# Going Off-Label: Prescribing Hepatitis C Medications Outside of FDA Guidelines

Balancing the complexities—and sometimes urgency—of hepatitis C treatment with the available research (or lack thereof) on safety, efficacy and drug-drug interactions is a delicate science for physicians treating patients who also have HIV, advanced liver disease or other major health challenges

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Hepatitis C is not one to exist in a vacuum. Rather, the virus is often linked with other major comorbidities, such as HIV coinfection, a past liver transplant, improperly functioning kidneys and decompensated cirrhosis, which is an advanced form of liver disease.

And yet the two currently available direct-acting antiviral (DAA) medications to treat hep C—the protease inhibitors (PIs) Incivek (telaprevir) and Victrelis (boceprevir)—are only approved by the U.S. Food and Drug Administration (FDA) to treat monoinfected people with hepatitis C and those who have the milder, earlier form of liver disease, compensated cirrhosis. Furthermore, the drugs are only indicated for people with genotype 1 of the virus (although the other genotypes are actually easier to treat).

Once a drug is FDA-approved in the United States, physicians are at their discretion to use it "off-label," for purposes that fall outside of those that pharmaceutical companies researched thoroughly enough to submit to the FDA, and which then gained the agency's approval.

"As physicians, we can use whatever we want," said Andrew Aronsohn, MD, an assistant professor of medicine at the University of Chicago Medical Center, adding that if a drug is off-label, "we don't have the FDA backing us on it,"

In the fast-changing and increasingly complex field of hepatitis C virus (HCV) treatment, this means health providers must rely more heavily on other medical research about the myriad health challenges and associated medications that, when combined with hep C therapy, may lead to serious adverse effects.

The result will be a medical game of chess for the coming years as the numerous second generation DAAs begin to hit the market—probably in 2014—but while further research into their use in various subcategories of patients lags behind for months, or even years.

Andrew Muir, MD, a hepatologist at Duke University, cowrote an essay with Aronsohn in the journal Gastroenterology about the direction of HCV treatment in which they expressed concern about the safety of off-label prescribing. Muir feels that the research into the current DAAs has been sufficient, but that the lag time between their release and the point when there was enough additional safety research has "led to an appreciation that the drug-drug interactions studies need to be done sooner."

Aronsohn says, "It's going to become easier and easier to treat monoinfected patients who are otherwise healthy," but he expresses concern that "there's a growing number of underserved populations," including coinfected people and those with kidney failure and decompensated cirrhosis, for whom treatment will remain a challenge.

Various pharmaceutical representatives, including those from Merck, Gilead Sciences and Bristol-Myers Squibb, declined to comment on off-label practices beyond expressing that physicians have leeway to prescribe as they see fit, but that the companies themselves only make recommendations that the drug be used according to the FDA-approved label.

Tracy Swan, the hepatitis/HIV project director at Treatment Action Group, categorized the current rush to bring new hep C drugs to market as "a highly capitalized space with incredible amounts of competition" between pharmaceutical companies. "And that's not fostering good sciences. It's not fostering drug development in a way that's truly responsible."

Muir, in contrast, says he is glad to find that pharmaceutical companies are indeed studying the newer therapies in HIV coinfected patients and those with advanced liver disease as the companies prepare for FDA approval among monoinfected people with hep C.

"I think we're probably doing a better job with the second generation of looking at some of these patients [with comorbidities] and trying to anticipate what some of the off-label indications are going to be and to study those ahead of time," Muir said. "In the first generation we were just trying to get the drugs out there so people could use them."

Just the same, Swan laments that, as of yet, there is still only one interferon-free hep C drug trial open to people coinfected with HIV. "We need more interferon-free trials in coinfected people," she says, "and in mono- and coinfected people with cirrhosis."

Once the drugs do hit the market, Muir says, it may be up to the medical team to remain vigilant when treating more complex cases. Health providers, he says, will need to educate themselves as much as possible about how to best care for their patients, and will also need to alert the FDA or other registries when drug-drug interactions or other adverse effects occur in their clinical practice.

"I don't think there's an easy answer there," as to how such education will occur, Muir says, pointing to various physicians' societies, such as the American Academy for the Study of Liver Diseases (AASLD) that have historically led the way in these efforts. Swan, for one, expressed her

frustration that the hep C community lacks an equivalent to the AIDS Clinical Trials Group Network, which is a clearinghouse for HIV research.

Another form of off-label prescribing in hepatitis C treatment that will be a major issue in the coming years will be when the DAAs are used in combination with one another when the FDA has only approved them as individual therapies, or perhaps when they're used in combination with a different drug. Gilead Sciences has rankled many in the hep C advocacy community by declining to further study its antiviral sofosbuvir along with Bristol-Myers Squibb's daclatasvir—a combination that cured more than 90 percent of the study population in a Phase II trial announced at the AASLD conference last October. Instead, Gilead is studying sofosbuvir with its own ledipasvir in Phase III trials, in hopes of striking gold with an FDA approval for a single-pill combination therapy.

'It's a shame Gilead is refusing to do the trial," Swan says. "I think it's costing them so much in good will that they should just do another trial. But they probably won't because they don't have to."

Nevertheless, physicians may still opt to go off-label and pair sofosbuvir with daclatasvir in the event that both are FDA approved as individual therapies. There will be some guesswork involved in more complex cases since, while there will be data on how each drug works in people with HIV and in those with cirrhosis, the drugs will have only been studied as a combination in HIV-negative people without cirrhosis.

The larger issue for prescribing combinations off label, however, is likely to be whether insurers will reimburse for multiple drugs that haven't received FDA approval as a combination therapy.

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