ILLUSTRATION BY TAJ FRANCIS

The sickle-cell drug boon

Promising treatments have many researchers wondering whether a new epoch of research for a long-neglected disease has finally arrived. **By Benjamin Plackett**

Elley Scott, a civil servant in Coventry, UK, remembers the day when doctors broke the news to her that her newborn son Akhil had sickle-cell disease. "When you're given the result, your heart just drops to the floor. I don't know how else to describe it," she says. Managing his disease has been a challenge ever since.

Sickle-cell disease is caused by a genetic mutation that deforms red blood cells into inflexible crescents that can block the circulation. Until 2017, the only drug approved to treat it was hydroxyurea, but Akhil, now 17 years old, doesn't take it. Although the drug is safe and effective for many people with the disease, he isn't so lucky — hydroxyurea actually makes things worse for him. Aside from pain relief, this effectively means that Akhil's sickle-cell disease has gone untreated.

But hope is on the horizon — the past few years have brought a flurry of new drugs for sickle-cell disease. First out of the pipeline was L-glutamine, which was approved by the US Food and Drug Administration in 2017. Two more drugs — crizanlizumab-tmca and voxelotor — received the regulator's approval in 2019. The European Medicines Agency hasn't approved L-glutamine, but it did sanction the use of crizanlizumab-tmca in 2020; voxelotor is still in clinical trials, and is yet to see use outside the United States.

Scientists anticipate that more drugs will soon be forthcoming. After decades of stagnation, research is finally beginning to bear fruit. "It feels like a glimmer of light," says Scott. But although the future now seems brighter for those coping with the disease, many are still asking why it was neglected for so long.

The underlying biology of sickle-cell disease starts with haemoglobin. This protein, found in red blood cells, transports oxygen around the body, grabbing the molecule in the lungs and later relinquishing it elsewhere. In sickle-cell disease, the haemoglobin molecules that do not contain oxygen often stick to each other and form large, repetitive chains. "That polymer becomes a rigid rod that builds within the red blood cell," explains Ahmar Zaidi, a paediatric haematologist who specializes in sickle-cell disease at the Children's Hospital of Michigan in Detroit. "That alters the red blood cell shape to the half-crescent moon that we typically talk about."

New pathologies, newer strategies

Hydroxyurea, originally developed as a form of chemotherapy, makes red blood cells bigger and helps them to stay rounder for longer, which is why the medication is effective in fighting the disease. The sickled cells clog

arteries as they catch on each other and on blood-vessel walls, restricting the oxygen supply to crucial organs and causing serious and long-lasting damage. These extremely painful blockages are said to be as excruciating as the pain from a heart attack.

Although haemoglobin polymerization remains the main cause of symptoms[1], it is just the first of three aspects of the disease's complex pathology that scientists are looking to target with drugs. Vasculopathy, which is the collective term for both excessive inflammation and the secretion of adhesive molecules from inner blood-vessel walls, is the second pathology that researchers are seeking to diminish, because it further reduces blood flow to organs. The third is an increased level of free haem — a precursor component of haemoglobin. For this characteristic of sickle-cell disease, antioxidant drugs are an option, because haem causes oxidative stress that can damage organs[2]. All three pathologies conspire to reduce the life expectancy of people with sickle cell. "The dream is that you get to a point where you're treating every aspect of this disease, which is why it's important we go after these three game plans," says Zaidi.

Voxelotor is one example of an anti-sickling drug. "This drug is all about how oxygen and haemoglobin interact with each other," explains Zaidi. It boosts the oxygen-carrying capacity of haemoglobin, making it cling to the molecule more tightly. This, in turn, decreases the opportunities for sickling because haemoglobins can polymerize only in their oxygen-depleted state. Studies have so far suggested that the drug also improves the shape of red blood cells[3], helping to undermine a key pathology of sickle-cell disease.

When it comes to vasculopathy, attention is focused on drugs that target a family of cell-adhesion molecules known as selectins. Blockages in the circulatory system of a person with sickle cell don't just consist of sickled red blood cells — platelets and white blood cells are also culprits. "Selectins are basically anchors on blood-vessel walls that act like Velcro for white blood cells to adhere to," says Zaidi. This is helpful in people without sickle-cell disease because they provide an exit point for white blood cells to leave the blood vessel and enter tissues where they might be needed to fight infection. But in people with sickle cell, these sticky areas give sickled red blood cells a convenient place to lodge themselves.

That's where selectin inhibitors come in; as the name suggests, these molecules tinker with the ability of selectins to form a viable docking place for white blood cells. "If you can interfere with this anchoring, then you can reduce the contribution of white blood cells to that traffic jam," says Zaidi. Last year, a phase-III clinical trial indicated that people who took the selectin inhibitor rivipansel within 30 hours of a pain crisis were ready to be discharged from hospital sooner than people who took a placebo.

In March, there was a call for applicants to take part in the first human trial of another drug, CSL889, which seeks to address the third aspect of sickle-cell disease: oxidative stress. CSL889 is a type of haemopexin protein that naturally occurs in the blood. Previous mouse-based studies have shown that administering doses of haemopexins can counteract both oxidative stress and inflammation by mopping up excess free haem[4]. People with sickle-cell disease have lower concentrations of haemopexins in their blood and a soon-to-launch human trial hopes to find out whether the success of animal studies holds true in humans. The pharmaceutical company behind the trial, CSL Behring, based in King of Prussia, Pennsylvania, hopes that CSL889 will reduce the frequency of pain crises.

Although preventing pain is important, Zaidi warns that clinical trials shouldn't limit themselves by measuring success only in terms of reduced crises. "We need to think of this disease as one of decreased life expectancy as well as one characterized by pain, and that's when you realize all three of these buckets — sickling, vasculopathy and oxidative stress — need to be tackled," he says. "If you're not in hospital or in pain then you might think you're doing well, but the disease is continuing beneath the surface. Your life expectancy is still low and so we need this multifaceted approach."

Although these new therapeutics are unquestionably good news for people such as Akhil Scott who live in wealthy nations, it could take many years before people in the disease's epicentre in Africa see any benefit, says Tom Williams, a clinical scientist at Imperial College London who is based in Kenya.

"The new drugs are being marketed at prices for the European and US markets," he says. "It will cost thousands of pounds per year per patient, which just isn't realistic. Finding a way to get these drugs to children in Africa will be key."

Funding change boosts research

Although the advent of new therapies is welcome, it has been a long time coming. One reason is that the biology of the disease is complex. Red blood cells flow to every organ in the body, meaning it's hard to predict which organs will be damaged by blockages. People also commonly experience other complications such as stroke and pulmonary hypertension. Treating the disease can be a frustrating game of whack-a-mole.

Another reason, some contend, is that the demographics of sickle-cell disease have kept it out of the research spotlight. Most people with sickle-cell disease are of African descent, and systemic racism could be to blame for the disease's neglect, says Lucia De Franceschi, a haematologist at the University of Verona in Italy who studies pathologies of red blood cells. "Discrimination deeply impacts this disease and the fact that people aren't talking about it and researching it as much," she says. "We talk far more about cystic fibrosis," she adds — a disease that, like sickle cell, is a single-gene defect, emerges during childhood and has a significant impact on life expectancy. But most people with cystic fibrosis are white.

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A 2020 study showed that on a per-person basis, US government spending on cystic fibrosis was more than three times greater than on sickle-cell disease[5]. Cystic fibrosis also benefits from a 75-fold advantage in philanthropic funding versus sickle-cell disease.

This disparity is slowly beginning to fade thanks to reformed economic policies — through schemes known as 'orphan drug designations', which give the drug developer privileges such as tax breaks. Orphan status is usually reserved for rare diseases, but it can also be granted in scenarios when the drug is for a neglected disease — such as sickle cell — and when the drug is not expected to generate enough profit to be worth the pharmaceutical company's investment. The onus is on the drug maker to seek this status, but many of the new sickle-cell drugs have been successful in this regard. L-glutamine, voxelotor and crizanlizumab-tmca have all been officially designated as orphan drugs. This amounts to a pivotal moment in how the disease is treated, even if getting the new drugs into sub-Saharan Africa is a challenge yet to be solved. "Sickle-cell disease", says Williams, "is finally coming out of the dark ages."

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