Peginterferon/Ribavirin-Experienced, Genotype 1a Patients With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

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\textsuperscript{a} For \textit{decompensated cirrhosis}, please refer to the appropriate section.

\textsuperscript{b} Includes genotype 1a RASs at amino acid positions 28, 30, 31, or 93 known to confer \textit{antiviral resistance to elbasvir}. Baseline testing for these RASs is recommended for patients receiving elbasvir/grazoprevir-based regimens.

\textsuperscript{c} Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

Recommended Regimens

Elbasvir/Grazoprevir

The daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) was evaluated in patients with a history of failed peginterferon/ribavirin therapy in the C-EDGE TE study. In this phase 3 trial, patients were randomized to 12 weeks or 16 weeks of elbasvir/grazoprevir, with or without ribavirin. Genotype 1 patients treated for 12 weeks without ribavirin had an overall SVR12 of 93.8\% (90/96), which was nearly identical to the response rate in patients treated for 12 weeks with added ribavirin (94.4\%, 84/89) (\textit{Kwo, 2017}). 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 (SVR12 with cirrhosis 95\% [19/20]; SVR12 without 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 RASs when assessed by population sequencing (25\% limit of detection). These RASs included substitutions at positions M28, Q30, L31, H58, and Y93. Among 21 genotype 1a patients with baseline NS5A...
RASs (>5 fold), only 52.4% (11/21) achieved SVR due to a higher relapse rate (Kwo, 2015).

A subsequent integrated analysis of phase 2 and phase 3 trials confirmed a lower SVR12 rate in treatment-experienced, genotype 1a patients with these specific baseline NS5A RASs (90%, 167/185) versus patients without baseline RASs (99%, 390/393) (Zeuzem, 2017). In patients treated with 12 weeks of elbasvir/grazoprevir without ribavirin, 64% (9/14) with baseline elbasvir NS5A RASs achieved SVR12 compared to 96% (52/54) among those without baseline RASs. Extension of therapy to 16 weeks or 18 weeks with the addition of weight-based ribavirin increased the response rate to 100% regardless of the presence of baseline NS5A RASs, suggesting this approach can overcome the negative impact of NS5A RASs seen with the 12-week regimen (Jacobson, 2015b).

Based on the known inferior response in patients with specific NS5A RASs, NS5A resistance testing is recommended in genotype 1a patients being considered for elbasvir/grazoprevir therapy. 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 relapse risk. A prospective real-world study confirmed high response rates based on this approach (Braun, 2019). Given the need for ribavirin and the prolonged duration of therapy in the presence of key NS5A RASs as well as multiple preferred regimens, elbasvir/grazoprevir plus ribavirin for 16 weeks has been removed as an alternative regimen. Lack of access to RAS testing or results should not be used as a means to limit access to HCV therapy.

**Sofosbuvir/Velpatasvir**

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naive and -experienced patients with genotype 1, 2, 4, 5, or 6 treated with sofosbuvir (400 mg)/velpatasvir (100 mg) as a daily 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 overall response rate among genotype 1 treatment-experienced patients was 99% (109/110), with 100% (78/78) among participants with genotype 1a and 97% (31/32) in those with genotype 1b. Among patients previously treated with peginterferon/ribavirin, 98% (50/51) achieved SVR12; 100% (48/48) of those previously treated with a DAA plus peginterferon/ribavirin achieved SVR12. The single treatment-experienced patient who did not respond to this regimen was a genotype 1b, black adult with cirrhosis and IL28 TT genotype. This individual had a persistently detectable HCV viral load during previous peginterferon/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%) versus the placebo group (77%).

**Glecaprevir/Pibrentasvir**

The EXPEDITION-1 trial investigated use of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 12 weeks in 146 patients with compensated cirrhosis infected with genotype 1, 2, 4, 5, or 6. Twenty-five percent (36/146) of enrolled patients were non-DAA treatment experienced. SVR12 was 98.9% (89/90) among genotype 1 patients. The single treatment failure occurred in a patient with genotype 1a who relapsed at post-treatment week 8 (Forns, 2017). Ninety-one percent of patients (133/146) had a Child-Pugh score of 5 and 9% (13/146) had a Child-Pugh score of 6. Twenty percent of patients had a platelet count <100 x 10^9/L and all but 1 participant had a normal albumin level. In this patient population with compensated cirrhosis, the regimen was safe and well tolerated. There were 11 serious adverse events; none were DAA-related and no adverse events led to discontinuation of the study drugs. Glecaprevir/pibrentasvir is a safe and highly efficacious 12-week regimen in patients with well-compensated cirrhosis.

**Alternative Regimen**

**Ledipasvir/Sofosbuvir + Ribavirin**

The double-blind, placebo-controlled, phase 2 SIRIUS trial enrolled genotype 1 patients with compensated cirrhosis who did not achieve SVR12 with peginterferon/ribavirin plus telaprevir or boceprevir. Participants were randomized to either 12 weeks of placebo followed by 12 weeks of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus ribavirin, or ledipasvir/sofosbuvir plus placebo for 24 weeks. The SVR12 rates were similar in the study arms: 96% (74/77) in the group that received ledipasvir/sofosbuvir plus ribavirin for 12 weeks (3 relapses), and 97% (75/77) in the group that
received ledipasvir/sofosbuvir for 24 weeks (2 relapses) (Bourliere, 2015).

These findings are further supported by a post hoc analysis of treatment-naive or -experienced, genotype 1 patients with compensated cirrhosis who were treated with ledipasvir/sofosbuvir in phase 2 and phase 3 studies (including the SIRIUS trial). In this analysis, ledipasvir/sofosbuvir for 12 weeks was inferior to ledipasvir/sofosbuvir plus ribavirin for 12 weeks. Safety and tolerability were similar in the groups and, apart from anemia, reported adverse events did not differ substantially between patients treated with or without ribavirin (Reddy, 2015). Due to the need for ribavirin, this regimen is recommended as an alternative for genotype 1 patients with compensated cirrhosis and a history of peginterferon/ribavirin treatment failure.

Baseline NS5A RASs adversely impact response to ledipasvir/sofosbuvir therapy. The magnitude of impact varies based on several 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 more than 350 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 a lower SVR12 compared to those without baseline RASs (Zeuzem, 2017). The SVR12 rates were 89% with RASs versus 96% in the absence of RASs with a 12-week course of ledipasvir/sofosbuvir plus ribavirin, and 87% versus 100%, respectively, with a 24-week course of ledipasvir/sofosbuvir without ribavirin. The impact of baseline RASs is likely greater in a genotype 1a only population.

Given the vulnerable nature of this population, baseline NS5A resistance testing should be considered for genotype 1a treatment-experienced patients with compensated cirrhosis prior to use of ledipasvir/sofosbuvir. If ledipasvir-associated RASs are detected, a different regimen should be used to optimize treatment response.

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**Related References**


