A clinical trial of gene therapy for HIV

Researchers in California and Australia have developed a gene therapy called OZ1. This therapy works by making CD4+ T-cells resistant to HIV infection. Results from previous and current clinical trials suggest that OZ1 is safe and has modest effectiveness. However, OZ1 is important in other ways, which we explain later in our report.

About OZ1

Researchers began their project by finding a virus to carry the genes they chose for therapy. The virus they selected was one that caused leukemia in mice. However, they removed the cancer-causing genes and inserted genes that did the following:

- cause CD4+ cells to make an enzyme that cuts up a specific part of HIV's genetic material; as a result, in cells treated with OZ1, HIV is unable to cause infection.

Study details

Researchers recruited 74 participants whose average profile at the start of the study was as follows:

- 92% male, 8% female
- age – 37 years
- CD4+ count – 700 cells
- viral load – less than 400 copies
- all participants were taking HAART

Researchers randomly assigned participants to one of two groups, as follows:

- OZ1 – 38 volunteers
- placebo – 36 volunteers

Researchers removed blood from the study volunteers and filtered out some bone marrow stem cells, identified as CD34+. They then infused the filtered blood back into participants. CD34+ bone marrow stem cells can develop into any one of a wide range of cells used by the immune system, including CD4+ cells.

The stem cells were collected and cultured and then infected with the weakened mouse virus that carried genes to help make them resist HIV infection. After they were infected, the stem cells were stimulated to produce more CD34+ cells for several days.

These cells were then infused back into participants based on their weight—5 million cells per kg of body weight. For instance, a person who weighed 70 kg would have received 350 million CD34+ cells. Each person received a single infusion of cells. On average, about 54% of the cells infused contained OZ1 genes.

Participants in the placebo group also received CD34+ cell infusions but without protective OZ1 genes.

Participants were highly motivated and able to undertake the 45 visits to study clinics over two years—a requirement of the study. HAART was interrupted during the study to assess the impact of uncontrolled HIV infection on the gene-enhanced cells.

Results

Four weeks after infusion, technicians detected HIV-resistant cells from blood cells in 94% of people in the OZ1 group. One year after the infusion, this figure fell to 12% and two years after the infusion it fell to 7%.
OZ1 recipients tended to have higher CD4+ and CD8+ counts than people who received placebo, but this difference did not reach statistical significance.

Eight weeks after participants underwent a treatment interruption, viral load was generally lower in the OZ1 group compared to placebo. Again, this difference was not statistically significant.

**Results—safety**

None of the participants assigned to receive OZ1 died or had severe heart, kidney or liver toxicity. Three serious complications did occur in the study but all in the placebo group.

The study protocol included an interruption of therapy. During this time, new outbreaks of the flu, herpes and oral yeast infections occurred in both groups.

**In perspective**

This study of OZ1 was the largest randomized controlled trial of gene therapy in HIV to have reached the phase II stage of development. The improvements in CD4+ counts and viral load were at best modest. Still, the results underscore a promising trend in those measures. Future gene therapy experiments need to find ways to do the following:

- get more CD34+ stem cells to take hold in the bone marrow
- prolong the life of CD4+ cells containing gene therapy
- demonstrate significant anti-HIV activity
- consider enrolling HIV positive people who have not yet started HAART

Further experiments with this and other forms of gene therapy for HIV are being planned in the United States.

**REFERENCE:**

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