Non-Nuke Lersivirine Promising in First-Time Treatment Takers

July 19, 2011 By Tim Horn

Two doses of lersivirine (UK-453061), ViiV Healthcare's experimental non-nucleoside reverse transcriptase inhibitor (NNRTI), achieved similar rates of viral load suppression compared with Sustiva (efavirenz), according to 48-week data from a Phase II study reported Tuesday, July 19, at the 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention in Rome.

While there were more reports of nausea among those using lersivirine, more central nervous system side effects were documented among those using Sustiva. Lersivirine also had a neutral effect on lipid levels in the study.

NNRTIs remain key components in antiretroviral (ARV) drug regimens. A major problem with the first approved NNRTIs was the emergence of mutations in HIV's reverse transcriptase gene, particularly K103N and Y181C, which led to resistance to the entire class. Hence there has been a need for "second generation" NNRTIs that not only have unique resistance profiles but also can be effectively combined with other ARVs.

Early results from studies of lersivirine suggest it will be useful in this regard, either as a first-line NNRTI option or as a compound to be used after resistance develops to already approved options—such as Sustiva or Viramune (nevirapine). Data also suggests lersivirine is effective against different HIV subtypes, such as subtype C, which is common in Africa (subtype B dominates in the United States and is most common among men who have sex with men and intravenous drug users).

Anton Pozniak, MD, of Chelsea & Westminster Hospital in London reported preliminary results from a clinical trial comparing two doses of lersivirine to Sustiva—all combined with Truvada (tenofovir plus emtricitabine)—in HIV-positive patients starting treatment for the first time.

The researchers randomized 195 people to receive 500 milligrams (mg) lersivirine once daily, 750 mg lersivirine once daily or standard doses of Sustiva. The primary goal of the study was an evaluation of volunteers with undetectable viral loads (less than 50 copies) at week 48, with the study continuing for a total of 96 weeks.

Study volunteers were, on average, 36 years old upon enrolling. Roughly 27 percent were female. About 33 percent of the study volunteers were in South Africa (Region B), whereas 66 percent

were enrolled at sites in the European Union, Latin America, Australia and Canada (Region A). Roughly 35 percent had non-subtype B strains of HIV.

About 33 percent had high viral loads—above 100,000—upon entering the study, and the average CD4 count was about 320.

After 48 weeks, 86 percent in the Sustiva group had undetectable viral loads, compared with 79 percent of those receiving either dose of lersivirine.

When looking at patients who entered the study with viral loads below 100,000 copies, results were roughly comparable: 88 percent among those receiving Sustiva, compared with 80 percent receiving 500 mg lersivirine and 86 percent receiving 750 mg lersivirine.

Among those with high viral loads, 82 percent of those receiving Sustiva had levels below 50 after 48 weeks, compared with 75 percent of those receiving 500 mg lersivirine. Among those in the 750 mg lersivirine group, only 62 percent had undetectable viral loads.

Efficacy rates were also explored by region. Among those in Region A, viral loads remained undetectable in 87 percent of patients using Sustiva, compared with 81 percent of those using 500 mg lersivirine and 84 percent of those using 750 mg lersivirine. In region B, efficacy rates were 83, 72 and 63 percent, respectively.

Of note, when the researchers combined pre-treatment viral load and region data, about 85 percent of those using Sustiva in Region A with viral loads in excess of 100,000 achieved and maintained undetectable viral loads, compared with similarly matched Group A patients using 500 mg lersivirine (81 percent) and 750 mg lersivirine (77 percent).

CD4 counts increased by 188 to 195 cells in all treatment groups after 48 weeks.

As for resistance mutations in those with virologic failure, the K103N mutation occurred in one of three patients who weren't able to control their HIV in the Sustiva group. Among those with virologic failure in the lersivirine groups, the M184V mutation—which confers resistance to lamivudine and emtricitabine—was common and the integrase mutations that arose were unique to lersivirine treatment.

The most common side effects were nausea (more common in the 750 mg lersivirine group), headache (more common in the 500 mg lersivirine group), abnormal dreams, dizziness and rash (all more common in the Sustiva group). Moderate-to-severe lab abnormalities were more common among those in the Sustiva group (13 percent) compared with those in either lersivirine group (3–5 percent).

Pozniak pointed out that lersivirine did not have any appreciable effects on total cholesterol, "bad" LDL cholesterol or triglycerides in the study.

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