You Say You Want a Revolution?

The hepatitis C pipeline: huge changes on the horizon

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Hepatitis C: Prepare to meet your match. The future is almost here.

This is the resounding message that thrilled the hep C medical and advocacy community throughout the mid-November annual meeting of the American Academy for the Study of Liver Diseases (AASLD) in Boston. Study after hopeful study showed that the pharmaceutical industry is poised to revolutionize hepatitis C virus (HCV) care over the coming years and begin to truly turn the tide in the battle against this notoriously difficult to treat chronic infection.

Tracy Swan, hepatitis/HIV project director at Treatment Action Group and one of the nation's leading hep C activists, says the meeting "was completely exciting," thanks to what she describes as a "blossoming cornucopia of drug development."

"It's also overwhelming because there's so much going on on so many levels," she says.

Those levels include a host of powerful direct acting antiviral (DAA) combination therapies in the pipeline that require shorter durations than the current standard of care and which have shown sustained virologic response (SVR, considered a cure) rates above 90 percent, with some even approaching 100 percent for certain segments of the population living with HCV.

The real clincher: These drugs don't need to be taken with interferon, meaning people taking hep C therapy won't have to endure that drug's often intolerable flu-like side effects, although many will still have to cope with headaches, nausea or skin rashes. Some treatment paradigms are able to cast aside ribavirin as well, which comes with its own host of adverse reactions.

The promising news extends even to harder-to-treat people with hep C—for example, those with genotype 1a of the virus, which is common in the United States. Recent clinical trials have provided information about how to better tailor therapies to various subtleties and complexities of individual cases of hep C, such as according to a person's genotype or whether he or she previously failed therapy (known as being a "null responder").

"We're getting to a point in time where [treatment] is going to be so personalized that for some [groups of] people it is going to be a 100 percent cure in 12 weeks," said Lorren Sandt, executive

director of the Caring Ambassadors Program in Oregon City, Oregon, who serves on the Hepatitis Community Advisory Board consulting on HCV therapy study design.

This is a stunning advancement in the field of hep C treatment considering that the current gold standard of therapy, a protease inhibitor in combination with interferon and ribavirin, must be taken for 48 weeks and leads to a cure in less than half of all cases.

“I think the hep C landscape will be dramatically different in four to five years,” says Kris Kowdley, MD, a clinical professor of medicine at the University of Washington in Seattle and the principal investigator of Abbott’s AVIATOR study, which made major headlines at the AASLD conference for its 90 percent-plus cure rates among people treated with a triple cocktail of DAAs plus ribavirin.

Kowdley says he anticipates incremental medical progress in the years leading up to that time. First, the “second generation” DAAs will come to market, bringing improved tolerability, lowered pill burden and reduced dosing frequency. These new drugs will likely have a high barrier to resistance, cause very few side effects and be effective more broadly across different genotypes of hep C. Also, the amount of time during which interferon must be a component of therapy may be shortened.

Finally, Kowdley sees a new era when clinicians such as himself can prescribe highly potent, completely interferon-free therapies of multiple DAAs taken with ribavirin.

Highlights of the AASLD conference include:

- Abbott’s interferon-free, three drug DAA regimen—ABT-450, ABT-333 and ABT-267—paired with ribavirin, led to a 93 percent SVR rate among null-responders and cured 97 percent of treatment-naive patients in just 12 weeks. Without ribavirin, the SVR rate was a still-robust 87 percent among those who had not previously taken hep C therapy. Abbott announced that its Phase III trials of the three compounds with and without ribavirin will include more than 2,000 patients with hep C genotype 1 from 29 countries. The study will aslo include participants with cirrhosis, who will all take the drugs with ribavirin.
- Bristol-Myers Squibb’s (BMS) daclatasvir and Gilead Sciences’ sofosbuvir boasted cure rates of 93 percent in hard to treat patients. A small study of daclatasvir combined with asunaprevir and BMS-791325, with treatments lasting 12 or 24 weeks, achieved an SVR of 94 percent among treatment naïve patients with genotype 1.
- A small study of sofosbuvir along with GS-5885 cured 100 percent of study participants after 12 weeks. Gilead has just begun a Phase III study of sofosbuvir and GS-5885, both with and without

ribavirin, for 12- and 24-week periods among genotype 1 patients. Twenty percent of the 800-patient study participants have evidence of cirrhosis.

TAG's Tracy Swan cautions, however, "Things never look as good in real life as they do in a clinical trial." She feels the AASLD data was especially rosy because researchers "cherry-picked" their study populations in favor of those who would bring the best results and lead to the kind of scene-stealing moments Abbott, BMS and Gilead enjoyed at the conference.

"So now it's gotten to the point where they have to get real," Swan says.

Getting real means the current study designs will include more participants with cirrhosis or transplanted livers, more previous null-responders and, perhaps most critically, patients coinfected with HIV. People with HIV experience drastically lowered chances of achieving an SVR with the current available therapies, and the complexities of taking hep C therapies in combination with HIV antiretrovirals is a tangled web that will require careful research.

"They're not moving as quickly as we'd like," said Swan of the major pharmaceutical companies' hep C therapy research in difficult to treat populations. "But nonetheless they're moving into coinfected people—and really into some of the groups that need [therapy] the most."

"For the most part we're pleased," said Sandt about the clinical trial designs she's consulted about. "A lot of the companies are really looking to try to do studies in not the typical avenue of a university. They're trying to do studies in more community-based clinics that don't normally do clinical trials so that they can enroll more real-world patients."

"Our plan is basically to come up with therapies that will meet critical unmet needs in these patient populations," says Steve Schnittman, MD, global development lead for HCV antivirals at BMS. "Obviously, we're approaching pretty good therapies. They key is to get all once-a-day therapies that can be applied in a fixed-dose combination with minimal interactions. We're not all quite there yet, but we're getting darn close."

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