Retreatment of Persons in Whom Prior Therapy Has Failed

This section provides guidance on the retreatment of a person with chronic HCV infection in whom prior therapy has failed. The level of the evidence available to inform the best regimen for each patient and the strength of the recommendation vary, and are rated accordingly (see Methods Table 2). In addition, specific recommendations are given when treatment differs for a particular group (eg, those infected with various genotypes). Recommended regimens are those that are favored for most patients in that subgroup, based on optimal efficacy, favorable tolerability and toxicity profiles, and duration. Alternative regimens are those that are effective but have, relative to Recommended regimens, potential disadvantages, limitations for use in certain patient populations, or less supporting data than Recommended regimens. In certain situations, an Alternative regimen may be an optimal regimen for a specific patient. Not Recommended regimens are clearly inferior compared to Recommended or Alternative regimens due to factors such as lower efficacy, unfavorable tolerability and toxicity, longer duration, and/or higher pill burden. Unless otherwise indicated, such regimens should not be administered to patients with HCV infection. Specific considerations of persons with HIV/HCV coinfection, decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh [CTP] class B or C), HCV infection post-liver transplant, and those with severe renal impairment or end-stage renal disease are addressed in other sections of the Guidance.

Recommended and Alternative regimens are listed in order of level of evidence. When several regimens are offered at the same level of evidence, they are listed in alphabetical order. Choice of regimen should be determined based on patient-specific data, including drug interactions. As always, patients receiving antiviral therapy require careful pretreatment assessment for comorbidities that may influence treatment response. All patients should have careful monitoring during treatment, particularly for anemia if ribavirin is included in the regimen (See Monitoring section).

The following pages include guidance for management of treatment-naive patients.

- Genotype 1
- Genotype 2
- Genotype 3
- Genotype 4
- Genotype 5 or 6

Last update: April 12, 2017

Treatment-experienced Genotype 1

Six highly potent oral DAA combination regimens are Recommended for patients with HCV genotype 1 infection, although there are differences in the Recommended regimens based on the viral subtype and the presence or absence of baseline NS5A resistance-associated substitutions (RASs), and the presence or absence of cirrhosis. With certain regimens, patients infected with genotype 1a may have higher rates of virologic failure than those infected with genotype 1b. HCV genotype 1 infection that cannot be subtyped should be treated as genotype 1a infection.

Approximately 10%-15% of HCV genotype 1-infected patients without prior exposure to NS5A inhibitors will have detectable HCV NS5A RASs at the population level prior to treatment. While the clinical impact of NS5A RASs remains to be fully elucidated, in patients with genotype 1a infection the presence of baseline NS5A RASs that cause a large reduction in the activity of NS5A inhibitors (>5 fold) adversely impacts response to NS5A-containing regimens (Zeuzem, 2017); (Jacobson, 2015b). These RASs include substitutions at positions M28, Q30, L31, and Y93 in genotype 1a and are found by population sequencing in roughly 5%-10% of patients. Given that baseline NS5A RASs are one of the

strongest pre-treatment predictors of treatment outcome with certain regimens in patients with genotype 1a infection, testing for these RASs prior to deciding on a therapeutic course is recommended in select situations (Zeuzem, 2015c).

The introduction of DAAs into HCV treatment regimens increased the risk of drug interactions with concomitant medications and now with combinations of DAAs, attention to drug interactions is all the more important (see Drug Interactions table). The product prescribing information and other resources (eg, http://www.hep-druginteractions.org) should be referenced regularly to ensure safety when prescribing DAA regimens. Important interactions with commonly used medications (eg, antacids, lipid-lowering drugs, anti-epileptics, antiretrovirals, etc) exist for all of the regimens discussed below.

The following pages include guidance for management of treatment-experienced patients with HCV Genotype 1.

- PEG-IFN/Ribavirin Experienced, Genotype 1a Patients Without Cirrhosis
- PEG-IFN/Ribavirin Experienced, Genotype 1a Patients with Compensated Cirrhosis
- PEG-IFN/Ribavirin Experienced, Genotype 1b Patients Without Cirrhosis
- PEG-IFN/Ribavirin Experienced, Genotype 1b Patients with Compensated Cirrhosis
- NS3 PI + Peg-IFN/Ribavirin Experienced, Genotype 1 Patients Without Cirrhosis
- NS3 PI + Peg-IFN/Ribavirin Experienced, Genotype 1 Patients with Compensated Cirrhosis
- NS5A Experienced Genotype 1 Patients
- Simeprevir Plus Sofosbuvir Experienced, Genotype 1 Patients
- Sofosbuvir plus Ribavirin, with or Without PEG-IFN, Experienced Genotype 1 Patients with or Without Cirrhosis

Last update: April 12, 2017

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

Recommended and Alternative Regimens by evidence level and alphabetically for:

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

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.

Last update: April 12, 2017

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

Recommended and Alternative Regimens by evidence level and alphabetically for:

Genotype 1a, PEG-IFN/Ribavirin Treatment-experienced, 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) plus weight-based ribavirin	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	24 weeks	I, A

Recommended and Alternative Regimens by evidence level and alphabetically for:

Genotype 1a, PEG-IFN/Ribavirin Treatment-experienced, with Compensated Cirrhosis ‡

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†		
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	24 weeks	I, A
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	I, B
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; for patients who are negative for the Q80K substitution by commercially available resistance assay. Other Recommended or Alternative regimens should be used for patients with compensated cirrhosis and HCV genotype 1a infection in whom the Q80K substitution is present.	24 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.

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.

Last update: April 12, 2017

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 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.

Last update: April 12, 2017

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.

Last update: April 12, 2017

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.

Last update: April 12, 2017

NS3 PI + Peg-IFN/Ribavirin Experienced, Genotype 1 Patients with Compensated 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, with Compensated Cirrhosis ‡

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based ribavirin	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	24 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) with or without weight-based ribavirin	24 weeks	IIa, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based ribavirin	12 weeks	IIa, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus 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.
‡ 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.

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. Based on data from the SIRIUS study, patients with cirrhosis in whom a prior protease inhibitor-containing regimen failed may also receive ledipasvir/sofosbuvir plus weight-based ribavirin for 12 weeks (Bourliere, 2015).

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.

Last update: April 12, 2017

NS5A Experienced Genotype 1 Patients

Recommended Regimens by evidence level and alphabetically for:

Genotype 1, NS5A Inhibitor Treatment-experienced Patients

RECOMMENDED	RATING
Deferral of treatment is recommended, pending availability of data for patients with HCV genotype 1, regardless of subtype, in whom previous treatment with any HCV nonstructural protein 5A (NS5A) inhibitors has failed, who do not have cirrhosis, and do not have reasons for urgent retreatment.	IIb, C
Testing for resistance-associated substitutions that confer decreased susceptibility to NS3 protease inhibitors and to NS5A inhibitors is recommended for patients with HCV genotype 1, regardless of subtype, in whom previous treatment with any HCV nonstructural protein 5A (NS5A) inhibitors has failed, and who have compensated cirrhosis,‡ or have reasons for urgent retreatment. The specific drugs used in the retreatment regimen should be tailored to the results of this testing as described below.	IIb, C
When using nucleotide-based (eg, sofosbuvir) dual DAA therapy a treatment duration of 24 weeks is recommended, and weight-based ribavirin, unless contraindicated, should be added.	IIb, C
If available, nucleotide-based (eg, sofosbuvir) triple or quadruple DAA regimens may be considered. In these settings treatment duration ranges from 12 weeks to 24 weeks (see text), and weight-based ribavirin, unless contraindicated, are recommended.	IIb, C

‡ For decompensated cirrhosis, please refer to the appropriate section.

Ledipasvir/sofosbuvir failures

Data on the retreatment of patients for whom prior treatment with ledipasvir/sofosbuvir has failed are very limited. In a pilot study, 41 patients with and without cirrhosis who did not achieve an SVR with 8 weeks or 12 weeks of ledipasvir/sofosbuvir were retreated with 24 weeks of ledipasvir/sofosbuvir (Lawitz, 2015b). SVR12 rates varied according to the presence or absence of NS5A inhibitor RASs. Among 11 patients for whom NS5A inhibitor RASs were not detected, SVR occurred in 11 of 11 (100%); in contrast, among 30 patients for whom NS5A inhibitor RASs were detected, SVR occurred in 18 of 30 (60%). Importantly, NS5B inhibitor RASs (eg, S282T) known to confer decreased activity of sofosbuvir were observed in 3 of 12 (25%) patients for whom the retreatment regimen was not successful (Lawitz, 2015b). Similarly, in the OPTIMIST-2 study in which patients with cirrhosis were treated with simeprevir and sofosbuvir, the presence of NS3 RASs, namely the Q80K substitution, led to a decreased SVR rate in patients with HCV genotype 1a infection. SVR occurred in 25 of 34 (74%) patients with HCV genotype 1a and the Q80K RAS and in 35 of 38 (92%) patients with HCV genotype 1a without the Q80K RAS (Lawitz, 2016b). Based on these data, retreatment for patients for whom an NS5A inhibitor-containing regimen has failed should be considered in the context of retreatment urgency and the presence or absence of RASs to inhibitors of NS3 and NS5A. Further, based on limited data, ribavirin is recommended as part of all retreatment regimens for patients in whom prior treatment with NS5A inhibitors has failed. Although no data exist, consideration may also be given to the addition of PEG-IFN to the retreatment regimen in patients who are eligible for this agent; PEG-IFN will have antiviral activity regardless of the RASs present.

Retreatment approach and potential regimens (including other NS5A regimen containing failures)

For patients with cirrhosis or other patients who require retreatment urgently, testing for RASs that confer decreased

susceptibility to NS3 protease inhibitors (eg, Q80K) and to NS5A inhibitors should be performed using commercially available assays prior to selecting the next HCV treatment regimen. For patients with no NS5A inhibitor RASs detected, retreatment with ledipasvir/sofosbuvir or sofosbuvir/velpatasvir, both with ribavirin, for 24 weeks is recommended. For patients who have NS5A inhibitor RASs detected and who do not have NS3 inhibitor RASs detected, treatment with simeprevir, sofosbuvir, and ribavirin for 24 weeks is recommended. For patients who have both NS3 and NS5A inhibitor RASs detected there are several small studies that provide some insight on salvage regimens. Limited data suggest a retreatment approach based on sofosbuvir combined with either elbasvir/grazoprevir or PrOD may be efficacious (Lawitz, 2015e); (Poordad, 2015a). In a retreatment arm of the C-SWIFT study, 23 patients who had failed shorter courses of elbasvir/grazoprevir plus sofosbuvir were retreated with 12 weeks of this combination plus weight-based ribavirin. In a per protocol analysis a 100% SVR12 rate was achieved (23/23), including SVR in 9/9 patients with dual NS3 and NS5A RASs (Lawitz, 2015e). A second phase II study of 22 patients, including 14 PrOD failures, evaluated retreatment with 12-24 weeks of PrOD plus sofosbuvir. Treatment duration and ribavirin usage were determined by cirrhosis status, HCV RNA response on therapy, and genotype subtype. SVR12 data was available on 15 patients with 14/15 (93%) attaining SVR12. Based on these limited data, patients with dual NS3 and NS5A class RASs may be retreated with elbasvir/grazoprevir plus sofosbuvir with weight-based ribavirin for 12 weeks or PrOD plus sofosbuvir for 12 weeks in genotype 1b and 24 weeks with weight-based ribavirin in those with genotype 1a. If these regimens are unavailable, retreatment should be conducted in a clinical trial setting, as an appropriate treatment regimen cannot be recommended at this time. Another approach in patients with prior non-response to NS5A-containing therapy has been studied in genoptype 1, 2, and 3 patients who did not respond to velpatasvir-containing regimens including sofobuvir/velpatasvir and sofosbuvir/velpatasvir/GS-9857 (Gane, 2016). Retreatment with sofosbuvir/velpatasvir with ribavirin for 24 weeks yielded high overall response rates (91% or 59/65). Among genotype 1 patients, 97% (33/34) achieved SVR. Baseline NS5A RASs did not appear to effect SVR rates. In 34 genotype 1 patients, 6 patients had NS5A RASs prior to retreatment, all of whom achieved SVR. Although data are extremely limited, retreatment with sofosbuvir/velpatasvir + ribavirin for 24 weeks should be considered in genotype 1 patients who have not responded to prior NS5A-based therapy, especially if there is urgency for treatment.

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.

Last update: April 12, 2017

Simeprevir Plus Sofosbuvir Experienced, Genotype 1 Patients

Recommended Regimens by evidence level and alphabetically for:

Genotype 1, Simeprevir Plus Sofosbuvir Treatment-experienced Patients

RECOMMENDED	RATING
Deferral of treatment is recommended, pending availability of data, for patients with HCV genotype 1 infection, regardless of subtype, in whom prior treatment with the HCV protease inhibitor simeprevir plus sofosbuvir has failed (no prior NS5A treatment), who do not have cirrhosis, and do not have reasons for urgent retreatment.	IIb, C

Recommended Regimens by evidence level and alphabetically for:

Genotype 1, Simeprevir Plus Sofosbuvir Treatment-experienced Patients

Testing for resistance-associated substitutions that confer decreased susceptibility to NS3 protease inhibitors and to NS5A inhibitors is recommended for patients with HCV genotype 1 infection, regardless of subtype, in whom prior treatment with the HCV protease inhibitor simeprevir plus sofosbuvir has failed (no prior NS5A treatment), who have compensated cirrhosis,‡ or have reasons for urgent retreatment. The specific drugs used in the retreatment regimen should be tailored to the results of this testing as described below.	II, C
When using nucleotide-based (eg, sofosbuvir) dual DAA therapy a treatment duration of 24 weeks is recommended, and weight-based ribavirin, unless contraindicated, should be added.	II, C
If available, nucleotide-based (eg, sofosbuvir) triple or quadruple DAA regimens may be considered. In these settings treatment duration ranges from 12 weeks to 24 weeks (see text), and weight-based ribavirin, unless contraindicated, are recommended.	II, C

‡ For decompensated cirrhosis, please refer to the appropriate section.

Simeprevir + sofosbuvir failures

Data suggest that approximately 5% to 10% of patients without cirrhosis and with HCV genotype 1 infection treated for 12 weeks with simeprevir plus sofosbuvir will experience treatment failure, typically due to viral relapse (Kwo, 2015). Failure rates in patients with cirrhosis treated for 24 weeks with this regimen are limited; however, treatment failure appears to be more common in persons infected with HCV genotype 1a and those with cirrhosis. Data from the OPTIMIST-1 and -2 studies indicate that treatment failure following a regimen of simeprevir plus sofosbuvir is associated with resistance to simeprevir and cross-resistance to other HCV NS3 protease inhibitors such as paritaprevir, telaprevir, and boceprevir; grazoprevir cross-resistance may also occur in the setting of D168 or A156 substitutions (Kwo, 2015); (Lawitz, 2017). On the other hand, only a single patient developed the signature sofosbuvir RAS S282T in the OPTIMIST trials supporting the rare occurrence of this substitution in clinical practice.

Data on retreatment of simeprevir plus sofosbuvir failures are extremely limited. Interim data from a cohort of 31 patients who had failed simeprevir plus sofosbuvir therapy indicated reasonable response rates to 12-24 weeks of ledipasvir/sofosbuvir therapy with or without ribavirin (Gonzales, 2015). In the subset of patients with SVR12 data available, 85% SVR12 was achieved in non-cirrhotic patients and 91% in cirrhotic patients. Given the lack of a standardized treatment approach and heterogeneous nature of the population, conclusions on the optimal retreatment regimen cannot be drawn.

Retreatment approach and potential regimens (including other NS5A regimen containing failures)

For patients with cirrhosis or other patients who require retreatment urgently, testing for RASs that confer decreased susceptibility to NS3 protease inhibitors (eg, Q80K) and to NS5A inhibitors should be performed using commercially available assays prior to selecting the next HCV treatment regimen. For patients with no NS5A inhibitor RASs detected, retreatment with ledipasvir/sofosbuvir or sofosbuvir/velpatasvir, both with ribavirin, for 24 weeks is recommended. For patients who have NS5A inhibitor RASs detected and who do not have NS3 inhibitor RASs detected, treatment with

simeprevir, sofosbuvir, and ribavirin for 24 weeks is recommended. For patients who have both NS3 and NS5A inhibitor RASs detected there are several small studies that provide some insight on salvage regimens. Limited data suggest a retreatment approach based on sofosbuvir combined with either elbasvir/grazoprevir or PrOD may be efficacious (Lawitz, 2015e); (Poordad, 2015a). In a retreatment arm of the C-SWIFT study, 23 patients who had failed shorter courses of elbasvir/grazoprevir plus sofosbuvir were retreated with 12 weeks of this combination plus weight-based ribavirin. In a per protocol analysis a 100% SVR12 rate was achieved (23/23), including SVR in 9/9 patients with dual NS3 and NS5A RASs (Lawitz, 2015e). A second phase II study of 22 patients, including 14 PrOD failures, evaluated retreatment with 12-24 weeks of PrOD plus sofosbuvir. Treatment duration and ribavirin usage were determined by cirrhosis status, HCV RNA response on therapy, and genotype subtype. SVR12 data was available on 15 patients with 14/15 (93%) attaining SVR12. Based on these limited data, patients with dual NS3 and NS5A class RASs may be retreated with elbasvir/grazoprevir plus sofosbuvir with weight-based ribavirin for 12 weeks or PrOD plus sofosbuvir for 12 weeks in genotype 1b and 24 weeks with weight-based ribavirin in those with genotype 1a. If these regimens are unavailable, retreatment should be conducted in a clinical trial setting, as an appropriate treatment regimen cannot be recommended at this time. Another approach in patients with prior non-response to NS5A-containing therapy has been studied in genoptype 1, 2, and 3 patients who did not respond to velpatasvir-containing regimens including sofobuvir/velpatasvir and sofosbuvir/velpatasvir/GS-9857 (Gane, 2016). Retreatment with sofosbuvir/velpatasvir with ribavirin for 24 weeks yielded high overall response rates (91% or 59/65). Among genotype 1 patients, 97% (33/34) achieved SVR. Baseline NS5A RASs did not appear to effect SVR rates. In 34 genotype 1 patients, 6 patients had NS5A RASs prior to retreatment, all of whom achieved SVR. Although data are extremely limited, retreatment with sofosbuvir/velpatasvir + ribavirin for 24 weeks should be considered in genotype 1 patients who have not responded to prior NS5A-based therapy, especially if there is urgency for treatment.

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.

Last update: April 12, 2017

Sofosbuvir plus Ribavirin, with or Without PEG-IFN, Experienced Genotype 1 Patients with or Without Cirrhosis

Recommended Regimen for:

Genotype 1 (regardless of subtype), Sofosbuvir Plus Ribavirin with or Without PEG-IFN Treatment-experienced Patients, Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with weight-based ribavirin	12 weeks	IIa, B

Recommended Regimen for:

Genotype 1 (regardless of subtype), Sofosbuvir Plus Ribavirin with or Without PEG-IFN Treatment-experienced Patients, Without Cirrhosis

Recommended Regimen for:

Genotype 1 (regardless of subtype), Sofosbuvir Plus Ribavirin with or Without PEG-IFN Treatment-experienced Patients, with Compensated Cirrhosis‡

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with weight-based ribavirin	24 weeks	IIa, B

‡ For decompensated cirrhosis, please refer to the appropriate section.

To date, clinical experience and trial data on the retreatment of sofosbuvir-experienced patients are very limited. However, retreatment after a sofosbuvir-containing treatment failure with a second course of treatment using sofosbuvir plus new agents, or retreatment with the same sofosbuvir-based regimen for a longer duration, have been reported.

Retreatment with ledipasvir/sofosbuvir in subjects with HCV genotype 1 infection, with or without cirrhosis, in whom a sofosbuvir-containing regimen failed has been evaluated in two small pilot studies utilizing ledipasvir/sofosbuvir for 12 weeks. With prior failures of 24 weeks of sofosbuvir plus ribavirin, high SVR rates were noted when patients were retreated with ledipasvir/sofosbuvir for 12 weeks (Osinusi, 2014). Ledipasvir/sofosbuvir plus ribavirin has also been evaluated in subjects in whom prior treatment with sofosbuvir plus PEG-IFN/ribavirin or sofosbuvir and ribavirin failed. In this study of 51 patients, retreatment with ledipasvir/sofosbuvir plus ribavirin for 12 weeks led to SVR12 in 100% of 50 patients with HCV genotype 1 infection; 1 virologic failure was observed in a patient determined to have HCV genotype 3 infection prior to retreatment (Wyles, 2015b). There are exceedingly limited data on the retreatment of such patients with cirrhosis. However, a post-hoc analysis of 352 previously treated patients with cirrhosis (240 of whom had prior protease inhibitor-based treatment failures) who were retreated with 12 weeks or 24 weeks of ledipasvir/sofosbuvir with or without ribavirin found that SVR12 was achieved in 95% to 98% (Reddy, 2015). Thus, for previously treated HCV genotype 1-infected patients with compensated cirrhosis, retreatment with 24 weeks of ledipasvir/sofosbuvir plus ribavirin is recommended.

There are no published data on retreatment of sofosbuvir-containing treatment failures with non-sofosbuvir based DAA regimens. In theory the lack of cross resistance between SOF and all other currently available DAAs suggests that such regimens may be efficacious in retreatment settings. However, given the lack of available data recommendations cannot be made. If use of non-sofosbuvir-based DAA regimens is being considered, those patients should be treated in line with the recommendations for pegylated interferon-experienced patients according to genotype subtype and cirrhosis status.

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.

Last update: April 12, 2017

Treatment-experienced Genotype 2

The following pages include guidance for management of treatment-experienced patients with HCV Genotype 2.

- PEG-IFN/Ribavirin Treatment-experienced, Genotype 2 Patients Without Cirrhosis
- PEG-IFN/Ribavirin Treatment-experienced, Genotype 2 Patients with Compensated Cirrhosis
- Sofosbuvir Plus Ribavirin Treatment-experienced, Genotype 2 Patients

Last update: April 12, 2017

PEG-IFN/Ribavirin Treatment-experienced, Genotype 2 Patients Without Cirrhosis

Recommended and Alternative Regimens by evidence level and alphabetically for:

Genotype 2, PEG-IFN/Ribavirin Treatment-experienced Patients, Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
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.

Sofosbuvir/velpatasvir

In the randomized, open-label ASTRAL-2 study, patients with HCV genotype 2 infection were treated with either 12 weeks of sofosbuvir plus velpatasvir (hereafter, sofosbuvir/velpatasvir) or sofosbuvir plus ribavirin (Foster, 2015a). Of the total of 266 patients, a minority (15%) had previously failed PEG-IFN/ribavirin and a similar proportion (14%) had cirrhosis. Overall, the combination of sofosbuvir/velpatasvir yielded a statistically significant superior SVR12 rate, 99% vs 94%. The only failure in the sofosbuvir/velpatasvir arm was a man who withdrew from the study after one day due to side effects (anxiety). In contrast, there were 6 virologic failures in the sofosbuvir plus ribavirin arm. Fatigue and anemia were more commonly reported in patients receiving sofosbuvir plus ribavirin. In light of the high SVR12 rate and fewer side effects with sofosbuvir/velpatasvir, regimens with peginterferon and/or ribavirin are no longer recommended for genotype 2 infection.

Daclatasvir plus sofosbuvir

The once-daily combination of daclatasvir (60 mg) plus sofosbuvir (400 mg) for 12 to 24 weeks has been shown to have efficacy in HCV genotype 2 infection, however available data in patients previously treated with PEG-IFN/ribavirin are very limited (Wyles, 2015); (Sulkowski, 2014a). For patients who require treatment and are unable to access sofosbuvir/velpatasvir, treatment with daclatasvir/sofosbuvir for 12 weeks is an alternative regimen with consideration of extension of therapy to 24 weeks in more difficult patients to treat 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.

Last update: April 12, 2017

PEG-IFN/Ribavirin Treatment-experienced, Genotype 2 Patients with Compensated Cirrhosis

Recommended and Alternative Regimens by evidence level and alphabetically for:

Genotype 2, PEG-IFN/Ribavirin Treatment-experienced Patients, with Compensated Cirrhosis ‡

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	DURATION	RATING

Recommended and Alternative Regimens by evidence level and alphabetically for:

Genotype 2, PEG-IFN/Ribavirin Treatment-experienced Patients, with Compensated Cirrhosis ‡

Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg)	16 weeks to 24 weeks	IIa, B

‡ 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.

Sofosbuvir/velpatasvir

In the randomized, open-label ASTRAL-2 study, patients with HCV genotype 2 infection were treated with either 12 weeks of sofosbuvir plus velpatasvir (hereafter, sofosbuvir/velpatasvir) or sofosbuvir plus ribavirin (Foster, 2015a). Of the total of 266 patients, a minority (15%) had previously failed PEG-IFN/ribavirin and a similar proportion (14%) had cirrhosis. Overall, the combination of sofosbuvir/velpatasvir yielded a statistically significant superior SVR12 rate, 99% vs 94%. The only failure in the sofosbuvir/velpatasvir arm was a man who withdrew from the study after one day due to side effects (anxiety). In contrast, there were 6 virologic failures in the sofosbuvir plus ribavirin arm. Fatigue and anemia were more commonly reported in patients receiving sofosbuvir plus ribavirin. In light of the high SVR12 rate and fewer side effects with sofosbuvir/velpatasvir, regimens with peginterferon and/or ribavirin are no longer recommended for genotype 2 infection.

Daclatasvir plus sofosbuvir

The once-daily combination of daclatasvir (60 mg) plus sofosbuvir (400 mg) for 12 to 24 weeks has been shown to have efficacy in HCV genotype 2 infection, however available data in patients previously treated with PEG-IFN/ribavirin are very limited (Wyles, 2015); (Sulkowski, 2014a). For patients who require treatment and are unable to access sofosbuvir/velpatasvir, treatment with daclatasvir/sofosbuvir for 12 weeks is an alternative regimen with consideration of extension of therapy to 24 weeks in more difficult patients to treat 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.

Last update: April 12, 2017

Sofosbuvir Plus Ribavirin Treatment-experienced, Genotype 2 Patients

Recommended Regimens by evidence level and alphabetically for:

Genotype 2, Sofosbuvir Plus Ribavirin Treatment-experienced Patients ‡

RECOMMENDED	DURATION	RATING
Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with or without weight-based ribavirin‡	24 weeks	IIa, C
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin‡	12 weeks	IIa, C

‡ 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.

To date, there are few data available to guide therapy in patients with HCV genotype 2 infection in whom prior treatment with sofosbuvir and ribavirin has failed. Prior studies of genotype 1 or 3 treatment failures have shown that adding ribavirin to sofosbuvir/velpatasvir leads to higher cure rates than just sofosbuvir/velpatasvir alone (Pianko, 2015). Extrapolating from this study, the addition of ribavirin is recommended.

The combination of daclatasvir and sofosbuvir is effective in patients with HCV genotype 2 infection, but there are limited data about this therapy in treatment-experienced patients with HCV genotype 2 infection (Sulkowski, 2014a); (Wyles, 2015). For patients in whom prior treatment with sofosbuvir and ribavirin failed who are ribavirin ineligible, the decision to treat with daclatasvir and sofosbuvir should be made on an individual patient basis with consideration of extension of therapy to 24 weeks with the addition of ribavirin, especially in 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.

Last update: April 12, 2017

Treatment-experienced Genotype 3

The following pages include guidance for management of treatment-experienced patients with HCV Genotype 3.

- PEG-IFN/Ribavirin Experienced, Genotype 3 Patients Without Cirrhosis
- PEG-IFN/Ribavirin Experienced, Genotype 3 Patients with Compensated Cirrhosis
- Sofosbuvir-experienced, Genotype 3 Patients

Last update: April 12, 2017

PEG-IFN/Ribavirin Experienced, Genotype 3 Patients Without Cirrhosis

Recommended Regimens by evidence level and alphabetically for:

Genotype 3, PEG-IFN/Ribavirin Treatment-experienced Patients, Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg)¶	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)¶	12 weeks	I, A

* 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.
¶ RAS testing for Y93H is recommended for cirrhotic patients and ribavirin should be included in regimen if present.

Daclatasvir plus sofosbuvir

In the ALLY-3 study, treatment-experienced patients without cirrhosis did well with an SVR12 rate of 94% (32/34) (Nelson, 2015).

Sofosbuvir/velpatasvir

The phase III ASTRAL-3 study evaluated the fixed-dose combination of sofosbuvir/velpatasvir for 12 weeks without

ribavirin in 277 genotype 3-infected patients, including 71 with prior treatment experience and 80 with cirrhosis (Foster, 2015a). Despite a high combined SVR12 rate of 95% (264/277), both prior treatment (90% SVR) and cirrhosis (91% SVR) had a moderate negative impact on treatment responses. The addition of ribavirin did appear to increase SVR12 rates in a phase II study of treatment-experienced genotype 3 patients treated for 12 weeks with 25 or 100 mg of velpatasvir combined with sofosbuvir (Pianko, 2015).

Baseline NS5A substitutions in genotype 3 also impact DAA treatment response, with the Y93H substitution being the most challenging. In the ALLY-3 study the Y93H was detected in 13 (9%) of patients with an SVR12 of 54% (7/13); including a 67% SVR12 in patients without cirrhosis. In the ASTRAL-3 study the Y93H was detected in 25 (9%) of patients with an SVR12 rate of 84% (21/25). Given that cirrhotic patients in whom prior treatment with PEG-IFN/ribavirin has failed are already recommended to have ribavirin added with or without extension of therapy depending on the specific regimen, baseline testing for NS5A RASs in genotype 3 would only impact treatment approaches for patients in whom prior treatment with PEG-IFN/ribavirin has failed without cirrhosis. Pending additional data, baseline NS5A RAS testing is recommended in all treatment-experienced genotype 3 patients without cirrhosis. If the Y93H substitution is identified, weight-based ribavirin should be added to the treatment course.

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.

Last update: April 12, 2017

PEG-IFN/Ribavirin Experienced, Genotype 3 Patients with Compensated Cirrhosis

Recommended and Alternative Regimens by evidence level and alphabetically for:

Genotype 3, PEG-IFN/Ribavirin Treatment-experienced Patients, with Compensated Cirrhosis [†]

RECOMMENDED	DURATION	RATING
Daily fixed-dose elbasvir (50 mg)/grazoprevir (100 mg) plus sofosbuvir (400 mg)	12 weeks	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin	12 weeks	I, B
ALTERNATIVE	DURATION	RATING

Recommended and Alternative Regimens by evidence level and alphabetically for:

Genotype 3, PEG-IFN/Ribavirin Treatment-experienced Patients, with Compensated Cirrhosis ‡

Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with weight-based ribavirin	24 weeks	IIa, B

‡ 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.

Daclatasvir plus sofosbuvir

Data are limited for treatment-experienced HCV genotype 3-infected patients with cirrhosis. In the ALLY-3 study, a suboptimal response to 12 weeks of daclatasvir plus sofosbuvir (SVR12 69% [9/13]) was seen (Nelson, 2015). In a follow-up study (ALLY-3+), 36 genotype 3 cirrhotic patients were randomized to daclatasvir plus sofosbuvir with ribavirin for 12 or 16 weeks. An on-treatment analysis showed similar SVR12 rates of 88% (15/17) and 89% (16/18), respectively, in the 12-week and 16-week treatment arms (Leroy, 2016). These data suggest at a minimum ribavirin should be included, if possible, for all cirrhotic patients treated with this regimen. For patients who are unable to access shorter duration or ribavirin-free regimens such as sofosbuvir plus elbasvir/grazoprevir or sofosbuvir/velpatasvir, treatment with daclatasvir plus sofosbuvir with ribavirin for 24 weeks is an alternative regimen that can be considered, especially for those who require immediate treatment.

Sofosbuvir/velpatasvir

The phase III ASTRAL-3 study evaluated the fixed-dose combination of sofosbuvir/velpatasvir for 12 weeks without ribavirin in 277 genotype 3-infected patients, including 71 with prior treatment experience and 80 with cirrhosis (Foster, 2015a). Despite a high combined SVR12 rate of 95% (264/277), both prior treatment (90% SVR) and cirrhosis (91% SVR) had a moderate negative impact on treatment responses. In the group with both cirrhosis and prior treatment the SVR12 rate was 89% (33/37). The addition of ribavirin did appear to increase SVR12 rates in a phase II study of treatment-experienced genotype 3 patients treated for 12 weeks with 25 or 100 mg of velpatasvir combined with sofosbuvir (Pianko, 2015). Based on this and analogous to the similar ALLY-3+ study, the addition of weight-based ribavirin (if not contraindicated) is recommended for cirrhotic genotype 3 patients when using sofosbuvir/velpatasvir pending additional data.

Baseline NS5A substitutions in genotype 3 also impact DAA treatment response, with the Y93H substitution being the most challenging. In the ALLY-3 study the Y93H was detected in 13 (9%) of patients with an SVR12 of 54% (7/13); including a 67% SVR12 in patients without cirrhosis. In the ASTRAL-3 study the Y93H was detected in 25 (9%) of patients with an SVR12 rate of 84% (21/25). Given that cirrhotic patients in whom prior treatment with PEG-IFN/ribavirin has failed are already recommended to have ribavirin added with or without extension of therapy depending on the specific regimen, baseline testing for NS5A RASs in genotype 3 would only impact treatment approaches for patients in whom prior treatment with PEG-IFN/ribavirin has failed without cirrhosis. Pending additional data, baseline NS5A RAS testing is recommended in all treatment-experienced genotype 3 patients without cirrhosis. If the Y93H substitution is identified, weight-based ribavirin should be added to the treatment course.

Elbasvir/grazoprevir plus sofosbuvir

In the C-ISLE study, patients (N=100) with genotype 3 infection and cirrhosis, including 53 who previously failed PEG-IFN/ribavirin, were randomized into 1 of 3 arms: elbasvir/grazoprevir plus sofosbuvir for 12 weeks, elbasvir/grazoprevir plus sofosbuvir plus weight-based ribavirin for 12 weeks, or elbasvir/grazoprevir plus sofosbuvir for 16 weeks (Foster, 2016b). All 3 arms had a 100% SVR on the per protocol analysis, with 17 patients in each arm. The efficacy was high regardless of the presence of baseline resistance association substitutions, including 3 patients with the Y93H.

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.

Last update: April 12, 2017

Sofosbuvir Experienced, Genotype 3 Patients

Recommended Regimens by evidence level and alphabetically for:

Genotype 3, Sofosbuvir-based Treatment-experienced Patients (No Prior NS5A Treatment)

RECOMMENDED	DURATION	RATING
Deferral of treatment is recommended, pending availability of data, for patients with HCV genotype 3, in whom previous treatment with a sofosbuvir-based regimen has failed (no prior NS5A treatment), who do not have cirrhosis,‡ and do not have reasons for urgent retreatment	NA	IIb, C
Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with weight-based ribavirin, regardless of cirrhosis status;‡ for patients who require urgent retreatment	24 weeks	IIb, C
Daily fixed-dose elbasvir (50 mg)/grazoprevir (100 mg) plus sofosbuvir (400 mg) with or without weight-based ribavirin, regardless of cirrhosis status;‡ for patients who require urgent retreatment	12 weeks to 16 weeks	IIb, C
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) plus	12 weeks	IIb, C

Recommended Regimens by evidence level and alphabetically for:

Genotype 3, Sofosbuvir-based Treatment-experienced Patients (No Prior NS5A Treatment)

weight-based ribavirin, regardless of cirrhosis status;‡ for patients who require urgent retreatment.		

‡ 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.

Daclatasvir plus sofosbuvir

In the ALLY-3 study, 7 patients previously treated with sofosbuvir-containing regimens (with ribavirin and/or PEG-IFN) were retreated with daclatasvir plus sofosbuvir for 12 weeks. Of these patients, 5 (71%) achieved an SVR12 (Nelson, 2015). Based on these limited data, 12 weeks of daclatasvir plus sofosbuvir may be insufficient, and extending the duration to 24 weeks of therapy and adding weight-based ribavirin is recommended.

Elbasvir/grazoprevir plus sofosbuvir plus ribavirin

The C-ISLE study included two patients who had failed prior sofosbuvir plus ribavirin. Both of these patients had a SVR12 (Foster, 2016b). Despite the paucity of data, this is a logical strategy, since all three directly acting antivirals in the regimen are known to have activity against genotype 3 infection and have shown high efficacy in other treatment-experienced patients with cirrhosis. The exact duration and need for ribavirin is not clear but due to the lack of extensive data, optimization with extended therapy and the addition of weight-based ribavirin is recommended when possible.

Sofosbuvir/velpatasvir

No data are available evaluating retreatment of patients with genotype 3 infection with sofosbuvir/velpatasvir, who previously failed treated with sofosbuvir plus ribavirin with or without PEG-IFN. However, retreatment with sofosbuvir/velpatasvir plus weight-based ribavirin for 12 weeks is a logical strategy in patients who require immediate treatment due to the general lack of treatment-emergent NS5B resistance substitutions in sofosbuvir regimen failures and the high efficacy of this regimen in phase 2 trials (Pianko, 2015).

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.

Last update: April 12, 2017

Treatment-experienced Genotype 4

The following pages include guidance for management of treatment-experienced patients with HCV Genotype 4.

- PEG-IFN/Ribavirin Experienced, Genotype 4 Patients Without Cirrhosis
- PEG-IFN/Ribavirin Experienced, Genotype 4 Patients with Compensated Cirrhosis

Last update: April 12, 2017

PEG-IFN/Ribavirin Experienced, Genotype 4 Patients Without Cirrhosis

Recommended Regimens by evidence level and alphabetically for:

Genotype 4, PEG-IFN/Ribavirin Treatment-experienced Patients, Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based ribavirin	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg); for patients who experienced virologic relapse after prior PEG-IFN/ribavirin therapy	12 weeks	IIa, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) and weight-based ribavirin; for genotype 4 patients with prior on-treatment virologic failure (failure to suppress or breakthrough) while on PEG-IFN/ribavirin	16 weeks	IIa, B
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	IIa, B

Paritaprevir/ritonavir/ombitasvir

PEARL-I was an open-label phase IIb study that included a cohort of 49 treatment-experienced patients with HCV genotype 4 infection without cirrhosis who received 12 weeks of paritaprevir, ritonavir, and ombitasvir (PrO) with or without weight-based ribavirin. In intention-to-treat analysis, SVR12 was achieved in 41 of 41 (100%) patients. This regimen was well tolerated with no serious adverse events reported (Hézode, 2015). The AGATE-II trial offered 100 treatment-naive and -experienced noncirrhotic patients with genotype 4 PrO plus weight-based ribavirin for 12 weeks. The SVR12 was 94%. These data continue to support the use of PrO plus ribavirin for 12 weeks in treatment-experienced genotype 4 patients (Esmat, 2015a).

Ledipasvir/sofosbuvir

In the SYNERGY trial, 20 patients with HCV genotype 4 infection were treated with ledipasvir/sofosbuvir for 12 weeks. Of these patients, 40% were treatment-experienced and 40% had advanced fibrosis. Preliminary data demonstrate efficacy, with 95% achieving SVR12 based on an intention-to-treat analysis (Kohli, 2015).

Sofosbuvir/velpatasvir

Velpatasvir is also active in vitro against genotype 4 and the combination of sofosbuvir/velpatasvir for 12 weeks was

evaluated in 116 genotype 4-infected patients included in the ASTRAL-1 study (Feld, 2015). 100% SVR12 was achieved, including 52 treatment-experienced patients.

Elbasvir/grazoprevir

An integrated analysis of all phase 2/3 elbasvir/grazoprevir studies demonstrated efficacy of this regimen for both treatment-naive (n=66) and -experienced (n=37) patients with genotype 4 HCV infection (Asselah, 2015). The overall SVR12 rate among treatment-experienced genotype 4 infected patients was 87% (32/37) with numerical response differences based on prior interferon treatment response (relapse vs on-treatment viral failure) and elbasvir/grazoprevir duration (12 vs 16 weeks) and/or ribavirin usage (no ribavirin vs ribavirin). Numbers within any specific subgroup are too small to make definitive recommendation; however, trends emerged that were used to guide the current recommendations pending additional data. No treatment failures were seen in patients who relapsed after prior PEG-IFN/ribavirin therapy, regardless of elbasvir/grazoprevir treatment duration or ribavirin usage. In contrast, response rates were numerically lower in patients with prior on-treatment virologic failure in the non-ribavirin-containing arms (12 weeks: 78%, 16 weeks: 60%) compared to ribavirin-containing treatment (12 weeks + ribavirin: 91%, 16 weeks + ribavirin: 100%). Given the lack of sufficient numbers to differentiate response between 12 weeks with ribavirin and 16 weeks with ribavirin, the use of 16 weeks plus ribavirin in genotype 4-infected patients with prior on-treatment virologic failure represents the most conservative approach.

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.

Last update: April 12, 2017

PEG-IFN/Ribavirin Experienced, Genotype 4 Patients with Compensated Cirrhosis

Recommended and Alternative Regimens by evidence level and alphabetically for:

Genotype 4, PEG-IFN/Ribavirin Treatment-experienced Patients, with Compensated Cirrhosis ‡

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based ribavirin†	12 weeks	I, A

Recommended and Alternative Regimens by evidence level and alphabetically for: **Genotype 4, PEG-IFN/Ribavirin Treatment-experienced Patients, with Compensated Cirrhosis** [‡]		
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg); for patients who experienced virologic relapse after prior PEG-IFN/ribavirin therapy	12 weeks	IIa, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) and weight-based ribavirin; for genotype 4 patients with prior on-treatment virologic failure (failure to suppress or breakthrough) while on PEG-IFN/ribavirin	16 weeks	IIa, B
Daily ledipasvir (90 mg)/sofosbuvir (400 mg) and weight-based ribavirin; for patients who are eligible for ribavirin.	12 weeks	IIa, B
ALTERNATIVE	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	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.

Paritaprevir/ritonavir/ombitasvir

The AGATE-I trial randomized 120 treatment-naive and -experienced patients with genotype 4 HCV and compensated cirrhosis to receive 12 weeks or 16 weeks of paritaprevir/ritonavir/ombitasvir (PrO) plus weight-based ribavirin. The SVR12 rates in the 12-week and 16-week arms were 96% and 100%, respectively. The regimens were well tolerated (Asselah, 2015a). Additionally, AGATE-II randomized 60 treatment-naive and -experienced genotype 4-infected patients with compensated cirrhosis to receive either 12 or 24 weeks of PrO plus weight-based ribavirin. The SVR12 rate from the 12-week arm, reported recently, was 97%. These data continue to support the use of PrO plus ribavirin for 12 weeks in treatment-experienced genotype 4 patients, including those with cirrhosis (Esmat, 2015a).

Ledipasvir/sofosbuvir

In the SYNERGY trial, 20 patients with HCV genotype 4 infection were treated with ledipasvir/sofosbuvir for 12 weeks. Of these patients, 40% were treatment-experienced and 40% had advanced fibrosis. Preliminary data demonstrate efficacy, with 95% achieving SVR12 based on an intention-to-treat analysis (Kohli, 2015).

Sofosbuvir/velpatasvir

Velpatasvir is also active in vitro against genotype 4 and the combination of sofosbuvir/velpatasvir for 12 weeks was evaluated in 116 genotype 4-infected patients included in the ASTRAL-1 study (Feld, 2015). 100% SVR12 was achieved, including 52 treatment-experienced patients.

Elbasvir/grazoprevir

An integrated analysis of all phase 2/3 elbasvir/grazoprevir studies demonstrated efficacy of this regimen for both treatment-naive (n=66) and -experienced (n=37) patients with genotype 4 HCV infection (Asselah, 2015). The overall SVR12 rate among treatment-experienced genotype 4-infected patients was 87% (32/37) with numerical response differences based on prior interferon treatment response (relapse vs on-treatment viral failure) and elbasvir/grazoprevir duration (12 vs 16 weeks) and/or ribavirin usage (no ribavirin vs ribavirin). Numbers within any specific subgroup are too small to make definitive recommendation; however, trends emerged that were used to guide the current recommendations pending additional data. No treatment failures were seen in patients who relapsed after prior PEG-IFN/ribavirin therapy, regardless of elbasvir/grazoprevir treatment duration or ribavirin usage. In contrast, response rates were numerically lower in patients with prior on-treatment virologic failure in the non-ribavirin-containing arms (12 weeks: 78%, 16 weeks: 60%) compared to ribavirin-containing treatment (12 weeks + ribavirin: 91%, 16 weeks + ribavirin: 100%). Given the lack of sufficient numbers to differentiate response between 12 weeks with ribavirin and 16 weeks with ribavirin, the use of 16 weeks plus ribavirin in genotype 4-infected patients with prior on-treatment virologic failure represents the most conservative approach.

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.

Last update: April 12, 2017

Treatment-experienced Genotype 5 or 6

Few data are available to help guide decision making for patients infected with HCV genotype 5 or 6. Thus, for those patients for whom immediate treatment is required, the following recommendations have been drawn from available data.

Recommended Regimens by evidence level and alphabetically for:

Genotype 5 or 6, PEG-IFN/Ribavirin Treatment-experienced Patients, with or Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	IIa, B
Daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	IIa, C

In the phase III NEUTRINO trial (Lawitz, 2013a), treatment-naive patients with HCV genotypes 1 (n=291), 4 (n=28), 5 (n=1), and 6 (n=6) were treated with sofosbuvir (400 mg daily) plus PEG-IFN (2a 180 µg weekly) and weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks. All six patients with HCV genotype 6 and the one patient with HCV genotype 5 achieved SVR12. The adverse event profile in these patients and in the larger study population was similar to that seen with PEG-IFN/ribavirin therapy.

Ledipasvir has in vitro activity against most HCV genotype 6 subtypes (exception 6e) (Wong, 2013); (Kohler, 2014). A small, two-center, open-label study (NCT01826981) investigated the safety and in vivo efficacy of ledipasvir/sofosbuvir for 12 weeks in treatment-naive and -experienced patients with HCV genotype 6 infection. Twenty-five patients (92% treatment-naive) who were primarily of Asian descent (88%) were infected with different subtypes of HCV genotype 6 (32%, 6a; 24%, 6e; 12%, 6l; 8%, 6m; 12%, 6p; 8%, 6q; 4%, 6r). Two patients (8%) had cirrhosis. The SVR12 rate was 96% (24/25). The 1 patient who experienced relapse had discontinued therapy at week 8 because of drug use. No patient discontinued treatment owing to adverse events.

Velpatasvir also has in vitro activity against HCV genotypes 5 and 6. The ASTRAL-1 study included 35 patients with genotype 5 and 41 patients with genotype 6, of those only 11 and 3, respectively, were treatment-experienced (Feld, 2015). All genotype 5 and 6 treatment-experienced patients treated with 12 weeks of sofosbuvir/velpatasvir achieved SVR12.

Because of their limited activity against HCV genotypes 5 and 6 in vitro and in vivo, neither boceprevir nor telaprevir should be used as therapy for patients with HCV genotype 5 or 6 infection.

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.

Last update: April 12, 2017