Treatment-Naive Genotype 3 With Compensated Cirrhosis

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

Treatment-Naive Genotype 3 Patients With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)[c]	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) when Y93H is present	12 weeks	IIa, B
Daily daclatasvir (60 mg)[d] plus sofosbuvir (400 mg) with or without weight-based ribavirin[c]	24 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.
[c] RAS testing for Y93H is recommended for cirrhotic patients. If present, ribavirin should be included in the regimen or sofosbuvir/velpatasvir/voxilaprevir should be considered.
[d] 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.

Recommended Regimens

Glecaprevir/Pibrentasvir

SURVEYOR-II—a partially randomized, open-label, multicenter, 4-part, phase 2 trial—compared 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, to glecaprevir/pibrentasvir plus ribavirin among 48 treatment-naive, genotype 3-infected participants with compensated cirrhosis. All patients treated with 12 weeks of glecaprevir/pibrentasvir, with or without ribavirin, achieved SVR12 (Kwo, 2016b). The presence of baseline NS3 and/or NS5A RASs had no impact on SVR12 rate regardless of inclusion of ribavirin in the treatment regimen; however the analysis was limited because few patients had NS5A RASs. These data indicate that 12 weeks of glecaprevir/pibrentasvir yields high SVR12 rates among treatment-naive, genotype 3-infected patients with compensated cirrhosis.

Sofosbuvir/Velpatasvir

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 3 infection in patients without cirrhosis or with compensated cirrhosis. ASTRAL-3 randomized

552 treatment-naive and -experienced patients (without cirrhosis or with compensated cirrhosis) to 12 weeks of sofosbuvir/velpatasvir or 24 weeks sofosbuvir plus ribavirin (Foster, 2015a). Among those with compensated cirrhosis, the SVR12 was 93% (40/43) in the sofosbuvir/velpatasvir arm compared to 73% (33/45) among those in the sofosbuvir plus ribavirin arm. Of the 250 participants who received sofosbuvir/velpatasvir, 43 (16%) had baseline NS5A RASs, of which 88% achieved SVR12 compared to 97% without baseline substitutions. Eighty-four percent (21/25) of those with Y93H achieved SVR12. Pending further data on optimal therapy in the setting of a baseline Y93 substitution, the addition of ribavirin is recommended for patients with compensated cirrhosis.

POLARIS-3 was a randomized, phase 3 trial that compared 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) to 12 weeks of sofosbuvir/velpatasvir among 219 DAA-naive participants with genotype 3 infection and cirrhosis (Jacobson, 2017). The SVR12 rate was 96% in both arms; 105/109 of those randomized to 12 weeks of sofosbuvir/velpatasvir achieved SVR. Four participants in the sofosbuvir/velpatasvir arm had the Y93H substitution; all achieved SVR12.

Alternative Regimens

Sofosbuvir/Velpatasvir/Voxilaprevir

POLARIS-3 was a randomized, phase 3 trial that compared 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) to 12 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg) among 219 DAA-naive participants with genotype 3 infection and cirrhosis (Jacobson, 2017). Thirty-one percent of participants were interferon treatment experienced. The SVR12 rate was 96% in both arms, 106/110 of patients randomized to 8 weeks of sofosbuvir/velpatasvir/voxilaprevir and 105/109 of those randomized to 12 weeks of sofosbuvir/velpatasvir. There were 2 virologic failures in each arm (2 relapses in the sofosbuvir/velpatasvir/voxilaprevir arm; 1 virologic breakthrough and 1 relapse in the sofosbuvir/velpatasvir arm). Baseline RASs had no effect on treatment response. Among the 6 participants with Y93H in the sofosbuvir/velpatasvir/voxilaprevir arm and 4 in the sofosbuvir/velpatasvir arm, all achieved SVR12. Additionally, no patients receiving sofosbuvir/velpatasvir/voxilaprevir with virologic failure developed RASs. Although an 8-week regimen was studied in POLARIS-3, a 12-week regimen of sofosbuvir/velpatasvir/voxilaprevir was approved by the FDA for the indication of retreatment of DAA-experienced patients and could be considered as an alternative regimen for patients with cirrhosis and Y93H.

Daclatasvir + Sofosbuvir

Daclatasvir (60 mg) plus sofosbuvir (400 mg) for 12 weeks was approved by the FDA for treatment of genotype 3 infection. The recommendation is based on ALLY-3, a phase 3 study of daclatasvir/sofosbuvir for 12 weeks among genotype 3-infected, treatment-naive or -experienced (interferon ± ribavirin, sofosbuvir plus ribavirin, or other anti-HCV agents) patients. The study included 101 treatment-naive patients and demonstrated an SVR12 rate of 90%. In treatment-naive patients without cirrhosis (Metavir F0-F3), 97% achieved SVR12, compared to 58% SVR12 in treatment-naive patients with cirrhosis (Metavir F4) (Nelson, 2015).

The results of the ALLY-3 study suggest that patients with genotype 3 infection and cirrhosis are likely to benefit from an extension of therapy. This has been confirmed in cohort studies, including the European compassionate-use program, which reported SVR12 rates of 70% vs 86% when daclatasvir/sofosbuvir was used for 12 weeks and 24 weeks in genotype 3-infected patients with cirrhosis, respectively. The role of ribavirin could not be clarified as only 4 patients received daclatasvir/sofosbuvir plus ribavirin for 12 weeks, all of which achieved SVR12. SVR12 was comparable between the 24-week arms irrespective of the addition of ribavirin (85.9% [116/135] without ribavirin; 81.3% [39/48] with ribavirin). SVR12 rates were also higher in those with compensated Child-Pugh A cirrhosis (85% to 90%) compared to 70.6% in Child-Pugh B/C. Again, the addition of ribavirin did not increase SVR12 rates in the 24-week treatment arms (Hézode, 2017). Seventy-three percent of patients were treatment-experienced, however earlier data suggested that SVR12 rates were higher in treatment-naive patients (91% to 100%) compared to treatment-experienced (81% to 82%). SVR12 rates were similar in patients who received ribavirin (88%, 29/33) and those who did not (86%, 42/49) (Hézode, 2017).

Baseline NS5A RASs significantly reduce SVR12 rates with a 12-week course of daclatasvir/sofosbuvir in genotype 3-infected patients. In an analysis of 175 genotype 3-infected patients with nucleotide sequence data from the ALLY-3 trial, the presence of a NS5A Y93H was associated with a reduced SVR12 rate; 54% (7/13) in those with the substitution compared to 92% in those without it (149/162). Although the small numbers make interpretation difficult, only 7% of participants (13/175) had NS5A Y93H, all of which were subtype 3a. SVR rates were numerically lower among those with both cirrhosis and Y93H. In noncirrhotic patients with Y93H, 67% (6/9) achieved SVR12 compared to 98% (125/128) among noncirrhotics without Y93H. In those with both cirrhosis and Y93H, 25% (1/4) achieved SVR12 compared to 71% (24/34) in those with cirrhosis but without the Y93H substitution (Daklinza PI, 2016).

Substitutions A30K, L31F, L31I in the genotype 3a replicon are associated with reduced daclatasvir susceptibility (Daklinza PI, 2016). In the ALLY-3 trial, participants with A30K and without cirrhosis achieved 100% SVR12 (9/9); those with cirrhosis had lower SVR12 rates (1/5) (Nelson, 2015). The impact of this single substitution is difficult to discern as 2/5 patients had compound substitutions with Y93H. Pending further data on optimal therapy, the addition of ribavirin for patients with cirrhosis is recommended in the setting of a baseline Y93 substitution.

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Related References

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