Integrase Inhibitors on the Upswing for HIV

BY SHERRY BOSCHERT

SAN FRANCISCO — For the first time, an integrase inhibitor is included in the preferred first-line antiretroviral regimens for adolescents and adults with HIV, and another integrase inhibitor may be starting phase II/III clinical trials.

Integrase inhibitors in recent years have become important tools for managing highly treated patients with drug-resistant HIV.

New data showing efficacy in previously untreated patients with HIV have moved the integrase inhibitor raltegravir into the starting lineup, Dr. Diane V. Havlir said at a meeting on the medical management of HIV and AIDS sponsored by the University of California, San Francisco.

New guidelines released by the Department of Health and Human Services on Dec. 1, 2009, include a combination of raltegravir plus tenofovir and emtricitabine (TDF/FTC) as one of five preferred first-line antiretroviral therapy options for previously untreated patients with HIV.

The pivotal trial (called STARTMRK) that boosted raltegravir into first-line therapy randomized 566 treatment-naive patients with HIV to 48 weeks of TDF/FTC plus either raltegravir or efavirenz, said Dr. Havlir, professor of medicine at the university and chief of the HIV/AIDS division at San Francisco General Hospital.

Results for the raltegravir and efavirenz groups showed similar rates of viral suppression (82% and 86%, respectively) and of serious adverse events (less than 2% each), and viral suppression was more rapid in the raltegravir group (Lancet 2009;374:796-806).

Longer follow-up data out to 96 weeks now show sustained suppression of HIV RNA levels with raltegravir.

The Food and Drug Administration approved raltegravir for first-line combination antiretroviral therapy in August 2009.

A separate analysis suggested that raltegravir therapy avoids most of the increases in total cholesterol and triglyceride levels seen with efavirenz, she added, making the combination regimen containing raltegravir useful for HIV-infected patients with a history of lipid or cardiovascular problems.

The raltegravir plus TDF/FTC regimen involves more complex dosing and a higher pill burden than a once-a-day formulation of efavirenz combined with TDF/FTC (Atripla), which is one of the other preferred first-line regimens in the new federal guidelines.

An investigational integrase inhibitor that could be used in once-daily dosing might overcome that disadvantage, and the agent, S/GSK1349572, has showed promise in a preliminary trial in previously untreated patients with HIV, Dr. Havlir said.

A 10-day trial of various doses of the integrase inhibitor S/GSK1349572 in three cohorts of 10 patients each (with 8 patients on the active drug and 2 on placebo in each cohort) found that a 50-mg/day dose of S/GSK1349572 reduced HIV-1 RNA levels by 2.5 $\log_{10}$ copies/mL, according to reports at an international AIDS meeting in South Africa earlier this year.

"It's my understanding that this is now going into phase II and III trials," Dr. Havlir said. "We certainly look forward to more data on this particular agent." ■

VITALS

Major Finding: The integrase inhibitor raltegravir has joined the preferred first-line agents in combination therapy for HIV. S/GSK1349572 showed promise in a preliminary trial.

Source of Data: STARTMRK trial, a double-blind trial in 566 patients with HIV randomized to raltegravir or efavirenz. Also, unpublished data from a randomized, placebo-controlled trial of S/GSK1349572 in 30 subjects.

Disclosures: Dr. Havlir has no conflicts of interest. STARTMRK was funded by Merck, which makes raltegravir. The S/GSK1349572 trial was funded by the drug's developer, GlaxoSmithKline.