Editing CCR5 gene to confer HIV resistance

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THE STUDY: Tebas P, Stein D, Tang WW, et al. Gene editing of CCR5 in autologous CD4 T cells of persons infected with HIV. *N Engl J Med* 2014; 370:901-910

BACKGROUND

The advent of zinc finger nucleases (ZFNs) restriction enzymes, designed to induce site-specific changes in DNA, has allowed modification or "editing" of the human genome. The discovery of ZFN has provided high specificity coupled with restrained activity; important attributes that had limited the applicability of earlier agents. Chemokine receptor 5 (CCR5) gene is critical in the pathogenesis of human immune-deficiency virus (HIV) as it encodes a trans membrane protein that mediates intracellular entry of HIV. Humans who are homozygous to a 32 base pair deletion in the CCR5 gene are resistant to HIV, while those who are heterozygous exhibit significantly delayed progression to AIDS.

WHY WAS THE STUDY CONDUCTED?

The discovery of the role of CCR5 has led to several potential therapeutic implications. For instance, it has been shown that the drug Maraviroc that binds selectively to the CCR5 leads to significantly reduced HIV viral load and increased CD4 counts compared to placebo. This study attempted to explore whether inducing partial acquired resistance to HIV through CCR5 modification by ZFNs' is safe and tolerable in HIV positive patients.

THE STUDY

This non-randomized and uncontrolled clinical trial enrolled twelve patients who had undetectable viremia during treatment with HAART. Six of these patients, designated as immune responders, had CD4 T cell counts over 450 cells per cubic millimeters at the screening time. In these patients, HAART was halted for 12 weeks as per study protocol. The non-immune responders' cohort constituted of six patients who had CD4 T cell counts between 200-500 cells per cubic millimeters, despite at least two years of treatment with HAART. All patients were infused with a one-time autologous CD4+ T-lymphocyte dose of 10 billion cells developed ex vivo by inducing a CCR5 modification using ZFN.

The study shows the safety of the technique (primary outcome) with one patient requiring emergency visit secondary to fever, chills and joint pain. The adverse effect was secondary to the transfusion reaction. The study also found a significantly increased CD4+ T cell count, increasing almost three-fold at one-week post transfusion. The decline in CD4 T cell count was significantly lower in the CCR5 modified cells compared with the unmodified cells. However, HAART had to be restarted before 12 weeks among all the immune responders.

WHAT IS THE WAY FORWARD?

This is the first clinical trial to show that infusion of ZFN-modified CCR5 cells in HIV patients is safe. The study is limited by a small sample size. Future studies will likely assess the efficacy and long-term outcomes of this promising new treatment before it can become routinely applicable in clinical settings.

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