Peginterferon/Ribavirin-Experienced, Genotype 4 Patients With Compensated Cirrhosis

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

Peginterferon/Ribavirin-Experienced, Genotype 4 Patients With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients who experienced virologic relapse after prior peginterferon/ribavirin therapy[b]	12 weeks	IIa, B
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[c]	12 weeks	IIa, B
ALTERNATIVE	**DURATION**	**RATING**
Daily ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based ribavirin	12 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] If the type of prior treatment failure (relapse vs breakthrough/nonresponse) is unknown, another recommended regimen should be used.
[c] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

Recommended Regimens

Sofosbuvir/Velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naive or -experienced patients with genotype 1, 2, 4, 5, or 6 treated with a daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks (Feld, 2015). The study included 116 patients with genotype 4. One hundred percent SVR12 was achieved, including 52 treatment-experienced patients and 27 with compensated cirrhosis (Feld, 2015).

Elbasvir/Grazoprevir ± Ribavirin

A 2015 integrated analysis of all phase 2 and phase 3 elbasvir (50 mg)/grazoprevir (100 mg) studies to date demonstrated efficacy of this regimen for both treatment-naive (n=66) and -experienced (n=37) patients with genotype 4 (Asselah, 2018c). The overall SVR12 among treatment-experienced, genotype 4 patients was 87% (32/37) with numerical response differences based on prior interferon treatment response (relapse vs on-treatment viral failure); elbasvir/grazoprevir duration (12 weeks vs 16 weeks); and/or ribavirin usage (inclusion or exclusion of ribavirin in the regimen). Numbers within any specific subgroup are too small to make definitive recommendations. Trends emerged, however, that were

used to guide the current recommendations pending additional data. No treatment failures were seen in patients who relapsed after prior peginterferon/ribavirin therapy, regardless of elbasvir/grazoprevir treatment duration or ribavirin usage. In contrast, response rates were numerically lower in patients with prior on-treatment virologic failure in the non-ribavirin-containing arms (12 weeks, 78%; 16 weeks, 60%) compared to ribavirin-containing treatment (12 weeks with ribavirin, 91%; 16 weeks with ribavirin, 100%).

Given the lack of sufficient numbers to differentiate response between 12 weeks with ribavirin and 16 weeks with ribavirin, the use of 16 weeks of elbasvir/grazoprevir plus ribavirin in genotype 4 patients with prior on-treatment virologic failure represents the most conservative approach and is an alternative recommendation.

Glecaprevir/Pibrentasvir

The phase 3, single-arm, open-label EXPEDITION-1 study investigated the safety and efficacy of a 12-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 patients with genotype 1, 2, 4, 5, or 6 and compensated cirrhosis (Forns, 2017). Overall, 25% of patients were treatment experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon). All 16 patients with genotype 4 (unknown number with prior treatment experience) achieved SVR12.

Alternative Regimen

Ledipasvir/Sofosbuvir + Ribavirin

In the open-label cohort, phase 2a SYNERGY trial, 21 patients with genotype 4 were treated with a 12-week course of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg). Forty percent of participants were treatment experienced and 40% had advanced fibrosis. Twenty patients completed the 12-week therapy and all achieved SVR12; 1 patient withdrew from the study (Kohli, 2015). A pooled analysis of the 12-week ledipasvir/sofosbuvir regimen (including the SYNERGY trial) reported an SVR12 of 94% (32/34) in treatment-experienced patients with genotype 4 (Asselah, 2018b). Due to the small number of patients overall and with cirrhosis, the addition of ribavirin to the 12-week regimen is recommended in patients with cirrhosis (Kohli, 2015). This is an alternative regimen due to the need for ribavirin.

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Related References

Asselah T, Kowdley KV, Zadeikis N, et al. Efficacy of glecaprevir/pibrentasvir for 8 or 12 weeks in patients with hepatitis C virus genotype 2, 4, 5, or 6 infection without cirrhosis. *Clin Gastroenterol Hepatol*. 2018;16(3):417-426.

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Feld JJ, Jacobson IM, Hézode C, et al. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. *N Engl J Med*. 2015;373(27):2599-2607.

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Kohli A, Kapoor R, Sims Z, et al. Ledipasvir and sofosbuvir for hepatitis C genotype 4: a proof-of-concept, single-centre, open-label phase 2a cohort study. *Lancet Infect Dis*. 2015;15(9):1049-1054.