PEG-IFN/Ribavirin Experienced, Genotype 1b Patients with Compensated Cirrhosis

Recommended and Alternative Regimens by evidence level and alphabetically for:

Genotype 1b, PEG-IFN/Ribavirin Treatment-experienced Patients, with Compensated Cirrhosis [‡]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based ribavirin	12 weeks	I, A
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)[†]	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 ledipasvir (90 mg)/sofosbuvir (400 mg)	24 weeks	I, A
Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with or without weight-based ribavirin	24 weeks	IIa, B
Daily simeprevir (150 mg) plus sofosbuvir (400 mg) with or without weight-based ribavirin	24 weeks	IIa, B

[†] 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.

Elbasvir/grazoprevir

The fixed-dose, once-daily combination of elbasvir (50 mg) and grazoprevir (100 mg) (hereafter, elbasvir/grazoprevir) was evaluated in patients who had previously failed PEG-IFN/ribavirin in C-EDGE TE. In this phase III trial, patients were randomized to receive elbasvir/grazoprevir for 12 or 16 weeks with or without ribavirin. Genotype 1 patients treated for 12 weeks without ribavirin had an overall high SVR rate of 93.8% (90/96), which was similar to response rates in patients treated for 12 weeks with ribavirin (94.4%, 84/89). Response rates were similar in the 16-week arms without ribavirin (94.8%, 91/96) and with ribavirin (96.9%, 93/96). A subset analysis of patients with compensated cirrhosis revealed

similar response rates to the population without cirrhosis when treated with elbasvir/grazoprevir without ribavirin for 12 weeks: SVR in cirrhosis 95% (19/20) vs no cirrhosis 94.9% (37/39).

The presence of certain baseline NS5A RASs appears to be the single best predictor of relapse with the 12-week elbasvir/grazoprevir regimen. In genotype 1a patients treated with elbasvir/grazoprevir, decreased efficacy was seen among those with baseline NS5A resistance-associated substitutions (RASs) when assessed by population sequencing (limit of detection 25%). These resistance-associated substitutions included substitutions at positions M28, Q30, L31, H58, and Y93. Among 21 genotype 1a-patients with baseline NS5A RASs (>5 fold), 11 patients achieved SVR (52.4%) due to higher relapse (Kwo, 2015). A subsequent integrated analysis of phase II and III trials confirmed a lower SVR in treatment-experienced genotype 1a patients with these specific baseline NS5A RASs (90%, 167/185) vs patients without baseline RASs (99%, 390/393) (Zeuzem, 2017). In patients treated with 12 weeks of elbasvir/grazoprevir without ribavirin, 64% (9/14) of patients with baseline elbasvir NS5A RASs achieved SVR, compared to 96% (52/54) of those without baseline RASs. Extension of therapy to 16 weeks or 18 weeks with the addition of weight-based ribavirin increased response rates to 100% regardless of presence of baseline NS5A RASs, suggesting this approach can overcome the negative impact of NS5A RASs seen in the 12-week arms (Jacobson, 2015b). Based on the known inferior response in patients with specific NS5A RASs, NS5A resistance testing is recommended in genotype 1a patients who are being considered for therapy with elbasvir/grazoprevir. If these RASs are present, 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 the risk of 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) has been evaluated in patients with cirrhosis in whom prior treatment with PEG-IFN/ribavirin, with or without HCV protease inhibitors (telaprevir or boceprevir), failed. In the ION-2 study, patients who had not responded to prior PEG-IFN/ribavirin were treated with ledipasvir/sofosbuvir. This regimen was given for 12 weeks or 24 weeks, with or without ribavirin (Afdhal, 2014b). This regimen was well tolerated in all groups, with no serious adverse events reported in the 12-week regimen with or without ribavirn. In the population with cirrhosis, patients treated for 24 weeks had higher SVR rates than those treated for 12 weeks, supporting the recommendation that HCV treatment-experienced patients with cirrhosis receive 24 weeks of treatment without ribavirin.

In SIRIUS, a double-blind placebo-controlled French study, patients with cirrhosis who did not respond to PEG-IFN/ribavirin plus telaprevir or boceprevir, were randomized to receive placebo for 12 weeks followed by ledipasvir/sofosbuvir plus ribavirin for 12 weeks or ledipasvir/sofosbuvir plus placebo for 24 weeks. The SVR rate was similar in each group, 74 of 77 (96%) in the group that received ledipasvir/sofosbuvir plus ribavirin for 12 weeks (3 patients with relapse) and 75 of 77 (97%) in the group that received ledipasvir/sofosbuvir for 24 weeks (2 patients with relapse). This observation was further supported by a meta-analysis of treatment-naive and -experienced patients with cirrhosis who were treated with ledipasvir/sofosbuvir in phase II and III studies (including the SIRIUS study). In this analysis, ledipasvir/sofosbuvir for 12 weeks was inferior to ledipasvir/sofosbuvir for 24 weeks and ledipasvir/sofosbuvir plus ribavirin for 12 weeks; no difference in SVR was detected between the latter two groups. Safety and tolerability were similar in each group, and with the exception of anemia, reported adverse events did not differ substantially between patients treated with or without ribavirin (Bourliere, 2015); (Reddy, 2015).

Baseline NS5A RASs adversely impact responses to ledipasvir/sofosbuvir therapy; though the magnitude of this impact varies based on a number of factors including virus (genotype subtype, specific RAS), regimen (companion drugs, use of ribavirin), and patient factors (treatment experience, presence of cirrhosis). In an analysis of over 350 HCV genotype 1 treatment-experienced patients with cirrhosis the presence of baseline ledipasvir RASs (defined as RASs resulting in a >2.5 fold-shift in ledipasvir EC_{50}) detected at a 1% level resulted in lower SVR12 rates compared to those without baseline RASs (Zeuzem, 2017). The SVR12 rates were 89% (RASs) versus 96% (no RASs) when ledipasvir/sofosbuvir plus ribavirin for 12 weeks was used and 87% versus 100%, respectively, with ledipasvir/sofosbuvir for 24 weeks. The impact is likely to be larger in a genotype 1a only population. Given the vulnerable nature of this population, baseline NS5A resistance testing should be considered in genotype 1a treatment-experienced patients with cirrhosis prior to use of ledipasvir/sofosbuvir. If ledipasvir associated RASs are detected consideration should be given to adding weight-based

ribavirin to the regimen and extending therapy to 24 weeks. This is based on a 100% SVR12 rate in 14 patients with cirrhosis and baseline ledipasvir RASs treated with 24 weeks of ledipasvir/sofosbuvir plus ribavirin (Sarrazin, 2016).

Paritaprevir/ritonavir/ombitasvir + dasabuvir

In the TURQUOISE-II study, patients with CTP class A cirrhosis were treated with PrOD and ribavirin for 12 weeks or 24 weeks (Poordad, 2014). Of the 380 patients enrolled in this study, 220 had received prior PEG-IFN/ribavirin therapy that failed. Among the treatment-experienced patients, SVR12 was achieved in 90.2% (110/122) of patients in the 12-week arm and 96.9% (95/98) of patients in the 24-week arm. In multivariate logistic regression analysis, both prior null response to PEG-IFN/ribavirin therapy and genotype 1a subtype were associated with lower likelihood of SVR in patients who received 12 weeks of therapy. Therefore, patients with HCV genotype 1a infection and cirrhosis should be treated for 24 weeks. Hemoglobin decline to less than 10 g/dL occurred in 7.2% of the 12-week arm and 11.0% of the 24-week arm; however, treatment discontinuation for adverse events was rare overall (2.1%). To address the need for ribavirin with this regimen in patients with HCV genotype 1b and cirrhosis, the TURQUOISE-III study evaluated the safety and efficacy of PrOD without ribavirin for 12 weeks in patients with HCV genotype 1b infection and compensated cirrhosis. Sixty patients (62% men, 55% treatment-experienced, 83% with the IL28B non-CC genotype, 22% with platelet counts <90 x 10^9/L, and 17% with albumin levels <3.5 g/dL) were enrolled. All patients completed treatment, and all patients achieved an SVR12. On the basis of this study, treating patients with HCV genotype 1b with PrOD without ribavirin is recommended, regardless of prior treatment experience or presence of cirrhosis (Feld, 2016). 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 suspected. 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

In the phase IIa COSMOS study, 167 participants received simeprevir (150 mg once daily) plus sofosbuvir (400 mg once daily) with or without weight-based ribavirin for 12 weeks or 24 weeks. Overall SVR12 was 92% (90% among 80 patients with prior PEG-IFN/ribavirin nonresponse and limited [Metavir F0-F2] fibrosis, and 94% among 87 patients with Metavir F3-F4 fibrosis), and the regimens were well tolerated confirming high efficacy and safety (Lawitz, 2014b). The OPTIMIST-2 phase III study subsequently evaluated the combination of sofosbuvir plus simeprevir for 12 weeks in patients with HCV genotype 1 infection who were HCV treatment-naive and -experienced and with cirrhosis (Lawitz,

2016b). In the OPTIMIST-2 study (a single-arm study), 79% (42/53) of treatment-experienced patients with HCV genotype 1 infection and cirrhosis who were treated with 12 weeks of simeprevir and sofosbuvir achieved SVR. Overall, in this population of patients with cirrhosis, the SVR rate was lower in patients with HCV genotype 1a with the Q80K substitution (74%; 25/34) than in patients with HCV genotype 1a without the Q80K substitution (92%, 35/38). Taken together, these studies support the evaluation of treatment-experienced patients with cirrhosis and HCV genotype 1a for the presence of the Q80K substitution. If the Q80K substitution is detected, a different treatment regimen should be used. If Q80K substitutions are not detected then a 24-week regimen should be used (Simeprevir PI, 2013); (Lawitz, 2014b).

Sofosbuvir/velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naive and treatment-experienced patients with HCV genotypes 1, 2, 4, 5, and 6 treated with sofosbuvir and velpatasvir (hereafter, sofosbuvir/velpatasvir) as a fixed-dose combination for 12 weeks (Feld, 2015). Patients in the placebo arm were eligible to roll over into a deferred therapy arm with the same regimen. The response rate among genotype 1 treatment-experienced patients was 99.1% (109/110) overall with 100% (78/78) in patients with subtype 1a infection and 96.9% (31/32) with subtype 1b. Specifically among patients previously treated with PEG-IFN/ribavirin, 50 of 51 (98%) achieved SVR, and among those previously treated with a DAA plus PEG-IFN/ribavirin, 48 of 48 (100%) achieved SVR. The single treatment-experienced patient who did not have a response to this regimen was a genotype 1b black patient with cirrhosis and IL28 TT genotype who had a persistently detectable HCV viral load during previous PEG-IFN/ribavirin therapy. This regimen was well tolerated and there was no significant difference in the rate of adverse events in the sofosbuvir/velpatasvir group (78%) when compared to the placebo group (77%).

Daclatasvir + sofosbuvir

The combination of daclatasvir and sofosbuvir has been studied in HCV genotype 1 treatment-experienced patients who have previously been treated with PEG-IFN/ribavirin in two observational early access programs in the United Kingdom and France (Foster, 2015); (Pol, 2017); (Foster, 2016). In the French cohort, patients were treated with daclatasvir and sofosbuvir with or without ribavirin for 12 weeks or 24 weeks. In patients treated with daclatasvir and sofosbuvir alone, a numerically higher rate of sustained virologic response at 4 weeks (SVR4) was seen in those treated for 24 weeks (12 weeks, 15/18 or [82.6%] vs 24 weeks, 75/78 or [96.1%]). Patients treated with daclatasvir, sofosbuvir, and ribavirin had high response rates in the 12-week and the 24-week treatment groups (100% and 97.1%, respectively), but only 4 patients were treated for 12 weeks. In the United Kingdom cohort, 235 HCV genotype 1-infected patients with decompensated cirrhosis (45% had prior IFN-based HCV treatment failures) were treated with 12 weeks of sofosbuvir plus ledipasvir or daclatasvir with or without ribavirin as part of a compassionate access program. The selection of daclatasvir or ledipasvir and the use of ribavirin was at the discretion of the treating physician; most patients (94.4%) had ribavirin in their regimen. Among patients treated with sofosbuvir plus ribavirin for 12 weeks, the SVR rate was 86% for those who received ledipasvir (n=164) and 82% for those who received daclatasvir (n=82). Based on these limited data, consideration should be given to the addition of ribavirin when treating more difficult-to-treat patients, such as those with cirrhosis.

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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