Breakthrough: Non-Interferon/Ribavirin Regimen Can Cure Hep C

April 4, 2011 By Tim Horn

In what is being heralded as a hepatitis C virus (HCV) treatment research breakthrough, a clinical trial evaluating two oral medications being developed by Bristol-Myers Squibb (BMS) suggests that at least some cases of chronic HCV infection can be cured without the use of either pegylated interferon or ribavirin (IFN/RBV).

The same study, reported Saturday, April 2, at the 46th annual meeting of the European Association for the Study of the Liver (EASL) in Berlin, also appeared to cure 10 people living with HCV treated with a quadruple regimen, consisting of BMS's BMS-650032 and BMS-790052 in combination with IFN/RBV.

Though a combination of IFN/RBV has long been the standard treatment for chronic HCV infection, both drugs are associated with side effects and neither drug works directly against the virus. The high rate of toxicities, compounded by their indirect mechanisms of action, help explain why current treatment isn't highly effective in a proportion of people living with HCV, particularly those with hard-to-treat genotype 1 infection.

Direct-acting antivirals (DAAs), drugs that directly target HCV, have been in development for several years. Not only can they potentially maximize treatment responses and reduce the amount of time someone needs to be treated for HCV, but they also have been eyed as a way of treating hepatitis C without the need for either IFN or RBV.

Numerous studies at EASL suggest that DAAs, including protease inhibitors, NS5A inhibitors and polymerase inhibitors, can substantially increase rates of sustained virologic responses (SVRs)—maintaining an undetectable HCV viral load for six months after stopping treatment, or a viral cure—when used in combination with IFN/RBV. Not only did a clinical trial evaluating BMS's protease inhibitor asunaprevir (BMS-650032) and NS5A inhibitor daclatasvir (790052) add to the encouraging news, but it also demonstrated that two DAAs used together, without IFN/RBV, can cure HCV in some patients.

The Phase II study looked at a cohort of 21 HCV genotype 1 null responders—patients who had very limited responses to previous treatment with IFN/RBV—of whom 19 had an unfavorable IL28B genotype, which predisposes HCV patients to treatment failure. The cohort was divided into two groups: Group A involved 11 patients treated with BMS-790052 plus BMS-650032 without IFN/RB

for 24 weeks; Group B involved 10 patients treated with both BMS drugs plus IFN/RBV for 24 weeks.

Nine of the 10 patients treated with quadruple therapy had an SVR after 24 weeks (SVR24), reported Anna Lok, MD, of the University of Michigan Medical Center at Ann Arbor and her colleagues. The one patient who didn't have an SVR24 was tested again 35 days later and found to have an undetectable HCV viral load, suggesting a possible cure rate of 100 percent in the small number of individuals who received four-drug treatment.

Of particular interest are the results among those treated with the DAAs without IFN/RBV. Four of the 11 patients had an SVR24—among the first individuals in a clinical trial to be successfully cured of HCV without today's standard-of-care drugs.

In the six patients who saw their HCV viral loads rebound during treatment with the DAAs, IFN/RBV was promptly added. Four of the patients then went on to achieve undetectable HCV viral loads. HCV resistance to both BMS-790052 and BMS-650032 was documented in all six patients who did not respond favorably to DAA therapy alone, though it is not clear what the implications of resistance are for those who potentially require retreatment with these or similar agents.

Many side effects were similar in both groups, including diarrhea, fatigue, headache, fever and difficulty sleeping. Most side effects, however, were mild to moderate in severity, and there were no discontinuations from the study due to adverse events. Moderate-to-severe drops in neutrophils, a type of white blood cell, was documented in six patients in the quadruple-therapy group, compared with no patients in the dual-DAA group.

Lok concluded that quadruple therapy can result in a high rate of cure in this difficult-to-treat population and that, based on the encouraging dual-DAA study results, that HCV infection can be cured without IFN or RBV.

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