STEVE BABULJAK/UCSF

Six-year-old twins Tylee and Taleeke both have sickle-cell disease.

BLOOD DISEASE

Medicine is in the blood

Sickle-cell disease is an ideal target for gene therapy, but economic and social barriers to treatment are rife.

BY ANNA NOWOGRODZKI

Elliott Vichinsky estimates that at least 30% of his adult patients with sickle-cell disease die from preventable causes. Red blood cells are supposed to be shaped like concave discs, but in people with sickle-cell disease, a mutation in a single gene collapses them into a crescent shape. The pointy sickles catch on each other and clog blood vessels. They cut off oxygen to limbs. They cause kidney failure, hypertension, lung problems and strokes — along with bouts of excruciating pain.

These are common and treatable complications, so why the high death rate? Vichinsky attributes it to a lack of infrastructure, such as care centres, to properly monitor adults with sickle-cell disease. This is partly because the disease mainly affects low-income minorities and people in developing countries. "If they were tracked before," says Vichinsky, "they would not be dead."

Gene therapy might offer a cure for sickle-cell disease, and clinical trials are already under way. "In the long run I think it will be able to cure the disease," says Vichinsky, a haematologist and oncologist at the University of California, San Francisco (UCSF) Benioff Children's Hospital in Oakland. The approach is promising because just a single gene needs correcting: the one for the β-globin subunit of haemoglobin, the body's oxygen ferry. But Vichinsky is concerned that the same problems that make current care ineffective will also plague this gene-therapy treatment. As his patients attest, sickle-cell care is often inadequate for reasons that have little to do with scientific advancement and lots to do with economics and racism.

For people with sickle-cell disease in the United States, paying for the treatment could be a challenge: it involves such hefty upfront costs that insurers might not be able to cover the treatment, even if it saves them money in the long term.

The only current cure for sickle-cell disease is a bone-marrow transplant from a matched healthy donor. The stem cells that serve as blood-cell factories — haematopoetic stem cells — are removed from the donor's bone marrow or blood, then infused into the recipient. If the transplant works, the donor's stem cells churn out non-sickle-shaped red blood cells, curing the disease. Donors can be a sibling or someone unrelated with the same bone-marrow type, but less than one-third of people with sickle-cell disease can find a matched donor.

Gene therapy could provide a cure for many more people because it doesn't rely on a donor: instead, stem cells are harvested from the patient's own bone marrow. As a further benefit, gene therapy avoids conflict between the donor's and recipient's cells. After a bone-marrow transplant, doctors have to suppress the recipient's immune system to prevent it from attacking the transplant, which leaves the patient vulnerable to infection. Even then, the donor cells might attack the recipient's cells, resulting in graft-versus-host disease — the leading cause of death after a bone-marrow transplant. Gene therapy eliminates this concern.

GENE THERAPY ON TRIAL

Mark Walters, a paediatrician at UCSF Benioff, is working on two gene-therapy clinical trials. One by Bluebird Bio in Cambridge, Massachusetts, is in phase I/II, and one by Bioverativ in Waltham, Massachusetts, will start soon.

For the Bluebird Bio trial, Walters has enrolled two people so far, and plans to enrol four or five in all at his institution — a total of 50 people will be recruited across the United States. The trial is using the gene-therapy drug LentiGlobin BB305 to insert a healthy version of the β-globin gene into people's blood stem cells. With the gene, the stem cells will make normal red blood cells instead of sickle-shaped ones.

Stem cells are harvested from each person in the trial, and they receive blood transfusions every 3–4 weeks to reduce the percentage of sickle cells in their blood, says Walters. "We don't want patients having complications in the middle of the trial or leading up to it."

It takes about a month for the new gene to be inserted into the patients' stem cells. After being collected up, the cells are shipped overnight by plane to a central manufacturing location, where they spend several days just multiplying. Then scientists put the β-globin gene into the stem cells using LentiGlobin BB305, a vector made from a virus. After quality-control testing, the improved stem cells are frozen and shipped back to UCSF Benioff.

In the meantime, the patients receive four days of intensive chemotherapy to wipe out any remaining stem cells with the old, problematic version of the gene. The improved stem cells

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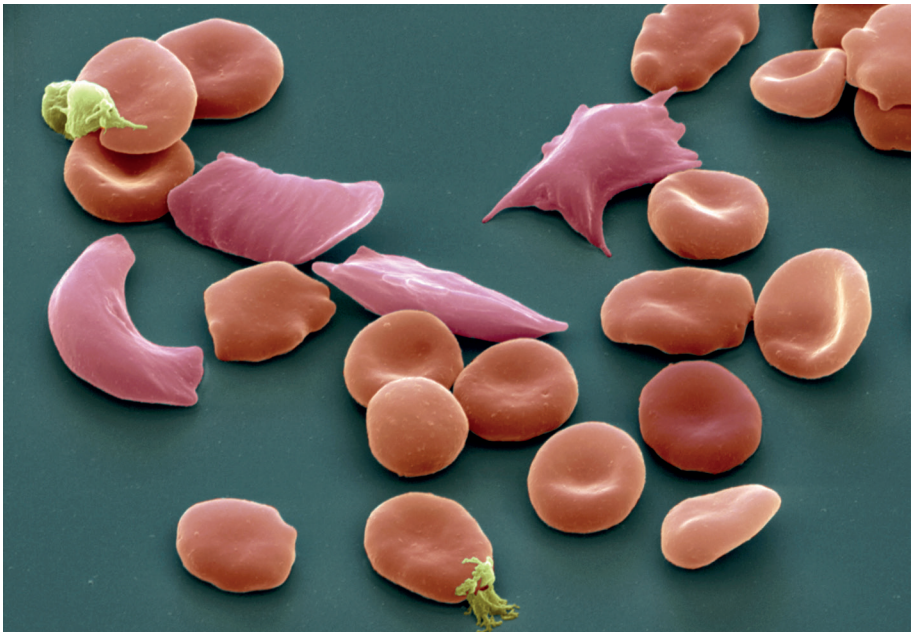

Normal red blood cells (red) compared with the elongated blood cells in sickle-cell disease (pink).

are then reinfused into the person around a day later, and their immune system regains its strength slowly. "It takes about three months to completely recover," says Walters.

A COSTLY ENDEAVOUR

The clinical trials will demonstrate whether gene therapy is effective at curing sickle-cell disease. But even if it is, the cost of treatment is likely to be very high. For example, voretigene neparvovec (Luxturna), a gene therapy for degenerative blindness, costs US$425,000 per eye. "We're looking upwards of $500,000 to $700,000" for sickle-cell gene therapy, spread over multiple years, says Stephanie Farnia, director of health policy and strategic relations at the American Society for Blood and Marrow Transplantation in Chicago, Illinois. And this is a disease for which more than 50% of patients in the United States rely on government health insurance such as Medicare and Medicaid.

In the long term, an expensive cure for sickle-cell disease would probably be cheaper than — and much more preferable to — dealing with 30–40 years of the disease's chronic, long-term effects. But even if the pharmaceutical company spreads the cost to insurers over 5–7 years, Farnia says, insurers, particularly government-funded ones, will probably not have sufficient capital to pay for everyone who wants the treatment. "The really tough part is these budgets do not have a lot of room in them for additional costs," Farnia says. It's like trying to pay for an entire 30-year mortgage in just five years, she says. "You're going to save a lot more money down the road, but can you come up with the money to do that?"

For a possible preview, Farnia suggests looking to chimeric antigen receptor T-cell (CAR-T) therapy — a type of immunotherapy that has shown promising results in treating certain types of cancer. US medical centres and hospitals are paying for CAR-T therapy up front to treat their patients, before knowing whether insurers will reimburse them for it. "And they have to hope they can figure out with payers that they get reimbursed for enough of that," Farnia says.

CHALLENGES AHEAD

There are other concerns with gene therapy as well. For one, more long-term monitoring is needed. The added gene slips in at random places in each stem cell's genome, so it has thousands of opportunities to land in the middle of another important gene. It could theoretically wind up in a gene that suppresses cancer. No one has yet observed a leukaemia caused by delivering treatments with the family of viral vectors that LentiGlobin BB305 belongs to, Walters says, but a stem cell is long-lived. "If you treat a child, it's going to be a source of blood for the next 50–60 years." No patients have been monitored for anywhere near that long after gene therapy.

Although gene therapy opens up bone-marrow transplants to more people than the one-third who have a suitable bone-marrow donor, it doesn't open it up to everyone. "It's still an intensive procedure," says Walters, particularly the high dose of chemotherapy that people receive before the stem cells are returned to their bodies. "Not everybody is well enough to go through it."

Recruiting for clinical trials might also be a problem. Current trials involve small numbers of people with sickle-cell disease, but if the treatments work, future trials will require many more participants. In the United States, sickle-cell disease is more common among black and Hispanic populations, and there is an ugly history of non-consensual medical research on black people, causing some to be wary of participating in clinical trials. And racial bias also gets in the way of treating the disease. "The hallmark of sickle-cell disease is pain, and it's excruciating pain. It's like putting a tourniquet on and depriving a limb of oxygen," says Walters. And unfortunately, doctors have been shown by multiple studies to be less likely to believe black people's claims to be in pain than white people's (see, for example, K. M. Hoffman *et al. Proc. Natl Acad. Sci. USA* **113**, 4296–4301; 2016).

> ***"Sickle-cell disease represents the best and worst of health care in the United States."***

Sickle-cell disease is a chronic condition. Management of chronic diseases isn't typically groundbreaking, and even among chronic diseases, sickle cell is typically neglected. "It's not received the attention or the national funding that it maybe should have received, because it's not as politically connected," says Walters.

Vichinsky argues that gene therapy should be part of a multidisciplinary programme that includes basic care, not a substitute for basic care. "We shouldn't push them into gene therapy just because there's no basic care available," he says. The US Centers for Disease Control and Prevention list 175 providers of paediatric care for sickle-cell disease in the United States, but only 44 providers of adult care. Vichinsky started his own adult programme because he had nowhere else to transfer his young patients when they became adults. "It has to do I think with money and ethnicity," he says.

Basic care for sickle-cell disease should be modelled on current programmes for cystic fibrosis or childhood cancer, says Vichinsky. He advocates that sickle-cell-disease medical centres should include multidisciplinary teams to monitor people for the degenerative effects of sickle cells across many different organ systems, such as the lungs, heart, kidneys, spleen and brain. That way, doctors could detect early warning signs of problems such as renal failure and hypertension.

He is optimistic, however, that sickle-cell gene therapy might act "as a kind of door opener to the field of gene therapy". There are a handful of gene-therapy drugs on the market, but sickle-cell disease's role as an early gene-therapy target, and the promise of that therapy, might attract interest in how best to care for people with this disease, and propel standards of care forward.

"Sickle-cell disease represents the best and worst of health care in the United States," Vichinsky says. Technologically advanced gene therapy is a hot research area, but not yet proven to work. Mundane chronic illness care is neglected, but it would save lives. "Most adults don't have access to multidisciplinary services," says Vichinsky. "I believe to some extent that gene therapy will actually stimulate the medical and scientific community to bring that to sickle cell." ■

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