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

Recommended and Alternative Regimens by evidence level and alphabetically for:

Genotype 1a, PEG-IFN/Ribavirin Treatment-experienced 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 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.

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 ribavirn.

Paritaprevir/ritonavir/ombitasvir + dasabuvir

In SAPPHIRE-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-naive 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-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. 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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