

**Criteria Grid**  
**Best Practices and Interventions for the Diagnosis and Treatment of Hepatitis C**

<b>Best Practice/Intervention:</b>	Matthews SJ. et al. (2012) Telaprevir: a hepatitis C NS3/4A protease inhibitor. <i>Clinical Therapeutics</i> , 34(9):1857-1882.			
<b>Date of Review:</b>	March 1, 2015			
<b>Reviewer(s):</b>	Christine Hu			
<b>Part A</b>				
<b>Category:</b>	Basic Science <input type="checkbox"/> Clinical Science <input type="checkbox"/> Public Health/Epidemiology <input type="checkbox"/> Social Science <input type="checkbox"/> Programmatic Review <input checked="" type="checkbox"/>			
<b>Best Practice/Intervention:</b>	<b>Focus:</b> Hepatitis C <input checked="" type="checkbox"/> Hepatitis C/HIV <input checked="" type="checkbox"/> Other: _____ <b>Level:</b> Group <input checked="" type="checkbox"/> Individual <input type="checkbox"/> Other: _____ <b>Target Population:</b> <u>People infected with HCV</u> <b>Setting:</b> Health care setting/Clinic <input checked="" type="checkbox"/> Home <input type="checkbox"/> Other: _____ <b>Country of Origin:</b> <u>USA</u> <b>Language:</b> English <input checked="" type="checkbox"/> French <input type="checkbox"/> Other: _____			
<b>Part B</b>				
	<b>YES</b>	<b>NO</b>	<b>N/A</b>	<b>COMMENTS</b>
<i>Is the best practice/intervention a meta-analysis or primary research?</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Provide an overview of the chemistry, mechanism of action, resistance, pharmacodynamic and pharmacokinetic properties, drug interactions, therapeutic efficacy, HIV/HCV coinfection, pharmacogenomics, tolerability, pharmacoeconomic issues, and dosing and administration of telaprevir for the management of patients infected with chronic HCV infection genotype 1 through the use of published literature
<i>The best practice/intervention has utilized an evidence-based approach to assess:</i>				

<i>Efficacy</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Summary of efficacy and tolerability of telaprevir in various Phase II clinical trials and Phase III clinical trials
<i>Effectiveness</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>The best practice/intervention has been evaluated in more than one patient setting to assess:</i>				
<i>Efficacy</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>Effectiveness</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

	<b>YES</b>	<b>NO</b>	<b>N/A</b>	<b>COMMENTS</b>
<i>The best practice/intervention has been operationalized at a multi-country level:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Search of literature from MEDLINE and BIOSIS
<i>There is evidence of capacity building to engage individuals to accept treatment/diagnosis</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>There is evidence of outreach models and case studies to improve access and availability</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Methodology clearly stated along with the search terms used for the study
<i>Are the best practices/methodology/results described applicable in developed countries?</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Telaprevir approved in US, Canada, Japan and Europe
<i>Are the best practices/methodology/results described applicable in developing countries?</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Developing countries may not have easy access to telaprevir given its cost and availabilities
<i>Evidence of manpower requirements is indicated in the best practice/intervention</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>Juried journal reports of this treatment, intervention, or diagnostic test have occurred</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<i>Clinical Therapeutics</i>
<i>International guideline or protocol has been established</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>The best practice/intervention is easily accessed/available electronically</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Purchase required for download from <a href="http://www.clinicaltherapeutics.com/">http://www.clinicaltherapeutics.com/</a>
<i>Is there evidence of a cost effective analysis? If so, what does the evidence say?</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Gellad et al compared cost-effectiveness of telaprevir with Peg-IFN and ribavirin

<p><b><i>Please go to Comments section</i></b></p>				<p>treatment regimen in HCV genotype 1 patients</p> <ul style="list-style-type: none"> <li>- telaprevir with Peg-IFN and ribavirin therapy would become cost-effective if weekly cost of telaprevir was &lt;\$1640</li> </ul> <p>Liu et al assessed cost-effectiveness of the triple therapy with a 'general' protease inhibitor</p> <ul style="list-style-type: none"> <li>- triple therapy with telaprevir believed to be no cost-effective due to high weekly cost of medication (\$4100)</li> </ul>
<p><i>How is the best practice/intervention funded?</i> <b><i>Please go to Comments section</i></b></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<p>Article was not funded</p>
<p><i>Other relevant information:</i> _____</p>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

## New Drug Review

# Telaprevir: A Hepatitis C NS3/4A Protease Inhibitor

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### ABSTRACT

**Background:** Telaprevir is a hepatitis C NS3/4A protease inhibitor approved by the US Food and Drug Administration as part of combination therapy for the management of chronic hepatitis C virus (HCV) genotype 1 infection.

**Objective:** The article reviews published literature on telaprevir, including its chemistry, mechanism of action, resistance, pharmacodynamic and pharmacokinetic properties, drug interactions, therapeutic efficacy, HIV/HCV coinfection, pharmacogenomics, adverse events, pharmacoeconomics, and dosing and administration.

**Methods:** English-language literature was included. Searches of MEDLINE and BIOSIS databases from 1975 through January 2012 were performed. Emphasis was placed on reference citations involving clinical trials, randomized controlled trials, and research in humans. Additional publications were found by searching the reference lists of identified articles and reviewing abstracts from recent scientific meetings. Search terms included, but were not limited to, *telaprevir*, *VX-950*, *hepatitis C virus genotype 1*, *resistance*, *pharmacology*, *pharmacokinetics*, *pharmacodynamics*, *drug interactions*, *pharmacogenomics*, *adverse events*, and *therapeutic use*.

**Results:** Review of the databases revealed 471 publications/abstracts on this subject. Of these, 85 were chosen based on the review criteria. Two Phase III studies investigated the efficacy and tolerability of telaprevir administered for 12 weeks (T12) when used with peginterferon alfa and ribavirin (PR) in treatment-naïve subjects. The ADVANCE study reported that patients who had an extended rapid virologic response (eRVR; an undetectable HCV RNA level at both 4 and 12 weeks of treatment) with triple therapy could be treated with PR for a total of 24 weeks (T12PR24 group) versus standard PR treatment for 48 weeks (PR48 group [control]). The proportions of patients who achieved sustained virologic response (SVR; undetectable HCV RNA concentration at 24 weeks after the completion of therapy) in the T12PR24 and PR48 groups were 89% and 44%, respectively. The ILLUMINATE study reported T12PR24

was noninferior to T12PR48 in patients with an eRVR to combination therapy. In the REALIZE study, patients with a history of relapse responded well to T12PR48 compared with PR48 (SVR, 83% vs 24%). Telaprevir is a substrate/inhibitor of cytochrome P450 (CYP3A4) and a substrate/inhibitor of P-glycoprotein and poses an important risk for drug interactions. Adverse drug events (ADEs) reported most commonly with triple therapy compared with the T or PR regimen alone were rash, pruritus, nausea, diarrhea, and anemia. The serious AEs most commonly reported during T + PR therapy were anemia, rash, and pruritus. Two reports concluded that T combined with PR was not cost-effective due to the high cost of telaprevir. One study reported that the combination of T + PR would be cost-effective if the treatment rate of HCV genotype 1 infected patients reached 50%.

**Conclusion:** Including telaprevir as part of triple therapy for the management of chronic HCV genotype 1 infection significantly increases the likelihood of achieving an SVR over standard dual drug therapy (PR) in both treatment-naïve and -experienced patients. However, due to the high cost, the use of triple therapy with telaprevir will likely be limited to patient groups known to respond poorly to dual therapy. (*Clin Ther.* 2012;34:1857–1882) © 2012 Elsevier HS Journals, Inc. All rights reserved.

**Key words:** anemia, hepatitis C genotype 1, telaprevir, rash.

### INTRODUCTION

Telaprevir\* is the second hepatitis C virus (HCV) NS3/4A serine protease inhibitor (PI) directly acting antiviral (DAA) agent approved by the US Food and Drug Administration (FDA) for use with a peginter-

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feron alfa (2a or 2b) and ribavirin for the management of chronic HCV infection in patients with genotype 1 (1a, 1b) (May 23, 2011).<sup>1</sup> It can be used in adult patients with chronic HCV infection with stable (compensated) liver involvement including cirrhosis. Patients may be naive to therapy or have failed previously interferon-based treatment. The medication is also approved in Canada,\* Japan,<sup>†</sup> and Europe.<sup>‡</sup> The first HCV NS3/4A DAA agent approved by the FDA was boceprevir (May 13, 2011).<sup>2</sup>

Worldwide, the burden of chronic HCV infection approximates 160 million individuals.<sup>3</sup> Approximately 2.9 million persons are infected with HCV in the United States as of 2011.<sup>4</sup> In patients in whom the acute infection does not spontaneously clear, disease may progress to chronic hepatitis and, over 20 to 30 years, the patients may be at risk for cirrhosis (15%–40%) and hepatocellular carcinoma (HCC).<sup>5</sup> Patients who have early onset chronic disease or who develop cirrhosis carry annual rates of HCC of 0.5% and 8%, respectively.<sup>6</sup> Data reviewing deaths in the United States between 1999 and 2007 show that more people died as a result of chronic HCV infection than from HIV disease.<sup>7</sup>

Prior to the availability of telaprevir, the standard regimen for the management of chronic HCV genotype 1 was a combination of a peginterferon alfa (2a or 2b) and ribavirin for a treatment period of 48 weeks.<sup>8</sup> Clinical outcome as determined by sustained viral response (SVR; defined as an undetectable plasma HCV RNA level at week 24 after the conclusion of therapy) is variable depending on the genotype of the HCV infecting the patient (genotypes 1–6). Response is lowest with genotype 1 (42%–52%) and is highest with genotype 2 or 3 (76%–82%).<sup>9–12</sup> With standard therapy, patients infected with genotypes 4 to 6 experience a SVR at the following rates: 4 (61%–69%), 5 (55%–60%), and 6 (74%–85.7%).<sup>13–19</sup> The high prevalence of HCV genotype 1 worldwide, combined with its overall poor response to standard therapy, makes it a prime target for new therapies.<sup>8</sup>

Used concurrently with peginterferon and ribavirin (triple therapy), telaprevir has been reported to suppress HCV RNA production in a small number of chronically HCV infected patients with genotypes 2 and 4.<sup>20,21</sup> Triple therapy did not show comparable HCV RNA suppression in patients infected with HCV

genotype 3, however.<sup>20</sup> Because the number of treated patients was small and the duration of therapy short in studies available to date,<sup>2–6</sup> larger controlled studies will need to be undertaken to investigate the activity of telaprevir in patients infected with other HCV genotypes. This review will investigate the chemistry, mechanism of action, resistance, pharmacodynamic and pharmacokinetic properties, drug interactions, therapeutic efficacy, HIV/HCV coinfection, pharmacogenomics, tolerability, pharmacoeconomic issues, and dosing and administration of telaprevir for the management of patients infected with chronic HCV infection genotype 1.

## METHODS

Literature for this review was obtained from searches of MEDLINE and BIOSIS from 1975 through January 2012. Review of the 2 databases revealed 471 publications/abstracts on this subject. Of these, 85 were chosen based on the review criteria. Emphasis was placed on reference citations involving clinical trial, randomized controlled trials, and research in humans. Telaprevir review articles and identical abstracts that were presented at multiple meetings were excluded. Further publications were identified from citations of resulting papers, and review of abstracts from scientific meetings. Search terms included, but were not limited to, *telaprevir*, *VX-950*, *MP-424*, *HCV genotype 1*, *resistance*, *pharmacology*, *pharmacokinetics*, *pharmacodynamics*, *drug interactions*, *pharmacogenomics*, *pharmacoeconomics*, *adverse events*, and *therapeutic use*.

## RESULTS

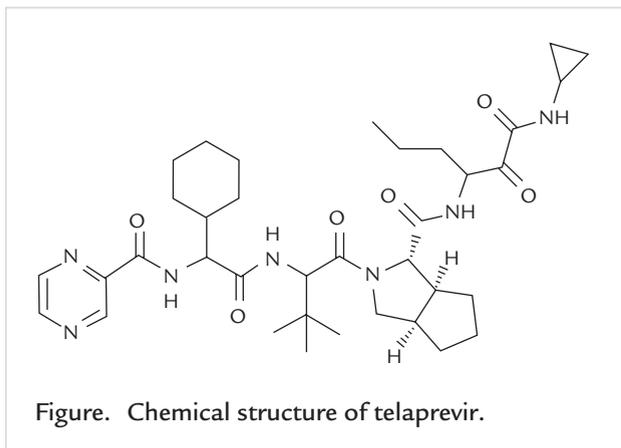
### Chemistry

The molecular formula and weight of telaprevir are C<sub>36</sub>H<sub>53</sub>N<sub>7</sub>O<sub>6</sub> and 679.85, respectively. The drug is only slightly soluble in water. Telaprevir interconverts to its *R*-diastereomer (VRT-127394) in plasma.<sup>1</sup> The chemical structure of telaprevir is presented in the **Figure**.

### Mechanism of Action

HCV is composed of a single-stranded, positive-sense RNA genome of ~9600 nucleotides in length.<sup>22</sup> After binding to the host cell ribosomes, the HCV RNA genome is translated into a large polyprotein, which is in turn converted into structural proteins (core, E1, E2, P7) and nonstructural proteins (NS2, NS3, NS4A, NS4B, and NS5B) in the endoplasmic reticulum of infected cells. The structural proteins are involved in the formation of a complete virion, its egress from the cell, and the ability to infect other cells. The nonstructural proteins are important for replication of the HCV

Trademarks: <sup>†</sup>Telaviv™, and <sup>‡</sup>Incivo™ (Vertex Pharmaceuticals Inc, Cambridge, Massachusetts).



RNA genome and the virus.<sup>22</sup> Telaprevir is a reversible HCV NS3/4A serine PI.<sup>23</sup> Nonstructural protein 3 (NS3) has both protease and helicase activity, and the viral NS4A cofactor protein is necessary for the proper functioning of NS3.<sup>24</sup> Telaprevir binds to the NS3/4A protease in 2 steps. Step 1 is characterized by a weak binding followed by the formation of a covalent bond between a site on the protease molecule (hydroxyl group of the catalytic serine) and telaprevir (keto-carbonyl group).<sup>23</sup> The dissociation of this complex is slow, with a  $t_{1/2}$  of 58 minutes (in vitro model).<sup>23</sup> By inhibiting HCV NS3/4A, telaprevir inhibits the formation of proteins necessary for the replication of the HCV RNA genome and virus. It accomplishes this by preventing the cleavage of genome-encoded polyprotein into active forms of the NS4A (serine protease cofactors), NS4B (membranous web-scaffold for replication complex), NS5A (RNA binding and assembly replication complex), and NS5B (RNA-dependent RNA polymerase) proteins.<sup>25</sup> It may also counteract the HCV NS3/4A protease ability to inactivate cellular proteins needed by host cells for innate immunity to HCV.<sup>26–29</sup> Telaprevir is selective for HCV NS3/4A and does not inhibit other serine proteases (in vitro model) (plasmin, factor Xa, thrombin, and kallikrein).<sup>23</sup> Other HCV DAA agents being developed target NS3/4A, NS5B, NS4B, and NS5A.<sup>25,30,31</sup> The American Association for the Study of Liver Diseases has developed guidelines for the use of the DAAs, including telaprevir.

### Resistance

Telaprevir must be used as a part of combination therapy for chronic HCV infection genotype 1 due to the rapid selection of resistant HCV quasispecies when used alone.<sup>32–34</sup> The HCV replication rate of its ge-

nome is high, and it is reproduced in a haphazard manner, resulting in the presence of viral mutations (quasispecies) in an individual patient. Kuntzen et al<sup>32</sup> determined the genome sequences of the HCV NS3 protease in 507 patients with chronic HCV genotype 1 (subtypes 1a and 1b) infection. Patients were naive to anti-HCV therapy. They tested the susceptibility of these strains to telaprevir. Of 362 subjects infected with HCV genotype 1a, low-level resistance variants (V [valine] 36 [position of the substitution] M [methionine replaces valine]-V36M, V36L, and T54S) were found in 0.6%, 1.7%, and 1.9% of patients, respectively. The moderate-to-high-level resistant mutation (R155K) was present in 0.8% of individuals. No patient was infected with a mutation at the A156 position (high-level resistance). One patient harbored a dual mutation strain of HCV NS3 protease (V23A + V36M; high-level resistance). Only the T54S mutation was found in 1.4% of the 145 individuals infected with genotype 1b, which may have been due to the fact that, to produce the V36M or R155K mutation, a dual substitution of amino acids must occur in patients infected with HCV genotype 1b.<sup>32,33</sup>

Sarrazin et al<sup>33</sup> reviewed the selection of mutation strains of HCV genotype 1 (1a, 1b) in a group of 34 patients receiving telaprevir monotherapy or placebo who were enrolled in a Phase Ib double-blind, placebo-controlled study. The following oral doses of telaprevir were administered: 450 mg q8h, 750 mg q8h, and 1250 mg q12h. Sequence analysis of the HCV protease catalytic domain was performed at baseline, end of dosing (14 days), and 7 to 10 days and 3 to 7 months after dosing. All HCV isolates were sensitive to telaprevir at baseline, and there were no resistant strains detected in the placebo group. Following an initial decline in HCV RNA plasma concentrations ( $3 \log_{10}$ ) over the first 2 days of telaprevir dosing, the ensuing response was classified as: breakthrough (HCV-RNA increase of  $>0.75 \log_{10}$  IU/mL from nadir [ $n = 13$ ]); plateau (increase  $\leq 0.75 \log_{10}$  IU/mL from nadir [ $n = 8$ ]); or continuous decline ( $n = 7$ ). In addition to the wild-type virus, the following mutations were found to have predominated in all patients at the end of 14 days of telaprevir dosing in the breakthrough group: V36A/M, T54A, and R155K/T (conferred low-level resistance [ $<25$ -fold increase in  $IC_{50}$  for telaprevir (50% inhibition concentration)]). The high-level resistant ( $>60$ -fold increases in  $IC_{50}$  for telaprevir) double mutation V36 + R155 was also found in a few patients ( $n$  not provided). Low-level resistant mutations were still

present after 7 to 10 days after dosing. At 3 to 7 months after dosing, wild-type virus predominated, low-level resistant mutations had decreased, and the high-level resistant double-mutations had disappeared. In the plateau group, the *A156V/T* mutation (high-level resistance) was most common in all patients. Wild-type and low-level resistant mutations were present in lower quantities. At 7 to 10 days after dosing, the wild type virus had increased, low-level resistant mutations had diminished, and high-level resistant mutation concentrations had precipitously fallen. At 3 to 7 months, wild-type virus predominated. In the continuous-decline group, no mutations were detectable at the end of the dosing period due to low HCV RNA concentrations, but wild-type and low-level mutations were found at the 7-to-10-day study period. At 3 to 7 months, wild-type virus predominated. Additional low-level resistant mutation *A156S* and high-level double mutations at positions *V36 + A156* were also identified in that study. A majority of patients receiving telaprevir 450 mg q8h or 1250 mg q12h were in the breakthrough or plateau groups, and the majority of the patients receiving telaprevir 750 mg q8h were in the continuous-decline group.

Kieffer et al<sup>34</sup> studied the selection of mutation strains of HCV genotype 1 in 20 treatment-naive patients (1a, n = 6; 1b, n = 14) treated with telaprevir monotherapy (n = 8), telaprevir + peginterferon alfa-2a (n = 8), or placebo + peginterferon alfa-2a (n = 4) for a total of 14 days.<sup>34</sup> The initial telaprevir oral dose of 1250 mg was followed by a dosage of 750 mg q8h. Peginterferon alfa-2a was dosed at 180 µg by subcutaneous injection. After completing the dosing phase, patients were offered the opportunity to go on standard therapy with peginterferon alfa-2a and ribavirin. The HCV RNA concentrations were noted to have declined by a median of 3.99 log<sub>10</sub> in the telaprevir monotherapy group, 5.49 log<sub>10</sub> in the telaprevir + peginterferon group, and 1.09 log<sub>10</sub> in the placebo + peginterferon group, from baseline to day 15 of the study. On day 15, HCV RNA concentrations were undetectable (<10 IU/mL) in 1 patient receiving telaprevir monotherapy and in 4 patients on telaprevir + peginterferon therapy. Sequence analysis of the HCV protease catalytic domain was performed at baseline and during dosing and at weeks 1, 12, and 24 after the last dose. No telaprevir-resistant mutations were found in the group receiving placebo + peginterferon alfa-2a. Patients on telaprevir monotherapy after an initial decline in HCV RNA plasma concentrations ex-

perienced either a rebound (a >50-IU/mL increase in HCV RNA level at day 15 [n = 4]) or continued decline (no increase in HCV RNA concentrations from nadir or <50 IU/mL at day 15 [n = 4]). Rebound occurred in 3 patients at day 8 (genotype 1a) and in 1 patient at day 12 (genotype 1a) of dosing. On day 4, wild-type virus predominated, but *V36A/M*, *R155K/T*, and *A156V/T* single mutations were isolated (5%–20%) as well. By day 15, the double mutation (*V36 + R155* [high-level resistance]) had replaced the single mutations. The 3 patients who were subsequently placed on peginterferon alfa-2a and ribavirin experienced a decrease in HCV RNA concentrations (undetectable, unquantifiable [ $<30$  IU/mL], and 86 IU/mL after 12 weeks) respectively. The 4 patients (genotype 1b) with continuous HCV RNA decline had only wild-type virus detected at day 4 of dosing. At a later time point (between days 8 and 15), mutation variants *A156V/T* predominated and *V36A/M* and *T54A* were found in low numbers in 2 patients. All 4 patients experienced undetectable HCV RNA concentrations at 12 and 24 weeks of peginterferon alfa-2a + ribavirin therapy. In the telaprevir + peginterferon alfa-2a group, no breakthrough was noted; however, the highly resistant mutation *A156T* was found in 1 patient (day 8-HCV RNA concentrations below the lower limit of quantification (LLOQ) at day 15) and the low resistant mutation *V36A* was noted in another (undetectable HCV RNA concentration while on peginterferon + ribavirin [PR]). All 8 patients responded to follow-on therapy with PR. Although the number of patients was small, this study observed that even highly resistant telaprevir mutations were controlled with PR therapy. Follow-up of patients with resistant HCV variants in the EXTEND trial and in 2 Phase III trials reported that virus with reduced susceptibility to telaprevir disappeared in a majority of cases over time after telaprevir was discontinued.<sup>35–40</sup> In the EXTEND study, 89% of patients no longer had detectable resistant variants, whereas 11% of patients still harbored resistant mutations after a median follow-up of 7 to 36 months.<sup>39</sup> In the ILLUMINATE (Illustrating the Effects of Combination Therapy with Telaprevir) and REALIZE (Retreatment of Patients with Telaprevir-based Regimen to Optimize Outcomes) trials, 55% (median follow-up, 43 weeks) and 58% (median, 46.4 weeks) of patients were free of detectable resistant variants versus 45% and 42%, respectively, who still had resistant variants detectable.<sup>36,37</sup>

### Pharmacodynamic Properties

The pharmacodynamic properties of telaprevir monotherapy were compared with those of peginterferon + placebo and telaprevir + peginterferon in a Phase I study by Forestier et al.<sup>41</sup> Twenty treatment-naïve patients with chronic HCV genotype 1 infection were divided into 3 groups. Group 1 (n = 4) received placebo + peginterferon alfa-2a (180 µg/wk); group 2 (n = 8) received a loading dose of telaprevir of 1250 mg followed by 750 mg q8h; and group 3 (n = 8) received telaprevir (same dose as in group 2) + peginterferon alfa-2a. All patients received the prescribed regimen for a total of 14 days. HCV RNA concentrations declined in a biphasic manner in all groups. By day 15, the HCV RNA concentrations had decreased from baseline by 1.09 log<sub>10</sub> (group 1), 3.99 log<sub>10</sub> (group 2), and 5.49 log<sub>10</sub> (group 3). HCV RNA concentrations were undetectable (<10 IU/mL) on day 15 in 0, 1, and 4 (50%) patients in groups 1, 2, and 3, respectively.

In another study, 20 Japanese patients with chronic HCV genotype 1b infection and a high viral load received telaprevir + peginterferon alfa-2b + ribavirin for 12 weeks.<sup>42</sup> Six patients had not responded to interferon monotherapy, and 4 had not responded to PR therapy. Patients were divided into 2 groups. Group 1 received telaprevir 750 mg q8h; group 2 received telaprevir 500 mg q8h. The numbers in each group were not delineated. The HCV RNA concentrations dropped quickly initially, followed by a slower second phase. Overall, the means change from baseline in HCV concentrations at day 7 and 14 were -5.0 and -5.7 log<sub>10</sub>, respectively. By 4 weeks, HCV RNA concentrations were undetectable (<1.2 log IU/mL) in 79% of patients (15/19) and reached 100% (13/13) by 12 weeks. Seven patients (5 with anemia, 1 with general malaise attributed to peginterferon, and 1 with rash) stopped all therapy due to adverse events (AEs). Subsequent to the discontinuation of triple therapy, HCV RNA concentrations remained below the level of detection (<1.2 log IU/mL) in 6 patients who stopped therapy due to AEs.

### Pharmacokinetic Properties

The pharmacokinetics of telaprevir are displayed in Table I.<sup>43–46</sup> Much of the data on the pharmacokinetics of telaprevir was derived from the FDA Antiviral Drugs Advisory Committee report from the manufacturer, published abstracts or the manufacturer package insert. Gender, age (19–70 years), weight and race does not affect telaprevir pharmacokinetics.<sup>47</sup> Our

search of the literature found no studies that presented telaprevir pharmacokinetics in children.<sup>1</sup>

### Absorption

Telaprevir is absorbed orally, with a T<sub>max</sub> between 2.5 and 5.0 hours after administration (Table I).<sup>20,43</sup> C<sub>max</sub>, C<sub>min</sub>, and AUC for telaprevir are higher when the medication is used with PR than when telaprevir is used as monotherapy. Telaprevir absorption is improved when it is administered with food with some fat included. Compared with a standardized breakfast (533 kcal, 21g fat) after a single 750-mg dose, the AUC<sub>0–∞</sub> in the fasting state and after a low-calorie/high-protein (fat, 9 g) meal and a low-calorie/low-fat (3.6 g) meal were reduced by 73%, 26%, 39%, respectively. A high-fat breakfast (56 g fat) increased the AUC<sub>∞</sub> by ~20% compared with a standardized meal.<sup>48</sup> Telaprevir is both a substrate and an inhibitor of P-glycoprotein.<sup>49</sup>

### Distribution

The apparent volume of distribution (Vd/F) of telaprevir is greater than the total body water (~252 L).<sup>47</sup> Protein binding in human plasma varies between 59% and 76% (telaprevir concentration range, 0.1–20 µM).<sup>50</sup> Binding was moderate to human serum albumin and α<sub>1</sub>-acid glycoprotein and low with human γ globulin.<sup>50</sup> Protein binding is concentration dependent, with binding decreasing at higher plasma concentrations of telaprevir (5 µM, 87%; 50 µM, 71%).<sup>50,51</sup>

### Metabolism

Telaprevir is a single diastereomer (S-configuration at position 21) and has been shown to epimerize in human plasma to the R-diastereomer (VRT-127394 [30-fold less active than telaprevir]) in vitro and in vivo.<sup>52</sup> Additional metabolites include an inactive M3 isomer of telaprevir (reduction at the α-ketoamide bond VRT-0922061) and pyrazinoic acid.<sup>47</sup> Telaprevir is a substrate and inhibitor of the cytochrome P450 (CYP) 3A4 isozyme, which makes it a candidate for drug interactions when combined with other agents metabolized by this isozyme (see Drug Interactions section).<sup>49</sup> Telaprevir does not inhibit CYP2D6, CYP2C19, CYP2C9, or CYP1A2.<sup>47</sup> Extensive liver metabolism takes place through reduction, hydrolysis, and oxidation of telaprevir.<sup>47</sup>

### Elimination

Telaprevir was eliminated in the feces (82%), expired air (9%), and urine (1%) after the administration of a single 750-mg dose of <sup>14</sup>C-telaprevir in healthy

Table I. Pharmacokinetic properties of multiple-dose telaprevir (TVR) 750 mg, a hepatitis C (HCV) NS3/4A protease inhibitor, administered every 8 hours. Data are mean (SD) unless otherwise noted.

Treatment/Study Group	C <sub>max</sub> , <sup>†</sup> ng/mL	C <sub>min</sub> , <sup>†</sup> ng/mL	T <sub>max</sub> , <sup>*</sup> h	AUC ng · h/mL
TVR				
Garg et al <sup>43</sup>				
Healthy volunteers (n = 6)	2808 (436) <sup>†</sup>	1386 (202) <sup>†</sup>	2.5 (1.5–4)	—
van Heeswijk et al <sup>44</sup>				
Healthy volunteers (n = 16)	3338 (766)	1903 (618)	—	20,810 (5230) <sup>‡</sup>
Foster et al <sup>20</sup>				
Chronic HCV genotype 2 (n = 8)	3261 (1818)	1605 (1106)	3.6 (1–4)	20,144 (11,129) <sup>§</sup>
TVR with peginterferon + ribavirin				
Foster et al <sup>20</sup>				
Chronic HCV genotype 1 and 2 (n = 4)	4318 (1518)	2164 (1398)	3.0 (3–4)	26,588 (10,908)
Marcellin et al <sup>45</sup>				
Chronic HCV genotype 1 (n = 8)	4523 (768)	2624 (507)	—	85,890 (17,610) <sup>‡¶</sup>
Chronic HCV genotype 2 (n = 11) <sup>  </sup>	4036 (728)	2476 (329)	—	80,420 (12,440) <sup>‡</sup>
Lawitz et al <sup>46</sup>				
Chronic HCV genotype 1 (n = 12)	—	2568 <sup>†</sup>	—	26,400 <sup>‡§</sup>

\*Median (range).

<sup>†</sup>Median or median (SD).<sup>‡</sup>AUC<sub>0–24</sub>.<sup>§</sup>AUC extrapolated to 8 hours.<sup>||</sup>TVR + peginterferon alfa-2b + ribavirin.<sup>¶</sup>n = 6.

subjects.<sup>47</sup> In the feces, the percentages of unchanged telaprevir and the R-diastereomer of telaprevir recovered were 31.9% and 18.8%, respectively.<sup>47</sup> The apparent total clearance was ~32.4 L/h, and the steady-state  $t_{1/2}$  was calculated to vary between 9 and 11 hours.<sup>47</sup> van Heeswijk et al<sup>53</sup> investigated the effect of severe renal impairment (creatinine clearance [CrCl] <30 mL/min) versus normal renal function (CrCl >80 mL/min) on the pharmacokinetic properties of a single dose (750 mg) of telaprevir in HCV-negative volunteers. There were 12 subjects in each group. The C<sub>max</sub> and the AUC<sub>0–∞</sub> were compared. The mean (SD) C<sub>max</sub> and AUC<sub>0–∞</sub> in the group with severe renal impairment versus the group with normal renal function were 2658 (1218) ng/mL and 20,260 (11,000) ng · h/mL, respectively, versus 2256 (636) ng/mL and 15,140 (6736) ng · h/mL. Analysis using the ratio of the least squares means revealed a 21% increase in the AUC<sub>0–∞</sub> in the group with renal impairment versus the group with normal renal function. Although renal

function plays a small role in the elimination of telaprevir, because the medication is used in combination with PR, renal function should be considered due to the ribavirin component of the regimen.

Adiwijaya et al<sup>54</sup> studied the pharmacokinetic properties of telaprevir in subjects with normal liver function compared with patients with mild to moderate cirrhosis of the liver (Child-Pugh grade A or B). Patients received a single dose of telaprevir 750 mg PO on day 1 followed by 750 mg q8h PO on days 2 to 5 in an open-label, Phase I study. Ten subjects were enrolled in each of 3 groups. Geometric least squares mean ratios of telaprevir C<sub>max</sub> and AUC<sub>0–8h</sub> were used to compare the pharmacokinetic properties in the healthy volunteers with those in patients with hepatic impairment. The results of the multiple-dose component of the study are presented. For the mild-impairment group, the C<sub>max</sub> and AUC<sub>0–8h</sub> were 10% and 15% lower compared with those in the healthy subjects. The investigators did not consider these numbers to be clinically

relevant. For the patients with moderate hepatic impairment, the  $C_{\max}$  and  $AUC_{0-8h}$  were 49% and 46% lower compared with those in the healthy subjects. The manufacturer recommends that telaprevir not be used in patients with chronic HCV infection and moderate to severe hepatic impairment at this time.<sup>1</sup>

### Drug Interactions

Much of the data related to drug interactions between telaprevir and other medications were available only in abstract form. Because telaprevir is a substrate and an inhibitor of CYP3A4 and a substrate and inhibitor of P-glycoprotein, there is risk for interactions with other agents that rely on the CYP3A4 isozyme for metabolism and P-glycoprotein for elimination.<sup>49</sup> As a substrate for CYP3A4 isozymes, plasma telaprevir concentrations may increase in the face of coadministration with CYP3A4 inhibitors. Likewise, as an inhibitor of CYP3A4, telaprevir may increase the concentrations of agents metabolized by this isozyme. Concurrent use of telaprevir with the following medications is contraindicated based on the inhibition of metabolism by telaprevir: ergot medications, cisapride (not available in the United States), alfuzosin, atorvastatin, lovastatin, simvastatin, pimozide, agents used for pulmonary hypertension (sildenafil or tadalafil), oral midazolam, and triazolam.<sup>1,47,49,55,56</sup> In addition, the doses of agents that are processed by P-glycoprotein (ie, digoxin) may need to be reduced in the face of inhibition by telaprevir.<sup>49</sup> Agents that induce CYP3A4 or P-glycoprotein may reduce the plasma concentrations of telaprevir and require a dosage adjustment.<sup>55</sup> The coadministration of telaprevir and St. John's wort or rifampin is contraindicated because the latter 2 agents reduce telaprevir concentrations.<sup>1,47,55</sup> In addition, estrogen-containing oral contraceptives may be ineffective if administered concurrently with telaprevir because telaprevir may decrease the concentration of ethinyl estradiol in these products.<sup>57</sup> Clinicians must take into consideration the potential for drug interactions when starting or discontinuing telaprevir therapy or adding or stopping a new medication during telaprevir administration. Drug interactions with medications for the management of patients with HIV disease are discussed in the HCV/HIV coinfection section. It is suggested that clinicians refer to the manufacturer's package insert for a more complete review of medications that may interact with telaprevir.<sup>1</sup>

### Efficacy and Tolerability

#### Phase II Clinical Trials

Five Phase II studies have investigated the efficacy and tolerability of the combined use of telaprevir with PR in chronic HCV genotype 1 infected patients.<sup>45,46,58-60</sup> Lawitz et al<sup>46</sup> performed an open-label trial in 12 treatment-naïve patients with chronic HCV genotype 1 (1a,  $n = 9$ ; 1b,  $n = 3$ ) infection. Patients were excluded if they had HIV disease or any cause of serious liver disease, including decompensated disease, documented cirrhosis, hepatitis B infection, or a history of alcohol or substance abuse. All patients received telaprevir (1250-mg single dose followed by 750 mg q85), peginterferon alfa-2a (180  $\mu$ g SC once per week), and weight-adjusted ribavirin ( $<75$  kg, 1000 mg/d;  $\geq 75$  kg, 1200 mg/d) for a total of 28 days. At the end of the 28 days, all patients were offered the opportunity to continue PR for an additional 44 weeks. The primary goal of the study was to assess the tolerability of telaprevir when combined with PR. The dose of ribavirin could be adjusted based on new-onset anemia. Sequence analysis of HCV NS3 was performed at baseline, during the 28-day study period, and at 2 and 12 weeks after the end of telaprevir dosing. The study included 6 men (age range, 21-55 years) and 6 women (age range, 27-57 years). Compared with baseline, HCV RNA concentrations fell by 4  $\log_{10}$  in all patients and by  $>5 \log_{10}$  in 10 patients. At the end of the 28-day study period, the HCV RNA concentrations were undetectable ( $<10$  IU/mL), and no patient experienced a viral breakthrough during the study period. All 12 patients elected to continue therapy with PR, and 8 patients had an SVR (undetectable HCV RNA concentrations at 24 weeks after the end of therapy in patients with undetectable concentrations at the end of therapy). Two patients had a viral breakthrough (detectable HCV concentrations at any time after day 28), and 2 were lost to follow-up. Wild-type virus was present at baseline in all patients. The V36M mutation (low-level resistance) appeared in 1 patient on day 2, but the variant was undetectable at the day 8 study time point. At day 8, 2 patients had detectable HCV concentrations. One had only wild-type virus, and 1 had a mixture of virus types (wild type, 7%; V36M mutation [low-level resistance], 77%; A156T mutation [higher-level resistance], 11%; 36/156 mutation [higher-level resistance], 5%). See Resistance section for definitions of levels of resistance. These variants were below the level of detection at day 28 in both patients. In 1 pa-

tient who experienced a viral breakthrough, the HCV NS3 sequence analysis was performed at 16 and 24 weeks. At the 16-week mark, 90% of virus was *R155K*, and 10% was wild-type virus. By 24 weeks, 40% of virus was *R155K* and 60% was wild type. In the second patient (24 weeks follow-up), 14% of virus was the *R155K* variant and 86% was wild-type virus. Patients reported most frequently fatigue, flulike symptoms, headache, nausea, depression, pruritus, and anemia. Rash was noted in 4 patients, and 2 had an erythematous rash (mild), with the rash described as moderately pruritic in 2 patients. Laboratory abnormalities included anemia in 4 patients and neutropenia (mild) in 1.

Marcellin et al<sup>45</sup> performed a multicenter, prospective, randomized open-label study in 30 centers in Europe. That study explored the efficacy and tolerability of telaprevir administered at 8- or 12-hour intervals with peginterferon alfa-2a or -2b and ribavirin in patients with chronic HCV genotype 1. Patients were naive to therapy. Patients were excluded from the study if they met any of the following criteria: confirmed cirrhosis, hepatocellular carcinoma, hepatitis B infection, HIV infection, and/or a history of drug abuse, including alcohol abuse. Patients were grouped by genotype 1 subtype (1a, *n* = 82; 1b, *n* = 78; 1c, *n* = 1) and by baseline HCV RNA viral load (< or  $\geq$ 800,000 IU/mL). Patients received telaprevir 750 mg q8h and ribavirin + peginterferon alfa-2a (*n* = 40 [group A]) or 2b (*n* = 42 [group B]) or telaprevir 1125 mg q12h and ribavirin + peginterferon alfa-2a (*n* = 40 [group C]) or 2b (*n* = 39 [group D]). The peginterferon alfa-2a regimens included 180  $\mu$ g SC once weekly, with ribavirin dosage calculated by patient weight (1000–1200 mg/d). Peginterferon alfa-2b was dosed at 1.5  $\mu$ g/kg/wk SC + ribavirin 800 to 1200 mg/d. All patients received telaprevir with PR for 12 weeks. Subsequently, patients who had undetectable HCV RNA concentrations (<10 IU/mL) at weeks 4 through 20 received an additional 12 weeks of PR therapy (total, 24 weeks). Patients who did not meet these criteria received an additional 24 weeks of PR therapy (total, 48 weeks). Patients were monitored for viral breakthrough (1.0 log<sub>10</sub> increase in HCV RNA concentration over the lowest measured value, or a >100-IU/mL increase in HCV RNA level if the concentration had been <25 IU/mL). Relapse rates were determined based on a detectable HCV RNA concentration at any time during the follow-up period (24 weeks after the end of ther-

apy) in patients who had undetectable concentrations at the completion of therapy. The primary end point was the rate of SVR in each group. The study groups were comparably matched (median age, 45 years; 50% male; 91% white, 3% black, and 2.5% Asian). The percentages of patients achieving SVR were 85%, 81%, 83%, and 82% in groups A, B, C, and D, respectively. There were no statistically significant differences between the 4 groups in the percentages achieving SVR ( $P \geq 0.787$ ), between dosing intervals (data were pooled for this analysis) ( $P = 0.997$ ), or by type of peginterferon administered ( $P = 0.906$ ). The percentages of patients who achieved SVR and were treated with 24 weeks of PR were 96.7%, 92.9%, 100%, and 99.5% in groups A, B, C, and D, respectively. Twenty-nine patients were treated with PR for 48 weeks, and the SVR rates were 83.3%, 70%, 75%, and 88.9%. Fourteen patients experienced viral breakthrough (1, 6, 3, and 4 patients, respectively). Eleven of 14 patients infected with genotype 1a had a viral breakthrough versus 3 of 14 patients infected with genotype 1b. A relapse occurred in 3, 2, 3, and 1 patient in groups A, B, C and D. The most commonly reported AEs were rash, pruritus, flulike symptoms, headache, asthenia, anemia, and fatigue. A total of 8.1% of patients stopped therapy due to an AE. The most common reasons for stopping therapy were rash (4.3%) and anemia (2.5%). The use of erythropoietin was allowed for the treatment of anemia during the study.

McHutchison et al<sup>58</sup> performed a randomized, parallel-group, double-blind, placebo-controlled study in US patients infected with chronic HCV genotype 1 infection (the PROVE 1 study). Patients were naive to treatment. In addition to efficacy and tolerability, the study investigated whether therapy could be shortened by the addition of telaprevir to a regimen of PR. Exclusion criteria included the presence of decompensated liver disease, HCC, and biopsy-proven cirrhosis. Patients were divided into 4 groups (1 received standard therapy [placebo + PR], and 3 received 1250-mg telaprevir on day 1 and then 750 mg q8h + peginterferon alfa-2a 180  $\mu$ g SC once weekly + ribavirin [ $<75$  kg weight, 1000 mg/d;  $>75$  kg weight, 1200 mg/d]). The standard-therapy group received PR at the above doses for 48 weeks (PR48). All of the telaprevir regimens included telaprevir + PR for  $\geq$ 12 weeks. The T12PR12 group had treatment stopped after 12 weeks, the other 2 groups (T12PR24, T12PR48) continued PR for an additional 12 or 36 weeks. In the PR 48

Table II. Findings from the PROVE studies of telaprevir.

Study/Parameter	T12PR12	T12PR24	T12PR48	PR48 (Control)	Regimens Without Ribavirin
PROVE 1 <sup>58</sup>					
n	17	79	79	75	—
SVR, %	35	61	67	41	—
<i>P</i> *	NP	0.02	0.002	—	—
Relapse, %	33	2	6	23	—
PROVE 2 <sup>59</sup>					T12P12
n	82	81	—	82	78
SVR, %	60	69	—	46	36
<i>P</i> *	0.12	0.004	—	—	0.20
Relapse, %	30	14	—	22	48
PROVE 3 <sup>60</sup>					T24P24
n	—	115	113	114	111
SVR, %	—	51	53	14	24
<i>P</i> *	—	<0.001	<0.001	—	0.02
Relapse, %	—	30	13	53	53

NP = not provided as per protocol; P = peginterferon; PR = peginterferon + ribavirin; PROVE = Protease Inhibition for Viral Evaluation study; SVR = sustained virologic response; T = telaprevir.

\*For SVR (T vs PR48).

group, if the HCV RNA concentration did not decrease by 2 log<sub>10</sub> units by 12 weeks or was not below the level of detection (<10 IU/mL) by week 24, therapy was discontinued. A rapid virologic response (a week-4 undetectable HCV RNA concentration) was a requirement for continuation in the telaprevir 12-week and 24-week groups. A detectable HCV RNA concentration at any time during weeks 4 to 10 (T12PR12) or weeks 4 to 20 (T12PR24) required that these patients continue PR for a total of 48 weeks. These patients were counted as a failure in the intent to treat analysis. Patients were monitored for viral breakthrough which was defined as a 1.0 log<sub>10</sub> increase in HCV RNA concentration over the lowest measured value or a > 100 IU/mL HCV RNA level increase if the concentration had become undetectable previously. Patients experiencing a viral breakthrough were removed from telaprevir or placebo and continued on PR therapy for a total of 48 weeks. Relapse rates were determined based on a detectable HCV RNA concentration at any time during the follow-up period (24 weeks after the end of therapy) in patients who had undetectable concentrations at the completion of therapy. The primary end

point was the percentage of each group that achieved SVR (undetectable HCV RNA concentrations at 24 weeks after the end of therapy in patients with undetectable concentrations at the end of therapy). The study groups were comparably matched, with a mean age of 48 years; 63% were male and 77% were white. The SVR and relapse rates are listed in Table II. The SVR in the T12PR24 and the T12PR48 groups were 61% and 67% versus 41% in the PR48 group (*P* = 0.02 and *P* = 0.002, respectively). The SVRs in the T12PR24 and T12PR48 groups were comparable (*P* = 0.51). The SVR with T12PR12 was 35%. The SVRs in black patients (historically poor responders to PR) were 11% in the PR48 group versus 44% in the telaprevir groups. Relapse occurred in 23%, 33%, 2%, and 6% of patients in the PR48, T12PR12, T12PR24, and T12PR48 groups, respectively. Twelve patients (7%) treated with telaprevir experienced a viral breakthrough during weeks 1 to 12. Ten of the 12 patients never achieved an undetectable level of HCV RNA prior to breakthrough. Ten patients infected with HCV genotype 1a demonstrated the presence of the V36M and R155K variants, and A156T predominated in

1 patient with HCV genotype 1b. One patient had a breakthrough attributed to a wild-type virus. AEs most commonly attributed to the telaprevir group included rash, nausea, diarrhea, and pruritus. Twenty-one percent of patients in the telaprevir groups discontinued therapy due to an AE versus 11% in the PR48 group. Rash was maculopapular in appearance, and all cases of severe rash resolved on discontinuation of telaprevir. Decrease in hemoglobin was noted during the 12 weeks of telaprevir therapy and returned to baseline levels within 4 weeks after telaprevir discontinuation. The use of erythropoietin was not allowed during the first 12 weeks of the study.

Hézode et al<sup>59</sup> performed a multicenter, randomized, placebo-controlled study in Europe in patients infected with chronic HCV genotype 1 (the PROVE 2 study). The study included a group that did not receive ribavirin as part of the therapy. Patients were naive to treatment, and the study was partially double-blind in design. Patients with biopsy-proven cirrhosis of the liver were excluded. Patients were randomly assigned to 1 of 4 treatment groups and assessed for efficacy and AEs. Patients in the control group received placebo + PR for 12 weeks, followed by 36 weeks of PR alone (PR48). The T12PR12 group received telaprevir + PR for 12 weeks. The T12PR24 group received telaprevir + PR for 12 weeks, followed by an additional 12 weeks of PR. The T12P12 group received 12 weeks of telaprevir + peginterferon alfa-2a and was not blinded because the researchers would have been able to discern the absence of ribavirin due to the lack of the expected drug-induced anemia. The automatic stop rules as outlined in the study above were applied to the PR48 group. Patients in the telaprevir groups who showed detectable HCV RNA concentrations at the last study visit before the established end-of-treatment date were continued on PR for a total of 48 weeks and counted as treatment failures. Telaprevir and PR doses were identical to those in the PROVE 1 study. The other study groups were double-blinded up to week 10. Efficacy assessment included serial plasma HCV RNA concentration changes, viral breakthrough, and relapse as defined in the PROVE 1 study. Primary analysis for efficacy was the comparison of SVR between the control group and the groups that received the telaprevir-containing regimens. Patients were well matched into the study groups, with a median age of 45 years; 60% were men and 95% were white. The SVR and relapse rates are listed in **Table II**. The SVR in the T12PR24 group was

69% versus 46% in the PR48 group ( $P = 0.004$ ). The SVR between the T12PR12 (60%) and T12P12 (36%) versus the PR48 group were comparable ( $P = 0.12$  and  $P = 0.20$ , respectively). The rate of SVR was greater in the T12PR24 group compared with the T12P12 group ( $P = 0.003$ ). Relapse, as defined previously, occurred in 22%, 30%, 14%, and 48% of patients in the PR48, T12PR12, T12PR24, and T12P12 groups, respectively. After an SVR was achieved, 2 patients experienced a relapse, 1 at 48 weeks after end of treatment (T12 PR24) and 1 at 36 weeks after the end of treatment (T12 P12). Viral strains in these patient were present at baseline. Viral breakthrough was experienced by 1% (PR48), 1% (T12PR12), 5% (T12PR24), and 24% (T12P12) of patients in the respective groups by 12 weeks of the study. Analysis of the NS3 protease sequence revealed that 5%, 41%, and 55% of breakthrough virus represented wild-type, low-level (<25-fold increase in  $IC_{50}$  for telaprevir), and high-level (>60-fold increase in  $IC_{50}$  for telaprevir) resistance, respectively. AEs most commonly attributed to telaprevir included rash (usually maculopapular) and pruritus. Grade 3 (severe) rash was observed in 3% to 7% of patients in the telaprevir groups. Twelve percent of patients in the telaprevir groups discontinued therapy due to an AE versus 7% in the PR48 group. Decreases in hemoglobin ( $-3.1$  to  $-3.9$  g/dL) were noted during the 12 weeks of telaprevir therapy. The use of erythropoietin was not allowed during telaprevir-containing treatment. Adjustments to ribavirin or peginterferon alfa-2a therapy were allowed based on laboratory findings.

McHutchison et al<sup>60</sup> randomly assigned patients chronically infected with HCV genotype 1 who failed to achieve SVR after standard PR therapy to 1 of 4 treatment groups (the PROVE 3 study). Patients with decompensated liver disease, hepatitis B infection, HCC, HIV infection, or low white blood cell or platelet counts were excluded. The study included a group who did not receive ribavirin as part of the therapy. The groups included PR48 (PR + placebo for 24 weeks and 24 additional weeks of PR alone), T12PR24 (telaprevir + PR for 12 weeks and 12 additional weeks of PR + placebo), T24PR48 (telaprevir + PR for 24 weeks followed by 24 weeks of PR alone), and T24P24 (telaprevir + peginterferon alfa-2a for a total of 24 weeks). The telaprevir and PR doses were identical to those outlined above.<sup>58,59</sup> To prevent continued therapy in patients unlikely to respond to therapy, 4 stop rules were for-

mulated. Study medications were discontinued in patients who met these criteria, and these patients were listed as nonresponders in the final analysis. The primary outcome was SVR as defined previously and analysis was intent to treat. The mean age was 51 years, 89% were white, and 68% were men. Cirrhosis was present in 16% of patients. The SVR and relapse rates are listed in **Table II**. The SVR in the T12PR24 group was 51% versus 14% in the PR48 group ( $P < 0.001$ ). The rates of SVR with T24PR48 (53%) and T24P24 (24%) were higher when compared with the PR48 group ( $P < 0.001$  and  $P < 0.02$ , respectively). Relapse (in patients with an undetectable HCV RNA [ $<10$  IU/mL] at end of treatment) occurred in 53%, 30%, 13%, and 53% of patients in the PR48, T12PR24, T24PR48, and T24P24 groups, respectively. Viral breakthrough at 24 weeks (undetectable HCV RNA concentrations occurring during treatment with detectable levels before end of treatment) was experienced by 3% (PR48), 13% (T12PR24), 12% (T24PR48), and 32% (T24P24) of patients in the respective groups. Viral strains with resistance to telaprevir were found during viral breakthrough analysis. AEs most commonly attributed to telaprevir included rash (maculopapular) and pruritus. Grade 3 (severe) rash was observed in 3% to 5% of patients in the telaprevir groups and 0% in the PR group. Five percent of patients in the telaprevir groups discontinued therapy due to rash versus 0% in the PR group. Fifteen percent of telaprevir-treated patients discontinued therapy due to an AE versus 4% in the PR48 group. Decrease in hemoglobin was more common in the telaprevir groups than in the PR group, and levels recovered when therapy was stopped. The use of erythropoietin was not allowed.

The Phase II studies reported that the combination of telaprevir with PR may increase the likelihood of SVR in patients infected with chronic HCV infection.<sup>45,46,58–60</sup> Marcellin et al<sup>45</sup> reported comparable efficacy in patients receiving telaprevir + PR q8 or q12. They also noted that peginterferon alfa-2a and -2b had similar rates of SVR in study patients. Because all of the other Phase II studies administered telaprevir on an 8-hour schedule, more study will be necessary to confirm the effectiveness of the q12h regimen. These Phase II studies (PROVE 1 and 2) reported that the addition of telaprevir to PR may improve the likelihood of achieving SVR in treatment-naïve patients with chronic HCV genotype 1 infection (T12PR24, 61% and 69%) compared with conventional PR48 therapy

alone (41% and 46%).<sup>58,59</sup> In patients who have failed PR therapy, SVR was also improved with T12PR24 and T24PR48 (51% and 53%) compared with PR48 therapy alone (14%).<sup>60</sup> These studies indicated that a shorter duration of therapy may be possible when telaprevir is added to a regimen of PR. The interim analysis of a study designed to follow up patients enrolled in the Phase II studies reported that 99% of patients (122/123) experiencing SVR would continue to have undetectable HCV RNA concentrations at a median of 22 months' follow-up (range, 5–35 months).<sup>39</sup> It is clear that ribavirin is necessary to achieve the improved SVR when telaprevir is used in combination with peginterferon alfa.<sup>59,60</sup> The PROVE 3 study reported that the addition of telaprevir to PR therapy in patients who have failed prior PR therapy improves the likelihood of achieving SVR, especially in patients with a history of relapse. AEs are manageable, with the need for discontinuation of therapy occurring at a higher rate in the telaprevir groups than in the PR48 groups.

Limitations of these studies included the relatively small numbers of patients in each treatment arm and the exclusion criteria, which limit the applicability of the results to a select group of patients with chronic HCV infection. These results may not be applicable to members of various ethnic groups (eg, black, Asian, Hispanic) because these groups were underrepresented in these studies.

### **Phase III Clinical Trials**

The ADVANCE (A New Direction in HCV Care: A Study of Treatment-Naïve HCV Patients with Telaprevir) study was an international effort that included 123 sites and enrolled treatment-naïve patients who were chronically infected with HCV genotype 1 (1a, 58%; 1b, 41%).<sup>35</sup> Patients with compensated liver cirrhosis were eligible. Patients with decompensated liver disease, HCC, hepatitis B surface antigen, HIV infection, low white blood cell and platelet counts, and/or hemoglobin concentrations  $<12$  g/dL (women) and  $<13$  g/dL (men) were excluded from the study. The trial was randomized, double-blind, and placebo controlled. Patients were grouped by genotype 1 subtype (a, b, and unknown) and by baseline HCV RNA viral load ( $<$  and  $\geq 800,000$  IU/mL). Patients were randomly assigned to 1 of 3 treatment groups (PR48, T12PR, or T8PR). Members of the standard-therapy group were assigned to receive 12 weeks of combined PR + placebo followed by 36 weeks of PR alone (total,

Table III. Findings from Phase III studies of telaprevir in hepatitis C virus (HCV).

Study	T8PR24*	T8PR48 <sup>†</sup>	T12PR24	T12PR48	PR48 (Control)
ADVANCE <sup>35</sup>					
n	207	157	210*	153 <sup>†</sup>	361
SVR, %	83	50	89	54	44
ILLUMINATE <sup>37‡</sup>					
n	—	—	162*	160/118	—
SVR, %	—	—	92	88/64	—
Relapse, %	—	—	6	3/11	—
Kumada et al <sup>61</sup>					
n	—	—	126	—	63
SVR, %	—	—	73	—	49.2
Relapse, %	—	—	16.7	—	22.2
Hayashi et al <sup>62§</sup>					
n	—	—	109/32	—	—
SVR, %	—	—	88.1/34.4	—	—
Relapse, %	—	—	7.3/40.6	—	—

ADVANCE = Telaprevir in Genotype 1 Treatment-naive Patients study; ILLUMINATE = Illustrating the Effects of Combination Therapy with Telaprevir study; PR = peginterferon + ribavirin; SVR = sustained virologic response; T = telaprevir.

\*Patients with extended rapid virologic response (undetectable HCV RNA concentrations at 4 and 12 weeks of treatment).

<sup>†</sup>Patients without extended rapid virologic response.

<sup>‡</sup>For T12PR48, data on eRVR/non-eRVR groups.

<sup>§</sup>Data on relapsers/nonresponders.

48 weeks [PR48]). The T12PR group received telaprevir combined with PR for a total of 12 weeks, and the T8PR group received telaprevir for the first 8 weeks, followed by placebo for 4 weeks. Peginterferon alfa and ribavirin were administered for the entire 12 weeks. The 2 telaprevir groups were subdivided into 2 based on patients' response to initial therapy (response-guided therapy [RGT]). Patients assigned to each of the telaprevir groups who achieved an extended rapid virologic response (eRVR; undetectable HCV RNA concentration [ $<10$  IU/mL] at 4 and 12 weeks) continued on PR for an additional 12 weeks (24 weeks total) (T12PR24 and T8PR24). Patients with detectable HCV RNA concentrations at 4 or 12 weeks received an additional 36 weeks of PR (total, 48 weeks) (T12PR48 and T8PR48). Patients received telaprevir at a dosage of 750 mg q8h with food, peginterferon alfa-2a 180  $\mu$ g/wk SC, and weight-adjusted ribavirin ( $<75$  kg, 1 g/d;  $\geq 75$  kg, 1.2 g/d). Therapy was automatically discontinued if the following criteria were met: (1) an HCV RNA concentration decreased by  $<2$

$\log_{10}$  from baseline at week 12; (2) an HCV RNA concentration of  $>1000$  IU/mL at week 4 in patients receiving telaprevir (PR was continued); and (3) a detectable HCV RNA level between weeks 24 and 40. The primary end point of the study was SVR. Patients' characteristics in the treatment groups were well matched. The median age was 49 years; 58% of patients were men, 88% were white, 8.7% were black, and 1.7% were Asian; and 21% had cirrhosis or bridging fibrosis. For statistical analysis, the investigators chose to combine T12PR groups (24 + 48 weeks) and the T8PR groups (24 + 48 weeks) and compare the SVR results with the PR48 group. The SVR rates in the combined groups were 75% (T12PR), 69% (T8PR), and 44% (PR), respectively ( $P < 0.001$ ; both telaprevir groups vs the PR group). Relapse (as defined earlier) occurred in 9% (T12PR), 9% (T8PR), and 28% (PR). The SVR results for the uncombined eRVR and non-eRVR groups are presented in Table III. The rates of SVR in patients who had an eRVR, by treatment group, were as follows: 89% in the T12PR24 group,

83% in the T8PR24 group, and 97% in the PR48 group (no statistics provided). In contrast, the rates of SVR in patients in the non-eRVR groups were 54% (T12PR48) and 50% (T8PR48) (no statistics provided). Subgroup analysis of response in patients with baseline indicators of poor response revealed the following results. SVR was achieved in 62% (T12PR), 58% (T8PR), and 25% (PR) of black patients. The SVR rates in patients with genotype 1a were 71% (T12PR), 66% (T8PR), and 41% (PR); genotype 1b, 79% (T12PR), 74% (T8PR), and 48% (PR) (no statistics provided). The rates of SVR in patients with a baseline HCV RNA concentration of  $\geq 800,000$  IU/mL were 74% (T12PR), 66% (T8PR), and 36% (PR) (no statistics provided). Virologic failure (VF) was defined by the stop rules mentioned previously and occurred in 8% (T12PR), 13% (T8PR), and 32% (PR) of patients. High-level resistant variants as defined earlier (eg, V36M + R155K) caused VF during the first 12 weeks of telaprevir treatment. After 12 weeks, wild-type virus and lower-level resistant variants predominated. VF was more common in the T8PR group (10%) versus the T12PR group (5%). The most common AEs were rash, gastrointestinal complaints, and anemia. AEs resulted in the discontinuation of therapy during the telaprevir or placebo phase of the study in 7% (T12PR), 8% (T8PR), and 4% (PR) of patients. Rash and anemia were most commonly listed as the cause of stopping telaprevir regimens. Seven percent of the T12PR group and 5% of the T8PR group stopped therapy due to rash. Rash resolved with the discontinuation of telaprevir and was described as eczematous in appearance. Anemia caused the discontinuation of therapy in 1% (T12PR), 3% (T8PR), and  $<1\%$  (PR) of groups. Erythropoietin use was not allowed in this study, and anemia was managed using ribavirin dosage adjustments.

ILLUMINATE was an international, randomized, open-label, noninferiority trial that compared the efficacy and tolerability of 24 weeks versus 48 weeks of telaprevir/PR regimens for the management of chronic, stable genotype 1 (1a, 72%; 1b, 27.5%) HCV infected patients.<sup>37</sup> A noninferiority trial is designed to determine whether a new therapy is not less effective than the standard treatment by more than a certain amount. Exclusion criteria were similar to those in the ADVANCE study, except that patients with active cancer within the previous 5 years were excluded. Patients were treatment naive and were assigned to differing durations of therapy based on response to treatment at

4 and 12 weeks (RGT). All patients received telaprevir (750 mg q8h PO), peginterferon alfa-2a (180  $\mu$ g SC once a week), and weight-adjusted ribavirin (as outlined previously) for 12 weeks, followed by PR alone. Patients who achieved undetectable HCV RNA concentrations ( $<10$ – $15$  IU/mL) at weeks 4 and 12 (eRVR) were randomly assigned to complete a total PR regimen of 24 (T12PR24) or 48 (T12PR48) weeks. Patients not achieving eRVR were assigned to a third group (T12PR48). SVR was assessed at 24 weeks in all patients and at 48 weeks in the T12PR24 group. VF was defined as  $<2$  log<sub>10</sub> units of detectable HCV RNA at 12 weeks or a detectable HCV RNA concentration at any time between the 24- and 36-week time points. An HCV RNA concentration of  $>1000$  IU/mL at week 4 constituted VF. Automatic stop rules included stopping all medications if VF was noted at week 12 or between weeks 24 and 36. If the HCV RNA concentration was  $>1000$  IU/mL at week 4, telaprevir therapy was discontinued. Noninferiority between the SVR response in patients with eRVR assigned to T12PR24 versus T12PR48 was set as the primary efficacy outcome of the study. The margin for noninferiority was set at  $-10.5\%$ . Patients were well matched in the 3 treatment groups. Approximately 60% of patients were male, 78% were white, and 14% were black, and in the remaining 8%, race/ethnicity was not specified. The median age was 51 years. Bridging fibrosis or cirrhosis was present in 16.3% and 11.3% of patients, respectively. Sixty-five percent of patients had eRVR, and 18.5% of patients were withdrawn from the study because of withdrawn consent or AEs. The SVR percentages in the eRVR groups (T12PR24 and T12PR48) were 92% and 88%, respectively (95% CI,  $-2$  to 11) (Table III). These results met the defined noninferiority criteria for the study. The rate of SVR in the non-eRVR group (T12PR48) was 64%. Relapse rates were noted in 6% (T12PR24), 3% (T12PR48) of patients with an eRVR, and 11% (T12PR48) patients without an eRVR. In patients with eRVR, baseline HCV RNA concentration was not a factor in the achievement of SVR. Overall, 74% of white patients and 60% of black patients experienced SVR ( $P = 0.02$ ). SVR was achieved in 88% of black patients who achieved eRVR in either treatment group (T12PR24 or T12PR48). In patients with bridging fibrosis or cirrhosis and eRVR, 82% (T12PR24) and 88% (T12PR48) of patients had SVR ( $P = \text{NS}$ ). VF occurred in 8% of patients overall, and patients carried HCV variants with reduced suscepti-

bility to telaprevir. After a median follow-up of 43 weeks, of patients without SVR and with baseline telaprevir-resistant HCV variants, 55% no longer carried these strains. During the 12 weeks of telaprevir + PR therapy, 7% of patients discontinued all study medications (1% due to rash and 1% due to anemia). Telaprevir alone was discontinued in 12% of patients (2% anemia and 7% rash). Erythropoietin use was not allowed in the study. Rash was severe in 5% of patients. The rash was usually eczematous in appearance, occurred within the first 8 weeks of therapy, and usually responded to topical treatment.

Zeuzem et al<sup>36</sup> performed REALIZE (a double-blind, randomized, placebo-controlled study), which investigated the efficacy and tolerability of telaprevir + PR containing regimens in patients chronically infected with HCV genotype 1 (1a, 45%; 1b, 45%; unknown, 10%) who had failed to achieve a SVR with PR alone. Patients were excluded from the study if they had active cancer, decompensated liver disease, low hemoglobin (as defined in the ADVANCE study), and/or a low white blood cell or platelet count. Patients were stratified by HCV RNA concentrations (< or  $\geq$ 800,000 IU/mL) and type of previous response to PR therapy. Responses were defined as follows: *no response*, a  $<2\text{-log}_{10}$  reduction in HCV RNA concentrations after 12 weeks of treatment; *partial response*, a  $\geq 2\text{-log}_{10}$  reduction in HCV RNA concentrations after 12 weeks of treatment but with detectable HCV RNA; and *relapse*, undetectable HCV RNA concentration ( $<10$  IU/mL) at the end of treatment but with detectable HCV RNA at a subsequent time point. Telaprevir, peginterferon alfa-2a, and ribavirin were administered at the same dosages and regimens as in the ADVANCE and ILLUMINATE studies. Patients were randomly assigned to 1 of the following 3 treatment groups: (1) the control group received PR + placebo for 16 weeks, followed by PR for 32 weeks (PR48); (2) the T12PR48 group received telaprevir + PR for 12 weeks, followed by PR + placebo for 4 weeks, then 32 weeks of PR alone; and (3) the lead-in T12PR48 group received PR + placebo for 4 weeks, then telaprevir + PR for 12 weeks, followed by PR alone for 32 weeks (T12PR48 lead-in). Stop rules included stopping all therapy if a patient had a  $<2\text{-log}_{10}$  reduction in HCV RNA concentrations after 12 weeks of treatment in the T12PR48 or control groups, or at 16 weeks in the lead-in T12PR48 group. Therapy was also stopped if HCV RNA concentrations were detectable at week 24

or 36. In addition, telaprevir therapy was discontinued if HCV RNA concentrations exceeded 100 IU/mL at weeks 4, 6, and 8 after telaprevir was started. Patients could continue on PR therapy. The primary end point of the study was the percentage of patients in whom SVR was achieved. Secondary end points reviewed the effect of the lead-in period on SVR, the number of patients with undetectable HCV RNA concentrations at 4 and 8 weeks, change from baseline in  $\log_{10}$  HCV RNA concentrations, and the percentage of patients who relapsed after the completion of therapy. Baseline characteristics were comparable in the 3 study groups. Sixty-nine percent were male, 92% were white, 5% were black, and 3% were Asian. The mean age was 51 years. A diagnosis of cirrhosis was present in 26% of patients. Twenty-eight percent of patients had no response, 19% had a partial response, and 53% had a relapse during previous PR therapy. The results of the study are outlined in Table IV. Overall, SVR occurred in 64% (T12PR48), 66% (lead-in T12PR48), and 17% (PR48) of patients ( $P < 0.001$  for both telaprevir groups vs control). Patients with a history of relapse on prior therapy had the best SVR responses (83% [T12PR48], 88% [lead-in T12PR48], and 24% [control];  $P < 0.001$  for both telaprevir groups compared with control). Partial responders had the next-best response, followed by the no-response group, which had the lowest SVR. The rate of SVR in the no-response group was 29% (T12PR48), 33% (lead-in T12PR48), and 5% (PR48). The SVR percentage was comparable between the T12P48 and the lead-in T12PR48 groups and the 3 response groups (no statistics provided). The baseline HCV viral load did not affect the attainment of a SVR (no statistics provided). However, according to the investigators, the presence of advanced liver fibrosis significantly decreased the response to therapy (SVR) in the no-response and partial-response groups (no statistics provided). VF was observed in each group (control  $>$  no response  $>$  previous partial response  $>$  relapse). HCV variants with reduced susceptibility to telaprevir were discovered in 73% of VFs and relapses. By  $\sim 46$  weeks of follow-up, these variants were no longer detected in 58% of patients. The most common AEs reported during telaprevir + PR therapy were fatigue, gastrointestinal effects, pruritus, anemia, and rash. Anemia was managed using dosage adjustments of ribavirin. The use of erythropoietin was not allowed. Thirteen percent of patients in the 2 telaprevir groups discontinued therapy due to AEs versus 3% in the control

Table IV. Findings from the REALIZE study of telaprevir in hepatitis C virus.<sup>36</sup>

Group	T12PR48*	T12PR48 Lead-in*	PR48 (Control)
Overall response			
n	171	175	22
SVR, %	64	66	17
Relapse, %	7	9	NA
No response			
n	72	75	37
SVR, %	29	33	5
Relapse, %	27	25	60
Partial response			
n	49	54	27
SVR, %	59	54	15
Relapse, %	21	25	0
Relapse			
n	145	141	68
SVR, %	83	88	24
Relapse, %	7	7	65

NA = not available; PR = peginterferon + ribavirin; REALIZE = Re-treatment of Patients with Telaprevir-based Regimen to Optimize Outcomes study; SVR = sustained virologic response; T = telaprevir.

\*For SVR,  $P < 0.001$  versus control.

group. Four percent of patients discontinued telaprevir due to rash versus 0% of the control group.

Kumada et al<sup>61</sup> performed a multicenter, prospective, randomized, open-label study in Japanese patients with stable chronic HCV genotype 1 (1b, 98.9%) infection who were naive to prior therapy. Patients with hepatitis B surface antigen; decompensated liver cirrhosis, HCC or other cancer, and/or other causes of liver disease; depression or schizophrenia; chronic kidney disease; and/or blood abnormalities (as listed previously) were excluded. Patients were randomly assigned to 1 of 2 groups in a 2:1 ratio. Group 1 ( $n = 126$ ) received 12 weeks of the following therapy: telaprevir 750 mg q8h PO, peginterferon alfa-2b (median dose, 1.5  $\mu\text{g}/\text{kg}/\text{wk}$ ; range, 1.25–1.739  $\mu\text{g}/\text{kg}$ ), and ribavirin (adjusted to weight), followed by PR for an additional 12 weeks (T12PR24). Group 2 ( $n = 63$ ) received PR therapy at the doses listed previously for a total of 48 weeks. The primary end point was the per-

centage of patients achieving SVR. The 2 groups were well matched based on baseline demographic characteristics, with 52.4% being male, and had a median age of 54 years. The percentages of patients achieving SVR were 73% in group 1 and 49.2% in group 2 ( $P = 0.002$ ) (Table III). Relapse occurred in 16.7% of group 1 and 22.2% of group 2 ( $P = 0.4272$ ). AEs were common in both groups, with 16.7% (group 1) and 22.2% (group 2) stopping all drug therapy. The prevalences of anemia, elevated serum uric acid/hyaluronic acid, thrombocytopenia, and malaise were higher ( $>10\%$ ) in group 1 versus group 2. The prevalence of anemia was higher in group 1 versus group 2 (grades 1 and 2,  $P = 0.0045$ ; grade 3,  $P = 0.0055$ ). Anemia resolved within 12 weeks of the completion of therapy. Skin reactions (rash, erythema, or drug eruptions) occurred in both groups. Three patients in group 1 experienced a serious skin reaction. Reactions included 1 case of Stevens-Johnson syndrome (onset day 35 of treatment), 1 case of DRESS (drug rash with eosinophilia and systemic symptoms), and 1 case of erythema multiforme. All cases were treated successfully and patients recovered in 9 to 14 weeks.

Hayashi et al<sup>62</sup> performed an open-label study investigating the efficacy and tolerability of telaprevir + PR therapy in Japanese patients who had relapsed (relapser group) ( $n = 109$ ) or were nonresponders (non-responder group) ( $n = 32$ ) to previous interferon-based treatment. The exclusion criteria were the same as listed in the previously mentioned study, with the addition of HIV infection. A *relapser* was defined as a patient who had been previously treated with either interferon or peginterferon therapy with or without ribavirin and had achieved undetectable HCV RNA concentrations ( $<1.2 \log_{10}$  IU/mL). *Nonresponders* were defined as patients who failed to achieve an undetectable HCV RNA concentration for  $>24$  weeks during treatment with interferon or peginterferon with or without ribavirin. Eligible patients had chronic stable HCV genotype 1 infection (1a, 1.6%; 1b, 98.4%). All patients in both treatment groups received 12 weeks of the following therapy: telaprevir 750 mg q8h PO, peginterferon alfa-2b (median dose, 1.5  $\mu\text{g}/\text{kg}/\text{wk}$ ), and ribavirin (adjusted to weight and baseline hemoglobin), followed by peginterferon + ribavirin for an additional 12 weeks (T12PR24). The initial dose of ribavirin was adjusted based on patients' baseline hemoglobin concentrations in an effort to decrease the incidence of anemia. A change in the dose of telaprevir

was not allowed and erythropoietin was not used for increasing hemoglobin levels. Stop rules were applied based on changes in HCV RNA concentrations. The primary end point was percentage of patients who achieved SVR. The 2 groups were well matched based on baseline demographic characteristics; 56.8% were male, and the median age was 57 years. The rate of SVR in the relapser group was 88.1% versus 34.4% in the nonresponder group (Table III). Relapse occurred in 7.3% of patients in the relapser group and 40.6% of patients in the nonresponder group. AEs were common in both treatment groups. All medications were discontinued in 17.4% of patients in the relapser group versus 12.5% in the nonresponder group. Anemia resulted in discontinuation of all medications in 10.1% and 9.4% of patients in the relapser and nonresponder groups, respectively. One patient in the relapser group died, with a “possibly related” to telaprevir designation and a “probably related” classification for PR. Overall, skin rash and drug eruption occurred in 39% and 24.2% of patients. Severe (grade 3) reactions occurred in 6.4% and 6.3% of patients in the relapser and nonresponder groups, respectively. Seven of the 9 reactions occurred within the first 8 weeks of therapy, making an association with telaprevir likely.

The ADVANCE study reported that patients with chronic HCV infection genotype 1 who experienced eRVR with combined telaprevir + PR therapy could be treated for 24 weeks with PR versus the standard treatment of 48 weeks of PR-based therapy (RGT).<sup>35</sup> The lower SVR response to the T8PR24/48 regimens favored the use of triple therapy with telaprevir for a total of 12 weeks. Patients without eRVR would need to receive the T12PR48 regimen. Patients with historically negative predictive baseline factors (eg, black patients and/or those with bridging fibrosis, cirrhosis, older age, diabetes, and/or high baseline HCV levels) responded well to telaprevir-based therapy. The ILLUMINATE study reported that 24-week therapy with PR (T12PR24) was noninferior to 48 weeks of PR (T12PR48) in treatment-naïve patients with eRVR to combination therapy.<sup>37</sup> The REALIZE study did not stratify patients using RGT guidelines, and all patients received T12PR48 therapy.<sup>36</sup> Patients with a history of relapse responded well to T12PR48 therapy, and dosing guidelines approved by the FDA allow for the duration of therapy to be determined by response.<sup>1,36</sup> The investigators believed that the lead-in period did not affect SVR rate (T12PR48, 64%; lead-in T12PR48,

66%; statistics not provided).<sup>36</sup> The study by Hayashi et al<sup>62</sup> reported similar rates of SVR as in the REALIZE study in relapsers, although the patients received PR for a total of 24 weeks (T12PR24, 88.1%; T12PR48, 83%; and T12PR48 lead-in, 88%) (Tables III and IV).<sup>36</sup> In addition, the SVR response was similar in the no-response groups, although Hayashi et al<sup>36</sup> treated patients with PR for a total of 24 weeks versus 48 weeks in the REALIZE study (T12PR24, 34.4%; T12PR48, 29%; and T12PR48 lead-in, 33%).<sup>36,62</sup> The Phase III studies addressed some of the limitations discussed in the Phase II study section, including a larger number of patients and the inclusion of more difficult-to-treat patients (black patients and/or those with cirrhosis). Minority patients, women, and patients who were coinfecting with HIV were noticeably underenrolled in these studies.

### Special Populations

#### HIV/HCV Coinfection

Some patients with HCV are coinfecting with HIV. In the United States, 20% to 30% of patients with HIV are also infected with HCV.<sup>63–65</sup> In Spain, the percentage of coinfecting patients is 42%.<sup>66</sup> The current standard of care for HIV/HCV coinfection includes a combination of peginterferon (alfa-2a or -2b) plus ribavirin for 48 weeks, regardless of genotype.<sup>67</sup> Response to therapy (SVR) with PR varies between 14% and 38% in patients coinfecting with HCV genotype 1.<sup>68–72</sup> Although telaprevir has not been approved for use in HIV/HCV coinfecting patients, a Phase II study has reached the 24-week assessment point and is available as an abstract.<sup>1,73</sup> The study was a randomized, placebo-controlled, double-blind, parallel-group trial. Patients were randomly assigned to 1 of 3 groups. All 3 groups had a triple-therapy subgroup, with telaprevir 750 mg q8h + peginterferon alfa-2a 180 µg/wk + ribavirin 800 mg/d for 12 weeks, followed by 36 weeks of PR alone (T12PR48) and a control subgroup (placebo for 12 weeks + PR for 48 weeks [PR48]). Group 1 did not receive antiretroviral therapy (ART) (T12PR48, n = 7; and PR48, n = 6). Group 2 received ART that consisted of efavirenz (EFV)/tenofovir/emtricitabine (T12PR48, n = 16; PR48, n = 8) and group 3 received ART that included ritonavir-boosted atazanavir (ATV/r)/tenofovir/emtricitabine (T12PR48, n = 15; PR48, n = 8). Patients in group 2 (EFV group) received telaprevir at a dose of 1125 mg q8h due to EFV induction of telaprevir metabolism.<sup>1,74</sup> Patient baseline

characteristics included a mean age of 46 years, with 88% male, 27% black, and mean CD4 counts of 690 cells/mm<sup>3</sup> (group 1) and 562 cells/mm<sup>3</sup> (groups 2 and 3). In group 1, 86% of patients in the T12PR48 group had undetectable HCV RNA concentrations (<25 IU/mL) at 24 weeks versus 33% in the PR48 group. In group 2 (EFV treated), 75% of patients in the T12PR48 group and 50% in the PR48 group had undetectable HCV RNA concentrations at 24 weeks. In group 3 (ATV/r treated), 67% of patients in the T12PR48 group and 75% of the PR48 group had undetectable HCV RNA concentrations at 24 weeks. A total of 74% and 55% of patients in the T12PR48 and PR48 groups, respectively, had undetectable HCV RNA concentrations after 24 weeks. In addition, 63% of patients in the T12PR48 groups and 4.5% of patients in the PR48 groups experienced eRVR when data from each group were combined. Two patients, 1 in each group (EFV and ATV/r) had a viral breakthrough during telaprevir therapy. AEs included nausea, vomiting, dizziness, depression, pruritus, and abdominal pain and were more common in the T12PR48 groups than in the PR48 groups. An increase in bilirubin occurred in group 3 receiving ATV/r (27% vs 0%). Three patients (groups 2 and 3) had  $\geq 1$  study drug stopped due to a severe adverse reaction (jaundice, cholelithiasis, hemolytic anemia). No severe rashes have been noted to this point in the study. Although the number of patients is small, the results are encouraging and the study is ongoing.

Because telaprevir is a substrate and inhibitor of CYP3A, there is a concern that it will interact with ART agents that are metabolized by this isozyme and potentially result in AEs. Patients in the study mentioned previously appeared to have tolerated the combination of telaprevir + PR and the ART included in the trial.<sup>73</sup> Telaprevir has been reported to increase the AUC<sub>24h</sub> of tenofovir by 30%, which is similar to the effect of other PIs when used concurrently.<sup>44</sup> Low-dose ritonavir does not boost telaprevir activity when used concurrently.<sup>43</sup> Concurrent telaprevir did not appreciably affect the pharmacokinetic properties of ATV/r, whereas the AUC of telaprevir was decreased by 20%. This change was not considered clinically significant.<sup>74</sup> The serum bilirubin increased in 27% of patients receiving ATV/r and telaprevir versus 0% in patients receiving telaprevir without ATV/r. A pharmacokinetic study in healthy subjects that combined telaprevir with a ritonavir-boosted antiretroviral PI noted the follow-

ing effects on the AUCs of these agents: darunavir, 40% decrease; fosamprenavir, 47% decrease; and lopinavir, unchanged.<sup>74</sup> In contrast, with the concurrent administration of ritonavir-boosted darunavir, fosamprenavir, and lopinavir, telaprevir AUCs were reduced by 35%, 32%, and 54%, respectively.<sup>74</sup> The combination of telaprevir with these PIs should be avoided. Dierynck et al<sup>75</sup> performed an in vitro study to investigate whether telaprevir would affect the antiviral activity of amprenavir, atazanavir, darunavir, and lopinavir on HIV-1. Telaprevir demonstrated a small antagonistic effect when combined with atazanavir (not considered significant), but no effect on the antiviral activity of the other PIs was reported. In a study in healthy volunteers, telaprevir increased the AUC<sub>0-12h</sub> of raltegravir by 31%.<sup>76</sup> Raltegravir did not affect telaprevir pharmacokinetic properties. The interaction was most likely due to an increased absorption of raltegravir based on the inhibition of intestinal P-glycoprotein by telaprevir and is not considered clinically significant.

Drug interactions can also occur between ART and peginterferon and/or ribavirin. Didanosine and stavudine increase the risk for mitochondrial toxicity (eg, lactic acidosis) when used with ribavirin.<sup>71,77</sup> The risk for anemia is increased when peginterferon and ribavirin are used with zidovudine.<sup>78</sup> It is suggested that clinicians refer to the manufacturer's package insert for a more complete review of potential interactions between ART and telaprevir.<sup>1</sup>

#### *Pharmacogenomic Issues*

The question of when to add telaprevir to standard PR therapy is important due to the increased cost and AEs attributed to its use. A recently discovered association between polymorphisms near the interleukin (IL)-28B gene may predict how a patient infected with chronic HCV infection genotype 1 will respond to therapy with PR.<sup>79</sup> The IL-28B gene is located on chromosome 19 and codes for interferon  $\lambda$ -3. Two single-nucleotide polymorphisms (SNPs) have been most studied (rs12979860 and rs8099917).<sup>79,80</sup> For SNP rs12979860, the favorable genotype (SVR more likely) is designated as CC and the less favorable are designated as CT and TT IL-28B type. For SNP rs8099917, the favorable genotype (SVR more likely) is designated as TT and the less favorable are designated as TG and GG IL-28B type. Thompson et al<sup>79</sup> investigated the association of SNP rs12979860 with SVR in patients

infected with HCV genotype 1 who were treated with standard therapy (PR for 48 weeks). They found a higher likelihood of achieving SVR in white patients with the CC genotype (69%) versus those with non-CC genotypes (CT, 33%; TT, 27%) and that the IL-28B type was a predictor of pretreatment response to standard therapy.<sup>79</sup> In a group of HCV/HIV coinfecting patients, the IL-28B SNP rs8099917 genotype was associated with treatment success and failure in patients receiving standard PR therapy (genotype 1).<sup>81</sup> Patients with the G allele were more likely to fail therapy than those with the TT genotype ( $P < 0.0001$ ). In the group of patients achieving SVR, 90% had the TT genotype and 10% had either the TG or GG genotype. In another study, the rs12979860 SNP outperformed the rs8099917 SNP as a predictor of SVR in HIV/HCV coinfecting patients when compared with standard PR therapy.<sup>82</sup>

Chayama et al<sup>80</sup> investigated the utility of 2 SNPs (rs8099917 and rs1127354) in the prediction of response to triple therapy (T12PR24) in HCV genotype 1 infected Japanese patients. The rs1127354 is a polymorphism of the inosine triphosphatase (ITPA) gene associated with anemia due to ribavirin.<sup>83</sup> In the study, 94% of patients with the TT genotype achieved SVR versus 50% of patients with non-TT genotypes (GT or GG). The ITPA polymorphism was not predictive of a response. The impact of the rs12979860 SNP of the IL-28B gene on the likelihood of achieving a SVR at the US sites in the ADVANCE study was assessed in the treatment-naïve white population.<sup>84</sup> Telaprevir administration improved the SVR rate in all genotype groups versus the standard-therapy group (PR). In the T12PR group, the rates of SVR were 90% (CC), 71% (CT), and 73% (TT), and in the PR group they were 64% (CC), 25% (CT), and 23% (TT). In contrast, an analysis of the REALIZE study results on the impact of IL-28B polymorphism genotype rs12979860 on the rate of SVR reported no predictive difference in outcome between the 3 groups.<sup>85</sup> Although these findings are intriguing, current guidelines fall short of recommending IL-28B testing in all patients infected with HCV genotype 1 to help guide the choice of therapy.<sup>86</sup>

### Tolerability

Because telaprevir is used in combination with PR, AEs will include those seen with peginterferon monotherapy (fatigue and flulike symptoms) plus additional AEs that can be attributed to telaprevir administration

(Table V).<sup>1,35–37,58–62,87</sup> The prevalences of AEs that are more commonly associated with telaprevir versus PR regimens are as follows: rash (56% vs 34%), pruritus (47% vs 28%), nausea (39% vs 28%), diarrhea (26% vs 17%), and anemia (36% vs 17%).<sup>1</sup> The most-cited causes of stopping telaprevir when used in combination with PR are rash, anemia, fatigue, pruritus, nausea, and vomiting which occurred in ~14% of patients.<sup>1</sup> The most common serious AEs occurring during telaprevir + PR therapy are anemia, rash, and/or pruritus.<sup>1,35–37,58–62</sup>

### Anemia

In the Phase II and III studies, the study protocols did not allow for the adjustment of the dose of telaprevir nor the administration of blood transfusions or erythropoietin during the administration of telaprevir.<sup>35–37,58–62</sup> Anemia was primarily managed by adjusting ribavirin therapy (dose modification or holding or stopping therapy) based on baseline hemoglobin concentrations or changes in hemoglobin concentrations during therapy. Median hemoglobin decreased by ~3.0 g/dL in the PR groups and by 3.5 to 4.0 mg/dL during the 12 weeks of telaprevir + PR therapy.<sup>58,59</sup> Overall, 36% of subjects receiving telaprevir and 17% of subjects receiving PR had a hemoglobin concentration of  $\leq 10$  g/dL during clinical trials.<sup>1,35–37,58–62</sup> Fourteen percent and 5% of patients had a hemoglobin level of  $< 8.5$  g/dL while receiving telaprevir + PR or PR monotherapy, respectively.<sup>1</sup> Of patients receiving combination telaprevir + PR, 2% to 4% had telaprevir stopped due to anemia during clinical trials.<sup>1,35–37,58,60</sup> Hemoglobin concentrations returned to baseline on discontinuation of telaprevir.<sup>1,58,60–62</sup> Dose adjustment of ribavirin in response to anemia in the telaprevir + PR groups did not affect the likelihood of achieving SVR compared with PR-only regimens.<sup>47,61,88</sup>

### Rash

Overall, rash of all grades occurred more frequently with telaprevir + PR regimens (56%) than with PR monotherapy (34%).<sup>1</sup> Pruritus was also common but was not always associated with a rash.<sup>1,58</sup> The rash has been described as maculopapular or eczematous in appearance, with a typical onset within 4 weeks of beginning therapy but a rash can occur at any time during and possibly after therapy with telaprevir is completed.<sup>1,35,47,58–60</sup> In the ILLUMINATE study, two thirds of all cases of rash occurred within the first 8 weeks of therapy initiation.<sup>37</sup> Biopsy of the rash does not show

Table V. Tolerability of telaprevir in Phase III trials.

Parameter	ILLUMINATE <sup>37</sup>									
	ADVANCE <sup>35</sup>			T12PR24, Randomly Assigned (n = 162)	T12PR48		Kumada et al <sup>61</sup>		Hayashi et al, <sup>62</sup> T12PR24	
	T12PR24 (n = 363)	T8PR24 (n = 364)	PR (Control) (n = 361)		Randomly Assigned (n = 160)	Not Randomly Assigned (n = 118)	T12PR24 (n = 126)	PR48 (Control) (n = 63)	Relapsers (n = 109)	Non-Responders (n = 32)
Discontinuations due to ADRs, %*	10	10	7	1	12	10	16.7	22.2	17.4	12.5
ADR, no. (%)										
Fatigue	207 (57)	211 (58)	206 (57)	110 (68)	111 (69)	81 (69)	NR	NR	NR	NR
Pruritus	181 (50)	165 (45)	131 (36)	95 (59)	83 (52)	55 (47)	23 (18.3)	13 (20.6)	20 (18.3)	2 (6.3)
Nausea	156 (43)	146 (40)	112 (31)	71 (44)	76 (48)	61 (52)	32 (25.4)	7 (11.1)	24 (22)	4 (12.5)
Headache	148 (41)	156 (43)	142 (39)	61 (38)	57 (36)	51 (43)	48 (38.1)	32 (50.6)	42 (38.5)	10 (31.3)
Anemia	135 (37)	141 (39)	70 (19)	68 (42)	66 (41)	38 (32)	115 (91.3)	46 (73)	96 (88.1)	32 (100)
Rash	133 (37)	129 (35)	88 (24)	60 (37)	62 (39)	47 (40)	48 (38)	18 (28.6)	39 (35.6)	16 (50)
Insomnia	117 (32)	116 (32)	111 (31)	50 (31)	62 (39)	44 (37)	40 (31.7)	17 (27)	34 (31.2)	11 (34.4)
Diarrhea	102 (28)	115 (32)	80 (22)	48 (30)	54 (34)	38 (32)	34 (27)	19 (30.2)	31 (28.4)	7 (21.9)
Pyrexia	95 (26)	108 (30)	87 (24)	NR	NR	NR	98 (77.8)	46 (73)	90 (82.6)	30 (93.8)
Anorexia	NR	NR	NR	NR	NR	NR	42 (33.3)	17 (27)	56 (51.4)	15 (46.9)
Vomiting	NR	NR	NR	NR	NR	NR	37 (29.4)	9 (14.3)	26 (23.9)	8 (25)
Abdominal discomfort	NR	NR	NR	NR	NR	NR	23 (18.3)	12 (19)	22 (20.2)	6 (18.8)

ADR = adverse drug reaction; ADVANCE = Telaprevir in Genotype 1 Treatment-naive Patients study; ILLUMINATE = Illustrating the Effects of Combination Therapy with Telaprevir study; NR = not reported; PR = peginterferon + ribavirin; T = telaprevir.

\*Telaprevir discontinued.

the presence of a vasculitis.<sup>47</sup> Mild to moderate rashes (grade 1 to 2) can usually be treated without stopping telaprevir. Topical agents including emollients and topical/oral antiallergic/antipruritic agents can be utilized to manage rash.<sup>1,37,60–62</sup> Grade 3 rash (severe, involving 50% of the body with vesicles or bullae or ulcerations [not Stevens-Johnson syndrome]) was noted to occur in 3% to 10% of patients receiving telaprevir + PR and in up to 4.8% of patients receiving PR.<sup>1,58–62</sup> Kumada et al<sup>61</sup> noted the highest rates of grade 3 skin reactions (telaprevir + PR, 10.3%; PR, 4.8%). Four to seven percent of patients in telaprevir groups had treatment stopped due to rash versus 0% of patients in the PR groups.<sup>1,36,58–60</sup> Telaprevir administration has been associated with serious skin reactions in a small number of patients. These have included Stevens-Johnson syndrome, DRESS, and erythema multiforme.<sup>1,35,47,61,89</sup> Patients experiencing any of these skin conditions should have telaprevir discontinued permanently. Rashes resolve on stopping telaprevir, but recovery may be prolonged depending on the severity of the reaction.<sup>1,61,89</sup> If telaprevir is stopped because of a rash, it should not be given again.<sup>1,90</sup>

#### Laboratory Effects

The incidence of laboratory changes that are more commonly associated with telaprevir + PR versus PR regimens are as follows: lymphocyte count decreased to  $<500$  cells/mm<sup>3</sup> (15% vs 5%), depressed platelet count (47% vs 36%) ( $<50 \times 10^3$  cells/mm<sup>3</sup>: telaprevir + PR, 3%; PR, 1%), elevated serum uric acid (73% vs 29%), and elevated serum bilirubin (any grade) (41% vs 28%).<sup>1</sup> Kumada et al<sup>61</sup> noted hyperuricemia in 15.9% of patients receiving telaprevir + PR versus 3.2% in the PR group. Bilirubin concentrations of 2.6-fold above the upper limit of normal have been documented in 4% and 2% of telaprevir + PR and PR treated patients, respectively.<sup>1</sup> Bilirubin concentrations rose sharply during the first 1 to 2 weeks of telaprevir + PR therapy and returned to baseline between weeks 12 and 16.<sup>1</sup> An increase in hyaluronic acid was reported in 50.8% of telaprevir + PR-treated patients and 39.7% of PR-treated patients in the study by Kumada et al.<sup>61</sup> Hayashi et al<sup>62</sup> reported a similar rate of increase in hyaluronic acid concentrations in patients receiving telaprevir + PR (50.4%) as retreatment of chronic HCV infection.

#### Miscellaneous

AEs of the anorectal area were more commonly reported in the telaprevir + PR groups (29%) versus the PR groups (7%).<sup>1,47</sup> AEs included the appearance of hemorrhoids, anorectal discomfort, rectal burning, and anal pruritus and were graded as mild to moderate in severity. These reactions resolved on stopping telaprevir. Readers are encouraged to review the manufacturer's package insert for telaprevir for a complete discussion of AEs attributed to telaprevir administration.<sup>1</sup>

#### Pharmacoeconomic Considerations

Gellad et al<sup>91</sup> used a Markov model to compare the cost-effectiveness of a treatment regimen containing telaprevir in patients infected with HCV genotype 1 as initial therapy with 2 PR regimens. All patients in each group had the favorable IL-28B CC genotype. Three treatment strategies were compared. The PR strategies included a standard therapy arm (PR for 48 weeks) and a response-guided therapy PR arm in which PR was administered for 24 weeks in patients who had RVR (undetectable HCV RNA concentration [not defined] at 4 weeks of therapy). The telaprevir treatment arm was also based on RGT in that all patients received triple therapy with telaprevir + PR for 12 weeks. If a patient achieved eRVR, they would be treated with an additional 12 weeks of PR therapy (T12PR24), and if they failed to achieve eRVR, PR would be continued for an additional 36 weeks (T12PR48). The investigators concluded that under the established study parameters, the use of triple therapy with telaprevir was not cost-effective. Triple therapy with telaprevir would become cost-effective if the weekly cost of telaprevir was  $< \$1640$ .

Liu et al<sup>92</sup> assessed the cost-effectiveness of triple therapy with a "general" PI. Effectiveness data for telaprevir was taken from the ADVANCE study. A decision-analytic Markov model that simulated the effect of various treatments on the progression from mild to more severe liver disease was used. The researchers looked at 3 possible scenarios: (1) treating all patients with the standard regimen (PR for 48 weeks); (2) treating all patients with a PI-containing regimen; and (3) treating patients with guided PI-containing regimens. Guided therapy involved using a genetic test IL-28B genotype (CC, CT, or TT type).<sup>79</sup> Patients with the IL-28B CC genotype (favorable genotype) would receive PR therapy, and those with non-CC genotype (unfavorable genotype) would receive triple therapy.

Based on the parameters included in the study, the investigators determined that universal triple therapy and IL-28B guided triple therapy were cost-effective using the cost of the “general PI” in patients with advanced fibrosis. When triple therapy with telaprevir was analyzed in the model, the investigators believed that this combination was not cost-effective due to the high weekly cost of the medications (\$4100). In contrast, Chan et al<sup>93</sup> postulated that increasing the treatment rate in patients in the Veterans Health Administration who were infected with HCV genotype 1 to  $\geq 50\%$  with telaprevir or boceprevir could result in decreased morbidity and mortality from chronic infection.

### Dosage and Administration

Telaprevir is approved for concurrent administration with PR for the treatment of patients with chronic HCV infection genotype 1.<sup>1</sup> The patients should be instructed to take two 375-mg tablets (750 mg per dose) TID PO with food. The food should include some fat content (ie, 20 grams of fat) and be consumed within 30 minutes prior to taking telaprevir.<sup>1</sup> The dose of telaprevir must not be changed or interrupted during therapy. Telaprevir therapy must be stopped if peginterferon and/or ribavirin is discontinued. Each dose should be administered between 7 to 9 hours apart. Initial therapy includes telaprevir + peginterferon alfa (2a or 2b) + ribavirin administered for 12 weeks. At the conclusion of 12 weeks of combination therapy, telaprevir is stopped and PR is continued. Readers are encouraged to refer to the manufacturer’s information for dosages of peginterferon alfa (2a or 2b) and ribavirin.<sup>94,95</sup>

The duration of subsequent PR therapy is dependent on whether a patient is naive to anti-HCV therapy or has failed previous treatment with interferon + ribavirin regimens. If a patient is treatment naive, the duration of subsequent PR therapy will depend on HCV RNA concentrations measured at 4 and 12 weeks of telaprevir + PR therapy (RGT). If the HCV RNA concentrations are undetectable at weeks 4 and 12 (eRVR), PR is continued for an additional 12 weeks, for a total of 24 weeks of PR. If the HCV RNA level is  $\leq 1000$  IU/mL at week 4 and/or 12, PR is continued for an additional 36 weeks, for a total of 48 weeks of PR. RGT can be used only if the HCV RNA concentration is reported as “undetectable.” A report of a detectable,

but  $< \text{LLOQ}$ , concentration will require an additional 36 weeks of PR therapy.<sup>1,96</sup>

Treatment-naive patients with cirrhosis and an undetectable HCV RNA concentration at 4 and 12 weeks of telaprevir + PR therapy may gain additional response if treated for a total of 48 weeks with PR.<sup>1,47</sup> This recommendation is a result of the findings from ILLUMINATE, that is, 61.1% of T12PR24-treated patients with cirrhosis of the liver and eRVR achieved SVR, whereas 91.7% of T12PR48-treated patients with cirrhosis and eRVR achieved SVR.<sup>47</sup> Patients with a null response or prior partial response to interferon + ribavirin therapy should receive telaprevir + PR for 12 weeks, followed by PR for an additional 36 weeks (48 weeks of PR total).

### Stop Rules

To avoid continued HCV therapy in patients with little likelihood of responding to therapy, the following stop rules have been formulated: (1) HCV RNA concentrations  $> 1000$  IU/mL at week 4 or 12 (stop telaprevir and PR); and (2) HCV RNA detectable at week 24 (stop PR).<sup>1</sup>

Combination therapy (telaprevir + PR) for chronic HCV infection is contraindicated in women who are pregnant or are planning to become pregnant and in men with pregnant partners. These recommendations are the result of the ribavirin component, which may cause toxicity to the fetus. Women must use 2 effective methods of contraception during therapy. Women receiving telaprevir + PR therapy should use 2 nonhormonal forms of contraception during and for  $\geq 2$  weeks following the discontinuation of telaprevir.<sup>1</sup> Estrogen-containing oral contraceptives may not be effective in preventing pregnancy due to a telaprevir-induced decrease in the concentration of ethinyl estradiol in these products.<sup>57</sup> Two weeks after stopping telaprevir, hormonal oral contraceptives may be resumed as 1 of the 2 forms of contraception. The reader should also be cautioned to monitor for drug interactions when considering telaprevir-based therapy in any patient (see Drug Interactions and HIV/HCV Coinfection). Women who are breastfeeding must stop prior to using telaprevir.<sup>1</sup>

Telaprevir should not be used in patients with moderate or severe liver disease. The drug can be used in patients with reduced kidney function but has not been studied in patients with end-stage renal disease, in patients undergoing hemodialysis, or solid-organ trans-

plant recipients.<sup>1</sup> The manufacturer is currently recruiting participants in a study to assess the efficacy and tolerability of triple therapy with telaprevir in patients with chronic HCV infection genotype 1 who have undergone a liver transplantation.<sup>97</sup>

## CONCLUSIONS

Telaprevir is an important addition to the treatment of chronic HCV genotype 1 infection. When combined with PR in treatment-naïve patients, SVR rates improve significantly, even in patients with historically difficult-to-treat baseline characteristics, compared with standard therapy. In addition, patients who experience eRVR while receiving triple therapy with telaprevir not only have a higher rate of SVR but also can be treated with a shorter duration of PR (RGT). In patients who have failed prior interferon + ribavirin therapy, triple therapy with telaprevir improves the likelihood of achieving SVR, especially in patients who have relapsed during prior treatment. Unfortunately, the high cost, risk for serious AEs (anemia and rash), and the high risk for drug interactions argue for a judicious discourse to determine the role of telaprevir in the day-to-day management of this ubiquitous chronic disease.

A few studies in the United States have not found triple therapy with telaprevir to be cost-effective. These studies did not include the cost of the management of AEs such as anemia and rash. The addition of these costs will need to be taken into consideration in future studies. A number of other areas need to be investigated. At present, triple therapy with telaprevir has been studied in adult patients between the ages of 18 and 70 years. Thus, no data on dosing and tolerability in the pediatric or geriatric population are available. The efficacy and tolerability of telaprevir in HCV/HIV coinfecting patients is in the investigational phase. A study of the role of triple therapy in liver transplant recipients is currently recruiting patients. Another unknown is what to do if a patient fails triple therapy with telaprevir. New medications that attack HCV at a number of additional sites are under investigation and will likely present additional challenges and opportunities for the management of HCV infection in the near future.

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## CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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