New CCR5 Antagonist Shows Promise in Early Study

February 18, 2010 By Tim Horn

TBR-652, a CCR5 receptor antagonist being developed by Tobira Therapeutics, was safe and well tolerated in a small 10-day study reported on Wednesday, February 17, at the 17th Conference on Retroviruses and Opportunistic Infections (CROI) in San Francisco. Additionally, the drug holds promise against CCR2, a white blood cell receptor that has been tied to several inflammatory diseases.

According to Calvin Cohen, MD, of the New England Community Research Initiative of New England, who presented the Phase II TBR-652 data at CROI, the drug can be taken once a day, without a booster, and should not interact with many other HIV medications.

Cohen also pointed out that TBR-652 is an antagonist of the CCR2 receptor, found on the cell surface of monocytes, immature dendritic cells and memory CD4 cells. As explained by Cohen, CCR2 has been associated with and studied in a variety of inflammation-associated diseases—some of which are common in people living with HIV—including atherosclerosis, metabolic syndrome and insulin resistance.

To study the preliminary safety and antiviral activity of TBR-652, Cohen's group conducted Study 652-2-201, which randomized 54 HIV-positive patients to receive 10-day monotherapy doses of 25 mg, 50 mg, 75 mg, 100 mg, 150 mg or a placebo. All patients were HIV treatment-experienced, though they had been off antiretroviral therapy for at least six weeks and had never taken another CCR5 antagonist.

After 10 days of treatment, viral loads fell, on average, by 0.5 log in the 25 mg group, 1.3 logs in the 50 mg group, 1.6 logs in the 75 mg group, 1.2 logs in the 100 mg group and 1.5 logs in the 150 mg group. In the placebo group, the average viral load reduction after 10 days was 0.1 logs.

It is important to note that viral loads continued to decrease in most treatment groups until day 15 of the study—four days after the drug was discontinued. The largest viral load decline—a 1.8 log drop from baseline—was observed in the 75 mg group. Cohen also noted that all patients in the 75 mg dosing group achieved a decline in HIV-1 RNA of at least 1.0 log.

Most adverse side effects in the study were mild in severity. The most adverse ones included nausea, diarrhea, headache and fever, though none were reported in the 75 mg group.

During the question and answer period, Cohen noted that no patients in the study experienced an HIV tropism switch—the emergence of HIV using the CXCR4 receptor on CD4 cells instead.

As for CCR2 antagonism, Cohen noted increases in blood levels of monocyte chemoattractant protein-1 (MCP-1), a molecule that usually binds to the receptor. According to Cohen, this finding signifies that TBR-652 successfully occupied the CCR2 receptor. However, additional studies are needed to determine the clinical benefits of TBR-652's CCR2-blocking activity.

Cohen concluded by saying that "TBR-652 warrants further investigation as an unboosted, once-daily, oral CCR5 antagonist with potentially important anti-inflammatory effects."

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