

# Direct-Acting Antiviral Medications for Chronic Hepatitis C Virus Infection

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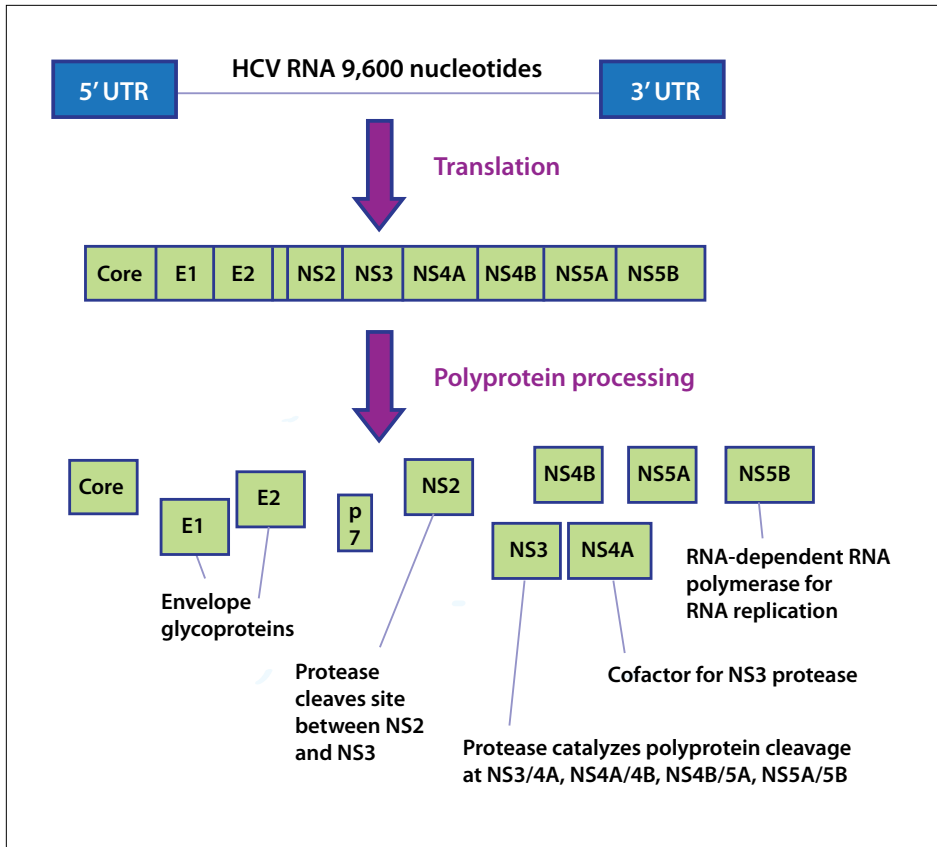
**Abstract:** Treatment of hepatitis C virus has traditionally been difficult because of low rates of treatment success and high rates of treatment discontinuation due to side effects. Current standard therapy consists of pegylated interferon  $\alpha$  and ribavirin, both of which have nonspecific and largely unknown mechanisms of action. New therapies are in development that act directly on the hepatitis C virus at various points in the viral life cycle. Published clinical trial data on these therapies are summarized in this paper. A new era of hepatitis C virus treatment is beginning, the ultimate goals of which will be directly targeting the virus, shortening the length of therapy, improving sustained virologic response rates, and minimizing side effects.

**H**epatitis C virus (HCV) is a major public health problem, with an estimated 180 million people infected worldwide. Up to 25% of chronically infected patients eventually develop cirrhosis and related complications, including hepatocellular carcinoma.<sup>1</sup> Chronic liver disease secondary to HCV thus remains the leading indication for liver transplantation in the United States.<sup>2</sup>

The goal of HCV treatment is to eradicate the virus and prevent the development of cirrhosis and its complications. Successful treatment of HCV has been defined in terms of sustained virologic response (SVR), which is the absence of detectable levels of viral RNA in the blood 24 weeks after completion of therapy. Currently, the standard treatment approach for HCV includes 24–48 weeks of treatment with pegylated interferon  $\alpha$  (pegIFN $\alpha$ ) in combination with ribavirin (RBV).<sup>3</sup> These drugs act on a variety of nonspecific pathways that affect the immune response to infection. The best treatment response is seen in patients with genotypes 2 and 3 HCV, in whom SVR rates of approximately 80% can be achieved with 24 weeks of therapy.<sup>4</sup> Patients with genotype 1 HCV remain the most difficult to treat, with SVR rates of approximately 40% after 48 weeks of therapy.<sup>5</sup> In addition to being ineffective in some patients,

## Keywords

Hepatitis C virus, direct-acting antiviral agents, specifically targeted antiviral therapy, sustained virologic response, telaprevir, boceprevir



**Figure 1.** Hepatitis C virus protein processing.  
HCV=hepatitis C virus;  
UTR=untranslated region.

pegIFN $\alpha$  and RBV are difficult to tolerate, and many patients treated with these drugs discontinue therapy due to adverse events.

For these reasons, clinicians need therapeutic agents that result in higher rates of SVR and are more tolerable to patients. Many new therapies in preclinical or clinical development act on targets in the viral life cycle to directly inhibit viral production. These drugs, which are referred to as specifically targeted antiviral therapy for hepatitis C or direct-acting antiviral (DAA) agents, are the topic of this paper.

### Viral Resistance

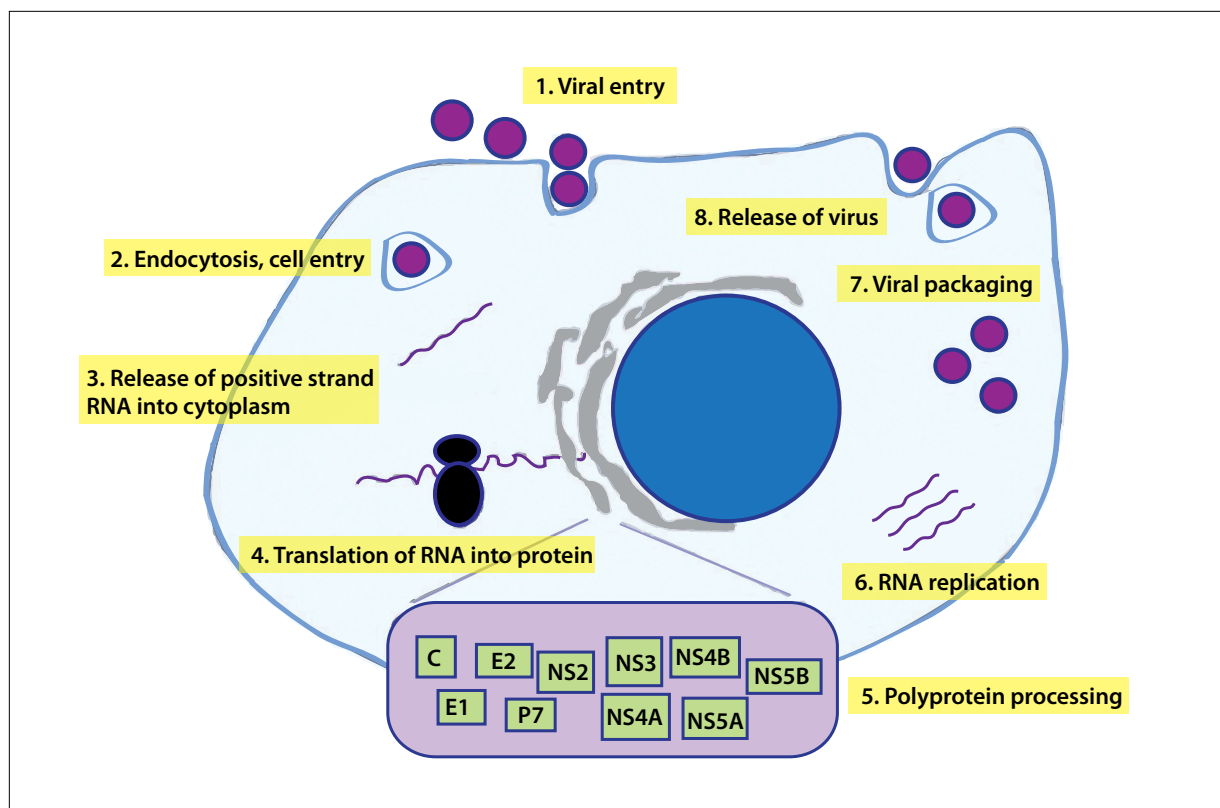
A major challenge in the development of new HCV therapies has been the emergence of resistance to DAA drugs. HCV has a high rate of replication, with  $10^{12}$  virions produced daily. The viral protein responsible for replication is NS5B RNA-dependent RNA polymerase (RdRp), which lacks proofreading ability and has a high error rate. Thus, many genetically distinct but closely related virus quasi species are circulating in the blood at any given time. In general, mutated viruses have less replication fitness than wild-type virus and are present in

much lower quantities. However, when subjected to selection pressure such as the addition of a drug, the quantity of wild-type virus decreases and the mutated virus gains replication fitness. Some of the resulting mutations lead to changes in the structure of the viral enzymes on which DAA drugs act, therefore causing the virus to be resistant to the DAA drug.<sup>6</sup> In other viral diseases, resistance can be overcome by using multiple drugs that target different mechanisms; as more drugs are developed, HCV therapy will likely involve a multidrug approach as well.

### Viral Life Cycle

To better understand the targets of new HCV therapies, basic knowledge of the HCV life cycle is helpful. HCV is a single-stranded RNA molecule approximately 9,600 nucleotides in length.<sup>7</sup> This RNA molecule is translated into a polyprotein consisting of approximately 3,000 amino acids, which are composed into structural and nonstructural proteins (Figure 1). The 4 structural proteins assemble new viral particles, and the 6 nonstructural proteins participate in viral replication.<sup>8</sup>

The viral life cycle provides potential therapeutic targets at every step (Figure 2). As the first step in this life



**Figure 2.** Hepatitis C viral life cycle.

cycle, the virus attaches to a receptor on the hepatocyte surface. The viral and cell membranes fuse, and the virus enters the cell via receptor-mediated endocytosis. The nucleocapsid is then released into the cytoplasm and free, positive-strand RNA is released into the cytoplasm, where it is translated into the polyprotein. Post-translational processing then occurs, followed by viral replication, assembly, and release.<sup>9</sup> HCV infection is somewhat unique in that DNA is not generated at any point in the life cycle; thus, the virus does not incorporate itself into the host DNA. As a result, it is possible to achieve successful clearance of the virus with a sustained effect.<sup>10</sup>

The specific proteins involved in the viral life cycle and descriptions of drugs being developed to target those proteins are detailed further below. Table 1 contains a list of drugs in various stages of development.

### ***Viral Entry***

Both proteins encoded by the virus and those on the cell surface are important for viral entry into cells. The viral structural proteins E1 and E2 interact with a variety of cell surface receptors, including glycosaminoglycans and low-density lipoprotein receptors. Fusion of the virus to

the receptor is mediated by viral proteins RdRp (NS5) and NS3.<sup>9</sup>

Several studies have investigated the use of molecules that prevent the attachment of viral particles to receptor molecules or that inhibit viral entry. Monoclonal and polyclonal antibodies are in development using this approach. Three monoclonal antibodies—HCV AB68, HCV AB6865, and bavituximab (Peregrine Pharmaceuticals)—and 1 polyclonal antibody, Civacir (Biotest Pharmaceuticals), are currently being evaluated in early-phase trials.<sup>11</sup>

### ***Translation***

Translation of HCV is controlled by the internal ribosome entry site (IRES), which is located at the 5' untranslated region of the virus and binds to the ribosome to initiate translation. The efficiency of IRES translation is thought to be affected by HCV core proteins NS4A and NS5B. Molecules in development that could potentially block this step of the viral life cycle include antisense oligonucleotides, strands of DNA or RNA that complementarily bind to messenger RNA and block translation. Early-phase studies of these molecules are underway. Ribozymes and specific small molecule inhibitors of HCV

**Table 1.** Direct-Acting Antiviral Drugs by Stage of Development

	Phase I	Phase II	Phase III
NS3A/4B protease inhibitors	BMS-850032	TMC435	Telaprevir (VX-950)
	ACH-1625	BI 201335	Boceprevir (SCH-503034)
	GS-9256	Vaniprevir (MK-7009)	
	ABT-450	Narlaprevir (SCH-900518)	
	IDX320	Danoprevir (ITMN-191, RG7227)	
	GS-9451		
	ACH-2684		
	MK-6172		
NS5B polymerase nucleoside inhibitors	INX-184	R7128	
		IDX184	
		PSI-7977	
		PSI-938	
NS5B polymerase non-nucleoside inhibitors	IDX375	GS-9190	
	ABT-333	Filibuvir (PF868554)	
		ANA-598	
NS5A inhibitors	PPI-461		
	GS-5885		
	BMS-824393		
Cyclophilin inhibitors		SCY-635	
		Debio 025	

IRES function could also potentially inhibit this step in the viral life cycle.<sup>9</sup>

### Post-Translational Processing

Once the viral genome has been translated, the proteins are then processed. The major enzymes involved in post-translational processing are the NS2-3 protease and the NS3/4A protease.<sup>9</sup> Inhibitors of the NS3/4A protease are the most extensively studied and successful DAA therapies to date. Two linear peptidomimetic ketoamides, boceprevir (SCH-503034) and telaprevir (VX-950), are currently

being developed to treat chronic HCV infection. Results from phase II studies of these agents are summarized below and in Table 2. A description of a phase III study is also summarized below, the results of which are anticipated soon. Approval of these medications is expected within the next 1–2 years.

Because the NS3/4A protease structure differs among HCV genotypes, protease inhibitors have different antiviral efficacy for different genotypes. The best antiviral effects are seen in patients with genotype 1 HCV. Further studies are required to determine effectiveness in other genotypes, although, preliminarily, it appears that protease inhibitors are less effective for genotypes 2, 3, and 4 HCV.<sup>12,13</sup>

### Boceprevir

**Major Studies** SPRINT-1 was a phase II, randomized, placebo-controlled study of treatment-naïve, genotype 1 HCV patients who were treated with boceprevir (800 mg TID) and pegIFN $\alpha$ -2b, with or without RBV. In addition to testing the efficacy of boceprevir, the study also evaluated a 4-week lead-in period during which patients were treated with pegIFN $\alpha$ -2b and RBV alone to see if this approach could reduce viral breakthrough. In part 1 of the trial, all patients received a standard dose of RBV (800–1,400 mg). Two treatment groups received boceprevir in combination with pegIFN $\alpha$ -2b and RBV for 28 or 48 weeks (PRB28 and PRB48); another 2 treatment groups received the lead-in regimen followed by either 24 or 44 weeks of treatment with boceprevir, pegIFN $\alpha$ -2b, and RBV (PR4/PRB24 and PR4/PRB44). The control group received pegIFN $\alpha$ -2b and RBV for 48 weeks (PR48).

Treatment groups PRB28 and PRB48 achieved SVR in 54% and 67% of patients, respectively. The lead-in treatment groups, PR4/PRB24 and PR4/PRB44, achieved SVR in 56% and 75% of patients, respectively. The PR48 control group achieved an SVR rate of 38%. In part 2 of the SPRINT-1 study, a treatment group receiving 48 weeks of triple therapy (PRB48) was administered a lower dose of RBV (400–1,000 mg). The SVR rate for this group was only 36%, with viral breakthrough occurring in 27% of patients, which was higher than the breakthrough rates (4–12%) observed in the other boceprevir treatment arms.<sup>14</sup>

To gather more data about boceprevir, several phase III studies of this drug are currently underway. For example, SPRINT-2 aims to assess the role of response-guided treatment with boceprevir. In this trial, all patients will receive a 4-week lead-in period with pegIFN $\alpha$  and RBV alone, followed by 1 of 3 treatment regimens: pegIFN $\alpha$  and RBV plus placebo for 44 weeks;

**Table 2.** Summary of Phase II Clinical Trials with NS3A/4B Protease Inhibitors Telaprevir and Boceprevir

Trial	Patient characteristics	Treatment regimen	SVR (%)	RVR (%)	Relapse (%)
SPRINT-1 (boceprevir)	520 HCV genotype 1, treatment naïve	PRB28	54	39	30
		PRB48	67	37	7
		PR4/PRB24	56	60	24
		PR4/PRB44	75	64	3
		PR48	38	8	24
		PRB48 (standard dose)	67	37	7
		PRB48 (low dose)	36	25	22
PROVE 1 (telaprevir)	250 HCV genotype 1, treatment naïve	T12PR12	35	59	33
		T12PR24	61	81	2
		T12PR48	67	81	6
		PR48	41	11	23
PROVE 2 (telaprevir)	323 HCV genotype 1, treatment naïve	T12P12	36	50	48
		T12PR12	60	80	30
		T12PR24	69	69	14
		PR48	46	13	22
PROVE 3 (telaprevir)	453 HCV genotype 1, all patients (treatment failure/relapse)	T12PR24	51	61	30
		T24PR48	54	50	13
		T24P24	24	47	53
		PR48	14	0	53
	Prior treatment failure alone	T12PR24	39		37
		T24PR48	38		4
		T24P24	11		68
		PR48	9		40
	Prior relapse alone	T12PR24	69		18
		T24PR48	76		0
		T24P24	42		46
		PR48	20		62

HCV=hepatitis C virus; RVR=rapid viral response; SVR=sustained virologic response.

boceprevir plus pegIFN $\alpha$  and RBV for 24 weeks, with an additional 20 weeks of treatment with pegIFN $\alpha$  and RBV alone if HCV RNA is detected during Weeks 8–24; or boceprevir plus pegIFN $\alpha$  and RBV for 44 weeks regardless of response during Weeks 8–24.

Another study, RESPOND-2, aims to assess response to boceprevir in patients who previously relapsed or failed to respond to standard treatment. Treatment groups in this study include a control arm that will receive pegIFN $\alpha$  and RBV for 48 weeks, a treatment arm that will receive 4 weeks of pegIFN $\alpha$  and RBV followed by response-guided therapy with 800 mg boceprevir plus pegIFN $\alpha$

and RBV, and a treatment arm that will receive 4 weeks of pegIFN $\alpha$  and RBV followed by 44 weeks of boceprevir plus pegIFN $\alpha$  and RBV.<sup>15</sup>

*Resistance* Several mutations conferring resistance to boceprevir have been identified in vitro, and additional mutations become apparent during boceprevir monotherapy at a dose of 400 mg 2–3 times daily. Resistant variants have been detected in the blood of HCV-infected patients as long as 4 years after treatment with boceprevir.<sup>16</sup> Whether the presence of resistant virus will be clinically meaningful and preclude successful re-treatment with

boceprevir has not been clearly determined. Presently, combination therapy with pegIFN $\alpha$  and RBV is necessary to prevent resistance and treatment failure.

**Adverse Events** Boceprevir is generally well tolerated. The most common side effects of boceprevir-containing triple therapy are those typically associated with pegIFN $\alpha$  and RBV treatment, such as flu-like symptoms, fatigue, and nausea. However, anemia was more common in SPRINT-1 among treatment groups that received boceprevir (52–56%) compared to the group that received standard treatment (35%). A large, multicenter trial is evaluating the role of erythropoietin versus RBV dose reduction for the management of treatment-related anemia.<sup>15</sup> Overall, treatment discontinuation was higher in the boceprevir groups than the control group, ranging from 9% to 19% in the groups that received boceprevir versus 8% in the control group.<sup>14</sup>

### Telaprevir

**Major Studies** Several phase II studies have now been reported with telaprevir. PROVE 1 was a phase II study in which patients received telaprevir in combination with pegIFN $\alpha$ -2a and RBV for 12 weeks followed by treatment with pegIFN $\alpha$ -2a and RBV alone for 0, 12, or 36 weeks (T12PR12, T12PR24, T12PR48). The control group received pegIFN $\alpha$ -2a and RBV for 48 weeks plus placebo for the first 12 weeks (PR48). Higher rates of SVR were seen in patients who received combination therapy followed by treatment with pegIFN $\alpha$ -2a and RBV for 12 or 36 weeks (61% and 67%, respectively) than in patients who received standard therapy (41%) or patients who received only 12 weeks of combination therapy without subsequent treatment with pegIFN $\alpha$ -2a and RBV (35%).<sup>17</sup>

PROVE 2 compared 3 telaprevir-containing treatment regimens: telaprevir with pegIFN $\alpha$ -2a alone for 12 weeks (T12P12), telaprevir with pegIFN $\alpha$ -2a and RBV for 12 weeks (T12PR12), and telaprevir with pegIFN $\alpha$ -2a and RBV for 12 weeks followed by pegIFN $\alpha$ -2a and RBV alone for an additional 12 weeks (T12PR24). SVR was achieved in 36%, 60%, and 69% of patients, respectively. The SVR achieved with standard treatment (PR48) was 46%. Relapse rates were highest in the T12P12 group (48%), followed by T12PR12 (30%), PR48 (22%), and T12PR24 (14%). PROVE 2 demonstrated that RBV is important in order to achieve higher SVR rates and lower relapse rates; the study also showed that triple therapy for only 12 weeks had unacceptable relapse rates.<sup>18</sup>

One challenge with telaprevir is the need to dose this drug every 8 hours, so the C208 study compared dosing of telaprevir every 8 hours (750 mg) with dosing every 12 hours (1,125 mg); both telaprevir treatment regimens

also included pegIFN $\alpha$ -2a and RBV. Comparable rates of SVR were found (81–85%) with the 2 dosing schedules, supporting further investigation of twice-daily dosing of telaprevir.<sup>19</sup>

PROVE 3 was a trial that enrolled genotype 1 HCV patients who had previously failed treatment, including prior nonresponders and relapsers. Treatment regimens included telaprevir with pegIFN $\alpha$ -2a and RBV for 12 weeks followed by pegIFN $\alpha$ -2a and RBV alone for 12 weeks (T12PR24), telaprevir with pegIFN $\alpha$ -2a and RBV for 24 weeks followed by pegIFN $\alpha$ -2a and RBV alone for 24 weeks (T24PR48), telaprevir with pegIFN $\alpha$ -2a alone for 24 weeks (T24P24), and standard therapy (PR48). SVR rates were highest in the T24PR48 and T12PR24 groups (53% and 51%, respectively); lower SVR rates were observed in the group treated with telaprevir and pegIFN $\alpha$ -2a alone (T24P24; 24%) and the control group (14%). This study confirmed the importance of RBV for achieving virologic response while minimizing relapse. The study also demonstrated higher response rates among patients who had previously relapsed compared to prior nonresponders; in the T24PR48 group, SVR was achieved in 76% of prior relapsers compared to 38% of prior nonresponders.<sup>20</sup>

Phase III study results are also expected for both treatment-naïve patients and patients who failed previous treatment. ADVANCE and ILLUMINATE are 2 of the phase III studies that will soon release results for treatment-naïve patients.

ILLUMINATE evaluated the clinical utility of extended rapid viral response (eRVR), defined as undetectable HCV RNA levels at Weeks 4 and 12. In this study, patients received telaprevir (750 mg every 8 hours) plus pegIFN $\alpha$ -2a and RBV; patients who achieved eRVR were randomized at Week 20 to continue receiving pegIFN $\alpha$ -2a and RBV for either 24 or 48 weeks of total treatment. Patients who did not achieve eRVR received a total of 48 weeks of treatment.

The ADVANCE study included the following treatment arms: telaprevir (750 mg every 8 hours) with standard pegIFN $\alpha$  and RBV for 8 weeks followed by pegIFN $\alpha$  and RBV alone for 16 or 40 weeks, telaprevir (750 mg every 8 hours) with pegIFN $\alpha$  and RBV for 12 weeks followed by pegIFN $\alpha$  and RBV alone for 12 or 36 weeks, and a control group treated with pegIFN $\alpha$  and RBV for 48 weeks. Patients in the telaprevir treatment arms who achieved eRVR received a total of 24 weeks of therapy; those who did not achieve eRVR received a total of 48 weeks of therapy.<sup>15</sup> Together, the ILLUMINATE and ADVANCE studies should provide more insight into how to use response-guided approaches to offer shorter versus longer courses of treatment.

Finally, the REALIZE trial evaluated prior nonresponders and patients who relapsed following standard



therapy. Patients in this trial received 12 weeks of telaprevir in combination with pegIFN $\alpha$  and RBV for a total of 48 weeks. In 1 group of patients, all drugs were started simultaneously; in a second group, pegIFN $\alpha$  and RBV were given alone for the first 4 weeks, after which telaprevir was added. These groups were compared to a control group that received standard treatment with pegIFN $\alpha$  and RBV for 48 weeks.<sup>15</sup>

**Resistance** The development of viral mutants during treatment with protease inhibitors has led to new insights into viral resistance. Patients treated with telaprevir monotherapy can develop mutations within 14 days. Mutations conferring resistance to telaprevir have been found at baseline, with additional mutations occurring during treatment. In general, viral strains with higher levels of telaprevir resistance have lower replication fitness; however, double mutants appear to have both high resistance levels and improved replication fitness.<sup>21</sup> When treatment with telaprevir ends, the wild-type virus increases rapidly in the first 7–10 days; by 3–7 months, the majority of circulating virus is wild-type virus. However, resistant virus has been detected at low levels in some patients up to 3 years following the completion of treatment.<sup>22,23</sup> As with boceprevir treatments, telaprevir-based regimens must include pegIFN $\alpha$  and RBV in order to prevent resistance and allow for successful completion of treatment.

**Adverse Events and Side Effects** As with boceprevir-based treatments, the most common side effects of telaprevir combination therapy are symptoms typically induced by pegIFN $\alpha$ . Telaprevir is also associated with anemia, with patients who receive telaprevir having an average hemoglobin reduction 0.5–1.0 g/dL lower than the control group. Higher rates of rash, pruritus, nausea, and diarrhea are also seen in the telaprevir treatment groups.<sup>17,18,20</sup> Rash was a common side effect of treatment in the PROVE 1 study; in the standard therapy arm, 40% of patients developed rash of any severity, compared to 53–61% of patients in the telaprevir treatment arms. Mild rash occurred in 37% of patients in the telaprevir treatment groups and 32% of patients in the control group. These rashes were maculopapular and initially difficult to distinguish from the rash associated with pegIFN $\alpha$  and RBV therapy.

Increased attention to the rash associated with telaprevir treatment has provided insight into the frequency of rash among patients receiving pegIFN $\alpha$  and RBV therapy. In PROVE 1, moderate and severe rash were present in 15% and 7% of patients who received telaprevir, respectively, compared to 8% and 1%, respectively, of patients who received pegIFN $\alpha$ -2a and RBV therapy. Rash led to treatment discontinuation in 7% of patients in

the telaprevir treatment arms compared to 1% of patients in the control arm.<sup>17</sup> Based upon experience gained in PROVE 1, later studies of telaprevir have included a rash management plan that includes close monitoring and potential discontinuation of telaprevir if the rash progresses.

### Replication

Once the viral genome has been translated, viral replication ensues. Viral replication is mediated largely by the nonstructural protein NS5B RdRp, and this polymerase has emerged as another important target of therapy.<sup>9</sup> NS5A is also a component of viral replication, although its exact mechanism is unclear. Agents targeting this protein are also in development.

NS5B RNA polymerase inhibitors come in 2 forms. The first are nucleoside analog inhibitors; these molecules mimic the natural substrates of the polymerase and become incorporated into the growing RNA chain, at which point they terminate replication. Because the active center of NS5B is highly conserved among genotypes, these agents should theoretically be able to achieve similar rates of response in all patients with HCV.<sup>9</sup>

**Nucleoside Inhibitors** One nucleoside inhibitor currently being studied in phase II trials is R7128, a pro-drug of PSI-6130 (an oral cytidine nucleoside analog polymerase inhibitor). In this study, R7128 (500 mg BID) was tested in combination with pegIFN $\alpha$ -2a and RBV for 28 days. Viral load reductions from baseline were found to be 2.6 log<sub>10</sub> IU/mL at Day 14 and 4.0 log<sub>10</sub> IU/mL at Day 28. Side effects of this treatment were similar to the side effects observed with standard-of-care treatment.<sup>24</sup> No evidence of resistance was seen with R7128 monotherapy for 14 or 28 days.<sup>25</sup> Interim analyses of phase II studies indicate that R7128 has potent antiviral activity, with RVR rates of approximately 60% when R7128 is dosed at 1,000 mg BID in combination with pegIFN $\alpha$  and RBV. Thus far, R7128 also appears to be safe and well tolerated.<sup>26</sup>

**Non-Nucleoside Inhibitors** The second class of NS5B inhibitors, the non-nucleoside inhibitors, bind to the enzyme itself to induce a conformational change that renders it ineffective. There are currently 4 sites on the enzyme that are being targeted for drug development in early-phase studies.<sup>9</sup>

### Combination Therapy

The ultimate goal of HCV treatment is to create a shorter, more effective treatment regimen consisting of oral medications that have a better side effect profile than pegIFN $\alpha$

and RBV. The initial studies in this area are exploring the combination of a protease inhibitor with a polymerase inhibitor.

The INFORM-1 study evaluated the combination of protease inhibitor R7227/ITMN-191 and polymerase inhibitor R7128 in patients with genotype 1 HCV. This randomized, controlled, double-blind, escalation dose trial included both treatment-naïve patients and non-responders. Patients were treated for 2 weeks, and viral load reductions with combination therapy ranged from 3.9 to 5.3 log<sub>10</sub> IU/mL. Among treatment-naïve patients receiving this combination therapy, HCV RNA levels were below the limit of quantification (43 IU/mL) in 88% of patients at 2 weeks.<sup>27</sup> Further studies with longer treatment durations are planned to determine whether this strategy can lead to SVR and whether it results in unacceptable rates of viral resistance.

## Summary and Next Steps

This is an exciting time in HCV treatment, with major developments of new drugs that can help clinicians manage a historically difficult-to-treat virus. Agents currently in development act on virtually every step in the viral life cycle. The first generation of protease inhibitors have been shown to increase the rates of treatment response in patients infected with genotype 1 HCV from approximately 40% to greater than 60%. Unfortunately, clinical trials have discovered that the use of protease inhibitors in isolation leads to the rapid development of mutations and viral resistance. The SPRINT-1 and PROVE 2 studies showed the importance of concomitant use of RBV to avoid both viral resistance and relapse after treatment. Once the protease inhibitors are approved, standard treatment will become triple therapy with a protease inhibitor, pegIFN $\alpha$ , and RBV.

For our patients, this advance will mean the possibility for better response rates. However, patients who were not eligible for treatment due to contraindications to pegIFN $\alpha$  and RBV therapy will still be ineligible for treatment in this new era. Additionally, the use of protease inhibitors in combination with pegIFN $\alpha$  and RBV appears to lead to higher discontinuation rates and more side effects. Therefore, more work is necessary to develop treatment combinations that minimize side effects while maximizing treatment response.

Data from the phase III protease inhibitor studies should guide patients and clinicians and also answer a number of questions, including the appropriate duration of treatment. The recently discovered interleukin (IL)-28B genotype predicts patients' treatment response to standard-of-care treatment, and the role of this predictor in relation to DAA agents needs to be understood.<sup>28</sup>

The protease inhibitors mark a major step forward, and other agents in development with different viral targets provide a path toward the ultimate goal of more potent and shorter courses of treatment.

After almost a decade without change, treatment for patients with genotype 1 HCV infection will undergo significant transformation when boceprevir and telaprevir are approved. These agents were specifically designed to target genotype 1 HCV, so patients infected with genotypes 2 and 3 HCV should continue to receive standard courses of pegIFN $\alpha$  and RBV, given these drugs' high rates of treatment response in this population. The current dilemma for patients with genotype 1 HCV infection is whether to proceed with current treatment with pegIFN $\alpha$  and RBV or wait for the approval of telaprevir and/or boceprevir. It would be very reasonable to proceed with pegIFN $\alpha$  and RBV therapy, especially in patients with factors associated with high rates of SVR, such as a favorable IL-28B genotype. In addition to potentially higher response rates with protease inhibitors, phase III studies are examining shorter courses of treatment for genotype 1 HCV patients. Delaying treatment until protease inhibitors are available may be particularly appropriate for patients with historically low response rates to standard treatment, including patients who are black and/or have cirrhosis.

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