

New Directions in Hepatitis C Therapy: A Look at the Evolving Therapeutic Arsenal

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Introduction

Chronic hepatitis C continues to be the most important cause of chronic liver disease in the United States, potentially resulting in cirrhosis, hepatocellular carcinoma, and the need for liver transplantation. The only US Food and Drug Administration-approved treatment for hepatitis C is combination therapy with pegylated interferon alfa and ribavirin (standard of care), which leads to a sustained virologic response (SVR) in approximately 80% of patients infected with hepatitis C virus (HCV) genotype 2, approximately 60% to 65% infected with genotype 3, and approximately 40% of patients infected with HCV genotype 1.^[1-3] If SVR is achieved, durable response is quite likely, providing patients with an excellent chance for long-term viral eradication.

In addition to a relatively low SVR rate in HCV genotype 1 patients, other challenges associated with the current anti-HCV treatment regimen are its side effects and the required duration of therapy, both of which interfere with patients' adherence to the full course of antiviral therapy. In fact, recent reports suggest that the inability to maintain the optimal dose of both pegylated interferon alfa and ribavirin, especially early in the course of treatment, is associated with a lower rate of response to the current standard of care therapy.^[3] This may explain, in part, the difference between response rates reported in randomized clinical trials (indicating the efficacy of treatment) compared with the response rates reported in clinical practices (indicating the effectiveness of treatment). To overcome these challenges, recent investigations have focused on optimal management of treatment-associated side effects such as anemia and depression.^[1-3]

In addition to managing side effects, research has also focused on developing models to predict low response probability in an effort to avoid futile treatment, and high response probability in an effort to support a full regimen for patients likely to achieve viral eradication. These predictive models are based on viral kinetic data at weeks 4, 12, and 24. Patients who achieve rapid virologic response (RVR; undetectable HCV RNA [< 10 IU/mL] by polymerase chain reaction [PCR] after 4 weeks of treatment) have an excellent chance of achieving SVR.^[1,2] In contrast, failure to achieve an early virologic response by week 12 of treatment (a minimum of 2-log drop in HCV RNA from the baseline value) is a reliable negative predictor of response to this combination therapy regimen.^[1,2] Furthermore, patients who continue to have detectable virus after 24 weeks of therapy are unlikely to achieve SVR and are considered "nonresponders" to combination therapy.

Although findings on viral kinetics and adherence can help clinicians individualize therapy and maximize SVR, many patients, especially those infected with HCV genotype 1, fail to respond to the current standard-of-care treatment. This has led to the development of new strategies and medications for HCV treatment. Although a number of approaches are under consideration, 3 strategies appear most promising: (1) improving the pharmacokinetics and side-effect profile of interferon; (2) improving the pharmacokinetics and side-effect profile of ribavirin; and (3) targeting viral enzymes required for HCV viral replication. This report discusses the most recent findings with regard to these new approaches to the treatment of HCV infection, with special focus on specifically targeted antiviral therapy for hepatitis C (STAT-C) regimens.^[4,5]

New Interferon Preparations

Given the required weekly injections of pegylated interferon alfa and its associated side effects, several agents have been developed to reduce the injection frequency. These include albinterferon, controlled-release recombinant interferon alfa, maxy-alfa interferon, oral interferon, and implantable mini-pump technology to deliver continuous interferon infusion.

Albinterferon* was developed by genetically fusing human albumin to interferon alfa. The concept is that this recombinant agent will have a longer sustainable half-life and thus allow a reduction in the frequency of interferon administration. Results from phase 2 clinical trials using 900-1200 mcg of albinterferon every 2 weeks in addition to weight-based dosing of ribavirin suggested similar efficacy but better health-related quality of life when compared with the standard combination regimen.^[6] Additional phase 3 clinical trials of this agent for the treatment of hepatitis C are currently ongoing.

Controlled-release recombinant interferon alfa* was developed as a biodegradable polymer delivery system for interferon alfa-2b. In early phase clinical trials, this novel interferon delivery system was administered every 2 weeks, and preliminary data suggest good pharmacokinetics and fewer side effects. The safety and efficacy of this drug are still under investigation.^[5,7]

Maxy-alfa interferon* has been developed with molecular biological techniques to improve the immunomodulatory effect of interferon alfa. Although preclinical data suggested enhanced antiviral effects in cell cultures, subsequent phase 1 clinical trial data were not encouraging.^[5]

Oral long-lasting interferon alfa* is another novel variant that seems to be more resistant to proteolytic degradation. In preclinical studies in animal models, oral administration resulted in good pharmacokinetics and safety profiles.^[5,8] Nevertheless, data from phase 1 clinical trials of this agent in humans are not yet available.^[5,8]

Finally, implantable mini-pumps are being developed to deliver interferon alfa or more potent forms of interferon, such as interferon omega. These mini-pumps* are used to infuse and deliver a steady flow of interferon to HCV-infected patients. Some of the mini-pumps must be changed every 3 months to remain functional.^[5,9] Although promising, data on these mini-pump technologies for interferon infusion in humans are not yet available.

As delivery systems and side-effect profiles for interferon preparations improve, HCV-infected patients will be able to be provided with more efficient options for antiviral therapy.

Ribavirin-Like Drugs

The efficacy of standard interferon alfa or pegylated interferon alfa improves significantly with the addition of ribavirin. As mentioned, the combination of these 2 drugs represents the current standard of care for the treatment of hepatitis C. Furthermore, preliminary studies using newer, targeted treatment for HCV suggest that both pegylated interferon alfa and ribavirin remain an essential part of a triple-drug combination regimen (as will be discussed later). In addition to enhancing the efficacy of pegylated interferon alfa, the addition of ribavirin to the treatment regimen also increases the side effects associated with combination therapy. The most important side effect of ribavirin is anemia, which is predominantly related to a hemolytic process. Another therapeutic agent, taribavirin,* an oral prodrug of ribavirin, was developed in an attempt to reduce this potentially serious side effect. Taribavirin, previously known as viramidine, is taken up preferentially by the liver and converted to ribavirin. Because of this hepatic preference, taribavirin is theoretically associated with a lower risk for anemia. Two large randomized clinical trials^[10,11] compared the

efficacy of 800-, 1200-, or 1600-mg daily doses of taribavirin with 1000- or 1200-mg daily doses of ribavirin, given in combination with pegylated interferon alfa, in treatment-naive chronic hepatitis C patients. Both studies showed that taribavirin was associated with lower rates of anemia as well as lower SVR rates. Data from clinical trials using higher doses of taribavirin in combination with pegylated interferon are not available.

Drugs Targeting Viral Enzymes

The current treatment regimens for HCV infection act predominantly through immunomodulatory mechanisms. Newer anti-HCV drugs in development, however, target several viral enzymes such as the NS3/4A serine protease, NS5B RNA-dependent RNA-polymerase, and, most recently, the cyclophilin proteins.

It is important to remember the ability of HCV to develop escape mutants. Mutations are common because the virus has a high rate of replication without a good repair mechanism. These mutations form the basis of the "escape mutants," which allow HCV to escape innate immunity and to resist the action of antiviral drugs.^[12] In a similar fashion, the use of monotherapy with new drugs designed to target HCV viral enzymes is expected to result in the development of viral resistance and the failure of these novel therapeutic agents as monotherapy. It is almost certain that in the near future, multidrug regimens will be required for the antiviral treatment of HCV infection using these targeted agents.

The most exciting group of anti-HCV therapies on the horizon are known as the STAT-C agents. These drugs are based on the model of antiretroviral therapy for HIV infection. Investigators had to overcome many challenges to develop the required targets for these therapeutic agents, including the need for a detailed knowledge of the hepatitis C replication cycle, development of an effective replication cell culture system or HCV replicon system, and a 3-dimensional structure analysis of important HCV enzymes (ie, the NS3/4A protease and NS5B polymerase). The following sections discuss the development of these agents and their potential role in the treatment of HCV infection.^[4,5,13,14]

Protease Inhibitors

BILN-2061 (ciluprevir). BILN-2061,* a potent inhibitor of the NS3/4A protease, was tested in a phase 1 clinical trial and showed a rapid reduction in viral load within the first 48 hours.^[15] Although BILN-2061 demonstrated potent antiviral activity against HCV genotype 1, the virologic response was less pronounced and more variable in HCV genotypes 2 and 3. Despite its potent antiviral effect, further development of this agent was halted because of concerns for potential cardiotoxicity seen in rhesus monkeys treated with higher doses of the drug for 4 weeks' duration.

VX-950 (telaprevir). Telaprevir* is a selective and potent inhibitor of the HCV NS3/4A serine protease. In a phase 1 clinical trial, patients with HCV genotype 1 were randomized to placebo or telaprevir monotherapy at doses of 450 mg or 750 mg every 8 hours or 1250 mg every 12 hours for 14 days.^[16] The majority of patients (79%) in this clinical trial had failed to respond (did not achieve SVR) to previous treatment to interferon-based regimens for hepatitis C. After 14 days of treatment, telaprevir administered at a dose of 750 mg every 8 hours resulted in a 4.4-log decline in HCV RNA from baseline. At 450 mg and 1250 mg per day dosing, the maximum viral suppression occurred at days 3 and 7. However, a subsequent increase in HCV RNA was attributed to the development of resistant variants of HCV. Subsequent analysis^[16] examined the efficacy of combining telaprevir with pegylated interferon alfa-2a. In this study, one cohort of subjects received telaprevir in combination with pegylated interferon alfa-2a for 14 days. At the end of the 14-day study period, a

5.5-log decline in HCV RNA was observed. Indeed, 75% of patients had undetectable HCV RNA (< 30 IU/mL) by day 14 of treatment. After the completion of 14 days of the study period, in an off-study follow-up protocol, all patients were given a combination of pegylated interferon alfa-2a and ribavirin for another 24 weeks.^[16] Nineteen of 20 patients who had originally received telaprevir monotherapy or telaprevir and pegylated interferon in combination continued standard combination therapy with pegylated interferon/ribavirin. At week 24, all patients became HCV RNA undetectable, which was sustained in 61%. These studies led to the development of triple combination protocols, involving telaprevir, ribavirin, and pegylated interferon alfa, which were tested in 2 large randomized clinical trials (PROVE 1 and PROVE 2).

PROVE 1, conducted in the United States, is a randomized, double-blind, placebo-controlled, clinical trial assessing the safety and efficacy of telaprevir 750 mg daily (given every 8 hours) in combination with pegylated interferon alfa-2a and ribavirin in patients with treatment-naive HCV genotype 1.^[17] The duration of treatment in this study ranged from 12 to 48 weeks. After 12 weeks of the triple-therapy regimen, pegylated interferon/ribavirin only was continued for 0, 12, or 36 weeks; the control group received the current standard of care (48 weeks of pegylated interferon/ribavirin). Patients randomized to the treatment arms receiving 12 or 24 weeks of therapy were eligible to stop treatment if they achieved an RVR at week 4 and maintained this response at weeks 10 and 20. Otherwise, all subjects received a full 48-week course of therapy. Interim analysis of this study showed an RVR rate of 79% in the triple therapy arm (vs 11% in the standard of care arm), and a week-12 virologic response (HCV RNA < 10 IU/mL) was seen in 70% of patients in the triple combination arm (vs 39% in the standard of care arm). This study also showed that the majority (67%) of patients who achieved RVR and discontinued treatment at week 12 maintained a virologic response 20 weeks after discontinuing treatment.

These findings support the notion that protease inhibitors, such as telaprevir, when used in a triple combination regimen in a select group of patients (those achieving RVR), may shorten the course of treatment. Although the total incidence of adverse events was similar in the triple combination and standard therapy arms, the triple combination arm had more discontinuations (11% vs 3%) and higher rates of gastrointestinal side effects and anemia. Final results of PROVE 1 and PROVE 2 are currently pending.^[18-22]

PROVE 2, conducted primarily in European centers, had a study design similar to PROVE 1 but included an arm that received telaprevir + pegylated interferon without ribavirin.^[23] In general, the results were similar to those of PROVE 1: the triple therapy arm resulted in significantly greater virologic response than standard therapy at 4, 12, and 24 weeks. However, patients in the treatment arm that received telaprevir/pegylated interferon without ribavirin were less likely to suppress HCV RNA and more likely to relapse than those who received the triple combination regimen.

PROVE 3 is an ongoing phase 2b study evaluating telaprevir-based therapy in patients with genotype 1 chronic hepatitis C who did not achieve an SVR with prior standard-of-care therapy. Results are pending. In addition, several phase 3 randomized, controlled trials are also being initiated to further establish the efficacy and safety of this triple therapy regimen (telaprevir/pegylated interferon/ribavirin) in HCV genotype 1, treatment-naive (ADVANCE [A New Direction in HCV Care: A Study of Treatment-Naive Hepatitis C Patients With Telaprevir]) and nonresponder (REALIZE [Re-treatment of Patients With Telaprevir-based Regimen to Optimize Outcomes]) patients.

SCH503034 (boceprevir). Boceprevir* is another NS3 serum protease inhibitor. In a phase 1 clinical trial, 61 patients infected with HCV genotype 1 who were nonresponders to previous

treatment with pegylated interferon alfa-based therapy were randomized to regimens with a variable duration sequence of boceprevir monotherapy or a combination of pegylated interferon alfa-2b and boceprevir at different doses (200 mg thrice daily or 400 mg thrice daily).^[24] This study showed that after 14 days, the combination of pegylated interferon alfa 2b and boceprevir given at a dose of 200 or 400 mg thrice daily was associated with an approximately 2.45 and 2.88-log drop in HCV RNA from baseline.

In addition, several clinical trials assessing the efficacy of boceprevir in a triple combination regimen are being conducted in HCV genotype 1 patients who are interferon-naïve and in patients who are considered nonresponders to previous treatment.^[4,5] SPRINT-1 (Serine Protease Inhibitor Therapy-1),^[25] a phase 2 randomized clinical trial conducted in HCV treatment-naïve genotype 1 patients, showed that HCV RNA was undetectable in more than 73% of those who received the triple therapy of boceprevir plus pegylated interferon and ribavirin at week 12 after initiation of treatment, compared with only 34% of the control group (who received standard doses of pegylated interferon and ribavirin). The treatment was tolerated well overall, although anemia was more common in the triple-therapy arm.

Other protease inhibitors. The antiviral activity of another HCV protease inhibitor, ACH-806 (also known as GS-9132),* has been tested in a phase 1 clinical trial.^[26] Preliminary analysis suggests that ACH-806 is associated with a 2.38-log decline in HCV RNA within 5 days of initiating therapy. However, the analysis also showed a reversible increase in serum creatinine, resulting in the halting of further development of this agent. Finally, ITMN-191* is another HCV NS3/4A protease inhibitor that has been tested in replication model(s).^[27] Phase 1 clinical trials with this agent were recently completed, but additional dosing studies are ongoing.

HCV RNA Polymerase Inhibitors

Another group of viral enzyme inhibitors comprise those agents that inhibit the HCV RNA-dependent RNA polymerase. Two classes of polymerase inhibitors are currently under development: nucleoside and nonnucleoside analogs.

Nucleoside analog polymerase inhibitors. NM283 (valopicitabine)* is a ribonucleoside analog that targets the viral RNA polymerase and is a viral RNA chain terminator. The efficacy and safety of valopicitabine alone or in combination with pegylated interferon alfa were assessed in phase 1 and 2 clinical trials. In patients with HCV genotype 1 who were nonresponders to previous treatment, combination therapy with pegylated interferon + valopicitabine 800 mg daily resulted in a 3.32-log reduction in HCV RNA after 24 weeks of treatment. In another study assessing this combination in treatment-naïve HCV genotype 1 patients, 4.56- and 4.41-log reductions in HCV RNA were noted after 24 and 36 weeks of treatment, respectively. Both trials required protocol amendments that reduced the dose of valopicitabine to 400 mg daily. At the end of 48 weeks of therapy, the efficacy was not significantly different from the standard-of-care therapy, although more frequent dose-dependent gastrointestinal side effects were noted. In fact, the higher dose of valopicitabine was associated with more significant side effects, specifically nausea and vomiting. Because of the gastrointestinal side-effect profile of valopicitabine and lack of clear gains in terms of efficacy, further development of this compound has been suspended.^[28-30]

A prodrug of R1479 and a potent inhibitor of the NS5B-RNA-dependent HCV RNA polymerase, R1626* is also being developed as a STAT-C agent. R1626 is an oral nucleoside analog that has been administered at doses ranging from 500 mg to 4500 mg twice daily for 14 days in treatment-naïve HCV genotype 1 patients. The largest mean reduction in serum HCV RNA of 3.7 logs was

observed with the 4500-mg twice daily dose of R1626.^[31,32] Additionally, recent data reported in treatment-naive HCV genotype 1 patients showed that 84% of patients who received triple therapy of R1626/pegylated interferon/ribavirin had undetectable HCV RNA at the end of treatment vs 65% who received standard treatment with pegylated interferon and ribavirin.^[33] Neutropenia (dose-dependent) was common in patients receiving R1626.

Nonnucleoside analog inhibitors. Several nonnucleoside analog inhibitors are also being developed. The mechanism of action of these drugs is different from that of the nucleoside analogs; therefore, cross resistance is unlikely.^[4,5]

The nonnucleoside polymerase inhibitor HCV-796* was studied in a phase 1 clinical trial at doses ranging from 50 mg per day to 1500 mg per day. Monotherapy trials of HCV-796 showed a 1.4-log decline in the HCV RNA viral load in patients receiving the higher doses of drug. Phase 2 clinical trials using a combination of HCV-796 and pegylated interferon alfa showed a mean viral reduction of 3.3 to 3.5 logs after 14 days of treatment. Subsequent phase 2 clinical trials of this agent were carried out in combination with pegylated interferon alfa-2a with or without ribavirin in both treatment-naive and nonresponder patients. Clinically significant elevations in liver enzyme levels were noted, resulting in discontinuation of further development of this compound as a potential treatment option for HCV infection.^[4,5,34]

Other protease/polymerase inhibitors. In addition to the protease and polymerase inhibitors described in this section, a number of other agents (protease inhibitors: ACH-1095;* polymerase inhibitors: PSI-6130,* R7128,* GS-9190,* BILB 1941,* A-831,* and A-689*) have also undergone testing in early phase clinical trials. The findings regarding these agents are preliminary and await additional analysis.^[4,5]

Cyclophilin Inhibitors

Cyclophilins are proteins widely found in human cells; they are involved in protein folding and stimulate the activity of the HCV NS5B-polymerase. The cyclophilin inhibitor DEBIO-25* has demonstrated antiviral effects against both HCV and HIV.^[35] The safety and efficacy of this class of drugs is currently pending.

Conclusion

We have witnessed many advances in our understanding of the life cycle of HCV and the enzymes critical for its replication over the past decade. Although efforts to optimize the current immunomodulatory therapy for HCV (pegylated interferon and ribavirin) have continued, newer, targeted treatments for HCV are being developed. It is becoming increasingly clear that these enzyme inhibitors are most effective when used in combination with the current standard of care, combination pegylated interferon and ribavirin. However, triple combination therapy regimens may not only enhance efficacy but also shorten the course of therapy. Current findings regarding the STAT-C class of agents suggest that protease inhibitors are at a more advanced stage of clinical development than polymerase inhibitors. Additionally, newer treatment options using cyclophilin inhibitors may provide further targets for combating hepatitis C infection. Nevertheless, clinical trials of these drugs suggest that their efficacy may increase along with the side-effect profile when used in these multidrug cocktails. It is important to balance increased efficacy and shorter treatment duration with increased toxicity and costs associated with additional drugs and toxicity monitoring. With these enthusiastic but cautious notes, we expect the next decade to bring tremendous advances in the treatment of HCV infection. Nevertheless, in achieving these advances, the safety, efficacy,

and effectiveness of these drugs must be established in addition to their cost effectiveness and positive impact on health-related quality of life.

**The US Food and Drug Administration has not approved this medication for this use.*

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