

Treatment-naive Genotype 3 with Compensated Cirrhosis

Recommended Regimens by evidence level and alphabetically for:

Genotype 3, Treatment-naive Patients, with Compensated Cirrhosis † ⓘ

RECOMMENDED	DURATION	RATING ⓘ
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	Ila, 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.

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

Daclatasvir + sofosbuvir

Daclatasvir with sofosbuvir for 12 weeks was approved by the FDA for treatment of HCV genotype 3 infection. The recommendation is based on ALLY-3, a phase III study of the once-daily NS5A inhibitor daclatasvir plus sofosbuvir for 12 weeks; the study included 101 treatment-naive patients and demonstrated an SVR12 rate of 90%. In treatment-naive patients without cirrhosis (Metavir F0-F3), 97% achieved SVR12, and in treatment-naive patients with cirrhosis (Metavir F4), 58% achieved SVR12 ([Nelson, 2015](#)). This suggests that patients with genotype 3 infection and cirrhosis are likely to benefit from an extension of therapy. This has been confirmed in cohort studies, including the European compassionate-use program, which reported SVR12 rates of 70% versus 86% when daclatasvir and sofosbuvir were used for 12 weeks and 24 weeks in HCV genotype 3-infected patients with cirrhosis, respectively. The role of ribavirin could not be clarified, as only 4 patients received daclatasvir plus sofosbuvir and ribavirin for 12 weeks, all of which achieved SVR12. SVR12 was comparable between the 24-week arms irrespective of the addition of ribavirin (85.9% [116/135] without compared to 81.3% [39/48] with ribavirin). SVR12 rates were also higher in those with compensated Child-Pugh A cirrhosis (85%-90% compared to 70.6% in Child B/C). Again the addition of ribavirin did not increase SVR12 rates in the 24-week arms ([Hézode, 2017](#)). 73% of patients were treatment-experienced, however earlier data suggested that SVR12 rates were higher in treatment-naive patients (91%-100%) compared to experienced (81%-82%). SVR12 rates were similar in those that received ribavirin (88%, 29/33) and those that did not (86%, 42/49) ([Hézode, 2017](#)).

The exact duration of therapy for a treatment-naive genotype 3 patient with compensated cirrhosis is not known. The phase III study, ALLY3+, investigated the combination of daclatasvir plus sofosbuvir and ribavirin for 12 weeks or 16 weeks in treatment-naive and -experienced genotype 3 patients with both stage 3 and compensated cirrhosis. Overall SVR12 rates were 86% with cirrhosis, the majority of which were treatment experienced. Extending the duration to 16 weeks did not have a strong impact with 88% (15/17) achieving SVR12 with 12 weeks and 89% (16/18) achieving SVR12 with 16 weeks. All 14 patients with stage 3 disease achieved SVR12 irrespective of treatment duration ([Leroy, 2016](#)).

Presence of baseline NS5A RASs significantly reduces rates of SVR12 with a 12-week course of daclatasvir plus sofosbuvir in genotype 3-infected patients. In analysis of 175 subjects infected with HCV genotype 3 and nucleotide sequence data in the ALLY-3 trial, the presence of a NS5A Y93H substitution was associated with a reduced SVR12 rate; 54% (7/13) compared to 92% (149/162). Although the small numbers make interpretation difficult, only 7% (13/175) had

NS5A Y93H substitution, all of which were subgenotype 3a. SVR rates were numerically lower in those with both cirrhosis and Y93H. In non-cirrhotic subjects with Y93H, 67% (6/9) achieved SVR12 compared to 98% (125/128) of those non-cirrhotic without Y93H. In those with both cirrhosis and Y93H, 25% (1/4) achieved SVR12 compared to 71% (24/34) in those with cirrhosis but without the substitution ([Daclatasvir PI, 2016](#)). Substitutions at A30K, L31F, L31I in genotype 3a replicon are associated with reduced daclatasvir susceptibility ([Daclatasvir PI, 2016](#)). In the ALLY-3 trial, subjects with A30K and without cirrhosis achieved 100% SVR12 (9/9), however those with cirrhosis had lower SVR12 rates (1/5) ([Nelson, 2015](#)). The impact of this single substitution is difficult to discern as 2/5 had compound substitutions with Y93H. Pending further data on optimal therapy in the setting of baseline Y93 substitution, the addition of ribavirin for patients with cirrhosis is recommended.

Additional real-world studies support the use of this regimen for treatment-naive, genotype-3 infected patients with advanced liver disease ([Welzel, 2016](#)).

Sofosbuvir/velpatasvir

Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of HCV genotype 3 infection in patients with and without cirrhosis. ASTRAL-3 demonstrated superiority of 12 weeks of sofosbuvir/velpatasvir to 24 weeks sofosbuvir plus ribavirin in 552 treatment-naive and -experienced subjects with and without cirrhosis ([Foster, 2015a](#)). In those with cirrhosis SVR12 was 93% (40/43) compared to 73% (33/45), respectively. Of the 250 subjects that received sofosbuvir/velpatasvir 43 (16%) had baseline NS5A RASs; of which 88% achieved SVR12 compared to 97% without baseline substitutions. 84% (21/25) with Y93H achieved SVR12. Pending further data on optimal therapy in the setting of baseline Y93 substitution, the addition of ribavirin for patients with cirrhosis is recommended.

Elbasvir/grazoprevir + sofosbuvir

C-SWIFT investigated the efficacy of triple therapy with the daily fixed-dose combination of elbasvir/grazoprevir and sofosbuvir (400 mg) for 8 weeks to 12 weeks in genotype 3 treatment-naive patients with and without compensated cirrhosis. 93% (14/15) of non-cirrhotic patients achieved SVR12 with 8 weeks and 100% (14/14) with 12 weeks of this combination. 91% (10/11) compensated cirrhotic subjects achieved SVR12 with 12 weeks of therapy ([Poordad, 2016](#)).

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 pangentypic regimen should be considered. When the correct combination or duration is unclear, expert consultation should be sought.

Last update: April 12, 2017