Peginterferon/Ribavirin-Experienced, Genotype 3 Patients With Compensated Cirrhosis

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

Peginterferon/Ribavirin-Experienced, Genotype 3 Patients With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose elbasvir (50 mg)/grazoprevir (100 mg) plus sofosbuvir (400 mg)	12 weeks	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)	12 weeks	IIb, B
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) plus weight-based ribavirin	12 weeks	I, B
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	16 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.

Recommended Regimens

Elbasvir/Grazoprevir + Sofosbuvir

The C-ISLE study evaluated the daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus sofosbuvir, with or without ribavirin, for 8 weeks to 16 weeks for treatment-naive or -experienced, genotype 3-infected patients with compensated cirrhosis. One hundred patients were enrolled, including 53 with a history peginterferon/ribavirin failure. Treatment-experienced participants were randomized to 12 weeks of elbasvir/grazoprevir plus sofosbuvir, 12 weeks of elbasvir/grazoprevir plus sofosbuvir and weight-based ribavirin, or 16 weeks of elbasvir/grazoprevir plus sofosbuvir (Foster, 2016b). All 3 arms had 100% SVR on the per protocol analysis, with 17 patients in each arm. The efficacy was high regardless of the presence of baseline RASs, including 3 patients with the Y93H substitution.

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 in patients with genotype 3 infection and cirrhosis.

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). Patients with genotype 3 infection, prior non-DAA treatment failure, and cirrhosis are among the most difficult to treat. For this reason, ribavirin is recommended for all patients receiving sofosbuvir/velpatasvir, making this an alternative regimen. Due to the low number of patients with the Y93H mutation in the POLARIS-3 study, we recommend 12 weeks of sofosbuvir/velpatasvir/voxilaprevir to optimize SVR12.

Alternative Regimens

Sofosbuvir/Velpatasvir + Ribavirin

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. Among those with both compensated cirrhosis and prior treatment, the SVR12 rate was 89% (33/37). 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 (Pianko, 2015).

In the POLARIS-3 study noted previously, the SVR12 rate in the 32 patients with prior peginterferon/ribavirin treatment failure and cirrhosis was 91% (29/32). Although the 2 virologic failures did not have Y93H at baseline, both developed treatment-emergent Y93H mutations (Jacobson, 2017). Based on this finding and analogous to the similar ALLY-3 study, the addition of weight-based ribavirin (if not contraindicated) is recommended for all treatment-experienced, genotype 3-infected patients with compensated cirrhosis when using sofosbuvir/velpatasvir pending additional data. Due to the need for ribavirin, this is recommended as an alternative regimen.

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 47 treatment-experienced participants with compensated cirrhosis who were treated for 16 weeks, the SVR rate was 96% (45/47). One of the virologic failures was a relapse and the other was viral breakthrough. The patient with viral breakthrough had low serum DAA levels at week 4 of the study, suggesting poor adherence. The patient with relapse did not have baseline NS3 or NS5A RASs but did have dual NS5A RASs emerge at the time of failure (Wyles, 2016a).

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