Peginterferon/Ribavirin-Experienced, Genotype 3 Patients Without Cirrhosis

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

**Peginterferon/Ribavirin-Experienced, Genotype 3 Patients Without Cirrhosis**

<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)²</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ALTERNATIVE</th>
<th>DURATION</th>
<th>RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily daclatasvir (60 mg)ᵇ plus sofosbuvir (400 mg)ᵃ</td>
<td>12 weeks</td>
<td>I, A</td>
</tr>
<tr>
<td>Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)ᶜ</td>
<td>16 weeks</td>
<td>IIa, B</td>
</tr>
<tr>
<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)⁻ when Y93H is present</td>
<td>12 weeks</td>
<td>IIb, B</td>
</tr>
</tbody>
</table>

ᵃ Baseline RAS testing for Y93H is recommended. If the Y93H substitution is identified, a different regimen should be used, or weight-based ribavirin should be added as an alternative option.

ᵇ The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

ᶜ This is a 3-tablet coformulation. Please refer to the prescribing information.

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**Recommended Regimen**

**Sofosbuvir/Velpatasvir**

The phase 3 ASTRAL-3 study evaluated the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks (without ribavirin) in 277 genotype 3-infected patients, including 71 with prior treatment experience and 80 with compensated cirrhosis (Foster, 2015a). Despite a high combined SVR12 rate of 95% (264/277), both prior treatment (90% SVR) and compensated cirrhosis (91% SVR) had a moderate negative impact on treatment response. The addition of ribavirin appeared to increase SVR12 rates in a phase 2 study that included treatment-experienced, genotype 3-infected patients treated for 12 weeks with sofosbuvir (400 mg) plus 25 mg or 100 mg of velpatasvir, with or without ribavirin (Planko, 2015).

The phase 3 POLARIS-2 study evaluated 12 weeks of sofosbuvir/velpatasvir versus 8 weeks of sofosbuvir/velpatasvir/voxilaprevir in patients (any genotype) who were either treatment naive or had a previous peginterferon/ribavirin treatment failure. Eighty-nine genotype 3-infected patients (all without cirrhosis) received the sofosbuvir/velpatasvir regimen and 97% (86/89) achieved SVR12 (Jacobson, 2017). There were no virologic failures. These findings confirm the efficacy of this 12-week regimen in genotype 3-infected patients without cirrhosis.
Baseline NS5A substitutions in genotype 3 infection impact DAA treatment response, with the Y93H substitution having the greatest effect. In the ALLY-3 study, the Y93H substitution was detected at baseline in 9% (13/147) of participants (Nelson, 2015). SVR12 in these patients was 54% (7/13), including an SVR12 of 67% (6/9) in patients without cirrhosis. In the ASTRAL-3 study, the Y93H substitution was detected in 9% (25/274) of patients with an SVR12 rate of 84% (21/25) (Foster, 2015a).

Pending additional data, baseline NS5A RAS testing is recommended in all treatment-experienced, genotype 3-infected patients without cirrhosis for whom sofosbuvir/velpatasvir is being considered. If the Y93H substitution is identified, a different regimen should be used, or weight-based ribavirin should be added as an alternative option.

**Alternative Regimens**

**Daclatasvir + Sofosbuvir**

The phase 3, open-label ALLY-3 study evaluated a 12-week course of daclatasvir (60 mg) plus sofosbuvir (400 mg) in treatment-naive or -experienced (interferon-based therapy or sofosbuvir plus ribavirin), genotype 3-infected patients without cirrhosis or with compensated cirrhosis. Treatment-experienced, genotype 3-infected patients without cirrhosis did well with an SVR12 rate of 94% (32/34) (Nelson, 2015).

Baseline NS5A substitutions in genotype 3 infection impact DAA treatment response, with the Y93H substitution having the greatest effect. In the ALLY-3 study, the Y93H substitution was detected at baseline in 9% (13/147) of patients (Nelson, 2015). The SVR12 in these patients was 54% (7/13), including an SVR12 of 67% (6/9) in patients without cirrhosis. In the ASTRAL-3 study, the Y93H substitution was detected in 9% (25/274) of patients with an SVR12 rate of 84% (21/25) (Foster, 2015a).

Pending additional data, baseline NS5A RAS testing is recommended in all treatment-experienced, genotype 3-infected patients without cirrhosis for whom daclatasvir plus sofosbuvir is being considered. If the Y93H substitution is identified, a different recommended regimen should be used, or weight-based ribavirin should be added as an alternative option.

**Glecaprevir/Pibrentasvir**

The SURVEYOR-II, part 3 trial evaluated the safety and efficacy of a 12-week or 16-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 treatment-naive or -experienced (standard or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon), genotype 3-infected patients without cirrhosis or with compensated cirrhosis. Among the 44 treatment-experienced patients without cirrhosis, the SVR rates were 91% (20/22) and 96% (21/22) for 12 weeks and 16 weeks, respectively. All patients who experienced treatment failure had baseline RAS mutations. One patient in the 12-week study arm had an A30K RAS at baseline and a treatment-emergent Y93H RAS at failure resulting in the A30K+Y93H double RAS, which confers 69-fold resistance to glecaprevir/pibrentasvir. This was also true in the single relapse in the 16-week study arm. The second patient with relapse in the 12-week arm had a baseline Y93H RAS, which persisted at the time of failure. The Y93H substitution does not confer high-fold resistance to this regimen (Wyles, 2017a).

Based on these data, the appropriate length of therapy is unclear for genotype 3-infected, peginterferon/ribavirin-experienced patients. Until further data are available, a 16-week duration of treatment is recommended as an alternative option, especially if a baseline A30K substitution is present.

**Sofosbuvir/Velpatasvir/Voxilaprevir**

The efficacy of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) in genotype 3 infection is supported by the phase 3 POLARIS trials, which investigated 8 weeks of sofosbuvir/velpatasvir/voxilaprevir in DAA-naive patients and 12 weeks in DAA-experienced patients. The 8-week
Peginterferon/Ribavirin-Experienced, Genotype 3 Patient...

regimen achieved noninferiority compared to a 12-week sofosbuvir/velpatasvir regimen in the POLARIS-3 study, which included 35 interferon-experienced patients with genotype 3 infection and cirrhosis (Jacobson, 2017). Thus, this regimen is recommended as an alternative option for patients with genotype 3 infection who have evidence of the Y93H RAS at baseline.

In the ASTRAL-3 study, which investigated 12 weeks of sofosbuvir/velpatasvir, the Y93H substitution was detected in 9% (25/274) of patients with an SVR12 rate of 84% (21/25) (Foster, 2015a). Due to the low number of patients with the Y93H mutation in the POLARIS-3 study and the difficult-to-treat nature of treatment-experienced, genotype 3-infected patients, we recommend 12 weeks of sofosbuvir/velpatasvir/voxilaprevir to optimize SVR12.

Last update: September 21, 2017

Related References


