A Landmark Permanent Treatment for Children Born with a Deadly Immune Disorder

In June 2022, the first stem cell gene therapy of Dutch origin was successfully given to a patient by researchers at the Leiden University Medical Centre (LUMC). A baby with severe congenital immune disorder (SCID) received the complex but one-time treatment, marking the first time stem cell gene therapy has treated this specific form of the disease.

Severe congenital immune disorder: a genetic error that compromises the immune system

SCID is a rare congenital disorder in which a genetic error in the blood stem cells causes newborns to have a non-functioning immune system, leaving them vulnerable to infections as harmless as the common cold. In the 1970s, the term "bubble boy syndrome" was coined after the experience of SCID patient David Vetter, who had to live within a sterile chamber for most of his life.

Fortunately, there are now treatments for the disorder, and children with the disease are no longer condemned to a life of isolation. Additionally, newborn screening for SCID is now widely used so that treatment can occur before any infections (1).

Without treatment, children with SCID often die before their first birthday. However, if treated within the first few months of life before developing a serious infection, the long-term survival rate is more than 90%.

The treatment: inserting good genes back into the body

SCID patients with a mutation in the recombination activation gene (RAG-1) lack T- and B lymphocytes, resulting in an immune system that is unable to protect the child and causing them to experience severe, life-threatening infections.

However, the Dutch stem cell gene therapy, created by Arjan Lankester, a professor of pediatrics and stem cell transplantation, and Frank Staal, a professor of stem cell biology, corrects this genetic error, thus allowing the growth of a functioning immune system. At three months old, the baby's stem cells were taken, and using a "crippled" virus as a vector, a good copy of the gene was inserted into the DNA of the cells. "We only use the property of the virus to build its own genome in the DNA of its host but remove all other properties. The virus is therefore just the wheelbarrow that brings the gene to the right place," Stall explained.

The repaired cells were then transferred back into the patient, who is doing well and left the hospital within a month. "The baby has endured the treatment without any problems, and their immune system responds well to the usual vaccinations for newborns. A fantastic result," Lankester said. The therapy is expected to have cured the child for life.

Stem cell transplantation: a common but imperfect SCID treatment

Hematopoietic stem cell transplantation — also called a bone marrow transplant —is the typical treatment for SCID and works by infusing donor hematopoietic stem cells into the child with SCID. Over time, the donor cells multiply and create an immune system for the child.

The therapy has several disadvantages, though, like finding a suitable donor, which is unavailable for half of SCID patients. Lankester explained that because stem cell transplantation is often the only chance of survival, tissue types that are only partial matches are often used, lowering the survival rate to 20% and reducing the overall quality of life. Additionally, the donor cell transplant could cause an unwanted reaction against the patient's body known as graft-versus-host-disease.

However, Lankester explained that stem cell gene therapy circumvents these problems because the patient is their own donor.

Enzyme replacement therapy is a third treatment option for children and adults with adenosine deaminase (ADA) SCID. The treatment involves regular injections of the missing ADA enzyme to boost its levels. However, the results are temporary, and the therapy doesn't permanently repair the immune system. For long-term results, stem cell transplantation or gene therapy are the best options.

Many ups and downs: creating the cure

Perfecting the process took Lancaster, Staal, and other LUMC researchers 15 years, mainly because the type of SCID they focused on caused mutations in a "very tricky gene:" RAG-1. "The process had many ups and downs," said Staal. "Both in terms of developing the therapy in the lab and also the paperwork to obtain permission for use in patients."

"It is fantastic to see that we have been able to help a patient," Lankester added. Ultimately, they hope to make this therapy available to patients throughout Europe.

The technology also makes the treatment process much easier for patients and their families. "Our motto is: the cells travel, not the patient. That way, patients and their families, who are already going through a hard time, don't have to move abroad for a few months. This is sometimes what happens with patients suffering from other forms of SCID."

Gene therapy: a promising technology

Gene therapy is an experimental treatment where genetic information is transferred into a person's cell to fight or prevent a specific disease and involves introducing the gene via a carrier known as a "vector." Altered viruses are the most common type of vector used in gene therapy due to their natural ability to deliver genetic material into cells. Although the technology is still relatively new, the success of treating a baby with SCID marks a huge milestone.

Staal and Lankester are now investigating how the technology could cure another form of the SCID gene, RAG-2. With over 20 different types of mutations that can cause the disorder, the LUMC therapy is the first to cure those caused by RAG-1.

Currently, several clinical gene therapy trials are taking place at children's hospitals in the United States and at the National Institute of Health for SCID. In 2019, St. Jude Children's Research Hospital announced they had cured babies with X-linked SCID via stem cell gene therapy.

Meanwhile, other researchers are looking at how the technology can treat diseases like hemophilia, Parkinson's, cancer, and HIV. However, as the treatments become more popular, will their cost allow affordable access?

SCID gene therapy: the cost of a cure

Staal explained that because the treatment is still in the research phase, it doesn't cost the patient anything. However, what the price tag will be long-term remains unclear. The process requires a special preparation facility and LUMC is one of the few Netherland hospitals that has a license to genetically modify cell products, meaning they are not dependent on the pharmaceutical industry and can somewhat reduce the price. Staal recently received a grant to study how society can best use the therapies and what reimbursement guidelines for policymakers should look like.

Fortunately, there is a recent example of covering costs for gene therapy to draw from. American biotechnology company Novartis gained U.S. Food and Drug Administration (FDA) approval in

2019 for its gene therapy treatment for spinal muscular atrophy. Tay Salimullah, the company's global head of value and access, said his company secured 80% coverage on Medicare and commercial plans in the U.S., while in Europe, Novartis created a program that guarantees up-front access for patients and honors reimbursement and pricing decisions in other countries.

The future of treating SCID

If treated early, a SCID diagnosis, though serious, is no longer a death sentence. Although there are many forms of SCID, the stem cell gene therapy created by researchers at LUMC provides hope for families whose child has a RAG-1 form of the disorder, offering a cure for life. With clinical trials happening in the United States and other SCID causing genes being researched, stem cell gene therapy could continue to be a life changing option for the other forms of the disease.

References:

1. Slatter MA, Gennery AR. Advances in the treatment of severe combined immunodeficiency. Clin Immunol. 2022 Aug 5:109084. doi: 10.1016/j.clim.2022.109084. Epub ahead of print. PMID: 35940359.