The 2017 Hepatitis C Treatment Pipeline

The major players in the hep C pharmaceutical market are still reaching for improved treatments, with two key approvals expected this year.

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Even as greater competition has pulled hepatitis C virus (HCV) drug prices down (at least somewhat) from scandalously stratospheric levels, a handful of pharmaceutical companies remain in feverish pursuit of more advanced HCV therapies that may help them further tap into this still lucrative market.

The current crop of preferred treatments is already highly effective, with cure rates typically in the 95 to 99 percent range, and are generally safe and well tolerated. But three main subgroups of people living with the virus may have a lower chance of a cure with today's available regimens: people with cirrhosis who were previously treated unsuccessfully with interferon-based hep C regimens, people with decompensated cirrhosis and those with genotype 3 of hep C—especially those with cirrhosis. There are also subgroups for whom no hep C treatments have been specifically approved.

Additionally, researchers are always looking to reduce the treatment time necessary to cure HCV, at the very least providing more people with the opportunity to take just eight weeks of therapy, as many with genotype 1 of hep C currently can with Gilead Sciences' blockbuster Harvoni (ledipasvir/sofosbuvir).

To follow is a review of the new drugs likely to emerge from the pipeline over the next couple of years. Click the hyperlinks for more details about any of the referenced studies.

Gilead

Since Gilead released the NS5B polymerase inhibitor Sovaldi (sofosbuvir) in December 2013, the pharmaceutical company has dominated the hep C market.

Gilead subsequently paired two additional drugs with Sovaldi to create two new single-tablet combination HCV regimens. Adding the NS5A inhibitor ledipasvir to Sovaldi created Harvoni, which was released in 2014 and is approved to treat those with genotypes 1, 4, 5 and 6 of hep C. Next, combining the pangenotypic (meaning it operates on all genotypes of HCV) NS5A inhibitor

velpatasvir with Sovaldi yielded Epclusa (sofosbuvir/velpatasvir), a regimen green-lighted in 2016. Unlike the previous two Gilead treatments, Epclusa is approved for those with all genotypes (1 through 6) of hep C. It is approved for those with or without cirrhosis, including the advanced form of the disease, decompensated cirrhosis.

Most recently, Gilead has added the pangenotypic NS3/4A inhibitor voxilaprevir to the components of Epclusa to further refine that treatment. In December 2016, the company applied for U.S. Food and Drug Administration (FDA) approval of a 12-week regimen of sofosbuvir/velpatasvir/voxilaprevir for those with all genotypes of the virus—including those without cirrhosis or with compensated cirrhosis—who have been treated previously with direct-acting antivirals (DAAs).

If given the thumbs-up, the triple-drug combination tablet would be the first once-daily single-tablet regimen approved for those who have failed a previous DAA treatment.

The FDA granted the triple combo tablet a breakthrough therapy designation for the treatment of those with genotype 1 of hep C who have failed a previous regimen containing a DAA from the NS5A inhibitor class. This designation is given to treatments that may offer a substantial improvement over currently approved therapies of serious diseases and expedites the treatment's approval process. A decision on the regimen is expected in early August.

The triple combo's FDA application is based on data from the POLARIS trials, including the Phase III POLARIS-1 and POLARIS-4 trials, each of which tested 12 weeks of the regimen among people with genotypes 1 through 6 of hep C who were previously treated with DAAs, including those who took an NS5A inhibitor. Ninety-seven percent of the participants achieved a sustained virologic response 12 weeks after completing therapy (SVR12, considered a cure).

Also backing the new drug application are the Phase III POLARIS-2 and -3 studies, which included people with cirrhosis and tested eight weeks of the triple-drug combo among first-timers to treatment. These studies saw 95 to 96 percent cure rates.

AbbVie

AbbVie currently manufactures Viekira Pak (ombitasvir/paritaprevir/ritonavir; dasabuvir), which was approved in 2014; Viekira XR (which has the same components of Viekira Pak but has simpler dosing), approved in 2016; and Technivie (ombitasvir/paritaprevir/ritonavir), approved in 2015. The components of these drugs include the NS5A inhibitor ombitasvir, the NS3/4A protease inhibitor paritaprevir, the HIV protease inhibitor Norvir (ritonavir), which is used to boost the level of other drugs, and the non-nucleoside NS5B polymerase inhibitor dasabuvir.

In February, the FDA granted priority review status to AbbVie's new drug application for the once-daily fixed-dose combination tablet of the NS3/4A protease inhibitor glecaprevir and the NS5A inhibitor pibrentasvir, known as G/P. The FDA's decision about the treatment will likely come in late June.

The FDA grants priority review, which shortens the process from 10 to six months, to therapies for serious diseases that may have safety or efficacy advantages over currently available treatments.

Unlike AbbVie's currently approved regimens, G/P is pangenotypic. Also, instead of a minimum 12 weeks of treatment, the new regimen stands to receive approval for an eight-week prescription, specifically for those without cirrhosis who have not been treated for hep C before.

The new drug application is based on eight clinical trials with a combined 2,300 participants with all genotypes of HCV, including people with chronic kidney disease. Recent results from such trials have been very promising, generally boasting cure rates of 95 percent or higher and favorable tolerability.

Among these trials are the Phase III CERTAIN-1 study of those who had genotype 1, did not have cirrhosis and were first-timers to treatment, which saw a 99 percent cure rate; the Phase II MAGELLAN-1 study of people with genotype 1 who had failed a previous treatment; the Phase II SURVEYOR-II trial of 12 or 16 weeks of G/P for those with genotype 3; and the Phase III ENDURANCE-4 trial of those with genotypes 4, 5 and 6 who did not have cirrhosis.

A recent Phase I study also found that G/P is safe to use with the HIV antiretroviral (ARV) regimens Genvoya (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide) and Triumeq (dolutegravir/abacavir/lamivudine) and that no dose adjustments are required.

Janssen

Janssen's only hep C drug on the market is Olysio (simeprevir), which was approved in 2013 and must be used in combination with Sovaldi (a pairing approved in 2014). Edged aside by Harvoni in particular, Olysio has failed to find a major niche for itself. Janssen remains behind in the development of advanced combination therapies.

In 2015, Janssen announced a partnership with Achillion to develop HCV therapies, focusing on the triple-drug treatment known as JNJ-4178, which includes Olysio, the NS5A inhibitor odalasvir and the NS5B polymerase inhibitor AL-335.

A Phase IIb trial of the JNJ-4178 regimen is testing six- and eight-week courses among those with genotypes 1, 2, 4, 5 and 6 who do not have cirrhosis, some of whom had been treated before.

Additionally, a Phase IIa trial is currently investigating six or eight weeks of odalasvir and AL-335 with or without Olysio among those with genotypes 1, 2 and 3 who had not been treated before, some of whom have cirrhosis. Interim findings presented last fall showed promising results among people with genotype 1 who did not have cirrhosis.

Investigational treatments must complete Phase III clinical trials before a pharmaceutical company can apply for approval from the FDA.

Merck

Merck's sole hep C treatment is Zepatier (elbasvir/grazoprevir), which includes the NS5A inhibitor elbasvir (50 mg) and the NS3/4A protease inhibitor grazoprevir. Zepatier was approved in 2016 to treat people with genotype 1 and 4 of hep C, including those with cirrhosis.

Merck currently has two regimens in Phase II clinical trials. Like Janssen, Merck is behind Gilead and Abbvie in getting new treatments to market .

One regimen is called MK-3682B, or MK-3 for short, which includes grazoprevir, the NS5A inhibitor ruzasvir and the HCV NS5B inhibitor uprifosbuvir (formerly MK-3682). Part B of the C-CREST 1 & 2 studies gave eight, 12 or 16 weeks of MK-3 to those with genotypes 1, 2 and 3 of hep C, some of whom had cirrhosis (some of those with genotypes 2 or 3 also received ribavirin). Cure rates were largely between 95 and 99 percent. In Part C of the C-CREST 1 & 2 studies, 16 weeks of MK-3 plus ribavirin cured almost all those who failed a previous cure attempt with other Merck regimens.

Merck is also investigating 12 weeks of treatment with a double-drug regimen of uprifosbuvir and ruzasvir plus ribavirin in a Phase II trial among those new to treatment with all genotypes of HCV, including people with cirrhosis and those coinfected with HIV.

Bristol-Myers Squibb

BMS manufactures Daklinza (daclatasvir), an NS5A inhibitor approved in 2015 that, like Olysio, must be combined with Sovaldi. The Daklinza/Sovaldi combo is approved for people with genotypes 1 and 3 of hep C.

The company has bowed out of the HCV-drug-development game.

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