

New Protease Inhibitor May Help When Others Fail

BY MITCHEL L. ZOLER
Philadelphia Bureau

WASHINGTON — A new protease inhibitor, tipranavir, was effective for controlling HIV infection in patients who had failed treatment with the standard protease inhibitors now on the U.S. market, in a phase III study with 620 patients.

Tipranavir's efficacy against HIV strains resistant to existing protease inhibitors (PI) was a welcome development, giving physicians a new way to treat patients no longer responding to standard combinations of antiretroviral drugs. Tipranavir is the first non-peptidic, dihydropyridone PI. Results from prior studies showed that it retains activity against dozens of HIV isolates that are highly resistant to all PIs now available, including amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir.

"Tipranavir appears to be a very promising agent for patients with highly PI-resistant virus," Joseph J. Eron Jr., M.D., commented at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy. "Long-term success with tipranavir is likely to require coadministration with other drugs that are active against a patient's specific HIV-1 variant," added Dr. Eron, director of the AIDS clinical trials unit at the University of North Carolina at Chapel Hill.

The study was sponsored by Boehringer Ingelheim Pharmaceuticals Inc., which makes tipranavir. Last October, the company submitted a license application to the Food and Drug Administration based on the results from this study and results from a second phase III study that have not yet been reported. Tipranavir is currently available to U.S. patients through a compassionate-use program.

The study enrolled patients who had a viral load of more than 1,000 copies/mL of HIV RNA, who had already been treated with at least two PI-based regimens of antiretroviral drugs, and who had received drugs from at least three classes of antiretroviral drugs (nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, and PIs). The primary strain of HIV that infected each patient had to have at least one primary mutation that conferred re-

sistance to PIs, but no more than two of the protease resistance-associated mutations.

Patients were randomized to either an optimized antiretroviral regimen that included a standard PI, or to an optimized regimen that included 500 mg tipranavir b.i.d plus 200 mg ritonavir b.i.d (a PI often added to a regimen to boost serum levels of the primary PI). About a third of all patients had the relatively new drug enfuvirtide, an HIV fusion inhibitor, included in their regimen.

After 24 weeks of treatment, 41.5% of patients treated with tipranavir had at least a 1.0-log drop in their viral load, compared with baseline, the study's primary end point, compared with 22.3% of patients in the control arm—a statistically significant difference, reported Charles B. Hicks, M.D., associate director of the AIDS research and treatment center at Duke University in Durham, N.C.

The overall average drop in viral load among all patients was 0.88 log in the tipranavir group and 0.28 log in the control group. Viral load dropped to completely undetectable levels in 25.1% of patients in the tipranavir group, compared with 10% of those in the control group.

One additional analysis highlighted the improved responses of patients who were placed on two drugs that were active against their infection. Among the patients who received enfuvirtide along with tipranavir, 32.8% had their viral load drop to an undetectable level, compared with 14.3% of patients in the control group who were treated with enfuvirtide, Dr. Hicks said at the meeting, sponsored by the American Society of Microbiology.

The incidence of adverse events was similar in the two study groups, 22.8% among those treated with tipranavir and 18.1% among the control patients. The rate of elevations of liver enzymes or serum lipids was higher in patients treated with tipranavir, but these were mostly transient and asymptomatic. Two patients in the tipranavir group stopped treatment because of a rise in liver enzymes.

The results were a "proof of concept that in an advanced patient population treatment with tipranavir is superior to boosting another PI," commented Michael S. Saag, M.D., professor of medicine at the University of Alabama, Birmingham. ■

Two New Anti-HIV Drugs Provide Effective Combo

BY MITCHEL L. ZOLER
Philadelphia Bureau

WASHINGTON — The best strategy for using two of the newest anti-HIV drugs, tipranavir and enfuvirtide, may be to use them together because each appears to work better when coupled with at least one other active antiretroviral drug, several experts recommended at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy.

After enfuvirtide, an HIV-fusion inhibitor that's administered as a subcutaneous injection, was approved by the Food and Drug Administration in early 2003, "a lot of physicians shied away from using it, perhaps because it's an injectable or perhaps because they didn't have other drugs to partner with it," said Michael S. Saag, M.D., professor of medicine at the University of Alabama, Birmingham.

"Finding the right time to pull the trigger and use enfuvirtide is a challenge, but waiting too long can cut patient responsiveness to the drug," Dr. Saag added. "With tipranavir becoming available, there will be a lot more use of enfuvirtide."

A new analysis of the data collected during the phase III trials that led to enfuvirtide's licensing highlighted the importance of starting enfuvirtide treatment sooner rather than later, said Calvin J. Cohen, M.D., an internist in group practice in Boston.

This posthoc analysis identified four factors that were each associated with enfuvirtide treatment leading to a marked drop in a patient's viral load:

1. Starting enfuvirtide treatment when the patient had a CD4 count of more than 100 cells/ μ L.
2. Starting treatment when a patient's viral load was less than 100,000 RNA copies/mL.

3. Having at least two active antiretroviral drugs in the regimen.

4. Treating patients who had previously been treated with no more than 10 antiretroviral drugs.

"Delaying initiation of enfuvirtide may be associated with a reduced likelihood of response," Dr. Cohen said at the meeting, sponsored by the American Society for Microbiology. "In some cases, it may be in the patients' best interest to use enfuvirtide when tipranavir is available."

Both Dr. Saag and Dr. Cohen have been investigators in studies using enfuvirtide that were sponsored by Trimeris Inc. and Roche Laboratories Inc., the companies that market enfuvirtide, and both have also served as speakers for these companies.

Study results presented at the meeting on the new protease inhibitor tipranavir also suggested that this drug would work best when coupled with at least one other active antiretroviral drug. Because tipranavir will likely be used on patients infected with HIV that's become resistant to standard protease inhibitors, these viruses are also often resistant to the other drugs that are frontline agents for treating HIV. When tipranavir is begun, enfuvirtide may be one of the few agents left that's still effective against a patient's infection.

"Long-term success with tipranavir is likely to require coadministration with other drugs that are active against a patient's specific HIV variant, which may include drugs from new classes such as enfuvirtide," Joseph J. Eron Jr., M.D. said at the meeting. Dr. Eron, director of the AIDS clinical trial unit at the University of North Carolina at Chapel Hill, has worked in studies of tipranavir sponsored by Boehringer Ingelheim Pharmaceuticals Inc., which makes tipranavir, and he has served as a speaker for Roche and Trimeris. ■

Thorough Anal Exam Crucial, Especially in HIV Disease

BY ROBERT FINN
San Francisco Bureau

SAN FRANCISCO — A look at the epidemiology of anal cancer demonstrates the need for thorough anal exams, particularly in individuals of both sexes with HIV disease. Joel M. Palefsky, M.D., said at a meeting on HIV management sponsored by the University of California, San Francisco.

Prior to the HIV epidemic, reported rates of anal cancer among men who have sex with men (MSM) were as high as 35/100,000, about the same as the rate of cervical cancer among women before universal screening.

Now, data suggest that MSM with HIV

disease have anal cancer rates as high as 100/100,000, or about 10 times the rate of cervical cancer among screened women, which has declined to about 8/100,000, said Dr. Palefsky of the university.

Visual inspection of the anal opening is not sufficient, he said, although this step should certainly not be dispensed with. Visual inspection can, for example, turn up the diffuse, hyperpigmented, flat plaques of Bowen's disease. "Most of the action is occurring intraanally, where you need special techniques to see what's going on."

Two centimeters inside the anal canal is a transformation zone where the rectal columnar epithelium meets the anal squamous epithelium. This transformation zone is quite similar to the cervical trans-

formation zone, and similarly, that's where most disease occurs.

Anal and cervical disease have many other similarities as well, especially in their association with human papilloma virus (HPV) infection.

After visual inspection, the next step is an anal Pap smear, which must be done without lubricant. Moisten a Dacron (not cotton) swab with tap water or saline and insert it past the anal-rectal junction as far as it will go. As it's pulled out, it will capture a good sample of cells from the transformation zone, which can then be examined cytologically and tested for HPV. Virtually everyone with HIV disease—regardless of gender—will have HPV infection, some with as many as 10 virus types.

A Pap smear tests for dysplasia, not cancer, so the next step is a digital rectal exam, which is a good cancer-screening tool, Dr. Palefsky said. Put a lubricated finger in the anal canal and feel for subcutaneous masses that would not otherwise be visible.

Next, perform an anoscopy with a standard plastic anoscope. Cancerous and precancerous lesions in the anus appear quite similar to what one would see in the cervix.

Dr. Palefsky cautioned against dismissing standard-seeming warts, especially in individuals with HIV disease. These patients often have high-grade disease mixed in with these warts. "We recommend sampling, through biopsy, lesions of different appearance when patients have multiple lesions, which is often the case." ■