Dispatches From the Front: Hep C To Waive the White Flag

A recent liver conference made it more clear than ever that the means to blow hepatitis C off the map is just within reach.

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You could call the numerous pharmaceutical companies developing hepatitis C drugs the allied forces, lining up their arsenals at the front, ready for a massive showdown against a doomed viral axis. That is, if the companies weren't all so competitive against one another to claim the ultimate victory title as the holder of the most powerful, far-reaching series of weapons. At stake is billions of dollars in drug sales, not to mention the chance to cure millions of people worldwide who are infected with a virus that can lead to progressive liver disease, liver cancer, transplants and death.

At the 64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD) in Washington, DC, in early November, Big Pharma put on its best show to both grab the headlines and give greater focus to exactly how the treatment landscape is likely to change as the new generation of game-changing direct-acting antivirals are released over the course of the next couple of years.

"It was incredibly upbeat," Douglas Dieterich, MD, a professor of medicine in liver diseases at Mount Sinai Hospital in New York City, says of the hepatic symposium. "It was wild, actually. All the good news, it was just all over the place. The enthusiasm was unbridled."

Both Gilead Sciences' nucleotide analogue inhibitor sofosbuvir—widely considered the leader of the pack, especially come the likely approval in late 2014 of a tablet coformulated with the company's NS5A inhibitor ledipasvir—as well as Janssen's NS3/4A protease inhibitor simeprevir are in line to receive U.S. Food and Drug Administration (FDA) approval in the next few weeks. Clinicians may prefer to warehouse the vast majority of their hepatitis C patients until the FDA approves combination therapies, such as sofosbuvir and ledipasvir, that ditch interferon and its notorious flu-like side effects and that have very high cure rates. But for those in more urgent need of treatment, AASLD provided important information on likely outcomes with both simeprevir and sofosbuvir.

AbbVie, Bristol-Myers Squibb, Boehringer Ingelheim and Merck are nipping at Gilead's heels, each of them developing combination therapies that boasted 90 percent-plus cure rates in studies

announced at the conference. The conference also gave liver specialists the first look at promising research into treatment outcomes for pre- and post-transplant people with hep C. Further studies have provided much-needed information about the use of therapy in particularly hard-to-treat groups, including those coinfected with HIV and people with advanced liver disease.

Companies have levied considerable heft to develop effective therapies for genotype 1 of hepatitis C in particular; it is the most common form in the United States and the most difficult to treat. Janssen's Phase III QUEST-1, QUEST-2 and PROMISE studies treated this group with simeprevir, pegylated interferon and ribavirin for 12 weeks, an interval which is fast becoming the new gold standard treatment length across the industry. Eighty percent of treatment-naive study participants and 79 percent of those who had relapsed after a previous treatment attempt achieved a sustained virologic response 12 weeks after completing therapy (SVR12, considered a cure). This is an improvement over an average cure rate of about 70 percent with the currently available therapies, Incivek (telaprevir) and Victrelis (boceprevir), which must be taken for 24 to 48 weeks.

Dismissing talk that sofosbuvir will ultimately eclipse simeprevir, Gaston Picchio, PhD, Janssen's hepatitis disease area leader, stresses the longevity of the hep C fight ahead.

"People think that as soon as the first single-tablet, fixed-dose combination comes out everyone that needs to be treated will be treated. And then from a business opportunity, even from a public health opportunity, the problem is gone," he says.

Instead, he says, parent company Johnson & Johnson's global reach will open opportunities over the next 15 to 20 years of tackling the disease around the world. Furthermore, Janssen recently acquired an NS5A inhibitor from GlaxoSmithKline and is collaborating with BMS, Gilead and Vertex on research into combinations with those companies' drugs.

If approved by the FDA, sofosbuvir will be licensed for use without interferon among those with genotypes 2 and 3 of hep C (the approval would still dictate interferon use with the other genotypes). Gilead's Phase III VALENCE trial of sofosbuvir and ribavirin cured an average of 93 percent of those with genotype 2 and 85 percent of those with genotype 3 after a respective 12 and 24 weeks of treatment. Treatment-experienced genotype 3s with cirrhosis faired much worse than the other subcategories in the trial, however, achieving a cure rate of just 60 percent.

The Phase IIa COSMOS trial provided key information for physicians looking to prescribe interferon-free therapies off-label as soon as sofosbuvir and simeprevir hit the shelves. Twelve or 24 weeks of simeprevir and sofosbuvir, either with or without ribavirin, for the most part yielded cures in the mid-90 percent range in various study groups with genotype 1, which included both treatment-naive participants and null responders to previous treatment. The participants had liver disease ranging in severity from non-existent up to compensated cirrhosis.

Dieterich says he is eager to treat many of his patients with the simeprevir and sofosbuvir combo, and that he may use what's known as a "ladder protocol," in which he adds lower-dose interferon

to the mix in sicker, harder-to-treat patients.

Meanwhile, Ype de Jong, MD, PhD, a visiting clinical fellow in the laboratory of virology and infectious disease at The Rockefeller University in New York City, says, “I would love to start sofosbuvir/simeprevir with a lot of my patients, but I think we’re going to run into a lot of trouble with getting reimbursed for the drugs.” With no specific FDA approval and a lack of any Phase III trial data for the combo, he says, insurers may be reluctant to go out on a limb and pay for the medications, which are likely to come with a tremendous price tag.

For the lion’s share of his hep C patients, however, de Jong says he will hold out until late 2014 or early 2015 for the approval of an NS5A inhibitor—in particular BMS’s daclatasvir or Gilead’s ledipasvir—which will open the door for interferon- and ribavirin-free combinations with near-perfect cure rates.

Dieterich described the results of the Phase II LONESTAR study of the sofosbuvir and ledipasvir combination pill, with or without ribavirin, as “astonishing”: a 97 percent cure rate among those with genotype 1 of the virus after eight or 12 weeks of treatment. Meanwhile, the Phase II ELECTRON study of the two drugs plus either ribavirin or the non-nucleoside polymerase inhibitor GS-9669 cured 100 percent of hard-to-treat study participants who had failed previous treatment and had advanced liver fibrosis or cirrhosis.

Making another strong showing was AbbVie, with its Phase IIb PEARL-1 trial, which cured 90 to 95 percent of participants with genotype 1b of the virus through a combination of the NS3/4A protease inhibitor ABT-450/r, which is co-dosed with low-dose ritonavir, and the NS5A inhibitor ABT-267. The company has fully enrolled its sprawling Phase III program, which includes more than 2,300 participants in 25 countries and will research a coformulated pill of ABT-450/r and ABT-267 in combination with the non-nucleoside polymerase inhibitor ABT-333 and ribavirin for 12 weeks of treatment (except for one group of cirrhotic participants that will receive 24 weeks of therapy).

Downplaying any concerns that pill burden may play against AbbVie’s fortunes when going face-to-face with Gilead’s single-pill coformulated powerhouse, Barry Bernstein, MD, who heads up AbbVie’s hep C drug development program, says, “We think we’ll be very competitive from what we consider to be the most important attribute of the regimen, and that’s SVR rates.” Pill burden, he points out, has not appeared to drag on the success of the AbbVie drugs.

Not to be outdone, BMS announced at AASLD that the company had filed for the world’s first all-oral, interferon- and ribavirin-free regulatory approval in Japan. The filing was based on a Phase III study that cured 80 to 87 percent of genotype 1b’s after 24 weeks of treatment with daclatasvir and the NS3 protease inhibitor asunaprevir. In another Phase IIb trial, the dual combination therapy plus the NS5B polymerase inhibitor BMS-791325 cured 92 percent of treatment-naive participants with genotypes 1a or 1b.

Eric A. Hughes, MD, PhD, who directs BMS’s hep C clinical development unit, says the ribavirin-free

status of the company's combination therapies helps maintain their competitiveness. In addition, he says, daclatasvir, asunaprevir and BMS-791325 will be studied as a coformulated pill in Phase III studies.

As a dark horse in the running, Merck showed an impressive 96 to 100 percent cure rate in interim data from Phase II trial of treatment-naive genotype 1a's and 1b's with less advanced liver disease taking the NS3/4A protease inhibitor MK-5172 and the NS5A inhibitor MK-8742 with or without ribavirin for 12 weeks.

All the Byzantine complexity of this vast army of players and their numerous, overlapping means of attacking hepatitis C aside, Ype de Jong sees the matter relatively simply:

"It just seems that that combination of sofosbuvir with an NS5A is going to treat everyone almost," he says. "And we just have to fine-tune in the coming year what duration [of therapy] cirrhotics or advanced fibrotics really need. But I am optimistic that it's going to be over soon."
