



# Hepatitis C Agents

## Therapeutic Class Review (TCR)

January 10, 2012

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## FDA-APPROVED INDICATIONS

Drug	Mfr	FDA-Approved Indications
<b>Interferons</b>		
interferon alfacon-1 (Infergen®) <sup>1</sup>	Three Rivers	<p>Chronic hepatitis C</p> <ul style="list-style-type: none"> <li>▪ In adults (&gt;18 years old) with compensated liver disease and anti-HCV serum antibodies and/or HCV RNA</li> <li>▪ Combination therapy with ribavirin is preferred unless a patient cannot take ribavirin. <ul style="list-style-type: none"> <li>– Safety and efficacy data are not available for use of interferon alfacon-1 with or without ribavirin for the treatment of patients co-infected with hepatitis B or HIV</li> </ul> </li> </ul> <p>Patients with the following characteristics are less likely to benefit from treatment of interferon alfacon-1 and ribavirin: response of &lt;1-log<sub>10</sub> drop HCV RNA on previous treatment, genotype 1, high viral load (&gt;850,000 IU/mL), African American race, and/or presence of cirrhosis.</p>
peginterferon alfa-2a (PEGASYS®) <sup>2</sup>	Roche	<p>Chronic hepatitis C</p> <ul style="list-style-type: none"> <li>▪ Alone or in combination with ribavirin in patients ≥ 5 years old with compensated liver disease who have not been previously treated with interferon alfa</li> <li>▪ Includes patients with histological evidence of cirrhosis (Child-Pugh class A)</li> <li>▪ Includes adult patients with clinically stable HIV disease and CD4 counts &gt; 100 cells/mm<sup>3</sup></li> </ul> <p>Monotherapy is not recommended unless a patient has a contraindication to or significant intolerance to ribavirin. Combination therapy provides substantially better response rates than monotherapy. Safety and efficacy have not been demonstrated for treatment longer than 48 weeks. Safety and efficacy have not been established in liver or other organ transplant recipients.</p> <p>Chronic hepatitis B</p> <ul style="list-style-type: none"> <li>▪ Treatment of HBeAg-positive and HBeAg-negative chronic hepatitis B in adults with compensated liver disease and evidence of viral replication and liver inflammation</li> </ul>
peginterferon alfa-2b (PEGIntron™, PEGIntron™ Redipen®) <sup>3</sup>	Schering	<p>Chronic hepatitis C</p> <ul style="list-style-type: none"> <li>▪ For patients with compensated liver disease in combination with ribavirin and an approved Hepatitis C Virus (HCV) NS3/4A protease inhibitor in adult patients (≥18 years old) with HCV genotype 1 infection.</li> <li>▪ For patients with compensated liver disease in combination with ribavirin in patients with genotypes other than genotype 1, pediatric patients (3-17 years of age), or in patients with genotype 1 infection where the use of an HCV NS3/4A protease inhibitor is not warranted based on tolerability, contraindications or other clinical factors.</li> </ul> <p>Monotherapy should only be used in the treatment of chronic hepatitis C in patients with compensated liver disease if there are contraindications to or significant intolerance of ribavirin and is indicated for use only in previously untreated adult patients. Combination therapy provides substantially better response rates than monotherapy.</p>

**FDA-Approved Indications (continued)**

Drug	Mfr	FDA-Approved Indications
<b>Ribavirin</b>		
ribavirin (Copegus™) <sup>4</sup>	generic	<p>Chronic hepatitis C</p> <ul style="list-style-type: none"> <li>In combination with peginterferon alfa-2a (PEGASYS) in patients <math>\geq 5</math> years of age with compensated liver disease and have not been previously treated with interferon alfa</li> <li>Includes patients with histological evidence of cirrhosis (Child-Pugh class A)</li> <li>Includes adult patients with clinically stable HIV disease and CD4 count <math>&gt; 100</math> cells/mm<sup>2</sup></li> </ul> <p>Safety and efficacy have not been demonstrated for treatment longer than 48 weeks. The safety and efficacy have not been established in liver or other organ transplant recipients, patients with decompensated liver disease or previous non-responders to interferon therapy.</p>
ribavirin (Rebetol®) <sup>5</sup>	generic Schering	<p>Chronic hepatitis C</p> <ul style="list-style-type: none"> <li>In combination with interferon alfa-2b (pegylated [PEG-Intron] or nonpegylated [Intron-A®]) in patients (<math>\geq 3</math> years of age) with compensated liver disease</li> </ul> <p>Combination therapy with ribavirin/peginterferon alfa-2b is preferred over ribavirin/interferon alfa-2b as this combination provides substantially better response rates. Patients with the following characteristics are less likely to benefit from retreatment after failing a course of therapy: previous nonresponse, previous peginterferon treatment, significant bridging fibrosis or cirrhosis, and genotype 1 infection. No safety and efficacy data are available for treatment of longer than one year.</p>
ribavirin (Ribasphere™, Ribasphere Ribapak) <sup>6,7,8</sup>	generic	<p>Chronic hepatitis C</p> <p>Capsules</p> <ul style="list-style-type: none"> <li>In combination with interferon alfa 2b (pegylated and nonpegylated) in patients <math>\geq 3</math> years of age with compensated liver disease</li> </ul> <p>Combination therapy with ribavirin/peginterferon alfa-2b is preferred over ribavirin/interferon alfa-2b as this combination provides substantially better response rates. Patients with the following characteristics are less likely to benefit from retreatment after failing a course of therapy: previous nonresponse, previous peginterferon treatment, significant bridging fibrosis or cirrhosis, and genotype 1 infection. No safety and efficacy data are available for treatment of longer than one year.</p> <p>Tablets</p> <ul style="list-style-type: none"> <li>In combination with peginterferon alfa-2a (PEGASYS) in adults with compensated liver disease and adults who have not been previously treated with interferon alpha.</li> <li>Patients in whom efficacy was demonstrated included patients with compensated liver disease and histological evidence of cirrhosis (Child-Pugh class A) and patients with HIV disease that is clinically stable and CD4 count <math>&gt; 100</math> cells/mm<sup>2</sup>.</li> </ul> <p>Safety and efficacy data are not available for treatment longer than 48 weeks. The safety and efficacy of ribavirin and peginterferon alfa-2a therapy has not been established in liver or other organ transplant recipients, patients with decompensated liver disease or previous non-responders to interferon. Safety and efficacy have not been demonstrated for treatment longer than 48 weeks</p>

**FDA-Approved Indications (continued)**

Drug	Mfr	FDA-Approved Indications
<b>Oral Protease Inhibitors</b>		
boceprevir (Victrelis™) <sup>9</sup>	Merck/Schering	<p>Chronic hepatitis C genotype 1 infection</p> <ul style="list-style-type: none"> <li>▪ in combination with peginterferon alfa and ribavirin, in adult patients (≥18 years of age) with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy.</li> <li>▪ Boceprevir should only be used in combination with peginterferon and ribavirin; monotherapy should not be considered.</li> </ul>
telaprevir (Incivek™) <sup>10</sup>	Vertex	<p>Chronic hepatitis C genotype 1 infection</p> <ul style="list-style-type: none"> <li>▪ in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease, including cirrhosis, who are treatment naive or who have been previously treated with interferon-based treatments, including prior null responders, partial responders and relapsers.</li> <li>▪ Telaprevir must only be used in combination with peginterferon alfa and ribavirin; monotherapy should not be considered.</li> <li>▪ A high proportion of previous null responders (especially those with cirrhosis) did not achieve Sustained Virologic Response (SVR) and had telaprevir resistance-associated substitutions emerge on treatment. Efficacy has not been established for patients who have previously failed therapy with a treatment regimen that includes telaprevir or other HCV NS3/4A protease inhibitors.</li> </ul>

**OVERVIEW**

Hepatitis C virus (HCV) infection is the most common chronic blood-borne infection in the United States. An estimated 4.1 million Americans are infected with HCV.<sup>11</sup> The prevalence is nearly twice as high in men as in women. African-Americans have an anti-HCV prevalence rate of three percent, twice as high as in white Americans. Individuals with a history of injection drug use have the highest risk of HCV. In the United States, an estimated 14 percent of those with chronic HCV may be co-infected with human immunodeficiency virus (HIV).<sup>12</sup>

Transmission of HCV occurs primarily through exposure to infected blood, most commonly as a result of injectable drug use. Less common causes include unsafe medical practices, occupational exposure to infected blood, birth from an infected mother, and sex with an infected person or multiple sexual partners.<sup>13,14</sup> Transmission from blood products and organ transplants was virtually eliminated by the introduction of a more sensitive test for antibody to HCV in 1992.

Chronic HCV infection results in cirrhosis in five to 20 percent of patients infected for over 20 years.<sup>15,16</sup> Of those who develop cirrhosis, approximately 30 percent will develop end-stage liver disease over the next ten years, and one to two percent per year will develop hepatocellular carcinoma.<sup>17</sup> HCV infection is the most common reason for liver transplantation and results in 8,000 to 10,000 deaths yearly in the United States.<sup>18,19,20</sup>

The standard measure of virological cure for hepatitis C treatment is the sustained virologic response (SVR).<sup>21</sup> SVR is defined as undetectable serum HCV RNA six months after discontinuation of treatment. When suppression of viral replication has been maintained for six months after treatment, the patient can be considered cured of chronic hepatitis C. As a part of monitoring therapy, early virologic response (EVR), defined as a greater than 2-log<sub>10</sub> decrease in HCV RNA compared to baseline or

undetectable HCV RNA, is assessed after 12 weeks of combination therapy. If EVR is not achieved, the likelihood of SVR is less than two percent.<sup>22</sup>

There are six HCV genotypes and more than 50 subtypes. Hepatitis C viral genotype has been shown to be an important predictor of treatment response and also dictates dose and duration of treatment with combination therapy.<sup>23</sup> Genotype 1 accounts for 70 to 80 percent of all HCV infections in the United States and is associated with the lowest SVR of any genotype when treated with peginterferon + ribavirin therapy, 40 to 50 percent.<sup>24</sup> With triple combination therapy with an oral protease inhibitor, peginterferon and ribavirin, rates of SVR for genotype 1 for treatment naïve patients are higher than dual combination therapy with peginterferon and ribavirin. Nearly all other HCV infections are due to genotypes 2 and 3, which have SVR of greater than 80 percent when treated with peginterferon + ribavirin dual combination therapy.<sup>25,26,27</sup>

The introduction of the long-acting peginterferons led to higher response rates (when given with ribavirin) than are possible with interferon alfa and ribavirin.<sup>28,29</sup> Peginterferon alfa plus ribavirin has also been shown to yield higher SVR rates than peginterferon alfa monotherapy.<sup>30</sup> Dual therapy with peginterferon and ribavirin for 48 weeks (genotype 1, 4, 5 and 6) or 24 weeks (genotype 2 and 3) was the standard of care until October 2011.<sup>31</sup> The 2011 American Association for the Study of Liver Diseases (AASLD) Practice Guidelines Update on the treatment of Genotype 1 Hepatitis C Virus infection changed the recommended regimen for genotype 1 HCV infection. Triple therapy with boceprevir or telaprevir in combination with peginterferon alfa and weight-based ribavirin is recommended for treatment-naïve patients. For patients previously treated with standard interferon or peginterferon alfa and ribavirin, and who had a virologic relapse or were partial responders, the new recommendation is retreatment with either boceprevir or telaprevir, with peginterferon alfa and weight-based ribavirin. Retreatment with telaprevir, peginterferon alfa and weight-based ribavirin may be considered for prior null responders to a course of standard interferon or peginterferon alfa and/or weight-based ribavirin (patients whose HCV RNA level did not decline by at least 2-log<sub>10</sub> IU/mL at treatment week 12).<sup>32</sup>

The likelihood of a patient achieving an SVR after treatment with peginterferon alfa and ribavirin and of spontaneous viral clearance is associated with the patient's IL28B genotype. IL28B is a gene related to the interferon system. Polymorphisms probably influence the gene product in the immune response to the hepatitis C virus but the specific mechanism remains unclear. The carriage of two C alleles (CC) at rs12979860 most strongly, but not fully, predicts SVR, while carriage of one or two unfavorable alleles (CT or TT) does not completely predict failure to respond (there are other polymorphisms near the gene for IL28B that also predict SVR).<sup>33</sup> In one study, among patients infected with genotype 1 hepatitis C virus who were treated with peginterferon and ribavirin, SVR was achieved in 69 percent, 33 percent and 27 percent of Caucasians who carried the CC, CT and TT genotypes, respectively (p <0.0001 for CC versus CT and TT). A similar trend is reported among black patients, 48 percent, 15 percent and 13 percent for CC, CT and TT genotypes, respectively.<sup>34</sup> The predictive value of IL28B genotype testing is also strong in studies examining the efficacy of the protease inhibitors plus peginterferon and ribavirin.<sup>35</sup> The addition of a protease inhibitor, boceprevir or telaprevir, improves SVR rates across all genotypes. In a phase 3 study of telaprevir in treatment naïve patients, those tested for IL28B genotype were retrospectively analyzed. For patients with the CC genotype, 90 percent of patients treated with triple therapy achieved a SVR compared to 64 percent of those treated with peginterferon alfa plus ribavirin. For patients with the CT and TT genotype, 71 and 73 percent of triple therapy-treated patients compared to 25 and 23 percent of peginterferon plus

ribavirin-treated patients achieved a SVR, respectively. IL28B genotype was also predictive of obtaining a rapid virologic response and thus potentially treatment duration.<sup>36,37</sup> The 2011 AASLD practice guidelines state that there is insufficient data to support withholding protease inhibitors from patients with a favorable genotype because of the potential for abbreviated therapy and the trend for higher SVR rates observed in the telaprevir study. In conclusion, they state that there is insufficient data to determine whether IL28B testing can be used to recommend selection of peginterferon plus ribavirin over a protease inhibitor-based regimen with a favorable genotype or in deciding upon the duration of therapy with either regimen. The guideline recommends that testing may be considered when the patient or providers wish additional information on the probability of treatment response or on the probable treatment duration needed (Class 2a, Level B).<sup>38</sup>

The older non-pegylated interferons are now primarily used for other disease states and in selected special patient populations such as those with chronic hepatitis C with decompensated cirrhosis who are candidates for liver transplantation according to the 2009 AASLD practice guidelines. The older non-pegylated interferons will not be considered in this review.

## PHARMACOLOGY

Most interferon compounds are naturally occurring small proteins and glycoproteins produced and secreted by cells in response to viral infections and other synthetic or biological inducers. Peginterferons are produced by binding the large inert polyethylene glycol moiety to interferon molecules, thus decreasing renal clearance, altering metabolism, and increasing the half-life of the interferon molecule.<sup>39</sup> Because of their long half-lives, peginterferon can be administered subcutaneously (SC) once weekly. Interferon alfacon-1 (Infergen) is a non-naturally occurring, synthetic type-I interferon alfa.<sup>40</sup>

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Once bound to the cell membrane, interferons initiate a complex sequence of intracellular events including the induction of certain enzymes, suppression of cell proliferation, immunomodulating activities such as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells, and inhibition of virus replication in virus-infected cells.

Ribavirin is a nucleoside analog with antiviral activity.<sup>41</sup> Ribavirin is phosphorylated intracellularly to the triphosphate metabolite. Once phosphorylated, ribavirin disrupts cellular purine metabolism by inhibiting inosine monophosphate dehydrogenase, which leads to a decrease in guanosine triphosphate. Ribavirin may also act as a potent RNA virus mutagen and increase the mutation rate of RNA viruses. Typically, RNA viruses have a high mutation rate that enables the virus to evolve rapidly and escape host immune mechanisms; however, the high mutation rate is also associated with the production of nonviable virions. Ribavirin monotherapy is not effective for the treatment of chronic hepatitis C, and ribavirin should not be used alone for this indication.<sup>42,43</sup> The mechanism of inhibition of HCV RNA by combination therapy with interferon alfa and ribavirin has not been established.<sup>44</sup>

**Boceprevir (Victrelis) and telaprevir (Incivek) are hepatitis C virus (HCV) NS3/4A protease inhibitors.**

## PHARMACOKINETICS

The half-life of interferon alfa is approximately five to eight hours. Dosing these agents three times weekly results in undetectable blood levels of interferon during the remaining four days of the week.

Pegylation of the interferons has extended the mean steady-state half-life to 40 hours for peginterferon alfa-2b (PEGIntron) and 160 hours for peginterferon alfa-2a (PEGASYS), allowing these agents to be given once weekly.<sup>45,46</sup> The shorter half-life of peginterferon alfa-2b (PEGIntron) results in undetectable levels at day seven while peginterferon alfa-2a (PEGASYS) accumulates over time with multiple dosing. The pharmacokinetic profile of interferon alfacon-1 (Infergen) has not been completed in patients with chronic hepatitis C.<sup>47</sup>

In patients with end-stage renal disease undergoing hemodialysis, there is a 25 to 45 percent reduction in clearance of peginterferon alfa-2a (PEGASYS).<sup>48</sup> There is a 44 percent reduction in peginterferon alfa-2b (PEGIntron) clearance in patients with creatinine clearance (CLCR) less than 30 mL/min.<sup>49</sup> Dose reductions for both peginterferons are necessary for patients with moderate renal impairment.

The terminal half-life of ribavirin (Copegus) with multiple dosing is 120 to 170 hours. The half-life of ribavirin (Rebetol) has been reported as 298 hours. Ribavirin (Rebetol) is metabolized by phosphorylation and degradation prior to being renally eliminated.

Bioavailability of boceprevir has not been studied, however, boceprevir may be taken without regard to meals.<sup>50</sup> Boceprevir is administered as an approximately equal mixture of two diastereomers, SCH534128 and SCH534129, which rapidly interconvert in plasma. The predominant diastereomer, SCH534128, is pharmacologically active and the other diastereomer is inactive. Boceprevir primarily undergoes metabolism through the aldoketoreductase-mediated pathway to ketone-reduced metabolites that are inactive against HCV.

Telaprevir absorption is significantly reduced when administered during fast or with a low-fat meal. Telaprevir should always be taken with food (not low fat). Telaprevir is extensively metabolized in the liver, involving hydrolysis, oxidation, and reduction. Multiple metabolites were detected in feces, plasma, and urine. Estimated half-life of telaprevir is 9-11 hours.

## CONTRAINDICATIONS/WARNINGS

### interferons<sup>51,52,53</sup>

#### *Contraindications*

Peginterferon alfa and interferon alfa are contraindicated in patients with autoimmune hepatitis or hepatic decompensation or hypersensitivity to any of the product components.

Peginterferon alfa-2a (PEGASYS) is contraindicated in hepatic decompensation (Child-Pugh score > 6 [class B and C]) in cirrhotic chronic hepatitis C patients before treatment. Peginterferon alfa-2a (PEGASYS) is contraindicated in hepatic decompensation (Child-Pugh score  $\geq$  6) in cirrhotic chronic hepatitis C patients co-infected with HIV before treatment.

Peginterferon alfa-2b (PEGIntron) is contraindicated in hepatic decompensation (Child-Pugh score > 6 [class B and C]) in cirrhotic chronic hepatitis C patients before treatment or during treatment.

Benzyl alcohol is associated with an increased incidence of neurologic and other complications in neonates and infants, which are sometimes fatal; therefore, peginterferon alfa-2a (PEGASYS) is contraindicated in neonates and infants.

Peginterferon alfa-2b (PEGIntron) is contraindicated in known hypersensitivity reactions, such as urticaria, angioedema, bronchoconstriction, anaphylaxis, Stevens-Johnson syndrome, and toxic

epidermal necrolysis to interferon alpha or any other product component. Peginterferon alfa-2a (PEGASYS) is contraindicated with hypersensitivity with peginterferon alfa-2a or any other component.

Contraindications for interferon alfacon-1 (Infergen) include known hypersensitivity to alpha interferons, autoimmune hepatitis, and decompensated hepatic disease (Child-Pugh score  $\geq 6$  [Class B and C]).

The combination of peginterferon or interferon alfacon-1 plus ribavirin are contraindicated in women who are pregnant or may become pregnant, men whose female partners are pregnant, patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia) and in patients with creatinine clearance  $< 50$  mL/minute.

Peginterferon alfa-2a and ribavirin combination is contraindicated when given concurrently with didanosine due to reports of fatal hepatic failure and peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis.

### **Warnings**

All of the alpha interferons indicated for HCV, including peginterferons and interferon alfacon-1 (Infergen), have the following black box warning: alpha interferons cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Serious and severe infections due to bacterial, fungal or viral pathogens have been reported with the alpha interferons, including some fatal infections. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many, but not all cases, these disorders resolved after stopping interferon therapy.

Life-threatening or fatal neuropsychiatric events including suicides, suicidal and homicidal ideation, depression, and relapse of drug addiction/overdose may manifest in patients receiving therapy with peginterferon alfa or interferon alfacon-1 (Infergen). Adverse neuropsychiatric events reported with alpha interferons include aggressive behavior, psychoses, hallucinations, bipolar disorder, and mania. These reactions may occur in patients with or without previous psychiatric illness. Patients on therapy should receive close monitoring for the occurrence of depressive symptomatology. Patients with persistently severe or worsening neuropsychiatric signs or symptoms should be withdrawn from therapy. These agents should be used with extreme caution in patients with a history of psychiatric illness.

Additionally, peginterferon (Peg-Intron) should be used with extreme caution in patients with a history of psychiatric disorders. Interferon alfa may be associated with exacerbated symptoms of psychiatric disorders with concurrent psychiatric and substance use disorders. If interferon treatments is deemed necessary in patients with a prior history or existence of psychiatric disorder or with a history of substance use disorders, treatment requires individualized drug screening strategies and frequent psychiatric symptom monitoring. Early intervention for re-emergence or development of neuropsychiatric symptoms and substance abuse is recommended.

Interferon alfa suppresses bone marrow function and may result in severe cytopenias, including neutropenia and lymphopenia and very rare events of aplastic anemia. It is advised that complete blood counts be obtained pretreatment and monitored routinely during therapy. Interferon alfa should be discontinued in patients who develop severe decreases in neutrophils ( $<0.5 \times 10^9/L$ ) or platelet

counts (<25 X 10<sup>9</sup>/L). Severe neutropenia and thrombocytopenia occur with a greater incidence in HIV co-infected patients than monoinfected patients and may result in serious infections or bleeding. Serious bacterial, fungal, and viral infections, some fatal, have been observed in interferon-treated patients. Some infections have been associated with severe neutropenia.

Interferon alfa should be used with caution in patients with cardiac disease. Chest pain, changes in blood pressure, supraventricular arrhythmias, and myocardial infarctions have occurred. Patients with a significant history or unstable cardiac disease should not be treated with peginterferon and ribavirin therapy.

Interferon alfa also affects the endocrine system, either causing or aggravating hyperthyroidism or hypothyroidism as well as hyperglycemia or hypoglycemia. New onset diabetes including Type 1 Diabetes Mellitus has been reported. One study showed thyroid dysfunction occurring in 11.8 percent of 254 patients being treated for chronic hepatitis C with interferon alfa plus ribavirin combination therapy.<sup>54</sup> Neither interferon alfa dosage nor the virologic response to treatment was related to the incidence of thyroid dysfunction, of which two-thirds was hypothyroidism, and one-third was hyperthyroidism.

Pulmonary disorders, colitis (ulcerative and hemorrhagic/ischemic), and pancreatitis have also occurred following use of an interferon alfa. Decreases in or loss of vision, retinopathy, retinal vessel thrombosis, optic neuritis, serious retinal detachment, and papilledema are induced or aggravated by treatment with interferon alfa. Cerebral vascular events, both thrombotic and hemorrhagic, have been reported with patients receiving interferon alfa therapy; events occurred in patients with few or no other risk factors for stroke, including patients less than 45 years of age. Due to fever and flu-like symptoms from peginterferon, use caution when using peginterferon in patients with debilitating medical conditions, such as those with a history of pulmonary disease such as chronic obstructive pulmonary disease.

Patients with chronic hepatitis C with cirrhosis may be at risk of hepatic decompensation and death when treated with alpha interferons. Initiation of interferon alfa therapy has been reported to cause transient liver abnormalities, which can result in increased ascites, hepatic failure, or death in patients with poorly compensated liver disease. Therapy should be discontinued for any patient developing signs and symptoms of liver failure. There are very little data regarding use of interferon alfa in immunosuppressed patients or transplant recipients.

Patients with cirrhosis due to chronic hepatitis C and also infected with HIV who receive highly active antiretroviral therapy (HAART) and interferon alfa-2a with or without ribavirin appear to be at increased risk for the development of hepatic decompensation compared to patients not receiving HAART. Patients' clinical status and hepatic function should be closely monitored and peginterferon should be immediately discontinued in patients with hepatic decompensation.

Interferon alfa should be used with caution in patients with a history of autoimmune disease.

## **ribavirin**<sup>55,56,57,58</sup>

### ***Contraindications***

Ribavirin is contraindicated in patients with hemoglobinopathies (e.g., thalassemia major, sickle cell anemia).<sup>59</sup> Ribavirin is contraindicated in patients with known hypersensitivity to ribavirin or to any component of the product. Coadministration of ribavirin (Rebetol) and didanosine is contraindicated

because exposure to the active metabolite of didanosine (dideoxyadenosine 5'-triphosphate) are increased. Fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in patients receiving both didanosine and ribavirin.

Ribavirin is contraindicated in females who are pregnant and in the male partners of females who are pregnant. Ribavirin is Pregnancy Category X. Ribavirin exposure may cause birth defects and/or death of the exposed fetus. Ribavirin therapy should not be started unless a negative pregnancy test has been obtained immediately prior to the initiation of ribavirin therapy. Patients should use a minimum of two effective forms of contraception during therapy and for six months after treatment has stopped. Monthly pregnancy testing should be performed during and for six months after therapy has been discontinued. Ribavirin is genotoxic and mutagenic and should be considered a potential carcinogen.

Ribavirin is contraindicated in patients with autoimmune hepatitis, hepatic decompensation (Child-Pugh score >6; class B or C) in cirrhotic patients with chronic hepatitis C before or during therapy, and hepatic decompensation (Child-Pugh score  $\geq$ 6) in cirrhotic chronic hepatitis C patients with co-infected with HIV before or during therapy.

Using ribavirin without interferon therapy is not effective for the treatment of hepatitis C.

### **Warnings**

The primary toxicity of ribavirin is hemolytic anemia. Hemolytic anemia was observed in approximately ten percent of patients treated with interferon alfa plus ribavirin in clinical trials and usually occurred within one to two weeks of initiation of ribavirin therapy. Cardiac and pulmonary events have occurred in approximately ten percent of patients with hemolytic anemia. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin. **Caution should be exercised in starting treatment in any patient with an increased risk of severe anemia (e.g., history of gastrointestinal bleeding).**

Patients with estimated creatinine clearance < 50 mL/minute should not receive ribavirin.

## **Oral Protease Inhibitors – boceprevir (Victrelis) and telaprevir (Incivek)**

### **Contraindications**

All contraindications to peginterferon alfa and ribavirin also apply since boceprevir and telaprevir must be administered with peginterferon alfa and ribavirin. Due to the ribavirin in the triple combination therapy, boceprevir and telaprevir plus peginterferon/ribavirin are contraindicated in pregnant women and in men whose female partners are pregnant. Because ribavirin may cause birth defects and fetal death, avoid pregnancy in female patients and female partners of male patients. Patients must have a negative pregnancy test prior to therapy; use two or more forms of contraception, and have monthly pregnancy tests.

The triple combination with boceprevir or telaprevir is contraindicated in patients who have concurrent drug therapy with drugs that are highly dependent on CYP 3A4/5 for clearance, and for which elevated plasma concentrations are associated with serious and/or life threatening events. The following drugs are contraindicated with boceprevir and telaprevir: alfuzosin (increased alfuzosin levels resulting in hypotension or cardiac arrhythmias), dihydroergotamine, ergonovine, ergotamine, methylergonovine (potential for acute ergot toxicity characterized by peripheral vasospasm or ischemia), cisapride and pimozide (potential for cardiac arrhythmias), simvastatin and lovastatin

(potential for myopathy, including rhabdomyolysis), sildenafil and tadalafil when used for the treatment of pulmonary arterial hypertension (potential for PDE5 inhibitor-associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope), orally administered triazolam and midazolam (prolonged or increased sedation or respiratory depression). Boceprevir is also contraindicated with drospirenone, carbamazepine, phenobarbital, and phenytoin. Telaprevir is also contraindicated with atorvastatin.

Potent CYP 3A4/5 inducers may significantly reduce boceprevir plasma concentrations. The following drugs are contraindicated with concurrent administration of boceprevir due to the potential for reduced efficacy of boceprevir: carbamazepine, rifampin, phenytoin, phenobarbital, and St. John's wort.

Coadministration with potent CYP 3A4 inducers may significantly reduce telaprevir plasma concentrations and lead to loss of efficacy. The following drugs are contraindicated with concurrent administration of telaprevir due to the potential for reduced efficacy of telaprevir: rifampin and St. John's wort.

### **Warnings**

The addition of boceprevir or telaprevir to peginterferon alfa and ribavirin is associated with an additional decrease in hemoglobin concentrations. Boceprevir in triple combination therapy is associated with additional worsening of neutropenia compared with peginterferon alfa and ribavirin alone.

Serious skin reactions, including Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) and Stevens-Johnson Syndrome (SJS) occurred in less than one percent of patients receiving telaprevir. If a serious skin reaction occurs, all components of telaprevir combination therapy must be discontinued immediately and the patient referred for urgent medical care.

Rash develops in a significant proportion of telaprevir-treated patients. The rash observed with telaprevir is typically a maculopapular and papular lichenoid rash. It is similar to that reported with pegylated interferon and ribavirin. Patients with mild to moderate rash should be followed for progression of rash or development of systemic symptoms. If the rash becomes severe or if systemic symptoms develop, telaprevir should be discontinued. If the rash does not improve within seven days, sequential or simultaneous interruption or discontinuation of ribavirin and/or peginterferon alfa should be considered. If telaprevir is discontinued due to rash, it must not be re-started.

### **Risk Evaluation and Mitigation Strategy (REMS)**

The FDA no longer requires a medication guide to be given to the patient with each prescription for peginterferon alfa-2a (PEGASYS or Peg-Intron) or ribavirin (Rebetol or Copegus).<sup>60,61,62,63</sup> Both boceprevir and telaprevir require a medication guide be given to the patient with each prescription.<sup>64,65</sup>

## **DRUG INTERACTIONS<sup>66,67</sup>**

Concomitant use of peginterferon alfa and theophylline may result in a significant increase in theophylline concentrations. Consider monitoring theophylline levels and adjusting theophylline therapy accordingly during peginterferon therapy. Peginterferon alfa has also been reported to inhibit activity of CYP 450 enzymes, although this interaction is thought to be of minimal clinical significance.

Peginterferons have synergistic toxicities when given with myelosuppressive agents, such as antineoplastics and zidovudine.

Ribavirin may reduce phosphorylation of lamivudine, stavudine, and zidovudine based on in vitro studies. No pharmacokinetic or pharmacodynamic interactions were observed in small studies when ribavirin and lamivudine, stavudine or zidovudine were coadministered as a part of a multiple drug regimen for the treatment of HCV/HIV co-infected patients. Ribavirin and didanosine coadministration may result in increased exposure to didanosine and its metabolites; closely monitor for toxicities and consider discontinuation with worsening toxicities.

Ribavirin coadministered with azathioprine has resulted in pancytopenia with marked decreases in red blood cells, neutrophils, and platelets. Bone marrow suppression has been reported to occur within three to seven weeks after the concomitant administration with peginterferon and ribavirin with azathioprine. In the eight reported cases, myelosuppression was reversible over four to six weeks upon withdrawal of all three agents and did not recur upon reintroduction of either treatment alone.

Telaprevir is a strong inhibitor of CYP3A4 and P-glycoprotein (P-gp). Co-administration of telaprevir with drugs that are metabolized by CYP3A4, or are substrates for P-gp transport, may result in increased plasma concentrations with increased pharmacologic effects or adverse reactions. Telaprevir is primarily metabolized by CYP3A4 and is a substrate for P-gp. Coadministration of telaprevir with drugs that inhibit CYP3A and/or P-gp may increase telaprevir plasma concentrations; drugs that induce CYP3A4 may reduce telaprevir concentrations and its efficacy. The potential for drug-drug interactions must be considered prior to and during therapy.

Boceprevir is a strong inhibitor of CYP3A4/5 and is partly metabolized by CYP3A4/5.

Both oral protease inhibitors, boceprevir and telaprevir, have extensive drug interactions with significant need for increased monitoring and/or dosage adjustments. Both protease inhibitors may have drug interactions with the following drug classes and drugs and may require increased monitoring or dosage adjustment (list is not all inclusive): anti-arrhythmics, digoxin, azole antifungals, colchicine, systemic or inhaled corticosteroids, bosentan, efavirenz, methadone, ethinyl estradiol, alprazolam, and IV midazolam.

For telaprevir, additional drug classes and drugs impacted by concurrent administration include (list is not all-inclusive): warfarin, anticonvulsants, calcium channel blockers, macrolides, protease inhibitors indicated for HIV, and tenofovir. Drug classes and drugs that may interact with boceprevir include the following (list is not all-inclusive): clarithromycin, ritonavir, atorvastatin, immunosuppressants, salmeterol, buprenorphine, and drospirenone. See prescribing information for specific recommendations and details for either oral protease inhibitor.

## ADVERSE EFFECTS

Drug	Depression	Fever	Injection Site Reaction	Anemia	Neutropenia	Withdrawal Rate
<b>Monotherapy</b>						
interferon alfacon-1 (Infergen) <sup>68</sup> n=231	26	61	23	4	19	nr
peginterferon alfa-2a (PEGASYS) <sup>69</sup> n=559	18	37	22	2	21	11
peginterferon alfa-2b (PEGIntron) <sup>70</sup> n=297	29	22	47	0	6	10-14
<b>Dual Combination therapy</b>						
interferon alfacon-1 (Infergen) <sup>71</sup> n=486	25-27	13-17	12-15	27	24-34	21
peginterferon alfa-2a (PEGASYS) <sup>72</sup> + ribavirin n=451	20	41	23	11	27	11
<b>Peginterferon alfa-2a (PEGASYS)<sup>73</sup> + ribavirin n=55</b>	<b>nr</b>	<b>nr</b>	<b>44</b>	<b>nr</b>	<b>nr</b>	<b>13</b>
peginterferon alfa-2b (PEGIntron) <sup>74</sup> + ribavirin n=511 adults	31	46	75	12	26	10-14
peginterferon alfa-2b (PEGIntron) <sup>75</sup> + ribavirin n=107 pediatric patients	1	80	29	11	33	2

nr = not reported

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive.

**Adverse Effects (continued)**

Drug	Rash	Dysgeusia	Fatigue	Anemia	Neutropenia	Withdrawal Rate
<b>Triple Combination therapy</b>						
boceprevir (Victrelis) plus peginterferon alfa-2b/ribavirin n=1,225	17	35	58	50	25	13
peginterferon alfa-2b/ribavirin n=467	191	16	59	30	19	12
telaprevir (Incivek) plus peginterferon alfa/ribavirin n=1,797	56	10	56	36	15	14
peginterferon alfa/ribavirin n=493	34	3	50	17	5	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive.

Nearly all patients receiving peginterferon alfa plus ribavirin will experience at least one adverse effect as a result of peginterferon alfa (such as neutropenia, thrombocytopenia, depression, thyroid disorders, irritability) and/or ribavirin (such as hemolytic anemia, fatigue, itching, rash, sinusitis). Adverse events tend to be more severe in the initial stages of treatment and can often be managed with analgesics, NSAIDs, and antidepressants. Growth factors, such as erythropoietin and filgrastim (Neupogen®), are sometimes used to counteract the adverse effects of ribavirin and peginterferon alfa.

Treatment adherence enhances SVR in patients with genotype 1 HCV.<sup>76</sup> Therefore, management of adverse effects to maintain patients on at least 80 percent of interferon or peginterferon alfa and ribavirin therapy for at least 80 percent of the duration of therapy will likely increase the chance for SVR.

**SPECIAL POPULATIONS****Pediatrics**

An estimated 240,000 children in the United States in 2002 had antibodies to HCV.<sup>77</sup> The seroprevalence is 0.2 percent for children ages six to 11 years and 0.4 percent for those 12 to 19 years of age.<sup>78</sup> New HCV infections in children are primarily the result of perinatal transmission.<sup>79</sup> The 2009 AASLD practice guidelines for the treatment of hepatitis C recommend that children ages two to 17 years receive the same methods of diagnosis, testing, and treatment criteria as adults. The 2009 guidelines recommend the following as standard treatment for children ages two to 17 years: peginterferon alfa-2b (PEGIntron) 60 mcg/m<sup>2</sup> SC weekly with ribavirin 15 mg/kg daily for 48 weeks.

In December 2008, peginterferon alfa-2b (PEGIntron) plus ribavirin was approved by the FDA for the treatment of chronic hepatitis C in previously untreated pediatric patients (ages  $\geq 3$  years). The SVR rate for peginterferon alfa-2b plus ribavirin for 48 weeks for genotype 1, 4 or high viral load and genotype 3 was 55 percent.<sup>80</sup> In a small published trial, safety and efficacy of peginterferon alfa-2b (PEGIntron) plus ribavirin have been evaluated in 30 children (ages three to 16 years) with detectable HCV for a minimum of three years.<sup>81</sup> Patients were given peginterferon alfa-2b 1 mcg/kg weekly plus ribavirin 15 mg/kg per day for 24 weeks for genotypes 2 or 3 and 48 weeks for genotypes 1 or 4. SVR was achieved by 50 percent of patients (100 percent of genotype 3; 12/27 patients with genotypes 1 or 4). For EVR at week 12, 52 percent of patients were HCV RNA negative. Three patients discontinued therapy due to adverse effects. Dose reductions of peginterferon alfa-2b were required in 23 percent of patients due to neutropenia.

In August 2011, peginterferon alfa-2a (PEGASYS) plus ribavirin was approved by the FDA for the treatment of chronic hepatitis C in previously untreated pediatric patients 5 to 17 years of age. In a study that randomized 114 patients to receive either peginterferon alfa-2a, 180 mcg/1.73m<sup>2</sup> times once weekly plus ribavirin 15 mg/kg (n=55) or peginterferon alfa-2a (same dosage) plus placebo (n=59) for 48 weeks, reported SVR rates were 53 percent in the peginterferon alfa plus ribavirin group versus 21 percent in the peginterferon alfa monotherapy group ( $p < 0.001$ ).<sup>82</sup> For those patients with genotype 1 HCV, SVR was obtained in 47 percent and 17 percent of the combination and monotherapy groups, respectively. Neutropenia or anemia lead to dose modification in about 30 percent of children. At the two-year follow-up visit, in the 82 percent of combination therapy and 86 percent of monotherapy patients available for analysis of durability of response, virologic response was 100 percent in both groups.

Another published study evaluated peginterferon alfa-2a (PEGASYS) in a trial with 14 children ages two to eight years with chronic hepatitis C.<sup>83</sup> Peginterferon alfa-2a (PEGASYS) dosing was based on body surface area (BSA)  $\times$  180 mcg and administered as once weekly subcutaneous injection for 48 weeks. Pharmacokinetics were evaluated and compared to adult data and determined that dosing based on BSA produced adequate drug levels. SVR was achieved in 43 percent of patients with genotype 1. No serious adverse events were noted.

The weight and height gain of pediatric patients treated with peginterferon alfa-2b (PEGIntron) and ribavirin lags behind that predictive by normative population data for the entire length of treatment.<sup>84</sup> After about six months post-treatment, subjects had weight gain rebounds similar to that predicted by their average baseline weight. After about six months post-treatment, height gain stabilized and subjects treated with peginterferon alfa-2b and ribavirin had an average height percentile of 44 percentile, which was less than the average of the normative population and less than their average baseline height (51 percentile). Severely inhibited growth velocity ( $<$  three percentile) was observed in 70 percent of patients while on treatment. Of the subjects experiencing severely inhibited growth, 20 percent had continued inhibited growth velocity ( $<$  third percentile) after six months of follow-up.

Pediatric patients treated with peginterferon alfa-2a and ribavirin (PEGASYS) show a delay in weight and height increases after 48 weeks of therapy compared with their baseline. Both weight and height for age z-scores as well as the percentiles of the normative population for subject weight and height decrease during treatment.<sup>85</sup> On follow-up at two years post-treatment, most patients had returned to their baseline normative growth curve percentiles but 16 percent of patients remained 15 percentiles or more below their baseline weight curve and 11 percent remained 15 percentiles or more below their baseline height curve.

Benzyl alcohol is associated with an increased incidence of neurologic and other complications in neonates and infants, which are sometimes fatal; therefore, peginterferon alfa-2a (PEGASYS) is contraindicated in neonates and infants.

Interferon alfacon-1 (Infergen) has not been shown to be safe and effective in children less than 18 years old.<sup>86</sup>

Suicidal ideation or attempts occurred more frequently among pediatric patients, primarily adolescents, compared to adult patients (2.4 versus one percent) during treatment with ribavirin and off-therapy follow-up.<sup>87</sup>

**Safety and effectiveness of boceprevir (Victrelis) and telaprevir (Incivek) have not been established in pediatric patients.<sup>88,89</sup>**

### **Pregnancy<sup>90,91,92,93,94,95</sup>**

Ribavirin is Pregnancy Category X. Ribavirin exposure may cause birth defects and/or death of the exposed fetus. Ribavirin is contraindicated in females who are pregnant and in the male partners of females who are pregnant.

Peginterferon alfa-2a (PEGASYS), peginterferon alfa-2b (PEGIntron), and interferon alfacon-1 (Infergen) are Pregnancy Category C.

**Boceprevir and telaprevir are Pregnancy Category B; however, both oral protease inhibitors require combination therapy with ribavirin and peginterferon.**

### **Ethnicity**

African Americans are less likely than non-Hispanic whites to respond to interferon-based therapies. The reasons for this difference are not known.<sup>96</sup> The 2009 AASLD guidelines have included a section regarding the treatment of hepatitis C in African Americans.<sup>97</sup> The treatment recommendations for African Americans are the current optimal treatment regimen including peginterferon and ribavirin. African Americans who have neutropenia at baseline should not be excluded from hepatitis C treatment (Class IIa, Level B recommendation).

A small open-label trial enrolled 100 black patients and 100 non-Hispanic white patients with chronic hepatitis C.<sup>98</sup> Patients were treated with peginterferon alfa-2b (PEGIntron) 1.5 mcg/kg weekly SC and ribavirin for 48 weeks. Ribavirin was given as 1,000 mg daily for the first 12 weeks then reduced to 800 mg daily for the remaining treatment period. Genotype 1 HCV was present in 98 percent of both groups. SVR was achieved in 19 percent of the black patients and 52 percent of the non-Hispanic white patients ( $p < 0.001$ ) who initiated treatment. Blacks also had a lower rate of early virologic response at 12 weeks (40 versus 69 percent,  $p < 0.001$ ) and at the end of treatment (20 versus 58 percent,  $p < 0.001$ ). Discontinuations were 19 and 21 patients in the blacks and non-Hispanic whites, respectively. Dose reductions occurred in 22 black patients and 24 non-Hispanic white patients. Compliance was similar between the two groups. The two groups had similar severity and type of adverse effects. This study was supported by Schering-Plough.

In an open-label, multicenter trial located in the US, peginterferon alfa-2a (PEGASYS) 180 mcg weekly and ribavirin 1,000 to 1,200 mg per day were given to 196 African-Americans and 205 white Americans with chronic hepatitis C genotype 1.<sup>99</sup> Baseline characteristics were similar between the two groups although the African-Americans had higher body weights, higher prevalence of diabetes and

hypertension, and lower ALT levels ( $p < 0.001$  for all). SVR was 28 percent for African-Americans and 52 percent for white Americans ( $p < 0.0001$ ). Differences in the two groups were observed as early as week four. At week 24, 45 and 74 percent of the African-Americans and white Americans, respectively, had undetectable HCV RNA and continued on therapy until week 48. Relapse rates, after therapy was completed, were similar between the two groups (32 and 25 percent,  $p = 0.3$ ). The discontinuation rate, serious adverse events, and dose modifications were similar between the two groups.

In one of the largest cohorts of African-American patients studied with chronic hepatitis C infection, investigators compared weight-based ribavirin and flat-dose ribavirin in combination with peginterferon alfa-2b (PEGIntron) in a randomized, open-label U.S.-based study.<sup>100,101</sup> Peginterferon alfa-2b (PEGIntron) 1.5 mcg/kg weekly was given to 387 African-Americans with hepatitis C genotype 1. Patients were randomized to either a fixed dose of ribavirin 800 mg daily or a weight-based ribavirin dosing regimen. In the weight-based ribavirin regimen, patients received ribavirin 800 mg daily if they weighed less than 65 kg; 1,000 mg if they weighed between 65 and 85 kg; 1,200 mg if they weighed between 86 and 104 kg; and 1,400 mg if they weighed between 105 and 124 kg. A total of 362 patients were included in the primary efficacy analysis. The discontinuation rates were 42.6 percent (86/202) of patients randomized to the flat dose ribavirin group and 40 percent (74/185) of patients randomized to the weight-based dosing of ribavirin. The primary endpoint was SVR rate that was defined as the absence of detectable serum HCV RNA 24 weeks after treatment completion. SVR rates were 21 percent of those in the weight-based group and in 10 percent of those in the fixed-dose group ( $p = 0.0006$ ). Anemia, defined as a drop in hemoglobin to below 11 gm, occurred in 47 percent of patients in the weight-based dose arm and in 29 percent of those in the fixed-dose arm. While dose reductions and anemia were more common in the group receiving weight-based RBV, discontinuation rates were similar in both groups.

The LATINO study, a prospective, multicenter, open-label, nonrandomized trial, was conducted to better understand how previously untreated Latino patients with HCV genotype 1, responded to treatment with peginterferon alfa-2a plus ribavirin as compared to non-Latino whites.<sup>102</sup> All patients ( $n = 569$ ) were treated with peginterferon alfa-2a 180 mcg/week plus ribavirin 1,000 or 1,200 mg/day for 48 weeks. Patients were then followed through 72 weeks. The data showed that Latino patients achieved SVR, defined as undetectable HCV RNA 24 weeks after the end of treatment, at a lower rate than non-Latino whites (33 percent versus 49 percent,  $p < 0.001$ ). Treatment was generally well tolerated, with similar rates of withdrawals between the groups. However, concern was noted in a letter to the editor regarding patient selection. At baseline, higher percentages of patients in the Latino group had cirrhosis (13 percent versus 10 percent) and an alanine aminotransferase quotient of greater than three (20 percent versus 18 percent) which might indicate more advanced disease at baseline. Furthermore, the rates of obesity and diabetes, which are risk factors for the lack of a SVR, were higher in the Latino group.<sup>103</sup> Evaluations of liver biopsies were obtained within 18 months of baseline and at week 72.<sup>104</sup> Liver fibrosis was assessed by the Ishak-modified histologic activity index scoring system. Paired biopsy data were available for 157 Latinos and 201 non-Latinos. Both groups had improvement in Ishak activity at week 72. Improvement rates were higher in the non-Latinos than Latinos (59 percent versus 47 percent,  $p = 0.03$ ). Histologic response was higher in non-Latinos than in Latinos regardless of virologic response.

## Co-infected HCV/HIV patient

For the co-infected HIV/HCV patient, to provide the best chance for SVR with HCV, the patient should be on a stable antiretroviral regimen, with maximal CD4 benefit, prior to initiating HCV therapy.<sup>105</sup> For patients co-infected with HIV, the guidelines from AASLD (2009) recommend initial treatment with peginterferon plus ribavirin for 48 weeks.<sup>106</sup> When possible, patients receiving zidovudine or didanosine should be switched to another antiretroviral agent before beginning therapy with ribavirin (Class 1, Level C). The 2006 American Gastroenterological Association (AGA) technical review reports that three of four clinical trials support combination therapy with peginterferon plus ribavirin for 48 weeks regardless of genotype.<sup>107</sup> In this patient population, risks must be weighed against the potential limited benefits as co-infected patients do not respond to therapy as well as mono-infected patients.

In 2007, recommendations for the care of patients co-infected with HIV and HCV were updated by the HCV-HIV International Panel.<sup>108</sup> Patients should be treated with the standard doses of peginterferons and weight based dosing of ribavirin. Predictions for SVR can be estimated based on negative serum HCV RNA at week four of treatment.<sup>109</sup> Patients who achieve a reduction  $< 2\text{-log}_{10}$  IU/mL in HCV RNA at week 12 and/or the presence of detectable viremia at week 24 should consider therapy discontinuation since the likelihood of successful therapy is very low. This is the same treatment decisions considered in mono-infected patients. Patients with HCV genotypes 2 or 3 with a rapid virologic response at week four may benefit from a 24 week treatment, whereas patients with HCV genotypes 1 or 4 with early virologic response at week 12 might benefit from prolonged therapy (60-72 weeks). Acute HCV infection in HIV-positive patients should be treated for 24 weeks with a combination of peginterferon plus weight based dosing of ribavirin.

In an open-label, multicenter, controlled trial, randomized trial to compare the safety and efficacy of two interferons, 133 patients with HIV/HCV co-infection were randomized to peginterferon alfa-2a plus ribavirin or interferon alfa-2a plus ribavirin for 48 weeks.<sup>110</sup> The percentage of patients with HCV genotype 1 was 78 percent. Eighty-six percent of patients were receiving stable antiretroviral therapy for HIV with 60 percent of patients had fewer than 50 copies of HIV-1 RNA/mL. The primary outcome measures were the virologic response at week 24 that was defined as an HCV RNA level of less than 60 IU/mL and safety. The secondary outcome measures included SVR. A total of 66 subjects were randomized to receive peginterferon alfa-2a 180 µg weekly for 48 weeks, and 67 subjects were randomized to receive interferon alfa-2a 6 million IU three times weekly for 12 weeks followed by 3 million IU three times weekly for 36 weeks. Both groups received ribavirin according to a dose-escalation schedule. At week 24, virologic response was observed in 44 percent and 15 percent of the peginterferon and interferon treatment groups, respectively ( $p<0.001$ ). The SVR rates after completion of 48 weeks of therapy were 27 percent and 12 percent, respectively ( $p=0.03$ ). SVR rates for genotype 1 patients were 14 percent and 6 percent for the peginterferon and interferon groups, respectively ( $p=NS$ ). Twelve percent of each group withdrew due to abnormal laboratory values or adverse events. Safety profiles of the two drugs were similar.

In a randomized trial with 868 patients infected with both HCV and HIV, safety and efficacy of peginterferon alfa-2a (PEGASYS) plus either ribavirin or placebo were compared to interferon alfa-2a plus ribavirin.<sup>111</sup> In this treatment-naïve patient population, patients were on highly active antiretroviral therapy (HAART) and had CD4 counts greater than 100 cells/mL<sup>3</sup>. Patients were given one of the following three regimens for 48 weeks: peginterferon alfa-2a 180 mcg weekly plus ribavirin 800

mg per day, peginterferon alfa-2a plus placebo, or interferon alfa-2a 3 million IU three times weekly plus ribavirin. The overall SVR was significantly higher among patients receiving peginterferon alfa-2a plus ribavirin compared to those receiving interferon alfa-2a plus ribavirin (40 versus 12 percent, odds ratio, 5.40; 97.5% CI, 3.20 to 9.12;  $p<0.001$ ) or peginterferon alfa-2a plus placebo (40 versus 20 percent, odds ratio, 2.89; 97.5% CI, 1.83 to 4.58;  $p<0.001$ ). Peginterferon alfa-2a plus placebo had significantly higher SVR rates than interferon alfa-2a plus placebo (20 versus 12 percent; odds ratio, 0.53; 97.5% CI, 0.30 to 0.91;  $p=0.008$ ). For patients with genotype 1, SVR was highest with peginterferon alfa-2a plus ribavirin (29 percent) followed by peginterferon alfa-2a (14 percent) and interferon alfa-2a plus ribavirin (7 percent). SVR rates for genotypes 2 or 3 were 62 percent for peginterferon alfa-2a plus ribavirin, 36 percent for peginterferon alfa-2a plus placebo, and 20 percent for interferon alfa-2a plus ribavirin. Significantly more patients withdrew from treatment in the peginterferon alfa-2a plus ribavirin (39 percent) compared to the interferon alfa-2a plus ribavirin (25 percent,  $p<0.001$ ).

A trial evaluated the prolonged use of peginterferon alfa-2a (PEGASYS) plus ribavirin in HIV/HCV co-infected patients from Spain.<sup>112</sup> Patients ( $n=110$ ) were given peginterferon alfa-2a 180 mcg weekly plus ribavirin 800 mg daily for 12 weeks. EVR was achieved in 70 patients (63.6 percent). Patients that achieved EVR continued therapy for an additional 12 or 36 weeks depending on their genotype. Patients not achieving EVR randomized to a total of 48 weeks or 72 weeks of therapy, regardless of genotype. SVR was achieved in 41.8 percent of the overall study population. None of the 11 patients allocated to the 48-week extended arm achieved SVR, and only one patient of the 16 patients allocated to the extended arm of 72 weeks achieved SVR. The drop-out rate was 68 percent in the extended therapy group. Authors concluded that extending therapy in HIV/HCV co-infected patients without EVR does not provide additional benefit.

The PEGASYS Ribavirina España Coinfección (PRESCO) study evaluated short and extended duration of treatment for chronic hepatitis C using peginterferon alfa-2a (PEGASYS) 180 mcg weekly plus weight-based ribavirin 1,000 to 1,200 mg daily in 389 HIV-seropositive patients.<sup>113</sup> Patients with hepatitis C genotype 1 or 4 received treatment for 12 or 18 months; patients with genotypes 2 and 3 received combination therapy for six or 12 months. End of treatment response and SVR were defined as undetectable HCV RNA at the end of therapy and 24 weeks after completion of treatment, respectively. End of treatment response was reported in 262 patients (67.3 percent) who comprised the following patient subtypes: 106 patients (55 percent) with genotype 1, 137 patients (90 percent) with genotypes 2 or 3; and 19 patients (41 percent) with genotype 4. Six patients were lost to follow-up during the 24-week observation period. Of the remaining patients ( $n=256$ ), 62 patients (24 percent) relapsed. Overall SVR was achieved in 194 patients (49.7 percent). The best independent predictors of relapse were baseline HCV RNA level  $> 500,000$  IU/mL (relative risk=4.81; 95% CI, 1.52 to 15.22;  $p=0.008$ ) and lack of rapid virologic response (RVR) defined as undetectable HCV RNA at week four (relative risk=2.94; 95% CI, 1.22 to 7.09;  $p=0.02$ ). Additionally, highly active antiretroviral therapy (HAART) was associated with a greater risk of HCV relapse. In summary, higher baseline HCV RNA, lack of RVR, and concomitant use of HAART were identified as independent predictors of relapse.

Peginterferon alfa-2b (PEGIntron) is currently not FDA-approved for the treatment of HIV-HCV co-infected patients.<sup>114,115</sup> There are two trials published for peginterferon alfa-2b plus ribavirin that demonstrate overall SVR rates of 38 to 44 percent. The 2009 AASLD practice guidelines for the treatment of hepatitis C do not differentiate the two peginterferons in the recommendations.<sup>116</sup>

Specific data to base definitive recommendations on the doses and duration of therapy for HIV/HCV co-infected patients do not exist at this time.

Safety and efficacy of interferon alfacon-1 (Infergen), alone or in combination with ribavirin, have not been proven in patients co-infected with HIV-1 or hepatitis B.

Safety and efficacy of telaprevir in the co-infected HCV/HIV patient have not been established. Safety and efficacy of telaprevir in the co-infected HCV/HBV patient have not been studied.

Safety and efficacy of boceprevir in the co-infected HCV/HIV patient with genotype 1 have not been established. Safety and efficacy of boceprevir in the co-infected HCV/HBV patient with genotype 1 have not been studied.

### **Patients who have not responded, partially respond or who have relapsed following initial treatment**

There are three classifications used for patients who have received previous therapy for chronic HCV but who failed treatment. Those whose HCV RNA level did not decline by at least  $2\text{-log}_{10}$  IU/mL by treatment week 12 are classified as null responders. Those whose HCV RNA level had dropped by at least  $2\text{-log}_{10}$  IU/mL at week 12, but still had detectable HCV RNA at week 24 are classified as partial responders. Relapsers are defined as patients who have had undetectable HCV RNA during therapy and then develop measurable HCV RNA within the six months after the completion of therapy.

Few trials with heterogeneous populations have evaluated the use of the peginterferons for patients who have relapsed or not responded to initial therapy.<sup>117,118,119</sup> Relapsers have a higher rate of response in retreatment trials than patients who do not respond to initial treatment. Retreatments of nonresponders with peginterferon plus ribavirin has produced SVR rates of 13 to 18 percent. The 2009 AASLD guidelines state that patients who have relapsed are likely to respond to the same regimen given a second time, but they will still experience an unacceptable rate of relapse.<sup>120</sup> Data on retreatment of relapsers to peginterferon and ribavirin have not been published. Approximately 30 percent of patients treated with pegylated interferon and ribavirin are unable to clear virus from the serum. Retreatments with peginterferon and ribavirin in non-responders is not recommended even if a different type of peginterferon is administered according to the 2009 AASLD guidelines (Class 3, Level B). There is no convincing evidence that switching to alternative interferon is effective.

Phase 3 trials of the protease inhibitors included evaluations of treatment-experienced patients with genotype 1 chronic HCV infection. For both boceprevir and telaprevir, studies showed that retreatment with triple therapy was superior to retreatment with peginterferon plus ribavirin in obtaining a SVR.<sup>121,122</sup> Patients who had relapsed have higher response rates (SVR) on retreatment compared to those with a prior partial response. Null responders have the lowest response rate; retreatment of null responders with the telaprevir containing triple therapy regimen produced SVR rates of 28 percent.

The 2011 AASLD guidelines for treatment of genotype 1 HCV infection recommend retreatment of patients who had virologic relapse or were partial responders after a prior course of nonpegylated or pegylated interferon alfa and/or ribavirin treatment with triple therapy (boceprevir or telaprevir and peginterferon alfa plus weight-based ribavirin) (Class 1, Level A). Re-treatment with telaprevir, peginterferon alfa and weight-based ribavirin may be considered for prior null responders (Class 2b, Level B).<sup>123</sup>

Interferon alfacon-1 (Infergen) also has been investigated to treat patients who fail initial therapy. The sustained HCV RNA response rate among prior nonresponders was 13 percent at 48 weeks, and the sustained alanine aminotransferase (ALT) response rate for nonresponders was 12 percent (24 weeks) and 17 percent (48 weeks).<sup>124,125,126,127,128</sup>

## Renal Impairment<sup>129</sup>

Persons with GFR > 60mL/min with HCV are treated with standard regimens of peginterferon and ribavirin. According to the 2009 AASLD guidelines, patients with severe chronic kidney disease (CKD) not on hemodialysis may be treated with reduced doses of peginterferon (alfa-2a 135 mcg/week or alfa-2b 1 mcg/kg/week) and ribavirin 200-800 mg daily with careful monitoring for adverse effects (Class 2a, level C). Patients on dialysis may be considered for treatment with standard interferon (alfa-2a or alfa-2b) 3 mU three times weekly or reduced dose peginterferon (alfa-2a 135 mcg/week or alfa-2b 1 mcg/kg/week) (Class 2b, level C). Ribavirin at a reduced dosage may be used with careful monitoring for anemia and other adverse effects (Class 2b, level C).

According to the prescribing information, the peginterferon alfa-2b (PEGIntron) dose should be reduced by 25 percent for patients with moderate renal impairment (CrCl 30 to 50 mL/minute). For patients with severe renal dysfunction (CrCl 10 to 29 mL/minute), including those on hemodialysis, peginterferon alfa-2b dose should be reduced by 50 percent. If renal function decreases during treatment, peginterferon alfa-2b should be discontinued. When peginterferon alfa-2b and ribavirin are given in combination, patients with impaired renal function and patients over age of 50 years should be more carefully monitored for the development of anemia.

The peginterferon alfa-2a (PEGASYS) dosage should be reduced to 135 mcg once weekly in patients with a CrCl < 30 mL/minute, including those with endstage renal disease and those on hemodialysis. Signs and symptoms of toxicity should be closely monitored and if severe or if laboratory abnormalities develop, the dose may be reduced to 90 mcg until symptoms abate. There is no data available on dosage adjustments for renal failure in pediatric patients.<sup>130</sup>

The recommended dosage for ribavirin (Copegus) in patients with renal impairment is: for CrCl 30 to 50 mL/minute, alternating doses of 200 mg and 400 mg every other day; for CrCl < 30 mL/minute and those on hemodialysis, 200 mg daily.<sup>131</sup> The prescribing information for Rebetol states that ribavirin should not be used in patients with a CrCl < 50 mL/minute.<sup>132</sup>

Interferon alfacon-1 plus ribavirin should not be administered to patients with creatinine clearance <50 mL/minute.

No dosage adjustment of telaprevir is required for patients with mild, moderate or severe renal impairment. Telaprevir has not been studied in patients with end stage renal dysfunction or those on hemodialysis.

No dosage adjustment is required for boceprevir with renal impairment.

## Hepatic Impairment<sup>133</sup>

Patients with compensated cirrhosis (Child-Turcotte-Pugh [CTP] class A) may be treated with standard treatment with close monitoring for adverse effects (Class 1, Level A). Patients with decompensated cirrhosis should be referred for consideration for liver transplantation (Class 1, Level B). Interferon-based therapy may be considered for patients with decompensated cirrhosis (CTP class B and C) if the

patients have already been accepted as candidates for liver transplantation and are treated by experienced clinicians (Class 2b, Level C). For liver transplant recipients who have recurrent histologic disease, use peginterferon alfa either with or without ribavirin is the preferred regimen when treating hepatitis C (Class 2a, Level B). For peginterferon alfa-2a, dose should be reduced to 135 mcg/week when patient experiences progressive elevations of ALT above baseline values. After dose reduction or a period of withheld therapy to allow ALT flares to subside, peginterferon alfa-2a may be resumed.

In patients with decompensated cirrhosis (bilirubin level > 1.5 mg/100mL; prothrombin time > 15 seconds [international normalized ratio (INR)  $\geq$  1.7]; albumin level < 3.4 g/100mL; history of ascites, bleeding esophogastric varices, or hepatic encephalopathy), antiviral therapy is not recommended. These patients should be referred for evaluation as liver transplant candidates.<sup>134</sup>

Safety and efficacy of boceprevir has not been studied in patients with decompensated cirrhosis or in patients with an organ transplant. No dose adjustment of boceprevir is required for patients with mild, moderate or severe hepatic impairment.

No dosage adjustment is necessary for patients with mild hepatic impairment (Child-Pugh A, score 5-6). Telaprevir is not recommended for use in patients with moderate or severe hepatic impairment (Child-Pugh B or C, score  $\geq$  7) because there is little information on its pharmacokinetics, safety or the appropriate dosage in this population.

## Other

The safety and efficacy of interferon alfas, alone or in combination with ribavirin, for the treatment of chronic HCV infection in liver or other organ transplant recipients have not been established.

The safety and efficacy of telaprevir in solid organ transplant recipients have not been established.

The safety and efficacy of boceprevir alone or in combination with peginterferon alfa and ribavirin for the treatment of chronic hepatitis C genotype 1 infection in liver or other organ transplant recipients have not been studied.

## DOSAGES

### Monotherapy

Drug	Dosage	Duration of Therapy	Dosage Forms
interferon alfacon-1 (Infergen) <sup>135</sup>	IFN-naïve patients: 9 mcg SC three times weekly (if not tolerated, dosage reduction to 7.5 mcg may be necessary)	24 weeks	SDV: 9 mcg/0.3 mL, 15 mcg/0.5 mL
	IFN relapsers or nonresponders: 15 mcg SC three times weekly	48 weeks	
peginterferon alfa-2a (PEGASYS) <sup>136</sup>	Age ≥18 years: 180 mcg SC once weekly (consideration should be given to discontinuing therapy after 12-24 weeks if the patient has failed to demonstrate EVR defined as undetectable HCV RNA or at least 2-log <sub>10</sub> reduction from baseline in HCV RNA titer after 12 weeks)	48 weeks	SDV: 180 mcg/1 mL prefilled syringes: 180 mcg/0.5 mL <b>Autoinjector: 180 mcg/0.5 mL, 135 mcg/0.5 mL</b> <u>Convenience packs</u> 4 SDV: 180 mcg/1 mL (with syringes)
peginterferon alfa-2b (PEGIntron) <sup>137</sup>	Age ≥18 years: 1 mcg/kg SC once weekly (consideration to discontinue therapy if < 2-log reduction of HCV- RNA at 12 weeks, or if HCV-RNA remains detectable after 24 weeks of therapy)	1 year	SDV: powder for injection (with diluent and syringes) 50, 80, 120, 150 mcg Redipen: 50, 80, 120, 150 mcg/0.5 mL

SDV = single dose vial

Dose modifications may be necessary due to adverse effects such as neutropenia, thrombocytopenia, depression, progressive increases in ALT values over baseline, and impaired renal function. Consult prescribing information for dosage adjustments.

### Combination Therapy

The AASLD 2011 guidelines recommend that patients with genotype 1 HCV infection be treated for 24 to 48 weeks with triple therapy containing boceprevir or telaprevir in combination with peginterferon and weight-based ribavirin. The protease inhibitors cannot be used alone. The total duration of therapy depends on viral response, whether the patient has cirrhosis and whether the patient is treatment naïve or has been previously treated with an interferon and/or ribavirin. For boceprevir-containing regimens, all three drugs should be discontinued if the HCV RNA level is >100 IU/mL at treatment week 12 or detectable at treatment week 24. For telaprevir-containing regimens, all three drugs should be stopped if the HCV RNA level is >1,000 IU/mL at treatment weeks 4 or 12 and/or is detectable at treatment week 24.<sup>138</sup> The 2009 guidelines recommend that patients with genotypes 2 and 3 be treated for 24 weeks using peginterferon weekly plus ribavirin 800 mg daily in divided doses.

Genotype 1 infected patients should only be treated with dual therapy (peginterferon alfa plus ribavirin), without an HCV protease inhibitor, if there are contraindications, significant intolerance or other clinical factors that would preclude use of a protease inhibitor. The recommended duration of treatment when peginterferon alfa and ribavirin are chosen as a two drug regimen for genotype 1 HCV is 48 weeks. Discontinuation should be considered if the patient does not achieve at least a 2-log<sub>10</sub> drop or loss of HCV RNA at 12 weeks or if HCV RNA remains detectable after 24 weeks.<sup>139,140</sup>

Peginterferon alfa-2a + ribavirin should be discontinued in patients who develop hepatic decompensation during treatment.

Interferon alfacon-1 (Infergen) - Patients who fail to achieve at least a 2- $\log_{10}$  drop at 12 weeks or undetectable HCV-RNA at week 24 are highly unlikely to achieve SVR and discontinuation of therapy should be considered.

### Dosages (continued)

Drug	Dosage	Duration of Therapy	Availability
<b>Dual Combination therapy</b>			
interferon alfacon-1 (Infergen) <sup>141</sup>	15 mcg SC daily plus ribavirin (1,000 mg per day if <75 kg or 1,200 mg per day if ≥75 kg)	48 weeks	SDV: 9 mcg/0.3 mL, 15 mcg/0.5 mL
peginterferon alfa-2a (PEGASYS) + ribavirin <sup>142</sup>	Genotypes 1, 4: 180 mcg SC once weekly plus ribavirin (1,000 mg per day if <75 kg or 1,200 mg per day if ≥75 kg)	48 weeks	SDV: 180 mcg/1 mL Autoinjector: 180 mcg/0.5 mL, 135 mcg/0.5 mL Convenience packs
	Genotypes 2, 3: 180 mcg SC once weekly plus ribavirin 400 mg twice daily	24 weeks	4 SDV: 180 mcg/1 mL (with syringes)
	Co-infection with HIV (regardless of genotype): 180 mcg SC once weekly plus ribavirin 400 mg twice daily	48 weeks	4 prefilled syringes: 180 mcg/0.5 mL
	Age 5 to 17 years: 180 mcg/1.73 m <sup>2</sup> SC once weekly plus ribavirin 15 mg/kg/day orally with food in two divided doses	Genotype 1: 48 weeks  Genotypes 2&3: 24 weeks	
peginterferon alfa-2b (PEGIntron) + ribavirin <sup>143</sup>	Age ≥18 years: 1.5 mcg/kg SC once weekly plus ribavirin 800 to 1,400 mg per day, based on body weight, in two divided doses Age 3- 17 years: 60 mcg/m <sup>2</sup> /week plus ribavirin 15 mg/kg/day orally with food in two divided doses Patients who reach their 18th birthday while receiving therapy should remain on the pediatric dosing regimen.	Genotype 1: 48 weeks  Genotypes 2 & 3 : 24 weeks  Retreatment of prior treatment failure: 48 weeks, for all genotypes.	SDV: powder for injection (with diluent and syringes) 50, 80, 120, 150 mcg Redipen: 50, 80, 120, 150 mcg/0.5 mL
<b>Triple Combination therapy</b>			
boceprevir (Victrelis) plus peginterferon/ribavirin	800 mg administered orally three times daily (every 7 - 9 hours) with food (a meal or light snack); therapy is initiated after 4 weeks of peginterferon and ribavirin therapy	24 – 44 weeks in combination with peginterferon and ribavirin	200 mg capsule
telaprevir (Incivek) plus peginterferon/ribavirin	750 mg administered orally three times daily (every 7 - 9 hours) with food (not low fat)	12 weeks in combination with peginterferon and ribavirin	375 mg tablet

## ribavirin

Drug	Adult Dosage	Availability
ribavirin (Copegus)	As listed above for combination therapy.	Tablet: 200 mg
ribavirin (Rebetol)		Capsule: 200 mg Oral solution: 40 mg/mL
ribavirin (Ribapak)		Unit Dose Packs: 400-400 (56 X 400 mg tablets) 400-600 (28 X 400 mg + 28 X 600 mg tablets) 600-600 (56 X 600 mg tablets)
ribavirin (Ribasphere)		Capsules: 200 mg Tablets: 400, 600 mg

Dose modifications may be necessary due to adverse effects such as neutropenia, thrombocytopenia, depression, progressive increases in ALT values over baseline, and impaired renal function. Consult prescribing information for dosage adjustments.

## CLINICAL TRIALS

### Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class and chronic hepatitis C for the FDA-approved indications. Randomized, controlled comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Due to the chronic nature, course of disease progression, and treatment duration for hepatitis C, most of the comparative trial data involve study designs that lack blinding. Studies performed in the United States were given preference since genotype 1 is most common in the US and has been associated with lower SVR. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Clinical trials evaluating the pegylated products versus the non-pegylated products with and without ribavirin have been completed.<sup>144,145,146,147</sup>

### peginterferon alfa-2b (PEGIntron) + ribavirin versus peginterferon alfa-2a (PEGASYS) plus ribavirin in early virological response at 12 weeks

A randomized Romanian trial compared the efficacy of two peginterferons plus ribavirin with early virologic response in 116 patients with chronic hepatitis C.<sup>148</sup> Patients were given peginterferon alfa-2a (PEGASYS) 180 mcg weekly plus ribavirin or peginterferon alfa-2b (PEGIntron) 1.5 mcg/kg weekly plus ribavirin. Ribavirin was dosed according to body weight. The patient population had treatment-naïve

patients as well as relapsers and nonresponders. The PEG-Intron group had more relapsers and nonresponders. EVR was assessed after 12 weeks of therapy and was defined as at least 2- $\log_{10}$  reduction in viral load from baseline. The EVR at 12 weeks was 82.2 percent and 67.2 percent for the PEGASYS and PEG-Intron groups, respectively ( $p=0.08$ ). There were no significant differences in EVR between the two groups for the treatment naïve patients (89.6 versus 75.2 percent,  $p=0.61$ ). No significant differences in EVR were noted for the relapsers or the nonresponders either. This study lacked blinding and enrolled a heterogeneous patient population.

Peginterferon alfa-2a (PEGASYS) 180 mcg weekly and peginterferon alfa-2b (PEGIntron) 1.5 mcg/kg weekly, both with ribavirin, were compared in an open-label trial evaluating the early virologic response at 12 weeks in 385 adults with chronic hepatitis C genotype 1 with high viral loads.<sup>149</sup> Patients weighing less than 75 kg received ribavirin 1,000 mg daily, and patients weighing more than 75 kg received 1,200 mg daily. Five patients that were randomized did not receive any study drug. Therefore, only 380 patients were included in the intent-to-treat analysis. The mean HCV RNA levels were similar in both peginterferon groups throughout the study period. The early virologic response rate was defined as  $> 2\text{-}\log_{10}$  reduction in HCV-RNA concentration at week four or undetectable HCV-RNA at week 12. EVR was achieved in 66 percent of the peginterferon alfa-2a (PEGASYS) group and 63 percent of the peginterferon alfa-2b (PEGIntron) group. Patients on peginterferon alfa-2b (PEGIntron) plus ribavirin had a higher rate of discontinuation due to adverse effects (5.7 percent versus 1 percent). The study concluded that a substantial percentage of patients infected with HCV genotype 1 and high viral load can achieve EVR when treated with peginterferon and ribavirin.

A prospective, non-randomized, open-label trial performed in Spain enrolled 183 treatment-naïve patients with chronic hepatitis C.<sup>150</sup> Patients were given peginterferon alfa-2a plus ribavirin or peginterferon alfa-2b plus ribavirin. SVR rates were similar with 65.9 percent and 62 percent ( $p=0.64$ ) of patients receiving peginterferon alfa-2a and peginterferon alfa-2b, respectively, without differences according to genotype. In the patients with HCV genotype 1 ( $n=117$ ), the SVR rates were 50.8 percent and 46.6 percent of patients receiving peginterferon alfa-2a and peginterferon alfa-2b, respectively ( $p=0.713$ ). Rapid virological response at four weeks, early virological response at 12 weeks, and transient virological response were also similar. The rate of withdrawals due to treatment-related adverse events was 13.2 and 10.9 percent of patients in the peginterferon alfa-2a and peginterferon alfa-2b, respectively. The number of patients requiring dose modifications was similar in both groups. Authors concluded that peginterferons plus ribavirin have similar efficacy due to similar SVR rates.

### **peginterferon alfa-2a (PEGASYS) plus ribavirin (Copegus) versus peginterferon alfa-2b (PEG-Intron) plus ribavirin (Rebetol) for 48 weeks**

The Individualized Dosing Efficacy versus Flat Dosing to Assess Optimal PegInterferon Therapy (IDEAL) study was a randomized, open-label trial comparing peginterferon alfa-2b (PEG-Intron) with ribavirin (Rebetol) and peginterferon alfa-2a (PEGASYS) with ribavirin (Copegus) in treatment-naïve patients with chronic hepatitis C genotype 1.<sup>151,152</sup> Two comparisons were evaluated in the study: peginterferon alfa-2b 1 mcg/kg weekly plus ribavirin 800 to 1,400 mg daily (low dose peginterferon group,  $n=1,016$ ) versus peginterferon alfa-2b 1.5 mcg/kg weekly plus ribavirin 800 to 1,400 mg daily (standard dose peginterferon group,  $n=1,019$ ) and peginterferon alfa-2b 1.5 mcg/kg weekly plus ribavirin 800 to 1,400 mg daily versus peginterferon alfa-2a 180 mcg weekly plus ribavirin 1,000 to 1,200 mg daily ( $n=1,035$ ). Ribavirin dosing for the peginterferon alfa-2b was according to FDA-approved labeling. Weight-based ribavirin dosing for use with peginterferon alfa-2a was not FDA-

approved when the study was initiated. Therefore, ribavirin dosing with for the peginterferon alfa-2a group was calculated to deliver a mean of 13 mg/kg/day on the basis of data derived from previous trials and from the product information from the European Medicines Agency. All treatments were 48 weeks in duration followed by 24 weeks of follow-up observation. All groups had similar baseline characteristics including baseline HCV RNA levels, body weight and African American race. The primary endpoint of SVR was similar among the groups in the intent-to-treat population with 39.8, 38, and 40.9 percent of patients achieving SVR in peginterferon alfa-2b 1.5 mcg/kg - RBV group, peginterferon alfa-2b 1 mcg/kg - RBV group, and peginterferon alfa-2a - RBV group, respectively (all p=NS). At the end of treatment (48 weeks), peginterferon alfa-2a with ribavirin had a higher response rate at 64.4 percent compared to 53.2 and 49.2 percent, respectively for peginterferon alfa-2b 1.5 mcg/kg with ribavirin and peginterferon alfa-2b 1 mcg/kg with ribavirin (standard dose peginterferon versus low dose peginterferon alfa-2b, p=0.04; standard dose peginterferon alfa-2b versus peginterferon alfa-2a, p<0.001). Relapse rate was also higher with peginterferon alfa-2a (31.5 percent) compared to 23.5 percent with standard dose peginterferon alfa-2b (8 percent difference, 95% CI, -13.2 to -2.8) and 20 percent with low dose peginterferon alfa-2b (standard dose peginterferon versus low dose peginterferon, 3.5 percent difference (95% CI, -1.6% to 8.6%). Due to the differences in FDA-approved ribavirin regimens, there are some notable differences among the groups in regards to ribavirin dosing and dosing adjustments. The mean ribavirin dose was significantly lower in the peginterferon alfa-2b groups (standard dose: 12.4 mg/kg/day; low dose: 12.6 mg/kg/day) compared to peginterferon alfa-2a (13.4 mg/kg/day) (p<0.001 for standard dose peginterferon alfa-2b group versus peginterferon alfa-2a; p≤0.001 for low dose peginterferon alfa-2b versus peginterferon alfa-2a groups). The peginterferon alfa-2a arm had greater dose reductions for adverse effects compared to the peginterferon alfa-2b arms per the approved labeling. Dose reductions with ribavirin were required prior to the administration of erythropoietin for the treatment of ribavirin-related anemia. Overall adverse effects reported were similar among the three groups. Discontinuation rates were 13, 10, and 13 percent for low dose peginterferon alfa-2b, standard dose peginterferon alfa-2b, and peginterferon alfa-2a, respectively. The manufacturer of PEG-Intron supported the study.

An Italian clinical trial compared the safety and efficacy of peginterferon alfa-2a plus ribavirin and peginterferon alfa-2b plus ribavirin for the treatment of chronic hepatitis C.<sup>153</sup> Patients were treatment naïve and were stratified by HCV genotype. Treatment duration was 24 or 48 weeks depending on HCV genotype. Patients were randomized to peginterferon alfa-2a 1.5 mcg/kg/week plus ribavirin 800 to 1,200 mg per day (n=212) or peginterferon alfa-2b 180 mcg/week plus ribavirin 800 to 1,200 mg per day (n=219). Baseline characteristics were similar between the two groups. By intention to treat, the two groups showed similar rates of treatment-related serious adverse events (both one percent) and discontinuation rates for adverse effects (seven versus six percent, respectively). Overall, SVR was higher in the peginterferon alfa-2a group than in the peginterferon alfa-2b group (66 percent versus 54 percent, respectively, p=0.02). For HCV genotypes 1 and 4, the SVR was 48 percent versus 32 percent, respectively (p=0.04). For the 143 patients with genotype 2, the SVR was 96 percent versus 82 percent, respectively (p=0.01).

In an Italian study of 320 consecutive, treatment-naïve patients with chronic hepatitis C, peginterferon alfa-2a 180 mcg weekly and peginterferon alfa-2b 1.5 mcg/kg weekly plus ribavirin were compared. Ribavirin was administered based on body weight. Duration of therapy was determined by genotype with genotypes 1 or 4 requiring 48 weeks of therapy and genotypes 2 and 3 requiring 24 weeks of therapy.<sup>154</sup> The primary outcome was SVR. Overall SVR were higher with peginterferon alfa-2a group

(68.8 percent) compared to peginterferon alfa-2b (54.4 percent;  $p=0.008$ ). Higher SVR rates were obtained in peginterferon alfa-2a than peginterferon alfa-2b among patients with genotype 1/4 (54 percent versus 39.8 percent;  $p=0.04$ ), with genotype 2/3 (88.1 percent versus 74.6 percent;  $p=0.046$ ), without cirrhosis (75.6 percent versus 55.9 percent;  $p=0.005$ ), and with baseline levels HCV RNA  $>500,000$  IU/mL (69 percent versus 46.2 percent;  $p=0.002$ ). SVR rates in the two groups were not statistically different among patients with baseline HCV RNA  $\leq 500,000$  IU/mL (68.4 percent versus 65.7 percent;  $p=0.727$ ) or in patients with cirrhosis (42.4 percent versus 46.1 percent;  $p=0.774$ ).

In an open-label, Egyptian trial, peginterferon alfa-2a/ribavirin and peginterferon alfa-2b/ribavirin were compared in 117 patients with chronic hepatitis C with genotype 4.<sup>155</sup> Patients were randomized to receive a weekly dose of peginterferon alfa-2a 180 mcg or peginterferon alfa-2b 1.5 mg/kg/week and a daily dose of ribavirin of 1,000-1,200 mg for 48 weeks. Overall SVR was 59.9 percent. SVR rate for peginterferon alfa-2a (70.6 percent) were higher than for peginterferon alfa-2b (54.6 percent;  $p=0.017$ ). Relapse rates were significantly lower with peginterferon alfa-2a (5.1 versus 15.7 percent;  $p=0.0019$ ). Tolerability was similar.

### **peginterferon alfa-2a (PEGASYS) plus ribavirin (Copegus) versus peginterferon alfa-2b (PEG-Intron) plus ribavirin (Rebetol) for 48 weeks in chronic hepatitis C/HIV co-infected patients**

In a prospective, randomized, open-label study, the efficacy and safety of peginterferon alfa-2b weight based dosing (80 to 150 mcg/week) and peginterferon alfa-2a 180 mcg/kg/week for 48 weeks were compared in 182 patients co-infected with HCV and HIV.<sup>156</sup> Patients were treatment-naïve for HCV therapy. All patients received ribavirin 800 to 1,200 mg daily for 48 weeks. Overall, SVR rates were 42 percent for peginterferon alfa-2b and 46 percent for peginterferon alfa-2a ( $p=0.65$ ). For genotypes 1 and 4, SVRs rates were 28 percent versus 32 percent ( $p=0.67$ ) for peginterferon alfa-2b and peginterferon alfa-2a, respectively. For genotypes 2 and 3, SVR rates were 62 percent and 71 percent ( $p=0.6$ ) for peginterferon alfa-2b and peginterferon alfa-2a, respectively. At 12 weeks, EVR was 70 percent in peginterferon alfa-2b group and 80 percent in the peginterferon alfa-2a group ( $p=0.13$ ). Discontinuation due to adverse effects occurred in eight percent on peginterferon alfa-2b and 13 percent on peginterferon alfa-2a ( $p=0.47$ ).

### **interferon alfacon-1 (Infergen) versus interferon alfacon-1 (Infergen) plus ribavirin**

Forty treatment-naïve subjects with chronic hepatitis C were randomized to two treatment groups: interferon alfacon-1 9 mcg daily or interferon alfacon-1 9 mcg daily plus ribavirin 1,000 or 1,200 mg daily.<sup>157</sup> All subjects received 48 weeks of open-label therapy except for non-genotype 1 subjects in the combination treatment group, who received only 24 weeks of therapy. The proportion of subjects with genotype 1 infection was approximately 50 percent in each group. SVR was exhibited in 20 and 40 percent of subjects in the monotherapy and combination therapy groups, respectively ( $p=NS$ ). For patients with genotype 1, SVR was 10 and 18 percent in the monotherapy and combination therapy groups, respectively ( $p=NS$ ). Study discontinuations due to adverse events related to study drug were 20 and 25 percent, respectively. A total of four serious adverse events occurred, two in each treatment group, only one of which was determined to be study drug-related.

## boceprevir (Victrelis) and peginterferon plus ribavirin

A randomized, double-blind study (SPRINT-2) evaluated the addition of boceprevir to peginterferon-ribavirin for the treatment of HCV genotype 1 in previously untreated adults.<sup>158</sup> All patients received peginterferon alfa-2b 1.5 mcg/kg weekly and ribavirin with weight-based dosing for the initial four weeks. Group 1 received placebo in addition to peginterferon + ribavirin for 44 weeks. Group 2 received boceprevir plus peginterferon + ribavirin for 24 weeks, and those with a detectable HCV RNA level between weeks eight and 24 received placebo plus peginterferon + ribavirin for an additional 20 weeks. Group 3 received boceprevir plus peginterferon + ribavirin for 44 weeks. A total of 938 non-Black and 159 Black patients were treated. In the nonblack population, the SVR was 40 percent in group 1 (125/311 patients), 67 percent in group 2 (211/316 patients;  $p < 0.001$ ), and 68 percent in group 3 (213/311 patients;  $p < 0.001$ ). In the Black cohort, the SVR was 23 percent in group 1 (12/52 patients), 42 percent in group 2 (22/52 patients;  $p = 0.04$ ), and 53 percent in group 3 (29/55 patients;  $p = 0.004$ ). SVR were similar for patients receiving boceprevir for 24 and 44 weeks. For patients in group 2, a total of 44 percent of patients received peginterferon-ribavirin for 28 weeks. Dose reductions due to anemia occurred in 13 and 21 percent of group 1 and boceprevir-treated patients, respectively. The manufacturer of boceprevir supported the study.

In a randomized, double-blind clinical trial (RESPOND-2), the effect of the combination of boceprevir and peginterferon + ribavirin was assessed in patients with chronic HCV genotype 1 who had previously been treated.<sup>159</sup> All patients received peginterferon alfa-2b 1.5 mcg/kg weekly and ribavirin with weight-based dosing for the initial four weeks. Patients were then randomized to placebo plus peginterferon + ribavirin (group 1) for 44 weeks, group 2 received boceprevir plus peginterferon + ribavirin for 32 weeks, and patients with a detectable HCV RNA at week eight received placebo plus peginterferon + ribavirin for an additional 12 weeks; and group 3 received boceprevir plus peginterferon + ribavirin for 44 weeks. A total of 403 patients were treated. SVR was achieved in 59 percent of group 2 and 66 percent of group 3 (both boceprevir groups  $p < 0.001$ ) compared to 21 percent in the control group or group 1. Among patients with an undetectable HCV RNA level at week eight, the rate of SVR was 86 percent after 32 weeks of triple therapy and 88 percent after 44 weeks of triple therapy. For patients ( $n = 102$ ) with a decrease of  $< 1\text{-log}_{10}$  HCV RNA at treatment week 4, SVR rates were zero percent for the control group (group 1), 33 percent and 34 percent for group 2 and 3, respectively. Anemia was significantly more common in the groups receiving boceprevir than in the control group. The manufacturer of boceprevir supported the study.

## telaprevir (Incivek) and peginterferon plus ribavirin<sup>160</sup>

A randomized, double-blind study (ADVANCE) evaluated the addition of telaprevir for the first eight or 12 weeks of peginterferon-ribavirin for the treatment of HCV genotype-1 in previously untreated adults.<sup>161</sup> All patients received peginterferon alfa-2a 180 mcg weekly and ribavirin with weight-based dosing. Group 1 received telaprevir in addition to peginterferon + ribavirin for eight weeks followed by peginterferon + ribavirin for a total of 24 or 48 weeks. Group 2 received telaprevir plus peginterferon + ribavirin for 12 weeks, followed by peginterferon + ribavirin for a total of 24 or 48 weeks. Patients with undetectable HCV-RNA at four and 12 weeks (eRVR) were treated for a total of 24 weeks; those who did not have undetectable HCV-RNA at both four and 12 weeks received peginterferon + ribavirin for 48 weeks. Group 3 was treated with placebo plus peginterferon + ribavirin for 12 weeks followed by interferon + ribavirin for a total course of 48 weeks. A total of 1,088 subjects were enrolled; nine percent were Black. The overall SVR was 72 percent in group 1, 79 percent in group 2, and 46 percent

in group 3. Overall SVR was obtained in 62 percent (16/26) of Black patients. Group 2 had higher SVR rates among subjects with demographic or disease characteristics associated with poorer response compared to group 1. More patients in group 1 experienced virologic breakthrough after week 12 while receiving peginterferon + ribavirin (16 percent) than those in Group 2 (10 percent). Obtaining an eRVR predicted SVR. An eRVR was obtained in 58 percent of Group 2 patients versus eight percent of control group patients. Of those with an eRVR, 92 percent (195/212) of Group 2 patients and 93 percent (27/29) of group 3 patients achieved a SVR. Of patients who did not obtain an eRVR, extending the duration of peginterferon + ribavirin to 48 weeks resulted in higher SVR rates (61 percent of group 2 patients and 42 percent of control patients in this subgroup obtained a SVR). On treatment virologic failure and relapse occurred in seven and four percent, respectively of Group 2 patients compared to 29 and 24 percent of control patients.

A randomized, open-label, supportive clinical trial (ILLUMINATE), compared the SVR rates in treatment-naïve patients achieving eRVR when treated with 12 weeks of telaprevir in combination with peginterferon + ribavirin for either 24 weeks or 48 weeks. A total of 540 subjects were enrolled. A total of 352 (65 percent) achieved eRVR and of those, 322 (60 percent) were then randomized to either 24 weeks (n=162) or 48 weeks (n=160) of peginterferon + ribavirin. The SVR rates were 92 percent in the 24 week group versus 90 percent in the 48 week group. In the subgroup with cirrhosis at baseline (n=61), 30 patients achieved an eRVR and were randomized to either 24 (n=18) or 48 (n=12) weeks of peginterferon + ribavirin. The SVR rates in these patients were 67 percent (12/18) in the 24 week treatment group versus 92 percent (11/12) in the 48 week treatment group.

A randomized, double-blind, placebo-controlled study (REALIZE) was conducted in 662 previously treated adults.<sup>162</sup> Patients were enrolled if they were a prior relapser (HCV-RNA undetectable at end of treatment following a peginterferon + ribavirin regimen but HCV-RNA detectable within 24 weeks of follow-up), a prior null responder (those that achieved a  $<2\text{-log}_{10}$  drop in HCV-RNA level at week 12 of prior therapy) or a prior partial responder ( achieved  $\geq 2\text{-log}_{10}$  drop in HCV RNA at week 12 of prior therapy but never achieved undetectable HCV RNA while on treatment). Subjects were randomized 2:2:1 to one of two telaprevir containing arms (with and without a peginterferon + ribavirin four-week lead-in) or to a control group. Group 1 received telaprevir and peginterferon + ribavirin for 12 weeks followed by peginterferon + ribavirin for a total duration of 48 weeks. Group 2 received peginterferon + ribavirin for four weeks (lead-in), followed by telaprevir and peginterferon + ribavirin for 12 weeks, followed by peginterferon + ribavirin for a total duration of 48 weeks. Group 3 received placebo + peginterferon + ribavirin for 16 weeks followed by peginterferon + ribavirin for a total duration of 48 weeks. There was no significant difference between groups 1 and 2 (with/without lead-in) in SVR rates, virologic failure, virologic breakthrough or relapse rates so the data were pooled. SVR rates in prior relapsers were 86 percent versus 22 percent for telaprevir-containing regimens and placebo-containing regimens, respectively. SVR rates in partial and null responders were 59 and 32 percent in group 1/2 versus 15 and five percent in the control group.

### Variations in dose or duration of therapy

Due to the lack of treatment success in many patients, studies have been conducted with the peginterferons and ribavirin that adjust the doses or treatment duration in an effort to improve SVR or reduce adverse effects and maintain similar SVR. Numerous studies have been completed which evaluated various doses of peginterferon and/or ribavirin. Some studies have also been completed

which evaluated various lengths of therapy in specific patient groups such as treatment duration based on genotype and response to therapy at either week four or 12 of treatment.

The Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) trial evaluated if long-term treatment with peginterferon alfa-2a would reduce the development of cirrhosis, liver cancer, or liver failure.<sup>163</sup> Patients (n=1,050) with chronic hepatitis C and advanced fibrosis who had not had a response to previous therapy with peginterferon and ribavirin were randomized to receive 90 micrograms of peginterferon weekly for 3.5 years or no treatment. The outcomes studied were death, liver cancer, or liver failure, and for those who did not have cirrhosis initially, the development of cirrhosis. At the end of the study, 34.1 percent of the treated group and 33.8 percent of the control group had experienced at least one outcome (hazard ratio, 1.01; 95% CI, 0.81 to 1.27; p=0.90). Patients in the treated group had significantly lower blood levels of the hepatitis C virus and improvement in liver inflammation (p<0.001). However, there was no major difference in rates of any of the primary outcomes between the groups. The study concluded that long-term therapy with peginterferon did not reduce the rate of disease progression in patients with chronic hepatitis C and advanced fibrosis, with or without cirrhosis, which had not had a response to initial treatment with peginterferon and ribavirin. Additionally, maintenance peginterferon therapy for four years did not reduce the incidence of hepatocellular carcinoma.<sup>164</sup> The cumulative incidences of HCC in treated and control patients with cirrhosis after seven years were 7.8 percent and 24.2 percent, respectively (hazard ratio [HR], 0.45; 95% CI, 0.24 to 0.83).

## META-ANALYSIS

An adjusted indirect analysis evaluated randomized controlled trials with peginterferons with ribavirin when compared to conventional interferon with ribavirin for the treatment of chronic hepatitis C.<sup>165</sup> The analysis found no statistically significant differences between combination therapy with ribavirin with peginterferon alfa-2a and peginterferon alfa-2b for SVR, discontinuations due to adverse effects, anemia, depression or flu-like symptoms. Closer evaluation of the studies did not reveal any difference in the result.

A systematic review evaluated the direct comparative randomized studies of the peginterferon alfa-2a and peginterferon alfa-2b to assess the benefits and harms of the two treatments.<sup>166</sup> Searches were performed with the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and LILACS through July 2009. Twelve randomized clinical trials, including 5,008 patients, that compared peginterferon alpha-2a plus ribavirin versus peginterferon alfa-2b plus ribavirin were identified. Overall, peginterferon alpha-2a significantly increased the number of patients who achieved SVR versus peginterferon alfa-2b in eight trials (47 percent versus 41 percent; risk ratio 1.11, 95% CI, 1.04 to 1.19; p=0.004). Subgroup analyses of risk of bias, viral genotype, and treatment history yielded similar results. Discontinuations in 11 trials did not reveal any significant differences between the two peginterferons.

## SUMMARY

Triple therapy with peginterferon alfa plus ribavirin and an oral protease inhibitor (boceprevir or telaprevir) is recommended for the treatment of genotype 1 chronic hepatitis C infection according to the 2011 AASLD practice guideline update. Genotype 1 infected patients should only be treated with dual therapy (peginterferon alfa plus ribavirin), without an HCV protease inhibitor, if there are contraindications, significant intolerance or other clinical factors that would preclude use of a protease

inhibitor. The current AASLD recommendation for genotype 2 and 3 chronic hepatitis C infection is dual therapy with peginterferon plus ribavirin. The two long-acting peginterferon products, peginterferon alfa-2a (PEGASYS) and peginterferon alfa-2b (PEGIntron) are similar in terms of safety and efficacy based on a limited number of comparative studies.

The two new oral protease inhibitors, boceprevir (Victrelis) and telaprevir (Incivek), are add-on therapy to peginterferon and ribavirin therapy. The protease inhibitors enhance the SVR rates with triple combination therapy compared to peginterferon plus ribavirin. Direct comparative data are not available for telaprevir and boceprevir. Initiate telaprevir therapy at the same time as peginterferon and ribavirin whereas initiate boceprevir after four weeks of peginterferon + ribavirin. The total duration of telaprevir therapy is 12 weeks whereas treatment regimens for boceprevir continue the protease inhibitor for at least 24 weeks in HCV-RNA responders; both are followed by dual peginterferon + ribavirin for variable durations based on response parameters. Monotherapy with either protease inhibitor should not be considered in the treatment of chronic hepatitis C.

Interferon alfacon-1 (Infergen) may be useful in treating nonresponders and relapsers, although there is a relative paucity of data supporting its use. The 2009 AASLD practice guidelines for the diagnosis, management, and treatment of hepatitis C do not specify any role of interferon alfacon-1 (Infergen) in the management of chronic hepatitis C.

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