

Oral Regimen Sustains Hepatitis C Viral Response to 24 Weeks

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AMSTERDAM, the Netherlands — A regimen of 3 direct-acting antiviral drugs plus ritonavir and ribavirin produced sustained virologic response rates in more than 90% of a broad range of patients infected with hepatitis C 24 weeks after therapy, results from a new clinical trial show.

Kris Kowdley, MD, from the Liver Center of Excellence in the Digestive Disease Institute at Virginia Mason Medical Center in Seattle, Washington, presented the results here at the International Liver Congress 2013.

The randomized, open-label, multicenter phase 2b trial, known as Aviator, shows that the sustained virologic responses seen at 12 weeks with an all-oral interferon-free regimen, presented last year at the annual meeting of the American Association for the Study of the Liver Diseases by Dr. Kowdley, are sustainable.

In the Aviator trial, noncirrhotic patients with genotype 1 hepatitis C virus who were treatment-naïve or had not responded to peginterferon and ribavirin were treated with combinations of direct-acting antiviral drugs with or without ribavirin for 8, 12, or 24 weeks.

The direct-acting antiviral drugs were once-daily ABT-450r (an NS3/4A protease inhibitor boosted with ritonavir), once-daily ABT-267 (an NS5A inhibitor), and twice-daily ABT-333 (a non-nucleoside NS5B inhibitor).

The 571 patients were predominantly white, and the mean age was 48 to 53 years. The majority, 59% to 71%, had hepatitis C genotype 1a, and mean baseline viral load was 6.6 log₁₀ hepatitis C RNA. Overall, 27% to 34% of treatment-naïve patients had genotype IL28B CC, whereas only 2% to 4% of the null responders did.

Patients coinfecting with HIV or hepatitis B were excluded from the study.

For the 79 treatment-naïve patients who received the regimen consisting of 3 direct-acting antiviral drugs plus ribavirin for 12 weeks, 96% achieved sustained virologic response rates at 24 weeks (99% achieved this at 12 weeks).

High Response Rates

Response rates were no higher with 24 weeks of treatment than with 12 weeks of treatment. Even with only 8 weeks of treatment, 88% of patients achieved sustained virologic response rates at 24 weeks and 89% achieved this at 12 weeks.

For the null responders who received the triple-drug plus ribavirin regimen, 93% of the 45 patients who received 12 weeks of treatment achieved sustained virologic response, as did 95% of the 43 patients who received 24 weeks of treatment.

With the triple-drug plus ribavirin regimen, the achievement of sustained virologic response was similar in the treatment-naive and null-responder patients, regardless of sex, genotype (1a or 1b), host IL28B genotype, severity of liver fibrosis, or baseline RNA level.

Of the 247 patients who received the triple-drug plus ribavirin regimen for 12 or 24 weeks, 4 (1.6%) discontinued the study because of drug-related adverse effects.

Of 4 serious adverse effects noted in the analysis, 1 arthralgia was possibly related to therapy. More common adverse effects, reported in more than 10% of patients, were headache, fatigue, nausea, insomnia, and diarrhea. Of the patients with grade 3/4 laboratory abnormalities, 6 had elevated total bilirubin and 1 had elevated alanine aminotransferase, which resolved with continuation of the drugs.

Dr. Kowdley told Medscape Medical News that results from the Aviator trial highlight 2 key points. "First, prolonging the therapy for another 12 weeks does not appear to improve the sustained virologic response. Second, greater treatment exposure does not seem to increase the risk of resistance; we're not seeing a drop off or more breakthroughs, because the number of breakthroughs has remained at 0. That's a really important point."

With the triple-drug plus ribavirin regimen, which is the optimal regimen, "sustained virologic response at 24 weeks remains very durable, compared with sustained virologic response at 12 weeks. That is true in both the null responders and treatment-naive patients.... So for those patients who do end up, for whatever reason, being on 24 weeks, we can feel, I think, reasonably confident that the resistance risk is not increased," Dr. Kowdley said.

A concern all along has been the high pill burden of this all-oral regimen. Dr. Kowdley said he expects that, for upcoming trials, reformulations will combine the once-daily ABT-267, ABT-450, and ritonavir into 1 pill, while keeping the twice-daily ABT-333 and the ribavirin separate. "I would say that in the phase 3 program and going forward, the pill burden should be lower," he predicted.

The sustained virologic response for treatment-naive patients is "extremely impressive," said Mark Thursz, MD, from Imperial College in London, the United Kingdom, and secretary general of the European Association for the Study of the Liver. Similarly, for null responders, Dr. Thursz, who was not involved in the study, said he is "quite excited" by the "really high sustained virologic responses."

He remarked that, in general, the protease inhibitors in development to treat hepatitis C virus have "much cleaner profiles than the current ones that we're using," but he added that "it's not quite time to bury the interferon yet."

However, "the vital signs are not looking good for either boceprevir or telaprevir." In light of the drugs now in trials, "it's time to move on," Dr. Thursz said.

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