ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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The Future of Hepatitis C Virus Therapeutics

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G&H How have we advanced in the treatment of hepatitis C virus infection?

PK In the last quarter of 2013, we saw the approval of simeprevir (Olysio, Janssen) and sofosbuvir (Sovaldi, Gilead) for the treatment of hepatitis C virus (HCV) infection in treatment-naive patients and treatment nonresponders. Simeprevir is a nonstructural (NS) 3 protease inhibitor (PI) that has a more favorable adverse event profile than first-generation PIs telaprevir (Incivek, Vertex) and boceprevir (Victrelis, Merck). Simeprevir is associated with a minimal degree of photosensitivity but not the anemia that is seen with other PIs. It also has a more convenient dosing schedule of once instead of thrice daily. Like the first-generation PIs, simeprevir is used in combination with peginterferon and ribavirin. Its overall sustained viral response (SVR) rate has been reported to be approximately 80%. The vast majority of patients infected with genotype 1 HCV who received the drug were able to be treated for just 24 weeks, which is also an improvement over first-generation PIs. A limitation to simeprevir therapy, however, is that its efficacy is compromised in patients with the genotype 1a Q80K polymorphism. The US Food and Drug Administration (FDA) mandates that patients be assessed for the Q80K polymorphism before being prescribed simeprevir.

Sofosbuvir, a polymerase inhibitor, is the first new class of direct-acting antiviral (DAA) agents to be approved. This new polymerase class is pangenotypic, meaning that it has potent antiviral activity across all the HCV genotypes. Sofosbuvir plus ribavirin was approved for treatment of infections caused by HCV genotypes 1 through 4.

Besides representing a new class of drugs, the other very important aspect about sofosbuvir is that the duration of therapy is just 12 weeks when used in combination with peginterferon and ribavirin for treatment of genotype 1 HCV infection. The overall SVR rate is 89%, and, in the cirrhotic population infected with genotype 1 HCV, the SVR rate is 80%. Among approved therapies, these are the highest SVR rates that have been reported for genotype 1 HCV infection. Also, the 12-week treatment course is significantly shorter than the 24 to 48 weeks of treatment required by first-generation PIs.

For genotypes 2 and 3 HCV infection, sofosbuvir provides an all-oral, interferon-free regimen. Sofosbuvir plus ribavirin can be given for 12 weeks in patients infected with genotype 2 HCV but for 24 weeks for patients infected with genotype 3 HCV. SVR rates in patients infected with genotype 2 HCV are quite high—above 90%.

The group that still requires additional strategies is patients infected with genotype 3 HCV and cirrhotics who failed therapy that included peginterferon. The SVR rate after 24 weeks of treatment is only approximately 60%.

G&H How is the problem of anemia being addressed?

PK Anemia remains an issue and is attributed to peginterferon and mainly ribavirin, but ribavirin-free regimens are being developed. The combination of sofosbuvir and ledipasvir leads to high SVR rates in genotype 1a/b patients, and the addition of ribavirin did not improve SVR rates. Both ABT-450 plus ombitasvir and asunaprevir plus daclatasvir have proven to be effective ribavirin-free regimens in patients infected with genotype 1b HCV.

Ribavirin-free regimens especially would be used in anemic patients and patients who have advanced kidney disease and renal disease because ribavirin-related anemia

is magnified when the creatinine clearance or the glomerular filtration rate is lower.

G&H How well do the newly approved agents handle emergence of resistant viral strains?

PK Resistance and cross-resistance of simeprevir are similar to those of other PIs, although the response rate is high and resistance relatively low in treatment-naive patients who do not carry the genotype 1a Q80K polymorphism. As for sofosbuvir, it is a polymerase inhibitor, which is a chain terminator. This means that the mutations required to become resistant to sofosbuvir render HCV poorly fit to replicate; therefore, mutations are not able to propagate. Thus, sofosbuvir has a high barrier to resistance.

When a patient receives sofosbuvir-based therapy and does not achieve a sustained response, the patient is typically experiencing a relapse and not treatment breakthrough. If a patient relapses while receiving sofosbuvir-based therapy, preliminary data suggest that retreatment is possible with the addition of other DAAs, such as a NS5A inhibitor.

G&H Is triple therapy that includes a DAA the new treatment paradigm?

PK Triple therapy historically refers to peginterferon-based therapy with ribavirin and a DAA. By next year, this treatment strategy essentially will be obsolete. We will be evolving toward all-oral therapies that are combinations of 2 or more DAAs. Most patients will likely be successfully treated with this type of all-oral therapy.

Combinations that have been studied in phase 2 trials of patients with genotype 1 HCV infection include sofosbuvir plus ledipasvir, sofosbuvir plus simeprevir, the PI ABT-450 plus the NS5A inhibitor ombitasvir in combination with the nonnucleoside inhibitor dasabuvir, and the NS3 PI asunaprevir and the NS5A inhibitor daclatasvir. Some of these combinations have included ribavirin. All have been associated with SVR rates above 90%.

As these DAAs are approved, treatment durations are going to be shortened. The preliminary evidence suggests that some patients with mild disease might only need 8 weeks of treatment and that patients with more advanced disease (cirrhosis) may require either longer durations of therapy or a greater combination of potent DAAs.

G&H How can identifying the infected population be improved?

PK We have 2 key concerns. One concern is recognizing that a large pool of infected persons has not yet been identified. The other concern is establishing a system to efficiently identify infected persons, make the diagnosis, and offer therapy. The Centers for Disease Control and Prevention announced 2 years ago that all persons born between the years of 1945 to 1965—the at-risk birth cohort—should undergo a 1-time screening for HCV infection. Evolving strategies are needed to find the best method to identify and diagnose infected persons.

One very interesting report, delivered at last year's annual meeting of the American Association for the Study of Liver Diseases, described an emergency room in Alabama that offered 1-time screening to persons in the at-risk birth cohort during a 6- to 8-week period. The facilitators were able to provide new diagnoses with rapid onsite testing to a high percentage of patients. Approximately 11% of persons screened were positive for HCV infection. This is a novel approach because the persons who come to the emergency room often are those who are not engaged in a healthcare system. This is one strategy that gives clinicians an opportunity to identify the persons who need therapy for HCV infection.

G&H What research in HCV medicine are you particularly excited about?

PK For HCV medicine, the future essentially has arrived. We will, probably by the end of this year, have combinations of highly effective therapies that will allow us to treat the vast majority of patients infected with HCV, and therapy will be free of the limitations imposed by interferon. This is very important because many persons with chronic HCV infection have contraindications to the standard of care used for the past 15 to 20 years. The new therapies in the pipeline provide hope for HCV-infected patients with psychiatric, inflammatory, autoimmune, pulmonary, and renal disorders.

All of these patients, who previously could not take interferon-based therapies, can now be offered therapies that are associated with high SVR rates. In fact, the FDA has already approved use of sofosbuvir and ribavirin for 24 weeks in patients in whom interferon is contraindicated. This decision was based on a large study of patients with HIV/HCV coinfection. The study regimen resulted in an overall SVR rate of 76%. Furthermore, the adverse effects reported were minimal. In addition, the regimen was safe in patients with HIV who were on complicated highly active antiretroviral therapy.

Because sofosbuvir is excreted in the urine, the drug-drug interaction problems that were previously seen with older therapies are far fewer with combination sofosbuvir and ribavirin. More of these types of results will be seen as DAA combinations are studied. Once therapy is interferon-free for the majority of HCV-infected patients, the so-called special populations, such as HIV/HCV-coinfected patients, will not necessarily be so special. These patients

will be able to take therapies that provide a sustained response comparable to that of other HCV populations. The one group that remains a challenge is patients with liver cirrhosis, particularly those with advanced cirrhosis. Research is now focused on this population.

In addition, we are now able to give hope to some patients with liver cancer who are undergoing liver transplantation. Sofosbuvir plus ribavirin can be given to select patients before liver transplantation to clear HCV and prevent reinfection after liver transplantation. Patients with posttransplant HCV infection represent one of the most problematic populations. Being rid of the virus before transplantation clearly not only improves graft and patient survival but also markedly reduces the resources required to care for patients who have chronic HCV infection following liver transplantation.

Drug combinations other than those I have mentioned here are being studied now, so further reports of progress will be coming. With the rate of advancement in HCV therapeutics, we may, in the United States within the next 20 to 30 years, be able to talk about HCV infection as being part of history and not a current disease.

Dr Kwo has no relevant conflicts of interest to disclose.

Suggested Reading

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