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Patient response to Harvoni unaffected by baseline RAS in NS5A

Sarrazin C, et al. *Gastroenterology.* 2016;doi:10.1053/j.gastro.2016.06.002.

July 8, 2016

Baseline resistance-associated substitutions in *NS5A* had minimal effects on the response of patients to Harvoni in hepatitis C virus infection genotype 1, according to a recent study. Further, when resistance-associated substitution (RAS) effects were apparent, researchers found that increased intensity or duration of treatment could overcome them.

"The impact of HCV baseline RASs on SVR may depend on the susceptibility/fitness of the RASs, the patient population, the specific regimen and treatment duration," **Christoph Sarrazin, MD,** of the medical clinic at Goethe University Hospital, and colleagues wrote. "In this analysis, the baseline prevalence and effects of NS5A inhibitor, [nucleotide inhibitor], and [protease inhibitor] RASs on virologic response to ledipasvir and sofosbuvir with and without ribavirin in a large number of patients (n = 2,144) from multiple studies from the ledipasvir/sofosbuvir phase 2/3 development program were investigated."

In recent years, direct-acting antivirals have increased the rates of sustained virologic response in patients infected with HCV infection genotype 1, with some patients reaching SVR rates of 94% to 99% in certain studies. However, pre-existing mutations that show in vitro resistance to ledipasvir or sofosbuvir in some patients may influence outcome. In untreated patients, these mutations may persist at low levels, but may emerge under the pressure of DAAs.

To test this, Sarrazin and colleagues analyzed data of 2,144 patients in phase 2 or 3 studies of HCV infection genotype 1a or bin which patients were provided the combination of ledipasvir (90 mg) and sofosbuvir (400 mg) once daily, with or without ribavirin twice daily. The researchers then conducted deep sequence and population analyses of the HCV *NS3*, *NS5A*, and *NS5B* genes on the blood samples collected at baseline.

They found 16% of patients showed detectable baseline RAS in *NS5A*. For patients with HCV genotype 1b, baseline RAS in *NS5A* had no significant effect on SVR 12 weeks after end of treatment with ledipasvir/sofosbuvir (Harvoni, Gilead), whereas patients with HCV genotype 1a showed a small effect. The RAS in *NS5A* that increased the half maximal effective concentration 50 to ledipasvir by more than 100-fold reduced the SVR12 rate in treatment-naive patients who were given ledipasvir/sofosbuvir for 8 weeks (P =.011), but not 12 weeks. Moreover, baseline *NS5A* RAS reduced the percentage of treatment-experienced patients with SVR12 to 12 weeks ledipasvir/sofosbuvir ($P < .001$), but not 24 weeks.

In total, 2.5% of patients had baseline *NS5B* nucleotide inhibitor RAS, and they all achieved an SVR12.

Additionally, 53.7% of patients previously treated with protease inhibitors had RAS in *NS3*, and 96.5% achieved an SVR12.

"Ledipasvir/sofosbuvir is an effective, simple, and safe single tablet regimen for the treatment of genotype 1 chronic HCV, with SVR rates of [94% to 99%] in phase 3 clinical trials," Sarrazin and colleagues wrote. "Overall, the presence of pre-existing RASs in the *NS5A* gene had no significant impact on treatment outcome in genotype 1b-infected patients, and a minimal impact on treatment outcome in genotype 1a-infected patients with SVR rates [greater than] 90 percent. The presence of pre-existing RASs in the *NS5B* and *NS3* genes had no impact on treatment outcome." – *by Rafi Naseer*

Disclosures: Sarrazin reports grant support from the German Centre for Infection Research and fees for advisory boards or speaking activities from Abbott, AbbVie, Achillion, Bristol-Meyers Squibb, Gilead Sciences, Janssen, Merck and Roche. Please see the full study for a list of all other researchers' relevant financial disclosures.

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