New Studies Under Way of Sangamo's Possible 'Functional Cure' Gene Therapy

January 10, 2012

Sangamo BioSciences has begun new clinical studies of its promising gene therapy SB-728-T, a potential "functional cure" for HIV infection, according to a January 9 announcement by the company.

SB-728-T is a zinc finger DNA-binding protein transcription factor (ZFP TF). It disrupts the gene responsible for making CCR5 co-receptors on the surface of CD4 cells, to which HIV bonds. When CD4 cells can't produce functional co-receptors, it is much harder for HIV to infect them.

The aim of SB-728-T therapy is to grow a new population of CD4 cells that are resistant to HIV infection, and thus make antiretroviral (ARV) therapy unnecessary.

The rationale for using SB-728-T comes from the case of Timothy Brown, an HIV-positive man with leukemia who received two stem cell transplants from a donor who inherited two mutated CCR5 genes (CCR5 delta32), from his father and mother, and was genetically unable to produce CD4 cells that carry functional CCR5 co-receptors. Such individuals rarely become infected with HIV. And in cases where only one mutated CCR5 gene is inherited, HIV infection can occur, but the disease tends to progress slowly.

In Brown's case, not only did the stem cell therapy cure his cancer, but it also appears to have cured his HIV infection. All efforts to locate HIV in the man's body have been unsuccessful.

Sangamo is hoping that treating a person's own stem cells with SB-728-T and then reinfusing them will, over time, replace HIV-susceptible cells with HIV-resistant CD4s and reduce the need for continuous antiretroviral therapy. Though such genetic modifications of stem cells have not yet been tried, the company is exploring the effects of SB-728-T on patients' own CD4 cells.

"We are delighted to be able to open these two important clinical studies ahead of schedule," said Geoff Nichol, MB ChB, Sangamo's executive vice president of research and development. "Data from earlier Phase 1 trials demonstrated a statistically significant relationship between the number of circulating [CD4s] in which both CCR5 genes are modified and the reduction in HIV viral load in infected subjects during an interruption of antiretroviral therapy. Both of these new [Phase II]

clinical trials are specifically designed to confirm and further investigate these findings."

The new studies employ two approaches to increase the number of infused CD4 cells in which both CCR5 gene copies are modified using SB-728-T. The first study, an extension of an ongoing trial (SB-728-902), will explore the effect of SB-728-T treatment on viral load in people living with HIV who inherited one CCR5 delta32 genetic mutation. The second study (SB-728-1101), involving people living with HIV without the CCR5 delta32 mutation, involves a pre-infusion course of chemotherapy to significantly enhance the proliferation of the gene-modified CD4 cells in the body.

In the extension of the SB-728-902 trial, up to 20 HIV-positive volunteers with one copy of the CCR5 delta32 deletion who are currently receiving ARV therapy will be enrolled and will receive a single intravenous infusion of 5 billion to 30 billion SB-728-T-modifed CD4 cells. Two months later, these volunteers will undergo a 16-week ARV treatment interruption. HIV treatment will be restarted if the patients' CD4 cells drop below 350 or if their viral loads are above 100,000 for three weeks in a row. After 16 weeks, only those who maintain undetectable viral loads will be permitted to remain off therapy.

The SB-728-1101 trial will mainly evaluate the safety and tolerability of Cytoxan (cyclophosphamide) chemotherapy, administered one day before being infused with SB-728-T-modified CD4 cells. Cytoxan is a chemotherapeutic drug used to temporarily reduce the numbers of CD4 cells in the body, which then rapidly repopulate once the drug is discontinued.

Chemotherapeutic "conditioning" therapy has been used to enhance engraftment of cells in the treatment of cancer and for numerous autoimmune diseases. The drug has been previously used in people living with HIV, with studies demonstrating that while the drug does reduce CD4s, it does not have a long-term effect on CD4 cell counts.

In addition to safety, the study will evaluate the effect of Cytoxan—administered intravenously at a dose of either 200 milligrams (mg), 500 mg or 1,000 mg—on SB-728-T engraftment, the effect of SB-728-T treatment on viral load following ARV therapy interruption, the change in CD4 cell counts and the long-term persistence of SB-728-T. At least nine people living with HIV receiving ARV therapy will be enrolled in the study.

Six weeks after receiving the infusion of SB-728-T-modifed CD4 cells, patients with CD4 cell counts of at least 500 will undergo a 16-week treatment interruption. Therapy will be reinstituted in the event the CD4 cell count falls below 500 or viral load exceeds 100,000 for three weeks.

To learn more about the extension of the SB-728-902 study, including enrollment information, click here (look for "Cohort 5" references). Recruitment information for SB-728-1101 is not yet available.

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