Transplanting Hope: Stem Cell Experiment Raises Eyebrows at CROI

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Not every remarkable HIV treatment discovery makes the front page of the morning papers. Take, for example, a single-patient study presented at the 15th annual Conference on Retroviruses and Opportunistic Infections (CROI) in Boston that went largely unnoticed by news outlets but is now generating excitement among activists and researchers.

The intriguing study involves an HIV-positive German man with leukemia who has regrown a new immune system after receiving a stem cell transplant and has since kept his viral load undetectable. In fact, sensitive tests have been unable to detect the virus in the patient's blood or tissues. According to the CROI report, presented by Gero Hütter, MD, of the Medical University of Berlin and his colleagues, the key to the transplant's success was the stem cells provided by a donor whose immune system was genetically resistant to HIV infection.

Nobody, least of all the authors of the study, is using the "c" word to describe the results. What's more, stem cell transplants are hardly ready for prime time, given that it is first necessary to destroy a person's existing immune system with a potentially lethal course of chemotherapy and radiation to make room for the new cells, at a cost of up to $250,000. Yet the study has generated a great deal of interest among some who are familiar with it. Top AIDS researcher Michael Lederman, MD, a professor of medicine at Case Western Reserve University in Cleveland, says, "I think this is really exciting."

Others, such as staff scientist Tae-wook Chun, PhD, of the National Institute of Allergy and Infectious Diseases (NIAID), in Bethesda, Maryland, caution that the experiment may not amount to a breakthrough. He says, "It's interesting, but the bigger picture is that doing stem cell transplants is not a realistic approach for curing AIDS."

Such caution may be warranted. After all, researchers have been saying for twenty-five years that we're just ten years away from an effective vaccine. But activists like Richard Jefferys, from New York City's Treatment Action Group (TAG), argue that it's vital for researchers and advocates not to overlook hopeful research findings such as this one, or give up on the possibility of a cure. "I think it's well worth shining a spot light on," says Jefferys. "[People living with HIV and activists] have to be the ones pushing back a little bit and saying that life-long therapy is fine for now but we can do better."

Rebirth of an HIV-resistant immune system

“Doing better” is just what Dr. Hütter had in mind when confronted with the need to perform a stem cell transplant on his patient, a 40-year-old HIV-positive man diagnosed with acute myeloid leukemia, a potentially fatal cancer of the immune system. Rather than simply performing a transplant that would increase the patient’s chance of cancer survival, Dr. Hütter’s group decided to go for double or nothing and attempt a transplant that would also increase the patient’s chances of surviving HIV.

All that was required was a simple phone call. He asked the blood and tissue bank if any of their stem cell donors had a particular genetic defect, called the CCR5 delta-32 deletion. This defect prevents CD4 cells from developing a receptor, called CCR5, on their surfaces. People who inherit this genetic mutation from both parents have CD4 cells that lack the CCR5 entirely and, as a result, are highly resistant to infection with HIV. People who inherit the mutation from one parent can be infected, but because they have fewer CCR5 receptors on their CD4 cells, tend to have slower disease progression. Dr. Hütter found a very lucky match—a suitable donor with the delta-32 deletion from both parents.

As is standard in stem cell transplants, Dr. Hütter’s team prepared the patient to receive the cells by first ablating, or destroying, most of his immune cells. This process, also called conditioning, is usually performed using intensive chemotherapy and radiation. As Dr. Lederman explains it, “You need to make room [for new immune cells to grow].”

Conditioning can be a brutal process. It requires a lengthy hospitalization and can cause numerous and potentially life-threatening side effects. This is part of the reason that stem cell transplants for conditions like leukemia are typically only performed when patients have failed to respond to standard treatment. The other reason is the cost, which in the United States typically ranges from $100,000 to $250,000.

The Berlin stem cell transplant has been a success so far. According to Dr. Hütter, the patient’s immune system has not rejected the transplant. In fact, 100 percent of his post-treatment immune system cells were grown out from the transplanted stem cells. Nor has there been a return of the leukemia, though this is always a possibility, even following a successful stem cell transplant.

Most exciting is the fact that the patient, who went off of his antiretroviral medication for the transplant procedure, has been able to remain off of the drugs for more than 285 days. Moreover, when the researchers looked for evidence of virus in blood and rectal tissue biopsies, not only was his viral load undetectable, more sensitive methods for detecting viral particles, known as proviral DNA, were also unable to find evidence of HIV.

Cautious optimism or reckless hope?

Experts stress that it is far too early to call the experiment a cure. For one thing, post-transplant survival in people who are battling leukemia is far from a sure thing. And as Chun points out, an immune system with CD4 cells lacking the CCR5 receptor is still susceptible to virus that uses another receptor dubbed CXCR4. If the German transplant patient has CXCR4-using virus

anywhere in his body, it can potentially reseed his immune system with HIV.

Chun, who is working on techniques for eradicating HIV in the laboratory of NIAID director Anthony Fauci, MD, has good reason to be cautious. It was not long after researcher David Ho claimed in 1996 that protease inhibitors had given us the tool to eradicate HIV that we learned of the virus' ability to hide out for years in the immune system, meaning that antiretroviral therapy, at least as we currently know it, is a lifelong proposition for most people with HIV.

Dr. Lederman, on the other hand, takes a more optimistic view. Despite the dangers and costs associated with stem cell transplants, he says it may be worthwhile to consider the procedure in people with HIV who do not otherwise require a transplant, such as for leukemia, but in whom none of the current or experimental antiretrovirals are working and who have low CD4 counts and uncontrolled virus. "I think such an approach is entirely defensible, especially in light of this experiment that we see here," says Lederman.

When asked if he is planning additional experiments in other patients with HIV and leukemia, Dr. Hütter says while such patients are rare, he would certainly consider it.

Dr. Lederman also believes that if Dr. Hütter's experiment continues to look successful, it could have implications for other experimental approaches that wouldn't require the dangers of a stem cell transplant. Dr. Lederman points to technologies like gene therapy and "RNA silencing" as promising methods for artificially knocking out the delta-32 gene responsible for producing CCR5 receptors.

Inspired by such experiments are non-profit groups like the Linda Grinberg Foundation for AIDS and Immune Research (FAIR). Martin Delaney, a long time AIDS activist and the current president of FAIR, says that he and other groups are planning a conference for the end of the year to chart out the scientific steps that may open up the path to a cure. According to Delaney, FAIR and the Foundation for AIDS Research (amfAR) are very interested in studies like Dr. Hütter's and plan to make grants to scientists who propose research that will take us down that path.

Delaney, who was among the first people to notice Dr. Hütter's poster at CROI and point it out to other activists and researchers, remains steadfast in his hope about a cure, a hope that some may consider fruitless. Although he refuses to respond to experiments like Dr. Hütter's with pessimism, Delaney does understand the caution with which most researchers greet such proof-of-concept studies. He says, "I understand that [caution], because they're case studies, rather than controlled clinical trials. But I think that's where the cure is going to first appear. It's not going to appear out of a controlled trial."

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