NS5A Experienced Genotype 1 Patients

Recommended Regimens by evidence level and alphabetically for:

Genotype 1, NS5A Inhibitor Treatment-experienced Patients

RECOMMENDED	RATING
Deferral of treatment is recommended, pending availability of data for patients with HCV genotype 1, regardless of subtype, in whom previous treatment with any HCV nonstructural protein 5A (NS5A) inhibitors has failed, who do not have cirrhosis, and do not have reasons for urgent retreatment.	IIb, C
Testing for resistance-associated substitutions that confer decreased susceptibility to NS3 protease inhibitors and to NS5A inhibitors is recommended for patients with HCV genotype 1, regardless of subtype, in whom previous treatment with any HCV nonstructural protein 5A (NS5A) inhibitors has failed, and who have compensated cirrhosis,‡ or have reasons for urgent retreatment. The specific drugs used in the retreatment regimen should be tailored to the results of this testing as described below.	IIb, C
When using nucleotide-based (eg, sofosbuvir) dual DAA therapy a treatment duration of 24 weeks is recommended, and weight-based ribavirin, unless contraindicated, should be added.	IIb, C
If available, nucleotide-based (eg, sofosbuvir) triple or quadruple DAA regimens may be considered. In these settings treatment duration ranges from 12 weeks to 24 weeks (see text), and weight-based ribavirin, unless contraindicated, are recommended.	IIb, C

‡ For decompensated cirrhosis, please refer to the appropriate section.

Ledipasvir/sofosbuvir failures

Data on the retreatment of patients for whom prior treatment with ledipasvir/sofosbuvir has failed are very limited. In a pilot study, 41 patients with and without cirrhosis who did not achieve an SVR with 8 weeks or 12 weeks of ledipasvir/sofosbuvir were retreated with 24 weeks of ledipasvir/sofosbuvir (Lawitz, 2015b). SVR12 rates varied according to the presence or absence of NS5A inhibitor RASs. Among 11 patients for whom NS5A inhibitor RASs were not detected, SVR occurred in 11 of 11 (100%); in contrast, among 30 patients for whom NS5A inhibitor RASs were detected, SVR occurred in 18 of 30 (60%). Importantly, NS5B inhibitor RASs (eg, S282T) known to confer decreased activity of sofosbuvir were observed in 3 of 12 (25%) patients for whom the retreatment regimen was not successful (Lawitz, 2015b). Similarly, in the OPTIMIST-2 study in which patients with cirrhosis were treated with simeprevir and sofosbuvir, the presence of NS3 RASs, namely the Q80K substitution, led to a decreased SVR rate in patients with HCV genotype 1a infection. SVR occurred in 25 of 34 (74%) patients with HCV genotype 1a and the Q80K RAS and in 35 of 38 (92%) patients with HCV genotype 1a without the Q80K RAS (Lawitz, 2016b). Based on these data, retreatment for patients for whom an NS5A inhibitor-containing regimen has failed should be considered in the context of retreatment urgency and the presence or absence of RASs to inhibitors of NS3 and NS5A. Further, based on limited data, ribavirin is recommended as part of all retreatment regimens for patients in whom prior treatment with NS5A inhibitors has failed. Although no data exist, consideration may also be given to the addition of PEG-IFN to the retreatment regimen in patients who are eligible for this agent; PEG-IFN will have antiviral activity regardless of the RASs present.

Retreatment approach and potential regimens (including other NS5A regimen containing failures)

For patients with cirrhosis or other patients who require retreatment urgently, testing for RASs that confer decreased susceptibility to NS3 protease inhibitors (eg, Q80K) and to NS5A inhibitors should be performed using commercially available assays prior to selecting the next HCV treatment regimen. For patients with no NS5A inhibitor RASs detected, retreatment with ledipasvir/sofosbuvir or sofosbuvir/velpatasvir, both with ribavirin, for 24 weeks is recommended. For patients who have NS5A inhibitor RASs detected and who do not have NS3 inhibitor RASs detected, treatment with simeprevir, sofosbuvir, and ribavirin for 24 weeks is recommended. For patients who have both NS3 and NS5A inhibitor RASs detected there are several small studies that provide some insight on salvage regimens. Limited data suggest a retreatment approach based on sofosbuvir combined with either elbasvir/grazoprevir or PrOD may be efficacious (Lawitz, 2015e); (Poordad, 2015a). In a retreatment arm of the C-SWIFT study, 23 patients who had failed shorter courses of elbasvir/grazoprevir plus sofosbuvir were retreated with 12 weeks of this combination plus weight-based ribavirin. In a per protocol analysis a 100% SVR12 rate was achieved (23/23), including SVR in 9/9 patients with dual NS3 and NS5A RASs (Lawitz, 2015e). A second phase II study of 22 patients, including 14 PrOD failures, evaluated retreatment with 12-24 weeks of PrOD plus sofosbuvir. Treatment duration and ribavirin usage were determined by cirrhosis status, HCV RNA response on therapy, and genotype subtype. SVR12 data was available on 15 patients with 14/15 (93%) attaining SVR12. Based on these limited data, patients with dual NS3 and NS5A class RASs may be retreated with elbasvir/grazoprevir plus sofosbuvir with weight-based ribavirin for 12 weeks or PrOD plus sofosbuvir for 12 weeks in genotype 1b and 24 weeks with weight-based ribavirin in those with genotype 1a. If these regimens are unavailable, retreatment should be conducted in a clinical trial setting, as an appropriate treatment regimen cannot be recommended at this time. Another approach in patients with prior non-response to NS5A-containing therapy has been studied in genoptype 1, 2, and 3 patients who did not respond to velpatasvir-containing regimens including sofobuvir/velpatasvir and sofosbuvir/velpatasvir/GS-9857 (Gane, 2016). Retreatment with sofosbuvir/velpatasvir with ribavirin for 24 weeks yielded high overall response rates (91% or 59/65). Among genotype 1 patients, 97% (33/34) achieved SVR. Baseline NS5A RASs did not appear to effect SVR rates. In 34 genotype 1 patients, 6 patients had NS5A RASs prior to retreatment, all of whom achieved SVR. Although data are extremely limited, retreatment with sofosbuvir/velpatasvir + ribavirin for 24 weeks should be considered in genotype 1 patients who have not responded to prior NS5A-based therapy, especially if there is urgency for treatment.

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.

Last update: April 12, 2017