Treatment-Naive Genotype 1a With Compensated Cirrhosis

Recommended and alternative regimens listed by pangenotypic, evidence level and alphabetically for: Treatment-Naive Genotype 1a 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 glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	8 weeks	I, B
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
ALTERNATIVE	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)[c]	12 weeks	1, A

[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] Should only be used with documented absence of RAS

Recommended Regimens

Sofosbuvir/Velpatasvir

The daily fixed-dose combination sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 1 infection in treatment-naive persons based on ASTRAL-1. This placebo-controlled trial involved a 12-week course of sofosbuvir/velpatasvir administered to 624 participants with genotype 1, 2, 4, 5, or 6 infection who were treatment naive (n=423) or previously treated with interferon-based therapy, with or without ribavirin or a protease inhibitor (n=201) (Feld, 2015). Of the 328 genotype 1 participants included, 323 achieved SVR12 with no difference in SVR12 rate observed by subtype (98% 1a; 99% 1b). Of 121 participants (all genotypes) classified as having cirrhosis, 99% achieved SVR12 (120/121).

The presence of baseline NS5A RASs (at 15% cutoff)—reported in 11% of genotype 1a and 18% of genotype 1b participant samples tested—did not influence SVR12 rate for genotype 1 (Hézode, 2018). Of the 2 virologic failures in ASTRAL-1 (<1% of treated participants), both were genotype 1 and had baseline RASs. There was no significant difference in the rates of adverse events in the sofosbuvir/velpatasvir versus placebo groups.

The phase 3 POLARIS-2 study randomized 941 DAA-naive participants with genotype 1, 2, 3, 4, 5, or 6 infection—19% of whom had cirrhosis—to receive 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) or 12 weeks of sofosbuvir/velpatasvir (Jacobson, 2017). Of participants treated with sofosbuvir/velpatasvir, 99% (170/172) with genotype 1a infection and 97% (57/59) with genotype 1b achieved SVR with a single relapse observed with each subtype. A real-world, pooled analysis of 12 cohort studies demonstrated an SVR rate of 98.3% (349/355) among adults with genotype 1 and compensated cirrhosis who were treated with 12 weeks of sofosbuvir/velpatasvir (Mangia, 2020).

Glecaprevir/Pibrentasvir

EXPEDITION-1 investigated the use 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 DAA-naive (75%) or DAA-experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) participants with compensated cirrhosis. Among the 146 participants with genotype 1, 2, 4, 5, or 6 infection given 12 weeks of glecaprevir/pibrentasvir, 99% (145/146) achieved SVR12. The single relapse occurred in a genotype 1a participant; SVR12 rate among these participants was 98% (47/48) (Forns, 2017).

EXPEDITION-2, a study of glecaprevir/pibrentasvir in 153 adults with HIV/HCV coinfection with genotype 1, 2, 3, 4, 5, or 6 infection, utilized 8 weeks of treatment for participants without cirrhosis and 12 weeks for those with cirrhosis (the recommended durations approved by the FDA). The overall SVR12 rate was 98%. There were no observed virologic failures among the 94 participants with genotype 1 infection (Rockstroh, 2018). In EXPEDITION-1 and EXPEDITION-2, neither subtype (1a versus 1b) nor the presence of baseline RASs impacted SVR12 rates in DAA-naive genotype 1 participants.

EXPEDITION-8 evaluated glecaprevir/pibrentasvir for a reduced duration of 8 weeks in treatment-naive participants with compensated cirrhosis and genotype 1 (n=95, genotype 1a), 2, 4, 5 or 6 infection. Participants with a prior history of decompensation, hepatocellular carcinoma, and HIV and/or HBV coinfection were excluded from this study. SVR12 rate was 99% with no virologic failures (Brown, 2020).

Ledipasvir/Sofosbuvir

The fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) was approved by the FDA for the treatment of genotype 1 infection in treatment-naive persons based on 2 registration trials: ION-1 (865 treatment-naive participants; those with cirrhosis were included) and ION-3 (647 treatment-naive participants; those with cirrhosis were excluded). ION-1 investigated length of treatment (12 weeks versus 24 weeks) and the need for ribavirin (Afdhal, 2014a). SVR12 rates were 97% to 99% across all study arms with no difference in SVR12 rates based on length of treatment, use of ribavirin, or genotype 1 subtype. Sixteen percent of participants enrolled were classified as having cirrhosis. There was no difference in SVR12 rates in those with cirrhosis (97%) versus those without cirrhosis (98%).

Alternative Regimen

Elbasvir/Grazoprevir

The recommendation for use of daily fixed-dose elbasvir (50 mg)/grazoprevir (100 mg) in persons with cirrhosis with genotype 1 infection is based on 92 persons (22% of the study cohort) in the phase 3 C-EDGE trial who had Metavir F4 disease (Zeuzem, 2015f). SVR12 rate was 97% in this subgroup of participants with cirrhosis. A similar 97% (28/29) SVR12 rate had previously been demonstrated in genotype 1 treatment-naive persons with cirrhosis treated with 12 weeks of elbasvir/grazoprevir without ribavirin in the open-label phase 2 C-WORTHY trial, which enrolled both participants with both HCV monoinfection and HIV/HCV coinfection (Lawitz, 2015c). Presence or absence of cirrhosis does not appear to alter the efficacy of the elbasvir/grazoprevir regimen (Zeuzem, 2017); (Lawitz, 2015c).

The presence of certain baseline NS5A RASs significantly reduces SVR12 rates with a 12-week course of the elbasvir/grazoprevir regimen in persons with genotype 1a infection (Zeuzem, 2017). Baseline NS5A RASs were identified in 12% (19/154) of participants with genotype 1a infection who were enrolled in the C-EDGE study, of which 58% (11/19) achieved SVR12 compared with 99% (133/135) in participants without these RASs (Zeuzem, 2017). Among treatment-naive participants, the presence of baseline NS5A RASs with a >5-

fold reduced sensitivity to elbasvir was associated with the most significant reduction in SVR12 rate with only 22% (2/9) of persons with genotype 1a infection with these RASs achieving SVR12.

Recommendations for prolonging treatment duration to 16 weeks with inclusion of ribavirin for treatment-naive persons with genotype 1a infection and baseline NS5A RASs are based on extrapolation of data from the C-EDGE TE trial. In this phase 3 open-label trial of elbasvir/grazoprevir that enrolled treatment-experienced participants, among 58 participants with genotype 1a infection who received 16 weeks of therapy with elbasvir/grazoprevir plus ribavirin, there were no virologic failures (Kwo, 2017). Subsequent integrated analysis of elbasvir/grazoprevir phase 2 and 3 trials demonstrated an SVR12 rate of 100% (6/6) in persons with genotype 1 infection with pretreatment NS5A RASs treated with elbasvir/grazoprevir for 16 weeks or 18 weeks plus ribavirin (Jacobson, 2017b); (Thompson, 2015).

Based on known inferior response among people with baseline NS5A RASs, NS5A resistance testing is recommended for those with genotype 1a infection who are being considered for elbasvir/grazoprevir therapy. If baseline RASs are present (ie, substitutions at amino acid position 28, 30, 31, or 93), another recommended regimen should be selected.

Related References

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Additional Reading

- Persons With HIV/HCV Coinfection
- Persons With Renal Impairment
- Management of Acute HCV Infection

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