Gene therapy promotes transfusion independence for severe beta-thalassemia

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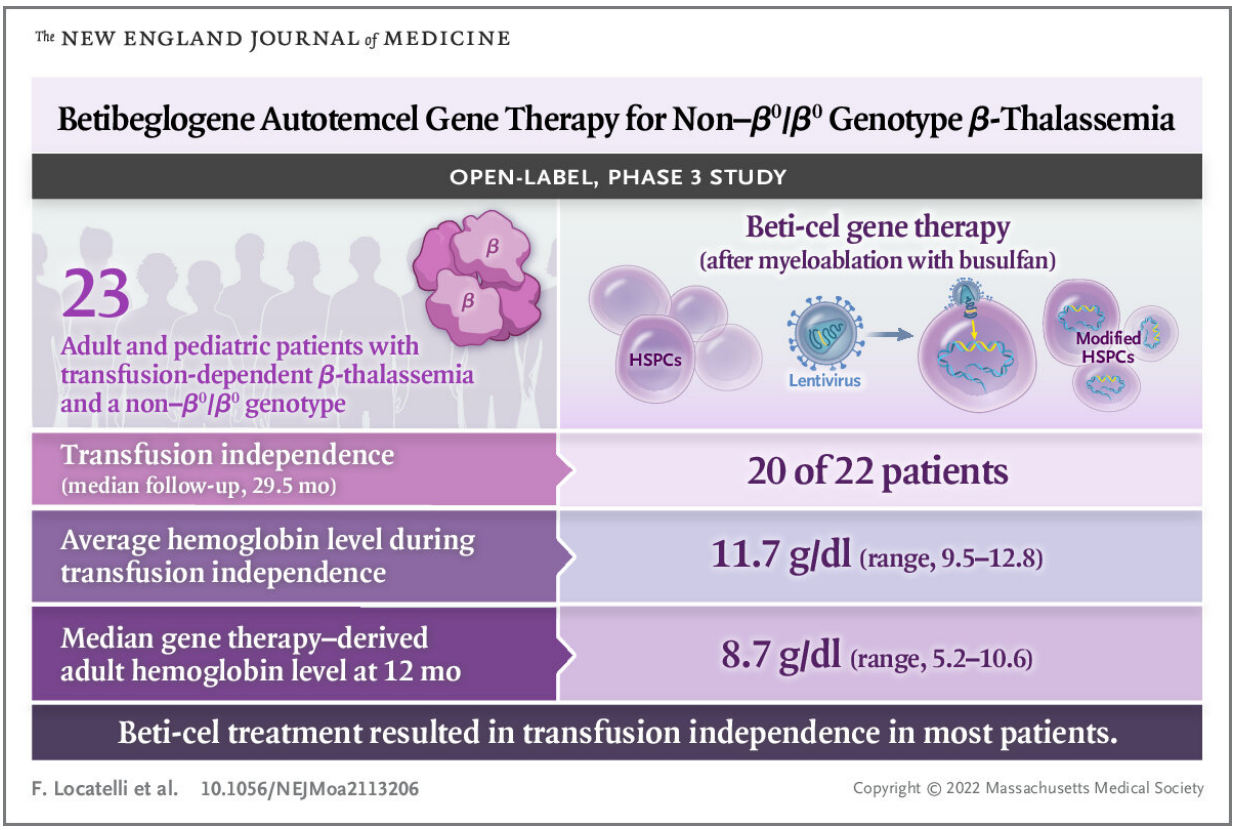

Graphical abstract. Credit: DOI: 10.1056/NEJMoa2113206

A novel gene therapy promoted transfusion independence in more than 90 percent of adult and pediatric patients with transfusion-dependent beta-thalassemia, according to a recent clinical trial published in the *New*

England Journal of Medicine.

The therapy represents a potentially curative treatment option for patients who must otherwise rely on life-long red blood cell transfusions.

"This approach provides a potential cure for patients with transfusion dependent beta-thalassemia without the need for an allogeneic donor, and these extremely encouraging results will give hope to patients otherwise not eligible for cure of their disease," said Jennifer Schneiderman, MD, '06 MS, associate professor of Pediatrics in the Division of Hematology, Oncology and Stem Cell Transplantation and a co-author of the study.

Alexis Thompson, MD, MPH, former section chief of Hematology in the Department of Pediatrics and associate director for Equity and Minority Health at the Robert H. Lurie Comprehensive Cancer Center of Northwestern University, was a co-author of the study.

Transfusion-dependent beta-thalassemia is an inherited blood disorder where the body doesn't make a normal amount of hemoglobin which carries oxygen throughout the body. It is the most severe form of beta-thalassemia and is most commonly diagnosed in children. Patients rely on red blood cell transfusions and regular iron chelation for their entire life, which can increase the risk of developing long-term adverse effects due to increased iron intake despite chelation.

The only available treatment option for patients is an allogeneic hematopoietic stem cell transplant, the infusion of hematopoietic stem cells that help reestablish normal blood cell production. However, not all patients will have an allogeneic donor, when a donors human lecukocyte antigens—proteins that indicate to the body's immune system which cells do and don't belong—match those of the patient.

The therapy can also cause significant negative side effects, such as graft-versus host disease (when the donor bone marrow or stem cells attack the recipient), long-term immune suppression or graft failure, underscoring a dire need for more effective and safe therapeutic interventions.

For the current phase 3 clinical trial, Schneidermanm and colleagues evaluated Betibeglogene autotemcel (beti-cel) gene therapy in adult and pediatric patients with transfusion-dependent beta-thalassemia and a non–β0/β0 genotype. A total of 23 patients were enrolled with a median follow-up period of 29 months.

The novel therapy consists of an autologous hematopoietic stem cell transplant with modified hematopoietic stem cells. Specifically, it contains autologous CD34+ hematopoietic stem cells and progenitor cells transduced with the BB305 lentiviral vector encoding the beta-globin gene.

"Patients undergo collection of their own stem cells, which are sent out for manufacturing, and upon return the patient is admitted for chemotherapy and infusion of the gene-modified cells. The goal is that once the cells begin working, normal hemoglobin production will occur, rendering the patient transfusion independent," said Schneiderman, who is also a member of the Lurie Cancer Center.

Post follow-up, the investigators found that 91 percent of patients were rendered transfusion independent, and eighty-six percent of these patients were children under the age of 12 years.

According to the authors, while risks of an autologous stem cell transplant do exist due to the chemotherapy administration, the long-term risks of graft-versus host disease and need for immune suppression do not.

"These data suggest that in most patients with transfusion-dependent beta-thalassemia and a non–β0/β0 genotype, one-time infusion of beti-cel is potentially curative through transfusion independence and the attainment of near normal hemoglobin levels," the authors wrote.

More information: Franco Locatelli et al, Betibeglogene Autotemcel Gene Therapy for Non–β0/β0 Genotype β-Thalassemia, *New England Journal of Medicine* (2021). DOI: 10.1056/NEJMoa2113206

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