Peginterferon/Ribavirin-Experienced, Genotype 1a Patients Without Cirrhosis

<table>
<thead>
<tr>
<th>RECOMMENDED</th>
<th>DURATION</th>
<th>RATING</th>
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<tbody>
<tr>
<td>Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for</td>
<td>12 weeks</td>
<td>I, A</td>
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<td>patients without baseline NS5A RASs&lt;sup&gt;a&lt;/sup&gt; for elbasvir</td>
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<td>Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8 weeks</td>
<td>I, A</td>
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<tr>
<td>Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)</td>
<td>12 weeks</td>
<td>I, A</td>
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<tr>
<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)</td>
<td>12 weeks</td>
<td>I, A</td>
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<sup>a</sup> Includes genotype 1a RASs at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance to elbasvir. Baseline testing for these RASs is recommended for patients receiving elbasvir/grazoprevir-based regimens.

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

Elbasvir/Grazoprevir

The phase 3 C-EDGE TE trial evaluated the daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) in patients with a prior peginterferon/ribavirin treatment failure. Patients were randomized to elbasvir/grazoprevir for 12 weeks or 16 weeks, with or without ribavirin. Genotype 1 patients treated for 12 weeks without ribavirin had an overall SVR12 of 93.8% (90/96), which was nearly identical to the rate seen in those treated for 12 weeks with ribavirin (94.4%, 84/89) (<sup>Kwo, 2017</sup>). SVR rates were similar in the 16-week arms without ribavirin (94.8%, 91/96) and with ribavirin (96.9%, 93/96).

The presence of certain baseline NS5A RASs appears to be the single best predictor of relapse with the 12-week elbasvir/grazoprevir regimen. In genotype 1a patients treated with elbasvir/grazoprevir, decreased efficacy was seen among those with baseline NS5A RASs when assessed by population sequencing (25% limit of detection). These RASs included substitutions at positions M28, Q30, L31, H58, and Y93. Among 21 genotype 1a patients with baseline NS5A RASs (>5 fold), only 52% (11/21) achieved SVR12 due to a higher relapse rate (<sup>Kwo, 2015</sup>).

A subsequent integrated analysis of phase 2 and phase 3 trials confirmed a lower SVR12 in treatment-experienced, genotype 1a patients with these specific baseline NS5A RASs (90%, 167/185) versus patients without baseline RASs (99%, 390/393) (<sup>Zeuzem, 2017</sup>). In patients treated with 12 weeks of elbasvir/grazoprevir without ribavirin, 64% (9/14) with baseline elbasvir NS5A RASs achieved SVR12, compared to 96% (52/54) among those without these baseline RASs. Extension of therapy to 16 weeks or 18 weeks with the addition of weight-based ribavirin increased the response rate to 100% regardless of the presence of baseline NS5A RASs, suggesting this approach can overcome the negative
impact of NS5A RASs seen with the 12-week regimen (Jacobson, 2015b).

Based on the known inferior response in patients with specific NS5A RASs, NS5A resistance testing is recommended for genotype 1a patients being considered for elbasvir/grazoprevir therapy. If these RASs are present, treatment extension to 16 weeks with the addition of weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [≥75 kg]) is recommended to decrease relapse risk. A prospective real-world study confirmed high response rates based on this approach (Braun, 2019). Given the need for ribavirin and the prolonged duration of therapy in the presence of key NS5A RASs as well as multiple preferred regimens, elbasvir/grazoprevir plus ribavirin for 16 weeks has been removed as an alternative regimen. Lack of access to RAS testing or results should not be used as a means to limit access to HCV therapy.

**Glecaprevir/Pibrentasvir**

The phase 3 ENDURANCE-1 trial enrolled 703 treatment-naive or -experienced patients (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) with genotype 1 and no cirrhosis. Participants were randomized to 8 weeks or 12 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 (Zeuzem, 2016). Of those enrolled, 43% had genotype 1a, 85% had fibrosis stage F0 or F1, and 38% were treatment experienced. Ninety-nine percent of the treatment-experienced patients had previously received interferon-based therapy and 1% had received sofosbuvir-based treatment. Overall SVR12 rates for the intention-to-treat population were 99% (348/351) in the 8-week arm and 99.7% (351/352) in the 12-week arm. The 8-week arm met the predefined study criteria for noninferiority. A single patient experienced on-treatment virologic failure (genotype 1a, day 29). There were no documented relapses in either study arm. This regimen was well tolerated with rare adverse events leading to discontinuation (0.1%); no significant laboratory abnormalities were noted.

**Ledipasvir/Sofosbuvir**

The daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) has been evaluated in patients without cirrhosis and a history of treatment failure with peginterferon/ribavirin, with or without HCV protease inhibitors (telaprevir or boceprevir). In the ION-2 study, patients who had not responded to prior peginterferon/ribavirin therapy were treated with ledipasvir/sofosbuvir, with or without ribavirin, for 12 weeks or 24 weeks. In the population without cirrhosis, the overall SVR12 rate was 98%. Specifically, in patients without cirrhosis and a history of peginterferon/ribavirin failure, 94% (33/35) achieved SVR12 after 12 weeks of ledipasvir/sofosbuvir treatment, and 100% (38/38) achieved SVR12 in the ledipasvir/sofosbuvir plus ribavirin study arm (Afdhal, 2014b). This regimen was well tolerated in all groups with no serious adverse events reported for the 12-week regimen, with or without ribavirin.

**Sofosbuvir/Velpatasvir**

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naive or -experienced patients with genotype 1, 2, 4, 5, or 6 who were treated with sofosbuvir (400 mg)/velpatasvir (100 mg) as a daily fixed-dose combination for 12 weeks (Feld, 2015). Patients in the placebo arm were eligible to roll over into a deferred therapy arm with the same regimen. The overall response rate among genotype 1, treatment-experienced patients was 99% (109/110), with 100% (78/78) in participants with genotype 1a and 97% (31/32) in those with genotype 1b. Among patients previously treated with peginterferon/ribavirin, 98% (50/51) achieved SVR; 100% (48/48) of those previously treated with a DAA plus peginterferon/ribavirin achieved SVR. The single treatment-experienced patient who did not respond to this regimen was a genotype 1b, black adult with cirrhosis and IL28 TT genotype. This individual had a persistently detectable HCV viral load during previous peginterferon/ribavirin therapy. The regimen was well tolerated and there was no significant difference in the rate of adverse events in the sofosbuvir/velpatasvir group (78%) vs the placebo group (77%).

**Last update:** November 6, 2019

**Related References**


