Unique Patient Populations: Patients Who Develop Recurrent HCV Infection Post-Liver Transplantation

Genotype 1 or 4

Recommended Regimens by evidence level and alphabetically for:

Treatment-naive and -Experienced Patients, with HCV Genotype 1 or 4 Infection in the Allograft, Including Those with Compensated Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with weight-based ribavirin	12 weeks	I, A
Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated)	12 weeks	I, B

Recommended Regimens by evidence level and alphabetically for:

Treatment-naive Patients, with HCV Genotype 1 or 4 Infection in the Allograft, and with Compensated Liver Disease, Who Are Ribavirin Ineligible

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	24 weeks	I, B
Daily daclatasvir (60 mg) plus sofosbuvir (400 mg)	24 weeks	II, C

Recommended Regimen for:

Treatment-naive and -Experienced Liver Transplant Recipients, with Decompensated Cirrhosis (Child Turcotte Pugh [CTP] Class B or C), Who Have HCV Genotype 1 or 4 Infection in the Allograft

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated)	12 weeks	I, B

Alternative Regimen for:

Patients with HCV Genotype 1 Infection in the Allograft, Including Those with Compensated Cirrhosis

ALTERNATIVE	DURATION	RATING
Daily simeprevir (150 mg) plus sofosbuvir (400 mg) with or without weight-based ribavirin	12 weeks	I, B

Alternative Regimen for:

Patients with HCV Genotype 1 Infection in the Allograft, Including Those with Early-stage Fibrosis (Metavir Stage F0-F2)

ALTERNATIVE	DURATION	RATING
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) with weight-based ribavirin	24 weeks	I, B

Genotype 2

Recommended Regimens by evidence level and alphabetically for:

Treatment-naive and -Experienced Patients, with HCV Genotype 2 Infection in the Allograft, Including Those with Compensated Cirrhosis

RECOMMENDED	DURATION	RATING
Daily daclatasvir (60 mg) plus sofosbuvir (400 mg), with low initial dose of ribavirin (600 mg, increased as tolerated)	12 weeks	II, A
Daily sofosbuvir (400 mg) and weight-based ribavirin	24 weeks	II, C

Recommended Regimen for:

Treatment-naive and -Experienced Patients, with HCV Genotype 2 Infection in the Allograft, Including Those with Compensated Cirrhosis, Who Are Ribavirin Ineligible

RECOMMENDED	DURATION	RATING
Daily daclatasvir (60 mg) plus sofosbuvir (400 mg)	24 weeks	II, C

Recommended Regimen for:

Treatment-naive and -Experienced Liver-Transplant Recipients, with Decompensated Cirrhosis (Child Turcotte Pugh [CTP] Class B or C), Who Have HCV Genotype 2 Infection in the Allograft

RECOMMENDED	DURATION	RATING
Daily sofosbuvir (400 mg) and ribavirin (initial dose 600 mg/day, increased monthly by 200 mg/day as tolerated to weight-based dose)	24 weeks	II, C

Genotype 3

Recommended Regimen for:

Treatment-naive and -Experienced Patients, with HCV Genotype 3 Infection in the Allograft, Including Those with Compensated Cirrhosis

RECOMMENDED	DURATION	RATING
Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated)	12 weeks	II, A

Recommended Regimen for:

Treatment-naive and -Experienced Patients, with HCV Genotype 3 Infection in the Allograft, Including Those with Compensated Cirrhosis, Who Are Ribavirin Ineligible

RECOMMENDED	DURATION	RATING
Daily daclatasvir (60 mg) plus sofosbuvir (400 mg)	24 weeks	II, C

Daclatasvir + sofosbuvir

In the phase III ALLY-1 study (Poordad, 2016), daclatasvir (60 mg daily) was administered in combination with daily sofosbuvir (400 mg) and ribavirin (initial dose, 600 mg) for 12 weeks to treatment-naive and -experienced patients who predominantly had HCV genotype 1 infection, in two specific populations: those with advanced cirrhosis (Child Turcotte Pugh [CTP] class B or C; n=60) and those with recurrent HCV infection posttransplant (n=53). Rate of sustained virologic response of 12 weeks (SVR12) was 83% among those with advanced cirrhosis and 94% among those with recurrent HCV infection posttransplant. In the population with advanced cirrhosis, SVR12 rate was 76% among patients with HCV genotype 1a and 100% among patients with HCV genotype 1b. In the population with advanced cirrhosis, SVR12 rate was 94% among patients with CTP class B cirrhosis and 56% among patients with CTP class C cirrhosis. Among subjects with HCV genotype 3, SVR12 rates were 83% and 91%, respectively, in those with advanced cirrhosis and recurrent HCV infection posttransplant.

Fontana and colleagues (Fontana, 2016) reported on the use of daclatasvir-containing regimens with either sofosbuvir (n=77) or simeprevir (n=18) or both (n=2) for 24 weeks in 97 liver-transplant recipients with severe recurrent HCV infection. 93% of the patients had HCV genotype 1, 31% had biopsy-proven cirrhosis, 37% had severe cholestatic HCV, and the proportion with CTP A/B/C was 51%/ 31%/12%. The mean MELD score was 13.0 + 6.0 and 35% of the cohort received ribavirin. The SVR12 rate was 87% overall, 91% in the group that received daclatasvir and sofosbuvir with or without ribavirin, and 72% in the group that received daclatasvir and simeprevir with or without ribavirin. Although 8 patients died during or after therapy from graft dysfunction, CTP and MELD scores were stable or improved in 87% and 83% of patients, respectively. There were 3 virologic breakthroughs and 2 relapses in patients treated with daclatasvir and simeprevir. These data along with those from others suggest that daclatasvir should preferentially be combined with sofosbuvir rather than simeprevir in liver-transplant recipients, particularly in those with advanced liver disease (EASL, 2015a). Herzer and colleagues (Herzer, 2015) described 6 liver-transplant recipients with recurrent HCV infection, 4 (67%) of whom achieved SVR with a regimen of daclatasvir plus simeprevir with ribavirin. Overall, daclatasvir-containing regimens appear to be well tolerated, with anemia noted when ribavirin was used. Cyclosporine and tacrolimus increase daclatasvir area under the curve by 40% and 5%, respectively; these changes are not clinically significant. Daclatasvir does not cause clinically meaningful changes in calcineurin inhibitor, mammalian target of rapamycin (mTOR) inhibitor, steroid, or mycophenolate levels.

Ledipasvir/sofosbuvir

The SOLAR-1 study was a large, multicenter, randomized controlled trial that included liver-transplant recipients (n=223) across a broad spectrum of histologic and clinical severity of recurrence (n=111 with Metavir fibrosis stage F0-F3; n=51 with HCV genotype 1 or 4 and compensated CTP class A cirrhosis; n=61 with decompensated CTP class B or C cirrhosis). Study participants were randomly assigned to receive fixed-dose combination ledipasvir (90 mg) and sofosbuvir (400 mg) (hereafter ledipasvir/sofosbuvir) and weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [≥ 75 kg]) for either 12 weeks or 24 weeks. On an intention-to-treat basis, SVR was achieved in 96% of patients with Metavir fibrosis stages F0 to F3 and in 96% of those with compensated cirrhosis, in both the 12- and 24-week arms; all patients received ribavirin. Ribavirin dose was weight based for patients with Metavir fibrosis stage F0 to F3 and CTP class A cirrhosis. For patients with CTP class B or C cirrhosis, ribavirin was initiated at 600 mg daily followed by dose escalation as tolerated (Charlton, 2015b). Only 2% of patients discontinued treatment owing to adverse events. Efficacy was lower in patients with CTP class B cirrhosis (85% SVR12) or CTP class C cirrhosis (60% SVR12), with no increase in SVR observed in patients who received 24 weeks of treatment. Mortality rate was 10% during the study among patients with CTP class B or C cirrhosis. Very similar results were achieved using an identical study design in the SOLAR-2 study, which was conducted in Europe, Australia, and New Zealand. SOLAR-2 included 168 posttransplant patients without cirrhosis (fibrosis stage F0-F3) or with compensated cirrhosis (Child Turcotte Pugh [CTP] A) treated for 12 weeks (n=86) or 24 weeks (n=82). There were also 160 pre- and posttransplantation patients with decompensated cirrhosis (CTP B/C) treated for 12 weeks (n=78) or 24 weeks (n=82). SVR12 rates in posttransplant non-cirrhotic or compensated cirrhosis were 95% for 12 weeks of therapy and 98% for 24 weeks of therapy. Among patients with more severe disease, SVR12 rates were 85% for 12 weeks of therapy and 88% for 24 weeks of therapy.

As the importance of ribavirin cannot be ascertained from the SOLAR study, in which all patients received ribavirin, the safest presumption is that ribavirin may contribute to the high SVR12 rates observed. In a previous study of a similar patient population to that of the SOLAR study, 40 patients with recurrent HCV infection following liver transplantation were treated for 24 weeks with sofosbuvir plus ribavirin, with SVR12 achieved in 70% (Charlton, 2015b). Although the basis for attenuated SVR rate observed in patients with more advanced HCV infection post-liver transplant is not known, these results, together with those of the sofosbuvir compassionate-use program, (Forns, 2015) suggest that the optimal period to initiate therapy may be the first 6 months to 12 months posttransplant to minimize the likelihood of having to treat patients with more advanced liver disease.

No data on ledipasvir/sofusbuvir are available for patients with HCV genotype 3 infection in the posttransplant setting. Very limited phase II data are available from a single-center study (ELECTRON-II) that examined ledipasvir/sofosbuvir used with (n=26) or without (n=25) ribavirin for 12 weeks in treatment-naive patients with HCV genotype 3 infection; 15% of patients had cirrhosis. All 26 (100%) patients in the ribavirin-containing arm achieved SVR12 compared with 16 of 25 (64%) of those in the ribavirin-free arm. Although these data raise the possibility that the addition of ledipasvir to

sofosbuvir and ribavirin may shorten the course of therapy for persons with HCV genotype 3 infection, the high effective concentration (EC_{50}) of ledipasvir for HCV genotype 3 (Wong, 2013); (Kohler, 2014) and the homogenous patient population studied limit the generalizability of this study. Until further data are available to confirm these findings, a recommendation for use of this regimen cannot be made at this time (Gane, 2013).

Paritaprevir/ritonavir/ombitasvir + dasabuvir

In a multicenter study of 34 liver-transplant recipients with mild recurrence (Metavir fibrosis stage F0-F2) of HCV genotype 1 infection, fixed-dose combination paritaprevir (150 mg), ritonavir (100 mg), and ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) (PrOD) and weight-based ribavirin was given for 24 weeks and achieved an SVR24 rate of 96% (Kwo, 2014). Because of the drug-drug interactions between ritonavir and calcineurin inhibitors, prospective dose adjustments were needed for cyclosporine and tacrolimus. Interactions between ritonavir and other medications commonly taken by liver-transplant recipients are also possible and will require detailed consideration when using this regimen. The efficacy and tolerability of this regimen in patients with more advanced HCV infection post-liver transplant are unknown.

Simeprevir + sofosbuvir

The GALAXY study prospectively assessed the use of simeprevir with sofosbuvir with or without weight-based ribavirin for 12 to 24 weeks in 46 non-cirrhotic patients with HCV genotype 1 (O'Leary, 2016). The SVR12 rate was 100% with simepevir and sofosbuvir for 12 weeks, 81.8% with simeprevir and sofosbuvir with ribavirin, and 91.7% with simeprevir and sofosbuvir with ribavirin for 24 weeks. A retrospective multicenter analysis of sofosbuvir (400 mg daily) plus simeprevir (150 mg daily) with or without ribavirin in 77 recipients reported an SVR4 rate of 92% (Pungpapong, 2015). Another recent multicenter retrospective study of 151 patients with recurrent HCV genotype 1 treated with simeprevir and sofosbuvir alone (n=119) or with ribavirin (n=32) was reported (Brown, 2016). The duration of therapy was 12 weeks for most patients but 15 did receive 24 weeks of therapy. Allograft cirrhosis had developed in 64.2% and 39.7% of patients had decompensated hepatic function. The overall SVR was 88% and 7% experienced virological relapse. Serious adverse events were reported in 11.9% and 3 deaths were not related to therapy. In healthy volunteers, the coadministration of single-dose cyclosporine with simeprevir resulted in a 19% increase in cyclosporine concentrations and simeprevir concentrations similar to historical data (see simeprevir prescribing information). However, in an interim analysis of an ongoing study in HCV-infected individuals (TMC435HPC3016), concomitant use of simeprevir (plus daclatasvir and ribavirin) with cyclosporine at steady state resulted in an approximately 6-fold increase in plasma concentrations of simeprevir compared with historical data of simeprevir in the absence of cyclosporine. This interaction may be caused by inhibition of organic ion-transporting polypeptide 1B1 (OATP1B1), p-glycoprotein (P-gp), and cytochrome P450 3A (CYP3A) by cyclosporine. Given these findings, simeprevir should not be coadministered with cyclosporine.

In healthy volunteers, the coadministration of single-dose tacrolimus with simeprevir did not result in a notable change of tacrolimus concentrations (see simeprevir prescribing information). In an ongoing study, concomitant use of simeprevir with tacrolimus resulted in a 2-fold increase in plasma concentrations of simeprevir compared with historical data (see simeprevir prescribing information). Based on phase I studies, a 2-fold increase in simeprevir concentrations is unlikely to be clinically significant.

Clinicians may consider the use of sofosbuvir plus simeprevir in patients receiving tacrolimus with therapeutic drug monitoring, particularly in those expected to have difficulty tolerating ribavirin (eg, patients with impaired renal function or anemia) or who are unable to forego proton pump inhibitor therapy (proton pump inhibitors attenuate ledipasvir absorption). A further option in patients who are ribavirin intolerant is 24 weeks of ledipasvir/sofosbuvir.

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

Elbasvir/grazoprevir

Although fixed-dose combination elbasvir and grazoprevir (hereafter, elbasvir/grazoprevir) have been extensively studied in patients with HCV infection with genotypes 1 and 4 who have compensated liver disease, there are no reports of this combination in liver-transplant recipients. The actual impact of elbasvir or grazoprevir on immunosuppression pharmacokinetics is unknown. For this reason, elbasvir and grazoprevir are not recommended for the treatment of HCV infection in liver-transplant recipients. Data regarding the safety and efficacy of elbasvir and grazoprevir in patients with advanced liver disease are available only from a phase II open-label study of grazoprevir (50 mg)/elbasvir (50 mg), given for 12 weeks in 30 HCV genotype 1 patients with CTP class B cirrhosis (Jacobson, 2015). This grazoprevir dose used in this study is lower than the grazoprevir dose in the commercially available fixed-dose formulation (50 mg vs 100 mg). The great majority of patients had CTP scores of 7 or 8 (28/30). The SVR12 rate was 90%. One patient died of liver failure at posttreatment week 4. MELD scores improved in 15 treated patients, were unchanged in 9, and increased in 6. It is possible that patients receiving elbasvir/grazoprevir will undergo liver transplantation prior to completing therapy. Continuation of elbasvir/grazoprevir following liver transplantation is not recommended. Similarly, although elbasvir/grazoprevir is well tolerated and effective in patients with renal insufficiency, which is common in liver-transplant recipients, the likely drug-drug interactions with immunosuppression agents outweigh the benefits of low renal metabolism of grazoprevir and elbasvir.

Sofosbuvir/velpatasvir

There are no reports of the safety of efficacy of sofosbuvir/velpatasvir fixed-dose combination in liver-transplant recipients. In the non-transplant setting, discussed in detail in the initial and retreatment sections of this guidance, of 624 patients with HCV genotypes 1a (34%), 1b (19%), 2 (17%), 4 (19%), 5 (6%), and 6 (7%) who were randomly assigned to receive fixed-dose combination of sofosbuvir/velpatasvir or placebo for 12 weeks were reported in the ASTRAL-1 study (Feld, 2015). All patients with genotype 5 (n=35) received active treatment. One third of patients were treatment experienced. Nineteen percent had CTP Class A cirrhosis. The 95% confidence interval for SVR12 was 98 to >99%. The side-effect/adverse-event profile of sofosbuvir/velpatasvir was similar to placebo. In a separate study (ASTRAL-3) (Foster, 2015a), among patients with HCV genotype 3 (n=552), the rate of sustained virologic response in the sofosbuvir/velpatasvir group was 95% (95% CI, 92 to 98), which was superior to the rate of 80% (95% CI, 75 to 85) for patients receiving sofosbuvir plus ribavirin for 12 weeks. In a third study (ASTRAL-4) (Curry, 2015b), 267 patients with HCV genotypes 1, 2, 3, 4, and 6 in patients with decompensated cirrhosis (90% CTP Class B or C) in which 55% of patients were treatment experienced, SVR12 was achieved in 83% in those who received sofosbuvir/velpatasvir for 12 weeks, 94% in those who received sofosbuvir/velpatasvir with ribavirin for 12 weeks, and 86% in those who received sofosbuvir/velpatasvir for 24 weeks. Among patients with genotype 1, the SVR was 88% and 96% with sofosbuvir/velpatasvir for 12 weeks without and with ribavirin respectively, and 92% with sofosbuvir/velpatasvir for 24 weeks. Posttreatment virologic relapse occurred in 12% and 9% in the groups that did not receive ribavirin vs 2% of the 12-week group of sofosbuvir/velpatasvir with ribavirin. Although the ASTRAL-4 study was not powered to generate statistical significance, the results suggest that sofosbuvir/velpatasvir with ribavirin for 12 weeks is the optimal choice for patients with genotypes 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.

Velpatasvir is a substrate for CYP3A4, CYP2C8, and CYP2B6 and a weak (P-gp, OATP) to moderate (breast cancer resistance protein, BCRP) transport inhibitor and 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). However, based on the lack of real-world experience of the pharmacokinetics of sofosbuvir/velpatasvir in liver-transplant recipients and because alternatives with similar projected efficacy are available for which interactions with immunosuppression agents have been reported, we do not recommend the use of velpatasvir in transplant recipients at this time.

Table. DAA Interactions with Calcineurin Inhibitors

	Cyclosporine	Tacrolimus
Sofosbuvir	4.5-fold ? in SOF AUC, but GS-331007 metabolite unchanged; no a priori dose adjustment, but monitor CSA levels and titrate CSA dose as needed	No interaction observed; no a priori dose adjustment, but monitor TAC levels and titrate TAC dose as needed
Ledipasvir	No data; no a priori dose adjustment, but monitor CSA levels and titrate CSA dose as needed	No data; no a priori dose adjustment, but monitor TAC levels and titrate TAC dose as needed
Daclatasvir	No interaction observed; no a priori dose adjustment, but monitor CSA levels and titrate CSA dose as needed	No interaction observed; no a priori dose adjustment, but monitor TAC levels and titrate TAC dose as needed
Simeprevir	5.81-fold ? in SIM AUC; combination is not recommended	85% ? in SIM AUC; no a priori dose adjustment, but monitor TAC levels and titrate TAC dose as needed
PrOD	5.8-fold ? in CSA AUC; modeling suggest using 1/5 of CSA dose during PrOD treatment, monitor CSA levels and titrate CSA dose as needed	57-fold ? in TAC AUC; modeling suggests TAC 0.5 mg every 7 days during PrOD treatment, monitor TAC levels and titrate TAC dose as needed
PrO	4.3-fold ? in CSA AUC; modeling suggest using 1/5 of CSA dose during PrO treatment, monitor CSA levels and titrate CSA dose as needed	86-fold ? in TAC AUC; modeling suggests TAC 0.5 mg every 7 days during PrO treatment, monitor TAC levels and titrate TAC dose as needed
Elbasvir / Grazoprevir	15-fold ? in GZR AUC and 2-fold ? in EBR AUC; combination is not recommended	43% ? in TAC; no a priori dose adjustment, but monitor TAC levels and titrate TAC dose as needed
Velpatasvir	No interaction observed; no a priori dose adjustment, but monitor CSA levels and titrate CSA dose as needed	No data; no a priori dose adjustment, but monitor TAC levels and titrate TAC dose as needed

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 duration is unclear, expert consultation should be sought.

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