Who’s Afraid of Adding Ribavirin to Hep C Treatment?

The antiviral drug, which for some people can be a beneficial adjunct to the new crop of hep C medications, has gotten a bad rap.

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The modern era of highly effective, highly tolerable direct-acting antiviral (DAA) treatments for hepatitis C virus (HCV) is upon us at last. Long gone are the days when the standard treatment was the dreaded interferon, which causes onerous flu-like side effects, paired with the anemia-fueling antiviral drug ribavirin.

So what is ribavirin still doing in the picture? Weren’t regimens like Harvoni (ledipasvir/sofosbuvir), Viekira Pak (ombitasvir/paritaprevir/ritonavir; dasabuvir) and Epclusa (sofosbuvir/velpatasvir) supposed to kick it to the curb?

It turns out, for some subgroups of the hep C population, ribavirin remains a useful adjunct to the current crop of DAAs when it comes to maximizing cure prospects. And while ribavirin’s various side effects can be quite pronounced when it is prescribed with interferon, pairing ribavirin with today’s DAAs greatly mitigates such side effects.

“There’s no question that ribavirin is much better tolerated in the absence of interferon,” says Jordan J. Feld, MD, a clinician-scientist at the Toronto Centre for Liver Disease, of the hep C drug market. “My experience with ribavirin is that it definitely adds side effects to the DAAs. But the DAAs are so well tolerated, so it’s not too bad.”

Feld is the lead author of a recent scientific paper published in the journal Liver International that examines the role ribavirin continues to play both in maximizing cure rates for harder-to-treat individuals with HCV and shortening the necessary length of treatment in some cases.

Greatly reduced side effects:

According to Feld’s paper, the adverse health events that were common when ribavirin was prescribed with interferon—fatigue, headache, nausea, cough, rash, indigestion, insomnia and shortness of breath—occur much more infrequently when the drug is combined with DAAs. Additionally, the severity and frequency of anemia are significantly reduced when ribavirin is given with DAAs rather than interferon.

What's more, when given with DAAs, ribavirin does not appear to affect individuals' ability to complete treatment. In clinical trials of the current crop of DAAs, the rate of those quitting treatment because of adverse health events was the same, about 3 percent, regardless of whether study participants took ribavirin.

With proper monitoring, physicians can even adjust the ribavirin dose during treatment to try to lessen any side effects that do arise, including anemia.

Who should still consider taking ribavirin?

Whether ribavirin is likely a helpful addition to currently available DAAs depends on various factors that tend to be associated with lower HCV cure rates. These factors include an individual's hep C genotype, the severity of fibrosis (or liver scarring, the most advanced cases of which are known as cirrhosis) and the DAA regimen itself.

The exact mechanism by which ribavirin helps cure hep C is poorly understood. But the apparent benefit of adding the drug to a DAA regimen is that ribavirin helps prevent what is known as viral relapse, or a return of the virus shortly after treatment.

Research suggests that those who likely stand to benefit most from adding ribavirin to Harvoni in particular are individuals with genotype 1a and compensated cirrhosis (the less advanced form of cirrhosis) who have failed a previous hep C treatment and who have drug-resistant virus. The same findings appear to hold true for prescribing Zepatier (grazoprevir/elbasvir).

When it comes to Epclusa, which is approved to treat all genotypes, the benefit of adding ribavirin is apparently the greatest for those with decompensated cirrhosis, particularly those with genotype 3.

Feld says he would alter the current American Association for the Study of Liver Diseases (AASLD) hep C treatment guidelines to recommend drug-resistance testing when considering Harvoni for those with genotype 1a who have failed a previous interferon-based therapy. And if they do have drug-resistant virus, he believes physicians should strongly consider adding ribavirin to their DAA regimens.

For people with decompensated cirrhosis, the more advanced form of the severe liver disease, recent research in those with genotype 1 suggested they may boost their chances of a hep C cure by adding ribavirin to a 12-week regimen of Epclusa.

Ribavirin can also offer some people with hep C the choice of shortening their time on DAA treatment. For those with genotype 1 who have been treated before and have compensated cirrhosis, AASLD guidelines for Harvoni use recommend a 12-week course with ribavirin or 24 weeks without.

Interestingly, Feld reports that when he presents patients with the option of these two treatment approaches, they tend to choose the 24-week ribavirin-free option. He attributes this phenomenon

to word of mouth about ribavirin's bad side effects, a bad rap he believes is a holdover from the interferon era.

Feld says that a compromise for people choosing between a shorter treatment versus avoiding ribavirin is to have them begin by taking both Harvoni and ribavirin; if ribavirin proves to be too much of a burden, they can just drop that drug and continue on Harvoni for 24 weeks instead of 12.

Will Newly Approved Regimens End the Ribavirin Era?

"This is a field that is changing incredibly rapidly," says Feld. "Although there's definitely still a role for ribavirin now, I think we're all hopeful that's a short-lived role."

In the coming months, two new hep C regimens that can treat people with all six genotypes of HCV are poised for likely FDA approval. Both have boasted generally excellent cure rates, in the high 90 percent range. Neither was studied with ribavirin in advanced trials.

From Feld's perspective, the lack of data about ribavirin's potential effect on the efficacy of these regimens deprives physicians like him of a guide for maximizing cure prospects for harder-to-treat patients. On the other hand, the reality may be that these new treatments are so effective that they simply won't need ribavirin to boost cure rates, even for highly complex cases. So their FDA approvals may signal another milestone in the phasing out of ribavirin from the hep C arsenal.

"When you start getting cure rates that are above 95 percent, it's hard to show that anything adds to that," says Feld. The HCV regimens coming out of the pipeline, he says, "are looking like they're going to cure the majority of people—even potentially [those with] with highly resistant virus."

A decision about AbbVie's new double-DAA treatment, glecaprevir/pibrentasvir, known as G/P, is expected at the end of June. The regimen, which received priority review status from the FDA because it likely represents an advancement over current hep C treatments, has shown promise in treating those who have failed a previous cure attempt.

The FDA is set to issue a decision about Gilead Sciences' sofosbuvir/velpatasvir/voxilaprevir in early August. The triple-drug regimen has the same components as Gilead's Epclusa plus the drug voxilaprevir. If approved, it would be the first once-daily, single-tablet regimen for those who have failed a previous treatment. (G/P involves taking three tablets once daily.)

The FDA has already recognized that Gilead's triple-drug regimen may offer an advancement for those with resistance to the NS5A inhibitor DAA class (which includes the ledipasvir and velpatasvir components of Harvoni and Epclusa, respectively), granting it a review-expediting breakthrough therapy designation for this purpose.

Even considering the apparent broad-based high efficacy of these new regimens, Feld anticipates that, just for good measure, he will still add ribavirin for the rare patient of his who has failed two previous treatments—even without clinical trial data to guide him. He will also continue using

ribavirin for those with decompensated cirrhosis, who will not be able to take either of the new regimens coming down the pike.

To KO the most difficult cases of hep C, it’s best, Feld says, “to throw the kitchen sink at them.”

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