation, treatment of transplant recipients from HCV-positive donors, and post-transplant drug-drug interactions, please see Patients Who Develop Recurrent HCV Infection Post Liver Transplantation.

Recommended Regimens

Glecaprevir/Pibrentasvir

The phase 3, open-label, single arm MAGELLAN-2 study evaluated a 12-week course of the pangenotypic regimen of glecaprevir/pibrentasvir in 100 liver (n=80) and kidney (n=20) transplant recipients with genotypes 1-6 infection who were at least 3 months post transplant. Cirrhotic patients were excluded. SVR12 was achieved in 98% of patients; a single patient experienced virologic failure (Reau 2018). The safety profile was excellent with 1 treatment discontinuation for an adverse event not considered to be therapy related. One rejection episode occurred in a liver transplant recipient. While glecaprevir/pibrentasvir is an effective pangenotypic regimen as demonstrated in the nontransplant population, there were no genotype 5 transplant recipients in the study.

There are potential drug-drug interactions with cyclosporine. Review the DAA interactions with calcineurin inhibitors table in the post liver transplantation section before prescribing HCV DAA therapy to a renal transplant recipient.

Ledipasvir/Sofosbuvir

A recent phase 2, open-label clinical trial evaluated the safety and efficacy of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) in 114 kidney transplant recipients who were more than 6 months post transplant (Colombo, 2017). Enrolled patients had genotype 1 (91%) or 4 infection; 69% were treatment naive and 15% had compensated cirrhosis. Patients were randomized to 12 weeks or 24 weeks of ledipasvir/sofosbuvir. Median eGFR prior to treatment was 50 mL/min for patients in the 12-week study arm and 60 mL/min for those in the 24-week arm. Overall SVR12 was 100% (114/114). Adverse events were common (64%) and serious adverse events occurred in 13 patients (11%); a single participant discontinued treatment because of an adverse event. Four patients with an eGFR >40 mL/min at baseline experienced a decrease to <30 mL/min during therapy. The eGFR increased to >30 mL/min at the last visit recorded in 3 of these patients; 1 patient who had interrupted study treatment had a final eGFR of 14.4 mL/min. All but 1 of the 6 patients with compensated cirrhosis whose eGFR decreased to <40 mL/min continued study treatment without

interruption; none permanently discontinued study treatment.

Several additional reports have described successful outcomes with combination direct-acting antiviral (DAA) therapy in kidney transplant recipients (Saxena, 2017); (Sawinski, 2016). One study evaluated treatment safety and efficacy among 20 HCV-infected kidney transplant recipients (88% genotype 1; 50% with advanced fibrosis; 60% treatment-experienced with an interferon-based regimen) who received sofosbuvir-based therapy. Various regimens were used, including simeprevir plus sofosbuvir (n=9); ledipasvir/sofosbuvir (n=7); sofosbuvir plus ribavirin (n=3); and daclatasvir plus sofosbuvir (n=1). SVR12 was 100% (Sawinski, 2016). Two patients required dose reductions due to anemia associated with ribavirin use. However, no significant changes in serum creatinine or proteinuria, or graft rejection were seen before or after treatment. Forty-five percent of patients required dose reduction of immunosuppressive agents while on antiviral therapy.

Real-world data from the ongoing HCV-TARGET study have also demonstrated the efficacy of DAA therapy in patients with kidney transplant and in those with dual liver and kidney transplant (Saxena, 2017). Various regimens were used, including sofosbuvir/ledipasvir ± ribavirin (85%); sofosbuvir plus daclatasvir ± ribavirin (9%); and ombitasvir/paritaprevir/ritonavir plus dasabuvir ± ribavirin (6%). SVR12 was 95% in those with kidney transplant and 91% in dual liver and kidney transplant recipients.

No change in calcineurin inhibitor dose is needed for patients receiving ledipasvir/sofosbuvir. Review the DAA interactions with calcineurin inhibitors table in the post liver transplantation section before prescribing HCV DAA therapy to a renal transplant recipient.

Sofosbuvir/Velpatasvir

There are no published clinical trials regarding the use of the fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) in kidney transplant recipients. There are, however, significant data addressing the efficacy and safety of this regimen in the nontransplant and liver transplant settings.

In liver transplant recipients (discussed in Patients who Develop Recurrent HCV Infection Post Liver Transplantation), the safety and efficacy of sofosbuvir/velpatasvir for 12 weeks was evaluated in 79 patients (n=5 with cirrhosis; n=4 DAA experienced) with genotype 1-4 infection (Agarwal, 2018). Treatment was well-tolerated with 99% of patients completing treatment. SVR12 rates by genotype were 93% genotype 1a (n=15); 96% genotype 1b (n=22); 100% genotype 2 (n=3); 97% genotype 3 (n=35); and 100% genotype 4 (n=4).

In the nontransplant setting (discussed in detail in the Initial and Retreatment sections), the phase 3, double-blind, placebo-controlled ASTRAL-1 study demonstrated an overall SVR of 99% among 742 treatment-naive or -experienced patients with genotype 1, 2, 4, 5, or 6 infection (Feld, 2015). In the phase 3, open-label ASTRAL-3 study, 552 treatment-naive or -experienced patients with genotype 3 (with or without compensated cirrhosis) were randomized in a 1:1 ratio to 12 weeks of sofosbuvir/velpatasvir or 24 weeks of sofosbuvir plus weight-based ribavirin. SVR12 was 95% for the sofosbuvir/velpatasvir treatment arm, which was superior to the SVR12 80% among patients receiving sofosbuvir plus ribavirin for 24 weeks (Foster, 2015a).

No change in calcineurin inhibitor dose is needed for patients receiving sofosbuvir/velpatasvir. Review the DAA interactions with calcineurin inhibitors table in the post liver transplantation section before prescribing HCV DAA therapy to a renal transplant recipient.

Sofosbuvir/Velpatasvir/Voxilaprevir

To date, there are no published clinical trials evaluating use of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) in kidney transplant recipients. There are, however, significant data addressing the efficacy and safety of this regimen in the nontransplant setting (Degasperi, 2019); (Llaneras, 2019); (Bourliere, 2017); (Jacobson, 2017); (Soriano, 2017); (Saxena, 2016).

Two phase 3, open label, randomized clinical trials were conducted to determine the safety and efficacy of

sofosbuvir/velpatasvir/voxilaprevir in nontransplant patients previously treated with a DAA regimen. The POLARIS-1 study included nontransplant patients who had previously received a regimen containing and NS5A inhibitor. Patients were randomized to 12 weeks of sofosbuvir/velpatasvir/voxilaprevir or placebo. SVR for patients on active treatment was 96%. POLARIS-4 compared 12 weeks of sofosbuvir/velpatasvir/voxilaprevir to 12 weeks of sofosbuvir/velpatasvir in non-NS5A inhibitor DAA-experienced nontransplant patients (Bourliere, 2017). Overall, 69% of participants were previously exposed to sofosbuvir plus ribavirin ± peginterferon, and 11% were exposed to sofosbuvir plus simeprevir. Cirrhosis was common, 46% in both study arms. SVR12 rates were 98% with sofosbuvir/velpatasvir/voxilaprevir and 90% with sofosbuvir/velpatasvir.

Velpatasvir is a substrate for CYP3A4, CYP2C8, and CYP2B6, a weak inhibitor of P-gp and OATP transporters, and a moderate inhibitor of the breast cancer resistance protein (BCRP) membrane transporter. As such, velpatasvir is moderately affected by potent inhibitors and, to a greater extent, potent inducers of enzyme/drug transporter systems (Mogalian, 2016). Based on this profile, which is similar to ledipasvir, clinically significant drug-drug interactions would not be expected for coadministration of sofosbuvir/velpatasvir with common immunosuppressive agents (eg, tacrolimus, cyclosporine, corticosteroids, mycophenolate mofetil, or everolimus). Review the DAA interactions with calcineurin inhibitors table in the post liver transplantation section before prescribing HCV DAA therapy to a renal transplant recipient.

Alternative Regimen

Elbasvir/Grazoprevir

Data from small, real-world studies evaluating elbasvir/grazoprevir are available. One such study evaluated 11 kidney transplant recipients with significant kidney function impairment (GFR <40 mL/min) treated with elbasvir/grazoprevir for 12 to 16 weeks. SVR12 was 100% (Eisenberger, 2019).

There are significant drug-drug interactions with cyclosporine. Review the DAA interactions with calcineurin inhibitors table in the post liver transplantation section before prescribing HCV DAA therapy to a renal transplant recipient.

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Related References

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