Sangamo’s Gene Therapy Continues to Show Well in Study

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Genetically modifying CD4 cells to knock out the CCR5 coreceptor resulted in significant CD4 count gains and, in some patients, a notable reduction in viral load while off antiretroviral (ARV) therapy, according to new data from a clinical trial reported in two presentations at the 51st Interscience Conference on Antimicrobial Agents and Chemotherapy in Chicago.

“The data obtained in our treatment interruption studies are very exciting and represent significant progress toward a ‘functional cure’ for HIV/AIDS,” said Carl June, MD, director of translational research at the Abramson Family Cancer Research Institute at the University of Pennsylvania School of Medicine and a study investigator, in a press release from Sangamo. “The statistically significant relationship between estimated modification of both copies of the CCR5 gene and viral load during the treatment interruption suggests that the next step is to increase the frequency of the modified cells in HIV-infected patients with the ultimate hope that if we do, we will achieve a ‘functional cure’ and eliminate the need for continued [ARV treatment].”

After HIV binds to the CD4 protein on CD4 cells the virus must then latch onto another receptor on the cell’s surface—either CCR5 or CXCR4. Usually, when people contract HIV, their virus starts off using the CCR5 receptor. Later on, as HIV disease progresses, the virus can switch to the CXCR4 receptor—this occurs in about 50 percent of treatment-experienced patients.

Selzentry (maraviroc), a U.S. Food and Drug Administration (FDA)–approved ARV, works by blocking the interaction between CCR5 and HIV, ultimately retarding the virus’s ability to infect CD4 cells. SB-728-T, a zinc finger DNA-binding protein transcription factor, goes one step further—it blocks the gene responsible for making CCR5, mimicking a naturally occurring human mutation that renders individuals largely resistant to the virus.

This mutation, dubbed CCR5 delta-32, appears to have no deleterious effect in the human body. In addition, a study published in Blood in December 2010 reported an effective cure when an HIV-positive person with leukemia received a bone marrow transplant from a “matched” donor with this delta-32 CCR5 mutation inherited from both parents. (When the mutation is inherited from one parent, CCR5 is produced, but at low quantities and is associated with slower HIV disease progression. When the mutation is inherited from both parents, which is very rare, little or no CCR5 is expressed on CD4 cells, rendering the cells impervious to forms of HIV that use the CCR5 receptor to enter cells.)

Sangamo's gene therapy approach has both therapeutic and curative potential. At present, only Sangamo's therapeutic-focused CCR5-knockout SB-728-T has entered clinical trials.

Therapy involves removing CD4 cells from patients' blood, treating the cells with SB-728-T to knock out the CCR5 gene, multiplying the cells in the lab, then transplanting the HIV-resistant genetically modified cells back into the body.

Fully curing HIV will be a bit more complicated, as it ultimately requires replacing the entire CD4 population with HIV-resistant cells, not merely creating a small reservoir of protected cells. A curative approach will likely involve removing and treating stem cells with CCR5 and possibly CXCR4 knockout genes, administering high-dose chemotherapy to wipe out the existing HIV-susceptible immune system, followed by transplanting the modified stem cells to rebuild an immune system that is resistant to the virus.

Preliminary data from evaluations of of SB-728-T were reported earlier this year at the 18th Conference on Retroviruses and Opportunistic Infections (CROI) in Boston. Data involving another nine patients were reported by Ronald Mitsuyasu, MD, of the University of California at Los Angeles, on Saturday, September 17, at ICAAC.

Similar to the earlier report, infusion—involving 10, 20 or 30 billion genetically modified CD4 cells—was well tolerated in the nine patients reviewed by Mitsuyasu. No unexpected side effects were reported; injection site reactions and flu-like symptoms following the infusions were the most common complications.

The modified cells were successfully engrafted in the patients—all had entered the study with fewer than 450 CD4 cells, despite years of otherwise successful ARV therapy use—and the cells persisted for nearly a year (and up to 561 days in one patient). Follow-up blood samples, collected 28 days after the infusions were administered, indicated that the modified cells made up 0.2 to 2.8 percent of the patients' CD4 cells.

CD4 counts increased, on average, by 163 cells by the end of the study, and most patients exhibited sustained improvements in their CD4:CD8 cell ratio, an indicator of immunologic health that is infrequently documented in ARV therapy clinical trials.

The modified cells also took up residence in rectal tissue—a major reservoir of virus in the body—suggesting, as predicted, that the cells were proliferating and remaining impervious to HIV infection. Ninety days post-infusion, approximately 6 percent of the cells in rectal tissue samples were CCR5 deficient.

Additional data from the study were reported at ICAAC on Sunday, September 18, this time involving six patients who entered the trial with CD4s higher than 450 and who agreed to undergo a 12-week treatment interruption after receiving their infusion. These results came from experiments conducted at the University of Pennsylvania Medical Center in Philadelphia and at Albert Einstein College of Medicine in New York.

Here too there was persistent engraftment of the gene-modified cells, along with overall improvements in CD4 counts and CD4:CD8 ratios, as good trafficking to rectal tissue.

In three of the six subjects, significant viral load reductions—between 0.8 and 2.0 log below pre-ARV therapy levels—were documented during the treatment interruption phase of the study.

Viral load levels also went undetectable in one patient, though he entered the study with a natural CCR5 delta-32 mutation on one copy of his CCR5 gene.

Not surprisingly, study volunteers who had the highest percentage of CCR5-deleted CD4 cells in blood samples following the infusion experienced the greatest reductions in viral load during the treatment interruption. This observation has prompted Sangamo and independent researchers exploring SB-728-T to consider increasing the number of gene-modified CD4 cells infused into patients, potentially turning a therapeutic candidate into a functional cure—essentially doing away with the need for antiretroviral therapy, at least for extended periods of time.

Sangamo says it plans to continue expanding its clinical trials and exploring mechanisms to enhance engraftment and maximize the impact of the HIV-resistant cells on viral load and the overall immune system of people living with HIV. “The ground-breaking clinical data that we and our collaborators are generating continue to validate our highly specific ZFN technology as a platform for development of novel therapeutic products,” said Geoffrey Nichol, Sangamo’s executive vice president of research and development.

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