Maraviroc Less Effective but Safe for Some

August 17, 2006 By Tim Horn

August 17, 2006 (AIDSmeds)—Results from a clinical trial presented at the XVI International AIDS Conference (IAC) indicate that maraviroc, Pfizer's experimental entry inhibitor,may be of limited benefit in HIV-positive people with a specific formof HIV. However, these data also challenge some concerns that patientswith this particular form of the virus seen in later stages HIV diseasewill be harmed by maraviroc and a similar entry inhibitor vicriviroc.

After HIV binds to the CD4 protein on T-cells,the virus must then latch onto another receptor on the cell's surface –either CCR5 or CXCR4. Earlier in the course of HIV disease, most peoplehave HIV that uses the CCR5 receptor. Later on, as HIV diseaseprogresses, the virus can switch to the CCR4 receptor, although it isnot clear why this happens. The virus' tendency to use CCR5 or CXCR4 isknown as "tropism."

Some people have mixed populationsof virus in their blood, with some of their HIV using CCR5 and othervirus targeting CXCR4. These viruses are known as dual- or mixed-tropicHIV.

Maraviroc and vicriviroc are specifically activeagainst virus that uses the CCR5 receptor. These agents are desperatelyneeded by patients with limited treatment options due to resistanceto currently available agents. Of central concern, however, is the factthat, because many of these patients have been infected for severalyears, they are more likely to have CXCR4-tropic virus ordual/mixed-tropic virus.

While experts agree thatmaraviroc and vicriviroc are not likely to be effective againstCXCR4-tropic virus, they have hoped that these drugs will be effectiveagainst dual/mixed-tropic HIV.

This crucial questionwas raised in a maraviroc study, the results of which were reportedtoday at IAC by Howard Mayer, MD, of Pfizer. It was a 24-week studydesigned to evaluate the effects of maraviroc in patients with HIV thatis either CXCR4-tropic or dual/mixed-tropic.

The studyenrolled 186 HIV-positive patients, 167 of whom had dual/mixed-tropicvirus (the rest had CXCR4-tropic virus). A tropism test that determinedwhether or not a patient's virus is CCR5-tropic, CXCR4-tropic, ordual/mixed-tropic was used to screen patients.

The patients were quite advanced in their HIV disease – the average CD4 count was less than 50 and the average viral load upon entering the study was above 100,000.

Studyvolunteers were randomized to three treatment groups. In the firstgroup, patients received optimized background therapy (OBT) – acombination of approved HIV drugs that patients' viruses were believedto be at least partially sensitive to – plus placebo. The second grouptook oral maraviroc once a day plus OBT. The third group took oralmaraviroc twice a day plus OBT.

While Pfizer was likelyhoping that the addition of maraviroc to OBT would prove to bevirologically beneficial for patients with dual/mixed-tropic virus, itwas not to be. After 24 weeks of treatment, viral loads decreased by0.97 log in the placebo plus OBT group, 0.91 in the once-dailymaraviroc plus OBT group, and 1.20 log in the twice-daily maravirocplus OBT group. The differences between these groups were notstatistically significant, meaning that the slightly better viral loaddrop in the twice-daily maraviroc group could have been due to chance.

Dr.Mayer also reported undetectable viral load results. By the end of thestudy, 15.5% in the placebo group had viral loads below 50, compared to21.1% in the once-daily maraviroc group and 26.9% in the twice-dailymaraviroc group. Again, these differences were not statisticallysignificant, although the trend toward better viral load results in thetwice-daily maraviroc group is notable.

Encouragingly,average CD4 count increases were significantly greater in the maravirocgroups. CD4 counts increased by 59.6 cells in the once-daily maravirocgroup and by 62.4 cells in the twice-daily maraviroc group. In theplacebo group, CD4 counts increased, on average, by 35 cells.

Itis also important to note that some patients who entered the study withdual/mixed-tropic virus only had detectable CXCR4-tropic virus in theblood by the end of the study. Some experts have speculated that theemergence of CXCR4-tropic virus during entry inhibitor therapy wouldresult in more rapid disease progression. However, patients who endedthe study with CXCR4-tropic virus actually ended up with significantlygreater CD4 cell counts, suggesting that while therapy with a CCR5inhibitor may not result in significantly greater viral load reductionsin patients with mixed/dual-tropic or CXCR4-tropic virus, it does notappear to be harmful.

As for side effects, maravirocwas well tolerated with few differences in the types, frequency, orseverity of adverse events among all three treatment groups. Whilethere were seven deaths in the study, none of these were considered tobe related to the study drug.

In preparing for the FDAapprovals of maraviroc and vicriviroc, laboratories are beginning toemploy tropism assays and to learn more about their use (Trofile™, from Monogram Biosciences, is emerging as one such test). Thesestudy results underscore the likely importance of these tests, in orderto help treatment-experienced patients determine if they are likely torespond to these new entry inhibitors. Patients with CCR5-tropic virusmay be expected to respond well to maraviroc or vicriviroc treatment,whereas those with CXCR4-tropic or dual/mixed-tropic virus may not.

Maravirocis now in the final stage of clinical development. The Phase IIIclinical trials of maraviroc

currently under way are focusing onpatients with CCR5-tropic virus, including those starting HIV treatmentfor the first time and those in need of new treatment options. Resultsreported thus far from studies involving patients with CCR5-tropicvirus have been encouraging.

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