New drug may treat rare diseases that make exposure to sunlight painful

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It sounds like the stuff of a vampire novel, but for people with a group

of rare genetic disorders, exposure to sunlight can cause excruciating pain.

Now, an experimental medication is showing promise for helping them better tolerate the light of day.

In an early clinical trial, researchers tested the drug for patients with either of two related conditions: erythropoietic protoporphyria (EPP) and X-linked protoporphyria (XLP).

Both belong to a group of eight rare genetic disorders called porphyrias. Studies estimate that EPP and XLP affect one in every 75,000 to 200,000 white people. Both conditions arise from certain genetic abnormalities that cause a chemical called protoporphyrin to build up in the blood and the lining of the blood vessels.

The trouble comes when a person with EPP or XLP goes into the sun: That light activates protoporphyrin in the blood vessels, which triggers inflammation, cell damage and severe pain.

Both disorders usually become apparent in childhood—which, clearly, takes a toll on kids' quality of life, said Dr. Robert Desnick, one of the researchers on the new trial.

"They call themselves shadow-jumpers, because they have to run from one shady spot to another to avoid the sun," said Desnick, a professor of genetics and genomic sciences at the Icahn School of Medicine at Mount Sinai, in New York City.

Standard sunscreen offers no protection, he said, though zinc oxide sun block can help. Traditionally, the main way to manage the disorders has been staying indoors and, when outside, covering up in sun-protective clothing.

But in 2019, the U.S. Food and Drug Administration approved the first treatment for adults with EPP: a drug called Scenesse. It's a hormonal medication delivered through an implant placed just under the skin. It increases the skin's pigmentation, which allows people with EPP to have more pain-free time outdoors.

The implant naturally dissolves and has to be replaced by a health care provider every two months.

In contrast, the new drug, called dersimelagon, is taken by mouth. Desnick said that makes it easy to adjust the dose to (in future studies) make the medication suitable for children.

It could also make treatment more accessible for people who cannot easily get to medical appointments for new Scenesse implants.

As it stands, only certain doctors can provide the implants. While availability is improving, some patients still have to travel for the treatment, said Dr. Angelika Erwin, a physician at the Cleveland Clinic who treats porphyrias.

Beyond that, it's always good to have more than one treatment option, said Erwin, who was not involved in the new trial.

"If you only have one option and you develop side effects, you have nothing to fall back on," she explained.

For the trial, published April 12 in the *New England Journal of Medicine,* Desnick and his colleagues recruited 102 adults with EPP or XLP. The patients were randomly assigned to take either dersimelagon (at a higher or lower dose) or placebo tablets every day for 16 weeks.

Like Scenesse, the oral drug works by boosting the skin's pigmentation.

Overall, the study found, the medication increased the amount of time patients could spend in the sun before developing "prodromal" symptoms.

Those are warning signs—like tingling or a burning sensation in the skin—that tell people they need to find shade fast, Desnick said.

About one-quarter of people with EPP develop such symptoms within 10 minutes of sun exposure, he said, and a majority have them within 30 minutes.

In the trial, patients on dersimelagon were able to increase their time in the sun by about an hour per day, on average, versus the placebo group.

"To someone without EPP, that might not seem like much," Erwin said. But for people with these conditions, she said, that extra time could make a big difference in quality of life.

The drug did have side effects—most often nausea, freckles and headaches. The nausea and headaches were short-lived and "well-tolerated," Desnick said. (Some people did not like the freckles, though, he noted.)

Mitsubishi Tanabe Pharma, the drug company developing dersimelagon, funded the trial.

Whether and when the drug might gain approval remains to be seen. But a larger trial is underway, and it includes kids as young as 12, Desnick noted.

Eventually, Erwin said, the hope would be to have an option for younger children, too. While the conditions take a toll on anyone's quality of life, she noted, they are particularly hard on children, who just want to play

outside and do all the usual kid things.

More information: The United Porphyrias Association has more on EPP and XLP.

Manisha Balwani et al, Dersimelagon in Erythropoietic Protoporphyrias, *New England Journal of Medicine* (2023). DOI: 10.1056/NEJMoa2208754