Do Interferon-Free Hep C Treatments Have Side Effects?

With interferon quickly becoming a thing of the past, what kind of side effects still remain in the new hepatitis C regimens—and how do you remedy them?

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Interferon, long a mainstay of hepatitis C virus (HCV) treatment, is currently singing its swan song. As the loathed weekly injectable drug finally makes an exit, it will take along with it a host of flu-like side effects that have made attempts to cure hep C a misery and kept droves of people who are living with the virus from even trying.

But what about side effects that still remain in interferon-free hep C therapies? No drug is without its risks and "potential adverse events," to borrow the term used in medical journals.

Kris Kowdley, MD, a clinical professor of medicine at the University of Washington in Seattle, who has been involved with much of the research of the forthcoming crop of drugs and who has treated a host of patients with the current therapies, says that the outlook is quite rosy for those considering the two currently available interferon-free therapies as well as the combination regimens likely to be approved at the end of the year.

"Essentially the side effects, when you compare them to the first-generation protease inhibitors—boceprevir [Victrelis], telaprevir [Incivek]—the side effects are negligible with any of these new treatments," Kowdley says.

The main adverse event culprit, according to Kowdley, is ribavirin, a drug that may not be required for some of the upcoming regimens. But even the effects of ribavirin aren't so much of a problem for people undergoing treatment and are pretty easily managed. And overall the crop of drugs waiting in the wings has proved quite tolerable—to wit, relatively few participants in clinical trials for the new drugs wound up dropping out because of side effects.

While even a short list of potential side effects for a particular hep C therapy might give one pause, Andrew Muir, MD, chief of gastroenterology at Duke University, stresses that in the case of interferon-free regimens, "Everything we're talking about is generally mild and well tolerated."

Treatment Options That Don't Include Interferon

Right now, there are two options for treatment that nix interferon. For those with genotype 1 of the virus who are interferon intolerant (which many clinicians argue includes those who simply do not want to take the drug) or who are not eligible to take interferon for various reasons, the American Association for the Study of Liver Diseases (AASLD) recommends the analog polymerase inhibitor Sovaldi (sofosbuvir) and the NS3/4A protease inhibitor Olysio (simeprevir) plus ribavirin for 12 weeks, or Sovaldi plus ribavirin for 24 weeks as an alternative. People with genotype 2 can opt for 12 weeks of Sovaldi and ribavirin, and those with genotype 3 can take this combination for 24 weeks. Genotypes 4 through 6, which are rarer in the United States, should see more options become available between October and December, when the U.S. Food and Drug Administration (FDA) is slated to decide on three new crops of drugs, all of which are slated for use without interferon.

For those taking Sovaldi and ribavirin, fatigue and headache are the most common side effects, occurring in more than 20 percent of cases, according to the drug's prescribing information.

In the COSMOS study of Sovaldi and Olysio plus ribavirin, the most common side effects were fatigue, headache, nausea, anemia, itching, dizziness, rash and photosensitivity (sensitivity to sunlight, or a tendency to burn more easily).

For his patients taking this regimen, Kowdley says, "We recommend them to avoid direct sunlight, and we certainly recommend that they use high efficacy sunblock. But part of it is we live in Seattle, so it's not a big problem, but it doesn't seem to be a very serious issue."

Gilead Sciences' fixed-dose, once-a-day combination tablet of Sovaldi and the investigatory NS5A inhibitor ledipasvir is considered the next big thing. With an approval date set for October 10, the combination could bring 12-week, or possibly even eight-week dosing that doesn't require interferon, and which might be able to sidestep ribavirin as well. Gilead's FDA application is for those with genotype 1, who make up 75 percent of the U.S. hep C population, but physicians may be able to prescribe the combo pill off-label to those with other genotypes. Side effects in various trials of the pill were fatigue, headache, insomnia and nausea, which tended to be more common when the combination was used with ribavirin.

AbbVie is the other major player, with a decision on the company's "3D regimen" expected in December. The combination therapy consists of a fixed-dose combination of the protease inhibitor ABT-450 and ritonavir co-formulated with the NS5A inhibitor ombitasvir (ABT-267), as well as the non-nucleoside polymerase inhibitor dasabuvir (ABT-333), with or without ribavirin. Fatigue and headache were the most commonly reported in a large Phase III trial.

Lastly, there's Bristol-Myers Squibb's NS5A replication complex inhibitor daclatasvir and the NS3 protease inhibitor asunaprevir. The company expects a decision from the FDA by the end of the year on that combination's use in those with genotype 1b. The most common side effects in the HALLMARK-DUAL study were headache, fatigue, diarrhea and nausea. (BMS has also filed for approval of daclatasvir's use with other hep C drugs to treat multiple genotypes of the virus.)

Treating Side Effects

Kowdley says that additional therapies to counteract other side effects of interferon-free hep C regimens are rarely needed, and if so the remedies are typically over-the-counter and fairly simple.

For anemia, the primary adverse effect of ribavirin, Kowdley has found that today's short treatment lengths mean that any effects that ribavirin has on the blood are almost never significant enough to warrant interventions along the lines of adjusting the dose of the drug, giving a blood transfusion or prescribing the hormone erythropoietin.

This doesn't mean, however, that ribavirin is without side effects. In fact, side effects are more common in ribavirin-containing hep C regimens than in those without. However, the difference in side effects in terms of number and severity is not that great.

"In my opinion," Kowdley says, "the added benefit with regard to a potential [cure] easily overcomes the potential limitation of those regimens that contain ribavirin."

Cough and rash are also common ribavirin side effects. Cough can be treated with Robitussin or some other anti-cough medicine. For rash, Kowdley will in very rare occasions advise hydrocortisone, but otherwise he says that moisturizing with an emollient cream—Eucerin is an example of a brand name—should do just fine. David Bernstein, MD, chief of the division of hepatology at North Shore University Hospital in Manhasset, New York, says he sometimes will advise using an antihistamine such as Benadryl for rash.

In the event of nausea resulting from hep C regimens, Bernstein says, "We usually recommend that patients take the medication with food. It tends to occur on an empty stomach. But it's generally not severe."

If Bernstein's patients have trouble with insomnia, he may prescribe a sleeping aid. For headache, he says that typical over-the-counter drugs like Tylenol or Advil should do the trick.

All this said, Kowdley stresses that there is still one last profound potential side effect to consider, a potentially life-altering effect that he has seen in numerous patients in his vast clinical experience.

As he puts it: "We're seeing all kinds of reports of euphoria, increased energy, almost insomnia because of having so much more energy than ever before."
