Patients Who Develop Recurrent HCV Infection Post Liver Transplantation

Post Liver Transplantation: Genotype 1-6

### Recommended regimens listed by evidence level and alphabetically for:

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

<table>
<thead>
<tr>
<th>RECOMMENDED</th>
<th>DURATION</th>
<th>RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)</td>
<td>12 weeks</td>
<td>I, B</td>
</tr>
<tr>
<td><strong>Genotype 1, 4, 5, or 6 only:</strong> Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)</td>
<td>12 weeks</td>
<td>I, B</td>
</tr>
<tr>
<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)</td>
<td>12 weeks</td>
<td>I, B</td>
</tr>
</tbody>
</table>

*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 evidence level and alphabetically for:

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

<table>
<thead>
<tr>
<th>RECOMMENDED</th>
<th>DURATION</th>
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</tr>
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<tr>
<td><strong>Genotype 1, 4, 5, or 6 only:</strong> Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with ribavirin starting at 600 mg and increased as tolerated to weight-based dose*</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)</td>
<td>12 weeks</td>
<td>I, B</td>
</tr>
<tr>
<td>Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)</td>
<td>12 weeks</td>
<td>I, C</td>
</tr>
</tbody>
</table>

*a* Ribavirin was only studied with ledipasvir/sofosbuvir, however, for patients with multiple negative baseline characteristics, 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.

*b* Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.
### Treatment-Naive and -Experienced Patients With Genotype 1-6 Infection in the Allograft and Decompensated Cirrhosis

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<th>RATING</th>
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</thead>
<tbody>
<tr>
<td>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})</td>
<td>12 to 24 weeks(^{c})</td>
<td>I, B</td>
</tr>
<tr>
<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) starting at 600 mg and increased as tolerated(^{b})</td>
<td>12 to 24 weeks(^{c})</td>
<td>I, B</td>
</tr>
</tbody>
</table>

\(^{a}\) 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.

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

<table>
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<tr>
<th>RECOMMENDED</th>
<th>DURATION</th>
<th>RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)(^{b})</td>
<td>12 weeks</td>
<td>I, C</td>
</tr>
</tbody>
</table>

\(^{a}\) 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.

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**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 or 12 weeks of...
gqeaprevir/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 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.

**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 (Kwo, 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.
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**

The safety and efficacy of the fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was evaluated in 79 (n=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 uncompensated 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 plus weight-based ribavirin. 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 and with and 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 uncompensated 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).

**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.

**Treatment of Transplant Recipients with Organs from HCV-Viremic Donors**

With the large disparity between patients in need of an organ transplant and available donors, transplant programs are turning to the use of HCV-positive donors to increase the donor pool and reduce waiting time. All donors undergo HCV-antibody testing (anti-HCV); those who are positive undergo HCV-RNA testing using a sensitive assay. Donors who are HCV antibody positive but HCV RNA negative pose a negligible risk for transmission of HCV to a recipient, with one exception—if a donor had a very recent HCV exposure and is not yet viremic (Levitsky, 2017); (Bari, 2018). Such donors, as defined by US Public Health Service (PHS) guidelines based on HCV exposure risk, pose a low risk for transmission of HCV and standard post-transplant monitoring of the recipients to detect HCV transmission is required (Seem, 2013b); (Levitsky, 2017). Donors who are HCV RNA positive (with or without anti-HCV) pose the highest risk for transmission of the virus to recipients. In the past, HCV-RNA-positive donors were primarily used in recipients with chronic hepatitis C. With the advent of safe and effective DAAs, however, organs from HCV-RNA-positive donors may be considered for use in recipients without chronic HCV infection.

No published data are available on the long-term consequences to HCV-negative recipients transplanted with organs from HCV-infected donors, but limited short-term data from liver, kidney, heart, and lung transplant programs are encouraging. Among 10 HCV-negative liver transplant recipients from HCV-infected donors, 100% achieved SVR12 with 12 to 24 weeks of various DAA regimens (Kwong, 2019). Noteworthy was the high rate of acute cellular or antibody-mediated rejection (30%) during or after DAA therapy.

In a multicenter Spanish study, 4 anti-HCV and HCV-RNA-positive (by rapid test) kidney transplant recipients were treated with glecaprevir/pibrentasvir starting the day of transplantation and for 8 weeks post transplant; 100% achieved SVR12 (Franco, 2019). In a study of 44 HCV-naive lung (n=36) and heart transplant (n=8) recipients from HCV-infected donors, treatment was administered preemptively with sofosbuvir/velpatasvir starting within hours of transplantation and continued for 4 weeks. Among the initial 35 patients with at least 6 months of follow-up post transplantation, 100% achieved SVR and had excellent graft function (Woolley, 2019).

Among 20 HCV-uninfected kidney transplant recipients who received organs from HCV-RNA-positive donors and were treated with 12 weeks of elbasvir/grazoprevir (± sofosbuvir), 100% achieved SVR (Goldberg, 2017). In a 1-year follow-up study, kidney function in those who received kidneys from HCV-infected donors was better than matched controls who had HCV uninfected donors (Reese, 2018).

While early results are encouraging, the overall number of published cases is small and treatment approaches variable. Risks include DAA treatment failure with possible severe or rapidly progressive liver disease, as highlighted by the lung transplant experience at the University of Toronto. Two of 8 DAA-treated patients relapsed, with emergence of complex RASs in 1 patient and the development of fibrosing cholestatic hepatitis in the other (Feld, 2018). Due to the limited and
heterogeneous experience and lack of longer-term safety data, strong consideration should be given to performing these transplants under IRB-approval protocols as recommended by the American Society of Transplantation consensus panel (Levitsky, 2017). Whether under an IRB-approved protocol or not, a rigorous process for informed consent is recommended. Importantly, such recipients must be assured of access to HCV treatment (and retreatment, if necessary) after transplantation. Moreover, transplant programs need to ensure that these patients have long-term follow-up to monitor for potential late consequences of HCV exposure and graft function.

### Recommendations When Considering Use of HCV-RNA-Positive Donor Organs for HCV-Negative Recipients

<table>
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<tr>
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**Informed consent should include the following elements:**

- Risk of transmission from an HCV-viremic donor (and if PHS-defined high risk, the potential risks for other viral infections)
- Risk of liver disease if HCV treatment is not available or treatment is unsuccessful
- Benefits, specifically reduced waiting time and possibly lower waiting list mortality
- Unknown long-term consequences (hepatic and extrahepatic) of HCV exposure (even if cure attained)
- Risk of graft failure
- Risk of HCV transmission to partner

**Transplant programs should have a programmatic strategy to:**

- Document informed consent
- Assure access to HCV treatment and retreatments, as necessary
- Insure long-term follow-up of recipients (beyond SVR12)

Treatment may be initiated preemptively (ie, immediately after transplantation without confirmation of viremia in the recipient) or early (ie, within days to weeks once HCV viremia is documented in the recipient). There has been no head-to-head comparison of these strategies so there are insufficient data to recommend one approach over the other. However, the goal should be to undertake therapy early enough to avoid the development of acute or chronic hepatitis but when the patient is clinically stable and taking medications orally, and treatment interruptions are unlikely. Importantly, since genotyping of HCV-viremic donors is not routinely performed, if a preemptive treatment approach is used, only pangenotypic regimens should be utilized. If treatment is delayed until the recipient has quantifiable HCV RNA, the recipient’s genotype can be used to guide DAA treatment choices.

Selection of the DAA therapy should follow the same principles as those for transplant recipients (above). Selection of regimens that avoid the use of ribavirin (to reduce ribavirin-associated side effects) and regimens that do not require baseline RAS testing may be preferred. Thus, although there are data supporting the safety and efficacy of elbasvir/grazoprevir among HCV-negative kidney transplant recipients of allografts from HCV-viremic donors, the regimen is designated an alternative regimen due to the necessity for baseline RAS testing.
### Recommendations for Treatment of Organ Recipients from HCV-RNA-Positive Donors

<table>
<thead>
<tr>
<th><strong>Timing of DAA Therapy</strong> - Considerations for preemptive versus delayed initiation of therapy</th>
<th><strong>RATING</strong></th>
</tr>
</thead>
</table>
| • Oral delivery of DAA therapy is assured.  
  ◦ There are limited data on the efficacy of DAAs given crushed via a nasogastric tube.  
  ◦ Nothing-by-mouth status may affect the absorption of some DAAs.  
• Preemptive therapy requires a pangenotypic regimen as donor genotyping is not routinely performed.  
• Delayed therapy involves awaiting documentation of viremia post transplantation and tailoring treatment to genotype or using a pangenotypic regimen. | II, B |

### Recommended and alternative\(^a\) regimens listed by evidence level and alphabetically for:

#### Treatment of Organ Recipients from HCV-RNA-Positive Donors

<table>
<thead>
<tr>
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<td>Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)(^b)</td>
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<td><strong>Genotype 1, 4, 5, or 6 only:</strong> Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)</td>
<td>12 weeks</td>
<td>I, C</td>
</tr>
<tr>
<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)</td>
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</tbody>
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<tr>
<th><strong>ALTERNATIVE</strong></th>
<th><strong>DURATION</strong></th>
<th><strong>RATING</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Genotype 1 and 4 only:</strong> Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs(^c) for elbasvir</td>
<td>12 weeks</td>
<td>I, C</td>
</tr>
</tbody>
</table>

\(^a\) Other considerations in selection of the DAA regimen:

- Presence of renal dysfunction in the post-transplant period as sofosbuvir-inclusive regimens are not recommended if creatinine clearance is <30 mL/min
- Presence of liver dysfunction (eg, elevated bilirubin) as protease inhibitors should be avoided
- Specific drugs that are contraindicated or not recommended with specific DAA agents, including but not limited to:
  ◦ High-dose antacid therapy (eg, twice daily proton pump inhibitor)
  ◦ Amiodarone (contraindicated with sofosbuvir-inclusive regimens)
  ◦ Specific statins (eg, atorvastatin)
- Consideration of immunosuppressive drugs and DAA interactions (see below)

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

\(^c\) Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance.
Recommended and alternative regimens listed by evidence level and alphabetically for:

Treatment of Organ Recipients from HCV-RNA-Positive Donors

Organs from HCV-RNA-positive donors may also be used in transplant candidates who have chronic HCV infection or had chronic HCV infection and achieved SVR. The management approach to these anti-HCV-positive transplant candidates should be the same as anti-HCV-negative transplant patients.

Drug Interactions Between DAAs and Calcineurin Inhibitors

The interaction of 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 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

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

AUC=area under the curve
Related References


Reese PP, Abt PL, Blumberg EA, et al. Twelve-month outcomes after transplant of hepatitis C-infected kidneys into


