How did the advent of boceprevir (Victrelis, Merck) and telaprevir (Incivek, Vertex) impact the efficacy of hepatitis C virus therapy?

The chance of clearing the virus and achieving a sustained virologic response (SVR) nearly doubled with the addition of these protease inhibitors. This improvement gave many people in the field of medicine a sense of renewal, as we finally have new agents to add to the interferon and ribavirin regimen that was the standard treatment for hepatitis C virus (HCV) infection for more than 10 years.

What are the benefits of protease inhibitor–based therapy?

These are potent drugs that allow patients with HCV infection to achieve much better outcomes. Because protease inhibitor–based therapy yields higher SVR rates, it offers the possibility of viral clearance both for patients who have never been treated before and for patients who have failed prior peginterferon and ribavirin therapy. The efficacy of protease inhibitor–based therapy in the latter group is particularly noteworthy, as successful treatment in these individuals was previously almost impossible. Once patients had been treated with peginterferon and ribavirin and were deemed to be nonresponders or relapsers, clinicians formerly could do very little other than observe these patients. However, we can now re-treat them with protease inhibitors, and these patients can frequently achieve SVR, which is a tremendous milestone.

Given these benefits, why are some patients still not receiving protease inhibitor–based therapy?

With the breakthrough offered by the new protease inhibitors, there was initial excitement about treating HCV infection, but I think providers learned fairly quickly that they still needed to have a well-organized team to manage these cases. While triple therapy for HCV infection does yield greater efficacy and an improved chance of achieving SVR, this therapy is still very intensive, so clinics need to have a dedicated team (involving physicians, nurses, and medical assistants) that can answer patients’ questions and help patients to manage treatment side effects. Given this requirement, there is probably still some hesitation about getting fully engaged in HCV therapy, especially treatment of complex patients—such as those who have comorbid conditions, marginal hepatic function, and/or early cirrhosis—as management of these patients remains quite demanding.

Which patients should definitely receive HCV therapy now? Are there any patients who should not receive treatment?

Clinicians should consider protease inhibitor–based therapy for treatment-naïve patients with chronic HCV infection if they have a liver biopsy indicating active inflammation and some degree of fibrosis (F2 or greater); these individuals run the risk of developing more advanced disease if they are left untreated. (On the other hand, patients with chronic HCV infection...
who have very mild inflammation and minimal fibrosis on biopsy may be able to wait for future therapies that will possibly be even more effective, shorter in duration, and/or more tolerable.) Another group that should probably be treated with protease inhibitor–based therapy includes patients who were previously treated but who did not achieve SVR; studies have shown that previously treated patients can do quite well with triple therapy regimens, and these patients likely have moderately advanced disease that could progress if left untreated. The only patients who absolutely should not be treated are those with severe comorbid conditions such as advanced cardiovascular disease, pulmonary disease, uncontrolled diabetes, advanced renal dysfunction, and uncontrolled depression or other psychiatric conditions.

**G&H Which HCV-infected patients remain most challenging to treat?**

**JSG** The most difficult group to treat includes patients with chronic renal failure who are on dialysis; in addition to their renal dysfunction, these patients frequently have problems with ribavirin-induced anemia. The second group that is difficult to treat includes patients with advanced fibrosis or early cirrhosis; these patients tend to have hypersplenism, lower platelet counts, and baseline anemia, all of which make it challenging to treat them without precipitating an acute decompensation of their liver function.

**G&H How frequently are such patients seen in clinical practice?**

**JSG** Depending on the practice, they may be seen quite frequently. In my practice, we have a large population of patients who have cirrhosis but are not yet eligible for liver transplantation; these patients have not had any life-threatening complications from their cirrhosis and portal hypertension, but they are outside of most treatment guidelines. These patients often present with low platelet counts, low white blood cell counts, and slight anemia. While treatment of such patients is challenging, I have had success with triple therapy in some of these cases; with very aggressive monitoring and very careful dosing of their medicines, these patients can receive treatment, and some of these patients have achieved SVR.

**G&H Can you briefly comment on some of the data from SPRINT-2 and RESPOND-2?**

**JSG** The SPRINT study showed that a triple therapy regimen including boceprevir can yield superior SVR rates in patients infected with genotype 1 HCV. In the RESPOND study, the most striking finding was that nonresponders still had an opportunity to achieve SVR; this result is tremendously exciting, as it means that patients who previously had no good treatment options can now undergo triple therapy and potentially clear their virus.

**G&H How can clinicians address some of the patient management challenges that occur when administering protease inhibitor–based therapy?**

**JSG** Hepatologists need to have a capable clinical staff of nurses or medical assistants who are well versed in the most common adverse events associated with protease inhibitor–based therapy. Clinics also need to have a very clear-cut, well-organized mechanism within the office to identify problems early, as well as a plan of action to keep patients on therapy. Instead of abruptly discontinuing treatment, some side effects can be managed with either dose reduction of 1 of the patient’s medicines or the addition of another medication to ameliorate some of the patient’s symptoms.

Modifying HCV therapy in this manner involves a degree of trial and error, so clinicians may find it helpful to collaborate with a more experienced clinic that can act as a resource. Rather than immediately discontinuing therapy because of concern about a laboratory abnormality or an adverse event, a clinician could talk to someone at an expert center and get some advice, which might allow him or her to continue the patient’s treatment using a modified regimen.

**G&H How can community gastroenterologists and hepatologists become more comfortable administering HCV therapy?**

**JSG** Clinicians who are seeking to gain experience in treating patients with HCV infection should team up with a more experienced clinician in a larger hepatology center or a liver transplant program. If a specialist has treated 500 cases, he or she is going to have a far greater experience profile and greater knowledge about various adverse events—both common adverse events and more obscure adverse events—and that knowledge can be quite enlightening for a less experienced clinician. Commonly, if a community gastroenterologist is treating an HCV-infected patient and the patient experiences an adverse event, the community gastroenterologist’s first reflex is to stop the therapy in order to prevent any potential harm to the patient. In the hands of an experienced team, however, therapy can often be modified in a way that allows the patient to continue therapy despite this adverse event. By collaborating with a more experienced physician, commu-
nity gastroenterologists and hepatologists can build experience and gain confidence in managing HCV therapy.

The corollary is that specialists should be open to consulting on cases and sharing their expertise. For example, I work in a specialty clinic, and we make our nursing and clinical staff available to other offices in the area. We also give inservices to area clinicians during which we share tips for managing the anemia, neutropenia, depression, and gastrointestinal upset that can occur during HCV therapy.

**G&H** If a community gastroenterologist has not previously been treating HCV infection, where should he or she begin?

**JSG** I would suggest starting with patients who are otherwise well nourished, healthy, and fit; patients should be free of advanced fibrosis, cirrhosis, or portal hypertension, and they should not have any significant comorbid problems—no cardiovascular disease, pulmonary disease, kidney disease, underlying depression, or diabetes. These “easier” patients will still experience drug interactions or other adverse events, but such problems are likely to be mild adverse events that can be easily managed. Thus, these patients will most likely be able to complete the full course of therapy, continue working during treatment, and maintain a fairly normal lifestyle.

**G&H** Which HCV-infected patients should be referred to a specialty clinic?

**JSG** The patients who should be referred to a specialist include those who experienced problems when treated with antiviral therapy in the past, patients with advanced fibrosis on biopsy, individuals with early signs of portal hypertension, and other complex cases such as patients who have diabetes, lung disease, or other problems that would make adherence to therapy more difficult.

**G&H** Given the recent approval of boceprevir and telaprevir, should clinicians treat patients now with currently available therapies, or should they wait for new agents that are still in development?

**JSG** At one end of the spectrum, we have mild cases—patients who have been infected for 10 years or longer but still have biopsy-proven mild disease, minimal inflammation, and minimal-to-no fibrosis; these patients may want to wait for future therapies that are in the pipeline, with the caveat that we never know exactly when upcoming therapies are going to be released. On the other hand, if patients are symptomatic, eager to be treated, and have moderate disease on biopsy, then I would think about treating them now. With protease inhibitor–based triple therapy, they have a very good chance of achieving SVR, in which case no further treatment would be needed. Other factors that clinicians may want to consider when making this decision include the patient population, the sophistication of the patient, and the availability of research studies.

**Suggested Reading**


