Change Has Arrived: Treating Hepatitis C with Protease Inhibitors—the New Standard of Care

Treating patients with the hepatitis C virus (HCV) is about to be changed forever. Over 170 million people are infected with HCV worldwide and this number grows as more and more patients are diagnosed with hepatitis C daily. Current standard of care (SoC) treatment for chronic hepatitis C consists of pegylated interferon (Peg IFN) and ribavirin (RBV). Success rates for viral eradication—sustained virological response (SVR), for patients infected with HCV genotype 1 (G1), the most common HCV genotype in the United States are less than 50%. New drugs, known as direct acting antivirals (DAAs), have been in development for over a decade, and the initial two of these, boceprevir and telaprevir, both protease inhibitors, have just been FDA approved (May 2011). Treating HCV with the addition of protease inhibitors to SoC is very promising with SVRs of approximately 70–75% in recent studies. This article, the first in this series, will review the burden of hepatitis C, the HCV lifecycle, and the studies behind the new therapies in an effort to preview how patients will likely be treated in the near future.

INTRODUCTION

The wait for new drugs in the fight against hepatitis C (HCV) is finally over. It is estimated that over 170 million people are chronically infected with hepatitis C worldwide (1). While some patients have achieved a sustained virologic response (SVR), defined as a nondetectable HCV RNA 24 weeks after treatment termination, also synonymous with a cure, many have failed to achieve SVR or have simply put off treatment feeling that a less than 50% chance for a cure is not worth the potential side effects. Current treatment of naïve hepatitis C patients with pegylated interferon and ribavirin yields an SVR of approximately 45% (2). New treatments have been shown to increase SVR to approximately 75% (3). This breakthrough is expected to have a profound effect on low-
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**THE HEPATITIS C VIRUS LIFECYCLE**

In order to understand how the new protease inhibitors work against HCV, one must first understand the structure of the virus and its lifecycle. The HCV genome consists of 9600 bases, which encode a single polyprotein of 3,000 amino acids (4). This polyprotein consists of four structural and six nonstructural proteins (see Figure 1) (5). The nonstructural proteins are essential for the virus to replicate and have therefore been the target of new antiviral medications.

When a patient is infected with the hepatitis C virus it attaches to plasma lipid particles in the blood and migrates to the liver. The viral particles have proteins on their surface that bind to receptors on the surface of liver cells, making the liver its target organ. Once the receptors are engaged, the liver cell internalizes the virus. Inside the liver, the outer coating of the virus dissolves and the genetic material is released. A single positive RNA containing strand remains and contains enough information to replicate itself. In order to do so, the viral RNA travels to the endoplasmic reticulum where proteins are made. The viral RNA then interacts with the ribosome on the outer surface of the endoplasmic reticulum and translates genetic information to produce viral proteins 3000 amino acids long (6).

Here the four structural proteins (Core, E1, E2, and p7) attach to liver cell receptors. The structural proteins are freed from the chain by liver enzymes. The remaining nonstructural proteins are freed by viral proteases. Then NS2 cysteine protease interacts with NS3 serine protease to separate from the polyprotein. NS3 works with NS4A to separate and NS3 acts like a knife cleaving the four remaining proteins leaving them free to perform their specific roles. NS4B and NS5A form the site for HCV viral replication in a membranous web. NS5B the viral polymerase plays a key role and is therefore the other area being studied to develop polymerase inhibitors. During replication negative RNA is produced from positive RNA to form the double stranded intermediate, which then serves as a copier producing thousands of copies of the genome. The virus is then packaged into new viral particles and these are transported out of the cell to infect new liver cells. The cycle is repeated and up to 1 trillion copies of the virus can be made each day (7).

*(continued on page 16)*

**Figure 1: Targets for Protease and Polymerase Inhibition (5)**
Although there are currently over 50 drugs in clinical trials aimed at increasing HCV cure rates, the most successful drug class to date is the protease inhibitor. Telaprevir and boceprevir are two orally effective DAA inhibitors of the nonstructural NS3/NS4A HCV serine protease. Understanding the life cycle of the hepatitis C virus as described above is essential to understanding how these drugs can halt viral replication. This section provides a review of the pivotal clinical trials that led to FDA approval, and changed the landscape of HCV treatment.

**TELAPREvir**

This drug was studied in a series of trials titled PROVE 1-3. PROVE stands for PROtease inhibition for Viral Evaluation. PROVE 1 was a phase 2b randomized, double blind, placebo controlled trial involving 250 treatment naïve, genotype 1 patients with chronic HCV infection (continued on page 21)
This study took place across 37 centers in the US and compared telaprevir based therapy groups of 12, 24, and 48 week durations with a standard 48 week Peg-IFN alfa-2a/RBV control group (see Figure 2). The objectives of the study were threefold: 1. Assess the SVR rate in telaprevir-based therapy. 2. Evaluate whether or not telaprevir could shorten the duration of current therapy. 3. Assess the safety and efficacy of therapy with telaprevir.

Patients in the 24 and 48 week telaprevir based treatment groups achieved 61% and 67% SVR respectively while those in the standard care group achieved just 41%.

PROVE 2 was a multicenter, randomized, partially double blind, placebo controlled phase 2b clinical trial involving 323 treatment naïve patients with chronic genotype 1 HCV infection (9). This study was done across 28 centers in Europe to compare telaprevir based therapy groups of 12 and 24-week durations with and without ribavirin against a standard 48 week control group (see Figure 3).

In the 24-week telaprevir based regimen there was a significantly higher SVR rate (69%) with a shortened treatment duration compared with the control group (46%). Also, this study showed that ribavirin is a necessary part of the treatment regimen.

All PROVE studies cite pruritus, rash, and anemia as the most common adverse events in the telaprevir based groups. In PROVE 2, rash led to discontinuation of all study drugs in 7% of patients. PROVE 3 will be discussed below as its population involved both nonresponders and relapers.

Two additional large phase III trials have confirmed the results of the PROVE 1 and 2 studies. More importantly, these trials determined that patients who achieved an undetectable HCVRNA at both weeks 4 and 12, known as an extended rapid viral response (eRVR) are eligible for a shortened course of therapy. This is known as “response guided therapy” (RGT) and utilizes the concept that the earlier HCV RNA becomes undetectable, the higher the likelihood of achieving SVR. A new Direction in HCV Care: a Study of Treatment Naïve Hepatitis C Patient with Telaprevir (ADVANCE) trial evaluated two different telaprevir based treatment regimens compared with SoC in approximately 1050 previously untreated genotype 1 patients (Figure 4a) (10). The SVR was the highest, 75%, in patients receiving 12 weeks of triple therapy followed by another 12 weeks of SoC. (T12PR24). The Illustrating the Effects of Combination Therapy with Telaprevir (ILLUMINATE) study was designed to compare 24 to 48 weeks of SoC treatment after beginning with an initial 12 weeks triple therapy, utilizing RGT. This trial enrolled 540 genotype 1 patients and did not have a SOC arm (Figure 4b) (11). The results demonstrated that SVR rates in the patients with an eRVR who were randomized into either the T12PR24 or T12 PR48 were virtually the same—92% and 88% respectively.

**BOCEPREVIR**

This drug has been studied in the SPRINT 1 and 2 studies along with the RESPOND 1 and 2 trials. The Serine PRotease INhibitor Therapy-1 study was a phase II trial that investigated an 800mg dose of boceprevir in com-
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<thead>
<tr>
<th>Week 4</th>
<th>Week 28</th>
<th>Week 48</th>
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<td>PR48</td>
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Figure 5: SPRINT-1 Study Design (12). (P) = Peg-IFN = pegylated interferon alfa-2b, (R) = RBV = ribavirin, (B) = boceprevir

Combination with PegIFN and ribavirin in 595 previous untreated HCV genotype 1 patients (12). The study included four boceprevir based treatment regimens of different treatment duration, including a 4-week pegIFN-ribavirin lead-in and a low dose ribavirin arm compared with SOC (Figure 5). The highest SVR rate of 75% was observed with the pegIFN/RBV lead-in which is followed by 44 weeks of triple therapy. In patients receiving 48 weeks of triple therapy with no lead-in, SVR was 66% therefore showing a lead in phase with PegIFN and RBV may be beneficial. Safety data from the study indicated that the most common adverse events reported were fatigue, anemia, nausea, and headache. Treatment discontinuation owing to adverse events was between 9 and 19% in the boceprevir arms compared to only 8% in the control arm.

SPRINT 2 divided patients into 2 cohorts by race: black and nonblack (see Figure 6). There were 316, 311, and 311 nonblack patients in the Boceprevir RGT, boceprevir/PR48, and 48/PR (control) arms respectively, and there were 52, 55, and 52 black patients in those groups (13). All groups had a 4-week lead-in with Peg/RBV. SVR achieved in the nonblack cohort was 68% in the boceprevir/PR48 group vs. 40% in the control arm. In the group with African American patients, the highest SVR was 53% achieved in the
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Boceprevir/PR48 group compared to 23% in the control arm. 44% of patients received the shorter 28-week course of therapy. In general, the boceprevir-containing arms had more patients with anemia (49% vs. 29%). Erythropoietin was allowed in the study and was used in 43% of the cases. 2% of the patients discontinued treatment due to anemia.

HOW TO APPROACH PREVIOUS RELAPSERS OR NONRESPONDERS

Each of the new protease inhibitors has at least one large study already looking into this topic and many more are sure to follow. Patients who have been previously treated for at least 12 weeks and did not achieve an early virologic response (EVR) defined as a > 2-log decrease in viral load from the pretreatment level are termed nonresponders. Those who achieved an undetectable HCV RNA at end of treatment (EOT) but then had detectable HCV RNA during follow up (did not achieve SVR) are known as relapers. The PROVE 3 trial was a randomized, partially placebo controlled, partially double blind phase 2 clinical trial which looked at 453 HCV genotype 1 infected patients who did not achieve SVR with an initial full course of Peg-IFN/RBV treatment (14). This study was done across 41 centers in the U.S., 6 in Canada, 3 in the Netherlands, and 3 in Germany (see Figure 7).

Overall SVR rates in the telaprevir based groups of 12 and 24 weeks were 51% and 53% vs. 14% in the control group. In previous nonresponders 39% of patients achieved an SVR in 24 weeks of total treatment, and in relapsers this went up to 69%. Current standard of care leads to only a 9% SVR in nonresponders and 20% SVR in relapsers. The ReTreatment of Patients with Telaprevir Based Regimen to Optimize Outcomes (REALIZE) (Figure 8) study was a trial of telaprevir-based treatment for patients with genotype 1 HCV infection who failed to achieve SVR with prior therapy with pegIFN and ribavirin. There were 662 patients were enrolled in this trial and SVR (continued on page 26)
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**Figure 8:** Realize (15). (P) = Peg-IFN = pegylated interferon alfa-2b, (R) = RBV = ribavirin, (B) = boceprevir

Rates were 86% in prior relapsers, 57% in partial responders, and 31% in null responders in the telaprevir groups (compared with 24%, 15%, and 5% in the control arm) (15). A lead in phase did not appear to be beneficial in this study.

RESPOND 1 evaluated the safety and efficacy of boceprevir with pegIFN in genotype 1 patients who had been null responders to prior peg-IFN/ribavirin. This study evaluated varying doses of boceprevir but the drug safety monitoring board recommended that all patients who showed a response be switched to boceprevir 800 mg PO TID because lower doses appeared less effective and there was more resistance to boceprevir when ribavirin wasn’t given (16). This study suggested that in patients with prior treatment failures an SVR could be achieved using boceprevir and that a lead in period of initial therapy with just P/R might provide additional benefit.

RESPOND 2 excluded null responders from the trial (those who did not achieve a >2 log HCV RNA decrease from baseline at week 12 during the first course of therapy). SVR rates here were 59%, 66%, and 21% in the boceprevir/RGT, Boceprevir/PR48, and control arms respectively (17). Again previous relapers responded better than previous nonresponders, defined in this study as patients who achieved a >2 log drop but kept detectable HCV RNA throughout therapy, also known as a partial responder. The main side effects seen in this trial were anemia and dysgeusia (Figure 9).

**THE FUTURE OF HEPATITIS C TREATMENT**

Researchers continue to examine ways to make hepatitis C treatment more effective and feasible. Most experts agree that eventually a combination of drugs: protease inhibitors, polymerase inhibitors, and ribavirin may replace the need for interferon for at least some patients, and these trials are already in their early stages. In the meantime, a protease inhibitor combined with PegIFN plus RBV is now the new SOC. Infectious disease physicians, primary care physicians, gastroenterologists, dermatologists, hematologists, psychiatrists, and hepatologists will need to work out a new system of caring for and monitoring these patients who will be on complex treatment regimens. The understanding of the hepatitis C virus lifecycle has allowed treatment options to grow tremendously over the last 10 years. The fruit of this research and development has finally come to the market and the management of hepatitis C will be changed forever.

**References**


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