Integrase Inhibitors Show Promise in HIV Therapy

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SAN FRANCISCO — The expected introduction of the integrase inhibitors will usher in the most exciting time in HIV treatment since the advent of highly active antiretroviral therapy, Dr. George Beatty predicted at a meeting on HIV management sponsored by the University of California, San Francisco.

The drug that is furthest along in trials, MK-0518, is "one of the most potent things I have ever seen," said Dr. Beatty, commenting on recent trial results. "Clearly, MK-0518 can really kick butt."

In the initial study in patients, MK-0518 (Merck) reduced viral loads by 2 log10 in just 10 days, a finding that was consistent with recent, double-blind trials, said Dr. Beatty, director of the HIV clinical trials group at the University of California, San Francisco, who did not participate in the trials and who said he had no conflicts of interest regarding the manufacturer.

All of the studies were presented at HIV meetings in 2006.

In the most recent of those studies, treatment-experienced patients with serious drug-resistant disease were randomly assigned to receive one of three doses of the new drug or placebo in addition to continuing their optimized background therapy. There were about 40 patients in each group.

At 16 weeks, 50% of the patients who were treated with MK-0518 had a viral load below 50 copies/mL, regardless of which dose they received, compared with only about 20% of patients on placebo.

At 24 weeks, 67% of the patients who were on active therapy had a viral load below 50 copies/mL.

The response rate was even more impressive in the subgroup whose background medications included enfuvirtide, also known as T20, an anti-HIV entry inhibitor. Overall, 90% of those patients achieved a viral load below 50 copies/mL at 24 weeks.

The patients in this trial were difficult to treat, with resistance to at least one drug in each of the three main classes of HIV medication, Dr. Beatty noted.

"It's sexy data," he said, of all the trials of MK-0518 to date.

Integrase inhibitors prevent DNA created by the retrovirus from becoming incorporated into the host cell DNA, thereby blocking reproduction.

MK-0518 is currently available through an expanded access research program to patients whose infection was previously uncontrolled.

A second integrase inhibitor that is "close on the heels" of MK-0518 in development is GS-9137 (Gilead), Dr. Beatty said. This drug also has shown the ability to reduce viral load by 2 log10 in about 10 days.

"It appears that Merck has not cornered the market on potency, and that this degree of potency is a class effect," he said.

One difference between the two drugs is that MK-0518 requires twice daily dosing, while GS-9137 uses once daily dosing.

Also, MK-0518 is metabolized by glucuronidation, so it does not appear to have any significant drug-drug interactions.

GS-9137, on the other hand, is metabolized by cytochrome P3A, so it may interact with other drugs.

Also, GS-9137 can be boosted with ritonavir, while MK-0518 cannot.

So far, the drugs appear to be very well tolerated. However, one patient in the MK-0518 trial developed abnormal liver enzymes that appeared to be drug related.

In vitro data suggest that when resistance does develop, it is broad resistance to all drugs in the class, Dr. Beatty added. ■

Effect of Nonadherence to HIV Therapy Is Variable

SAN FRANCISCO — Adherence to highly active antiretroviral therapy remains important, even though treatment may be more forgiving of nonadherence than some have suggested, Dr. Kristen M. Ries said at a meeting on HIV management sponsored by the University of California, San Francisco.

In 1999, adherence to a HAART regimen was said to require 95% compliance; if the patient was not compliant to that degree, his or her infection was likely to become resistant to treatment. That figure is still quoted today.

But the situation is probably not that simple. The study that produced the 95% figure used data from patients who were taking a single protease inhibitor or who had taken many nonnucleoside reverse transcriptase inhibitors, not data from those on HAART, said Dr. Ries, who is clinical director of the infectious diseases and HIV clinics at the University of Utah Hospital, Salt Lake City.

Rates of resistance and treatment failure actually vary somewhat depending on the regimen and the particular drugs used, she said.

In general, it has been estimated that for every 10% decrease in adherence there is a doubling of the viral load and a 20% increase in disease progression, and Dr. Ries said that she thinks "that is generally true." But patients are individuals and so are the drugs.

According to current data, a single protease inhibitor selects for resistance at about 85% adherence. A nonnucleoside reverse transcriptase inhibitor is more forgiving of individual missed doses, but nonadherence is more likely to result in viral mutations that will render the entire class ineffective.

"Nonadherence is still more predictive of treatment failure than most everything else, at least in my hands," she said.

Physicians who treat HIV patients should take these individual drug characteristics into consideration when deciding which regimen to prescribe, she said.

Nonadherence to a nonnucleoside reverse transcriptase inhibitor is more likely to result in viral mutations that will render the entire class ineffective.

Adherence to a HAART regimen is difficult because the regimens are complicated, and studies show that many patients on chronic medications are not adequately adherent, Dr. Ries said.

One way to improve patient adherence is to get to know the patient before prescribing, so that knowledge can be applied to choosing a regimen.

It also helps to educate the patient before he or she starts therapy, because a patient who does not trust a regimen or is not committed will be less adherent, she advised.

Another approach is to always ask the patient about adherence using specific questions, such as: "How many doses did you miss last week?" Most patients will admit that they have missed doses if they are asked in a nonjudgmental manner, but they are probably unlikely to volunteer the information.

Nonadherence "is really chronic relapsing behavior, and it goes on and on," she added. "There's no way to predict adherence until you actually do it." ■

Early Treatment of HIV May Be Beneficial, Despite Uncertainties

SAN FRANCISCO — Treating a recently infected HIV patient may provide some benefit, particularly if that treatment begins before or within a few weeks of antibody seroconversion, Dr. Frederick Hecht said at a meeting on HIV management sponsored by the University of California, San Francisco.

So what should physicians do in practice?

"What I recommend is that we put this in lay language and inform patients of both the risks and the benefits, and the still uncertainties of treating early," said Dr. Hecht of the department of medicine at UCSF. "There may be some benefit, based on the data, but it is not completely conclusive."

The current model of acute HIV infection is that T-cell destruction varies in different tissues in the body, and that the worst destruction occurs in the gut, where the majority of the body's T cells reside, particularly memory T cells that express the chemokine (C-C motif) receptor 5 (CCR5) that is a coreceptor for HIV.

Data from simian modeling with simian immunodeficiency virus show that T-cell depletion in the gut occurs very rapidly in infection, and that early treatment can preserve some of these memory T cells, which may allow better immune-system control of HIV over a longer term.

Clinical data in humans on whether early treatment can preserve T cells and reduce viral loads, however, have been conflicting.

Therefore, Dr. Hecht and his colleagues looked at a cohort of 395 patients who were identified early in the course of the infection, and compared the 58 patients who received early treatment with the 337 patients who were not treated as quickly (J. Infect. Dis. 2006;194:725-33).

The early-treatment patients were those who had been treated with at least a three-drug regimen for at least 12 weeks, with the drugs stopped for 4 weeks before the patients' data were examined. The mean duration of treatment was 1.5 years.

The analysis showed that the 13 patients who began their acute treatment within 2 weeks of their seroconversion had significantly lower viral loads, compared with the untreated patients (mean difference between groups, 0.68 log10 copies/mL), and that difference continued for the entire 72 weeks after their treatment ended.

The treated patients also had a slightly higher mean CD4 cell count than did the untreated patients (about 100 cells/mcL higher), and this increase also persisted.

In the 45 patients who began treatment more than 2 weeks after—but within 6 months of—seroconversion, there were lower viral loads and higher CD4 counts at 24 weeks after treatment stopped.

But that advantage waned over time. At 72 weeks, there was no longer any significant difference in viral load, and there was a diminished, albeit still significant, difference in CD4 cell count.

Another reason to consider treating patients early is that doing so will reduce their viral load, which is generally very high acutely, and will thereby reduce the chance that they will spread the virus to others, Dr. Hecht said.

"Acute HIV infection really is an important period for HIV transmission," he said. ■