More Details of TBR-652's Antiviral and Anti-Inflammatory Potential Reported

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TBR-652, which blocks CCR5 receptors and is being developed by Tobira Therapeutics, not only has promising activity against HIV but may also have important disease-reducing anti-inflammatory properties, according to an update from a Phase II study of the drug reported Monday, July 19, at the XVIII International AIDS Conference in Vienna.

As was initially explained in a presentation at the 17th Conference on Retroviruses and Opportunistic Infections (CROI) earlier this year in San Francisco, and was reiterated by David Martin, PharmD, of Tobira in Vienna, TBR-652 can be taken once a day, without a booster, and should not interact with many other HIV medications.

In addition to blocking CCR5 receptors—the same mechanism of action as ViiV Healthcare's Selzentry (maraviroc)—TBR-652 stymies CCR2, a receptor found on the cell surface of monocytes, immature dendritic cells and memory CD4 cells. As summarized by Martin, 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.

Preliminary safety and antiviral activity of TBR-652 were initially reported at CROI and reported again in Vienna. Study 652-2-201 randomized 54 HIV-positive patients to receive 10-day monotherapy doses of 25 milligram (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 blocker.

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.

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.

Most of the 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.

Martin’s presentation in Vienna provided more information about TBR-652’s CCR2 antagonism, which is being determined by measuring blood levels of monocyte chemoattractant protein-1 (MCP-1)—a molecule that usually binds to the CCR2 receptor—the inflammatory high-sensitivity C-reactive protein (hsCRP) and the pro-inflammatory cytokine interleukin-6.

MCP-1 levels rose in the TBR-652-treated patients and were generally tied to the dose used—the highest dose (150 mg) group experienced the greatest increase in blood concentrations of MCP-1. This, Martin explained, indicates that the drug is acting as it should on the CCR2 receptor.

The average hsCRP level among all study participants dropped, but it’s difficult to interpret this finding because it was largely attributed to one patient who had an extremely high level of hsCRP upon entering the study that decreased dramatically during the trial.

Limited information was available for IL-6 changes because of sensitivity issues with the assay used.

Additional studies are needed to further explore the anti-inflammatory properties of TBR-652, including the clinical benefits of the drug’s dual-mechanism activities.

Martin noted in his concluding remarks that a Phase IIb study is expected to start in early 2011 with a variety of sub-studies to evaluate TBR-652’s influence on immunologic, cardiovascular and metabolic outcomes.
