Peginterferon/Ribavirin-Experienced, Genotype 4 Patients With Compensated Cirrhosis

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

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<th>RECOMMENDED</th>
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<td>12 weeks</td>
<td>I, A</td>
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<tr>
<td>Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients who experienced virologic relapse after prior peginterferon/ribavirin therapy</td>
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<tr>
<td>Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)(b)</td>
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\(a\) For decompensated cirrhosis, please refer to the appropriate section.
\(b\) This is a 3-tablet coformulation. Please refer to the prescribing information.
\(c\) Please see statement on FDA warning regarding the use of paritaprevir/ritonavir/ombitasvir ± dasabuvir in patients with cirrhosis.

Recommended Regimens

Sofosbuvir/VELpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naive or -experienced patients with genotype 1, 2, 4, 5, or 6 infection treated with a daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks (Feld, 2015). The study included 116 patients with genotype 4 infection. One hundred percent SVR12 was achieved, including 52 treatment-experienced patients and 27 with compensated cirrhosis (Feld, 2015).
Elbasvir/Grazoprevir ± Ribavirin

A 2015 integrated analysis of all phase 2 and phase 3 elbasvir (50 mg)/grazoprevir (100 mg) studies to date demonstrated efficacy of this regimen for both treatment-naive (n=66) and -experienced (n=37) patients with genotype 4 infection (Asselah, 2018c). The overall SVR12 rate among treatment-experienced, genotype 4-infected patients was 87% (32/37) with numerical response differences based on prior interferon treatment response (relapse vs on-treatment viral failure); elbasvir/grazoprevir duration (12 weeks vs 16 weeks); and/or ribavirin usage (inclusion or exclusion of ribavirin in the regimen). Numbers within any specific subgroup are too small to make definitive recommendations. However, trends emerged that were used to guide the current recommendations pending additional data. No treatment failures were seen in patients who relapsed after prior peginterferon/ribavirin therapy, regardless of elbasvir/grazoprevir treatment duration or ribavirin usage. In contrast, response rates were numerically lower in patients with prior on-treatment virologic failure in the nonribavirin-containing arms (12 weeks, 78%; 16 weeks, 60%) compared to ribavirin-containing treatment (12 weeks with ribavirin, 91%; 16 weeks with ribavirin, 100%).

Given the lack of sufficient numbers to differentiate response between 12 weeks with ribavirin and 16 weeks with ribavirin, the use of 16 weeks of elbasvir/grazoprevir plus ribavirin in genotype 4-infected patients with prior on-treatment virologic failure represents the most conservative approach and is an alternative recommendation.

Glecaprevir/Pibrentasvir

The phase 3, single-arm, open-label EXPEDITION-1 study investigated the safety and efficacy of 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 patients with genotype 1, 2, 4, 5, or 6 infection and compensated cirrhosis (Forns, 2017). Overall, 25% of patients were treatment experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon). All 16 patients with genotype 4 infection (unknown number with prior treatment experience) achieved SVR.

Alternative Regimens

Paritaprevir/Ritonavir/Ombitasvir + Ribavirin

The AGATE-I trial randomized 120 treatment-naive or -experienced patients (interferon-based regimens) with genotype 4 infection and compensated cirrhosis to 12 weeks or 16 weeks of the daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus weight-based ribavirin. The SVR12 rates in the 12-week and 16-week arms were 96% and 100%, respectively. The regimens were well tolerated (Asselah, 2015a).

The phase 3, open-label, partly randomized AGATE-II trial included a cohort of 60 treatment-naive or -experienced (interferon-based regimens), genotype 4-infected patients with compensated cirrhosis. These participants were randomized to 12 weeks or 24 weeks of paritaprevir/ritonavir/ombitasvir plus weight-based ribavirin. The SVR12 rate from the 12-week arm was 97%.

These data support the use of paritaprevir/ritonavir/ombitasvir plus weight-based ribavirin for 12 weeks in treatment-experienced genotype 4 patients, including those with compensated cirrhosis (Esmat, 2015a). Due to the number of treatment options that exist, including those that do not use ribavirin, this is an alternative rather than a recommended option.

Ledipasvir/Sofosbuvir + Ribavirin

In the open-label cohort, phase 2a SYNERGY trial, 21 patients with genotype 4 infection were treated with a 12-week course of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg). Forty percent of participants were treatment experienced and 40% had advanced fibrosis. Twenty patients completed the 12-week therapy and all achieved SVR12; 1 patient withdrew from the study (Kohli, 2015). A pooled analysis of the 12-week ledipasvir/sofosbuvir regimen (including the SYNERGY trial) reported an SVR12 rate of 94% (32/34) in treatment-experienced patients with genotype 4...
infection (Asselah, 2018b). Due to the small number of patients overall and with cirrhosis, the addition of ribavirin to the 12-week regimen is recommended in patients with cirrhosis (Kohli, 2015). This is an alternative regimen due to the need for ribavirin.

**Last update:** September 21, 2017

**Related References**

Asselah T, Hassanien T, Qadish RB, et al. *A randomized, open-label study to evaluate efficacy and safety of ombitasvir/paritaprevir/ritonavir co-administered with ribavirin in adults with genotype 4 chronic hepatitis C infection and cirrhosis.* Journal of Hepatology. 2015;62(S861).


