Protease Inhibitor Therapy Post–Liver Transplantation in the Treatment of Hepatitis C Virus Infection

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G&H What is the current consensus regarding the use of protease inhibitors in liver transplant recipients?

SN Because of potential drug interactions that may occur with antirejection medications, use of protease inhibitors (PIs) is not recommended in liver transplant recipients. The serum levels of tacrolimus—the most widely used antirejection medication—are increased 70-fold when this drug is administered with the PI telaprevir (Incivek, Vertex). However, several presentations given at recent meetings, such as the 63rd annual meeting of the American Association for the Study of Liver Diseases in Boston, Massachusetts this past November and, more recently, the 48th annual meeting of the European Association for the Study of the Liver in Amsterdam, The Netherlands this past April, reported on successful use of PIs in patients with recurrent hepatitis C virus (HCV) infection.

G&H What advantages does adding a direct-acting antiviral agent have on current standard treatment in patients with HCV infection?

SN Several single-center studies have reported a sustained virologic response (SVR) rate of 30–35% for standard therapy with peginterferon (peg-IFN) and ribavirin. The addition of telaprevir to the standard regimen increases the SVR rate by 25–30% (ADVANCE trial). Hence, it is reasonable to assume that the SVR rate will also be higher in patients post–liver transplantation if a triple drug regimen is used. In addition, this regimen may potentially shorten treatment duration. In phase III telaprevir studies, the SVR rate was not affected by ribavirin dose reduction. Ribavirin is frequently associated with anemia in liver transplant recipients because of tacrolimus-induced renal dysfunction. Being able to use a lower dose of ribavirin is a distinct advantage in the management of these patients.

G&H What is the unique mechanism of action of direct-acting antiviral agents?

SN Direct-acting antiviral agents (DAAs) target specific nonstructural proteins of HCV, inhibiting viral replication. Telaprevir and boceprevir (Victrelis, Merck), the 2 PIs that were approved by the US Food and Drug Administration in May 2011, target the NS3/4A serine protease complex of HCV. A second-generation PI, simeprevir (TMC 435), is expected to be approved within the next few months. A more potent class of drugs targeting NS5b also will likely be approved in the near future. NS5b inhibitors are more active against all genotypes and have a high barrier to resistance. Another class of drugs that targets NS5a is likely to increase the efficacy of NS5b-based regimens. In the future, NS5b inhibitors will replace IFN as the backbone of anti-HCV therapy. Unlike the currently available PIs, these new drugs are better tolerated and likely to be dosed once a day.

G&H What is your view of the use of pharmacogenomics in evaluating treatment response in patients with chronic HCV infection?

SN At least 4 large clinical trials have confirmed the validity of pharmacogenomics in assessing HCV treatment...
response. The most widely studied gene polymorphism is at locus rs12979860 upstream of the interleukin-28B (IL-28B) gene. IL-28B encodes for IFN gamma (IFN-λ)–3. The presence of the C allele in the IL-28B gene predicts response to IFN. Patients with 2 C alleles (CC) have the best response followed by patients with the CT or TT genotype. African Americans have a lower frequency of the C allele, which partly explains the lower response rate to IFN in African American patients. Pharmacogenomic testing is widely available and can be used as a factor to assess benefit versus risk while initiating HCV therapy. PIs are more effective in patients with higher IFN responsiveness, so the presence of the C allele will be also useful in the current era of triple therapy.

In liver transplant recipients, the use of IL-28B is more complicated because these patients have an additional set of genes in the donor liver (allograft). There are data showing that if both donor and recipients are IL-28B CC-concordant, the SVR rate with peg-IFN and ribavirin is close to 80%. The donor IL-28B cannot be tested in routine clinical practice unless donor sera are stored. The IL-28B CC genotype is also associated with spontaneous clearance of HCV infection. Although rare, HCV spontaneously clears post–liver transplantation in some patients, suggesting a role of innate immunity via the allograft.

The role of IL-28B in the era of new drugs, especially in IFN-free regimens, is being debated. Some preliminary evidence suggests that a higher cure rate, even with IFN-free regimens, is achieved in patients with IL-28B CC, highlighting the role of innate immunity in clearing the infection.

The clinical focus on IL-28B has also highlighted the role of IFN-λ in clearing HCV infection. Encouraging reports suggest that IFN-λ–1 (IL-29 gene) is effective in treating genotype 1 patients who are infected with HCV. IFN-λ–1 has the advantage of expressing fewer systemic adverse effects than IFN-α.

CXC chemokine IFN-γ-inducible protein (IP)-10 levels could add another layer of stratification in assessing treatment response. Studies have shown that IP-10 levels are higher in patients who do not respond to IFN. Adding IP-10 to IL-28B allele testing could enhance predictability of IFN responsiveness, especially in non-CC IL-28B types.

**G&H Are there patients who should receive prophylactic therapy?**

**SN** Although this is an interesting concept, enough data support the observation that once SVR is achieved, the chance of relapse is extremely low (<1%) when using IFN-based regimens. The long-term durability of SVR in an all-oral IFN-free regimen remains to be proven. The question of need for prophylaxis can arise in the peritransplant period in patients with active HCV infection. One example in which prophylaxis might be considered would be in a patient undergoing transplant while receiving antiviral therapy because, although serum HCV RNA levels are undetectable, SVR has not been achieved. In our experience, some of these patients relapse after transplantation, especially if they have received only a few weeks of treatment. I believe we will see this type of scenario more often as non-IFN regimens become available and more widely used in decompensated patients who are awaiting liver transplantation.

Another example in which prophylaxis might be useful is in patients with detectable HCV RNA in the serum who are undergoing transplantation. In this scenario, the question is whether new agents will prevent infection of the graft. Because some of the new drugs are well tolerated and are associated with fewer drug interactions, they could be started on the day of liver transplantation and continued for a finite period after liver transplantation. Hopefully, studies will be conducted to address the value of this strategy in the near future.

Many centers now wait for the development of fibrosis before initiating antiviral therapy in patients with recurrent HCV infection. Early treatment is likely to become more common in the future when more effective and safer therapy becomes available.

**G&H What second-generation PIs look most promising?**

**SN** Simeprevir also is a NS3/4A inhibitor, but it has a better dosing schedule than similar agents and is associ-
ated with a lower risk of anemia. Hence, use of ribavirin should be easier in treatment regimens that include simeprevir. Simeprevir is also metabolized by a different pathway than telaprevir, and it is less likely to interact with tacrolimus.

**G&H What is the future for monoclonal antibodies in the prevention of recurrent HCV infection?**

**SN** Hepatitis B immunoglobulin has helped facilitate successful liver transplantations in patients with hepatitis B virus (HBV) infection since the mid-1990s; however, similar antibodies have not found much success regarding HCV infection. The role of monoclonal antibodies will be limited in the future, especially if we can achieve a close to 90–100% cure rate in the post-liver transplant setting. Also, monoclonal antibodies are unlikely to work without adding a DAA. In regard to HBV infection, the trend in recent years has been to wean patients off immunoglobulins and maintain drug prophylaxis. Unlike HBV infection, HCV infection can be cured, and it appears that a finite period of drug therapy or prophylaxis in the peritransplantation period is likely the best approach.

**G&H What forward-thinking strategies are being considered to address viral resistance with the use of the currently available PIs?**

**SN** Resistance of HCV is an important issue. Currently available PIs are not useful as single agents because of the rapid emergence of resistance. Multidrug regimens will address the concerns about resistance to a large extent, as the resistance variants to 1 drug will be susceptible to another class of drugs. Clinical trials with new NS5a, NS5b, and PI combinations have proven that drugs targeting different proteins of HCV can eradicate the virus without development of resistance. Because the new drugs are developing at a rapid pace, it is reasonable to wait for the best combination therapy rather than try single agents, especially in patients with mild disease.

**G&H In your opinion, how will use of PIs change the epidemiology of HCV?**

**SN** We know eradication of HCV will improve survival in, for instance, patients with liver cirrhosis. PIs in combination with peg-IFN and ribavirin have cured HCV infection in several of my patients with cirrhosis, thus delaying or eradicating the need for liver transplantations. Also, many of these patients have a lower risk of hepatocellular carcinoma. As we are able to cure more patients with safer and more effective therapies, we will be able to decrease the number of patients who progress to end-stage liver disease.

Current therapy is not suitable in patients with decompensated cirrhosis (ie, Child-Pugh Class B or higher). The newer IFN-free regimens are likely to be safe in these patients and hopefully will help delay the need for liver transplantation. We have seen a remarkable improvement in liver histology in patients with HBV receiving long-term therapy with oral agents; thus, it is likely that we will see a similar improvement in patients with HCV infection. It is not uncommon for decompensated patients with HBV-associated cirrhosis to improve after viral suppression. Within the next few years, such improvement may also be possible in patients with HCV infection.

The biggest concern, however, is that the vast majority of at-risk persons in the United States have not been treated or even diagnosed for HCV infection. Of the estimated 5 million persons who are HCV-seropositive, only half a million or so have received any form of treatment. The new Centers for Disease Control and Prevention recommendation of screening all persons born between 1945 and 1965 will likely lead to the diagnosis and treatment of more patients. Obviously, successful treatment of larger numbers of patients could potentially alter the prevalence of end-stage liver disease due to HCV.

**Suggested Reading**
