Treatment-naive Genotype 1a with Compensated Cirrhosis

Recommended and Alternative Regimens by evidence level and alphabetically for:

Genotype 1a, Treatment-naive Patients, with Compensated 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 sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
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 [†]	24 weeks	I, A
Daily simeprevir (150 mg) plus sofosbuvir (400 mg) with or without weight-based ribavirin; for patients in whom no Q80K substitution is detected	24 weeks	II, B
Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with or without weight-based ribavirin	24 weeks	IIa, B
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.
[†] Please see statement on FDA warning regarding the use of PrOD or PrO in patients with cirrhosis.
[‡] For decompensated cirrhosis, please refer to the appropriate section.
*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 C-WORTHY trial enrolled both HCV-monoinfected and HIV/HCV-coinfected patients. Recommendations for cirrhotic patients are based on 92 (22%) patients in the phase III C-EDGE trial who had Metavir F4 disease (Zeuzem, 2017). SVR12 was 97% in the subgroup of cirrhotic patients. A similar 97% (28/29) SVR12 rate had previously been demonstrated in genotype 1 cirrhotic treatment-naive patients treated with 12 weeks of elbasvir/grazoprevir without ribavirin in the open-label phase II C-WORTHY trial (Lawitz, 2015c). Presence or absence of compensated cirrhosis does not appear to alter the efficacy of the elbasvir/grazoprevir regimen (Lawitz, 2015c); (Zeuzem, 2017).

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%).

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). TURQUOISE-II enrolled treatment-naive and -experienced patients (261 patients with HCV genotype 1a) with CTP class A cirrhosis to receive either 12 weeks or 24 weeks of treatment with PrOD plus ribavirin. Overall, SVR12 rates were 89% in the 12-week arm and 95% in the 24-week arm (Poordad, 2014). This difference in SVR12 rate between arms was primarily driven by patients with null response to PEG-IFN/ribavirin; there was less difference in SVR rates in the patients with cirrhosis who were naive to therapy (92% and 95%, respectively) (paritaprevir/ritonavir/ombitasvir prescribing information); (Poordad, 2014). In 2016, an extended release formulation of PrOD was approved allowing once-daily dosing (RBV when needed remains twice daily) (PrOD PI, 2017).

In October 2015, the FDA released a warning regarding the use of the PrOD or PrO (without dasabuvir) in patients with cirrhosis. (This statement is based on our review of the limited data available from the FDA and will be updated if and when more data become available.) PrOD and PrO are contraindicated in patients with Child Turcotte Pugh (CTP) class B or C hepatic impairment (decompensated liver disease). The manufacturer's pharmacovigilance program reported rapid onset of liver injury and in some cases hepatic decompensation in patients with cirrhosis, including CTP class A compensated cirrhosis and decompensated cirrhosis, who were receiving PrOD or PrO. The liver injury and

decompensating events occurred largely during the first 4 weeks of therapy and primarily involved a rapid increase in total and direct bilirubin, often associated with a concomitant increase in liver enzyme levels. In most cases, early recognition and prompt discontinuation of PrOD or PrO resulted in resolution of injury, although some patients, including at least 2 patients with CTP class A compensated cirrhosis, died or required liver transplantation. Although cirrhosis carries a 2% to 4% annual risk of hepatic decompensation, the rapid onset of hepatic decompensation and in many cases its resolution with discontinuation of treatment with PrOD or PrO is suggestive of drug-induced liver injury. Although PrOD and PrO are contraindicated in patients with CTP class B or C cirrhosis and decompensated liver disease, predictors of these events in patients with CTP class A cirrhosis are currently unclear.

For patients with CTP class A cirrhosis, the unlikely but real possibility of drug-induced liver injury should be discussed with the patient. If the decision is made to initiate treatment with PrOD or PrO, close monitoring of total and direct bilirubin and transaminase levels every 1 week or 2 weeks for the first 4 weeks is recommended to ensure early detection of drug-induced liver injury. Also, educating patients about the importance of reporting systemic symptoms such as jaundice, weakness, and fatigue is strongly recommended. The regimen should be discontinued immediately if drug-induced liver injury is detected. If a patient is already taking PrOD or PrO and is tolerating the regimen, laboratory monitoring as above without discontinuation is recommended unless there are signs or symptoms of liver injury. If heightened monitoring cannot be provided in the first 4 weeks of therapy with PrOD or PrO in patients with cirrhosis, the use of these regimens is not recommended.

Simeprevir + sofosbuvir

The OPTIMIST-2 study was a single-arm, open-label trial investigating 12 weeks of simeprevir plus sofosbuvir in 103 treatment-naive and -experienced patients with cirrhosis (Lawitz, 2016b). The overall SVR12 rate was 83% (86/103), with 88% (44/50) of treatment-naive and 79% (42/53) of treatment-experienced patients achieving SVR12. In addition, patients infected with HCV genotype 1a and 1b without the Q80K substitution had similar SVR12 rates (84% [26/31] and 92% [35/38], respectively). However, patients with HCV genotype 1a infection and the Q80K substitution had lower SVR12 rates (74% [25/34]). Thus, extending treatment to 24 weeks, with or without ribavirin, is recommended for patients with cirrhosis receiving simeprevir plus sofosbuvir to decrease the risk of relapse. At this time it is unclear whether extending treatment, with or without the addition of ribavirin, will increase efficacy in genotype 1a-infected patients with the Q80K substitution. Given the lower response rate in patients with cirrhosis, it is reasonable to avoid this regimen in patients with this baseline substitution.

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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