Treatment-Naive Genotype 3 Without Cirrhosis

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

Treatment-Naive Genotype 3 Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	8 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A

[a] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

Recommended Regimens

Glecaprevir/Pibrentasvir

ENDURANCE-3 was a randomized (2:1) trial comparing 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 12 weeks of sofosbuvir (400 mg) and daclatasvir (60 mg) among 348 treatment-naive participants with genotype 3 infection without cirrhosis. The trial was later amended to include an open-label arm that evaluated glecaprevir/pibrentasvir for an 8-week duration among 157 treatment-naive participants with genotype 3 infection without cirrhosis. Participants receiving glecaprevir/pibrentasvir for 8 or 12 weeks achieved an SVR12 rate of 95% in an intention-to-treat analysis (222/233 participants receiving the 12-week regimen; 149/157 participants receiving the 8-week regimen) (Foster, 2017). Virologic failure was observed in 6 participants receiving the 8-week regimen (1 virologic breakthrough; 5 relapses) and in 4 participants in the 12-week arm (1 virologic breakthrough; 3 relapses). Both the 8- and 12-week glecaprevir/pibrentasvir regimens met noninferiority criteria for SVR12 compared to the standard of care arm of sofosbuvir/daclatasvir, which reported an SVR12 rate of 97%. While the baseline presence of the Y93H substitution did not affect SVR rates (10/10 with Y93H achieved SVR with an 8 week duration vs 165/171 without Y93H), the presence of the A30K substitution was associated with a lower SVR rate (14/18 with A30K achieved SVR with an 8 week duration vs 161/163 without A30K) (Krishnan, 2018). Of the 14 treatment-naive patients with genotype 3 without cirrhosis with baseline A30K who received a 12-week duration of glecaprevir/pibrentasvir, 13/14 achieved SVR. Given the small numbers, there is insufficient evidence at this time to recommend testing for RASs or extension of therapy in the setting of an A30K substitution.

In addition, data from real-world cohorts support the effectiveness of an 8-week regimen of glecaprevir/pibrentasvir therapy for treatment-naive, noncirrhotic patients with genotype 3 infection (Drysdale, 2019); (Sterling, 2019). Among treatment-naive patients with genotype 3, 99% (162/164) of patients in a German cohort (Berg, 2019) and 96% (46/48) of patients in an Italian cohort (D'Ambrosio, 2019) treated with 8 weeks of glecaprevir/pibrentasvir achieved SVR12. A meta-analysis of real-world cohorts that examined glecaprevir/pibrentasvir treatment response among adults demonstrated an SVR12 of 99.2% (n=320) among noncirrhotic participants with genotype 3 infection with 8 weeks of treatment (Lampertico, 2020).

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 demonstrated superiority of 12 weeks of sofosbuvir/velpatasvir to 24 weeks sofosbuvir plus ribavirin in 552 treatment-naive and -experienced patients without cirrhosis or with compensated cirrhosis (Foster, 2015a). Among treatment-naive, noncirrhotic patients, SVR12 rates were 98% (160/163) for sofosbuvir/velpatasvir compared to 90% (141/156) for sofosbuvir plus ribavirin.

The phase 3 POLARIS-2 study evaluated 12 weeks of sofosbuvir/velpatasvir in genotype 3-infected, noncirrhotic patients who were either treatment-naive or interferon-experienced. Eighty-nine genotype 3 patients received the sofosbuvir/velpatasvir regimen and 97% achieved SVR12 (86/89) (Jacobson, 2017). There were no virologic failures.

A subsequent open-label study conducted in Russia and Sweden demonstrated similar response rates in noncirrhotic genotype 3 patients (Isakov, 2019). Additionally, an observational cohort study from Germany supports the effectiveness of 12 weeks of sofosbuvir/velpatasvir among treatment-naive patients with genotype 3 infection (von Felden, 2018). Of 167 treatment-naive genotype 3 patients (25% cirrhosis in overall cohort), 162 were cured and there were no virologic failures. Other real-world data from cohorts across North America, Canada, and the United Kingdom also demonstrate high SVR rates with 12 weeks of sofosbuvir/velpatasvir among genotype 3, treatment-naive, noncirrhotic patients (Drysdale, 2019); (Mangia, 2019).

Another recent study provided information about the use of sofosbuvir/velpatasvir in patients with genotype 3b, a subtype rarely encountered in the United States. The single-arm, open-label, phase 3 trial of patients enrolled from Asia treated with sofosbuvir/velpatasvir reported an overall SVR of 86% among 84 patients with genotype 3 infection, with or without cirrhosis (Wei, 2019). Among patients with genotype 3a, 95% (40/42) achieved SVR12. In the subgroup of noncirrhotic patients with genotype 3b, 89% (25/28) achieved SVR12 with 12 weeks of sofosbuvir/velpatasvir. All patients with genotype 3b enrolled in this trial had NS5A RASs at A30K or L31M, or both. Another study among 90 noncirrhotic treatment-naive patients—most receiving opioid agonist therapy—treated with only 8 weeks of sofosbuvir/velpatasvir demonstrated an SVR rate of 96% (86/90) (Boyle, 2020). A real-world, pooled analysis of 12 cohorts that evaluated adults treated with 12 weeks of sofosbuvir/velpatasvir demonstrated an SVR of 98.3% (1649/1677) among participants with genotype 3, with or without compensated cirrhosis (Mangia, 2020).

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