ARSHAD ARBAB/EPA/SHUTTERSTOCK

A child with β-thalassaemia receives a blood transfusion.

CRISPR GENE THERAPY SHOWS PROMISE AGAINST BLOOD DISEASES

A study of sickle-cell anaemia is the first published account of using CRISPR to treat a heritable disease.

By Heidi Ledford

In 1949, biochemist Linus Pauling declared[1] sickle-cell anaemia the first "molecular disease", after discovering that the condition is caused by a flaw in the body's oxygen-carrying protein, haemoglobin. Now, more than 70 years later, cutting-edge genetic techniques could provide a molecular treatment.

In *The New England Journal of Medicine*[2,3], separate research teams report promising results from trials of two pioneering gene therapies that target the root cause of sickle-cell anaemia. Both aim to boost the production of an alternative form of haemoglobin, called fetal haemoglobin. One study does so using CRISPR–Cas9 genome editing — the first published account of using the gene-editing system to treat a heritable disease.

The other approach shuttles in the code for an RNA that alters expression of the fetal haemoglobin gene. Both treatments relieved participants of the debilitating episodes known as pain crises that come with sickle-cell disease.

"To have something like these two techniques is a great opportunity," says Renee Garner, a paediatrician at the Louisiana State University School of Medicine in New Orleans. "It would just open the doors of hope for these patients."

Both clinical trials have enrolled only a handful of participants, and it is too soon to say how long the effects will last — the first participant in the RNA study was treated nearly two-and-a-half years ago. The CRISPR–Cas9 approach is also being used to treat people with severe forms of a related genetic disorder called β-thalassaemia, and those participants have not required the blood transfusions usually needed to manage the disease.

Sickle-cell disease and β-thalassaemia are two of the most common genetic disorders caused by mutations in a single gene. Both conditions affect the production of β-globin, a component of haemoglobin. People with severe β-thalassaemia have anaemia; in sickle-cell anaemia, the blood cells become deformed, clump together and can clog blood vessels, sometimes starving tissues of oxygen and causing pain episodes. Each year, 60,000 people are diagnosed worldwide with a severe form of β-thalassaemia, and 300,000 are diagnosed with sickle-cell disease.

Both diseases can be cured by a bone-marrow transplant, although most people with the conditions cannot find a matched donor. In recent years, a variety of experimental gene-therapy approaches have burst onto the scene. Last year, the European Union approved a gene therapy called Zynteglo to treat β-thalassaemia. That approach uses a virus to shuttle a functioning copy of the β-globin gene into blood-producing stem cells. Bluebird Bio, a biotechnology company in Cambridge, Massachusetts, is conducting clinical trials of a similar approach in people with sickle-cell disease.

The CRISPR and RNA approaches take a different tack. They seek to boost expression of a form of haemoglobin that is normally produced in the fetus and then switched off after birth. Researchers had hypothesized that turning this fetal haemoglobin back on could compensate for the disabled β-globin produced by people with sickle-cell anaemia or β-thalassaemia.

Both studies suggest that this is the case. In one, a team that includes researchers from two Massachusetts companies — Vertex Pharmaceuticals in Boston and CRISPR Therapeutics in Cambridge — used CRISPR–Cas9 to alter a region of a gene called *BCL11A*, which is required to switch off production of fetal haemoglobin. By disabling this gene, the team hoped to turn fetal-haemoglobin production back on in adult red blood cells.

The other study's team — led by haematologist David Williams at Boston Children's Hospital and researchers from Bluebird Bio — used a snippet of RNA that switches off expression of the *BCL11A* gene in red blood cells.

The CRISPR–Cas9 publication reports data from two participants, one with β-thalassaemia and one with sickle-cell disease, but the trial has now treated a total of 19 people, says David Altshuler, chief scientific officer at Vertex. Williams' publication, meanwhile, reports data from six participants with sickle-cell disease, and his trial has since treated three more.

So far, the participants with β-thalassaemia have not needed blood transfusions, and those with sickle-cell disease have not reported pain crises since the treatment. Side effects from the therapies — which included infection and abdominal pain — were temporary.

In both cases, blood stem cells are removed from the marrow, then modified and reinfused into the patients. Before the cells are reintroduced, the participant is treated with drugs to ablate the remaining blood stem cells. This treatment can be difficult and risky.

Researchers are now hunting for gentler ways to prepare the bone marrow for such infusions, but until the therapies are made safer, they will probably be restricted only to people with severe disease that does not respond to conventional treatment, says haematologist David Rees at King's College Hospital, London. "Scientifically, these studies are quite exciting," he says. "But it's hard to see this being a mainstream treatment in the long term."

1. Pauling, L., Itano, H. A., Singer, S. J. & Wells, I. C. *Science* **110**, 543–548 (1949).
2. Frangoul, H. *et al. N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa2031054 (2020).
3. Esrick, E. B. *et al. N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa2029392 (2020).