Reengineered T Cells May Block Spread of HIV

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MINNEAPOLIS — A gene therapy appears to block the spread of HIV virus in humans, according to a study presented at the annual meeting of the American Society of Gene Therapy.

Three patients with drug-resistant strains of HIV have undergone the experimental treatment, which involves taking T cells from patients and reengineering them so they can paralyze HIV and prevent it from spreading to other cells.

"Preliminary analysis has shown a lower level of HIV in their blood stream than predosing levels, which, given the nature of a phase I clinical trial, is very encouraging," Boro Dropulic, Ph.D., chief scientific officer and founder, VIRxSYS Corp., Gaithersburg, Md., said in an interview.

The therapy consists of an HIV-1–based lentiviral vector that contains a 937-base antisense gene against the HIV envelope, *VRX496*, for autologous T-cell therapy, said Dr. Dropulic, who is conducting the research in collaboration with Johns Hopkins University in Baltimore and the University of Pennsylvania in Philadelphia.

Patients undergo leukopheresis with CD4-cell isolation. The vector that is used is based on a debilitated form of a lentivirus, which contains an antisense sequence that is targeted to the envelope gene.

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Its expression should inhibit the replication of HIV in a transduced cell.

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CD4 cells are transduced with the vector and subsequently expanded in culture for 8-11 days to more than 10 billion cells prior to reintroduction into the patient. The cells are given intravenously over 30 minutes.

Preclinical studies showed the feasibility of the approach in normal CD4 cells and in CD4 cells taken from 20 early- and late-stage patients. This is noteworthy, given the rapid emergence of drug-resistant strains of HIV, Dr. Dropulic said.

About 15% of newly transmitted virus is already resistant to at least one antiretroviral drug, which brings into question whether highly active antiretroviral therapy is a long-term solution to the AIDS crisis.

In the United States, where highly active antiretroviral therapy has become the standard of care, there are issues surrounding the toxicity of antiretroviral therapy and the spread of drug-resistant forms of HIV through the population, which limit the utility of these drugs, Dr. Dropulic said.

In the phase I, open-label clinical trial, five highly active antiretroviral therapy-resistant patients with CD4-cell counts between 200 and 500 cells/μL were serially enrolled to receive about 10 billion modified autologous CD4 cells in a single dose.

To date, three subjects have been infused and have completed early monitoring.

Adverse events were defined in part by a sustained 0.5-log increase in viral load or sustained 0.5-log increase in CD4 count within 3 weeks post dose.

Patients were monitored for the emergence of any replication-competent lentivirus. At baseline, subject one had an average viral load of 188,500, which fell to 70,006 by day 266.

Subject two's average viral loads were 54,000 at baseline and 8,600 at day 180; subject three's were 46,150 at baseline and 43,612 at day 90, Dr. Dropulic said.

There have been no adverse events, and all replication-competent lentivirus assays have been negative.

CD4 counts remain steady in all three patients, and there has been no evidence of change in the patients' T-cell repertoire, Dr. Dropulic said.

The second phase of the trial is designed to evaluate efficacy, and future trials are planned to examine the impact of single as well as multiple infusions. ■