Treatment-naive Genotype 1a Without Cirrhosis

Recommended and Alternative Regimens by evidence level and alphabetically for:

Genotype 1a, Treatment-naive Patients, Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg); for patients in whom no baseline NS5A RASs[§] for elbasvir are detected	12 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 non-black, HIV-uninfected, and whose HCV RNA level is <6 million IU/mL	8 weeks	I, B
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg), with weight-based ribavirin	12 weeks	I, A
Daily simeprevir (150 mg) plus sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg)	12 weeks	I, B
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based ribavirin; for patients who have baseline NS5A RASs[§] for elbasvir	16 weeks	IIa, B

[§] Includes G1a substitutions at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.
* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

For HCV genotype 1a-infected, treatment-naive patients without cirrhosis, there are six regimens recommended based on comparable efficacy, as outlined above. For cirrhotic patients, some are classified as Alternative regimens because compared to the Recommended, they have longer duration, potentially reduced efficacy, and/or limited supporting data.

Elbasvir/grazoprevir

The fixed-dose combination of elbasvir (50 mg) and grazoprevir (100 mg) (hereafter elbasvir/grazoprevir) can be recommended based on data from the phase III C-EDGE trial, which assessed the efficacy and safety of elbasvir/grazoprevir for 12 weeks in treatment-naive adults (genotypes 1, 4, and 6) (Zeuzem, 2017). Patients were enrolled from 60 centers in 9 countries on 4 continents. Three hundred and eighty-two patients (91% of study cohort) receiving 12 weeks of elbasvir/grazoprevir were infected with genotype 1 (50% genotype 1a, 41% genotype 1b). The

sustained virologic response rate at 12 weeks (SVR12) was 92% in treatment-naive patients with HCV genotype 1a infection (144/157) and 99% in genotype 1b (129/131) patients receiving 12 weeks of elbasvir/grazoprevir. Findings from this phase III study supported earlier phase II 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 non-cirrhotic HCV-infected 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.

Presence of certain baseline NS5A RASs significantly reduces rates of SVR12 with a 12-week course of the elbasvir/grazoprevir regimen in genotype 1a-infected patients (Zeuzem, 2017). NS5A RASs were identified at baseline 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 a larger than 5-fold shift to elbasvir was associated with the most significant reductions in SVR12 with only 22% (2/9) of genotype 1a patients with these RASs achieving SVR12. Recommendations for prolonging duration of treatment to 16 weeks with inclusion of ribavirin for treatment-naive genotype 1a patients with baseline NS5A RASs is based on extrapolation of data from the C-EDGE TE trial. In this phase III open-label trial of elbasvir/grazoprevir that enrolled treatment-experienced patients, among 58 genotype 1a patients who received 16 weeks of therapy with elbasvir/grazoprevir plus ribavirin, there were no virologic failures (Kwo, 2017).

Subsequent integrated analysis of the elbasvir/grazoprevir phase II and III trials have demonstrated SVR12 rates of 100% (6/6 patients) in genotype 1 patients with pre-treatments NS5A RASs treated with elbasvir/grazoprevir for 16/18 weeks plus ribavirin (Jacobson, 2015b); (Thompson, 2015). Based on known inferior response in patients with presence of baseline NS5A RASs, NS5A resistance testing is recommended in genotype 1a patients who are being considered for therapy with elbasvir/grazoprevir. If baseline RASs are present, ie, substitutions at amino acid positions 28, 30, 31, or 93, treatment extension to 16 weeks with the addition of weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [≥75 kg]) is recommended to decrease relapse.

Lack of RAS testing results or lack of access to RAS testing should not be used as a means to limit access to HCV therapy.

Ledipasvir/sofosbuvir

The fixed-dose combination of ledipasvir (90 mg) and sofosbuvir (400 mg) (hereafter, ledipasvir/sofosbuvir) was approved by the FDA for the treatment of HCV 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 arms, with no difference in SVR based on length of treatment, use of ribavirin, or HCV genotype 1 subtype. Sixteen percent of subjects 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 rate was 93% to 95% across all 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 2 ribavirin-free arms assessed baseline predictors of relapse and identified lower relapse rates in patients receiving 8 weeks of ledipasvir/sofosbuvir who had baseline HCV RNA levels below 6 million IU/mL (2%; 2/123), and was the same for patients with similar baseline HCV RNA levels who received 12 weeks (2%; 2/131). This analysis was not controlled and thus limits the generalizability of this approach to clinical practice. Published real-world cohort data generally show comparable effectiveness of 8 and 12 weeks 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 received it, assignment of duration was not randomized, and baseline characteristics may have varied between 8- and 12-week groups. Based on available data, shortening treatment to less than 12 weeks is Not Recommended for HIV-infected patients (see HIV/HCV Coinfection section) and African-American patients (Su, 2016); (Wilder, 2016); (O'Brien, 2014). For others, it should be done at the discretion of the practitioner with consideration taken of other potential negative prognostic factors.

Paritaprevir/ritonavir/ombitasvir + dasabuvir

The daily fixed-dose combination of paritaprevir (150 mg), ritonavir (100 mg), and ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) (PrOD) plus weight-based ribavirin was approved by the FDA for the treatment of HCV genotype 1a infection in treatment-naive patients based on three registration trials: SAPPHIRE-I (322 treatment-naive patients with genotype 1a HCV infection without cirrhosis), PEARL-IV (305 treatment-naive patients with genotype 1a without cirrhosis), and TURQUOISE-II (261 treatment-naive and -experienced patients with HCV genotype 1a and cirrhosis). The SAPPHIRE-I trial reported a high SVR12 rate (95.3%) with 12 weeks of PrOD and ribavirin (Feld, 2014). Overall, virologic failure was higher for patients with HCV genotype 1a (7 of 8 failures had genotype 1a) than patients with HCV genotype 1b (1 virologic failure). PEARL-IV was specifically designed to determine the role of PrOD with or without weight-based ribavirin for treatment-naive, HCV genotype 1a-infected patients without cirrhosis (Ferenci, 2014). SVR12 was lower in the ribavirin-free arm than in the ribavirin-containing arm (90% vs 97%, respectively) owing to higher rates of virologic failure (7.8% vs 2%, respectively), confirming the need for weight-based ribavirin for patients with HCV genotype 1a. In 2016, an extended release formulation of PrOD was approved allowing once daily dosing (RBV when needed remains twice daily) (PrOD PI, 2017).

Simeprevir + sofosbuvir

The OPTIMIST-1 and -2 trials investigated the safety and efficacy of simeprevir (150 mg) and sofosbuvir (400 mg) in chronically infected patients with HCV genotype 1 without and with cirrhosis, respectively. In the OPTIMIST-1 study, 310 treatment-naive and -experienced patients without cirrhosis were randomly assigned to 12 vs 8 weeks of the simeprevir plus sofosbuvir regimen (Kwo, 2016). The overall SVR12 rate was 97% (150/155) versus 83% (128/155), respectively, with a statistically significantly greater relapse rate in the 8-week arm. In the 12-week arm there was no difference in SVR12; treatment-naive and -experienced patients achieved SVR12 rates of 97% and 95%, respectively. There was also no difference in SVR12 based on genotype 1 subtype or presence of the baseline Q80K resistance substitution. A post-hoc analysis suggested that patients with a baseline HCV RNA level below 4 million IU/mL achieved the same SVR12 rate (96%) regardless of the length of treatment. This defined baseline HCV RNA level is different than the 6 million IU/mL defined in the ION-3 trial, suggesting these post-hoc analysis cut-offs are arbitrary and unlikely to translate to clinical practice. At this time an 8-week regimen of simeprevir and sofosbuvir cannot be recommended.

Sofosbuvir/velpatasvir

The fixed-dose combination of 12 weeks of sofosbuvir (400 mg) and velpatasvir (100 mg) (hereafter, sofosbuvir/velpatasvir) was approved by the FDA for the treatment of HCV genotype 1 infection in treatment-naive patients based on ASTRAL-1, a placebo-controlled trial that gave 12 weeks of sofosbuvir/velpatasvir to 624 participants with HCV genotypes 1, 2, 4, 5, and 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 in SVR observed by HCV genotype (98% 1a and 99% 1b). Of 121 participants (all genotypes) classified as having cirrhosis, 120 achieved SVR (99%). The presence of baseline NS5A resistance-associated substitutions (at 15% cut off), reported in 11% of genotype 1a and 18% of genotype 1b participant samples tested, did not influence SVR rate for genotype 1 (Hézode, 2016). Of the 2 virologic failures in ASTRAL-1 (<1% of treated participants), both were genotype 1 and had baseline RASs present. There was no significant difference in the rates of adverse events in the sofosbuvir/velpatasvir group and the placebo group.

Daclatasvir + sofosbuvir

Daclatasvir in combination with sofosbuvir for the treatment of HCV genotype 1 infection can be recommended based on data from the phase III ALLY-2 trial, which assessed the efficacy and safety of daclatasvir and sofosbuvir for 12 weeks in patients coinfected with HIV and HCV (genotypes 1-4) (Wyles, 2015). One hundred twenty-three (83%) patients receiving 12 weeks of therapy in the trial were infected with HCV genotype 1. Eighty-three (54%) of these patients were treatment-naive. The sustained virologic response (SVR) rate was 96% in treatment-naive patients with HCV genotype 1a infection (n=71) receiving 12 weeks of therapy. However, only 9 treatment-naive patients had cirrhosis. Similarly, in the phase IIb study of daclatasvir and sofosbuvir (A1444040) in 88 treatment-naive patients with HCV genotype 1a infection, 21 were

treated for 24 weeks (11 with ribavirin) and 67 were treated for 12 weeks (33 with ribavirin), and there were no virologic relapses. However, there were only 14 patients with cirrhosis in the 12-week and 24-week study arms (Sulkowski, 2014a). Because patients with cirrhosis were not adequately represented in these studies, the optimal duration of treatment for patients with cirrhosis remains unclear. Cohort studies of a compassionate-use program in Europe suggest that patients with cirrhosis may benefit from extension of therapy with daclatasvir and sofosbuvir to 24 weeks, with or without ribavirin (Welzel, 2016); (Pol, 2017). The phase III ALLY-1 trial investigated daclatasvir and sofosbuvir with ribavirin (initial dose of 600 mg, then titrated) in 60 patients with advanced cirrhosis (Poordad, 2016). Only 76% of patients with HCV genotype 1a (n=34) and 100% of patients with HCV genotype 1b (n=11) achieved an SVR at 12 weeks (SVR12). It is unclear how many treatment failures were among treatment-naive patients or those with CTP class A cirrhosis. More data are needed; however, owing to the risk of the emergence of resistance to nonstructural protein 5A (NS5A) inhibitor treatment at the time of failure, extending treatment to 24 weeks for all patients with HCV genotype 1a infection and cirrhosis is recommended, and the addition of ribavirin may be considered. In patients with favorable characteristics, a 12-week treatment course that includes weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [≥75 kg]) may be considered but is supported by limited data.

The safety profiles of all the Recommended regimens above appear favorable. Across numerous phase III programs, less than 1% of patients without cirrhosis discontinued treatment early and adverse events were mild. Most adverse events occurred in ribavirin-containing arms. Discontinuation rates were higher for patients with cirrhosis (approximately 2% for some trials) but still very low.

Mixed genotypes

Rarely, genotyping assays may indicate the presence of a mixed infection (eg, genotypes 1a and 2). Treatment data for mixed genotypes with direct-acting antivirals are sparse but utilization of a pangenotypic regimen should be considered. When the correct combination or duration is unclear, expert consultation should be sought.

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