TuSalud

The Pipeline: Waiting on the Promise of an Interferon-free Future

New hep C drugs are likely hitting the market in the very near future. But how long until interferon can be sent packing?

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In 2014, as the Affordable Care Act becomes the law of the land and a massive expansion of access to health insurance finally unrolls, another revolution in medical care promises to transform the treatment options for people living with hepatitis C. The current standard of care—one of the two approved protease inhibitors, plus ribavirin and the notorious interferon, with its flu-like side effects—will fall by the wayside. In its place will come simpler, shorter, far more easily tolerated regimens that boast much higher cure rates.

The end of this year will kick off a one- to two-year period during which as many as 10 new hep C drugs will likely hit the market. These promising medications, which have been causing much commotion at medical meetings over the past couple of years, will raise the current average cure rate of 50 to 75 percent to over 90 percent in many cases. They will also cut the current treatment time of 24 to 48 weeks down to as short as 8 to 12 weeks.

Most important, the era of the all-oral, interferon-free drug regimens will begin. However, this shift will not take place in one fell swoop. One of the complexities of conducting research on hep C therapies is that the population of those living with the virus is fractured into various subgroups, each with its own needs and its own reactions to treatment. First there are the different genotypes of the virus, then there are the particulars of the IL28B gene. Those who have failed a previous treatment attempt, called “null-responders,” represent their own unique challenges, as do people with varying ranges of liver disease, from mild fibrosis on up to cirrhosis, liver cancer and transplantation. And of course there is the thorny and pervasive matter of those who are coinfected with HIV.

Many argue the drug to beat is likely Gilead Sciences’ sofosbuvir. The nucleotide analogue inhibitor has boasted top-notch cure rates in its various trials, particularly when used in combination with other hep C drugs. With a likely approval from the U.S. Food and Drug Administration (FDA) by December 8, sofosbuvir will open the doors for those with genotypes 2 and 3 of the hep virus to receive interferon-free, all-oral therapy, along with ribavirin. As for those with genotypes 1, 4, 5 and 6, they will still have to include interferon in a sofosbuvir-based

treatment regimen until Gilead completes its research combining the drug with its NS5A inhibitor, ledipasvir. Current Phase III studies are examining the two therapies in a fixed-dose combination pill among participants with genotype 1, including those who have cirrhosis. Pending the study results, the company anticipates filing for FDA approval for the combination therapy in the first half of 2014.

Because the FDA approval process takes 12 months—eight under a priority review—all-oral, interferon-free regimens for those with genotype 1, the most difficult to treat, will most likely have to wait until the end of 2014. In the meantime, there may be opportunities for this group to enroll in clinical trials that will afford them earlier access to these combination therapies.

Then there is Janssen and Medivir's protease inhibitor simeprevir, which will likely receive FDA approval by late November. The drug will only be indicated for those with genotype 1 who have compensated liver disease (an earlier stage of liver disease), given in combination with ribavirin and interferon. However, earlier Phase II research of the drug in combination with sofosbuvir, among genotype 1 null responders who had mild to moderate fibrosis, demonstrated cure rates between 93 and 100 percent. For those who are in more urgent need of treatment and who can't wait a year or so, physicians may prescribe the two drugs off label, using the Phase II research as a guideline.

"I think the question there is, who's going to use those together off label?" says Michael Ninburg, executive director of Hepatitis Education Project in Seattle. "My guess would be only relatively sophisticated providers, and it would really only be necessary for folks who are at very advanced disease. Because if you are genotype 1, even if you're bridging fibrosis, you can probably wait eight months, 12 months, whatever it is, before these all-oral regimens are approved."

Another drug that has been studied in combination with sofosbuvir to great success is Bristol-Myers Squibb's NS5A inhibitor daclatasvir. BMS is currently completing Phase III trials of an interferon-free regimen of that drug with the company's NS3 protease inhibitor, asunaprevir, in people with genotype 1b. Also, a recent Phase II trial of those two drugs in combination with the polymerase inhibitor BMS-791325 cured about 90 percent of study participants with genotype 1. The company hopes to file for FDA approval of daclatasvir and asunaprevir in the first half of 2014.

AbbVie's triple drug combination also has the potential to be a major player, possibly besting a sofosbuvir-based regimen. The company is in the middle of a Phase III program investigating the protease inhibitor ABT-450 (which is "boosted" with ritonavir) and the NS5a inhibitor ABT-267 coformulated into a single, daily pill, plus the polymerase inhibitor ABT-333 in a single pill taken twice daily, either with or without ribavirin. Results from the collection of six studies, which include participants with genotype 1, are expected to arrive by late fall or early winter, followed by a regulatory filing in the second quarter of next year. In May 2013, the FDA designated the regimen as a "breakthrough therapy," which should expedite the review process. AbbVie is also currently conducting Phase II studies of the regimen among those with genotypes 2, 3 and 4.

Boehringer Ingelheim is attempting to build various combination therapies around its protease

inhibitor faldaprevir. The company has fully enrolled Phase III trials of the drug in combination with its non-nucleoside inhibitor, deleobuvir, and ribavirin. The company anticipates wrapping up this research by early to mid-2014. BI is also conducting Phase II trials of those two drugs in partnership with Presidio Pharmaceuticals' pan-genotypic NS5A inhibitor PPI-668, both with and without ribavirin.

Peter Piliero, MD, vice president of clinical development and medical affairs at BI, says that the diverse demands of the hep C population are driving the pharmaceutical industry to conduct research in correspondingly multifaceted patient populations. The result should be brighter future for many of those with harder-to-treat cases of hepatitis C.

"I feel like drug developers, other companies, including ours, are really trying to study a broad range of patient subgroups," Piliero says. "For example, null responders, co-infected—I think we're seeing those populations being studied because there's a real need to develop effective therapies for these groups as well."

Eric Hughes, MD, PhD, who is responsible for many of the late-stage hep C trials at BMS, says of his company's research, "We included people who traditionally have been excluded from studies in the past. We went specifically for the people who would benefit from the all-oral treatments."

"All pharmaceutical companies aren't the same," Ninburg says. "But I've definitely seen an effort on the part of most of the companies that are developing drugs to really try and be sensitive and inclusive of some of these populations that have been historically not included."

However, several notable subgroups will likely have to wait longer before interferon-free regimens are approved for their use. Studies will have to carefully ascertain the potential drug-drug interactions for those who are coinfected with HIV or who take immunosuppressants to prevent organ transplant rejection. Active drug users have also lacked a notable presence in much of the research.

People with advanced liver disease face a particularly urgent treatment conundrum. Blaire E. Burman, MD, a gastroenterology and hepatology fellow at the University of California, San Francisco, says the all-orals "should be used in the patients who need them the most"—specifically, those with cirrhosis or decompensated liver disease. "But that's the group we know the least about in terms of the safety of these medications," she says, because those with advanced liver disease have often been excluded from research in significant enough numbers.

As to which drugs will sink or swim in this fiercely competitive market, whoever assembles the most effective in-house combination therapy may assume a significant market share, particularly with a coformulated single pill, as Gilead is developing. However, cost will likely also play a major factor. Ninburg in particular perceives a scenario in which the drug companies that are comparatively behind in their drug development process may attempt to undercut Gilead and AbbVie on price in an effort to appeal more to insurance companies.

Once all these drugs are in the pharmacies and prescribed widely, a new period of fact-finding will help hone their use.

“The most information we gain is sort of the year after approval, when we really start to use these in practice,” Burman says—indicating, for example, that real-life clinical experience will likely provide key information about how best to treat those with advanced liver disease. “I think that’ll be interesting, and it’s hard to predict.”

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