The Hepatitis C Drug Pipeline Report: A Groundswell to Become a Sea Change

At the recent Conference on Retroviruses and Opportunistic Infections (CROI), researchers reveled in promising new data on forthcoming hepatitis C therapies. Shortly after, two pharmaceutical companies submitted their drugs to the FDA for approval.

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Frantic competition between the major pharmaceutical players has accelerated progress on new hepatitis C virus (HCV) therapies to a breakneck speed. At the October 2012 annual meeting of the American Association for the Study of Liver Diseases (AASLD), scientists were charged with excitement over the promise of a new paradigm in hep C treatment, one they predicted would arrive within a few years and would include simplified, all-oral, interferon-free therapies with high cure rates for broad swaths of the hep C population.

Only five months later, at the 20th Conference on Retroviruses and Opportunistic Infections (CROI) in Atlanta in March, it appeared that the revolution was even closer than earlier suspected, with predictions that game-changing combination therapies would hit the market by the second quarter of 2014.

To that end, two major players, Gilead Sciences and Medivir AB, have since announced their applications to the U.S. Food and Drug Administration (FDA) for approval of new hep C direct acting antivirals (DAAs).

The drug on the tip of everyone's tongue has been Gilead's nucleotide analogue inhibitor sofosbuvir, which boasts a thus-far unbeatable track record in clinical trials, most notably when it has been paired with another antiviral. First there were the promising results of its combination with Bristol-Myers Squibb's NS5A inhibitor daclatasvir. To much controversy, Gilead has declined to further study the combination in favor of pursuing a cocktail with its own NS5A inhibitor, ledipasvir. In a small study presented at CROI, the two drugs achieved 100 percent cure rates when taken with ribavirin. Two Phase III trials of sofosbuvir combined with ledipasvir, both with and without ribavirin, are underway.

"Essentially there has been no drug resistance" to sofosbuvir, says Daniel Fierer, MD, an assistant professor of medicine in infectious diseases at Mount Sinai School of Medicine in New York City. "It's as bulletproof a drug as you can get, and that is so rare. It's one pill, once a day; it's

incredibly potent; and there's no drug resistance. It's almost like, 'Pinch me, I'm dreaming.' No drug is that good, but this one seems to be that good."

While Gilead anticipates a regulatory filing for the fixed dose combination of sofosbuvir and ledipasvir by mid-2014, on April 8, the company announced it had submitted data from four Phase III studies of sofosbuvir to the FDA. If approved, the drug is poised to become a component, with ribavirin, of the first interferon-free, all-oral therapy, although only for genotypes 2 and 3 of the virus. Meanwhile, treatment for genotypes 1, 4, 5 and 6 will still require interferon, which often comes with flu-like side effects, although it will be taken for shorter durations. That said, sofosbuvir would slash the standard time of therapy from the current 24 to 48 weeks to only 12 to 16 weeks.

"It's pretty clear that sofosbuvir plus ribavirin alone, without interferon, is not adequate for people who have genotype 1, which is most of the people we see," says Kristen Marks, MD, a hep C clinician and researcher at Weill Cornell Medical College in New York. But she says the early data on its combination with ledipasvir and ribavirin shows promise for an excellent way to do away with interferon.

Meanwhile, Medivir AB announced March 28 that it had submitted the investigational NS3/4A protease inhibitor simeprevir, jointly developed with Janssen Pharmaceuticals, to the FDA for approval. Unlike sofosbuvir, however, the drug would only be approved for use with interferon across all genotypes, plus ribavirin.

Simeprevir also made waves at CROI. The drug was paired with sofosbuvir in an all-oral, interferon-free Phase IIa trial. Administered with ribavirin, the drugs were given to those with genotype 1 of the virus who had failed a previous treatment (null responders)—the most difficult to treat group—and who had mild to moderate fibrosis of the liver. Among three arms of the study, cure rates in an interim analysis ranged between 93 and 100 percent, although a fourth arm only cured two-thirds of the participants.

FDA approval for simeprevir, however, may not mean the drug will be put into wide use—especially if sofosbuvir eclipses other drug options as part of a blockbuster combination pill with ledipasvir. Physicians could prescribe simeprevir and sofosbuvir in combination, but they would have to do so off-label, since the FDA won't have approved them for use as a cocktail.

In fact, the issue of prescribing off-label combos to treat hep C is already on the radar for some doctors. Referring to simeprevir and Boehringer Ingelheim's NS3/4A protease inhibitor faldaprevir, which is also one of the major up-and-coming drugs, Fierer said, "Obviously they're really good drugs for what they are. But since we don't know if we can use them in combination with the other thing that's [coming] out, which is sofosbuvir, I am not going to be treating anybody with these new drugs. I'm going to sit on them. Because you're going to risk drug resistance in a quarter of them. I'm urging waiting in anybody who can wait—even people who have cirrhosis."

Those who do wait might have yet another treatment option: the NS3/4A protease inhibitor

ABT-450 by AbbVie (formerly Abbott). Attendees at CROI heard news of its recent trial in combination with ribavirin and Norvir (ritonavir) and either ABT-072 or ABT-333 for 12 weeks of therapy. Between 86 and 91 percent of the various configurations achieved an SVR, except for previous partial or null responders, of which only 47 percent were cured this time around.

Promise for the HIV-Hep C Coinfected Population

One of the subgroups of the hep C population that has been waiting for findings from research in the clinical trials of new DAAs is those who are coinfected with HIV. CROI had a good deal to offer in the form of hope that this group may soon have broadened treatment options. Also, pharmaceutical companies are more diligently studying how hep C drugs work in combination with the most common HIV ARVs than they did in preparation for the release of the current available therapies.

“I think as soon as interferon leaves the treatment paradigm for hepatitis C, HIV providers are going to be treating hepatitis C in both mono- and coinfected patients,” predicts Douglas Dieterich, MD, a professor of medicine at Mount Sinai.

In the meantime, Dieterich for one is still studying therapies that include interferon. He presented data from two studies in coinfected patients, one with simeprevir and another with faldaprevir.

Simeprevir, paired with pegylated interferon and ribavirin, cured between 75 and 90 percent of coinfected study participants with genotype 1 of hep C.

Faldaprevir was studied in combination with pegylated interferon and ribavirin among genotype 1 coinfected participants who either had not previously attempted treatment or had relapsed after previous hep C therapy. The study helped fill in a significant gap in scientific knowledge about drug-drug interactions between faldaprevir and the HIV antiretrovirals (ARVs) Prezista (darunavir) boosted with ritonavir, Sustiva (efavirenz) and Viread (tenofovir, which is a component of various ARV cocktails).

These hep C and HIV drugs proved safe in combination, although faldaprevir levels increased about 130 percent when paired with Prezista and dropped about 35 percent in combination with Sustiva. Preliminary results were promising, with 77 percent of the treatment-naive participants and 88 percent of those who had relapsed on a previous therapy clearing the virus early in the course of treatment.

Investigating a drug already on the market, Fierer conducted a study of Incivek (telaprevir) and found that adding the protease inhibitor to the standard regimen of pegylated interferon and ribavirin both improved the cure rate and cut in half the treatment time for acute hepatitis C infection (given within six months of their first elevated liver enzymes) among HIV-positive men.

“It’s not a big study, but it’s enough to be proof of principle that people who are experienced in treating acute infections and recognizing it can feel confident in using this [therapy],” Fierer said.

For the entire population of people with hepatitis C, CROI provided much reason for hope, especially if future research is conducted in a way that provides insights into safe and effective treatments for those who need them most.

“I think people are extremely positive, but still, I think there are still a lot of groups that we need to see data for,” says Marks, pointing to harder-to-treat cross-sections of the hep C populations that were largely excluded from earlier phases of drug trials, including null-responders, those with cirrhosis and those who have had or who need liver transplants.

“Overall, I think there’s tremendous enthusiasm,” she says. “I definitely think it’s the right time to test people for hepatitis C, because you can link them to care. And as they’re sort of learning about hepatitis C, you can educate them about what’s coming and prepare them for treatment. Soon there are going to be great options, I think, for everybody.”

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