Peginterferon/Ribavirin-Experienced, Genotype 4 Patients Without Cirrhosis

Recommended regimens listed by evidence level and alphabetically for:

<table>
<thead>
<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)</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)</td>
<td>8 weeks</td>
<td>I, B</td>
</tr>
<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>
<td>12 weeks</td>
<td>IIa, B</td>
</tr>
<tr>
<td>Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)</td>
<td>12 weeks</td>
<td>IIa, 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.

\[b\] If the type of prior treatment failure (relapse vs breakthrough/nonresponse) is unknown, another recommended regimen should be used.

Sofosbuvir/Velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naive or -experienced patients with genotype 1, 2, 4, 5, or 6 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. One hundred percent SVR12 was achieved, including 52 treatment-experienced patients (Feld, 2015).

Glecaprevir/Pibrentasvir

The phase 2, open-label, single arm SURVEYOR-II, part 4 study investigated the efficacy of 8 weeks 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 noncirrhotic patients with genotype 2, 4, 5, or 6. Patients were treatment naive or experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon). Forty-six genotype 4 patients accounted for 23% of the study population; only 27 of these patients (13% of the study population) were treatment experienced. The SVR12 was 93%; 3 patients had nonvirologic outcomes, including missed follow-up and study discontinuation. There were no virologic failures but the number of treatment-experienced patients was small (Asselah, 2018b).

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-naïve (n=66) and -experienced (n=37) patients with genotype 4 (Asselah, 2018c). The overall SVR12 among treatment-experienced, genotype 4 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. Trends emerged, however, 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 non-ribavirin-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 patients with prior on-treatment virologic failure represents the most conservative approach.

**Ledipasvir/Sofosbuvir**

In the open-label cohort, phase 2a SYNERGY trial, 21 patients with genotype 4 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 of 94% (32/34) in treatment-experienced patients with genotype 4 (Asselah, 2018b).

**Last update:** November 6, 2019

**Related References**


