Peginterferon/Ribavirin-Experienced, Genotype 3 Patients Without Cirrhosis

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

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\(^a\) 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 3A4 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.

### 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, 2018).

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
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**


