Shortening Treatment for Hepatitis C Virus Infection

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**G&H** How has treatment duration changed from the first direct-acting antiviral agents to those currently being used in patients with hepatitis C virus infection?

**SK** The first direct-acting antiviral (DAA) agents were serine protease inhibitors (telaprevir and boceprevir) used in combination with interferon and ribavirin. The duration of treatment was approximately 24 to 48 weeks. Two studies were conducted using a DAA agent alone for 12 to 24 weeks—the ELECTRON study from New Zealand on hepatitis C virus (HCV) genotype 3 infection, and the SPARE study from the United States on HCV genotype 1 infection (which I was the principal investigator of when I worked at the National Institutes of Health). The SPARE study demonstrated that HCV genotype 1 infection can be treated without the use of interferon. These 2 studies were the first to demonstrate the efficacy of a DAA agent in 6 months of first-line treatment for HCV genotypes 1 and 3 infection.

Subsequently, studies examined treatment regimens consisting of 2 DAA agents, such as ledipasvir plus sofosbuvir (Harvoni, Gilead) and ombitasvir/paritaprevir/ritonavir plus dasabuvir (Viekira Pak, AbbVie). Because 2 DAA agents were being used, researchers tried a shorter treatment duration (12 weeks). Early results revealed that almost all of the treated patients achieved sustained virologic response (SVR) or cure.

With such high response rates, researchers wondered whether treatment could be shortened for all patients. Thus, my colleagues and I conducted the SYNERGY trial, which was the first study to try to reduce DAA treatment duration for HCV infection to less than 12 weeks. Our goal was to see how much time it would take for all HCV RNA to be suppressed and completely eliminated from the liver and blood. We reasoned that increasing the potency of the drugs would increase the suppression of HCV replication, which would eliminate HCV RNA faster, helping us to reduce treatment duration. In this study, ledipasvir plus sofosbuvir was administered for 12 weeks, and all patients achieved SVR. In the second arm of the study, we added a third drug (protease inhibitor GS-9451 [vedroprevir, Gilead Sciences] or nucleoside analog GS-9669 [radalbuvir, Gilead Sciences]) to reduce treatment to 6 weeks, and almost all patients achieved SVR.

Subsequently, we conducted studies using the aforementioned 3-drug regimen for 4 weeks and then a 4-drug regimen (ledipasvir plus sofosbuvir and both GS-9451 and GS-9669) for 4 weeks. Around that time, other researchers conducted 4- and 6-week studies with recent data have shown that as the number of pills and weeks of treatment increase, adherence drops.
HCV drugs from Merck, Bristol-Myers Squibb, or Gilead Sciences (eg, the C-SWIFT study with sofosbuvir plus elbasvir/grazoprevir [Zepatier, Merck]). Treating patients without cirrhosis for 6 weeks with 3 drugs worked, but reducing treatment to 4 weeks did not. Based on these studies, we now know how short treatment can potentially be for patients with HCV genotype 1 infection.

However, it is important to keep in mind that, at this time, the treatment duration officially recommended by society guidelines is still 12 weeks for most HCV-infected patients; 8 weeks is used in rare cases, such as with ledipasvir plus sofosbuvir in patients with low HCV viral load and no cirrhosis or with glecaprevir plus pibrentasvir (Mavyret, AbbVie) in patients without cirrhosis.

G&H What are the main benefits of having a shorter HCV treatment duration?

SK The more medications patients have, the less adherent they likely are to treatment. Recent data have shown that as the number of pills and weeks of treatment increase, adherence drops. Shorter treatment can also save money and maximize resource utilization to treat more people. For example, if a disease can be treated in 4 weeks vs 12 weeks, the same amount of money can be used to treat 3 times as many people. Treatment expenses include all associated laboratory and outpatient visit costs, not only medication costs. Some countries with large populations of HCV-infected patients, such as Egypt and Mongolia, have been using government programs to treat all HCV-infected patients and could benefit enormously with a short-course regimen that is equally effective. HCV is a global disease that affects approximately 71 million people around the world; many resources will be needed to treat all of these patients and ensure improved global health.

G&H Are there any challenges with shortening HCV treatment?

SK A significant amount of research is needed to determine whether short-duration treatment (<6 weeks) can be effective in all HCV patients, as not all patients infected with HCV may respond to such regimens. For example, the SYNERGY trial showed that treatment for HCV genotype 1A infection cannot be shortened to less than 6 weeks, as the patients who responded to treatment less than 6 weeks were more likely to have HCV genotype 1B infection than 1A. Dr George Lau and his group from China conducted a small study on patients with HCV genotype 1B infection and no cirrhosis, and were able to use 3 different regimens that included sofosbuvir, a nonstructural 5A inhibitor, and a protease inhibitor for 3 weeks; SVR was achieved in all patients. Further research is needed to determine whether a regimen can be developed to treat all patients without cirrhosis regardless of genotype.

G&H Are there any other factors that appear to predict SVR with short-duration HCV treatment?

SK Most of these studies have been conducted with small sample sizes (20-30 patients each), so it is difficult to perform rigorous, meaningful statistical analysis. However, several factors have frequently been associated with achieving SVR with short-duration treatment. One factor is a low HCV viral load or RNA levels in the blood prior to initiation of treatment, as patients with a high viral load are likely to fail a short-duration treatment. Another factor is the presence of cirrhosis. Cirrhotic patients should not be considered for short-duration HCV treatment. Patients with a fibrosis stage less than 3 would be optimal for short-duration treatment. Finally, as mentioned previously, HCV genotype 1B infection (but not 1A) appears to be favorable for short-duration treatment. None of the shortened treatment strategies have evaluated other HCV genotypes, including 2 and 3; further research needs to be conducted before patients infected with these genotypes can be considered for short courses of therapy.

Retreatment studies have demonstrated high SVR, suggesting that the development of resistance is not a major concern with short-duration therapy.

G&H With shorter treatment, is there any concern regarding resistance?

SK The development of resistance to HCV drugs was a significant concern to short-course therapy at the beginning. We thought that if patients failed short courses (<6 weeks) of HCV therapy, they might develop resistance, making retreatment difficult. However, in the short-duration trials I have mentioned, which were conducted using DAA agents from different manufacturers, all patients were re-treated, most for 12 weeks with the same regimen or many times with the current standard of care (ledipasvir
plus sofosbuvir). Retreatment studies have demonstrated high SVR, suggesting that the development of resistance is not a major concern with short-duration therapy.

**G&H** Do you think that all HCV-infected patients will eventually use a short-duration treatment regimen?

**SK** Ideally, all patients should have a short duration of treatment. However, right now, doctors have to pick and choose treatments for different patient populations; as previously mentioned, certain factors seem to predict SVR with short-duration therapy, such as the absence of liver cirrhosis, HCV genotype 1B infection, and low HCV RNA levels prior to initiation of therapy. Critics of short-duration treatment believe that doctors should not have to pick and choose; the entire field of HCV therapy should be simplified by giving the same, quick treatment to cure all patients. Trying to select groups of patients becomes complicated and likely affects how doctors treat a large number of patients.

Having a treatment regimen that works on all HCV genotypes for 4 weeks or shorter would revolutionize HCV treatment. Currently, the patients who are driving the HCV epidemic in the United States are injection drug users and incarcerated people, who likely comprise more than half of the patients who are not being effectively treated. A short duration of treatment would be ideal to improve adherence in this difficult-to-engage patient population and prevent new infections from being spread by infected patients. These patients may have trouble being adherent to 12 weeks of treatment, especially if they become incarcerated, but 3 or 4 weeks of treatment would be highly pragmatic. That is the only way to control the spread of HCV transmission and halt the epidemic. Shorter-duration treatment would allow a larger number of patients, especially those who are marginalized, to be treated quickly and would utilize treatment as a means of preventing infection to break transmission cycles of HCV infection in the United States.

**G&H** Are there any studies currently being conducted using short-duration treatment for HCV infection?

**SK** Among treatment regimens approved for longer durations, no current studies are exploring shortening treatment to less than 8 weeks. However, it is likely that in the next year, some early studies may be initiated using short-duration treatment of drugs in development. To be competitive in the current marketplace, new drugs will need to have a short duration because there are already multiple regimens that cure nearly all patients after 12 weeks of treatment.

**G&H** What are the next steps for research in terms of short-duration HCV treatment?

**SK** The next step is to take the existing regimens and conduct studies in countries with highly prevalent HCV genotype 1B infection, such as Russia, China, Japan, Korea, and Mongolia. In addition, doctors could take some of the newer regimens under development, which may be more potent, and design phase 2 studies with both HCV genotype 1A– and 1B–infected patients, first in small studies and then following through with larger studies, to determine whether efficacy holds in a larger number of patients. It is important to remember that there are always differences between a 20-patient study and a 200-patient study. Researchers should make sure that treatment regimens can cure at least 95% of the patient population being studied.

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**Suggested Reading**


