

ADVANCES IN HCV

Current Developments in the Management of Hepatitis C Virus Infection

Interferon-Free Regimens and Direct-Acting Antiviral Agents



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G&H What attributed to the upsurge of hepatitis C infections in the latter half of the 20th century in the United States?

PP The high-risk population for hepatitis C virus (HCV) infection is the Baby Boom generation, born between 1945 and 1965. This population accounts for more than 75% of all the infected persons in the United States. This is the epidemiologic picture in our country, which is different than that in other parts of the world. High prevalence of HCV infection in the United States began in the late 1960s, which was the era of “free love” and drug experimentation in our culture. Prevalence peaked in the early to mid-1980s. Incidence of new infections began to fall when screening was instituted for potentially HIV-infected blood products. At that point, blood donors began to be screened for hepatitis B core antibody and abnormal alanine aminotransferase levels. They started to be questioned about whether they used illicit intravenous drugs, had sex with men who had sex with men, had multiple sex partners, or engaged in other high-risk behaviors. Persons who met the characteristics of being at high risk for HCV infection were excluded from being blood donors, and paid blood donorship was discontinued. The result was that the blood donation reservoirs were improved, and incidence of HCV infection began to fall. Incidence then fell dramatically with the introduction of the HCV enzyme-linked immunosorbent assay antibody test in 1992. By the late 1990s, new HCV infections became uncommon, and infections from blood products virtually disappeared.

G&H What challenges do interferon-based therapies present?

PP The challenges of interferon-based therapies are multiple. First, interferon-based therapy is inconvenient. It involves taking an injection, rather than a pill, once a week. The therapeutic course is prolonged; the average duration of therapy has been 48 weeks. The injections must be taken with pills, and the adverse effect profile of interferon-based therapy has been prohibitive for very many patients. Many patients either are not eligible for interferon because of preexisting comorbidities—which are common in this population—or patients demonstrate intolerance to the therapy.

The most common comorbidities in the Baby Boom population—persons now aged 48 to 68 years—are depression, substance abuse, obesity, and diabetes. In the United States, more than 120,000 veterans of foreign wars are infected with HCV. Most of these persons are Vietnam War veterans. These veterans actually were the surrogate population for study of HCV epidemiology in the United States, and they are the only subpopulation in the high-risk age group that has been adequately screened to date. The majority of these HCV-infected veterans have been found to be ineligible for interferon-based regimens because of 1 or another comorbidity, and, thus, they have not been treated.

Within the past 2 years, direct-acting antiviral (DAA) agents have been used in interferon-based regimens. So, although treatment strategies are changing, the contraindications and the problems associated with interferon-based therapy persist. Also, it has been

observed that, although first-generation DAAs significantly improved cure rates in genotype 1 HCV infection, they also increased the adverse effect profile. Thus, adverse effects, namely anemia and rash, were added to those that already existed. This made the therapeutic regimen more difficult for a patient to endure, although the sustained virologic response rates were improved. Although new DAAs are soon to be approved, peginterferon and ribavirin will still be required for the treatment of HCV genotype 1 infection.

The only interferon-free regimen that has been submitted for approval to the US Food and Drug Administration (FDA) is sofosbuvir (Gilead) plus ribavirin, which is for genotypes 2/3. Patients infected with HCV genotype 2 or 3 make up a relatively small population in the United States. Unfortunately, for patients with genotype 1, which is the main genotype seen in the United States, interferon-based regimens are still the only option. An advantage, however, is that the cure rate for treatment-naïve patients with genotype 1 who are treated with combination sofosbuvir, peginterferon, and ribavirin is 90%. The other advantage is that only 12 weeks of therapy is required, which is much more acceptable for patients than 48 weeks. Thus, it is a regimen that some patients, who have previously not been considered candidates because of reluctance to take long-duration therapies or because of intolerance, would now take.

G&H What are the most promising interferon-free regimens expected in the future?

PP The DAA regimen that is currently in phase 3 trials that would be closest to FDA approval is sofosbuvir plus ledipasvir, which is a nonstructural 5A protein (NS5A) inhibitor. Both agents are from Gilead. The phase 3 trials are likely to be completed this year. If all goes well, they could be submitted to the FDA for fast-track and approved by the end of 2014. The other regimen that is in phase 3 trials is more complicated but requires only 12 weeks of therapy. It is a combination of AbbVie's boosted protease inhibitor (PI) ABT-450, nonnucleoside NS5B polymerase inhibitor ABT-333, and NS5A inhibitor ABT-267. These 3 drugs have been formulated into a single pill, which would be combined with ribavirin and the nonnucleotide as an all-oral regimen. The timeline for potential approval is the same as for the sofosbuvir plus ledipasvir regimen. There are a number of all-oral regimens with timelines that are less clear, but many are already in phase 3 trials, including daclatasvir and asunaprevir with a nonnucleotide inhibitor (Bristol-Myers Squibb), faldaprevir and deleobuvir with ribavirin (Boehringer Ingelheim), and simeprevir (Janssen) and sofosbuvir with ribavirin (off-label use).

G&H How is treatment resistance being addressed?

PP Gilead has done a small study of PI failures using a combination regimen and has allowed patients who have failed prior PI therapy into its phase 3 trials of sofosbuvir. Thus, Gilead will have data on that patient population. If the regimen is effective in those who have had prior PI therapy, the regimen will be approved for such patients.

Another example of how treatment resistance is being addressed is a combination regimen using daclatasvir and sofosbuvir. This combination was studied by Dr Mark Sulkowski of Johns Hopkins University School of Medicine in Baltimore, Maryland, and the data were presented at this year's European Association for the Study of the Liver meeting. This study showed proof-of-concept that patients who had failed prior PI therapy could have an effective response with this other regimen.

As for cross-resistance, we only see cross-resistance to other PIs. Although cross-resistance from 1 PI to another is going to be seen, cross-resistance across classes from 1 PI to a nucleoside or nucleotide polymerase inhibitor is unlikely. This was demonstrated in the study by Sulkowski and colleagues.

G&H How will this new trend in therapy impact patients who are coinfecting with HIV and HCV?

PP Currently, the DAAs that are approved—telaprevir (Incivek, Vertex) and boceprevir (Victrelis, Merck Sharp & Dohme)—are not approved in HIV-infected patients. There have been studies on this topic, including one by Sulkowski and colleagues, which was recently published in the *Annals of Internal Medicine*. It showed that triple combination telaprevir regimens are effective in HIV-infected patients in some highly active antiretroviral therapy regimens. Approval for the regimen is unlikely, though, as telaprevir will soon be replaced by second-generation PIs that are given once daily and have little or no drug-drug interactions.

The new drugs sofosbuvir and simeprevir have not been studied in the phase 2 trials in any HIV/HCV coinfecting patients. However, interferon-free regimens are being studied, such as in the already mentioned phase 3 trials of sofosbuvir and ABT-450. If these studies show benefit, these drugs may get labeling for coinfecting patients. Issues may arise, though. For example, HIV drugs are often nucleoside polymerase inhibitors, and if nucleoside polymerase inhibitors for treatment of HCV infection are combined with polymerase inhibitors for treatment of HIV, hepatotoxicity or other mitochondrial toxicities could result.

G&H What impact will these new regimens have on the epidemiology of HCV infection?

PP I do not think HCV infection is going to be eradicated any time soon, but the potential is there if we have regimens that are interferon- and ribavirin-free, short, and effective in 98% of patients, including cirrhotics, nonresponders, and all the other populations, such as patients coinfecting with HIV and patients who have received liver transplant. I think it would take a decade or more to identify the entire infected population in the United States, but as word gets out that therapies are available, people will be more apt to get screened.

G&H What research are you most excited about?

PP I am most excited about using interferon-free regimens in patients with end-stage liver disease and post-transplant patients. If patients with end-stage liver disease can tolerate an oral medication, there is the potential to heal the liver and not require liver transplantation. Also posttransplant, we will no longer be dealing with the devastating effects of recurrent HCV infection. In the

realistic day-to-day practice of a hepatologist, the ability to produce liver regeneration in patients who otherwise would need liver transplantation and maintain health in patients posttransplant would be a major advance in care. Sofosbuvir and simeprevir, once available, will likely be used off-label in these difficult-to-treat patients because the regimens may be lifesaving.

Dr Pockros has received research grants and is a consultant for Gilead, Vertex, Genentech, Janssen, Boehringer Ingelheim, Bristol-Myers Squibb, and Abbott. He also is a speaker for Vertex, Merck, Genentech, Gilead, and Janssen.

Suggested Reading

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