Selzentry Treatment Failure: The Impact of Tropism Changes

September 20, 2007 By Tim Horn

Approximately two thirds of patients participating in Phase III studies of Pfizer's Selzentry (maraviroc) who experience treatment failure have HIV that has switched its tropism—a shift in the cellular receptors it uses to infect CD4s. While these new data further highlight an important mechanism of Selzentry-based regimen failure in treatment-experienced patients, results also show that CD4 cell counts remain increased and that such switches in tropism are often reversed after the CCR5-blocking entry inhibitor is discontinued.

The recently approved Selzentry works by preventing HIV's entry into CD4 cells. It does this by blocking one of two receptors—called CCR5—on CD4 cell surfaces. For Selzentry to be effective, however, a person's HIV must be tropic for CCR5, meaning that it uses the CCR5 receptor to infect these cells.

Some people have HIV that uses another CD4 cell receptor, called CXCR4. Still others have what is known as a "dual/mixed" (D/M) population of virus in their blood, referring to virus that can use either receptor or a mixture of CCR5 (R5)-using and CXCR4 (X4)-using HIV. There is some data to suggest that patients who experience a switch in their tropism—from R5-using to either D/M or X4-using HIV—progress more rapidly to AIDS.

There has also been some concern about the safety of Selzentry, given that it may exert what is known as "selective pressure" on HIV—snuffing out R5-using virus, thereby allowing D/M and X4-using virus to flourish. In turn, there are lingering questions regarding the risks of Selzentry, given the association between X4-using virus and more rapid disease progression.

The new information presented at ICAAC by Elna van der Ryst, MD, of Pfizer, based on 24-week data from the company's MOTIVATE studies, confirm that tropism switches do arise during therapy with Selzentry and are associated with treatment failure. Of the 751 patients who began Selzentry treatment with R5-using virus—disturbingly, 8 percent of patients saw their virus switch tropism between the time they were accepted into the study and the time they officially started the trial—98 volunteers experienced treatment failure during the first six months of study therapy. Sixty-three patients had D/M or X4-using virus at the time treatment failure was documented, whereas 35 still had R5-using virus when failure was documented.

A negative consequence of tropism switches is early treatment failure. Among those who experienced a tropism switch, 62 percent saw rebounds in their viral loads within 70 days, compared to 37 percent of those who maintained R5-using virus.

Additional data help to offset concerns of more rapid disease progression among patients who experience tropism switches while on Selzentry. Among those who maintained R5-using virus at the time failure was documented, CD4 counts were 61 and 138 cells higher in the once- and twice-daily Selzentry groups, respectively, compared to 15 cells higher in the placebo group. As for those who had documented tropism switches at the time failure was documented, average CD4 counts were still above baseline: an average 37-cell increase in the once-daily Selzentry groups, a 56-cell increase in the twice-daily Selzentry groups and a 67-cell gain in the placebo groups—with no statistically significant differences.

Dr. van der Ryst also noted that patients who had D/M or X4-using virus were no more likely to develop a new sign or symptom of AIDS, such as an opportunistic infection or a CD4 count below 200 cells, than those who maintained R5-tropic virus—further evidence of Selzentry safety, even when such switches occur.

Also of interest was the finding that many patients found to have D/M or X4-using virus during the study reverted to R5-using virus after Selzentry treatment was discontinued. Among 44 patients who experienced such tropism switches, stopped Selzentry and agreed to remain in the study, 30 had only R5-using virus in their blood at the time of their last study visit—approximately 203 days after starting the trial. While this finding suggests that retreatment with Selzentry—or another CCR5-blocking entry inhibitor—may be possible, this has not yet been tried.

Source:

van der Ryst E, Westby M. **Changes in HIV-1 co-receptor tropism for patients participating in the maraviroc Motivate 1 and 2 clinical trials** [Abstract H-715]. 47th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, 2007.

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