Treatment-Naive Genotype 1a Without Cirrhosis

Recommended and alternative regimens listed by pangenotypic, evidence level and alphabetically for: **Treatment-Naive Genotype 1a 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 ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients who are HIV-uninfected and whose HCV RNA level is <6 million IU/mL	8 weeks	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (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

The daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) is administered as three 100 mg/40 mg fixed-dose combination pills. Based on favorable data for 8 weeks of treatment among noncirrhotic patients in the phase 2 SURVEYOR-1 study (33/34 patients with SVR and no virologic failures) (Kwo, 2017b), ENDURANCE-1 enrolled 703 noncirrhotic, genotype 1 patients who were DAA-naive or in whom a previous interferon-based regimen failed. Participants were randomized to receive 8 or 12 weeks of glecaprevir/pibrentasvir (Zeuzem, 2018). Of those enrolled, 43% had genotype 1a, 85% had fibrosis stage 0 or 1, and 62% were treatment naive. Overall SVR12 rates for the intention-to-treat population were 99% (348/351) in the 8-week arm and 99.7% (351/352) in the 12-week arm. The 8-week arm met the predefined study criteria for noninferiority to the 12-week arm. A single patient experienced on-treatment virologic failure in this study (genotype 1a, day 29). Notably, there were no documented relapses in either study arm.

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, 145 (99%) achieved SVR12. The single relapse occurred in a genotype 1a patient; SVR for genotype 1a was 98% (47/48) (Forns, 2017).

EXPEDITION-2, a study of glecaprevir/pibrentasvir in 153 HIV/HCV-coinfected adults with genotype 1, 2, 3, 4, 5, or 6, utilized 8 weeks of treatment for noncirrhotic patients and 12 weeks for cirrhotic patients (the recommended durations approved by the FDA). The overall SVR12 was 98% and there were no observed virologic failures among the 94 patients with genotype 1 infection (Rockstroh, 2017). In EXPEDITION-1 and EXPEDITION-2, neither subtype (1a vs 1b) nor the presence of baseline RASs impacted SVR12 results in DAA-naive genotype 1 patients.

In an integrated analysis of 602 DAA-naive, noncirrhotic patients with genotype 1 infection treated with 8 weeks of glecaprevir/pibrentasvir in 6 phase 2 or 3 clinical trials, SVR12 was 99.2% (597/602) (Naganuma, 2019). Real-world cohorts from Germany (63% genotype 1a) and Italy (32% genotype 1a) show similarly high efficacy in treatment-naive, noncirrhotic patients with genotype 1 infection treated with 8 weeks of glecaprevir/pibrentasvir. Using a modified intention-to-treat analysis (excluding those not completing treatment or lost to follow-up), SVR was 100% in both the German (228/228) (Berg, 2019) and the Italian (307/307) (D'Ambrosio, 2019) cohorts.

Sofosbuvir/Velpatasvir

The fixed-dose combination of 12 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg) was approved by the FDA for the treatment of genotype 1 infection in treatment-naive patients 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 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 patients included, 323 achieved SVR with no difference observed by subtype (98% 1a; 99% 1b). Of 121 participants (all genotypes) classified as having cirrhosis, 120 achieved SVR (99%). 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 vs placebo groups.

The phase 3 POLARIS-2 study randomized 941 DAA-naive patients with genotype 1, 2, 3, 4, 5, or 6 infection—with or without compensated 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 for 12 weeks, 170/172 (99%) with genotype 1a and 57/59 (97%) with genotype 1b achieved SVR12 with a single relapse observed with each subtype.

In a single-arm, phase 3 study from Asia that included 375 treatment-naive and -experienced patients with genotype 1, 2, 3, 4, 5, or 6 infection (18% with cirrhosis) treated with 12 weeks of sofosbuvir/velpatasvir, SVR was achieved in 95% (362/375) (Wei, 2019). Of the 129 participants with genotype 1 infection (17% genotype 1a), 100% achieved SVR. A real-world, pooled analysis of 12 cohorts that evaluated adults treated with 12 weeks of sofosbuvir/velpatasvir demonstrated an SVR of 99.1% (1599/1613) among participants with genotype 1, with or without compensated cirrhosis (Mangia, 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 patients based on two registration trials: ION-1 (865 treatment-naive patients; those with cirrhosis were included) and ION-3 (647 treatment-naive patients; those with cirrhosis were excluded). ION-1 investigated length of treatment (12 weeks vs 24 weeks) and the need for ribavirin (Afdhal, 2014a). SVR12 was 97% to 99% across all study arms with no difference in SVR12 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 rate in those with cirrhosis (97%) versus those without cirrhosis (98%).

ION-3 excluded patients with cirrhosis and investigated shortening therapy from 12 weeks to 8 weeks (with or without ribavirin) (Kowdley, 2014). SVR12 rates were 93% to 95% across all study arms with no difference in SVR in the intention-to-treat analysis. However, relapse rates were higher in the 8-week arms (20/431)—regardless of ribavirin use—compared with the 12-week arm (3/216). Post hoc analyses of the ribavirin-free arms assessed baseline predictors

of relapse and identified lower relapse rates in patients who received 8 weeks of ledipasvir/sofosbuvir who had baseline HCV RNA levels <6 million IU/mL (2%; 2/123). The same held true for patients with similar baseline HCV RNA levels who received 12 weeks of treatment (2%; 2/131). This analysis was not controlled, which limits the generalizability of this approach to clinical practice.

Published, real-world cohort data generally show comparable effectiveness of 8-week and 12-week courses of ledipasvir/sofosbuvir in treatment-naive patients without cirrhosis (Backus, 2016); (Ingiliz, 2016); (Ioannou, 2016); (Kowdley, 2016); (Terrault, 2016). However, only about half of patients eligible for 8 weeks of treatment received it, assignment of duration was not randomized, and baseline characteristics may have varied between 8- and 12-week groups.

Real-world cohort studies of ledipasvir/sofosbuvir for treatment-naive, noncirrhotic black patients reported lower SVR12 rates with shorter duration therapy compared to white patients, although the absolute difference in SVR12 rates was <5% (Su, 2017); (Ioannou, 2016); (Wilder, 2016); (O'Brien, 2014). A subsequent real-world study among a Northern California Kaiser Permanente cohort of 436 black patients—most of whom were treated with an 8-week regimen—found similar SVR12 rates with 8 and 12 weeks of therapy (95.6% and 95.8%, respectively) (Marcus, 2018). Similarly, a Maryland Veterans Health Administration real-world cohort of black patients with predominantly genotype 1 infection found SVR12 rates of 93.7% (131/140) and 91.4% (332/363) with 8- and 12-week regimens, respectively (Tang, 2018). These data coupled with the availability of excellent rescue therapies for patients in whom initial DAA therapy fails support the use of 8 weeks of ledipasvir/sofosbuvir for black patients without cirrhosis and HCV RNA <6 million IU/mL.

Based on available data, shortening treatment to less than 12 weeks is not recommended for HIV/HCV-coinfected patients (see HIV/HCV Coinfection section). For others with potential negative prognostic factors, shortening treatment duration should be done at the discretion of the practitioner.

Alternative Regimen

Elbasvir/Grazoprevir

The fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) is recommended based on data from the phase 3 C-EDGE trial, which assessed the efficacy and safety of this regimen for 12 weeks in treatment-naive adults (genotypes 1, 4, and 6) (Zeuzem, 2015f). Patients were enrolled from 60 centers in 9 countries on 4 continents. Three hundred eighty-two patients (91% of the study cohort) were infected with genotype 1 (50% genotype 1a, 41% genotype 1b). The sustained virologic response rates at 12 weeks (SVR12) were 92% (144/157) in treatment-naive patients with genotype 1a infection and 99% (129/131) in genotype 1b patients. Findings from this phase 3 study support earlier phase 2 findings from the C-WORTHY trial in which SVR12 rates of 92% (48/52) and 95% (21/22) were demonstrated among genotype 1a and genotype 1b treatment-naive, noncirrhotic patients, respectively, who received 12 weeks of elbasvir/grazoprevir without ribavirin (Sulkowski, 2015b). The C-WORTHY trial enrolled both HCV-monoinfected and HIV/HCV-coinfected patients.

The presence of certain baseline NS5A RASs significantly reduces SVR12 rates with a 12-week course of elbasvir/grazoprevir in genotype 1a-infected patients (Zeuzem, 2017). Baseline NS5A RASs were identified in 12% (19/154) of genotype 1a-infected patients enrolled in the C-EDGE study, of which 58% (11/19) achieved SVR12 compared to an SVR12 rate of 99% (133/135) in patients without these RASs receiving 12 weeks of elbasvir/grazoprevir (Zeuzem, 2017). Among treatment-naive patients, the presence of baseline NS5A RASs with >5-fold reduced sensitivity to elbasvir was associated with the most significant reduction in SVR12 with only 22% (2/9) of genotype 1a patients with these RASs achieving SVR12.

In the phase 3 open-label C-EDGE TE trial of elbasvir/grazoprevir that enrolled treatment-experienced patients, 58 genotype 1a-infected patients received 16 weeks of therapy with elbasvir/grazoprevir plus ribavirin, and there were no virologic failures (Kwo, 2017). Subsequent integrated analysis of the elbasvir/grazoprevir phase 2 and 3 trials demonstrated an SVR12 rate of 100% (6/6) in genotype 1 patients with pretreatment NS5A RASs treated with elbasvir/grazoprevir plus ribavirin for 16 or 18 weeks (Jacobson, 2015b); (Thompson, 2015).

Based on known inferior response in patients with baseline NS5A RASs, NS5A resistance testing is recommended in

genotype 1a patients who are being considered for elbasvir/grazoprevir therapy. If baseline RASs are present (ie, substitutions at amino acid positions 28, 30, 31, or 93), another recommended regimen should be used (additional information is available in the RAS section).

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