Specifically Targeted Antiviral Therapy (STAT-C) for Patients With Chronic Hepatitis C

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Introduction

Chronic hepatitis C is one of the most common causes of chronic liver disease worldwide. It is estimated that, globally, approximately 170 million people are infected with hepatitis C, and that approximately 15% develop hepatitis C-related cirrhosis. Evidence suggests that the future burden of hepatitis C-related liver disease will increase with the increasing rates of liver-related mortality, morbidity, and liver cancer. Additionally, the economic burden of hepatitis C-related liver disease is estimated to be enormous. [1]

Several therapeutic regimens have been developed in an attempt to treat hepatitis C virus (HCV)-related liver disease. The current standard of care for the treatment of hepatitis C is combination therapy with pegylated interferon alfa and ribavirin. This combination regimen can be very effective in patients infected with HCV genotype 2, with more than 80% of patients achieving a sustained virologic response. The response rate is lowest among patients with genotype 1 disease, with approximately 40% achieving a sustained virologic response. [2]

The Challenge of Achieving a Sustained Virologic Response

Recent reports on viral kinetics suggest that rapid virologic clearance (undetectable HCV RNA by polymerase chain reaction after 4 weeks of treatment) has an excellent positive predictive value for sustained virologic response. [3] In contrast, the failure to achieve early virologic response by week 12 of treatment (a minimum of a 2-log drop in HCV RNA from the baseline value) is a reliable negative predictor of response to this combination therapy regimen. [3,4] Furthermore, recent reports suggest that maintaining the optimal dose of both pegylated interferon alfa and ribavirin is associated with the best response to combination therapy. Achieving this goal requires careful

and proactive management of side effects, including cytopenias and depression. [5]

Knowledge of these viral kinetic data and better management of side effects can ensure adherence to the optimal regimen and help clinicians maximize the efficacy of antiviral therapy. Despite these recent gains in the field, many patients fail to achieve a sustained virologic response or are unable to tolerate the side effects associated with these drugs, necessitating the development of new strategies in HCV therapy. Research has focused on the development of agents with novel mechanisms of action and on the modification of existing drugs. The anti-HCV regimens currently in development can be divided into 3 main categories, including specifically targeted antiviral therapy for HCV (STAT-C), immunomodulatory agents, and antifibrotic agents. Additionally, novel ribavirin-like drugs as well as interferons with more optimal pharmacokinetics (such as albumin-bound interferon) are also in development. [6] This report discusses the most recent data regarding the STAT-C regimens, with a view toward the potential future implications of these agents.

STAT-C Agents

The STAT-C regimens comprise the most exciting group of therapies on the horizon for hepatitis C. These agents are based on the model of antiretroviral therapy for HIV infection, targeting specific enzymes important in the replication of HCV. Investigators have overcome many challenges in the development of these compounds -- most important, the development of "enzyme inhibitors" required a detailed knowledge of the hepatitis C replication cycle. In turn, knowledge of these steps in the cycle of hepatitis C replication required the development of an effective replication cell culture system or HCV replicon system and a 3-dimensional structure analysis of important HCV enzymes such as the NS3-4A protease and NS5B polymerase. [7,8] Many HCV protease and polymerase inhibitors have been developed over the past 5 years and tested in phase 1 and 2 clinical trials.

Protease Inhibitors

BILN-2061. HCV NS3 is a serine protease that mediates polyprotein processing and that has a shallow hydrophobic binding region. BILN-2061 (Boehringer Ingelheim, Ingelheim, Germany), a potent inhibitor of NS3, was one of the first HCV protease inhibitors tested. A phase 1 clinical trial assessing the antiviral efficacy of BILN-2061 showed that this agent rapidly reduced viral load within the first 48 hours. Although

BILN-2061 demonstrated potent antiviral activity against HCV genotype 1, the virologic response was less pronounced and more variable in HCV genotype 2 and 3 patients. Despite early enthusiasm, further development has been halted because of concerns related to potential cardiotoxicity in animal models. [9,10]

VX-950. VX-950 (*Telaprevir*, Vertex Pharmaceuticals, Cambridge, Massachusetts) is a selective, specific, and potent peptidomimetic inhibitor of the HCV NS3-4A serine protease. In this phase 1 clinical trial, patients with HCV genotype 1 were randomized to placebo or to VX-950 monotherapy administered at doses of 450 mg or 750 mg every 8 hours or 1250 mg every 12 hours for 14 days. [11] Results of this preliminary study showed that VX-950 administered at a dose of 750 mg every 8 hours resulted in a 4.4-log drop in HCV RNA from baseline. In fact, this reduction in viral load occurred within the first 4 days of treatment. A subsequent study examined efficacy during dosing with VX-950 in combination with pegylated interferon alfa-2a. In this study, one cohort of subjects received VX-950 in combination with pegylated interferon alfa-2a for 14 days. At the end of the 14 days of the study period, a 5.5-log decline in HCV RNA was noted. In fact, 6 of 8 patients had undetectable HCV RNA (< 30 IU/mL) by day 14. After the completion of 14 days of the study period, in an off-study follow-on treatment, all patients were given a combination of pegylated interferon alfa-2a plus ribavirin for another 24 weeks. [12]

Of the 6 patients who have completed 24 weeks of combination therapy with pegylated interferon alfa-2a and ribavirin, 5 remain HCV RNA undetectable after 12 weeks of follow-up.[12,13]

In another larger study with longer duration, in a double-blind, placebo-controlled fashion (phase 2b PROVE1 clinical trial), the safety and efficacy of VX-950 in combination with pegylated interferon alfa-2a and ribavirin in treatment-naive HCV genotype 1patients are being assessed. [14] In this study, patients received at least 1 dose of VX-950 or placebo in addition to pegylated interferon alfa-2a plus ribavirin. An interim analysis presented during the 42nd Annual Meeting of the European Association for the Study of the Liver (EASL) showed that 88% of patients receiving the triple combination regimen achieved a rapid viral response (HCV RNA < 30 IU/mL); 79% achieved a rapid viral response as measured by HCV RNA levels < 10 IU/mL at week 4 of treatment. In comparison, 16% of patients who received the pegylated interferon alfa-2a, ribavirin, and placebo combination achieved a rapid viral response (HCV RNA < 30 IU/mL) and 11% achieved a rapid viral response as measured by HCV RNA < 10 IU/mL.

The virus remained undetectable after 20 weeks of follow-up (sustained virologic response "SVR 20") in 6 of 9 patients who completed their treatment. Although these data have not been fully analyzed, the occurrence of rash has been reported in some subjects. The final data regarding the efficacy and safety of this regimen are still pending. Additional trials investigating the efficacy of combination regimens involving VX-950, pegylated interferon-alfa, and ribavirin in patients who were nonresponders to standard therapy with pegylated interferon-alfa plus ribavirin are underway.

SCH503034. SCH503034 (Shering-Plough, Kenilworth, New Jersey) is another NS3 serum protease inhibitor. In a phase 1 clinical trial,[15] 61 patients infected with HCV genotype 1 who were nonresponders to previous treatment with pegylated interferon alfa were randomized to receive SCH503034 (100 mg twice daily, 200 mg twice daily, 400 mg twice daily, 400 mg thrice daily) or placebo for 14 days. Preliminary results showed that after 14 days of monotherapy, SCH503034 given at a dose of 400 mg thrice daily was associated with an approximately 2-log drop in HCV RNA from the baseline value. A follow-up study assessed the virologic response of combination SCH503034 plus pegylated interferon alfa-2b in patients infected with HCV genotype 1 who were previous nonresponders to pegylated interferon alfa-2b-based therapy. [16] Preliminary results suggested that the best viral response occurred when pegylated interferon alfa-2b was given in combination with SCH503034 400 mg thrice daily for 14 days; a 2.88-log reduction in HCV RNA occurred among patients in this treatment group. Ongoing phase 2 clinical trials are assessing the efficacy of SCH503034 given in combination with pegylated interferon alfa-2b ± ribavirin in HCV genotype 1 patients who are nonresponders to previous treatment. The results have not been fully reported to date.

Other Protease Inhibitors. The antiviral activity of ACH-806 (also known as GS-9132; Achillion Pharmaceuticals/Gilead Sciences), another HCV protease inhibitor, has been tested in a phase 1 clinical trial. In data presented at the recent EASL meeting in Barcelona, Spain, treatment with ACH-806 was associated with a 2.38-log drop in HCV RNA within 5 days of therapy.[17] It is important to note that there has been concern about an increase in beta-2-microglobulin and serum creatinine that was observed during this study. Finally, ITMN B (Intermune, Brisbane, California) is another HCV protease inhibitor that has been tested in replication model(s). [6] Although protease inhibitors represent an exciting class of compounds in development for the treatment of HCV infection, they have a short half-life and require dosing every 8 hours.

HCV RNA Polymerase Inhibitors

In addition to protease inhibitors, many other agents are being developed to target the HCV RNA-dependent RNA polymerase. One of these agents, NM283 (*Valopicitabine*, Idenix Pharmaceuticals, Cambridge, Massachusetts), is a ribonucleoside analog that targets the viral RNA polymerase and is a viral RNA chain terminator. Godofsky and colleagues [18] presented the results of a phase 1/2 dose-escalation trial of NM283 in the range of 50 mg per day to 800 mg per day. Results showed that the best response to NM283 occurred at a dose titrated between 400 mg and 800 mg/day. However, higher doses were associated with significant side effects, specifically nausea and vomiting. In a study presented at the recent EASL meeting, NM283 was administered in combination with pegylated interferon alfa-2a to HCV genotype 1 patients who were nonresponders to previous pegylated interferon alfa and ribavirin-based therapy. [19] Despite early enthusiasm, this trial failed to demonstrate an enhanced sustained virologic response in this difficult-to-treat group of patients with hepatitis C. A study assessing the safety and efficacy of this agent given in combination with pegylated interferon alfa and ribavirin is currently underway.

R1626 (Roche Pharmaceuticals, Basel, Switzerland), another nucleoside analog oral polymerase inhibitor, has been administered at doses ranging from 500 mg to 1500 mg twice daily for 14 days in treatment-naive HCV genotype 1 patients. The initial clinical trial involving this agent demonstrated a clinically significant approximately 1.2-log reduction in HCV RNA associated with the 1500-mg twice-daily dosing regimen.[20] A subsequent multiple ascending dose study of R1626 (500 mg, 1500 mg, 3000 mg, and 4500 mg twice daily for 14 days) was conducted in previously untreated patients with HCV genotype 1 infection. [21] Mean (median) HCV viral reductions of 0.3 (0.2), 1.2 (0.8), 2.6 (2.7), and 3.7 (4.1) log10 were observed for doses of 500 mg, 1500 mg, 3000 mg, and 4500 mg, twice daily, respectively.

The nonnucleoside polymerase inhibitor HCV-796 (ViroPharma, Exton, Pennsylvania and Wyeth Research, Philadelphia, Pennsylvania) has been studied in a phase 1 clinical trial at doses ranging from 50 mg per day to 1500 mg per day. Approximately a 1.2-log drop in the HCV RNA viral load was observed among patients receiving the higher doses (500-1500 mg/day). However, this drug seems to be associated with an increase in HCV RNA levels, which may be the result of the emergence of HCV variants. [22] A phase 2 clinical trial of this agent

given in combination with pegylated interferon alfa-2a with or without ribavirin in both treatment-naive and nonresponder patients is currently underway. In addition to these agents, several other polymerase inhibitors, including MK-0608, A-837093, and AG-021541, are also under development in the preclinical setting. [6]

Conclusion

In summary, research regarding the STAT-C agents suggests that protease inhibitors can achieve a greater than 2.5-log reduction in serum HCV RNA within 14 days when used as monotherapy. This is in contrast to polymerase inhibitors, which achieve about a 1-log reduction in HCV RNA when used in the same fashion and for the same duration of treatment. The efficacy of administering these STAT-C drugs in combination with interferon with or without ribavirin is currently being assessed in phase 2 clinical trials using double or triple combination therapy regimens.

It is likely that future strategies for treating hepatitis C will involve a cocktail of multiple agents that can target both the polymerase and protease enzymes of the hepatitis C virus. In the short term, it seems likely that these agents will be used in addition to the current standard of care, combination pegylated interferon and ribavirin. Despite our tremendous enthusiasm for the potential of these new therapeutic targets in hepatitis C, many questions remain unanswered. First, how many drugs can be combined to achieve optimal response and acceptable toxicity? Second, for what duration do we need to use these combination regimens to achieve an undetectable HCV RNA that will remain sustained in the long term? Furthermore, with these new agents, will the current viral kinetic data from combination therapy (rapid virologic and early virologic response) still be applicable? It is likely that the development of new drugs will increase costs, at least temporarily, and require close monitoring of both expected and unexpected side effects.

The introduction of these targeted antiviral therapies is expected to advance our therapeutic arsenal for patients with hepatitis C, especially nonresponders to the current standard of care and the more difficult-to-treat HCV genotype 1 patients. Nevertheless, it is critical that the efficacy and safety of these drugs be established and that their cost effectiveness and their impact on a patient's health-related quality of life be carefully assessed.

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