Treatment of HCV Genotype 3

This is a PDF version of the following document:
Module 5: Treatment of Chronic Hepatitis C Infection
Lesson 3: Treatment of HCV Genotype 3

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Introduction

Background: Approximately 10% of all hepatitis C virus infections in the United States result from genotype 3 infection. Accordingly, less extensive clinical trial data exists for genotype 3 than with genotype 1. Patients with HCV genotype 3, when compared with HCV non-3 genotypes, have relatively faster rates of fibrosis progression, higher prevalence of severe (Grade 3) steatosis, and a higher incidence of hepatocellular carcinoma. In the current direct-acting antiviral therapy era, patients with genotype 3 infection have been relatively difficult to treat compared with other genotypes, especially in patients with cirrhosis. Recent data with sofosbuvir-velpatasvir are very encouraging, with SVR rates of 97% in treatment-naive patients and 90% in treatment-experienced patients. The cost of recommended therapy for genotype 3 infection ranges from $74,760 to $295,000 (Figure 1). The following discussion regarding initial treatment and retreatment of patients with genotype 3 chronic hepatitis C assumes the patient and their clinician have already made the decision to initiate hepatitis C therapy.

Medications used to Treat Hepatitis C: The HCV Medications section on this web site provides detailed information for each of the FDA-approved medications listed in the treatment recommendations, including links to the full prescribing information and to patient assistance programs. Adherence with the treatment regimen is of paramount importance. Thus, patients should receive detailed counseling regarding the importance of adherence prior to starting therapy, as well as intensive monitoring and follow-up during therapy.

Genotype 3: Initial Treatment

Background: Clinical trials involving patients with genotype 2 or 3 infection have examined the efficacy of sofosbuvir plus weight-based ribavirin given for 12 to 16 weeks and have reported substantially lower SVR rates (30 to 60%) in patients with genotype 3 than with genotype 2 infection. The relatively lower SVR rates with genotype 3 were improved by using a 12-week course of sofosbuvir plus ribavirin plus peginterferon, or extending the all-oral sofosbuvir plus ribavirin regimen to 24 weeks. The dual DAA combination of daclatasvir plus sofosbuvir proved more efficacious than sofosbuvir plus ribavirin combination, but required a longer duration (16 or 24 weeks) in cirrhotic genotype 3 patients; the role of ribavirin remained unclear when duration was extended. Most recently, velpatasvir-sofosbuvir has demonstrated excellent SVR rates in treatment-naive genotype 3 patients, including those with compensated cirrhosis.

Factors to Consider Prior to Choosing Initial Treatment Regimen: For patients chronically infected with genotype 3 hepatitis C, three factors should be considered when choosing the initial treatment regimen and duration: baseline NS5A resistance (for naive cirrhotics or treatment-experienced non-cirrhotics, presence or absence of cirrhosis, and cost. The management of genotype 3 patients with decompensated cirrhosis, renal impairment, HIV coinfection, acute hepatitis C infection, or post-liver transplantation is not addressed in this lesson.

AASLD/IDSA Guidance (see Initial Treatment of HCV Infection**):** The following is a summary of joint recommendations issued by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA). The recommendations listed below are for patients with hepatitis C genotype 3 infection who are treatment naive.

Genotype 3: Initial Treatment
Table 1. Treatment-Naive Patients

Recommended regimens are listed in groups by level of evidence, then alphabetically.

Recommended for Genotype 3 patients without Cirrhosis

Daclatasvir *60 mg* once daily for 12 weeks*	+	**Sofosbuvir** *400 mg once daily for 12 weeks*

Rating: Class I, Level A
Note: *The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. See the daclatasvir prescribing information for details.

Recommended for Genotype 3 patients without Cirrhosis

Sofosbuvir-Velpatasvir
Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) one tablet once daily for 12 weeks

Rating: Class I, Level A

Recommended

Recommended for Genotype 3 patients with Compensated Cirrhosis

Sofosbuvir-Velpatasvir ±

Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) one tablet once daily for 12 weeks

Genotype 3: Retreating Persons who Failed Prior Therapy

Background: Genotype 3 infection has emerged as the most challenging of all HCV genotypes to treat in this interferon-free era, particularly in patients with prior treatment failure and cirrhosis. In treatment-experienced genotype 3 patients, clinical experience combined with limited data from clinical trials to date have suggested the regimen of sofosbuvir plus ribavirin may be suboptimal, with an estimated response rate of 80% among cirrhotics with the 24-week regimen. There are now several options for retreatment of patients with genotype 3 infection who failed either prior peginterferon plus ribavirin regimen or prior sofosbuvir-based therapy.

Factors to Consider Prior to Choosing Retreatment Regimen: For retreatment of patients with genotype 3 hepatitis C, several factors influence the regimen choice, including the prior regimen failed, presence or absence of cirrhosis, and medication cost. The retreatment of genotype 3 patients with decompensated cirrhosis, renal impairment, acute hepatitis C infection, or post-liver transplantation is not addressed in this lesson.

AASLD/IDSA Guidance (see Retreatment of Persons in Whom Prior Therapy has Failed**):** The following is a summary of joint recommendations issued by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA). The recommendations listed below are for patients with hepatitis C genotype 3 infection who are treatment experienced and failed prior therapy with either (1) peginterferon plus ribavirin or (2) sofosbuvir plus ribavirin.

Genotype 3: Retreatment

Table 2. Peginterferon plus Ribavirin Treatment-Experienced Patients

Recommended regimens are listed in groups by level of evidence, then alphabetically.

Recommended for Retreatment of Genotype 3 patients without Cirrhosis

Daclatasvir *60 mg* once daily for 12 weeks*	+	**Sofosbuvir** *400 mg once daily for 12 weeks*

RAV testing for Y93H is recommended and ribavirin should be included in regimen if present.

Rating: Class I, Level A

Note: *The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. See the daclatasvir prescribing information for detailed information.

Recommended for Retreatment of Genotype 3 patients without Cirrhosis

Sofosbuvir-Velpatasvir
Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) one tablet once daily for 12 weeks

RAV testing for Y93H is recommended and ribavirin should be included in regimen if present.

Rating: Class I, Level A

Recommended

Recommended for Retreatment of Genotype 3 patients with Compensated Cirrhosis

Sofosbuvir-Velpatasvir +

Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) one tablet once daily for 12 weeks

Genotype 3: Treatment Regimens under Study

Treatment Regimens under Study for Patients with HCV Genotype 3: The following list includes several treatment regimens under study that are not currently recommended in the AASLD/IDSA guidance.

- **Ledipasvir-Sofosbuvir**: In the ELECTRON-2 trial, 51 treatment-naive patients with genotype 3 HCV were randomized to receive ledipasvir-sofosbuvir (n = 25) or ledipasvir-sofosbuvir plus ribavirin (n = 25). The study included patients with cirrhosis, but only 15% of the genotype 3 patients had cirrhosis. In the treatment arm that included ribavirin, 25 (100%) achieved an SVR12, compared with 16 (64%) in the arm without ribavirin. In a separate study, investigators used a 12-week course of ledipasvir-sofosbuvir plus ribavirin for 50 treatment-experienced patients with genotype 3 HCV, including those with cirrhosis. Overall, SVR12 was achieved in 82% of the patients, including 89% in those without cirrhosis and 73% in those with cirrhosis. Although these data suggest some efficacy with this regimen, its comparability relative to the standard of care is not established and neither the FDA nor AASLD have approved its use for genotype 3 patients.
- **Paritaprevir-Ritonavir plus ABT-530 and Ribavirin**: This phase 2, open-label trial is examined a 12-week course of the paritaprevir-ritonavir plus the investigational pangenotypic NS5A inhibitor ABT-530, with ribavirin in 10 treatment-naive, non-cirrhotic patients with genotype 3a infection. Nine (90%) of the 10 patients achieved an SVR at post-treatment weeks 12 and 24.
- **Voxilaprevir (formerly GS-9857) plus Sofosbuvir plus Velpatasvir**: The regimen of the investigational NS3/4a protease inhibibitor, voxilaprevir, in combination with sofosbuvir and velpatasvir has been shown in phase 2 trial to have excellent SVR rates in treatment-naive and treatment-experienced patients with HCV genotype 1-6.
- **ABT-493 and ABT-530**: A next-generation NS3/4A protease inhibitor, ABT-493, which is distinctive in its pangenotypic activity is also being evaluated with ABT-530 in patients with genotype 2 or 3 infection.

Summary Points

- In the new direct-acting antiviral treatment era, genotype 3 has emerged as the most difficult genotype to treat.
- For treatment-naive patients without cirrhosis, two regimens are recommended with equal rating: (1) daclatasvir plus sofosbuvir for 12 weeks, or (2) sofosbuvir-velpatasvir for 12 weeks.
- For treatment-naive patients with compensated cirrhosis, two regimens are recommended: (1) sofosbuvir-velpatasvir for 12 weeks, or (2) daclatasvir plus sofosbuvir, with or without ribavirin for 24 weeks. Baseline NS5A genotype 3 resistance testing should be performed, and ribavirin should be added to sofosbuvir-velpatasvir or sofosbuvir plus daclatasvir if the Y93H mutation is detected. The sofosbuvir-velpatasvir has a higher rating and is much less expensive. .
- For treatment-experienced patients without cirrhosis, two regimens are recommended with equal rating: (1) daclatasvir plus sofosbuvir for 12 weeks, or (2) sofosbuvir-velpatasvir for 12 weeks. Baseline NS5A genotype 3 resistance testing should be performed, and ribavirin should be added to daclatasvir plus sofosbuvir or sofosbuvir-velpatasvir if the Y93H mutation is detected.
- For treatment-experienced patients with compensated cirrhosis, two regimens are recommended: (1) sofosbuvir-velpatasvir plus ribavirin for 12 weeks, or (2) daclatasvir plus sofosbuvir plus ribavirin for 24 weeks. The sofosbuvir-velpatasvir plus ribavirin has a higher rating and is much less expensive than daclatasvir plus sofosbuvir plus ribavirin.
- The recommended regimen for genotype 3 treatment-experienced patients who have failed prior treatment with sofosbuvir consists of (1) daclatasvir plus sofosbuvir plus ribavirin for 24 weeks, or (2) sofosbuvir-velpatasvir plus ribavirin for 12 weeks.
- For treatment-naïve patients with compensated cirrhosis and treatment-experienced non-cirrhotic patients, baseline NS5A genotype 3 resistance testing should be performed, and ribavirin added to sofosbuvir-velpatasvir or sofosbuvir plus daclatasvir if the Y93H mutation is detected.
- Regimens under study for genotype 3 include (a) ledipasvir-sofosbuvir, (b) paritaprevir-ritonavir plus the investigational NS5A inhibitor ABT-530, and (c) the combination of ABT-530 and ABT-493.

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Figures

Figure 1 Cost of Medication Regimens used to Treat Genotype 3 Chronic HCV

This figure shows the approximate cost of different regimens used for treatment-naive and/or treatment-experienced patients with genotype 3 chronic HCV. Cost based on available wholesale acquisition price data and estimates shown for patients without cirrhosis and with compensated cirrhosis.

Estimated Cost of Regimens for Treatment HCV GT 3 HCV	
Regimen and Duration of Therapy	**Cost of Regimen***
GT 3 HCV without Cirrhosis	
Daclatasvir + Sofosbuvir x 12 weeks	$147,000
Sofosbuvir-Velpatasvir x 12 weeks	$74,760
GT 3 HCV with Compensated Cirrhosis	
Sofosbuvir-Velpatasvir x 12 weeks +/- Ribavirin	$74,760
Daclatasvir + Sofosbuvir x 24 weeks +/- Ribavirin	$294,000
*Cost estimates based on Wholesale Acquisition Cost (WAC)	

Genotype 3: Initial Treatment
Table 1. Treatment-Naive Patients

Recommended regimens are listed in groups by level of evidence, then alphabetically.

Recommended for Genotype 3 patients without Cirrhosis

Daclatasvir *60 mg* once daily for 12 weeks*	+	**Sofosbuvir** *400 mg once daily for 12 weeks*		

Rating: Class I, Level A
Note: *The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. See the daclatasvir prescribing information for details.

Recommended for Genotype 3 patients without Cirrhosis

Sofosbuvir-Velpatasvir *Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) one tablet once daily for 12 weeks*

Rating: Class I, Level A

Recommended

Recommended for Genotype 3 patients with Compensated Cirrhosis

Sofosbuvir-Velpatasvir *Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) one tablet once daily for 12 weeks*	±	**Ribavirin** *1000 mg if <75 kg or 1200 mg if ≥75 kg for 12 weeks*		

RAV testing for Y93H is recommended for cirrhotic patients and ribavirin should be included in the regimen if the Y93H is present.
Rating: Class I, Level A

Recommended for Genotype 3 patients with Compensated Cirrhosis

Daclatasvir *60 mg* once daily for 24 weeks*	+	**Sofosbuvir** *400 mg once daily for 24 weeks*	±	**Ribavirin** *1000 mg if <75 kg or 1200 mg if ≥75 kg for 24 weeks*

RAV testing for Y93H is recommended for cirrhotic patients and ribavirin should be included in the regimen if the Y93H is present.
Rating: Class IIa, Level B
Note: (i) *The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively; see the daclatasvir prescribing

information for details. (ii) The ribavirin daily dose is given in two divided doses.

Source: AASLD/IDSA. Recommendations for testing, management, and treating hepatitis C. Initial treatment of HCV infection. [AASLD/IDSA Hepatitis C Guidance] - Accessed March 10, 2017.

Genotype 3: Retreatment
Table 2. Peginterferon plus Ribavirin Treatment-Experienced Patients

Recommended regimens are listed in groups by level of evidence, then alphabetically.

Recommended for Retreatment of Genotype 3 patients without Cirrhosis

Daclatasvir *60 mg* once daily for 12 weeks* + **Sofosbuvir** *400 mg once daily for 12 weeks*

RAV testing for Y93H is recommended and ribavirin should be included in regimen if present.

Rating: Class I, Level A

Note: *The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. See the daclatasvir prescribing information for detailed information.

Recommended for Retreatment of Genotype 3 patients without Cirrhosis

Sofosbuvir-Velpatasvir *Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) one tablet once daily for 12 weeks*

RAV testing for Y93H is recommended and ribavirin should be included in regimen if present.

Rating: Class I, Level A

Recommended

Recommended for Retreatment of Genotype 3 patients with Compensated Cirrhosis

Sofosbuvir-Velpatasvir *Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) one tablet once daily for 12 weeks* + **Ribavirin** *1000 mg if <75 kg or 1200 mg if ≥75 kg for 12 weeks*

Rating: Class I, Level B

Note: The ribavirin daily dose is given in two divided doses.

Recommended for Retreatment of Genotype 3 patients with Compensated Cirrhosis

Daclatasvir *60 mg* once daily for 24 weeks* + **Sofosbuvir** *400 mg once daily for 24 weeks* + **Ribavirin** *1000 mg if <75 kg or 1200 mg if ≥75 kg for 24 weeks*

Rating: Class IIa, Level B

Note: (i) *the dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. See the daclatasvir prescribing

information for details; (ii) the ribavirin daily dose is given in two divided doses.

Recommended

Source: AASLD/IDSA. Recommendations for testing, management, and treating hepatitis C. Retreatment of persons in whom prior therapy has failed. [AASLD/IDSA Hepatitis C Guidance] - Accessed March 10, 2017.

Genotype 3: Retreatment
Table 3. Sofosbuvir plus Ribavirin Treatment-Experienced Patients

Recommended regimens are listed in groups by level of evidence, then alphabetically.

Recommended for Genotype 3 patients, regardless of cirrhosis status

Daclatasvir *60 mg* once daily for 24 weeks*	+	**Sofosbuvir** *400 mg once daily for 24 weeks*	+	**Ribavirin** *1000 mg if <75 kg or 1200 mg if ≥75 kg x 24 weeks*

Rating: Class IIa, Level C
Note: *The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. See the daclatasvir prescribing information for details; the ribavirin daily dose is given in two divided doses.

Recommended for Genotype 3 patients, regardless of cirrhosis status

Sofosbuvir-Velpatasvir *Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) one tablet once daily for 12 weeks*	+	**Ribavirin** *1000 mg if <75 kg or 1200 mg if ≥75 kg for 12 weeks*

Rating: Class IIa, Level C
Note: The ribavirin daily dose is given in two divided doses.

Source: AASLD/IDSA. Recommendations for testing, management, and treating hepatitis C. Retreatment of persons in whom prior therapy has failed. [AASLD/IDSA Hepatitis C Guidance] - Accessed March 10, 2017.