Treatment-Naive Genotype 5 or 6

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

Treatment-Naive Genotype 5 or 6 Patients With and Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	8 weeks	I, A[c]
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, B
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)[d]	12 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.
[c] For compensated cirrhosis, rating is I, B.
[d] Not recommended for genotype 6e if subtype is known.

Recommended Regimens

Glecaprevir/Pibrentasvir

Based on favorable data for 12 weeks of treatment for noncirrhotic patients in the phase 2 SURVEYOR-2 study (100% SVR12 in 34 patients with genotype 4, 5, or 6) (Kwo, 2017b), ENDURANCE-4 enrolled 121 DAA-naive or -experienced (sofosbuvir plus ribavirin ± peginterferon) genotype 4, 5, or 6 patients without cirrhosis to receive 12 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg pills (Asselah, 2018b). Of those enrolled, 86% had fibrosis stage F0 to F1 and 68% were treatment naive. The genotype distribution was 63% genotype 4, 21% genotype 5, and 16% genotype 6. The overall SVR12 rate for the intention-to-treat population was 99% (120/121), including 99% (75/76) for genotype 4, 100% for genotype 5 (26/26), and 100% (19/19) for genotype 6.

Genotype 4, 5, and 6 patients were not included in the randomized study to compare an 8-week vs 12-week course for DAA-naive, noncirrhotic patients. However, part 4 of the SURVEYOR-2 study investigated an 8-week course of glecaprevir/pibrentasvir in DAA-naive patients without cirrhosis (Asselah, 2018b). In the intention-to-treat analysis, 2/2 with genotype 5 and 9/10 with genotype 6 achieved SVR12; there were no known virologic failures. Further, ENDURANCE-5,6 was a phase 3b, single-arm, open-label, multicenter study of the efficacy of glecaprevir/pibrentasvir among DAA-naive patients with genotype 5 (n=23) or 6 (n=61) infection. Participants without cirrhosis received an 8-week regimen; those with cirrhosis (11% of patients) received 12 weeks of treatment (Asselah, 2019). Overall SVR was 98% with 2 virologic failures; treatment failed in a patient with genotype 6f and cirrhosis, and in another noncirrhotic participant with genotype 5a.

In addition, EXPEDITION-1 investigated the use of glecaprevir/pibrentasvir in DAA-naive (75%) or -experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) patients with compensated cirrhosis. Of 146 patients with genotype 1, 2, 4, 5, or 6 given 12 weeks of glecaprevir/pibrentasvir, 99% (145/146) achieved SVR12, including 100% (2/2) with genotype 5 and 100% (7/7) with genotype 6 (Forns, 2017). Based on these studies, glecaprevir/pibrentasvir was approved for an 8-week course (noncirrhotic) and 12-week course (cirrhotic) of treatment for people with genotype 5 or 6 infection.

EXPEDITION-8 evaluated 8 weeks of glecaprevir/pibrentasvir among 280 treatment-naive patients with compensated cirrhosis and genotype 1, 2, 4, 5 (n=1) or 6 (n=9) infection. SVR12 was 99% with no virologic failures (Brown, 2018). Patients with a prior history of decompensation, hepatocellular carcinoma, and HIV or HBV coinfection were excluded from the study.

An integrated analysis of the 181 participants with genotype 5 or 6 from phase 2/3 studies including those above showed comparable response rates between 8 weeks and 12 weeks of treatment with no signal of poorer performance among cirrhotic patients with an 8-week regimen (Yao, 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 5 and 6 infection in patients with and without cirrhosis (Feld, 2015). ASTRAL-1 included 24 genotype 5 treatment-naive participants with and without cirrhosis, 96% (23/24) of whom achieved SVR12. The study also included 38 genotype 6 treatment-naive participants with and without cirrhosis, all of whom achieved SVR12. An additional 9 genotype 6 patients received sofosbuvir/velpatasvir in the POLARIS-2 phase 3 study, all of whom achieved SVR (Jacobson, 2017).

Two real-world cohort studies evaluated 12 weeks of sofosbuvir/velpatasvir among predominantly treatment-naive patients with genotype 6 infection. SVR was 100% in a cohort of patients (n=23) from Southwest China, none of whom had clinical cirrhosis (Wu, 2019). SVR was also 100% in a cohort of predominantly Vietnamese patients (n=43) residing in the United States, 12% of whom had cirrhosis (Nguyen, 2019). A real-world, pooled analysis of 12 cohorts that evaluated adults treated with 12 weeks of sofosbuvir/velpatasvir demonstrated an SVR of 98.5% (67/68) among participants with genotype 5 or 6 infection; all 13 participants with compensated cirrhosis achieved SVR (Mangia, 2020).

Ledipasvir/Sofosbuvir

Although there are limited data on patients with genotype 5 infection, the in-vitro activity of sofosbuvir and ledipasvir are quite good with EC50 of 15 nM and 0.081 nM, respectively. An open-label, single-arm study that included 41 genotype 5-infected patients demonstrated an overall SVR12 rate of 95% (39/41) (Abergel, 2016). The SVR12 rate was also 95% specifically among treatment-naive patients (20/21), of whom only 3 had cirrhosis but all achieved SVR12.

Ledipasvir has in-vitro activity against most genotype 6 subtypes, except for 6e (Wong, 2013); (Kohler, 2014). A small, 2-center, open-label study (NCT01826981) investigated the safety and in vivo efficacy of ledipasvir/sofosbuvir for 12 weeks in treatment-naive and -experienced patients with genotype 6 infection. Twenty-five patients (92% treatment-naive) who were primarily Asian (88%) had infection from 7 different subtypes (32% 6a; 24% 6e; 12% 6l; 8% 6m; 12% 6p; 8% 6q; 4% 6r). Two patients (8%) had cirrhosis. The SVR12 rate was 96% (24/25), and the single patient who experienced relapse had discontinued therapy at week 8 because of drug use. No patient discontinued treatment owing to adverse events (Gane, 2015).

In the largest US study, 60 patients with genotype 6 infection were randomized to 8 weeks (treatment-naive, no cirrhosis) or 12 weeks (treatment-naive or -experienced, with or without cirrhosis) of ledipasvir/sofosbuvir; SVR rates were 95% in both treatment groups (Nguyen, 2017). A real-world cohort of 92 treatment-naive patients with genotype 6 infection (predominantly Vietnamese patients residing in the United States, 51% with cirrhosis) was treated with 12 weeks of ledipasvir/sofosbuvir; SVR12 was 96.6% (Nguyen, 2019). Subtype data were not available.

A recent systematic review that examined the response to DAA therapy among persons with genotype 6 infection highlighted the heterogeneity of SVR rates in response to ledipasvir/sofosbuvir treatment across Asian countries (64% in Myanmar versus 100% in Vietnam) (Mettikanont, 2019). The reasons for this difference are likely multiple; the variable distribution of subtypes within the populations is a potential explanation. Pending more data, a conservative approach is recommended, with subtype 6e patients best treated with an alternative regimen.

Last update: October 24, 2022

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