Gene therapy restores immune function in children with rare immunodeficiency

An investigational gene therapy can safely restore the immune systems of infants and children who have a life-threatening, inherited disorder known as Severe Combined Immunodeficiency due to Adenosine Deaminase Deficiency, or ADA-SCID. The findings, published this year in the *New England Journal of Medicine*, were the result of an international collaboration between researchers in the United States, England, Switzerland, and Germany. 48 of 50 children who received the gene therapy retained their replenished immune system function two to three years later, and did not require additional treatments for their condition.

ADA-SCID is estimated to occur in approximately 1 in 200,000 to 1,000,000 newborns worldwide. The disease is caused by mutations in the *ADA* gene that impair the activity of the enzyme adenosine deaminase. This enzyme is found throughout the body, but is most active in lymphocytes. Adenosine deaminase is responsible for eliminating a molecule called deoxyadenosine, which is generated when DNA is broken down. Deoxyadenosine may be harmful to lymphocytes, and is typically converted to a benign molecule called deoxyinosine. Mutations in the ADA gene reduce or eliminate the activity of adenosine deaminase, and allow the buildup of deoxyadenosine to levels that are toxic to lymphocytes.

SCID is the most severe form of primary immunodeficiency, as its victims are highly vulnerable to severe infections. It is also known as the “bubble boy disease” because some patients are known for living in an isolated environment. If untreated, the disease is fatal, usually within the first two years of life. Patients with ADA-SCID can be treated with enzyme replacement therapy, but this treatment does not fully rebuild immune function and must be taken for life. Transplants of blood-forming stem cells, ideally from a genetically matched sibling donor, can provide a more lasting solution. However, most people lack such a donor. Stem cell transplants also carry risks such as graft-versus-host disease, as well as side effects from chemotherapy medications given to help the donor stem cells establish themselves in the patient’s bone marrow.

The new research evaluated an experimental gene therapy for ADA-SCID designed to be safer and more effective than previously tested gene-therapy strategies. This gene therapy involves inserting a normal copy of the *ADA* gene into the patient’s own blood-forming stem cells. First, stem cells are collected from the patient’s bone marrow or peripheral blood. Next, a harmless virus is used as a “vector,” or carrier, to deliver the normal *ADA* gene to these cells in the laboratory. The genetically-corrected stem cells then are infused back into the patient, who has received a low dose of the chemotherapy medication busulfan to help the cells establish themselves in the bone marrow and begin producing new immune cells.

The experimental gene therapy uses a modified lentivirus to deliver the *ADA* gene to cells. Previous gene-therapy approaches for ADA-SCID have relied on a different type of virus called a gamma retrovirus. Some patients who have received gamma retroviral gene therapies have later developed leukemia, which scientists suspect is due to the vector causing activation of genes that control cell growth. The lentiviral vector is designed to avoid this outcome and to enhance the effectiveness of gene delivery into cells.

The results come from three separate, non-randomized Phase 1/2 clinical trials, two conducted in the United States and one in the United Kingdom. The U.S. trials enrolled 30 participants with ADA-SCID ranging in age from 4 months to 4 years. The U.K. study enrolled 20 participants ranging in age from 4 months to 16 years. Most participants acquired and retained robust immune function following gene therapy — 96.7% after two years in the U.S. studies and 95% after three years in the U.K. study — and were able to stop enzyme replacement therapy and other medications. Of the two participants for whom gene therapy did not restore lasting immune

function, both restarted enzyme replacement therapy and one of them later received a successful stem cell transplant from a donor.

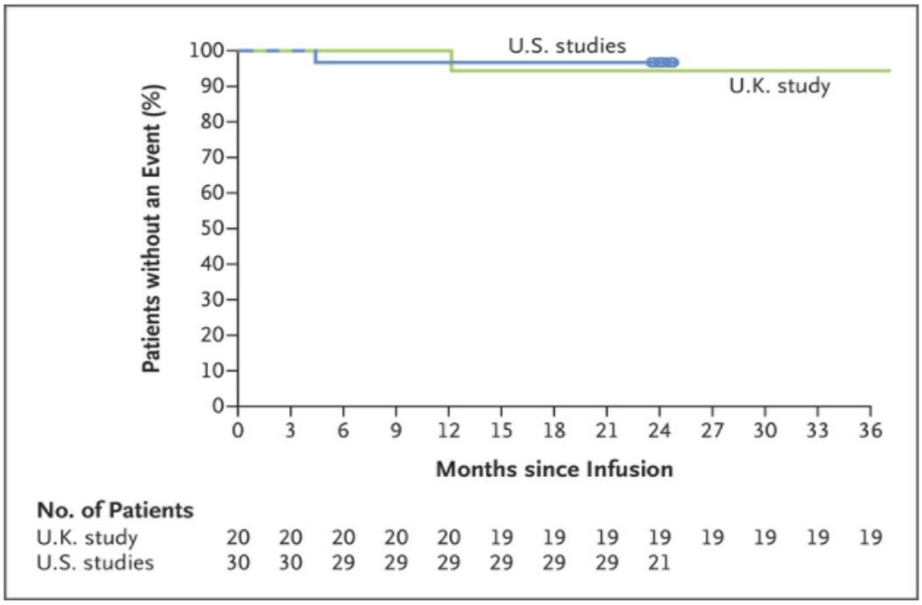

Figure 1. Event-free survival over 24 months (U.S.) and 36 months (U.K.) is shown. Events were defined as death, rescue stem-cell transplantation, or restarting of enzyme-replacement therapy. At 12 months, event-free survival was 97% among the patients in the U.S. studies and 100% among the patients in the U.K. study; it remained at 97% among the patients in the U.S. studies at 24 months and was 95% among the patients in the U.K. study at 24 and 36 months.

The lentiviral gene therapy appeared safe overall, although all participants experienced some side effects from the treatment. Most of the side effects were mild or moderate, and all were attributable to the chemotherapy that the participants received. Across the three studies, severe infection rates were generally low after gene therapy. Fifteen serious infections were observed in eight patients in the U.S. studies, while eight serious infections were observed in seven patients in the U.K. study. These included, but were not limited to, upper respiratory tract infection, pneumonia, influenza, otitis media, and urinary tract infection.

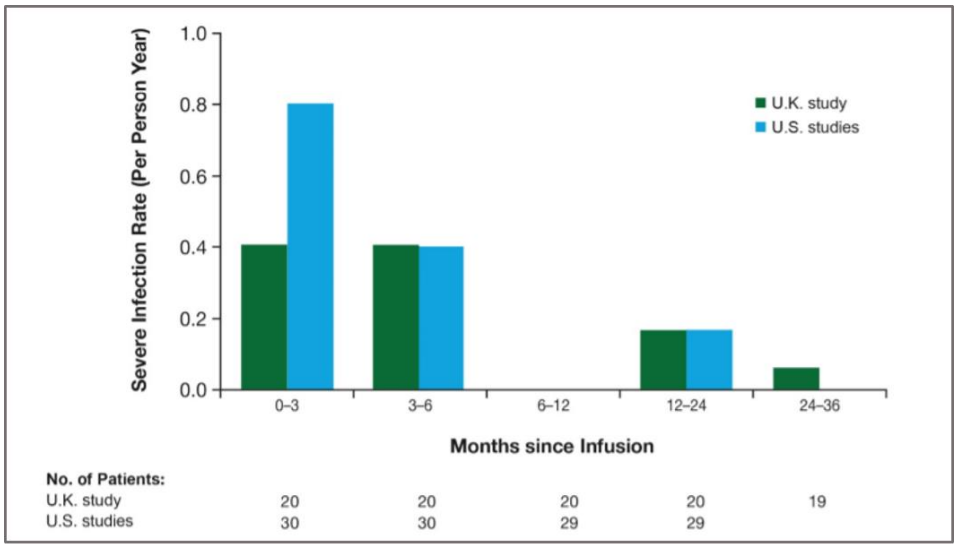

Figure 2. Severe infections were assessed up to 24 months (U.S.) or 36 months (U.K.) follow up. Starting at three months, post-treatment to last follow-up severe infection rates were similar in the U.S. and U.K. studies.

In all three studies, the median ADA enzyme activity in red cells increased sharply during the first 3 months and remained within or above levels observed in healthy children at the last follow-up visit.

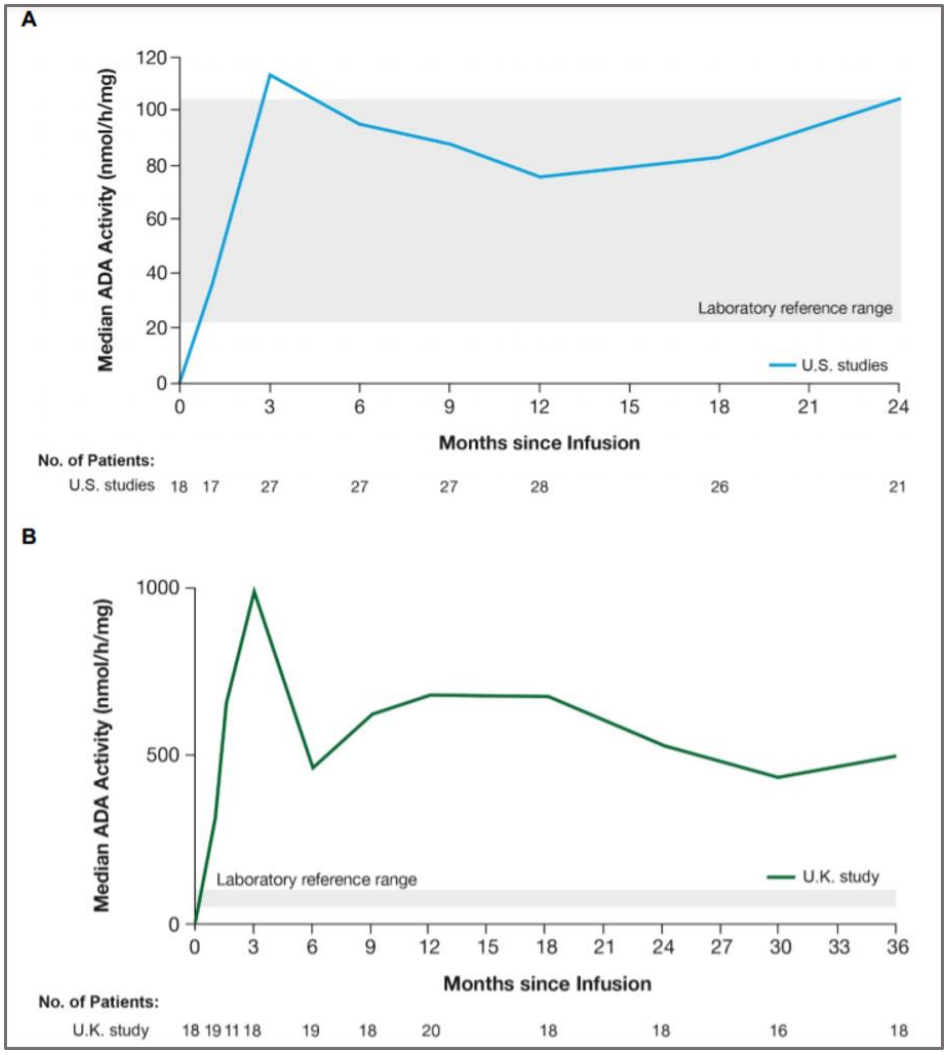

Figure 3. ADA activity over 24 months (U.S., Panel A) and 36 months (U.K., Panel B) in treated patients. Median adenosine deaminase (ADA) enzyme activity in peripheral red blood cells. Assays using different systems were employed at each of the sites.

At the final follow-up visit, lymphocyte counts in most patients had reached or come close to reaching the expected normal ranges for age for most lymphocyte populations. Median T-cell and B-cell counts decreased after withdrawal of enzyme-replacement therapy, but began to recover at month 3, with increases sustained through month 24 in the U.S. studies and through month 36 in the U.K. study. Reflective of improvements in B-cell function, the majority of patients had increases in serum IgM and IgA levels to within or above normal limits over time (data not shown).

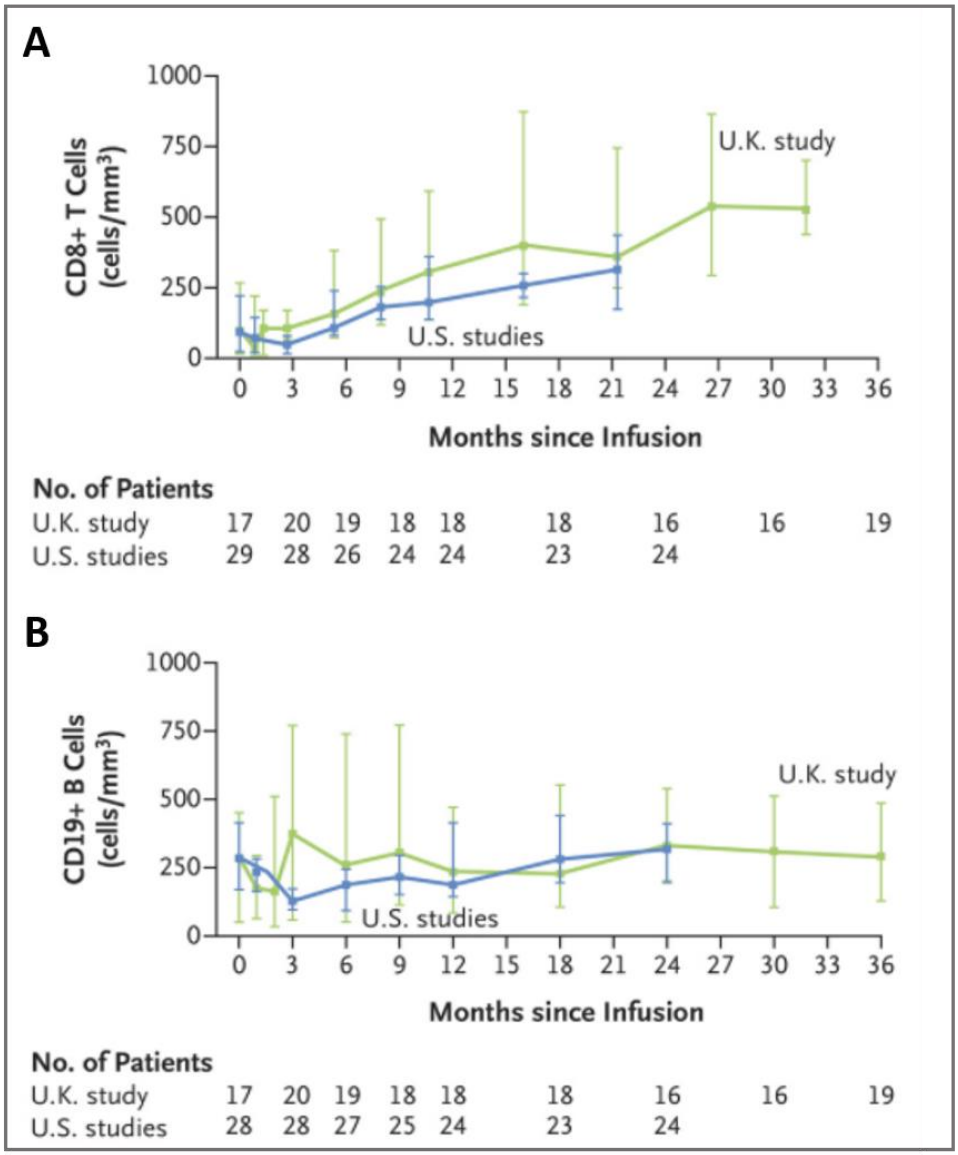

Figure 4. Median absolute lymphocyte counts over 24 or 36 months are shown.

Researchers observed similar outcomes in all three trials, although there were some differences between the studies. Stem cells were collected from bone marrow in the U.S. trials and from peripheral blood in the U.K. trial. In one of the U.S. trials, 10 children were treated with genetically corrected stem cells that had been frozen and later thawed, a process known as cryopreservation. The two other trials used fresh stem cell preparations. Efficacy results in U.S. patients who received the fresh formulation were similar to those in patients who received the cryopreserved formulation, as indicated by the median ADA activity and T-cell levels in the patients.

In the future, cryopreservation may allow stem cells to be more easily transported and processed at a manufacturing facility far from the patient's home and shipped back to a local hospital, reducing the need for patients to travel long distances to specialized medical centers to receive gene therapy. A trial of the cryopreserved treatment is now underway in the U.K. The investigational lentiviral gene therapy, which is licensed to Orchard Therapeutics in London, has not been approved for use by any regulatory authority.

References

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2. National Institutes of Health (2021 May 11). Gene therapy restores immune function in children with rare immunodeficiency. https://www.nih.gov/news-events/news-releases/gene-therapy-restores-immune-function-children-rare-immunodeficiency.
3. DB Kohn, KL Shaw *et al.* Lentiviral Gene Therapy with Autologous Hematopoietic Stem and Progenitor Cells (HSPCs) for the Treatment of Severe Combined Immune Deficiency Due to Adenosine Deaminase Deficiency (ADA-SCID): Results in an Expanded Cohort. *Blood* DOI: 10.1182/blood-2019-123432 (2019).