Researchers Explore CAR-T Therapy as a Potential Cure for HIV

A “living drug” could potentially eliminate HIV-infected cells, allowing for long-term remission without antiretroviral therapy.

November 28, 2022 By Liz Highleyman

The first clinical trial participant has been treated with an experimental CAR-T cell therapy, a “living drug” that could lead to a functional cure, or long-term HIV remission without antiretroviral drugs, according to an announcement from Caring Cross. The anti-HIV duoCAR-T therapy uses engineered T cells to target HIV-infected immune cells and potentially eliminate the viral reservoir. The study is currently recruiting participants in Sacramento and San Francisco.

“We have reached an important milestone with the dosing of the first participant in the Phase I/IIa clinical trial evaluating a potentially groundbreaking anti-HIV duoCAR-T cell therapy,” principal investigator Steven Deeks, MD, of the University of California San Francisco said in the press release. “Our primary goal for this clinical trial is to establish the safety of this promising therapeutic approach.”

Antiretroviral therapy can keep HIV replication suppressed as long as treatment continues, but the virus inserts its genetic blueprints into the DNA of human cells and establishes a long-lasting reservoir that is unreachable by antiretrovirals and invisible to the immune system. These so-called HIV proviruses can lie dormant in resting T cells indefinitely in the presence of antiretrovirals, but they usually start churning out new virus soon after the drugs are discontinued.

One approach for achieving long-term remission is to help the immune system recognize and fight HIV. Best known as a treatment for cancer, chimeric antigen receptor T-cell therapy, or CAR-T, reprograms a patient’s T cells to express synthetic receptors that recognize antigens—for example markers on tumor cells or bits of a virus. Six CAR-T therapies are currently approved to treat various blood cancers.

The CAR-T procedure involves collecting a sample of a patient’s CD4 and CD8 T cells and modifying them in a laboratory. An inactivated retrovirus vector is used to ferry synthetic receptors into the cells. The anti-HIV duoCAR-T contains receptors that recognize HIV-infected cells expressing the viral gp120 envelope protein. Because T cells are the primary target of HIV, the

CCR5 receptors found on normal T cells can also be edited out so most types of HIV can't use them to enter cells. The modified cells are then multiplied and reinfused back into the same individual. In some cases, patients receive chemotherapy beforehand to kill off some of their existing immune cells and make room for the new ones.

A previous study, published in 2019 in Science Translational Medicine, showed that anti-HIV duoCAR-T cells demonstrated the ability to potently suppress HIV and eliminate HIV-expressing cells in laboratory cultures and in mice while remaining resistant to HIV infection themselves.

A more recent study, published in the Journal of Clinical Investigation Insight, found that anti-HIV duoCAR-T cells can travel from the bloodstream to the spleen in humanized mice and eliminated immune cells infected with HIV. The researchers showed that the duoCAR-T cells "effectively sense and kill" HIV-infected CD4 T cells, monocytes and macrophages. The spleen and other lymphoid tissues contain numerous immune cells and are major viral reservoir sites.

In the video below, Rimas Orentas, PhD, scientific director at Caring Cross, explains how anti-HIV duoCAR-T works and reviews some of preclinical research that paved the way for the Phase I/II trial.

This open-label trial (NCT04648046)—the first study of anti-HIV duoCAR-T in humans—will evaluate safety and tolerability, identify an optimal dose and determine whether prior chemotherapy is needed. The first participant was treated in mid-August. So far, no treatment-related adverse events have been observed and "the participant is doing fine," according to study investigator Mehrdad Abedi, MD, of the University of California Davis.

The trial is enrolling adults living with HIV who have been taking antiretroviral therapy without interruption for at least a year, are currently on a stable regimen (certain medications are excluded), have had an undetectable viral load for a year and have a current CD4 count of at least 500 and have never fallen below 300. People with hepatitis B or C, chronic liver disease, tuberculosis, poorly controlled cardiovascular disease or certain types of cancer are excluded.

Participants will be enrolled in three successive cohorts. The first group will receive a single infusion of a low dose of anti-HIV duoCAR-T without prior chemotherapy; the initial participant received this regimen. The second cohort will receive non-ablative cyclophosphamide chemotherapy, which reduces but doesn't wipe out existing immune cells, followed by a single infusion of low-dose duoCAR-T. The third cohort will receive chemotherapy followed by an infusion of high-dose duoCAR-T. After their infusions, participants in all cohorts will stop taking antiretroviral medications in a closely monitored analytic treatment interruption.

"The study will require a lot of dedication from the patient because of the time commitment involved and the necessary steps required," co-investigator Paolo Troia-Cancio, MD, said in a University of California Davis press release.

If this and other trials are successful, CAR-T therapy could offer a promising new approach to a

functional cure for HIV. But CAR-T therapies for cancer can cause serious adverse effects, including life-threatening cytokine storms and neurological problems. What's more, the customized treatment is labor-intensive and expensive, which would limit its use for most of the 38 million people with HIV worldwide. For example, Gilead Sciences' Yescarta, a CAR-T therapy used to treat lymphoma, costs more than $350,000 for a single infusion.

Research is now underway in the cancer field to better manage side effects, scale up production and develop "off-the-shelf" CAR-T therapies that don't require the collection and modification of T cells from each individual patient. These advances could one day make this type of treatment more affordable and accessible for people living with HIV.

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