What caused the blood malignancies linked to gene therapy for sickle cell disease?

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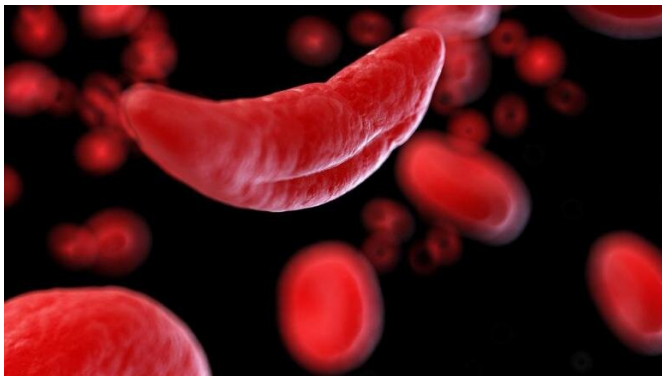

Credit: National Institutes of Health

Gene therapy trials for sickle cell disease have been showing great promise, even offering hope of a cure. But in early 2021, the trials ground to a halt after reports of blood malignancies in two people in a trial sponsored by bluebird bio. Investigations later concluded that the gene therapy delivery vectors were likely not to blame, and the trials have resumed, including one at Dana-Farber/Boston Children's Cancer and Blood Disorders Center. But the mystery remains: Why did these malignancies occur? And should these cases deter people with sickle cell disease from entering gene therapy trials?

"As a hematologist, I'm tremendously excited by gene therapy and the prospect of curative treatments for my patients," says Vijay Sankaran, MD, Ph.D., an attending physician at Dana-Farber/Boston Children's. "But for patients, cancer risk is a worry."

Clonal hematopoiesis in sickle cell disease?

It has been suggested that people with sickle cell disease may have an elevated risk for blood malignancies in general, especially as they get older. However, the cases reported in the gene therapy trials seemed to go beyond the expected "background" rate. In the February 15th issue of the *Journal of Clinical Investigation* (published online last month) Sankaran's lab, led by postdoctoral fellow Alex Liggett, Ph.D., explored one possible explanation: a potentially pre-leukemic condition called clonal hematopoiesis.

In clonal hematopoiesis, people acquire mutations causing some of their blood stem cells to multiply faster than others, forming distinct populations or "clones."

"Clonal hematopoiesis can increase the risk of blood cancers by up to 10-fold," says Sankaran. "It's been speculated that people with sickle cell disease may have a higher rate of clonal hematopoiesis, and that we should consider screening patients for it before enrolling them in gene therapy trials—or even if they aren't getting gene therapy."

Investigating clonal hematopoiesis

The study analyzed whole-genome sequencing data from more than 3,000 people with sickle cell disease and more than 71,000 people without the disease, looking for somatic mutations and clonal blood cell populations.

Somewhat surprisingly, the rate of clonal hematopoiesis in people with sickle cell disease was no greater than that in the general population. "This tells us that monitoring patients with sickle cell disease for clonal hematopoiesis, at least at levels we can detect with whole genome sequencing, is not going help us figure out the basis for the elevated cancer risk," says Sankaran.

David A. Williams, MD, chief of Hematology/Oncology at Boston Children's, was instrumental in launching the current sickle cell gene therapy trial at Boston Children's and was

coauthor on the study.

"These new data contribute significantly to the ongoing discussions about leukemia risk in individuals with sickle cell disease," he says. "It is critical that the field understands this risk more completely so we can improve the safety of our gene therapy approaches for these patients."

Beyond gene therapy: Exploring cancer risk in sickle cell disease

Sankaran notes that the study was unable to detect small clonal populations involving rare mutations. That's next on the agenda to explore as part of a large collaborative effort through the National Heart, Lung, and Blood Institute's Cure Sickle Cell initiative.

"Rare clones may arise as a result of the way cells are handled or processed in gene therapy," Sankaran says. "Or maybe something about the conditioning regimens used prior to gene therapy selects for rare clones. Until we study this, we won't know. Gene therapy is still experimental, and there are probably things we're going to learn."

Williams and Erica Esrick, MD, principal investigator on Boston Children's gene therapy trial, are now collaborating with investigators in the United Kingdom to study the effects of cell processing on the possible development of mutations in gene therapy recipients.

But separate from gene therapy, the study leaves many questions about cancer risk in people with sickle cell disease, especially those living well into adulthood. Their risk of myeloid blood cancers has not been well studied, but is believed to be five- to 10-fold higher than that in the general population. That risk is potentially as high as in patients with recognized leukemia predisposition syndromes, including many bone marrow failure disorders.

In the future, as more is learned, patients could be counseled as part of the Pediatric Cancer Genetic Risk Program at Dana-Farber/Boston Children's. "As people live longer with sickle cell disease, we have to be more aware of the long-term cancer risk," says Sankaran. "We need to learn more about these malignancies and start discussing this risk."

More information: L. Alexander Liggett et al, Clonal hematopoiesis in sickle cell disease, *Journal of Clinical Investigation* (2022). DOI: 10.1172/JCI156060

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