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In the News

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Resistance-Associated Gene Variants Found In Hep C Patients Who Received First-Generation DAAs

By Ashley Taylor

First-generation triple therapies for hepatitis C virus (HCV) infection are being phased out in favor of next-generation interferon-free direct-acting antiviral agents (DAAs).

When the old drugs are no longer available—the protease inhibitor telaprevir was discontinued last year and boceprevir will be discontinued at the end of this year—patients, including those in whom treatment with the first-generation drugs failed, will need to begin taking the next-generation drugs. One concern about this transition is that the new drugs might be less effective in HCV variants that are resistant to the old drugs, which, since a hepatitis C drug selects for viral variants that are resistant to it, are likely to be present in patients in whom first-generation therapies failed. Will the new drugs be less effective in this patient group—those for whom first-generation treatments failed—because of the resistance-associated variants (RAVs) that these patients harbor?

To determine the scope of this potential problem, Harald Farnik, MD, and colleagues at Wolfgang Goethe University, in Frankfurt, Germany, determined the frequencies of RAVs in patients infected with HCV genotype 1 who had already received interferon therapies, first-generation triple therapies—either telaprevir or boceprevir plus ribavirin and injected

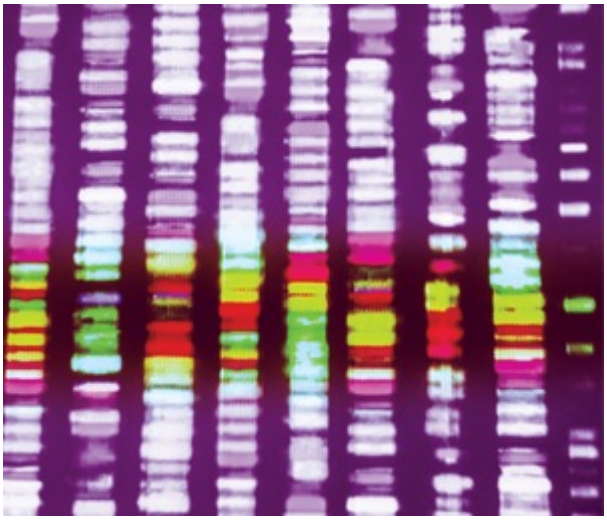
interferon—or no treatment. They found several RAVs with mutations in the NS3 protease and *NS5A* genes. The results, presented as a poster at the 2015 European Association for the Study of the Liver Congress (P0766), tell doctors which HCV variants the new drugs must be effective against.

“Drug resistance plays a key role in patients with failure to DAA-containing therapies,” Dr. Farnik said. “Some patients harbor RAVs within *NS3* and *NS5A* genes, which may affect treatment efficacy of protease and NS5A inhibitors.”

Among the DAAs, both ledipasvir-sofosbuvir (Harvoni, Gilead) and ombitasvir, paritaprevir, ritonavir and dasabuvir (Viekira Pak, AbbVie) act as NS5A inhibitors; Viekira Pak also inhibits NS3/4A protease.

In the study, patients were tested for RAVs associated with the first-generation drugs. But the new drugs will need to be effective against these RAVs, too.

“We can learn from the first-generation DAAs about how the next generation of DAAs will need to work in clinic,” said Matt Paulson, PhD, director of project and portfolio management at Assembly Biosciences, in New York City, who worked for Gilead developing DAAs and but was not involved in this study.



Among patients who were treatment-naive or who had already received pegylated interferon/ribavirin (PEG/R) treatment, the researchers found that the most frequent

resistance-associated variant was Q80K (in
which the amino acid glutamine was changed to lysine at amino acid position 80 within the protein), present in about 20% of patients infected with genotype 1a and around 1% of those infected with genotype 1b.

Five different RAVs were observed in patients previously treated with telaprevir and boceprevir. RAVs were more common in patients previously treated with telaprevir—the most frequent RAV was variation at R155 (20%) in genotype 1a patients and at A156 (9%) in genotype 1b—than in those previously treated with boceprevir, in whom the most frequent RAV was also R155 (12%) in genotype 1a and T54 (13%) in genotype 1b.

RAVs to NS5A inhibitors were found at frequencies under 4% and did not differ between patients who had received previous treatment and those who were untreated.

Clinical Implications Uncertain

The implication of having a given RAV for the effectiveness of a given drug regimen is unclear. A RAV's resistance to a particular drug means the drug will not work on that RAV; however, patients typically have many different strains of HCV—not a single variant—so the presence of a RAV in a patient generally does not in itself determine whether a treatment will work. Furthermore, the effectiveness of an HCV treatment depends not only on a patient's particular combination of variants but also on the other components of the therapy. For example, a 2013 study in *Virology* by researchers at Merck found that there was no association between patients' baseline RAVs (RAVs present before treatment) and the effectiveness of a boceprevir triple therapy. Patients' responsiveness to interferon treatment, in contrast, did predict treatment efficacy (444:329-336).

On the other hand, baseline NS5A RAVs are associated with poorer treatment responses to NS5A inhibitors, said Anita Howe, PhD, scientific lead of infectious diseases at Merck Research Laboratory and a co-author of the *Virology* paper. Because both Harvoni and Viekira Pak contain NS5A inhibitors, she said, baseline NS5A RAVs reduce the efficacy of both treatments.

"As for whether it's really relevant for current treatments, likely not," said Alexander Ploss, PhD, assistant professor of molecular biology at Princeton University, in Princeton, N.J., of the new results. Dr. Ploss said it was likely that the new drugs had already been tested in treatment-experienced individuals in clinical trials. Harvoni has been shown to work in patients previously treated with PEG/R and protease inhibitor triple therapies. Viekira Pak was shown to work in patients previously treated with PEG/R alone and with telaprevir triple therapy.

Dr. Ploss noted that because the new treatments include multiple DAAs, it would be more difficult for resistance to develop than it has been with the first-generation drugs, which contain a single DAA.

“For these combination therapies, it’s not necessary that all three inhibitors are working for the virus to shut down,” Dr. Ploss said. “It’s a fail-safe. If there are viral variants resistant to one, you still have the other drugs; even if there are viral variants resistant to two, there’s still the third drug that can eliminate the virus.”

Dr. Paulson owns stock in Gilead.