Genetic HIV Therapy Aided by Drug to Boost CD4 Infusion

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Sangamo BioSciences' promising genetic therapy for HIV is apparently augmented by the drug Cytoxan, which improves the chances that immune cells genetically altered to resist HIV will flourish in the body. Various results from Sangamo's SB-728-T program, in which the company is aiming to develop a functional cure for the virus, were presented by Gary Blick, MD, medical and research director of the CIRCLE CARE Center in Norwalk, Connecticut, at the Conference on Retroviruses and Opportunistic Infections (CROI) in Boston.

This news follows on the heels of a promising early safety study of Sangamo's zinc-finger nuclease (ZFN) technology that was published in The New England Journal of Medicine.

The Cytoxan-focused study discussed at CROI is a Phase 1/2 clinical trial called SB-728-1101. It is an open-label, dose-escalation, multi-center study primarily examining the safety and tolerability of increasing doses of Cytoxan (cyclophosphamide) given before an infusion of genetically altered CD4 cells.

Sangamo's genetic treatment involves drawing CD4s from HIV-positive study participants and then using the ZFN technique to edit the genes of immune cells to create a mutation on the gene for the CCR5 receptor, onto which most versions of HIV must latch in order to ultimately enter the cell. Consequently, the new cells have mutated CCR5 receptors, and therefore resist infection by the common form of HIV. The scientists then spur the growth of the cells outside the body and reinfuse them into the study participant, in hopes that enough HIV-resistant CD4s will populate the individual and allow him or her to control the virus without the need for daily antiretrovirals (ARVs).

Before they conduct the infusion in this study, the researchers administered Cytoxan, which lowers the CD4 population level in the body. After the drug is cut off, the body begins to rapidly renew its CD4 stores. The infusion of genetically altered cells is given during this upswing, with the goal of improving the cells' "engraftment." (This is a technique used in both cancer and autoimmune disease treatment.)

In this study, nine HIV-positive participants, who were all taking ARVs, received varying doses of Cytoxan.

Six weeks after receiving the infusion of CD4s, those who had a CD4 count of at least 500 stopped taking ARVs for 16 weeks. At the end of that period (the researchers presented preliminary data at CROI), those who have a viral load below 10,000 and a CD4 count greater than 500 can stay off ARVs until their viral load or CD4 levels cross those thresholds.

The participants who received higher doses of Cytoxan experienced better engraftment of the genetically altered CD4s and had greater increases in CD4 levels than found at the beginning of the study. Those who took the highest dose of Cytoxan have experienced a peak viral load that was nearly 99 percent lower than the peak level they experienced before going on ARV therapy. Out of the three participants taking this dose, two have been off ARVs for several weeks with detectable but stable levels of HIV.

Those cells modified by the ZFN technique survived longer in the presence of HIV than other CD4 cells.

Cytoxan was found to be safe and well tolerated at the doses used in the study. As the researchers expected, the increasing doses lead to nausea and vomiting, requiring the prophylactic use of an anti-emetic.

Sangamo also announced that a participant from another study of this ZFN technique has remained off ARVs for 31 weeks with an undetectable viral load. This study includes people with HIV who carry one of the two genes necessary to naturally effect the CCR5 genetic mutation.

“The achievement of over seven months of ongoing functional control of viral load without antiretroviral therapy and the progress that we are making in understanding how to best deploy this novel therapy are very exciting,” Gary Blick said in a release. “The data that have been generated over the course of the clinical investigation of SB-728-T demonstrate immune reconstitution, enhanced survival of the zinc finger nuclease-modified T cells in the presence of the virus and associated reductions in viral load and the levels of viral reservoir, all of which are necessary to provide functional control of the virus.”

To read the Sangamo press release, click here.
