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**
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.

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