

## **Therapeutic Class Overview Hepatitis C Polymerase Inhibitors**

### **Therapeutic Class**

- Overview/Summary:** Included in this review is sofosbuvir (Sovaldi®), a once-daily nucleotide analog inhibitor of hepatitis C virus (HCV) nonstructural protein 5B ribonucleic acid polymerase, which is essential for viral replication. The efficacy of sofosbuvir has been established in patients with HCV genotype 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/human immunodeficiency virus (HIV)-1 co-infection. The safety and efficacy of sofosbuvir have not been established in post-liver transplant patients or those who have previously failed therapy with a treatment regimen that includes HCV nonstructural protein 3/4A protease inhibitor. Sofosbuvir must be administered in combination with ribavirin or peg interferon alfa and ribavirin. Because of this, warnings and precautions that are associated with these agents are applicable to polymerase inhibitor combination treatment.<sup>1</sup>

Guidelines for the treatment of hepatitis C infection were updated prior to the Food and Drug Administration approval of sofosbuvir and do not address its place in therapy.<sup>2-7</sup> The American Association for the Study of Liver Diseases recommends the use of boceprevir or telaprevir in combination with peg interferon and ribavirin for chronic genotype 1 HCV infection.<sup>2</sup> Peg interferon alfa and ribavirin for 24 weeks for patients infected with HCV genotype 2 or 3 and for 48 weeks for patients infected with HCV genotype 4.<sup>3</sup> Clinical trials have demonstrated that when sofosbuvir is added to ribavirin or peg interferon alfa and ribavirin, sustained virologic response rates are significantly increased.<sup>1,8-12</sup>

**Table 1. Current Medications Available in Therapeutic Class<sup>1-3</sup>**

<b>Generic (Trade Name)</b>	<b>Food and Drug Administration Approved Indications</b>	<b>Dosage Form/Strength</b>	<b>Generic Availability</b>
Sofosbuvir (Sovaldi®)	Treatment of chronic HCV genotype 1 infection, including HCV/HIV-1 co-infection, in combination with peg interferon alfa and ribavirin; treatment of chronic HCV genotype 1 infection, including HCV/HIV-1 co-infection, in combination with ribavirin alone (without peg interferon alfa) in patients who are ineligible to receive an interferon-based regimen; treatment of chronic HCV genotype 4 infection, including HCV/HIV-1 co-infection, in combination with peg interferon alfa and ribavirin; treatment of chronic HCV genotype 2 or 3 infection, including HCV/HIV-1 co-infection, in combination with ribavirin; prevention of post-transplant HCV reinfection in combination with ribavirin in patients with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation), including patients with HCV/HIV-1 co-infection	Tablet: 400 mg	-

HCV=hepatitis C virus, HIV=human immunodeficiency virus

### **Evidence-based Medicine**

- The Food and Drug Administration (FDA) approval of the polymerase inhibitor sofosbuvir was based on the results of six clinical trials consisting of 1,947 patients who were treatment-naïve or had not responded to previous treatment with peg interferon alfa and ribavirin (treatment-experienced), including patients with hepatitis C virus (HCV) and human immunodeficiency virus co-infection. In addition, sofosbuvir was effective in patients who were not eligible for an interferon-based treatment regimen and in patients with hepatocellular carcinoma awaiting liver transplantation, addressing unmet medical needs in these populations.<sup>1,8,9</sup>

- The addition of sofosbuvir to standard therapy (i.e., ribavirin or peg interferon alfa and ribavirin) resulted in significantly higher sustained virologic response rates compared to standard therapy alone in adults with chronic HCV genotype 1, 2, 3 and 4 infections.<sup>1,8,9</sup>
- Several regimens not currently approved by the FDA are currently being evaluated in clinical trials. These include evaluation of sofosbuvir plus ribavirin in patients with recurrent HCV infection (any genotype) after liver transplantation; sofosbuvir plus peg interferon and ribavirin in treatment-experienced patients with genotype 2 or 3 HCV infection; and sofosbuvir plus simeprevir in difficult to treat groups of hepatitis C patients (prior null responders and treatment-naïve patients with advanced liver disease). Only the results of interim analyses from these studies are available at this time.<sup>11,12,16,17</sup>
- The most commonly reported adverse events in clinical studies of sofosbuvir and ribavirin were fatigue and headache. In patients treated with sofosbuvir, ribavirin and peg interferon alfa, the most commonly reported adverse events included fatigue, headache, nausea, insomnia, and anemia.<sup>1,8,9</sup>

### Key Points within the Medication Class

- According to Current Clinical Guidelines:<sup>2-7</sup>
  - The most efficacious therapy for the treatment of hepatitis C virus (HCV) genotype 1 is the use of boceprevir or telaprevir in combination with peg interferon alfa and ribavirin.
    - No one protease inhibitor is preferred or recommended over another.
    - No one peg interferon or ribavirin product is preferred or recommended over another.
    - Patients with genotype 2 or 3 infection may receive treatment for up to 24 weeks and patients with genotype 1 or 4 infection may receive treatment for up to 48 weeks.
  - Treatment guidelines were published prior to the availability of simeprevir and sofosbuvir and do not address the place in therapy of these two new agents.
- Other Key Facts:
  - Sofosbuvir is available as a 400 mg tablet and is dosed 400 mg once daily.<sup>1</sup>
  - The standard drug regimen for chronic hepatitis C requires 24 to 48 weeks of treatment, with self-injections of peg interferon alfa which is associated with a number of side effects including nausea, mood swings and severe flu-like symptoms. Sofosbuvir combination therapy shortens the treatment duration to only 12 week in genotype 1, 2 and 4 HCV infections and offers an interferon-free regimen in genotype 2 and 3 HCV infections.<sup>1-3</sup>
  - When added to standard therapy, sofosbuvir has been found to be well tolerated with no significant side effects beyond what is observed with peg interferon and ribavirin.<sup>1</sup>
  - Sofosbuvir is a substrate of P-glycoprotein (P-gp). Thus, coadministration of potent P-gp inducers such as rifampin and St. John's wort should be avoided. Nevertheless, there are fewer drug interactions with sofosbuvir compared to the HCV protease inhibitors.<sup>1,13-15</sup>
  - Compared to combination therapy with HCV protease inhibitors for the treatment of genotype 1 HCV infection, sofosbuvir combination therapy offers potential for improved efficacy, shorter duration of treatment that is not response-guided, no viral resistance, favorable safety profile, reduced pill burden, and fewer drug-drug interactions (no CYP450 hepatic metabolism).<sup>1,13-15</sup>

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## **Therapeutic Class Review Hepatitis C Polymerase Inhibitors**

### **Overview/Summary**

The hepatitis C virus (HCV) is an enveloped ribonucleic acid virus that is transmitted through exposure with infected blood. It causes chronic infection in 70 to 85% of infected persons and the Centers for Disease Control and Prevention estimates 3.2 million persons are chronically infected. Chronic HCV infection can lead to the development of active liver disease, and accounts for up to 40% of all patients undergoing liver transplantation.<sup>1,2</sup> There are seven genotypes of HCV (genotypes 1 to 7), with genotype 1 being the most common in the United States, followed by genotypes 2 and 3.<sup>2,3</sup> Genotyping is helpful in the clinical management of patients with hepatitis C for predicting the likelihood of response to treatment and in determining the optimal duration of treatment. Treatment goals for the management of chronic hepatitis C include preventing complications and death. Due to the slow evolution of chronic infection, it is difficult to demonstrate if treatment prevents complications of liver disease; therefore, response to treatment is defined by surrogate virological parameters. Sustained virologic response (SVR), defined as the absence of HCV ribonucleic acid (RNA) 24 weeks following discontinuation of treatment, has historically been the most important primary endpoint in clinical trials.<sup>2</sup> Recently, SVR 12 (undetectable HCV RNA 12 weeks after the end of therapy) has also been accepted as a primary endpoint for regulatory approval in the US due to concordance with SVR 24. Of note, SVR rates are lowest with genotype 1 as compared to the other identified genotypes.<sup>3</sup> Combination treatment with peg interferon alfa and ribavirin has been the standard of care for the treatment of chronic hepatitis C.<sup>2-6</sup> Newer treatment strategies which aim to improve efficacy, ease of administration, tolerability and patient adherence, as well as to shorten treatment duration are currently being developed and include the newly approved nonstructural protein 3 protease inhibitors, boceprevir, telaprevir, and simeprevir as well as nonstructural protein 5B polymerase inhibitor, sofosbuvir.<sup>8-11</sup> According to the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver, boceprevir or telaprevir in combination with peg interferon alfa and ribavirin is the recommended treatment for patients with genotype 1 chronic hepatitis C.<sup>3,4</sup> Treatment guidelines were published prior to the availability of simeprevir and sofosbuvir and do not address the place in therapy of these two agents. Overall, treatment guidelines do not give preference to one specific peg interferon or ribavirin product over another.<sup>2-7</sup> Furthermore, no one protease inhibitor is preferred over another and current recommendations for their use are in line with Food and Drug Administration (FDA)-approved indications and dosing.<sup>2-10</sup>

Included in this review is sofosbuvir (Sovaldi<sup>®</sup>), a nucleotide analog inhibitor of HCV nonstructural protein 5B RNA polymerase, which is essential for viral replication the hepatitis C. The efficacy of sofosbuvir has been established in patients with HCV genotype 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/human immunodeficiency virus (HIV)-1 co-infection. Prescribing information does not restrict sofosbuvir use to either treatment-naïve or experienced patients, and the specific FDA-approved indications are outlined in Table 2.<sup>11</sup> Compared to combination therapy with HCV protease inhibitors for the treatment of HCV genotype 1 infection, sofosbuvir combination therapy offers potential for improved efficacy, shorter duration of treatment that is not response-guided, no viral resistance, favorable safety profile, reduced pill burden, and fewer drug-drug interactions (no CYP450 hepatic metabolism).<sup>8-11</sup>

**Table 1. Medications Included Within Class Review**

Generic Name (Trade name)	Medication Class	Generic Availability
Sofosbuvir (Sovaldi <sup>®</sup> )	Hepatitis C virus NS5B polymerase inhibitor	-

### **Indications**

**Table 2. Food and Drug Administration Approved Indications<sup>11</sup>**

Indication	Sofosbuvir
Treatment of chronic HCV genotype 1 infection, including HCV/HIV-1 co-infection, in combination with peg interferon alfa and ribavirin; treatment in combination with ribavirin alone (without peg interferon alfa) can be considered for hepatitis C patients with genotype	✓

Indication	Sofosbuvir
1 infection who are ineligible to receive an interferon-based regimen	
Treatment of chronic HCV genotype 4 infection, including HCV/HIV-1 co-infection, in combination with peg interferon alfa and ribavirin	✓
Treatment of chronic HCV genotype 2 or 3 infection, including HCV/HIV-1 co-infection, in combination with ribavirin	✓
Prevention of post-transplant HCV reinfection in combination with ribavirin in patients with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation), including patients with HCV/HIV-1 co-infection	✓

HCV=hepatitis C virus, HIV=human immunodeficiency virus

There are additional factors that should be considered when initiating treatment with sofosbuvir. Sofosbuvir should be used in combination with ribavirin or peg interferon and ribavirin; it should not be used as monotherapy for the treatment of chronic hepatitis C. Treatment regimen and duration are dependent on both viral genotype and patient population. Treatment response varies based on baseline host and viral factors. The safety and efficacy of sofosbuvir have not been established in post-liver transplant patients or those who have previously failed therapy with a treatment regimen that includes hepatitis C virus (HCV) nonstructural protein 3/4A protease inhibitors. Available data is insufficient for dosing recommendations for patients with HCV genotype 5 or 6 infection.<sup>11</sup>

### Pharmacokinetics

**Table 3. Pharmacokinetics<sup>12</sup>**

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Sofosbuvir	Not reported	80	GS-461203	0.4

### Clinical Trials

The Food and Drug Administration approval of sofosbuvir was based on the results of five Phase 3 trials (N=1,724) in hepatitis C virus (HCV) mono-infected patients with HCV genotypes 1 to 6 and one Phase 3 trial (N=223) HCV/human immunodeficiency virus (HIV)-1 co-infected subjects with HCV genotype 1, 2 or 3 infection. Sofosbuvir dose was 400 mg daily, ribavirin dose was weight-based at 1,000 to 1,200 mg daily in two divided doses when given with sofosbuvir, and the peg interferon alfa dose was 180 µg weekly. Treatment duration was fixed in each trial and was not guided by patients' HCV ribonucleic acid (RNA) levels. Sustained virologic response (SVR), the primary endpoint, was defined as HCV RNA below the lower limit of quantification at 12 weeks after the end of treatment.<sup>11</sup>

NEUTRINO (N=327) was an open-label, single-arm Phase 3 trial that evaluated a 12-week regimen of sofosbuvir plus peg interferon alfa and ribavirin in treatment-naïve patients with HCV genotype 1, 4, 5, or 6 (of whom 98% had genotype 1 or 4). In this study, 90% of patients treated with sofosbuvir combination therapy achieved a SVR12 as compared to an adjusted historical response rate of 60% ( $P<0.001$ ) observed in studies of telaprevir and boceprevir. Rates of SVR12 did not differ greatly according to the HCV genotype. The rate of SVR was 92% among patients without cirrhosis and 80% among those with cirrhosis. A SVR occurred in 98% of patients with the CC genotype of IL28B (a marker for improved immune response to HCV), as compared to 87% of patients with the non-CC IL28B genotype.<sup>13</sup>

While sofosbuvir was not specifically studied in treatment-experienced patients with HCV genotype 1 infection, the estimated response rate in patient who previously failed treatment with peg interferon alfa and ribavirin is 71% according to the prescribing information. This is based on the observed response rate in NEUTRINO subjects with multiple baseline factors associated with a lower response to interferon-based treatment (i.e., IL28B non-C/C alleles, HCV RNA >800,000 IU/mL and F3 to F4 fibrosis).<sup>1</sup>

FISSION (N=499) was a randomized, open-label noninferiority Phase 3 trial that compared treatment with sofosbuvir plus ribavirin for 12 weeks to peg interferon alfa plus ribavirin for 24 weeks in treatment-naïve

patients with HCV genotype 2 or 3. A SVR12 was achieved in 67% of patients in both groups. Response rates in patients receiving sofosbuvir plus ribavirin were lower among patients with HCV genotype 3 than among those with HCV genotype 2 (56 vs 97%). Among patients with cirrhosis at baseline, 47% of patients receiving sofosbuvir plus ribavirin had a SVR compared to 38% of those receiving peg interferon alfa plus ribavirin.<sup>13</sup>

No resistance-associated mutations were detected among patients in either NEUTRINO or FISSION trials who received sofosbuvir and had a relapse after virological suppression; the precise reason for relapse is unknown.<sup>13</sup>

POSITRON (N=278) was a randomized, double-blinded Phase 3 trial that compared 12 weeks of treatment with sofosbuvir and ribavirin to placebo in patients with HCV genotype 2 or 3 who were interferon intolerant, ineligible or unwilling. A SVR was achieved in 78% of patients treated with sofosbuvir and ribavirin compared to 0% of those receiving placebo ( $P<0.001$ ). Response rates in patients receiving sofosbuvir and ribavirin were lower among patients with HCV genotype 3 than among those with HCV genotype 2 (61 vs 93%). Among patients with HCV genotype 3 receiving sofosbuvir and ribavirin, 21% of patients with cirrhosis achieved a SVR compared to 68% without cirrhosis. Among patients with HCV genotype 2 receiving sofosbuvir and ribavirin, 94% of patients with cirrhosis achieved a SVR compared to 92% without cirrhosis.<sup>14</sup>

FUSION (N=201) was a randomized, double-blinded Phase 3 trial that evaluated 12 or 16 weeks of treatment with sofosbuvir and ribavirin in patients with HCV genotype 2 or 3 who did not achieve SVR with prior interferon-based treatment (relapsers and nonresponders). Treatment with sofosbuvir and ribavirin resulted in higher rates of SVR in the 12-week (50%) and 16-week groups (73%) compared to historical control rate of 25%. Patients receiving 16 weeks of treatment had a significantly higher SVR rate than patients receiving 12 weeks of treatment (difference, -23%;  $P<0.001$ ). SVR in patients with HCV genotype 2 who received 12 weeks of treatment were lower than among those who received 16 weeks of treatment (86 vs 94%; difference of -8%; 95% confidence interval [CI], -24 to 9); however, the difference was not statistically significant. SVR rates in patients with HCV genotype 3 who received 12 weeks of treatment were significantly lower than among those who received 16 weeks of treatment (difference, -32%; 95% CI, -48 to -15). Among patients with cirrhosis who received 12 weeks of treatment, the SVR was 31% (60% with HCV genotype 2 and 19% with HCV genotype 3) compared to 61% among patients without cirrhosis (96% with HCV genotype 2 and 37% with HCV genotype 3). Among patients with cirrhosis who received 16 weeks of treatment, the SVR was 66% (78% with HCV genotype 2 and 61% with HCV genotype 3) as compared to 76% among patients without cirrhosis (100% with HCV genotype 2 and 63% with HCV genotype 3).<sup>14</sup>

VALENCE (N=419) is an unpublished randomized, placebo-controlled Phase 3 study that initially evaluated 12 weeks of treatment with sofosbuvir and ribavirin or placebo in naïve and treatment-experienced patients with HCV genotype 2 and 3. The treatment duration was subsequently extended to 24 weeks for patients with genotype 3 (N=250). In the sofosbuvir groups, SVR was achieved by 93% of patients with HCV genotype 2 receiving 12 weeks of therapy and 84% of patients with HCV genotype 3 receiving 24 weeks of therapy. SVR rates were >90% in treatment-naïve patients, regardless of HCV genotype or liver fibrosis. Among treatment-experienced patients with cirrhosis, the SVR was lower in patients with genotype 3 compared to genotype 2 (60 vs 88%).<sup>11</sup>

PHOTON-1 (N=223) is an unpublished open-label Phase 3 trial evaluating 12- or 24 weeks of treatment with sofosbuvir and ribavirin in treatment-naïve patients with genotype 1 and treatment-naïve and treatment-experienced patients with genotype 2 or 3 HCV who were all co-infected with HIV.<sup>11</sup> In this trial, 95% of patients were receiving antiretroviral therapy for their HIV infection. The most common HIV treatment regimens included emtricitabine/tenofovir administered with efavirenz, atazanavir/ritonavir, darunavir/ritonavir or raltegravir.<sup>15</sup> In this trial, SVR was achieved by 76% (87/114) of treatment-naïve patients with HCV genotype 1 receiving 24 weeks of therapy, 88% of treatment-naïve patients with HCV genotype 2 receiving 12 weeks of therapy, and 92% of treatment-experienced patients with HCV genotype 3 receiving 24 weeks of therapy. HIV rebound occurred in two patients (0.9%) on antiretroviral therapy.<sup>11</sup>

An unpublished open-label Phase 2 clinical trial evaluated sofosbuvir plus ribavirin in patients with HCV genotypes 1 to 6 and hepatocellular carcinoma prior to undergoing liver transplantation. Patients meeting the MILAN criteria (a single tumor  $\leq 5$  cm in diameter or  $\leq 3$  tumors each  $\leq 3$  cm in diameter and no extra hepatic manifestations of the cancer or evidence of vascular invasion of tumor) were treated for 24 to 48 weeks or until the time of liver transplantation. The post-transplant virologic response (pTVR) rate was 64% in the 36 evaluable patients who have reached the 12 week post-transplant time point. The safety profile of sofosbuvir and ribavirin was similar to that observed in Phase 3 clinical trials.<sup>11</sup>

An unpublished, ongoing, single-arm, open-label interferon-free Phase 2 pilot study is evaluating 24-week regimen of sofosbuvir plus ribavirin in naïve and treatment-experienced patients with recurrent HCV infection (any genotype) after liver transplantation. The interim SVR4 rate was 80.8% (21/26). There were no episodes of acute or chronic rejection. No drug interaction dose adjustments of immunosuppression have been required.<sup>16</sup>

LONESTAR-2 is an unpublished, ongoing open-label Phase 2 study evaluating a 12-week regimen of sofosbuvir 400 mg once daily added to peg interferon alfa (180  $\mu$ g/week) and weight-based ribavirin twice daily (1,000 or 1,200 mg/day) among 47 treatment-experienced patients with HCV genotype 2 or 3 infection. In this study 55% of patients had cirrhosis. SVR12 occurred in 83% (20/24) of genotype 3 patients achieved and 96% (22/23) of HCV genotype 2 patients.<sup>17</sup>

The COSMOS trial is an unpublished, ongoing, randomized, open-label, Phase 2a trial evaluating a once daily combination of simeprevir 400 mg and sofosbuvir 150 mg with and without ribavirin for 12 and 24 weeks in HCV genotype 1 patients. The four-point score METAVIR scale was used to quantify the degree of inflammation and fibrosis of the liver. Cohort 1 (N=80) included prior null responders with METAVIR scores F0 to F2 and Cohort 2 (N=87) included prior null responders and treatment-naïve patients with METAVIR scores F3 to F4. Only the results of an interim analysis are available at this time.<sup>18</sup>

In the Cohort 1, SVR12 was achieved by 96% (26/27) of patients receiving a 12-week simeprevir added to sofosbuvir and ribavirin regimen and 93% (13/14) of patients receiving a 12-week simeprevir and sofosbuvir regimen without ribavirin. In the Cohort 2, SVR4 was achieved by 93% (14/15) of patients receiving a 12-week simeprevir added to sofosbuvir and ribavirin regimen and 100% (14/14) of patients receiving simeprevir and sofosbuvir regimen without ribavirin. Treatment was found to be generally safe and well tolerated. There was little to no benefit from adding ribavirin in this difficult to treat groups of hepatitis C patients and 12 week treatment provided similar clinical benefit to 24 week treatment.<sup>18,19</sup>

**Table 4. Clinical Trials**

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<b>Treatment of Genotype 1, 2, 3, 4, 5, and 6 Chronic Hepatitis: Treatment-Naïve Patients</b>				
<p>Lavitz et al<sup>13</sup> (NEUTRINO and FISSION)</p> <p><b>NEUTRINO:</b> Sofosbuvir 400 mg once daily for 12 weeks</p> <p>and</p> <p>peg interferon alfa-2a 180 µg once weekly for 12 weeks</p> <p>and</p> <p>ribavirin 1,000 mg/day (weight &lt;75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks</p> <p><b>FISSION:</b> Sofosbuvir 400 mg once daily for 12 weeks</p> <p>and</p> <p>ribavirin 1,000 mg/day (weight &lt;75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks</p> <p>vs</p> <p>peg interferon alfa-2a 180 µg once weekly for 24 weeks</p> <p>and</p>	<p><b>NEUTRINO:</b> MC, OL, SG</p> <p>Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 1, 4, 5, or 6), serum HCV RNA levels of ≥10,000 IU/mL during screening, and who had never received treatment for HCV infection</p> <p><b>FISSION:</b> AC, MC, OL, R</p> <p>Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 2 or 3), serum HCV RNA levels of</p>	<p><b>NEUTRINO:</b> N=327</p> <p>12 weeks</p> <p><b>FISSION:</b> N=499</p> <p>24 weeks</p>	<p><b>NEUTRINO:</b> Primary: SVR12*</p> <p>Secondary: Not reported</p> <p><b>FISSION:</b> Primary: SVR12*</p> <p>Secondary: Not reported</p>	<p><b>NEUTRINO:</b> Primary: Treatment with sofosbuvir added to peg interferon alfa-2a and ribavirin achieved a SVR12 in 90% of patients (95% CI, 87 to 93). In addition, this regimen was found to be more effective in achieving a SVR12 compared to an adjusted historical response rate of 60% (<i>P</i>&lt;0.001) observed in studies of telaprevir and boceprevir.</p> <p>The rate of SVR12 was 92% (95% CI, 89 to 95) among patients without cirrhosis and 80% (95% CI, 67 to 89) among those with cirrhosis. A SVR12 occurred in 98% of patients with the CC genotype of IL28B, as compared to 87% of patients with the non-CC IL28B genotype.</p> <p>Rates of SVR12 were similar among various HCV genotypes: 89% for patients with genotype 1 (92% for genotype 1a and 82% for genotype 1b) and 96% for those with genotype 4. The single patients with genotype 5 and all six patients with genotype 6 achieved SVR12.</p> <p>Secondary: Not reported</p> <p><b>FISSION:</b> Primary: A SVR12 was achieved in 67% of patients in both sofosbuvir plus ribavirin group and peg interferon alfa-2a plus ribavirin group.</p> <p>Response rates in patients receiving sofosbuvir plus ribavirin were lower among patients with genotype 3 infection than among those with genotype 2 infection (56 vs 97%).</p> <p>Among patients with cirrhosis at baseline, 47% of patients receiving sofosbuvir plus ribavirin had a SVR12 compared to 38% of those receiving peg interferon alfa-2a plus ribavirin.</p>



Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ribavirin 800 mg/day in two divided doses for 24 weeks	≥10,000 IU/mL during screening, and who had never received treatment for HCV infection			Secondary: Not reported
<b>Treatment of Genotype 2 and 3 Chronic Hepatitis: Treatment-Naïve and Experienced Patients</b>				
<p>Jacobson et al<sup>14</sup> (POSITRON and FUSION)</p> <p><b>POSITRON:</b> Sofosbuvir 400 mg once daily for 12 weeks</p> <p>and</p> <p>ribavirin 1,000 mg/day (weight &lt;75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks</p> <p>vs</p> <p>placebo</p> <p><b>FUSION:</b> Sofosbuvir 400 mg once daily for 12 weeks</p> <p>and</p> <p>ribavirin 1,000 mg/day (weight &lt;75 kg) or 1,200 mg/day (weight of ≥75 kg) for 12 weeks</p>	<p><b>POSITRON:</b> DB, MC, PC, R</p> <p>Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 2 or 3), serum HCV RNA levels of ≥10,000 IU/mL during screening, and who are not candidates for interferon therapy</p> <p><b>FUSION:</b> AC, DB, MC, R</p> <p>Patients ≥18 years of age with confirmed diagnosis of</p>	<p><b>POSITRON:</b> N=278</p> <p>12 weeks</p> <p><b>FUSION:</b> N=201</p> <p>12 to 16 weeks</p>	<p><b>POSITRON:</b> Primary: SVR12*</p> <p>Secondary: Not reported</p> <p><b>FUSION:</b> Primary: SVR12*</p> <p>Secondary: Not reported</p>	<p><b>POSITRON:</b> Primary: Treatment with sofosbuvir plus ribavirin achieved a SVR12 in 78% of patients (95% CI, 72 to 83) compared to 0% among those receiving placebo (<i>P</i>&lt;0.001).</p> <p>Response rates in patients receiving sofosbuvir plus ribavirin were lower among patients with genotype 3 infection than among those with genotype 2 infection (61 vs 93%).</p> <p>Among patients with genotype 3 infection receiving sofosbuvir plus ribavirin, 21% of patients with cirrhosis achieved a SVR12 compared to 68% without cirrhosis.</p> <p>Among patients with genotype 2 infection receiving sofosbuvir plus ribavirin, 94% of patients with cirrhosis achieved a SVR12 compared to 92% without cirrhosis.</p> <p>Secondary: Not reported</p> <p><b>FUSION:</b> Primary: Treatment with sofosbuvir plus ribavirin resulted in higher rates of SVR12 in the 12-week group (50%; 95% CI, 40 to 60) and 16-week group (73%; 95% CI, 63 to 81) compared to historical control rate of 25%.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs  sofosbuvir 400 mg once daily for 16 weeks  and  ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight of ≥75 kg) for 16 weeks	chronic HCV infection (genotypes 2 or 3), serum HCV RNA levels of ≥10,000 IU/mL during screening, and who have previously not responded to treatment with an interferon containing regimen			<p>Patients receiving 16 weeks of treatment had a significantly higher rate of SVR than patients receiving 12 weeks of treatment (difference, -23%; 95% CI, -35 to -11; <math>P&lt;0.001</math>).</p> <p>Response rates in patients with genotype 2 infection who received 12 weeks of treatment were lower than among those who received 16 weeks of treatment (86 vs 94%; difference of -8%; 95% CI, -24 to 9); however, the difference was not statistically significant.</p> <p>Response rates in patients with genotype 3 infection who received 12 weeks of treatment were significantly lower than among those who received 16 weeks of treatment (difference, -32%; 95% CI, -48 to -15).</p> <p>Among patients with cirrhosis who received 12 weeks of treatment, the rate of response was 31% (60% with HCV genotype 2 infection and 19% with HCV genotype 3 infection), as compared to 61% among patients without cirrhosis (96% with HCV genotype 2 infection and 37% with HCV genotype 3 infection).</p> <p>Among patients with cirrhosis who received 16 weeks of treatment, the rate of response was 66% (78% with HCV genotype 2 infection and 61% with HCV genotype 3 infection) as compared to 76% among patients without cirrhosis (100% with HCV genotype 2 infection and 63% with HCV genotype 3 infection).</p> <p>Secondary: Not reported</p>

\*SVR12 was defined as HCV RNA level below the lower limit of quantification at 12 weeks after the end of treatment.

Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, MC=multicenter, OL=open-label, PC=placebo-controlled, R=randomized, SG=single-group

Miscellaneous abbreviations: HCV=hepatitis C virus, RNA=ribonucleic acid, SVR=sustained virologic response

**Special Populations****Table 5. Special Populations**<sup>11</sup>

Generic Name	Population and Precaution				
	Elderly/Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Sofosbuvir	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. No dosage adjustment required in the elderly.  Safety and efficacy in children <18 years of age have not been established.	No dosage adjustment required in mild or moderate renal impairment.  Safety and efficacy have not been established in severe renal impairment (eGFR <30 mL/minute) or ESRD requiring hemodialysis; no dose recommendation can be given.	No dosage adjustment required. Safety and efficacy have not been established in patients with decompensated cirrhosis.	B*	Unknown; use with caution.

eGFR=estimated glomerular filtration rate, ESRD=end stage renal disease

\*Ribavirin has a pregnancy category of X. Sofosbuvir must be used in combination with ribavirin or in combination with peg interferon alfa and ribavirin.

**Adverse Drug Events**

The safety of sofosbuvir is based on pooled Phase 3 clinical trial data (N=1,639) including patients who received sofosbuvir in combination with ribavirin (with or without peg interferon alfa) and patients who received peg interferon alfa and ribavirin combination therapy, or placebo alone. Table 6 below summarizes adverse events reported in ≥15% patients in any treatment arm.<sup>11</sup>

**Table 6. Adverse Drug Events (%)**<sup>11</sup>

Adverse Event(s)	Sofosbuvir
Fatigue	30* to 59 <sup>†</sup>
Headache	24 <sup>‡</sup> to 36 <sup>†</sup>
Nausea	13* to 34 <sup>†</sup>
Pruritus	11 <sup>‡</sup> to 27*
Insomnia	15 <sup>‡</sup> to 25 <sup>†</sup>
Anemia	6* to 21 <sup>†</sup>
Asthenia	5 <sup>†</sup> to 21*
Rash	8 <sup>‡</sup> to 18 <sup>†</sup>
Decreased appetite	6* <sup>‡</sup> to 18 <sup>†</sup>
Pyrexia	4* <sup>‡</sup> to 18 <sup>†</sup>
Chills	2* <sup>‡</sup> to 17 <sup>†</sup>
Neutropenia	<1* <sup>‡</sup> to 17 <sup>†</sup>
Influenza like illness	3 <sup>‡</sup> to 16 <sup>†</sup>
Myalgia	6 <sup>‡</sup> to 14 <sup>†</sup>
Irritability	10* <sup>‡</sup> to 13 <sup>†</sup>
Diarrhea	9 <sup>‡</sup> to 12* <sup>†</sup>

\*Sofosbuvir plus weight-based ribavirin for 24 weeks treatment regimen.

<sup>†</sup>Sofosbuvir plus peg interferon alfa and weight-based ribavirin for 12 weeks treatment regimen.<sup>‡</sup>Sofosbuvir plus weight-based ribavirin for 12 weeks treatment regimen.

**Contraindications/Precautions**

When sofosbuvir is used in combination with peg interferon alfa or ribavirin, contraindications to and precautions with those agents are applicable to combination therapies (Black Box Warnings associated with these agents are outlined below).<sup>11</sup>

Ribavirin may cause birth defects and/or death of the exposed fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Sofosbuvir combination treatment is contraindicated in women who are pregnant or may become pregnant and men whose female partners are pregnant.<sup>11</sup>

Drugs that are potent P-gp inducers in the intestine (e.g., rifampin, St. John's wort) may significantly decrease sofosbuvir plasma concentrations and may lead to a reduced therapeutic effect of sofosbuvir. Rifampin and St. John's wort should not be used with sofosbuvir.<sup>11</sup>

**Black Box Warning for Pegasys® (peg interferon alfa-2a) and Peg Intron® (peg interferon alfa-2b)<sup>20,21</sup>**

WARNING
Alfa interferon, including peg interferon alfa-2a and alfa-2b, may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping peg interferon alfa-2a or alfa-2b therapy.
Use with ribavirin: ribavirin may cause birth defects and/or death of the fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin causes hemolytic anemia. The anemia associated with ribavirin therapy may result in a worsening of cardiac disease.

**Black Box Warnings for Copegus® (ribavirin), Rebetol® (ribavirin) and Ribasphere®/Ribasphere® RibaPak® (ribavirin)<sup>22-24</sup>**

WARNING
Ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication.
The primary clinical toxicity of ribavirin is hemolytic anemia. The anemia associated with ribavirin therapy may result in worsening of cardiac disease and lead to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin.
Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple dose half-life of 12 days, and it may persist in non-plasma compartments for as long as six months. Therefore, ribavirin is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for six months after completion of therapy in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the six month post treatment follow up period.

**Drug Interactions**

**Table 7. Drug Interactions (Not All Inclusive)<sup>25</sup>**

Generic Name	Interacting Medication or Disease	Potential Result
Sofosbuvir	Carbamazepine, oxcarbazepine, phenobarbital, phenytoin	Coadministration may result in decreased plasma concentrations of sofosbuvir leading to loss of therapeutic effect of sofosbuvir. Coadministration is not recommended.
Sofosbuvir	Rifampin, rifabutin, rifapentine	Coadministration may result in decreased plasma concentrations of sofosbuvir leading to reduced therapeutic

Generic Name	Interacting Medication or Disease	Potential Result
		effect of sofosbuvir. Coadministration is not recommended.
Sofosbuvir	St. John's wort ( <i>Hypericum perforatum</i> )	Coadministration may result in decreased plasma concentrations of sofosbuvir leading to reduced therapeutic effect of sofosbuvir. Coadministration is not recommended.
Sofosbuvir	Tipranavir/ritonavir	Coadministration may result in decreased plasma concentrations of sofosbuvir leading to reduced therapeutic effect of sofosbuvir. Coadministration is not recommended.

**Dosage and Administration**

**Table 8. Dosing and Administration<sup>11</sup>**

Generic Name	Adult Dose	Pediatric Dose	Availability
Sofosbuvir	<p><u>Treatment of chronic HCV genotype 1 infection, including HCV/HIV-1 co-infection, in combination with peg interferon alfa and ribavirin; treatment in combination with ribavirin alone (without peg interferon alfa) can be considered for hepatitis C patients with genotype 1 infection who are ineligible to receive an interferon-based regimen:</u> Tablet: 400 mg once daily for 12 weeks (with peg interferon alfa and ribavirin) or 24 weeks (with ribavirin alone in patients ineligible to receive an interferon-based regimen)</p> <p><u>Treatment of chronic HCV genotype 4 infection, including HCV/HIV-1 co-infection, in combination with peg interferon alfa and ribavirin:</u> Tablet: 400 mg once daily for 12 weeks</p> <p><u>Treatment of chronic HCV genotype 2 or 3 infection, including HCV/HIV-1 co-infection, in combination with ribavirin:</u> Tablet: 400 mg once daily for 12 weeks (genotype 2) or 24 weeks (genotype 3)</p> <p><u>Prevention of post-transplant HCV reinfection in patients with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation), including patients with HCV/HIV-1 co-infection:</u> Tablet: 400 mg once daily for up to 48 weeks or until liver transplantation, whichever occurs first</p>	Safety and efficacy in children have not been established.	Tablet: 400 mg

HCV=hepatitis C virus, HIV=human immunodeficiency virus

**Clinical Guidelines**

**Table 9. Clinical Guidelines**

Clinical Guideline	Recommendation(s)
American Association for the Study of Liver Diseases: <b>An Update on Treatment of Genotype 1 Chronic Hepatitis C Virus Infection (2011)<sup>4</sup></b>	<ul style="list-style-type: none"> <li>The optimal therapy for hepatitis C virus (HCV) genotype 1 is the use of boceprevir or telaprevir in combination with peg interferon alfa and ribavirin.</li> <li>Boceprevir and telaprevir should not be used without peg interferon alfa and weight-based ribavirin.</li> </ul> <p><u>Treatment-naïve patients</u></p> <ul style="list-style-type: none"> <li>The recommended dose of boceprevir is 800 mg three times daily (every</li> </ul>

Clinical Guideline	Recommendation(s)
	<p>seven to nine hours) with food plus peg interferon alfa and weight-based ribavirin for 24 to 44 weeks, preceded by four weeks of lead in peg interferon alfa plus ribavirin alone.</p> <ul style="list-style-type: none"> <li>○ Patients without cirrhosis treated with boceprevir, peg interferon alfa and ribavirin, whose HCV ribonucleic acid (RNA) levels at weeks eight and 24 is undetectable, may be considered for a shortened duration of treatment of 28 weeks in total (four weeks lead in of peg interferon alfa and ribavirin, followed by 24 weeks of triple therapy).</li> <li>○ Triple therapy should be stopped if the HCV RNA level is &gt;100 IU/mL at treatment week 12 or detectable at treatment week 24.</li> </ul> <ul style="list-style-type: none"> <li>● The recommended dose of telaprevir is 750 mg three times daily (every seven to nine hours) with food (not low fat) plus peg interferon alfa and weight-based ribavirin for 12 weeks followed by an additional 12 to 36 weeks of peg interferon alfa plus ribavirin (without telaprevir).             <ul style="list-style-type: none"> <li>○ Patients without cirrhosis treated with telaprevir, peg interferon alfa and ribavirin, whose HCV RNA level at weeks four and 12 is undetectable should be considered for a shortened duration of therapy of 24 weeks.</li> <li>○ Triple therapy should be stopped if the HCV RNA levels is &gt;1,000 IU/mL at treatment weeks four or 12 and/or detectable at treatment week 24.</li> </ul> </li> <li>● Patients with cirrhosis treated with either boceprevir or telaprevir in combination with peg interferon alfa and ribavirin should receive therapy for a duration of 48 weeks.</li> </ul> <p><u>Treatment-experienced patients</u></p> <ul style="list-style-type: none"> <li>● Re-treatment with boceprevir or telaprevir, in combination with peg interferon alfa and weight-based ribavirin, can be recommended for patients who had virological relapse or were partial responders after a prior course of treatment with standard interferon alfa or peg interferon alfa and/or ribavirin.</li> <li>● Retreatment with telaprevir, in combination with peg interferon alfa and weight-based ribavirin, may be considered for prior null responders to a course of standard interferon alfa or peg interferon alfa and/or weight-based ribavirin.</li> <li>● Response-guided therapy of treatment-experienced patients using either a boceprevir- or telaprevir-based regimen can be considered for relapsers, may be considered for partial responders, but cannot be recommended for null responders.</li> <li>● Patients re-treated with boceprevir plus peg interferon alfa and ribavirin who continue to have detectable HCV RNA &gt;100 IU at week 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance.</li> <li>● Patients re-treated with telaprevir plus peg interferon alfa and ribavirin who continue to have detectable HCV RNA &gt;1,000 IU at weeks four or 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance.</li> </ul> <p><u>Adverse events</u></p> <ul style="list-style-type: none"> <li>● Patients who develop anemia on protease inhibitor-based therapy for chronic hepatitis C should be managed by reducing the ribavirin dose.</li> <li>● Patients on protease inhibitor-based therapy should undergo close monitoring of HCV RNA levels and the protease inhibitors should be discontinued if virological breakthrough (greater than one log increase in serum HCV RNA above nadir) is observed.</li> </ul>

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> <li>Patients who fail to have a virological response, who experience virological breakthrough or who relapse on one protease inhibitor should not be re-treated with other protease inhibitors.</li> </ul> <p><u>Use and Interpretation of HCV RNA Results During Triple Therapy</u></p> <ul style="list-style-type: none"> <li>An HCV assay with a lower limit of quantification of equal to or less than 25 IU/mL and a limit of HCV RNA detection of approximately 10 to 15 IU/mL should be used for monitoring response to therapy and decision making during triple therapy.</li> <li>Response-guided therapy should only be considered when no virus is detected by a sensitive assay four weeks after initiation of the HCV protease inhibitor.</li> </ul> <p><u>IL28B testing</u></p> <ul style="list-style-type: none"> <li>IL28B genotype is a robust pretreatment predictor of sustained virologic response (SVR) to peg interferon alfa and ribavirin as well as to protease inhibitor triple therapy in patients with chronic HCV genotype 1. Testing may be considered when the patient or provider wish additional information on the probability of treatment response or on the probable treatment needed.</li> </ul>
<p>Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office: <b>Update on the management and treatment of hepatitis C virus infection (2012)</b><sup>5</sup></p>	<p><u>Recommendations in patients being considered for HCV therapy</u></p> <ul style="list-style-type: none"> <li>All patients with chronic HCV infection should be evaluated for HCV antiviral treatment.</li> <li>Patients should be counseled on their likelihood of achieving SVR, based upon individual factors such as body mass index, genotype, race, stage of fibrosis, and viral load before initiating therapy.</li> <li>IL28B genotype testing can be performed before peg interferon-ribavirin therapy with or without a protease inhibitor, if the results would alter treatment decisions.</li> </ul> <p><u>Recommendations for treatment-naïve patients with genotype 1 infection</u></p> <ul style="list-style-type: none"> <li>Peg interferon alfa and ribavirin, in combination with boceprevir (800 mg three times daily with food) or telaprevir (750 mg three times daily with 20 grams of fat), is the standard of care for most treatment-naïve genotype 1-infected patients.</li> <li>If a telaprevir-containing regimen is used in treatment-naïve noncirrhotic patients who achieve an extended rapid virologic response (eRVR), telaprevir should be discontinued at week 12 and peg interferon-ribavirin should be continued for an additional 12 weeks. If HCV RNA is detectable at week four, but &lt;1,000 IU/mL and remains &lt;1,000 IU/mL or becomes undetectable at week 12, telaprevir should be discontinued at week 12, and peg interferon-ribavirin can be continued for another 36 weeks.</li> <li>If a telaprevir-containing regimen is used in treatment-naïve cirrhotic who achieve an HCV RNA that is undetectable or &lt;1,000 IU/mL at treatment weeks four and 12, telaprevir should be discontinued at week 12, and peg interferon-ribavirin can be continued for 36 more weeks.</li> <li>If a boceprevir-containing regimen is used in treatment-naïve noncirrhotics, if HCV RNA declines by <math>\geq 1 \log_{10}</math> during the four-week lead-in, and HCV RNA is undetectable at weeks eight to 24, treatment with boceprevir-peg interferon-ribavirin for 24 weeks is sufficient. If HCV RNA is detectable at week eight, but &lt;100 IU/mL at week 12, and negative at week 24, boceprevir-peg interferon-ribavirin should be continued until week 36, followed by peg interferon-ribavirin alone for 12 more weeks. If HCV RNA declines by <math>&lt; 1 \log_{10}</math> during the lead-in, boceprevir-peg interferon-ribavirin can be continued for 44 weeks.</li> </ul>

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> <li>• If a boceprevir-containing regimen is used in treatment-naïve cirrhotics, 44 weeks of boceprevir-peg interferon-ribavirin is required after the four-week lead-in.</li> </ul> <p><u>Recommendations for treatment of nonresponders and relapsers with genotype 1 infection</u></p> <ul style="list-style-type: none"> <li>• For patients who previously failed peg interferon-ribavirin, retreatment with boceprevir or ribavirin and peg interferon-ribavirin may be considered, particularly in patients who were relapsers.</li> <li>• If a boceprevir-containing regimen is used for retreatment of noncirrhotic prior partial responders or relapsers, the treatment duration is 36 weeks if HCV RNA is undetectable from weeks eight to 24. If HCV RNA is detectable at week 12, but &lt;100 IU / mL and is undetectable from weeks 24 to 36, boceprevir can be discontinued at week 36 and peg interferon-ribavirin can be continued for an additional 12 weeks.</li> <li>• If a boceprevir-containing regimen is used for re-treatment in cirrhotics, the treatment duration is 48 weeks if HCV RNA is detectable at week 12, but &lt;100 IU/mL, and becomes undetectable from weeks 24 to 36.</li> <li>• If a boceprevir-containing regimen is used for retreatment of prior null responders, the treatment duration is 48 weeks if HCV RNA is detectable at week 12, but &lt;100 IU/mL, and becomes undetectable from weeks 24 to 36.</li> <li>• If a telaprevir-containing regimen is used for retreatment of prior relapsers, and HCV RNA is undetectable from weeks four and 12, telaprevir should be discontinued at week 12 and peg interferon-ribavirin should be continued for an additional 12 weeks. If HCV RNA is detectable, but &lt;1,000 IU/mL at week four and/or 12, telaprevir can be discontinued at week 12, and peg interferon-ribavirin can be continued for an additional 36 weeks.</li> <li>• If a telaprevir-containing regimen is used for re-treatment of prior partial responders or null responders, and HCV RNA is &lt;1,000 IU/mL at weeks four and 12, telaprevir should be discontinued at week 12 and peg interferon-ribavirin should be continued for an additional 36 weeks.</li> </ul> <p><u>Recommendations for dose modification</u></p> <ul style="list-style-type: none"> <li>• Peg interferon alfa and ribavirin doses should be reduced in response to decreases in white blood cells, neutrophils, hemoglobin or platelets.</li> <li>• If ribavirin is stopped for seven or more days in patients concomitantly receiving boceprevir or telaprevir, then the protease inhibitor should also be permanently discontinued. The protease inhibitors should be either continued at full dose or discontinued.</li> <li>• A ribavirin dose reduction should be used as initial management of HCV treatment-related anemia in a symptomatic patient with a hemoglobin &lt;10 g/dL. Erythropoietin may be administered in patients with symptomatic anemia related to peg interferon-ribavirin therapy with or without protease inhibitors to limit anemia-related ribavirin dose reductions or dose discontinuations.</li> <li>• A peg interferon dose reduction should be used as initial management of HCV treatment-related neutropenia (an absolute neutrophil count of &lt;750, or as clinically indicated). Granulocyte colony-stimulating factor should not be given as primary therapy to prevent peg interferon alfa dose reductions.</li> </ul> <p><u>Recommendations for treatment monitoring</u></p> <ul style="list-style-type: none"> <li>• Patients should be monitored for treatment-related adverse effects at least every two weeks early in the course of therapy, and every one to two months during treatment as clinically indicated.</li> </ul>



Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> <li>• Assessment of treatment adherence and screening for depression, suicidal ideation, alcohol, and illicit drug use should be performed at every visit.</li> <li>• Patients should be counseled about avoiding pregnancy through the use of two forms of contraception during treatment and for six months posttreatment. If a patient is receiving a boceprevir- or telaprevir-containing regimen, two alternative effective methods of contraception, such as intrauterine devices and barrier methods, should be used in at-risk patients and partners during and for at least six months after treatment.</li> <li>• In patients receiving telaprevir-peg interferon-ribavirin, all treatment should be stopped if any of the following occur:             <ul style="list-style-type: none"> <li>○ HCV RNA level &gt;1,000 IU/mL at week four or 12.</li> <li>○ Detectable HCV RNA levels at week 24 or at any time point thereafter.</li> <li>○ HCV RNA rebounds at any time point (<math>\geq 1 \log_{10}</math> increase from the nadir HCV RNA).</li> </ul> </li> <li>• In patients receiving boceprevir-peg interferon-ribavirin, all treatment should be stopped if any of the following occur:             <ul style="list-style-type: none"> <li>○ HCV RNA level <math>\geq 100</math> IU/mL at week 12 with a boceprevir-containing regimen.</li> <li>○ Detectable HCV RNA levels at week 24 or at any time point thereafter.</li> <li>○ HCV RNA rebounds at any time point (<math>\geq 1 \log_{10}</math> increase from the nadir HCV RNA).</li> </ul> </li> <li>• Do not switch to the other protease inhibitor if virologic failure occurs with one protease inhibitor.</li> </ul> <p><u>Recommendations for groups with special considerations for therapy</u></p> <ul style="list-style-type: none"> <li>• Peg interferon alfa monotherapy may be used to treat patients with contraindications to ribavirin.</li> <li>• For patients who achieve RVR and have a low baseline viral load (HCV RNA &lt;400,000 IU/mL), 24-weeks of treatment with peg interferon-ribavirin may be sufficient.</li> <li>• Treatment can be deferred in patients with minimal inflammation and/or minimal portal fibrosis on liver biopsy.</li> <li>• HCV genotype 1-infected patients with compensated cirrhosis (Child-Pugh Class &lt;7), adequate neutrophils (<math>&gt;1.5 \text{ k/mm}^3</math>), and adequate platelet counts (<math>&gt;75 \text{ k/mm}^3</math>) should be considered for treatment with boceprevir (for 44 weeks) or telaprevir (for 12 weeks) combined with peg interferon-ribavirin at standard doses for 48 weeks.</li> <li>• Patients with cirrhosis continue to be at risk for hepatocellular carcinoma and should undergo routine screening regardless of viral clearance status.</li> </ul> <p><u>Recommendations for treatment-naïve and -experienced patients with genotype 2 or 3 infection</u></p> <ul style="list-style-type: none"> <li>• Treatment-naïve patients should be treated with peg interferon-ribavirin for 24 weeks.</li> <li>• For patients with low viral load (HCV RNA &lt;600,000 IU/mL) and mild fibrosis who achieve a RVR, 12 to 18 weeks of treatment may be sufficient.</li> <li>• For patients with genotype 3 infection and a high HCV RNA (&gt;600,000 IU/mL), steatosis or advanced fibrosis, treatment beyond 24 weeks may improve response.</li> <li>• Retreatment duration is 48 weeks.</li> </ul> <p><u>Recommendations in patients with genotype 4 infection</u></p>

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> <li>• Appropriate candidates with HCV genotype 4 infections should be treated with peg interferon alfa-2a 180 µg per week or peg interferon alfa-2b 1.5 µg / kg per week, plus ribavirin up to 1,400 mg per day for 48 weeks.</li> </ul> <p><u>Recommendations in patients with decompensated cirrhosis</u></p> <ul style="list-style-type: none"> <li>• Liver transplantation is the treatment of choice in patients with decompensated cirrhosis.</li> <li>• Antiviral therapy is contraindicated in most patients with decompensated cirrhosis.</li> <li>• Interferon-based therapy in combination with ribavirin can be considered for patients awaiting liver transplantation if they have a Child-Pugh score &lt;7 and a Model for End-Stage Liver Disease score ≤18.</li> <li>• If beginning antiviral therapy, the interferon dose should be reduced and growth factors may be used to for treatment-associated cytopenias.</li> </ul> <p><u>Recommendations in patients following solid organ transplantation</u></p> <ul style="list-style-type: none"> <li>• Interferon-based antiviral therapy is contraindicated in patients who have received a heart, lung or kidney transplant.</li> <li>• In patients with biopsy-proven chronic HCV disease following liver transplantation, peg interferon-ribavirin for 48 weeks may be considered.</li> <li>• Monitor antiviral therapy in post-liver transplant patients on antiviral therapy and discontinue if rejection is documented. Pre-emptive antiviral therapy early post-transplantation in patients without histological recurrence should be avoided.</li> </ul> <p><u>Recommendations in patients with renal disease</u></p> <ul style="list-style-type: none"> <li>• Considered modified doses of antiviral therapy with interferon (standard or pegylated).</li> <li>• Antiviral therapy for HCV treatment is not recommended in patients following renal transplant; however, it may be considered if patients develop fibrosing cholestatic hepatitis.</li> </ul> <p><u>Recommendations in patients with comorbid conditions</u></p> <ul style="list-style-type: none"> <li>• Antiviral therapy is not recommended in patients with a limited life expectancy. In addition, peg interferon-ribavirin, treatment should be avoided in comorbid conditions that may be exacerbated by treatment.</li> </ul> <p><u>Recommendations for patients on methadone</u></p> <ul style="list-style-type: none"> <li>• Antiviral therapy should be offered to patients enrolled in a methadone maintenance program who meet criteria for therapy. Coordinated HCV treatment between providers and substance abuse specialists should occur.</li> </ul> <p><u>Recommendations in patients with ongoing alcohol use</u></p> <ul style="list-style-type: none"> <li>• Encourage patients to decrease alcohol consumption or to abstain, and refer for behavioral intervention to reduce alcohol use. Antiviral therapy may be used in patients who are otherwise appropriate candidates, regardless of prior alcohol use. Alcohol reduces adherence and treatment response.</li> </ul> <p><u>Recommendations in obese patients and those with hepatic steatosis</u></p> <ul style="list-style-type: none"> <li>• Patients with a body mass index &gt;30 should be considered for antiviral treatment. Control comorbid conditions prior to initiation of antiviral therapy.</li> </ul> <p><u>Recommendations in patients with human immunodeficiency virus (HIV)/HCV coinfection</u></p>

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> <li>Patients with controlled HIV infection and evidence of liver disease on biopsy should be considered for HCV antiviral therapy. Treatment should consist of peg interferon-ribavirin at doses similar to those with HCV for a duration of 48 weeks.</li> </ul> <p><u>Recommendations in patients with acute HCV infection</u></p> <ul style="list-style-type: none"> <li>Observe patients for eight to 20 weeks from time of initial exposure to monitor for spontaneous resolution of infection.</li> <li>In patients who fail to resolve infection spontaneously, treatment with peg interferon alfa, with or without ribavirin for 24 to 48 weeks should be used, based on genotype and HCV RNA response during therapy.</li> </ul>
<p>American Association for the Study of Liver Diseases: <b>Diagnosis, Management, and Treatment of Hepatitis C: An Update (2009)<sup>2</sup></b></p>	<ul style="list-style-type: none"> <li>Treatment decisions should be individualized based on severity of liver disease, the potential for serious side effects, the likelihood of treatment response, the presence of comorbid conditions and the patient's readiness for treatment.</li> <li>Optimal therapy for chronic HCV infection is peg interferon alfa in combination with ribavirin.</li> <li>In genotypes 1 and 4, treatment with peg interferon alfa and ribavirin for 48 weeks is recommended. In patients who do not achieve an early virological response (early virologic response; <math>\geq 2</math> log reduction in HCV RNA at 12 weeks), treatment may be discontinued. Patients who do not achieve a complete early virologic response (undetectable HCV RNA at 12 weeks) should be re-tested at week 24, and if HCV RNA remains positive, treatment should be discontinued. Finally, for patients who have delayed virus clearance (HCV RNA test becomes negative between 12 and 24 weeks); consideration should be given to extending therapy to 72 weeks.</li> <li>In genotypes 2 or 3, treatment with peg interferon alfa and ribavirin for 24 weeks is recommended. Patients who receive treatment for 24 weeks and who have a negative HCV RNA measurement, should be retested for HCV RNA 24 weeks later to evaluate for a SVR. Regardless of genotype, patients with HCV-related cirrhosis who achieve a SVR should be monitored at six to 12 month intervals for hepatocellular carcinoma development.</li> <li>The same criteria for evaluating which patients should receive treatment can be used to determine which children, age two to 17 years of age, who are infected with HCV should receive treatment.</li> <li>Children should be treated with the combination of peg interferon alfa 2b, 60 <math>\mu\text{g}/\text{m}^2</math> weekly, and ribavirin 15 mg/kg daily for 48 weeks.</li> </ul>
<p>European Association for the Study of the Liver: <b>Management of Hepatitis C Virus Infection (2013)<sup>3</sup></b></p>	<p><u>Goals and endpoints of HCV therapy</u></p> <ul style="list-style-type: none"> <li>The goal of therapy is to eradicate HCV infection.</li> <li>The endpoint of therapy is SVR, defined by undetectable HCV RNA 24 weeks after the end of therapy; SVR usually equates to cure of infection in more than 99% of patients.</li> <li>Undetectable HCV RNA at 12 weeks after the end of therapy (SVR 12) has been accepted in the US and Europe given concordance with SVR 24 is 99%; however, this concordance needs to be further validated in ongoing clinical trials.</li> </ul> <p><u>Indications for treatment</u></p> <ul style="list-style-type: none"> <li>All treatment-naïve patients with compensated disease due to HCV should be considered for therapy.</li> <li>Treatment should be scheduled, not deferred, for patients with significant fibrosis (F3 to F4).</li> <li>In patients with less severe disease, indication for and timing of therapy can be individualized.</li> </ul>

Clinical Guideline	Recommendation(s)
	<p><u>First line treatment of chronic hepatitis C genotype 1</u></p> <ul style="list-style-type: none"> <li>• Triple therapy with boceprevir or telaprevir added to peg interferon alfa and ribavirin is the approved standard of care for chronic hepatitis C genotype 1. There is no head-to-head comparison to allow recommendation of boceprevir or telaprevir as preferred therapy.</li> <li>• Patients with cirrhosis should never receive abbreviated treatment with boceprevir or telaprevir regimens.</li> <li>• Selected patients with high likelihood of SVR to peg interferon alfa and ribavirin or with contraindications to boceprevir or telaprevir can be treated with dual therapy.</li> <li>• When lead-in is used to identify patients with peg interferon alfa sensitive infection, the possibility of continuation of dual therapy should have been discussed with the patient prior to initiation of treatment.</li> <li>• Both peg interferon alfa-2a (180 µg/week) and peg interferon alfa-2b (1.5 µg/kg/week) can be used in dual or triple therapy.</li> <li>• Ribavirin should be dosed following the peg interferon alfa label for triple therapy.</li> <li>• Ribavirin should be administered at a weight-based dose of 15 mg/kg/day in dual therapy.</li> </ul> <p><u>First line treatment of chronic hepatitis C genotypes 2, 3, 4, 5, and 6</u></p> <ul style="list-style-type: none"> <li>• The combination of peg interferon alfa and ribavirin is the approved standard of care for chronic hepatitis C genotypes 2, 3, 4, 5, and 6.</li> <li>• Ribavirin should be administered at a weight-based dose of 15 mg/kg/day for genotypes 4, 5 and 6, and at a flat dose of 800 mg/day for genotypes 2 and 3.</li> <li>• Patients with genotypes 2 and 3 with baseline factors suggesting low responsiveness should receive weight-based ribavirin at a dose of 15 mg/kg/day.</li> </ul> <p><u>Treatment monitoring</u></p> <ul style="list-style-type: none"> <li>• A real-time polymerase chain reaction-based assay with a lower limit of detection of &lt;15 IU/mL should be used to monitor triple therapy.</li> <li>• During triple therapy in HCV genotype 1 patients, HCV RNA measurements should be performed at weeks four, eight, 12, 24, and end of treatment when administering boceprevir, and at weeks four, 12, 24, and end of treatment when administering telaprevir.</li> <li>• During dual therapy in any HCV genotype, HCV RNA levels should be assessed at baseline, weeks four, 12, 24 and end of treatment.</li> <li>• The end-of-treatment virological response and the SVR at 12 or 24 weeks after the end of treatment must be assessed.</li> <li>• Whether the baseline HCV RNA level is low or high may be a useful criterion to guide treatment decisions during dual therapy. The safest threshold level for discriminating low and high baseline HCV RNA is 400,000 IU/mL.</li> <li>• Dual therapy for all HCV genotypes should be stopped at week 12 if the HCV RNA decrease is &lt;2 log<sub>10</sub> IU/mL and at week 24 if HCV RNA is still detectable.</li> <li>• Triple therapy with boceprevir should be stopped if HCV RNA is &gt;100 IU/mL at treatment week 12 or if HCV RNA is detectable at treatment week 24.</li> <li>• Triple therapy with telaprevir should be stopped if HCV RNA is &gt;1,000 IU/mL at weeks four or 12 of therapy.</li> <li>• Dual therapy duration should be tailored to the on-treatment virological response at weeks four and 12. The likelihood of SVR is directly proportional to the rapidity of HCV RNA disappearance.</li> </ul>

Clinical Guideline	Recommendation(s)
	<ul style="list-style-type: none"> <li>• For patients receiving dual therapy who achieve an RVR and who have low baseline viral titre (&lt;400,000 IU/mL), treatment for 24 weeks (genotype 1) or 16 weeks (genotype 2 or 3) can be considered. If negative predictors of response (i.e., advanced fibrosis/cirrhosis, metabolic syndrome, insulin resistance, hepatic steatosis) are present, published evidence for equal efficacy of shortened treatment is lacking.</li> <li>• Patients receiving dual therapy with genotypes 2 or 3, and with any adverse predictor of SVR, and who achieve an early virological response or a delayed virological response without an RVR, can be treated for 48 weeks.</li> <li>• Genotype 1 patients receiving dual therapy who demonstrate a delayed virological response can be treated for 72 weeks, provided that their HCV RNA is undetectable at week 24.</li> </ul> <p><u>Treatment dose reductions and stopping rules</u></p> <ul style="list-style-type: none"> <li>• The peg interferon alfa dose should be reduced if the absolute neutrophil count falls below 750/mm<sup>3</sup>, or the platelet count falls below 50,000/mm<sup>3</sup>. Peg interferon alfa should be stopped if the neutrophil count falls below 500/mm<sup>3</sup> or the platelet count falls below 25,000/mm<sup>3</sup> or if severe unmanageable depression develops.</li> <li>• If neutrophil or platelet counts rise, treatment can be restarted, but at a reduced peg interferon alfa dose.</li> <li>• If hemoglobin &lt;10 g/dL occurs, the dose of ribavirin should be adjusted downward by 200 mg at a time, and ribavirin should be stopped if hemoglobin falls below 8.5 g/dL.</li> <li>• Treatment should be stopped in case of a severe hepatitis flare or severe sepsis.</li> <li>• Boceprevir or telaprevir doses should not be reduced during therapy due to the risk of the development of antiviral resistance. If boceprevir or telaprevir have been stopped, they should never be reintroduced in the same course of treatment.</li> </ul> <p><u>Measures to improve treatment success rates</u></p> <ul style="list-style-type: none"> <li>• Full adherence to all antiviral drugs should be the aim in order to optimize SVR rates and to reduce the risk of emergence of specific drug resistance.</li> <li>• Body weight adversely influences the response to peg interferon alfa and ribavirin; therefore, a reduction of body weight in overweight patients prior to therapy may increase the likelihood of SVR.</li> <li>• Insulin resistance is associated with treatment failure for dual therapy; however, insulin sensitizers have no proven efficacy in improving SVR rates in these patients.</li> <li>• Counseling on abstaining from alcohol during antiviral therapy should be provided.</li> <li>• In dual therapy, recombinant erythropoietin can be administered when the hemoglobin level falls &lt;10 g/dL in order to reduce the need for ribavirin dose reduction.</li> <li>• In patients receiving boceprevir or telaprevir-based triple therapy, ribavirin dose reduction should be the initial response to significant anemia.</li> <li>• There is no evidence that neutropenia during peg interferon alfa and ribavirin therapy is associated with more frequent infection episodes, or that the use of granulocyte colony stimulating factor reduces the rate of infections and/or improves SVR rates.</li> <li>• Patients with a history and/or signs of depression should be seen by a psychiatrist before therapy. Patients who develop depression during therapy should be treated with antidepressants. Preventative antidepressant therapy</li> </ul>

Clinical Guideline	Recommendation(s)
	<p>in selected patients may reduce the incidence of this condition during treatment, without any impact on SVR.</p> <p><u>Post treatment follow up of patients who achieve an SVR</u></p> <ul style="list-style-type: none"> <li>• Noncirrhotic patients with SVR should be retested for alanine transaminase and HCV RNA at 48 weeks post-treatment, and then discharged if alanine transaminase is normal and HCV RNA is negative.</li> <li>• Cirrhotic patients with SVR should undergo surveillance for hepatocellular carcinoma every six months by means of ultrasound.</li> <li>• If present, portal hypertension and esophageal varices should be managed, though index variceal bleed is seldom observed in low-risk patients after the achievement of SVR.</li> <li>• Patients with ongoing drug use should not be excluded from HCV treatment on the basis of perceived risk of reinfection.</li> <li>• Following SVR, monitoring for HCV reinfection through annual HCV RNA assessment should be undertaken on people who inject drugs with ongoing risk behavior.</li> </ul> <p><u>Retreatment of nonsustained virological responders to peg interferon alfa and ribavirin</u></p> <ul style="list-style-type: none"> <li>• Patients infected with HCV genotype 1 who failed to eradicate HCV in prior therapy with peg interferon alfa and ribavirin should be considered for retreatment with the triple combination of peg interferon alfa, ribavirin and a protease inhibitor.</li> <li>• The previous response to interferon-based therapy is an important predictor of success of triple therapy. If the pattern of prior response to dual therapy is not clearly documented, the patient should not be treated with abbreviated response-guided therapy.</li> <li>• Patients with cirrhosis and prior null responders have a lower chance of cure and should not be treated with response-guided therapy with either boceprevir or telaprevir.</li> <li>• Patients infected with HCV genotypes other than 1 and who failed on prior therapy with non-pegylated interferon alfa, with or without ribavirin, can be re-treated with pegylated interferon alfa and ribavirin.</li> </ul> <p><u>Treatment of patients with severe liver disease</u></p> <ul style="list-style-type: none"> <li>• Patients with compensated cirrhosis should be treated, in the absence of contraindications, in order to prevent short to midterm complications.</li> <li>• Monitoring and management of side effects, especially those linked to portal hypertension, low platelet count, and low serum albumin should be done particularly carefully. Growth factors may be useful in this group.</li> <li>• Patients with cirrhosis should undergo regular surveillance for hepatocellular carcinoma, irrespective of SVR.</li> <li>• In patients awaiting liver transplantation, antiviral therapy, when feasible, prevents graft reinfection if an SVR is achieved.</li> <li>• Antiviral therapy may be started while awaiting liver transplantation, with the goal of achieving SVR or HCV RNA negativity before transplantation.</li> <li>• In patients with Child-Pugh B cirrhosis, antiviral therapy is offered on an individual basis in experienced centers, preferentially in patients with predictors of good response.</li> <li>• Patients with Child-Pugh C cirrhosis should not be treated with the current interferon alfa-based antiviral regimens due to a high risk of life-threatening complications.</li> <li>• Treatment can be started at low doses of peg interferon alfa and ribavirin,</li> </ul>

Clinical Guideline	Recommendation(s)
	<p>following a low accelerated dose regimen or at full doses. In the latter case, dose reductions and treatment interruptions are required in &gt;50% of cases.</p> <ul style="list-style-type: none"> <li>• Patients with post-transplant recurrence of HCV infection should initiate therapy once chronic hepatitis is established and histologically proven. Significant fibrosis or portal hypertension one year after transplantation predicts rapid disease progression and graft loss and indicates urgent antiviral treatment.</li> <li>• For patients with HCV genotype 1, protease inhibitor-based therapy can be used, but frequent monitoring and dose adjustment of tacrolimus and cyclosporine are required.</li> <li>• Graft rejection is rare but may occur during peg interferon alfa treatment. A liver biopsy should be performed whenever liver tests worsen on antiviral therapy.</li> </ul> <p><u>Treatment of special groups</u></p> <ul style="list-style-type: none"> <li>• Indications for HCV treatment in patients with human immunodeficiency virus (HIV) coinfection are identical to those in patients with HCV mono-infection. The same peg interferon alfa regimen should be used in HIV coinfecting patients. Longer treatment duration may be considered for patients with genotype 2 and 3 who exhibit slow early viral kinetics.</li> <li>• Patients coinfecting with HIV and HCV genotype 1 should be considered for telaprevir or boceprevir triple therapy regimen, but special care should be taken to minimize or avoid potential drug-drug interactions.</li> <li>• HIV patients with a diagnosis of acute HCV infection should be treated with peg interferon and ribavirin, with duration dependent on viral kinetics independent of HCV genotype.</li> <li>• Patients coinfecting with hepatitis B should be treated with telaprevir or boceprevir triple therapy regimen, following the same rules as mono-infected patients.</li> <li>• If hepatitis B virus replicates at significant levels before, during or after HCV clearance, concurrent hepatitis B virus nucleoside/nucleotide analogue therapy is indicated.</li> <li>• Patients on hemodialysis, particularly those who are suitable candidates for renal transplantation, should be considered for antiviral therapy.</li> <li>• Antiviral treatment should comprise peg interferon alfa at an appropriately reduced dose.</li> <li>• Ribavirin can be used at very low doses, but with caution.</li> <li>• Boceprevir or telaprevir can be used with caution in patients with impaired creatinine clearance, and dose adjustment is probably unnecessary.</li> <li>• Patients with HCV and end stage renal disease scheduled for kidney transplantation should undergo antiviral therapy prior to transplantation due to the increased risk of acute transplant rejection.</li> <li>• Interferon alfa-based antiviral treatment is associated with a significant risk of renal graft rejection, and it should be avoided unless there is a powerful indication for antiviral treatment (e.g., aggressive cholestatic hepatitis).</li> <li>• Regular alcohol consumption should be strongly discouraged.</li> <li>• Treatment of patients with active illicit drug abuse has to be individualized.</li> <li>• Patients with hemoglobinopathies can be treated with combination therapy but need careful monitoring.</li> </ul> <p><u>Follow up of untreated patients and of patients with treatment failure</u></p> <ul style="list-style-type: none"> <li>• Untreated patients with chronic hepatitis C and those who failed prior treatment should be followed regularly.</li> <li>• Non-invasive methods for staging fibrosis are best suited for follow-up</li> </ul>

Clinical Guideline	Recommendation(s)
	<p>assessment at intervals.</p> <ul style="list-style-type: none"> <li>Hepatocellular carcinoma screening must be continued indefinitely in patients with cirrhosis.</li> </ul> <p><u>Treatment of acute hepatitis C</u></p> <ul style="list-style-type: none"> <li>Peg interferon alfa monotherapy for 24 weeks is recommended in patients with acute hepatitis C and achieves SVR in &gt;90% of patients.</li> <li>Patients failing to respond to monotherapy should be retreated according to the standard of care for chronic hepatitis C.</li> </ul>
Centers for Disease Control and Prevention: <b>Hepatitis ABC Fact Sheet (2012)</b> <sup>7</sup>	<p><u>Hepatitis C</u></p> <ul style="list-style-type: none"> <li>For acute hepatitis C, antivirals and supportive treatments are used.</li> <li>Regular monitoring for signs of liver disease progression is required and some patients are treated with antiviral drugs.</li> </ul>
American Gastroenterological Association: <b>Medical Position Statement on the Management of Hepatitis C (2006)</b> <sup>6</sup>	<ul style="list-style-type: none"> <li>The treatment of choice is peg interferon plus ribavirin.</li> <li>Patients with genotypes 1 and 4 require 48 weeks of therapy with peg interferon and high daily doses of ribavirin (1,000 to 1,200 mg, depending on weight).</li> <li>Patients with genotypes 2 and 3 can be treated for only 24 weeks with peg interferon and 800 mg of ribavirin daily, with the following exceptions: <ul style="list-style-type: none"> <li>A longer duration of therapy may be considered on an individual patient basis taking into account factors such as elevated viral level, cirrhosis, or delayed response to therapy.</li> <li>Twelve weeks of therapy suffices in patients in whom HCV RNA levels are undetectable at week four.</li> <li>Patients with genotype 3, with high levels of HCV RNA or advanced fibrosis on liver biopsy, may require treatment for 48 weeks.</li> </ul> </li> </ul>

**Conclusions**

Sovaldi<sup>®</sup> (sofosbuvir) is a novel once-daily nucleotide analog inhibitor of hepatitis C virus (HCV) nonstructural protein 5B ribonucleic acid (RNA) polymerase, which is essential for viral replication the hepatitis C. The efficacy of sofosbuvir has been established in patients with HCV genotype 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/human immunodeficiency virus-1 co-infection.<sup>11</sup> The approval is likely to change the way in which hepatitis C is treated.

Similar to HCV protease inhibitors, sofosbuvir may be used in both treatment-naïve patients as well as those who have been previously treated with interferon-based treatment, including prior null responders, partial responders and relapsers.<sup>8-11</sup> Sofosbuvir must be administered in combination with ribavirin or peg interferon alfa and ribavirin. Because of this, warnings and precautions that are associated with these agents are applicable to polymerase inhibitor combination treatment. The safety and efficacy of sofosbuvir have not been established in post-liver transplant patients or those who have previously failed therapy with a treatment regimen that includes HCV nonstructural protein 3/4A protease inhibitors.<sup>11</sup>

The pivotal clinical trials demonstrate that treatment with sofosbuvir, in combination with ribavirin or peg interferon alfa and ribavirin, results in significantly higher sustained virologic response rates among adult patients with chronic hepatitis C genotype 1, 2, 3 and 4 infection compared to standard therapy alone.<sup>11,13,14</sup> Several regimens not currently approved by the Food and Drug Administration are currently being evaluated in clinical trials. These include evaluation of sofosbuvir plus ribavirin in patients with recurrent HCV infection (any genotype) after liver transplantation; sofosbuvir plus peg interferon and ribavirin in treatment-experienced patients with genotype 2 or 3 HCV infection; and sofosbuvir plus simeprevir in difficult to treat groups of hepatitis C patients (prior null responders and treatment-naïve patients with advanced liver disease). Only the results of interim analyses from these studies are available at this time.<sup>16-19</sup>



Combination treatment with peg interferon alfa and ribavirin has been the standard of care for the treatment of chronic hepatitis C.<sup>2-6</sup> Treatment guidelines recommend therapy with peg interferon alfa and ribavirin for 24 weeks for patients infected with HCV genotype 2 or 3 and for 48 weeks for patients infected with HCV genotype 4.<sup>2</sup> In the treatment of HCV genotype 1 infection, guidelines recommend HCV protease inhibitors boceprevir or telaprevir in combination with peg interferon alfa and ribavirin.<sup>3,4</sup> However, these treatment guidelines were published prior to the availability of simeprevir and sofosbuvir and do not address the place in therapy of these two agents.<sup>3-7</sup> To date, no head-to-head trials have been published to directly compare the efficacy of HCV polymerase inhibitor sofosbuvir and HCV protease inhibitors.

Compared to combination therapy with HCV protease inhibitors for the treatment of HCV genotype 1 infection, sofosbuvir combination therapy offers potential for improved efficacy, shorter duration of treatment that is not response-guided, no viral resistance, favorable safety profile, reduced pill burden, and fewer drug-drug interactions (no CYP450 hepatic metabolism).<sup>8-11</sup>

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