Rilpivirine Has Similar Efficacy and Better Tolerability Than Sustiva

July 22, 2010 By Tim Horn

Rilpivirine (TMC278) was similar to Sustiva (efavirenz) in two large clinical trials but demonstrated much fewer central nervous system (CNS) side effects, according to a presentation Thursday, July 22, at the XVIII International AIDS Conference (IAC), taking place July 18 to 23 in Vienna.

Rilpivirine is an experimental second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) being developed by Tibotec, a subsidiary of Johnson & Johnson. In a previous Phase IIb dose-ranging study, researchers found that rilpivirine, in people who'd never taken antiretroviral (ARV) therapy, had similar efficacy to Sustiva, but was more tolerable. Among those in the higher-dose group, however, there were signs that rilpivirine could negatively affect a person's heart rhythm. For this reason, Tibotec decided to pursue the lowest dose of the drug—25 milligrams (mg) once-daily—studied in the Phase IIb study. a lower dose of rilpivirine. This led some researchers and activists to be concerned that the drug's effectiveness might suffer.

In addressing this concern, Calvin Cohen, MD, from the Community Research Initiative New England, in Boston, presented the results of two large Phase III studies—ECHO and THRIVE—in a Thursday morning session.

ECHO is a 690-person study comparing 25 mg of rilpivirine once-daily plus Truvada (tenofovir plus emtricitabine) with Sustiva plus Truvada for 96 weeks in first-time treatment-takers. The THRIVE study, with 678 participants, has a similar design, but people are able to use Epzicom (abacavir plus lamivudine) or Combivir (zidovudine plus lamivudine) instead of Truvada. In his presentation, Cohen presented 48-week data on efficacy and safety.

The primary aim (endpoint) of the two-study analysis was the percentage of people with a viral load of less than 50 copies after 48 weeks of treatment. To be enrolled in either study, people had to have a viral load of 5,000 or higher, no NNRTI resistance, and full sensitivity to Truvada, Epzicom or Combivir. Characteristics of the participants were similar in both studies, with participants having an average CD4 count of roughly 250 and with about half of the participants having a viral load over 100,000 copies.

Cohen reported that rilpivirine efficacy was statistically similar in both studies compared with Sustiva. In an analysis where the two studies were pooled together, 84.3 percent of those taking rilpivirine had a viral load of less than 50 copies at week 48 compared with 82.3 percent of those

taking Sustiva. When Cohen and his colleagues analyzed the studies separately, rilpivirine performed a little better in the THRIVE study than in ECHO, but both studies met the primary endpoint and rilpivirine was ultimately determined to be not inferior to Sustiva. These results held up even in people who started the study with viral loads over 100,000 copies.

Twice as many people on rilpivirine did fail in the analysis due to either an inability to get their virus to undetectable levels or because they lost control of the virus at some point later in the study, dubbed virologic failures. Based on the analysis presented by Cohen, this appeared to be due to a higher virologic failure rate among those receiving rilpivirine-based therapy in the THRIVE study (11 versus 4.4 percent); virologic failure rates in the ECHO study were better balanced.

In people who had a virologic failure, 63 percent of those in the rilpivirine group and 54 percent of those in the Sustiva group developed NNRTI mutations. More than twice as many people taking rilpivirine developed HIV mutations confering resistance to the nucleosides—notably the M184 mutation known to decrease sensitivity to lamivudine and emtricitabine—compared with those receiving Sustiva (68 versus 32 percent, respectively).

Also of potential concern, 90 percent of the people on rilpivirine who had an emergence of NNRTI-resistant strains had cross-resistance to Intelence (etravirine), meaning that they might not be able to use this drug in later lines of therapy. The most frequent NNRTI mutation in the rilpivirine group was E138K (which confers some degree of resistance to Intelence), whereas the most frequent NNRTI mutation in the Sustiva group was K103N (a mutation that can be present without seriously jeopardizing a patient's chance of responding to Intelence).

In terms of tolerability and side effects, rilpivirine performed much better than Sustiva. While up to a third of those taking Sustiva had some form of a CNS side effect, such as insomnia or vivid dreams, roughly 15 percent of those taking rilpivirine had this type of side effect. What's more, though the overall number of people in both groups with elevations in liver enzymes or lipids (for example, cholesterol or triglycerides) was low, the percentage of people on Sustiva with these problems was 2 to 25 times higher than those on rilpivirine.

On another positive note, there was no sign of heart rhythm problems in people taking rilpivirine or Sustiva in either study.

Cohen concluded by pointing out the high response rate in both groups, the similarity in efficacy between rilpivirine and Sustiva, and the tolerability advantages of rilpivirine. He also noted that Tibotec is working with Gilead sciences to develop a single, once-daily pill of rilpivirine combined with Truvada.
