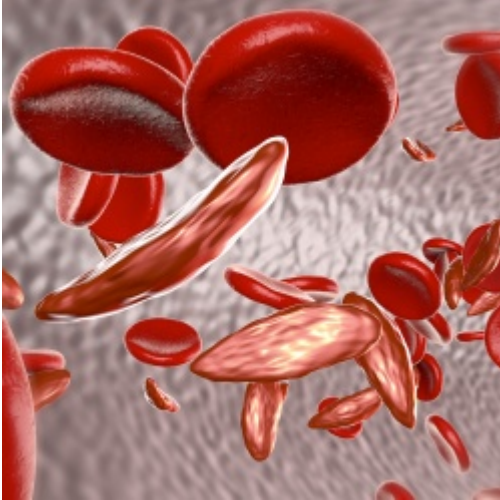


Did Gene Therapy Cure Sickle Cell Disease?



By *Jamie Wells, M.D.* — March 7, 2017



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A number of recent headlines imply a case study just published in the [New England Journal of Medicine](#) [2] proves that gene therapy has cured sickle cell disease—a genetic disorder that incurs tremendous pain, suffering and diminished life expectancy. Here, we will unpack the significance of the researchers' findings.

First, let's address why this news could be so groundbreaking to those afflicted and their loved ones.

Sickle Cell Disease is an inherited condition that causes a mutated hemoglobin—the protein within red blood cells (RBCs) that carries oxygen for delivery to vital tissues. Oxygen feeds our organs so they can stay healthy and perform their respective jobs. This Hemoglobin S (aka Sickle Hemoglobin) polymerizes on deoxygenation and rids the RBCs of their malleability. As a result, these malformed sickled cells are stiff and clump together thereby occluding vessels which in turn prompts organ damage.

Roughly 90,000 Americans have Sickle Cell Disease. (1) The natural course of the illness involves a complex cascade of events intermingled with crises often triggered by infections. Anemia is commonplace (and often profound) given these faulty cells get readily destroyed, over consumed and don't last as long as healthy RBCs. Vaso-occlusive Crises result from infarction and ischemia—in infants the hands and feet swell, in particular. Basically, adequate blood flow is halted wherever the obstruction takes place. Aggressive pain management and rehydration is essential.

Prophylactic antibiotics are a mainstay in an effort to stave off infection which can routinely catapult patients into a life-threatening crisis. By early childhood, they develop a functional

asplenia or ineffective spleen. So, they become especially susceptible to overwhelming infection by encapsulated bacteria—hence, why vaccination for pneumococcus and the like is so important. Sepsis can result. Parvovirus can cause an aplastic crisis.

Strokes. Pulmonary infarcts with subsequent hypoxia. Acute Chest Syndrome. Gallstones. Blood transfusions are frequent. Though the blood supply is well-tested for safety, recurrent transfusion can lead to issues like iron overload, for instance. This too must be treated. The list goes on of the challenges, battles and treatment complexities these patients endure. Because fetal hemoglobin has a higher oxygen carrying capacity, a disease-modifying drug like Hydroxyurea that increases its presence is used.

Allogeneic hematopoietic stem-cell transplantation represents the only cure, but less than 18% of those with severe disease have sibling donors who are a match. (2) This is also not without great risk, though those need to be weighed against how advanced the disease. Due to such limited progress in management of this condition, this team of researchers sought to examine whether “therapeutic ex vivo gene transfer into autologous hematopoietic stem cells referred to as gene therapy, may provide a long-term and potentially curative treatment for sickle cell disease.” (3)

What does this mean? They took samples from the bone marrow of a patient with severe disease. The cells here provide the origins of our blood components which includes our red blood cells. This is where the problem begins in generating the sickling. A cancer drug, busulfan, was used to condition the body— expected adverse effects from this occurred which resolved with standard care (e.g. anemia, low platelets, neutropenia and so on). Using a lentiviral vector, they transferred an anti-sickling gene into the patient’s stem cells (retrieved from the bone marrow) which get put back into the patient in the hope they will multiply and replace the cells made with the defective gene.

In a study funded in part by Bluebird Bio whose product is LentiGlobin BB305 (the antisickling gene therapy subject of this publication), the team concludes their patient “had complete clinical remission with correction of hemolysis and biologic hallmarks of the disease.” Furthermore, after fifteen months the antisickling protein remained high at approximately 50% and the patient had no crises or hospitalizations. Before, the patient required regular transfusions. After, all medications were stopped, no pain ones were needed, and the patient returned to full activities at school. (4)

Ongoing research is underway in a U.S. multi center, phase 1/2 clinical study. The intention is to use this gene therapy to treat those with severe sickle cell disease and another condition called beta-thalassemia. So far, in the few patients who have participated, their results seemingly support this work. Clearly, longer term follow-up and larger populations are crucial to understanding the significance of this report. Additionally, stem cell transplantation is no minor feat.

That said, for a disease that disables at such a young age, this option could be quite an extraordinary one if the success persists. ACSH’s Senior Fellow in Molecular Biology, Dr. Julianna LeMieux, puts the promise of gene therapy into even greater context for this and other disease entities: “This is an incredibly promising result, even with the obvious caveat that it is only one person. Sickle Cell is a disease that is ripe for genetic advances for a few reasons. First, the gene that is affected is known and can be replaced by the healthy variant. Also, the cells that are

needed to be altered are easily accessible in the bone marrow. In many diseases, this is not the case. But, this one success story is incredibly encouraging for the sickle cell community and for moving the field of curing diseases using genetic editing forward."

The team proved their concept. To know if "cure" is in this gene therapy's future, much more data needs to be acquired and study be implemented. Promising with cautious optimism might be the most apt description.

Source(s):

(1) (2) (3) (4) Jean-Antoine Ribeil, M.D., Ph.D. et al. [Gene Therapy in a Patient with Sickle Cell Disease](#) [2]. *N Engl J Med.* 376;848-855. March 2, 2017.

Note(s):

To learn more about "Orphan Diseases" or rare ones that afflict less than 200,000 (but in total impact 25 million Americans) and drug discovery challenges, review: [Did Pompe Disease Get a New Champion in President Trump?](#) [3] and [Pompe Disease, Newborn Screening and Inborn Errors of Metabolism](#) [4].

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