Continuing Changes in the Hepatitis C Treatment Landscape

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The Hepatitis C virus (HCV) treatment arena continues to evolve rapidly as pharmaceutical companies race to grab shares of an extraordinarily lucrative market currently dominated by Gilead Sciences. With two drugs approved by the U.S. Food and Drug Administration (FDA) in late July, AbbVie's Technivie (ombitasvir/paritaprevir/ritonavir) and Bristol-Myers Squibb's (BMS) Daklinza (daclatasvir), certain subgroups of the hep C population have new treatment options.

Daklinza for Genotype 3

The NS5A inhibitor Daklinza was approved for use in combination with Gilead's Sovaldi (sofosbuvir) to treat genotype 3 of hep C. The first treatment ever specifically approved for this genotype, the combo offers greater success rates for individuals without cirrhosis than do therapies that have been used off-label.

An estimated 12 percent of the U.S. hep C population has genotype 3.

The FDA's approval was based on the Phase III ALLY-3 study, in which 152 people with genotype 3 took Daklinza and Sovaldi for 12 weeks. Ninety percent of those who were new to treatment (called treatment naive) and 86 percent of those who had failed a previous cure attempt (treatment experienced) achieved a sustained virologic response 12 weeks after completing therapy (SVR12, considered a cure). Ninety-six percent of those who did not have cirrhosis were cured, regardless of whether they'd been treated before. For those who did have cirrhosis the news was not so rosy: Just 63 percent were cured.

BMS has priced Daklinza at $63,000 for the recommended 12-week course; with Sovaldi's $84,000 price tag, the cost for the two-drug regimen will be a $147,000.

Kris Kowdley, MD, director of the Liver Care Network and Organ Care Research at Swedish Medical Center in Seattle, says the two-drug combination is an excellent option for genotype 3s without cirrhosis, especially since the previous standard treatment was six months of Sovaldi and ribavirin, at a cost of $168,000. Nevertheless, he expresses concerns about his ability to secure approval from patients' insurers for payment for the Daklinza/Sovaldi combination, since the cost is still quite high.

Technivie for Genotype 4

Technivie effectively comprises one of the two pills in AbbVie's Viekira Pak (ombitasvir/paritaprevir/ritonavir; dasabuvir), which was approved to treat genotype 1 in December 2014. The FDA approved the combination of Technivie and ribavirin to treat people with genotype 4 of hep C who don't have cirrhosis. This marks the first time an interferon-free regimen has been approved for this genotype.

Only about 1 percent of Americans with hep C have genotype 4.

Paritaprevir is an NS3/4A protease inhibitor, ombitasvir is an NS5A inhibitor, and ritonavir is an HIV antiretroviral, marketed under the brand name Norvir, used to boost the body's levels of the other two drugs.

Technivie costs $76,653 for the recommended 12-week course.

In the Phase IIb PEARL-1 study, the treatment cured 100 percent of 42 treatment-naive and 49 treatment-experienced participants, none of whom had cirrhosis.

Genotypes 1 and 2

The story for genotype 1 has remained constant throughout 2015. Gilead's Harvoni (ledipasvir/sofosbuvir), which was approved in October 2014, is by far the most commonly prescribed treatment, offering cure rates of 94 to 99 percent in Phase III clinical trials. Viekira Pak is much less widely used, but not because of efficacy, since it cures 95 to 100 percent of those with genotype 1. AbbVie's regimen does require taking multiple pills each day, however, while the Harvoni is a once-a-day single-tablet regimen.

As for genotype 2, the American Association for the Study of Liver Diseases (AASLD) recommends treatment-naive people take 12 weeks of Sovaldi plus ribavirin, and 16 weeks if they have cirrhosis. Sixteen or 24 weeks are recommended for treatment-experienced people with genotype 2. Treatment-naive people with genotype 2 who have little or no fibrosis have a greater than 90 percent chance of a cure with this regimen. Among treatment-experience participants in the Phase III BOSON study, 16 and 24 weeks resulted in respective 87 percent and 100 percent cure rates.

For those treatment-naive genotype 2s who can't tolerate ribavirin, the AASLD recommends 12 weeks of Daklinza and Sovaldi, which in one recent trial cured 92 percent of those new to treatment.

On the Horizon

At the end of May, Merck filed a new drug application with the FDA for approval of the fixed-dose combination tablet of the NS3/4A inhibitor grazoprevir and the NS5A replication complex inhibitor elbasvir. Merck is hoping the FDA will green light the regimen for those with genotypes 1, 4, and 6 of the virus.

The FDA previously granted breakthrough status to grazoprevir/elbasvir for the treatment of those

with genotype 1 who have end-stage kidney disease and are on dialysis, and for those with genotype 4. The breakthrough designation means the treatment gets an expedited review process from the FDA, given that it may offer a substantial improvement over existing regimens. A decision is expected by the new year.

According to Andrew H. Talal, MD, MPH, a professor of medicine and hepatologist at the State University of New York at Buffalo, success rates for grazoprevir/elbasvir "look very promising." The treatment has cured more than 90 percent of most subgroups in clinical trials.

Whether newly approved medications can grab a significant share of the hep C market, Talal thinks, on the ultimate cost of the treatments, as well as companies' ability to negotiate favorable coverage policies from insurance carriers. (This assumes that new drugs offer roughly equivalent benefits to competing therapies in terms of efficacy, side effects and treatment duration.)

Unmet Needs

With so many new hep C drugs on the market, fewer subgroups of those living with the virus are still waiting for highly effective treatment options. One notable demographic that could benefit from further drug development, Kowdley points out, are those who have experienced a viral relapse after treatment with an NS5A inhibitor, which may be an indication that these individuals' virus is resistant to that class of drug. (This is presumably a very small subset of people.) Such resistance is a potential problem when someone is looking to take today's available treatments, because almost all preferred regimens include an NS5A inhibitor. (Harvoni, Viekira Pak and Technivie all contain medications in this class; as stated, Daklinza is an NS5A inhibitor.) An alternative treatment is the combination of Sovaldi and Janssen's Olysio (simeprevir). However, the pair costs $150,000 for 12 weeks of treatment, so getting insurance to cover it may be a particular challenge. There are also new "second-generation" NS5A inhibitors in the pipeline that may prove effective for those that have previously relapsed after treatment with a drug in that class.

For a HepMag.com feature on the treatment landscape for those with genotype 1, click here.
