

Treatment of HCV Genotype 2

Module 5: [Treatment of Chronic Hepatitis C Infection](#)

Lesson 2: [Treatment of HCV Genotype 2](#)

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Introduction

Background: In the United States, genotype 2 accounts for approximately 13 to 15% of all hepatitis C infections. Given the historically relatively high sustained virologic response (SVR) rates with the treatment of genotype 2, the data regarding retreatment of patients with genotype 2 in whom prior therapy failed is somewhat limited. The following discussion regarding initial treatment and retreatment of patients with genotype 2 chronic hepatitis C assumes the patient and their clinician have already made the decision to proceed with hepatitis C therapy. The FDA approval of the newest, highly effective, well-tolerated direct-acting antiviral agents (DAAs) has been complicated by the high price of these new agents. For the regimens included as preferred or alternative in the 2014 AASLD/IDSA/IAS-USA Guidance for genotype 2 infection, the cost of the treatment regimens range from approximately \$85,000 to \$113,000 ([Figure 1](#)). Although company-related drug assistance programs provides free medication to some low-income patients, getting medications paid for remains problematic for many clinicians and patients.

Medications Used to Treat HCV: 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. Accordingly, patients should receive detailed counseling regarding the importance of adherence prior to starting therapy and clinicians should provide intensive follow-up during therapy.

Genotype 2: Initial Treatment

Background: Historically, treatment of genotype 2 infection achieved higher sustained virologic response (SVR) rates than with genotype 1 infection, even with a shorter duration of therapy and lower doses of ribavirin. Until recently, the standard of care for treatment-naïve patients with genotype 2 hepatitis C has consisted of a 24-week course of peginterferon plus fixed-dose ribavirin, with SVR rates of 75 to 85%. In 2013, the FDA approved a 12-week course with the all-oral regimen of sofosbuvir plus ribavirin for the treatment of genotype 2 infection based on data from several studies showing SVR rates of approximately 95% with this regimen. The approval of this regimen represented a landmark introduction of interferon-free therapy for chronic hepatitis C. No hepatitis C protease inhibitors have received FDA approval for the treatment of genotype 2 HCV, but simeprevir has shown in vitro activity against HCV genotype 2.

Factors to Consider Prior to Choosing Treatment Regimen: For patients chronically infected with genotype 2 hepatitis C, two major factors determine the optimal treatment regimen and duration: (1) whether the patient has previously received and failed therapy and (2) the presence or absence of cirrhosis. Hepatitis C therapy in patients with decompensated cirrhosis, renal impairment,

HIV coinfection, acute hepatitis C infection, or post-liver transplantation is not addressed in this lesson.

AASLD/IDSA/IAS-USA 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 Disease (AASLD) and the Infectious Diseases Society of America, in collaboration with the International Antiviral Society USA (IAS-USA). The recommendations listed below are for initial treatment of patients with chronic hepatitis C genotype 2 infection. For initial therapy of genotype 2 infection the recommended duration of therapy is 12 weeks in patients without cirrhosis and 16 weeks for those with cirrhosis.

Genotype 2 Chronic HCV: Initial Treatment Treatment-Naive Patients with Genotype 2 Infection

Recommended regimen for Genotype 2 without cirrhosis

Sofosbuvir	+	Ribavirin
400 mg once daily x 12 weeks		1000 mg if <75 kg or 1200 mg if ≥75 kg x 12 weeks

Rating: [Class I](#), [Level A](#)

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

Recommended regimen for Genotype 2 with cirrhosis

Sofosbuvir	+	Ribavirin
400 mg once daily x 16 weeks		1000 mg if <75 kg or 1200 mg if ≥75 kg x 16 weeks

Rating: [Class IIb](#), [Level C](#)

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

Alternative regimens for Genotype 2

Note: No Alternative Regimens

Not recommended for Genotype 2

- **Peginterferon plus Ribavirin for 24 weeks**

Rating: [Class IIb](#), [Level A](#)

- **Monotherapy with Peginterferon, Ribavirin, or a Direct-Acting Antiviral**

Rating: [Class III](#), [Level A](#)

- **Telaprevir-, Boceprevir-, or Ledipasvir-containing regimens**

Rating: [Class III](#), [Level A](#)

Adapted from AASLD, IDSA, IAS-USA. Recommendations for testing, managing, and treating hepatitis C.

<http://www.HCVguidelines.org>. Accessed January 11, 2015.

Key Studies to Support Recommendations: The following key studies support the recommendations for treatment of patients with chronic hepatitis C and genotype 2 infection who are treatment naive or who have previously received treatment and had virologic relapse with a regimen that included peginterferon and ribavirin. Click on the study name (blue) to see more details and to view a PowerPoint slide summary.

- [FISSION](#): This phase 3 trial enrolled 499 treatment-naive patients with genotype 2 or 3 HCV infection and randomized treatment to 12 weeks of sofosbuvir plus weight-based ribavirin versus 24 weeks of peginterferon plus fixed-dose ribavirin. For patients with genotype 2 infection, 68 (97%) of 70 achieved an SVR12 with sofosbuvir plus ribavirin compared with only 78% with peginterferon plus ribavirin.
- [POSITRON](#): Patients in this multinational phase 3 trial were enrolled if they had genotype 2 or 3 infection and were (a) not willing to receive interferon, (b) not able to receive interferon, or (c) were intolerant to a previous course of interferon. A total of 278 patients were randomized to receive a 12-week course of sofosbuvir plus weight-based ribavirin versus placebo. For patients with genotype 2 infection, 101 (93%) of 109 achieved an SVR12 with sofosbuvir plus ribavirin.
- [VALENCE](#): In this phase 3 trial, investigators enrolled 419 patients with treatment-naive or treatment-experienced patients with genotype 2 or 3 HCV infection. Patients with genotype 2 received a 12-week course of sofosbuvir plus weight-based ribavirin versus placebo. For the treatment-naive patients with genotype 2 infection, 31 (97%) of 32 who received sofosbuvir plus ribavirin achieved an SVR12.

Genotype 2: Retreatment of Patients in whom Prior Therapy Failed

Background: Prior to the introduction of direct-acting antiviral agents, the SVR rates with treatment of genotype 2 infection was approximately 75% to 85%. Accordingly, less experience exists with retreatment of patients with genotype 2 than with genotype 1 infection. In particular, very limited data exist with retreatment of genotype 2 patients with cirrhosis. In 2013, the United States FDA approved a 12-week course with the all-oral regimen of sofosbuvir plus ribavirin for the treatment of genotype 2 infection; the description in the FDA approval does not differentiate initial treatment or retreatment. With a 12-week course of the dual regimen of sofosbuvir plus ribavirin, the SVR12 rates with retreatment have generally been higher than 85%. The 12-week retreatment triple regimen of sofosbuvir plus peginterferon and ribavirin achieved SVR rates of 96%. Due to the very high SRV rates with the use of sofosbuvir-containing regimens for genotype 2 infection, inadequate data exist regarding the optimal approach to patients with genotype 2 infection who have failed a sofosbuvir-containing regimen. No hepatitis C protease inhibitors have received FDA approval for the treatment of genotype 2 HCV, but simeprevir has shown in vitro activity against HCV genotype 2.

Factors to Consider Prior to Choosing Treatment Regimen: For retreatment of patients with genotype 2 hepatitis C, two major factors influence the optimal regimen for retreatment: presence or absence of cirrhosis and eligibility to receive interferon. The retreatment of genotype 2 patients with decompensated cirrhosis, renal impairment, HIV coinfection, acute hepatitis C infection, or post-liver transplantation is not addressed in this lesson.

AASLD/IDSA/IAS-USA 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 Disease (AASLD) and the Infectious Diseases Society of America, in collaboration with the International Antiviral Society USA (IAS-USA). The recommendations listed below are for patients with hepatitis C genotype 2 infection in whom prior peginterferon and ribavirin therapy failed.

Genotype 2 Chronic HCV: Retreatment Patients with Genotype 2 Infection in whom Prior Therapy has Failed

Recommended regimen for patients with Genotype 2 in whom prior Peginterferon and Ribavirin therapy failed

Sofosbuvir + **Ribavirin**
400 mg once daily x 12 or 16 weeks + *1000 mg if <75 kg or 1200 mg if ≥75 kg x 12 or 16 weeks*

Rating: [Class I](#), [Level A](#)

Note: (i) patients with cirrhosis may benefit by extension of therapy to 16 weeks; the decision to extend therapy should be made on a case-by-case basis, (ii) the ribavirin daily dose is given in two divided doses

Alternative regimen for patients with Genotype 2 who are eligible to receive interferon and in whom prior Peginterferon and Ribavirin therapy failed

Sofosbuvir + **Ribavirin** + [**Peginterferon alfa-2a** or **Peginterferon alfa-2b**]
400 mg once daily x 12 weeks + *1000 mg if <75 kg or 1200 mg if ≥75 kg x 12 weeks* + [*180 mcg subcutaneously once weekly x 12 weeks* or *1.5 mcg/kg subcutaneously once weekly x 12 weeks*]

Rating: [Class IIa](#), [Level B](#)

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

Not recommended for retreatment of genotype 2 patients in whom prior Peginterferon and Ribavirin therapy failed

- **Peginterferon plus Ribavirin with or without Telaprevir or Boceprevir**

Rating: [Class IIb](#), [Level A](#)

- **Fixed-dose combination Ledipasvir-Sofosbuvir**

Rating: [Class III](#), [Level A](#)

- **Monotherapy with Peginterferon, Ribavirin, or a Direct-Acting Antiviral**

Rating: [Class III](#), [Level A](#)

Adapted from AASLD, IDSA, IAS-USA. Recommendations for testing, managing, and treating hepatitis C.

<http://www.HCVguidelines.org>. Accessed January 11, 2015.

Key Studies to Support Recommendations: The following key studies support the recommendations for retreatment of patients with chronic hepatitis C and genotype 2 infection who previously failed therapy with peginterferon and ribavirin. Click on the study name (blue) to see more details and to view a PowerPoint slide summary.

- **FUSION**: The FUSION trial was a phase 3 trial that compared a 12-week and 16-week course of sofosbuvir plus ribavirin in treatment-experienced patients with genotype 2 or 3 HCV infection. For patients with genotype 2 infection, 31 (86%) of 36 achieved an SVR12 with the 12-week course and 30 (94%) of 32 had an SVR12 with the 16-week course. Of note, for the 19 patients with genotype 2 infection and cirrhosis, the SVR12 rates were higher with a 16-week course (76%) than with a 12-week course (60%).
- **VALENCE**: In this phase 3 trial, investigators enrolled 419 patients with treatment-naïve or treatment-experienced patients with genotype 2 or 3 HCV infection. Patients with genotype 2 received a 12-week course of sofosbuvir plus ribavirin versus placebo. For the treatment-experienced patients with genotype 2 infection, 37 (90%) of 41 achieved an SVR12. Among these treatment-experienced patients, with genotype 2 infection, SVR12 was obtained in 7 (78%) of 9 with cirrhosis compared with 30 (94%) of 32 without cirrhosis.
- **LONESTAR-2**: In the phase 2 LONESTAR-2 trial, treatment-experienced patients with genotype 2 or 3 infection received open-label sofosbuvir plus peginterferon plus ribavirin for 12 weeks. Among the treatment-experienced patients with genotype 2 infection, 22 (96%) of 23 achieved an SVR12. Of note, more than 50% of the patients in this study had cirrhosis and 13 (93%) of 14 patients with genotype 2 infection and cirrhosis obtained an SVR12.

Genotype 2: Future Treatment Options

Future Treatment Options for Patients with HCV Genotype 2: Moving forward, it is highly likely that use of peginterferon for genotype 2 infection will completely phase out. Relatively few studies are ongoing to examine future therapies for genotype 2, primarily because the extremely high SVR rates observed with a 12-week course of the all-oral regimen of sofosbuvir and ribavirin has generated a standard of success that will be very difficult to exceed, or even match. Future studies could potentially look at shorter-course (6 to 8 weeks), but would need to show an SVR rate of at least 95% to serve as an attractive alternative to sofosbuvir plus ribavirin.

- **Daclatasvir plus Sofosbuvir:** This investigational pangenotypic NS5A replication complex inhibitor is currently in phase 3 trials. In study AI444-040, a phase 2 trial involving patients with genotypes 1, 2, and 3, a 24-week course of daclatasvir 60 mg once daily plus sofosbuvir 400 mg once-daily, with or without ribavirin, produced SVR rates of 86% to 93% in patients with genotype 2 or 3, and was well-tolerated and safe. Additional phase 2 trials with daclatasvir in combination with sofosbuvir are ongoing. Daclatasvir for 12 weeks combined with peginterferon lambda and ribavirin for 12 or 24 weeks is under study in a phase 3 trial for patients with genotype 2 or 3 infection.

Summary Points

- The standard of care for initial treatment of hepatitis C genotype 2 consists of all oral therapy with sofosbuvir plus ribavirin, which typically achieves an SVR rate of 90% or better.
- When providing initial treatment of genotype 2 with sofosbuvir and ribavirin, the duration of therapy is 12 weeks in patients without cirrhosis and 16 weeks in those with cirrhosis.
- Data regarding retreatment of patients with genotype 2 and prior treatment failure are limited due to the relatively high SVR rates with the previously used peginterferon and ribavirin treatment regimen.
- For retreatment of patients with genotype 2 who previously failed therapy with peginterferon plus ribavirin, the recommended regimen is a 12 or 16 week course of sofosbuvir plus weight-based ribavirin, with the caveat that patients with cirrhosis may benefit from extending the treatment course to 16 weeks.
- High cost is the primary barrier to treatment with current recommended therapy for genotype 2 infection.

- The demand and interest for studies that examine future therapies for genotype 2 are somewhat limited given the very high SVR rates with the all-oral regimen of sofosbuvir plus ribavirin.

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Figures

Figure 1 Cost of Medication Regimens used to Treat Genotype 2 Chronic HCV

This figure shows the approximate cost of different regimens used for treatment-naive and/or treatment-experienced patients with genotype 2 chronic HCV. This chart does not show the cost of regimens not recommended for treatment in 2014. Cost based on available wholesale acquisition price data.

Estimated Medication Cost for Treatment of Genotype 2 Chronic HCV	
Regimen and Duration	Regimen Cost
Sofosbuvir + Ribavirin x 12 weeks	\$85,000
Sofosbuvir + Ribavirin x 16 weeks	\$113,000
Sofosbuvir + Ribavirin + Peginterferon alfa x 12 weeks	\$97,000