Treatment-naive Genotype 3 Without Cirrhosis

Recommended Regimens by evidence level and alphabetically for:

Genotype 3, Treatment-naive 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.

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 or 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).

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.

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 treatment-naive, non-cirrhotic subjects, SVR12 rates were 98% (160/163) compared to 90% (141/156), respectively. 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 pangenotypic regimen should be considered. When the correct combination or duration is unclear, expert consultation should be sought.

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