Early gene therapy results in Wiskott-Aldrich syndrome promising

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Sung-Yun Pai, M.D., Dana-Farber/Boston Children's Cancer and Blood Disorders Center. Credit: Dana-Farber/Boston Children's

Researchers reported promising preliminary outcomes for the first four children enrolled in a U.S. gene therapy trial for Wiskott-Aldrich syndrome (WAS), a life-threatening genetic blood and immune disorder, at the 57th annual meeting of the American Society of Hematology (abstract #260).

All four boys are alive and have improved between nine and 24 months following treatment, according to study principal investigator Sung-Yun Pai, MD, a pediatric hematologist-oncologist from Dana-Farber/Boston Children's Cancer and Blood Disorders Center. Since undergoing treatment, none of the boys of have experienced bleeding events or severe WAS-related infections. In addition, all four have experienced improvements in immunologic symptoms and variable improvements in platelet count. The two patients who had required medication to stimulate platelet production prior to undergoing gene therapy are no longer on those medicines.

It is too early, however, to draw conclusions about long-term outcomes. The study protocol calls for the children to be monitored for 15 years in order to assess the treatment's safety and efficacy.

WAS is caused by mutations that lead to the loss or dysfunction of the WAS gene, which is found on the X chromosome. The condition, which occurs only in boys, affects the development and function of T-cells and platelets, leaving patients vulnerable to bleeding, eczema and infections. The only curative treatment is a hematopoietic (blood-forming) stem cell transplant from a compatible donor. However, it is often difficult to identify an appropriate match.

The trial centers on a viral vector, which is used to insert functional copies of the WAS gene into a patient's hematopoietic (blood-forming)

stem and progenitor cells, which give rise to all cell types found in the blood and the immune system. These cells are collected from the patient, exposed to the vector in the laboratory and, once the vector inserts the gene and doctors have eradicated the patient's own blood system with chemotherapy, are returned to the patient via intravenous transfusion. The vector is a self-inactivating lentivirus—a member of a family of viruses that can insert genes into mammalian cells and drive expression of those genes—that has been engineered to avoid triggering the development of leukemia, a complication seen in previous gene therapy trials for immunodeficiency syndromes, including WAS.

The study's variable results to date raise questions about which factor is most important to the success of gene therapy for any given individual with WAS: the number of WAS gene copies the vector inserts into the patient's cells, the number of modified cells given to a patient, or how effectively the patient's native blood system is eliminated before the modified cells are infused.

"Putting the data that we have together, we get the sense that these factors all matter," said Pai, who presented the data on behalf of a team of investigators from the U.S., Turkey, Japan and Chile. "We suspect that infusing a few cells that each have two or three copies of the WAS gene may be better than infusing many cells with only one copy of the gene each. But with the very small number of patients we've treated to date, our data are only suggestive."

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