Selzentry Reanalysis Shows Potential as First-Line Treatment

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Selzentry (Celsentri; maraviroc) is comparable to Sustiva (efavirenz) in HIV-positive patients starting antiretroviral (ARV) treatment for the first time, according to a new analysis of a study that originally suggested that Selzentry was less effective than the standard-of-care non-nucleoside reverse transcriptase inhibitor (NNRTI). The latest review of the data, relying on a new enhanced-sensitivity tropism assay, was reported yesterday at the 2008 joint meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and Infectious Disease Society of America (IDSA).

Selzentry, manufactured by Pfizer, has already been proved safe and effective in clinical trials involving treatment-experienced patients.

Pfizer's MERIT study, originally reported by Michael Saag, MD, of the University of Alabama, at the fourth IAS Conference on HIV Pathogenesis, Treatment and Prevention in Sydney in 2007, is the first to test the CCR5-blocking entry inhibitor in patients beginning HIV therapy for the first time. The study randomized treatment-naïve patients to either Selzentry, using a 300 mg dose taken once or twice a day, or Sustiva, both used with Combivir (zidovudine plus lamivudine).

Sixteen weeks into the study, the once-daily Selzentry arm was discontinued due to inferior viral load responses.

Upon entering the study, patients had to have a pretreatment viral load above 2,000 and were required to have CCR5-tropic HIV—virus that targets CCR5 on the surface of CD4 cells as opposed to CXCR4, which typically arises in patients in more advanced stages of infection and typically renders Selzentry ineffective. Patients were screened for the study using an older version of Monogram Bioscience's Trofile assay, which can only detect CXCR4-using virus if it makes up more than 10 percent of the blood sample tested. Monogram's newer assay can detect CXCR4-using virus that makes up as little as 0.3 percent of the tested blood sample.

The average viral load and CD4 count at entry was 4.87 log and 250 cells, respectively. The average age was 37 years; roughly 71 percent of the study participants were male.

According to Dr. Saag's original presentation, based on data using the older Trofile assay, 69.3 percent of those in the Sustiva group, compared to 65.3 percent in the Selzentry group, had viral

loads below 50 copies after 48 weeks. Saag said this 4.2 percent difference was just large enough to suggest that Selzentry is inferior to Sustiva in terms of reducing viral load to undetectable.

In the reanalysis of the 48-week study data—dubbed MERIT ES (extra sensitive)—Saag and his colleagues used the new ultra-sensitive Trofile assay to retest blood samples of those who enrolled in the study.

Using the new tropism assay, 15 percent of the patients enrolled in the study were found to have a dual/mixed population of CCR5- and CXCR4-using HIV at the start of the study. They were then removed from the reanalysis, given that they technically shouldn't have entered the study in the first place. Saag's team then conducted a new comparison between Selzentry and Sustiva in a more pure population of patients with CCR5-using HIV.

Sixty-eight percent of patients in the Selzentry group, compared with 68 percent of patients in the Sustiva group, had viral loads below 50 copies after 48 weeks, according to the reanalysis.

In the MERIT ES population, there were fewer discontinuations in the Selzentry arm due to lack of efficacy than the rate seen in the original MERIT analysis. In MERIT ES, 9.3 percent of patients taking Selzentry discontinued due to lack of efficacy, compared to 4 percent of patients taking Sustiva. In the full study analysis originally reported by Saag, 11.9 percent of patients taking Selzentry stopped due to treatment failure, compared with 4.2 percent in the Sustiva group.

Patients were more likely to discontinue treatment due to side effects in the Sustiva group compared to the Selzentry group, according to both study analyses. This, Saag noted, was largely driven by a greater number of cases of central nervous system side effects and rash.

Pfizer has indicated to AIDSmeds.com that, in light of these more encouraging findings, discussions with regulatory agencies—such as the U.S. Food and Drug Administration—are ongoing regarding the possible approval of Selzentry for HIV-positive people starting therapy for the first time.
