ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

Six-Week Therapy for Hepatitis C Virus

David Bernstein, MD
Head, Liver Sub-Specialty Service Line
Vice Chair of Medicine for Clinical Trials
Chief, Division of Hepatology and Sandra Atlas Bass Center for Liver Diseases
Northwell Health
Professor of Medicine and Educational Sciences
Zucker School of Medicine at Hofstra/Northwell
Hempstead, New York

G&H How has the duration of hepatitis C virus treatment evolved over time?

DB Hepatitis C virus (HCV) treatment has seen a tremendous evolution, from interferon, which was an injectable therapy that was given for a year and caused significant side effects, to direct-acting antiviral (DAA) agents, which are oral medications that were first approved in 2014. Now, after many studies, refinement, and even newer oral agents, the vast majority of patients with HCV can be treated for either 8 or 12 weeks, depending upon genotype, degree of fibrosis, and whether the patients have been treated in the past. Currently, there are multiple recommendations for HCV treatment based upon the aforementioned factors, but the most common treatments are sofosbuvir/ledipasvir (Harvoni, Gilead), sofosbuvir/velpatasvir (Epclusa, Gilead), and glecaprevir/pibrentasvir (Mavyret, AbbVie). There is also the oral combination of sofosbuvir, velpatasvir, and voxilaprevir (Vosevi, Gilead), which can be used in patients who did not respond to the previously mentioned medications.

G&H What research has been conducted on even shorter HCV treatment durations?

DB DAA treatment has gone from 24 weeks to 12 weeks to select populations at 8 weeks. Once 8- and 12-week treatment became the standard of care, people wanted to try even shorter durations, such as 6 weeks or even 4 weeks. However, in chronic HCV, none of the studies of the aforementioned treatment regimens have shown the same efficacy with 6 weeks of treatment as with 8 or 12 weeks. On the other hand, in acute or recent HCV (ie, HCV with documented duration of less than 6 months), several small 6-week studies of sofosbuvir/ledipasvir and glecaprevir/pibrentasvir have shown significant success, with sustained virologic response rates varying from 90% to 100% (although 6-week therapy for acute disease is not approved by the US Food and Drug Administration [FDA]). Success with 6-week treatment has been seen only in patients with acute disease, so this therapy duration cannot be recommended for patients with chronic disease. Therefore, it is important to differentiate between acute and chronic disease.

G&H Could you expand on the differentiation between acute and chronic HCV infection?

DB A patient with acute HCV must be identified within 6 months of being infected. For example, a person using intravenous drugs, which is common among young people, may present with acute HCV, high transaminases, and perhaps jaundice. Most of the HCV patients whom doctors see were infected years ago because they received a blood transfusion before the blood supply was screened regularly, they took drugs years ago, or they have other risk factors. These patients usually present with normal or mildly elevated liver enzymes. Thus, the difference between acute and chronic disease is based on time and the ability to identify when the patient may have been exposed, and 6 months has been used as the cutoff.

G&H Among patients with acute HCV, are there any subgroups that seem to respond best to 6-week treatment?

DB We do not know. Most of the studies that have looked at 6 weeks of treatment in acute HCV are small. The studies are pangenotypic, which means that they include any of the various HCV genotypes. Several patients were coinfected with HIV. No patients had advanced fibrosis or cirrhosis. The vast majority of patients did very well. I think the numbers are too small to be able to predict which group responds better than another. While these small 6-week studies with either glecaprevir/pibrentasvir or sofosbuvir/ledipasvir show that this short duration may be highly effective, it is important to remember that treatment for acute HCV, regardless of duration, is not approved by the FDA.

When the dosing schedules of the 6-week studies of chronic HCV patients were examined, relapse rates were high.

G&H How is acute HCV usually managed then?

DB Thirty percent of the time, patients with acute HCV clear the virus on their own. However, that means that 70% of these patients develop chronic disease. Thus, when seeing a patient with acute disease, doctors have to decide whether the patient warrants treatment based upon his or her other medical conditions as well as on what the patient's follow-up likely will be. If a doctor does not think that a patient will come back and if the doctor thinks treatment would prevent spread in the community, I think that initiating treatment would be reasonable.

G&H In the studies that have been conducted on 6-week treatment of acute HCV patients, how safe was that treatment duration?

DB The therapies are extremely safe. Very few side effects have been reported with the 2 DAA regimens used in trials of acute HCV patients and, quite frankly, there have been very few side effects with the regimens that are currently being used for chronic HCV as well. This family of medications is incredibly effective and safe for use in the treatment of HCV.

G&H Have there been any challenges or concerns with treating HCV for only 6 weeks?

DB When the dosing schedules of the 6-week studies of chronic HCV patients were examined, relapse rates were high. Thus, the concern in treating patients for only 6 weeks is that they may relapse, meaning that they become negative on therapy but then when therapy is stopped, the virus may come back, leading to the difficult situation of having to re-treat patients.

G&H Is resistance a concern with a shorter duration of treatment?

DB That has not been shown. Most of the time with short durations of therapy, whether with 6 or even 4 weeks, the main concern is either nonresponse or a greater risk of relapse. Having said that, anecdotally (which is not in any way a scientific observation), all doctors have seen patients who were supposed to take therapy for 8 weeks but only took it for 6 weeks and did fine. Nevertheless, I do not think that there are enough data to support the use of a 6-week regimen in chronic HCV at this time. Providers should abide by the currently approved treatment durations of 8 and 12 weeks.

G&H Overall, what would be the benefits of a 6-week treatment for HCV?

DB If 6 weeks of therapy were as effective as 8 or 12 weeks, one benefit would be less expense. In addition, shorter therapy is always better for patients. They tend to have increased compliance with shorter durations, although most patients who are taking 8 or 12 weeks of treatment are already very compliant. On the other hand, if a patient is only taking a treatment for 6 weeks and misses a pill or two, that may have an effect on the overall response rate, whereas if the patient was taking a medication for 8 or 12 weeks, missing a dose or two may have less of an effect on the overall outcome.

G&H In the future, do you think a shorter treatment duration might become more widespread or eventually even become the standard of care?

DB I do not think so at this point. The current HCV therapies are highly effective, so I do not think that 6-week therapy will become the standard of care in chronic HCV; I think that 8 or 12 weeks of treatment will remain the

standard of care for chronic HCV. Before anyone can consider 6 weeks of therapy, more data are needed. To date, studies in acute disease have had a total of approximately 50 patients. It is difficult to make recommendations on treatment durations with such a small population. Larger studies are needed to be able to determine whether 6 weeks should become the standard of care for patients with acute HCV.

G&H Are there any studies currently underway on this issue?

DB I do not know, but it would surprise me if researchers were not looking into this. The challenge is, quite frankly, that it is difficult to find patients with acute HCV, although more are being seen with the opioid crisis across the country. However, it takes a long time to accrue patients for an acute HCV trial.

G&H Have you or your colleagues had any experiences treating patients with acute HCV for only 6 weeks?

DB We do not recommend 6 weeks of treatment in our practice or our health care system. We treat patients with chronic HCV for either 8 or 12 weeks. We also treat patients who have acute disease for either 8 or 12 weeks. Having said that, anecdotally, we have patients who have been treated for only 6 weeks, and they have done fine. However, that refers to a very small number of patients, and is not comparable to scientific or controlled findings.

G&H What follow-up care would be needed with 6-week treatment?

DB In patients treated for 8 or 12 weeks, doctors tend to obtain the viral load 3 months after therapy has been stopped to determine whether the patients have sustained virologic response. Then, depending upon the institution, most doctors will bring back patients either 6 months or a year later for confirmation. However, if a patient has been treated for only 6 weeks, I think more frequent testing is needed to evaluate for relapse.

Disclosures

Dr Bernstein has received research grants and has been a consultant to Gilead Sciences and AbbVie.

Suggested Reading

AASLD-IDSA. HCV guidance: recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org. Accessed September 16, 2020.

Deterding K, Spinner CD, Schott E, et al. Ledipasvir plus sofosbuvir fixed-dose combination for 6 weeks in patients with acute hepatitis C virus genotype 1 monoinfection (HepNet Acute HCV IV): an open-label, single-arm, phase 2 study. *Lancet Infect Dis*. 2017;17(2):215-222.

Emmanuel B, Wilson EM, O'Brien TR, Kottilil S, Lau G. Shortening the duration of therapy for chronic hepatitis C infection. *Lancet Gastroenterol Hepatol*. 2017;2(11):832-836.

Kohli A, Osinusi A, Sims Z, et al. Virological response after 6 week triple-drug regimens for hepatitis C: a proof-of-concept phase 2A cohort study. *Lancet*. 2015;385(9973):1107-1113.

Martinello M, Orkin C, Cooke G, et al. Short-duration pan-genotypic therapy with glecaprevir/pibrentasvir for 6 weeks among people with recent hepatitis C viral infection. *Hepatology*. 2020;72(1):7-18.