

Ongoing Challenges in the Management of Chronic Hepatitis C

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Introduction

It is now firmly recognized that chronic hepatitis C virus (HCV) infection is associated with substantial morbidity and mortality in infected individuals and that it clearly represents a global public health challenge. Hepatitis C is the most common chronic bloodborne infection in the United States and is believed to have infected as many as 2% of the world population, or more than 120 million persons.^[1] Despite substantial advancement in our understanding of its life cycle and modes of transmission, the lack of a prophylactic vaccine or a universally effective therapy has prevented and delayed control of this infectious epidemic.

Perhaps the most clinically significant aspect of chronic HCV infection is its ability to promote the development of progressive hepatic fibrosis and cirrhosis, which may in turn lead to severe complications and decreased survival.^[2] Several independent predictors of fibrosis progression in patients with chronic HCV infection have been identified, including male sex, daily alcohol consumption, and HIV coinfection,^[3,4] although the length (duration) of infection is by far the most significant predictor for advanced liver injury and cirrhosis. Viral eradication before the development of advanced disease is therefore an attractive goal in the treatment of HCV infection, as it may halt the progression or associated deadly complications, such as liver failure and hepatocellular carcinoma (HCC). Although the possibility of halting disease progression by achieving viral eradication in chronically infected patients has not entirely been proven beyond doubt, mounting supporting evidence of its validity has been generated, including a recent study suggesting improved overall survival in patients who achieve sustained virologic response (SVR) after receiving antiviral therapy.^[5,6]

Current Treatment Options

The efficacy of antiviral therapy in the setting of chronic HCV infection is measured by the likelihood of achieving an SVR (HCV RNA negativity 6 months after completion of therapy). Interferon alfa monotherapy was first used for the treatment of hepatitis C, but soon after, it was the addition of the nucleoside analog ribavirin to the regimen that greatly increased the chance of achieving an SVR.^[7,8] The addition of a polyethylene glycol moiety to the interferon molecule, pegylated interferon, extended its half-life and was shown to improve response rates. Several multinational, randomized controlled trials demonstrated that 48 weeks of once-weekly pegylated interferon plus daily ribavirin was associated with SVR rates of greater than 50% in a multiple genotype population and established the regimen as the "standard of care" for the treatment of chronic HCV infection.^[9,10] Since its approval and acceptance as the standard-of-care therapy for HCV infection, pegylated interferon plus ribavirin combination therapy was optimized in order to identify those patients who are not likely to benefit from treatment before or during therapy. Studies of viral kinetics established "stopping rules" at week 12 (early virologic response [EVR]) and week 24 of therapy. Failure to achieve an EVR, defined as undetectable HCV RNA or $> 2\text{-log}_{10}$ decrease in the level of HCV RNA from baseline after 12 weeks of therapy, is highly predictive of failure to attain an SVR, with a negative predictive value of 97% to 100%.^[11] The use of the EVR to guide discontinuation of therapy was found to decrease treatment duration and reduce associated antiviral costs significantly compared with a

full course of therapy.^[12] However, if patients continue on therapy past 12 weeks, it is also important to confirm negativity for HCV RNA at week 24, at the end of the course of therapy (week 48), and at 24 weeks post-therapy, as treatment failure can occur between weeks 24 and 72.^[13] Similarly, viral response at week 4 after initiation of treatment (rapid virologic response [RVR]) has been used to shorten the length of treatment in some patients who are highly likely to achieve SVR even with less than 48 weeks of therapy, given the high positive predictive value of RVR to identify those patients who will achieve SVR early in the course of treatment (RVR is defined as undetectable HCV RNA at 4 weeks after initiation of antiviral treatment).^[14,15]

In addition to monitoring viral response during therapy, several preexisting viral (HCV genotype and pretreatment HCV RNA level) and host (ethnicity, sex, and advanced histologic stage) factors were identified as important predictors for treatment outcome and have been used to counsel patients prior to initiation of treatment. Viral genotype is particularly important in determining the response to antiviral therapy. Patients with HCV genotype 1 infection have SVR rates of 42% to 46%, whereas those with genotypes 2 or 3 infection have SVR rates of 76% to 82%, and patients with genotype 4 have SVR rates of up to 70% after 48 weeks of therapy with the standard of care (or even 24 weeks of therapy for those with genotype 2 or 3 infection).^[7-11] The significance of this genotype-dependent response is even more highlighted given that in the United States, more than 70% of infected patients have HCV genotype 1 infection.^[16] Ethnicity is another highly significant factor affecting the SVR rate, wherein black patients are particularly disadvantaged compared with white patients in terms of the likelihood of achieving an SVR with the current standard of care (SVR rates in blacks range from 19% to 26% vs 39% to 52% in whites).^[17,18]

The identification of an effective antiviral therapy for HCV infection, followed by optimization of drug administration and our ability to identify patients who will benefit the most from these approaches, represents amazing progress achieved over a relatively short period of time considering that HCV was discovered only less than 20 years ago. Although this is a remarkable rate of progress in knowledge, many obstacles and challenges remain. The real battle to defeat this devastating chronic infection is only in its infancy.

Challenges in HCV Therapy

Simply stated, there are 2 major challenges to overcome with the currently available antiviral treatment strategy for HCV infection: its suboptimal efficacy and its significant toxicity. As antiviral therapy has improved over the past 2 decades, rates of SVR increased from 6% to 12% in the early 1990s to nearly 55% in the past 5 years.^[19] Even if "best response" is consistently achieved, as many as 45% of treatment candidates will fail to respond to therapy with the current standard of care and will be added to the "pool" of nonresponders to standard treatment. Moreover, subpopulations, including HIV-coinfected patients and black patients, have lower rates of SVR; greater than 60% of treatment candidates in these groups will "feed into" the nonresponder pool of patients.^[16,17,20,21] It is safe to assume that the nonresponder patient population is increasing in the United States and is likely to outnumber the treatment-naive population within the next 10 years. Nonresponders have a significantly higher incidence of cirrhosis and HCC,^[22,23] suggesting that lack of an effective intervention in this population may have serious consequences. Various therapeutic options have been attempted in nonresponders, with limited success, including re-treatment with combination of pegylated interferon plus ribavirin, longer duration therapy, higher induction dose of pegylated interferon, long-term maintenance pegylated interferon, and daily consensus interferon regimens.^[24-27]

The other main challenge is treatment-related adverse events. This is a major contributor to impaired antiviral response in HCV-infected patients because of the lack of adherence to the treatment regimen while experiencing side effects. Common adverse events associated with standard-of-care therapy include myalgias, headache, and other flu-like symptoms, as well as dermatologic, gastrointestinal, neuropsychiatric, and hematologic effects.^[7-10] Some adverse events, such as anemia, neuropsychiatric effects, and flu-like symptoms, compromise quality of life and may necessitate dose reductions.^[28] Discontinuation of therapy due to adverse events is common, occurring in up to 27% of patients in clinical trials; dose reductions have been reported in up to one third of patients.^[29] Effective management of treatment-related adverse events is therefore essential for improving adherence and increasing the likelihood of SVR.

Emerging Approaches to Face the Challenges

The emergence of specifically targeted antiviral therapy for HCV, referred to in the literature as STAT-C, will likely provide desperately needed ammunition to face some of the challenges reviewed earlier in this column. STAT-C is a group of pharmacologic agents that target specific enzymes important for viral replication, such as the protease and polymerase enzymes. Although a number of compounds are currently under investigation for the treatment of HCV infection, in terms of timeline, the STAT-C agents are anticipated to be the first to offer a paradigm shift in disease management.

Of several protease inhibitors under development, two have made significant progress through the process of clinical trial testing. Telaprevir (VX-950)*, a selective HCV NS3-4A serine protease inhibitor, has shown remarkable antiviral efficacy against HCV, especially when combined with pegylated interferon/ribavirin, while maintaining an acceptable safety profile. In early trials of treatment-naïve patients, it was reported that at 14 days after initiation of therapy, a 5.5- \log_{10} decline in HCV RNA occurred in those receiving the combination of telaprevir plus pegylated interferon, compared with only a 1.09- \log_{10} decline in patients receiving placebo plus pegylated interferon.^[30]

More recent phase 2 clinical trial data of telaprevir showed that these initial encouraging results will likely hold in larger groups of HCV-infected patients.^[31] In this trial (PROVE 1 study), overall SVR was achieved in 61% of HCV genotype 1 patients receiving the triple-drug regimen of telaprevir plus pegylated interferon and ribavirin, compared with 41% of those receiving the standard combination of pegylated interferon and ribavirin.^[31] Skin rashes were more frequent in the group receiving the triple-therapy regimen, although severe skin rashes occurred in only 7% of patients on triple therapy.^[32]

Boceprevir* (SCH 503034) is another NS3 protease inhibitor that is well tolerated and has so far demonstrated robust antiviral activity against HCV in phases 1 and 2 clinical trials.^[33,34] In a phase 2 randomized clinical trial (SPRINT-1 [Serine Protease Inhibitor Therapy-1]) in an HCV treatment-naïve genotype 1 population, HCV RNA was undetectable in more than 73% of patients receiving 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 receiving standard doses of pegylated interferon and ribavirin. Although anemia was more common in the triple-therapy group, the treatment was well tolerated overall.^[34]

Data for both of these agents (protease inhibitors) suggest that STAT-C offers a viable strategy to achieve viral eradication and should continue the process of development in order to establish its complete safety and efficacy profile.

Similarly, provocative and potentially exciting data were recently presented in relation to a polymerase inhibitor, R1626.* In phase 2 clinical trials of treatment-naive HCV genotype 1 patients, 84% of patients receiving the triple therapy of R1626/pegylated interferon/ribavirin had undetectable HCV RNA at the end of therapy compared with 65% of those receiving standard therapy with pegylated interferon and ribavirin. However, neutropenia is common in patients receiving R1626 and is dose-dependent.^[35]

Conclusion

Numerous challenges in eradicating HCV continue to face physicians and patients alike. Despite the dramatic decline in new HCV infections in the United States and worldwide, complications of end-stage liver disease and HCC in patients already infected will undoubtedly persist and continue to pose serious medical and socioeconomic burdens to individuals in the prime of their life. This trend could be altered dramatically or even reversed with the development of better tolerated and more effective therapy. The development of the STAT-C class of therapy is clearly a major advancement in the right direction.

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

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