Protease Inhibitor-to-Isentress Switch is Effective, Lipid Friendly

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Replacing a Norvir (ritonavir)–boosted protease inhibitor with Isentress (raltegravir) may be an effective option—with improvements in blood lipid levels—for HIV-positive individuals with undetectable viral loads, according to the results of two Spanish studies reported Monday, July 19, at the XVIII International AIDS Conference in Vienna.

One study indicated that it may even be possible to switch to once-daily dosing of Isentress, as opposed to the standard twice-daily dosing of the drug, while also warning that switches from a Norvir-boosted protease inhibitor (PI) to Isentress—either once or twice a day—may only be suitable for patients who don't have a history of resistance to nucleoside reverse transcriptase inhibitors (NRTIs).

As was noted by Jose Gattell, MD, of the Hospital Clinic in Barcelona, who presented the results of the SPIRAL study on behalf of his colleagues, Norvir-boosted PI-based therapy has been associated with a higher risk of cardiovascular disease due, at least in part, to lipid effects. Isentress, Gattell pointed out, may show a better lipid profile, all the while being as effective as Norvir-boosted PI-based therapy in selected patients.

Eugenia Vispo, MD, of the Hospital Carlos III in Madrid, who presented data from the ODIS study, went one step further. Not only has Isentress demonstrated good antiviral activity and safety when dosed twice-daily, but its long intracellular half-life—concentrations of the drug remain elevated inside cells for several hours—might allow once-daily administration of Isentress among those switching to the drug from a Norvir-boosted PI.

The SPIRAL Study

The SPIRAL study enrolled 282 people living with HIV, all of whom were on a Norvir-boosted PI plus two other antiretrovirals (ARVs) for at least six months and had an undetectable viral load for at least 180 days. Of these patients, 142 switched their Norvir-boosted PI for Isentress (400 mg taken twice daily), and 134 patients remained on their pre-study regimen.

The primary measurement of the study was the percentage of patients free of treatment failure, for any reason, through 48 weeks of follow-up. Treatment failure was defined as virologic rebound (two consecutive viral loads above 50 copies), discontinuation of study therapy, disease progression or death. A secondary measure of the study was the proportion of patients with

virologic failure at or before week 48 (the first of two consecutive viral loads above 50 copies at least two weeks apart).

Patients entering the study were, on average, 45 years old. Nineteen percent of those in the Isentress group were female, compared with 28 percent of those who continued Norvir-boosted PI therapy. Most patients entered the study using either Kaletra (lopinavir plus ritonavir) or Norvir-boosted Reyataz (atazanavir), with either Truvada (tenofovir plus emtricitabine) or Epzicom (abacavir plus lamivudine).

Before enrolling in the study, patients had been on an average of five ARV regimens. Thirty-eight percent had a history of virologic failure using previous regimens.

Eight-nine percent of those who switched to Isentress were free of treatment failure through week 48 of the study, compared with 87 percent of those who remained on Norvir-boosted PI therapy. As for virologic failure, this was avoided by 97 percent of those who switched to Isentress, compared with 95 percent of those who remained on Norvir-boosted PI treatment.

The average change in CD4 counts was similar in both groups. There was a 46-CD4 cell gain in the Isentress group and a 44-CD4 cell gain among those who remained on their Norvir-boosted PIs.

Adverse events, leading to study drug discontinuation, occurred in 2 percent of patients in both groups. Serious adverse events occurred in 4 percent of patients in both groups.

Of note, there were significant differences in blood lipid changes through week 48 of the study. Total cholesterol, for example, decreased by 11 percent in the Isentress group, compared with a 1.82 percent increase among those in the PI-treated group. Similarly, triglycerides decreased by nearly 21 percent in the Isentress group, compared with a 4.72 percent gain in the PI group. These differences were statistically significant, meaning they were too great to have occurred by chance.

The ODIS Trial

In the ODIS trial, Vispo's group randomized 311 patients to receive either twice-daily (73 patients) or once-daily (149 patients) Isentress, instead of their previously prescribed PI, after maintaining an undetectable viral load for at least six months. What's more, patients randomized to twice-daily Isentress who maintained an undetectable load for three months in the study were randomized again to either continue twice-daily dosing (35 patients) or switch to once-daily Isentress (38 patients).

The average age upon entering the study was 46 years. About 67 percent were male. The study volunteers had been receiving ARV therapy for an average of 101 months before entering the trial; 68 percent had a history of virologic failure; and 33 percent had a history of NRTI resistance. As with the SPIRAL study, almost all patients were on either Truvada or Epzicom upon entering the trial.

About 6 percent of the patients in the study experienced virologic failure—a rebound in viral load—after switching their PIs for Isentress. Among those in the once-daily Isentress group, 6.4

percent experienced virologic failure, compared with 2.9 percent of those in the twice-daily Isentress group. This difference, however, was not statistically significant.

As for those with prior virologic failure, the overall rate of virologic failure in ODIS was 8 percent. Among those in the once-daily Isentress group with a history of virologic failure, the rate was 8.7 percent. Among those in the twice-daily Isentress group with a history of virologic failure, the rate was 4.3 percent. Here, too, the difference was too small to be statistically significant.

There was, however, a statistically significant difference when looking at those with a history of previous NRTI resistance. Among those in the once-daily Isentress group with a history of NRTI resistance, 17.7 percent experienced virologic failure within 48 weeks of switching. Among those in the twice-daily Isentress group with a history of NRTI resistance, virologic failure occurred in 8.3 percent within 48 weeks of switching.

As was seen in SPIRAL, reductions in lipid levels were documented in ODIS.

In his conclusion of the SPIRAL study, Gattell remarked that, in patients with sustained virologic suppression on a Norvir-boosted protease inhibitor-based regimen, switching to Isentress demonstrated non-inferior efficacy and resulted in a better lipid profile.

Though the ODIS study lacked a control group involving patients who remained on a PI-based regimen for comparison purposes, Vispo also said that a switch from PIs to Isentress among people with undetectable viral loads effectively sustains viral suppression—as long as NRTI resistance has not be documented in the past. In this setting, she said, the efficacy of Isentress may not differ between providing the drug twice daily or once daily.

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