Treatment-naive Genotype 1b Without Cirrhosis

Recommended Regimens by evidence level and alphabetically for:

Genotype 1b, Treatment-naive 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 ledipasvir (90 mg)/sofosbuvir (400 mg); for patients who are non-black, HIV-uninfected, and whose HCV RNA level is <6 million IU/mL	8 weeks	I, B
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	I, 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.

For HCV genotype 1b-infected, treatment-naive patients without cirrhosis, there are six regimens of comparable efficacy, as outlined above. For cirrhotic patients, some are classified as Alternative regimens, because compared to the Recommended, they have longer duration, potentially reduced efficacy, and/or limited supporting data.

There are no significant differences demonstrated to date in treatment responses to daclatasvir and sofosbuvir, ledipasvir/sofosbuvir, or sofosbuvir/velpatasvir for HCV genotype 1 subtypes, thus the supporting evidence remains the same as for HCV genotype 1a-infected patients (see Genotype 1a). In the ALLY-2 arm of daclatasvir and sofosbuvir for 12 weeks in treatment-naive patients, only 12 were genotype 1b and all achieved SVR12 (Wyles, 2015). Furthermore, in the ALLY-1 study all 11 genotype 1b-infected patients with advanced cirrhosis achieved SVR12. Due to the limited numbers of genotype 1b patients represented in the phase III trials of this regimen, there is not enough evidence to support a different approach by subtype at this time.

For elbasvir/grazoprevir, 99% of genotype 1b (129/131) patients receiving 12 weeks achieved SVR in the phase III C-EDGE trial (Zeuzem, 2015c). In contrast to genotype 1a, the presence of baseline substitutions associated with NS5A resistance did not appear to affect response to elbasvir/grazoprevir. Thus, current data do not support extending the duration or adding ribavirin in genotype 1b patients with NS5A resistance-associated substitutions. PrOD (plus ribavirin for those with cirrhosis) was approved by the FDA for the treatment of HCV genotype 1b infection in treatment-naive patients based on three registration trials: SAPPHIRE-I (151 treatment-naive patients with HCV genotype 1b and without

cirrhosis), PEARL-III (419 treatment-naive patients, all with genotype 1b and without cirrhosis), and TURQUOISE-II (119 treatment-naive and -experienced patients with genotype 1b with cirrhosis). SAPPHIRE-I reported a high SVR12 rate (98%) with 12 weeks of PrOD and ribavirin in patients with HCV genotype 1b (Feld, 2014). Given the high SVR12 rates seen in SAPPHIRE-I, PEARL-III was specifically designed to determine the role of weight-based ribavirin with PrOD in treatment-naive patients with HCV genotype 1b without cirrhosis (Ferenci, 2014). SVR12 rate was 99% in both arms, confirming that there is no added benefit from the use of weight-based ribavirin for patients without cirrhosis who have HCV genotype 1b infection. GARNET, a phase 3b single-arm study of 163 genotype 1b patients without cirrhosis, demonstrated a 98% SVR rate with an 8-week duration of PrOD. When considering the generalizability of these results, it is important to note that 91% of the GARNET participants had fibrosis stage F0-F2, 93% had HCV RNA levels <6,000,000 IU/mL, and 96% were white. In addition, 2 of the 15 patients with fibrosis stage F3 experienced virologic relapse, suggesting that if used, an 8-week strategy should be reserved for those with early stage fibrosis (Welzel, 2016).

To date, there is no measurable difference demonstrated in treatment response to simeprevir plus sofosbuvir for HCV genotype 1 subtypes (with the exception of patients with genotype 1a with cirrhosis who also have the baseline Q80K substitution described above), thus the supporting evidence remains the same as for HCV genotype 1a-infected patients (see Genotype 1a).

The safety profiles to date of all recommended regimens above appear favorable. Across numerous phase III programs, less than 1% of patients without cirrhosis discontinued treatment early and adverse events were mild. Most adverse events occurred in ribavirin-containing arms. Discontinuation rates were higher for patients with cirrhosis (approximately 2% for some trials) but still very low.

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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