



Second chance

The results of phase III trials on etravirine are encouraging

by **Ashley Smith**

Further studies of etravirine continue to show its promise as a second-line drug. Etravirine, also known as TCM 125, is a new experimental non-nucleoside reverse transcriptase inhibitor (NNRTI). This class of drugs, which includes efavirenz (Sustiva) and nevirapine (Viramune), binds to the viral enzyme, reverse transcriptase, thereby rendering it inactive and inhibiting the transcription of the viral RNA into the viral DNA.

Like its counterparts, etravirine—which is manufactured by Tibotec—is used in conjunction with drugs from other classes, such as protease inhibitors and nucleoside reverse transcriptase inhibitors (NRTI) to prevent viral replication by disrupting the life cycle of the virus.

Etravirine's unique chemical structure allows for flexibility, which allows it to bind to reverse transcriptase even when the enzyme has several mutations.

What's most interesting and exciting about etravirine is its mutation tolerance. Many drugs used to treat HIV become ineffective due to viral genetic mutations. Efavirenz and nevirapine can tolerate relatively few mutations before the efficacy of the drug is compromised. By contrast, etravirine escapes this fate due to its unique chemical structure that allows for flexibility, which allows it to bind to reverse transcriptase even when the enzyme has several mutations. Etravirine has shown promise as a good second-line drug once the virus has become resistant to efavirenz.

Etravirine is currently undergoing clinical trials. In a phase II trial, 16 patients were given etravirine and then compared to a placebo group. The etravirine group showed an average of a 100-fold decrease in viral load and some patients fell below 400 copies/ml of blood. The virus showed no mutations in this seven-day course of monotherapy with the drug. Etravirine has also been shown to decrease viral loads in patients that have failed efavirenz or nevirapine. There was an average of just under a 10-fold change in viral load in these patients, regardless of dosage. The more mutations the virus has, the less effective etravirine was in decreasing viral load.

Not all the clinical trials have been so positive. A phase II clinical trial had to be stopped when the etravirine group of the study was doing worse than the control group, which was taking a protease inhibitor.

Still, etravirine has relatively few side effects when tested in trials. As with efavirenz and nevirapine, rashes were common; however, they appear to resolve a few days after treatment is started. There has been no research into the effects on a fetus or what the transmission rate was with mothers who are breastfeeding, so etravirine isn't recommended for pregnant woman or woman who are breastfeeding.

On September 20, 2007, the US Food and Drug Administration granted priority review to etravirine. That will allow for a timely analysis of the drug and its side effects, since it meets the requirement of medical urgency for its availability and usage. The expected approval date is January 2008. ☺

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