

PEG-IFN/Ribavirin Experienced, Genotype 1b Patients Without Cirrhosis

Recommended Regimens by evidence level and alphabetically for:

Genotype 1b, PEG-IFN/Ribavirin Treatment-experienced Patients, Without 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)	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 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	IIa, B

* 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).

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 without 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. In the population without cirrhosis, the overall response rate was 98% (95% confidence interval [CI], 96%-99%). Specifically, in patients without cirrhosis who did not respond to PEG-IFN/ribavirin, 33 of 35 (94%) achieved an SVR after treatment with ledipasvir/sofosbuvir for 12 weeks, and 38 of 38 (100%) patients achieved SVR after treatment with ledipasvir/sofosbuvir and ribavirin for 12 weeks ([Afdhal, 2014b](#)). This regimen was well tolerated in all groups, with no serious adverse events reported in the 12-week regimen with or without ribavirin.

Paritaprevir/ritonavir/ombitasvir + dasabuvir

In SAPPHERE-2, the daily fixed-dose combination of paritaprevir (150 mg), ritonavir (100 mg), and ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) (hereafter, PrOD) with weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [≥ 75 kg]) was investigated for treatment of patients with HCV genotype 1 infection, in whom previous PEG-IFN/ribavirin therapy failed ([Zeuzem, 2014](#)). In this phase III trial, patients who did not have cirrhosis and who were treated for a total of 12 weeks had a high overall rate of response with 286 of 297 (96.3%). Response rates did not differ substantially when stratified by subtype (genotype 1a, 96.0% [166/173]; genotype 1b, 96.7% [119/123]) or kinetics of prior response to PEG-IFN/ribavirin (relapse, 95.3% [82/86]; partial response, 100% [65/65]; null response, 95.2% [139/146]). In the PEARL-II study, 179 patients without cirrhosis and HCV genotype 1b infection, in whom previous therapy with PEG-IFN/ribavirin failed, were treated with PrOD with or without weight-based ribavirin for 12 weeks ([Andreone, 2014](#)). SVR rates were high in both arms: 100% (91/91) in the ribavirin-free arm and 96.6% (85/88) in the ribavirin-containing arm, supporting the recommendation that this regimen may be used without ribavirin for patients with HCV genotype 1b infection.

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-1 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-naïve and -experienced without cirrhosis ([Kwo, 2016](#)). In OPTIMIST-1, patients with HCV genotype 1 infection and no evidence of cirrhosis were randomized to 8 weeks or 12 weeks of treatment. Superiority in SVR12 was assessed for simeprevir plus sofosbuvir at 12 and 8 weeks versus a composite historical control SVR rate. The SVR12 in the 12-week arm was 97%, meeting superiority versus the historical control (87%); however, the 8-week arm only achieved an SVR12 of 83%, which did not meet superiority versus the historical control. Among those treated for 12 weeks, the SVR rate in PEG-IFN plus ribavirin treatment-experienced patients was 95% (38/40) and the SVR rate in patients with genotype 1a infection with the baseline Q80K substitution (96%; 44/46) was similar to that observed in patients without the Q80K substitution (97%; 68/70).

Sofosbuvir/velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naïve 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. 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 pangentypic regimen should be considered. When the correct combination or duration is unclear, expert consultation should be sought.

Last update: April 12, 2017