Patients Who Develop Recurrent HCV Infection Post Liver Transplantation

Post Liver Transplantation: Genotype 1-6

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

Treatment-Naive and -Experienced Patients With Genotype 1-6 Infection in the Allograft Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	12 weeks	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, B
Genotype 1, 4, 5, or 6 only: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, B

[a] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

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

Treatment-Naive and -Experienced Patients With Genotype 1-6 Infection in the Allograft With Compensated Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, B
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	12 weeks	I, C
Genotype 1, 4, 5, or 6 only: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A

[a] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

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

Treatment-Naive and -Experienced Patients With Genotype 1-6 Infection in the Allograft and Decompensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/ ribavirin starting at 600 mg and increased as tolerated[b]	12 to 24 weeks[c]	I, B
Genotype 1, 4, 5, or 6 only: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)[b]	12 to 24 weeks[c]	I, B

[a] Includes CTP class B and class C patients.
[b] The starting dose of ribavirin should be 600 mg/d and increased or decreased as tolerated. If renal dysfunction is present, a lower starting dose is recommended. Maximum ribavirin dose is 1000 mg/d if <75 kg and 1200 mg/d if ≥75 kg body weight.
[c] 24-week treatment duration is recommended if treatment experienced.

Recommended regimen for:

DAA-Experienced Patients With Genotype 1-6 Infection in the Allograft, With or Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)[b]	12 weeks	I, C

[a] Excludes CTP class B and class C patients.
[b] For patients with cirrhosis plus multiple negative baseline characteristic, consideration should be given to adding ribavirin. The starting dose of ribavirin should be 600 mg/d and increased or decreased as tolerated. If renal dysfunction is present, a lower starting dose is recommended. Maximum ribavirin dose is 1000 mg/d if <75 kg and 1200 mg/d if ≥75 kg body weight.

Glecaprevir/Pibrentasvir

The MAGELLAN-2 trial was an open-label, multicenter, single-arm, phase 3 study that evaluated a 12-week course of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills in 80 liver transplant recipients and 20 kidney transplant recipients without cirrhosis. All genotypes were represented except genotype 5; 57% of participants had genotype 1 and 24% had genotype 3. Except for genotype 3 patients (all of whom were treatment naive), treatment-experienced patients were included (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon). Eighty percent of patients had Metavir stage F0 or F1 fibrosis, 6% had F2, and 14% had F3. Cirrhotic patients were excluded. Any stable immunosuppressive regimen was allowed, except cyclosporine >100 mg/d and prednisone >10 mg/d. SVR was achieved in 98% (98/100) of patients with no virologic breakthroughs on treatment and 1 post-treatment relapse (Reau, 2018). There were no treatment discontinuations due to drug-associated adverse effects. One episode of mild rejection occurred that was assessed to be unrelated to drug interactions. A multicenter study from Japan treated 24 liver transplant recipients with recurrent HCV with 8 weeks or 12

weeks of glecaprevir/pibrentasvir (including 21% with F3/F4); 96% achieved SVR12. All 13 patients (genotype 1 or 2, without cirrhosis) treated for 8 weeks achieved SVR (Ueda, 2019). As data on the efficacy of glecaprevir/pibrentasvir in transplant recipients with cirrhosis and use of shorter treatment course (8 weeks versus 12 weeks) in those without cirrhosis are very limited, pending additional real-world data, a 12-week course is recommended regardless of stage. Additionally, for patients with cirrhosis plus other negative baseline factors, adding low-dose (600 mg) ribavirin may be a consideration.

Sofosbuvir/Velpatasvir

The safety and efficacy of the fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was evaluated in 79 (5 with cirrhosis, 4 DAA experienced) liver transplant recipients with genotype 1, 2, 3, or 4 (Agarwal, 2018). Treatment was well tolerated with 99% of patients completing treatment. Overall 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). Eighteen (23%) patients required a change in immunosuppression during treatment but none were for rejection or drug-drug-interactions. Most patients were on calcineurin inhibitor-based immunosuppression (71% on tacrolimus, 14% on cyclosporine).

In the nontransplant setting (discussed in detail in the Initial and Retreatment sections), the phase 3, double-blind, placebo-controlled ASTRAL-1 study reported on 742 treatment-naive or -experienced patients with genotype 1, 2, 4, 5, or 6 who were randomly assigned in a 5:1 ratio to sofosbuvir/velpatasvir or placebo for 12 weeks (Feld, 2015). All patients with genotype 5 (n=35) received active treatment. Thirty-two percent (201/624) of patients randomized to active therapy were treatment experienced and 19% (121/624) had compensated cirrhosis (CTP class A). The genotype distribution in the active treatment arm was 34% (n=210) genotype 1a; 19% (n=118) genotype 1b; 17% (n=104) genotype 2; 19% (n=116) genotype 4; 6% (n=35) genotype 5; and 7% (n=41) genotype 6. The overall SVR was 99% (95% CI, 98 to >99). The side effect/adverse event profile of sofosbuvir/velpatasvir was similar to placebo.

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% (95% CI, 92 to 98) for the sofosbuvir/velpatasvir treatment arm, which was superior to the SVR12 of 80% (95% CI, 75 to 85) for patients receiving sofosbuvir plus ribavirin for 24 weeks (Foster, 2015a).

The phase 3, open-label ASTRAL-4 study enrolled 267 treatment-naive or -experienced (55%) patients with genotype 1, 2, 3, 4, or 6 and decompensated cirrhosis (CTP class B at the time of screening). Patients were randomized in a 1:1:1 ratio to 12 weeks of sofosbuvir/velpatasvir, 12 weeks of sofosbuvir/velpatasvir plus weight-based ribavirin, or 24 weeks of sofosbuvir/velpatasvir. SVR12 rates were 83% (75/90) for the 12-week sofosbuvir/velpatasvir regimen, 94% (82/87) for the 12-week sofosbuvir/velpatasvir plus ribavirin regimen, and 86% (77/90) for the 24-week sofosbuvir/velpatasvir regimen (Curry, 2015b). Among patients with genotype 1, SVR12 rates were 88% and 96% with 12 weeks of sofosbuvir/velpatasvir without and with ribavirin respectively, and 92% with sofosbuvir/velpatasvir for 24 weeks. Virologic relapse occurred in 12% and 9% of patients in the 12-week and 24-week sofosbuvir/velpatasvir arms, respectively, compared to 2% in the 12-week sofosbuvir/velpatasvir plus ribavirin study arm. Although the ASTRAL-4 study was not powered to generate statistical significance, these results suggest that sofosbuvir/velpatasvir with ribavirin for 12 weeks is the optimal choice for patients with genotype 1 or 3 who have decompensated cirrhosis. The participant numbers were too small for genotypes 2, 4, and 6 to differentiate the comparative efficacy of the treatment arms. Reflecting the approach in nontransplant patients with decompensated cirrhosis, liver transplant recipients with hepatic decompensation are recommended to receive sofosbuvir/velpatasvir plus ribavirin for 12 to 24 weeks, depending upon presence of other negative prognostic features at baseline (ie, treatment experienced, genotype 3, presence of hepatocellular carcinoma).

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).

Ledipasvir/Sofosbuvir

The SOLAR-1 study was a large, US-based, multicenter, open-label, phase 2 trial that included 223 liver transplant recipients with genotype 1 or 4 whose baseline characteristics encompassed a broad spectrum of histologic and clinical severity of HCV recurrence. One hundred and eleven patients were Metavir stage F0 to F3, 51 had compensated CTP class A cirrhosis, and 61 had decompensated CTP class B or class C cirrhosis. Study participants were randomly assigned to 12 weeks or 24 weeks of a fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus ribavirin. The ribavirin dose was weight based for patients without cirrhosis or with compensated cirrhosis (1000 mg/d [<75 kg] to 1200 mg/d [≥ 75 kg]). For patients with CTP class B or class C cirrhosis, ribavirin was initiated at 600 mg/d followed by dose escalation as tolerated. Only 4% of enrolled participants discontinued treatment prematurely because of adverse events related to the study drugs (Charlton, 2015b). On an intention-to-treat basis, SVR was achieved in 96% (53/55) and 98% (55/56) of liver transplant patients without cirrhosis in the 12- and 24-week treatment arms, respectively. Among those with compensated cirrhosis, SVR was 96% in both the 12- and 24-week treatment arms. Efficacy was lower in patients with CTP class B or class C cirrhosis post liver transplantation. Among those with CTP class B cirrhosis, SVR rates were 86% and 88% in the 12- and 24-week treatment arms, respectively. Among patients with CTP class C cirrhosis, SVR rates were 60% and 75% in the 12- and 24-week treatment arms, respectively. Mortality rate during the study was 10% among patients with CTP class B or class C cirrhosis (Charlton, 2015b).

Similar results were achieved using an identical study design in the SOLAR-2 study, which was conducted in Europe, Australia, Canada, and New Zealand. The study included 168 liver transplant recipients with genotype 1 or 4 infection. Among the post-transplantation patients, 101 had no cirrhosis (Metavir stage F0 to F3), 67 had CTP class A compensated cirrhosis, 45 had CTP class B cirrhosis, and 8 had CTP class C decompensation. SVR rates in post-transplantation, noncirrhotic patients were 94% (49/52) and 100% (49/49) for 12 weeks and 24 weeks of treatment, respectively. Among patients with compensated cirrhosis after transplantation, SVR was 97% (33/34; 32/33) in both the 12- and 24-week treatment arms. For patients with CTP class B cirrhosis, comparable SVR rates were 95% (21/22) and 100% (23/23), respectively. Among those with CTP class C cirrhosis, SVR rates were 33% (1/3) and 80% (4/5), respectively. Considering both pre- and post-transplantation patients with CTP class B or class C cirrhosis, SVR rates were 85% (61/72) and 90% (70/78) for 12 weeks and 24 weeks of treatment, respectively.

An observational HCV-TARGET cohort study provides real-world data based on experience with 347 liver, 60 kidney, and 36 dual liver and kidney transplant recipients. Among the enrolled patients, 86% had genotype 1, 44% had cirrhosis, 26% had a history of liver decompensation, and 54% had a prior treatment failure with a non-NS5A inhibitor regimen (Saxena, 2017). Among the 279 participants treated with ledipasvir/sofosbuvir for 12 weeks or 24 weeks, the SVR rates were 97% (152/157) for those also taking ribavirin and 95% (116/122) for patients not taking ribavirin. Patients who received ribavirin were more frequently genotype 1a (versus genotype 1b), treatment experienced, and without renal dysfunction. The rate of therapy discontinuation due to an adverse event was 1.3%, highlighting the safety of the drug combination. Acute graft rejection occurred during or after cessation of therapy in 1.4% (6/415) of patients. These episodes were not judged to be a direct consequence of the antiviral regimen but serve to remind clinicians of the need to monitor immunosuppressive agent levels during direct-acting antiviral (DAA) therapy.

Another multicenter cohort of 162 patients (98% genotype 1) assessed treatment with ledipasvir/sofosbuvir (with or without ribavirin) for 8 weeks, 12 weeks, or 24 weeks. Duration of treatment and ribavirin use were provider determined. Overall SVR12 rates were 94% and 98% in those treated with ledipasvir/sofosbuvir without or with ribavirin, respectively (Kwok, 2016). SVR12 rates in patients treated for 8 weeks, 12 weeks, or 24 weeks with the ribavirin-free regimen were 86% (6/7), 94% (65/69), and 95% (39/41), respectively. SVR12 rates in the ribavirin-inclusive groups were 97% (38/39) and 100% (6/6) for 12 weeks and 24 weeks of treatment, respectively.

The multicenter ANRS CO23 CUPILT study investigators reported their experience with sofosbuvir plus an NS5A inhibitor (daclatasvir or ledipasvir ± ribavirin) among 512 liver transplant recipients with recurrent HCV who met inclusion criteria for analysis (Houssel-Debry, 2018). The genotype distribution of the participants was 70% (n=359) genotype 1, 1% (n=7) genotype 2, 18% (n=93) genotype 3, 10% (n=50) genotype 4, and <1% (n=3) genotype 5. Twenty-one percent had cirrhosis and 34% had prior treatment experience. The regimens and treatment durations were sofosbuvir plus an NS5A inhibitor without ribavirin for 12 weeks (n=156) or 24 weeks (n=239), and sofosbuvir plus an NS5A inhibitor and ribavirin

for 12 weeks (n=47) or 24 weeks (n=70). SVR12 rates were 94%, 99%, 96%, and 93%, respectively. Twenty patients experienced treatment failure and in a multivariate analysis, fibrosis stage, prior treatment, genotype, and baseline HCV viral load did not adversely impact SVR12 rates in the 4 treatment groups. The investigators concluded that 12 weeks of sofosbuvir plus an NS5A inhibitor without ribavirin was an effective regimen regardless of fibrosis stage, genotype, and prior treatment experience.

Collectively, these real-world experiences indicate high SVR rates can be attained without inclusion of ribavirin in liver transplant patients. However, all factors leading clinicians to include or exclude ribavirin cannot be discerned from these observational studies. The safest presumption is that ribavirin may contribute to the high SVR rates and be relevant for patients with unfavorable baseline characteristics (eg, cirrhosis, prior treatment experience). Thus, ribavirin-free therapy is recommended for patients with a favorable baseline profile and ribavirin-inclusive therapy is recommended for those with an unfavorable baseline profile.

Most clinical trials to date have focused on patients who were at least 6 months post transplantation, but there is no a priori reason not to consider earlier treatment if the patient is on stable immunosuppression and has recovered from postoperative complications. Treatment during the first 6 to 12 months post transplantation certainly seems reasonable to reduce the likelihood of treating patients with more advanced liver disease. A phase 2 study of prophylactic ledipasvir/sofosbuvir enrolled 16 genotype 1 liver transplant recipients (most with hepatocellular carcinoma as the indication). Treatment was initiated immediately preoperatively and continued for 4 weeks post transplantation (Levitsky, 2016). SVR12 post transplantation was attained in 88% (15/16) of patients. While these results are too preliminary upon which to base recommendations, the findings provide additional data on the safety of ledipasvir/sofosbuvir early in the post-transplantation period.

Sofosbuvir/Velpatasvir/Voxilaprevir

There is limited experience with sofosbuvir/velpatasvir/voxilaprevir in liver transplant recipients. In a single case report of a prior DAA regimen failure, successful treatment of recurrent HCV after liver transplant with sofosbuvir/velpatasvir/voxilaprevir was achieved (Cardona-Gonzalez, 2018). The patient had genotype 3 infection and acute hepatitis post liver transplant. He was treated with sofosbuvir/velpatasvir/voxilaprevir for 16 weeks with ribavirin added during the last 8 weeks of therapy. In a subsequent case series, 6 liver transplant recipients with HCV genotype 1 ± genotype 4 infection who had a previous DAA treatment failure were treated with sofosbuvir/velpatasvir/voxilaprevir. Participants received a 12-week course of therapy and all achieved SVR. Minor reductions in calcineurin inhibitor dosing were required but no adverse events or rejection episodes were reported (Higley, 2020).

Mixed Genotypes

Rarely, genotyping assays may indicate the presence of a mixed infection (eg, genotypes 1a and 2). Treatment data for mixed genotypes with DAAs 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.

Drug-Drug Interactions Between DAAs and Calcineurin Inhibitors

The interactions of DAA agents and calcineurin inhibitors are complex and unpredictable without formal studies of drug-drug interactions. A summary of drug-drug interactions between calcineurin inhibitors and DAAs with recommended dosing is provided in the table below. Based on the metabolism of grazoprevir and elbasvir, a 15-fold increase in grazoprevir AUC and a 2-fold increase in elbasvir AUC can be expected with cyclosporine coadministration. Therefore, this combination should be avoided. Since a 40% to 50% increase in tacrolimus level is predicted during coadministration with grazoprevir, no dosing adjustments are anticipated but tacrolimus levels should be monitored.

Table. DAA Interactions With Calcineurin Inhibitors

	Cyclosporine (CSA)	Tacrolimus (TAC)
Sofosbuvir (SOF)	4.5-fold ? in SOF AUC, but GS-331007 metabolite unchanged; no a priori dose adjustment	No interaction observed; no a priori dose adjustment
Ledipasvir	No data; no a priori dose adjustment	No data; no a priori dose adjustment
Elbasvir / grazoprevir (EBR/GZR)	15-fold ? in GZR AUC and 2-fold ? in EBR AUC; combination is not recommended	43% ? in TAC; no a priori dose adjustment
Velpatasvir	No interaction observed; no a priori dose adjustment	No data; no a priori dose adjustment
Glecaprevir / pibrentasvir (GLE/PIB)	5-fold ? in GLE AUC with higher doses (400 mg) of CSA; not recommended in patients requiring stable CSA doses >100 mg/day	1.45-fold ? in TAC AUC; no a priori dose adjustment; monitor TAC levels and titrate TAC dose as needed
Sofosbuvir / velpatasvir / voxila previr (SOF/VEL/VOX)	9.4-fold ? in VOX AUC; combination is not recommended	No data; no a priori dose adjustment
AUC=area under the curve		

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Related References

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