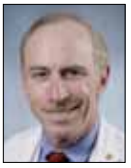
ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

Management of Patients Who Are Not Candidates for Protease Inhibitor Therapy



Paul J. Pockros, MD
Head of the Division of Gastroenterology and Hepatology
Director of the Center for Liver Diseases
Scripps Clinic
Director of Clinical Research
Scripps Translational Science Institute
La Jolla, California

G&H Which patients are not candidates for protease inhibitor therapy?

PJP Currently, protease inhibitor therapy is only approved for patients with genotype 1 hepatitis C virus (HCV) infection, so patients with other HCV genotypes require alternative therapies. For patients infected with HCV genotype 2 or 3, the approved therapy is pegylated interferon plus ribavirin for 24 weeks; alternatively, these patients could be enrolled in one of the clinical trials evaluating therapies for genotype 2 or 3 HCV infection. Similarly, patients with genotype 4 HCV infection are eligible for 48 weeks of therapy with pegylated interferon and ribavirin, or they can be enrolled in a clinical trial that accepts patients with genotype 4 HCV infection.

Even among patients with genotype 1 HCV infection, protease inhibitors are contraindicated in certain patients. Specifically, protease inhibitors are not approved for use in patients who have decompensated cirrhosis, patients who are co-infected with HIV, or patients who have undergone liver transplantation. I sometimes offer protease inhibitor therapy to certain patients in each of these groups, depending on their circumstances, but such therapy must be administered very carefully. For instance, I might treat a patient with decompensated cirrhosis if he or she is currently well compensated, has a low Model for End-Stage Liver Disease score, has already been approved for liver transplantation, has been very stable for years, and is desperate to be cured. I would usually treat such a patient with telaprevir (Incivek, Vertex) plus peginterferon and ribavirin because I am trying to get rid of the virus rapidly. My colleagues and I have treated 6 such patients at our institution. While we have treated these patients carefully, some patients have decompensated during therapy—usually due to interferon—and therapy had to be stopped. We have not had any deaths among these patients, but other clinics have had deaths, so extreme caution is warranted when treating such individuals.

Similarly, early data suggest that protease inhibitors may be used with caution in patients who are co-infected with HIV. For instance, studies of patients treated with telaprevir and efavirenz show that these drugs can be used safely in combination, but a higher dose of telaprevir must be administered. Data also suggest that ritonavir-boosted protease inhibitors can be administered with telaprevir but not with boceprevir (Victrelis, Merck), as drug-drug interactions have been observed with boceprevir. While these studies are encouraging, clinicians should bear in mind that protease inhibitors are not yet labeled for use in the setting of HIV co-infection.

Early data also suggest that protease inhibitors can be used in liver transplant recipients. However, clinicians need to be very careful treating patients who are receiving calcineurin inhibitors (CNI), as these drugs show a marked increase in concentration when a protease inhibitor is added. For instance, tacrolimus increases its concentration 70-fold, and cyclosporine increases its concentration 4.5–6-fold. For this reason, we prefer to use boceprevir in post-transplantation patients, as the effect on CNI levels is less dramatic. Successful treatment

of liver transplant recipients was recently demonstrated in the CUPIC study, the results of which were presented during the European Association for the Study of the Liver (EASL) Annual Meeting held in Barcelona, Spain in April 2012. In this study, a small number of patients were hospitalized at the start of therapy; the CUPIC investigators then reduced the patients' dose of cyclosporine or tacrolimus to a small dose given once a week, monitored levels of this drug, and added the protease inhibitor. The results of this study showed that treatment of transplant recipients was feasible and could achieve adequate reductions in viral loads; however, there was a high incidence of anemia, cytopenias, and infections, and there were even some deaths. Thus, treatment of these patients should only be performed in a transplant center where patients can be monitored closely and have an option for transplantation if they develop liver failure.

Finally, in addition to patients who cannot receive protease inhibitors for medical reasons, some patients do not receive protease inhibitor therapy because they elect to forgo treatment, typically because they want to avoid the side effects associated with peginterferon, ribavirin, and protease inhibitors. These patients are aware that HCV therapies are effective, but they also know that such drugs are difficult to tolerate because of the drugs' side effects, such as rash and anemia. In these cases, I perform a liver biopsy or assess the patient's degree of fibrosis via some other method, and then I manage the patient based on this assessment. In patients with advanced liver disease—Metavir scores of F3 or F4—I push patients to accept treatment, because I do not know how long it will be before new, interferon-free therapies will be available. If patients have milder disease—Metavir scores of F0 or F1—then I am more comfortable delaying therapy. I monitor these latter patients every 6–12 months, and I keep them up to date on the new therapies that are being developed.

G&H Do concerns about resistance limit the use of protease inhibitors?

PJP Resistance is a concern with protease inhibitors, as the development of resistance variants may limit the efficacy of future therapy. If a patient fails therapy with telaprevir or boceprevir, this failure is likely due to the development of viral breakthrough or failure to meet one of the futility milestones, which often occurs when patients develop a resistance variant. Thus, if a patient fails protease inhibitor therapy, it is more likely that he or she will develop a resistance variant.

Resistance is a particular concern in patients with genotype 1a HCV infection because genotype 1a HCV resistance variants seem to be common, and they occur with almost all of the protease inhibitors in development. The common genotype 1a HCV variants are R155K, V36M, D168Y, and R155K+V36M. If one of these variants emerges during therapy, then a patient could become resistant to subsequent protease inhibitor therapy.

However, available data suggest that resistance variants gradually disappear over time. Data from the Vertex database show that genotype 1a HCV variants disappear in approximately 12–16 months; genotype 1b HCV variants revert back to wild type even more quickly, in approximately 3 months. Also, re-treatment data suggest that most patients regain responsiveness to telaprevir therapy once their resistance variants have cleared; however, data on sustained virologic response (SVR) rates in these small re-treatment trials are not yet available.

While resistance is always a possible concern, I worry about resistance most in patients who are most likely to fail therapy—specifically, prior null responders, especially those with advanced fibrosis. Data from the REALIZE trial suggest that these patients have only a 30% chance of achieving SVR, which means that 70% of these patients could develop a resistance variant. If they have more severe fibrosis, then the chance of achieving SVR is even lower. Thus, I always discuss the possibility of resistance with these patients before starting therapy. In some patients, I also use a 4-week lead-in with peginterferon and ribavirin to determine if they are sensitive to interferon. If patients are sensitive to peginterferon and ribavirin and have a greater-than-1 $\log_{10}$ reduction in HCV RNA levels within the first 4 weeks of therapy, then they have an approximately 50% chance of clearing the virus. However, if patients are insensitive to peginterferon and ribavirin, then their chance of responding to therapy is almost zero. In the latter case, I often will not expose these patients to a protease inhibitor—either boceprevir or telaprevir—in order to avoid the risk of developing resistance.

G&H Are there some patients in whom any type of antiviral therapy is contraindicated?

PJP There are certainly patients who are not suitable candidates for interferon-based therapies. For example, I will not consider interferon-based therapy in patients over a certain age; my cutoff is generally 75 years. I have also encountered patients with absolute contraindications to interferon; these are patients who developed serious or life-threatening complications during prior exposure to interferon.

While these patients are not candidates for interferon-based therapy, they would still be candidates for interferon-free regimens. I think that everybody will be a candidate for some form of antiviral therapy once such therapy evolves to the point of being all oral, well tolerated, simple to take, and very effective. Unfortunately, such interferon-free regimens are not yet available.

In the meantime, I manage these patients by assessing their degree of fibrosis, determining whether they have cirrhosis, and treating them accordingly. If they have cirrhosis, I follow the guidelines from the American Association for the Study of Liver Diseases: I first perform an endoscopy to determine if they have varices; if they do, I treat them prophylactically with beta blocker therapy, band ligation, or other therapies, as appropriate. I also perform cross-sectional imaging—either via computed tomography ultrasound or magnetic resonance imaging—to screen for hepatocellular carcinoma. Finally, I monitor these patients at 6-month intervals for evidence of decompensation; if patients decompensate, then I evaluate them for liver transplantation.

G&H Do you think that new drugs could offer alternatives for patients who are not good candidates for protease inhibitor–based therapy?

PJP Yes. In the next 24 months, 2 new HCV regimens will probably be approved, but both will still require use of peginterferon and ribavirin, so they will not significantly broaden the population of patients who are eligible for treatment. Once an interferon-free regimen is available, however, such an option would open up the treatment-eligible population enormously. At that point, I think we will be able to treat everybody.

G&H Are there specific new drugs that look particularly promising?

PJP There are a number of drugs in several different classes that look promising. Among the protease inhibitors currently in development, the drug that is closest to approval is TMC435, also known as simeprevir (Tibotec/Janssen); it is on track to be approved in early 2014. Simeprevir is well tolerated, very potent, and dosed once daily. Data presented at the 2012 EASL meeting showed that this drug was very effective in patients who had failed previous treatment. Simeprevir will likely be used in combination with peginterferon and ribavirin, at least initially.

In the future, clinicians might also be able to use simeprevir in combination with a drug from a different class, possibly allowing for an all-oral regimen. One such drug that is close to approval is the NS5A inhibitor daclatasvir (Bristol-Myers Squibb). This drug is pan-genotypic, has a high barrier to resistance, and is dosed once daily. Daclatasvir is being evaluated for use with peginterferon and ribavirin, and it will hopefully be approved in 2014; an all-oral regimen with daclatasvir, a protease inhibitor, and ribavirin could also be considered.

Another promising drug is the polymerase inhibitor GS-7977 (Gilead). It is pan-genotypic, potent, and very safe; it also has a high barrier to resistance and is dosed once daily. GS-7977 is being tested as part of the first interferon-free regimen for genotype 2 or 3 HCV infection. If the trials currently being conducted yield positive results, GS-7977 will probably be approved by early 2014 for use in combination with ribavirin for genotype 2 or 3 HCV infection.

Currently, several trials of these new agents are ongoing. For instance, there is a phase II trial evaluating the protease inhibitor simeprevir plus the polymerase inhibitor GS-7977, with or without ribavirin, and this study could yield very positive data. In addition, early data presented at the 2012 EASL meeting demonstrated the efficacy of the NS5A inhibitor daclatasvir in combination with GS-7977; SVR rates were essentially 100% in all genotypes. This combination also showed no sensitivity to genotype 1a versus 1b HCV, and SVR rates were not dependent on interleukin-28B genotype. Thus, this combination looks very promising.

Suggested Reading

Pockros PJ. Drugs in development for chronic hepatitis C: a promising future. *Expert Opin Biol Ther*. 2011;11:1611-1622.

Naggie S, Sulkowski MS. Management of patients coinfected with HCV and HIV: a close look at the role for direct-acting antivirals. *Gastroenterology*. 2012;142:1324-1334.e3.

Saxena V, Terrault N. Hepatitis C virus treatment and liver transplantation in the era of new antiviral therapies. *Curr Opin Organ Transplant*. 2012;17:216-224.

Welzel TM, Zeuzem S. Mixing and matching drugs: what makes sense? *Clin Liver Dis*. 2011;15:657-664.

Gane E. Future hepatitis C virus treatment: interferon-sparing combinations. *Liver Int*. 2011;31(suppl 1):62-67.