NS3 PI + Peg-IFN/Ribavirin Experienced, Genotype 1 Patients Without Cirrhosis

Recommended Regimens by evidence level and alphabetically for:

Genotype 1 (regardless of subtype), HCV Nonstructural Protein 3 (NS3) Protease Inhibitor (telaprevir, boceprevir, or simeprevir) plus PEG-IFN/Ribavirin Treatment-experienced Patients, Without Cirrhosis

RECOMMENDED	DURATION	RATING
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
Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg)	12 weeks	IIa, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based ribavirin	12 weeks	IIa, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based ribavirin; for genotype 1a 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.

Ledipasvir/sofosbuvir

The safety and efficacy of ledipasvir/sofosbuvir was evaluated in subjects in whom prior treatment with an HCV protease inhibitor (telaprevir or boceprevir) plus PEG-IFN/ribavirin has failed (Afdhal, 2014b). SVR12 rates with 12- and 24-week regimens were high during both treatment durations (94% and 98%, respectively). Relapse rates in the ION-2 retreatment trial were numerically higher in the 12-week arms than in the 24-week arms. The pretreatment presence of cirrhosis or nonstructural protein 5A (NS5A) resistance-associated substitutions (RASs) were the major reasons for the higher relapse rate in the 12-week arm. Thus, patients with cirrhosis in whom a prior regimen of PEG-IFN, ribavirin, and an HCV protease inhibitor has failed should receive 24 weeks of ledipasvir/sofosbuvir, and patients without cirrhosis should receive 12 weeks of ledipasvir/sofosbuvir.

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/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. In this study, 100% (48/48) of subjects who had previously failed a protease inhibitor plus PEG-IFN/ribavirin achieved SVR12 (Feld, 2015). These data are supported by similarly high SVR rates seen in a preceding phase II open-label trail where 27/27 or 100% of patients achieved SVR12 after 12 weeks of therapy (Pianko, 2015).

Daclatasvir and sofosbuvir

The combination of daclatasvir and sofosbuvir was studied in 41 patients without cirrhosis in whom previous therapy with PEG-IFN, ribavirin, and an HCV protease inhibitor had failed. Of these patients, 21 were treated with daclatasvir and sofosbuvir for 24 weeks and 20 were treated with daclatasvir and sofosbuvir plus ribavirin for 24 weeks. Both groups had high cure rates and no additional benefit was seen with the inclusion of ribavirin (98% SVR12 overall) (Sulkowski, 2014a). Although data are limited, the addition of ribavirin can be considered in difficult-to-treat situations, such as in patients with cirrhosis (Pol, 2017).

Elbasvir/grazoprevir

Grazoprevir is a next-generation protease inhibitor that retains activity in vitro against many common protease inhibitor resistant substitutions (Summa, 2012); (Howe, 2014). The combination of grazoprevir (100 mg) plus elbasvir (50 mg) with expanded weight-based ribavirin (800-1400 mg) was evaluated in an open-label phase II study of 79 patients who had failed prior interferon-based HCV therapy including a protease inhibitor (Forns, 2015a). The majority of enrolled subjects had failed prior PEG-IFN/ribavirin plus either boceprevir (35%, n=28) or telaprevir (54%, n=43); importantly 83% experienced virologic failure with their prior PI-containing regimen and 44% had detectable NS3 RASs to early-generation PIs at study entry. Sustained virologic response 12 weeks after completion of therapy was attained in 96% of patients including in 93% (28/30) of genotype 1a patient and 94% (32/34) of those with cirrhosis. Baseline NS3 RASs did not appear to have a large impact on responses with a SVR12 rate of 91% (31/34). Presence of NS5A or dual NS3/NS5A substitutions was associated with lower SVR12 rates of 75% and 66%, respectively, but with only 3 failures in the entire study firm conclusions cannot be drawn. Consistent with the recommendations for other populations, extension of therapy to 16 weeks with ribavirin is recommended in patients with baseline NS5A RASs resulting in a >5-fold shift in elbasvir potency.

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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