Adding sotatercept to existing therapy shows promise in treating rare heart-lung condition

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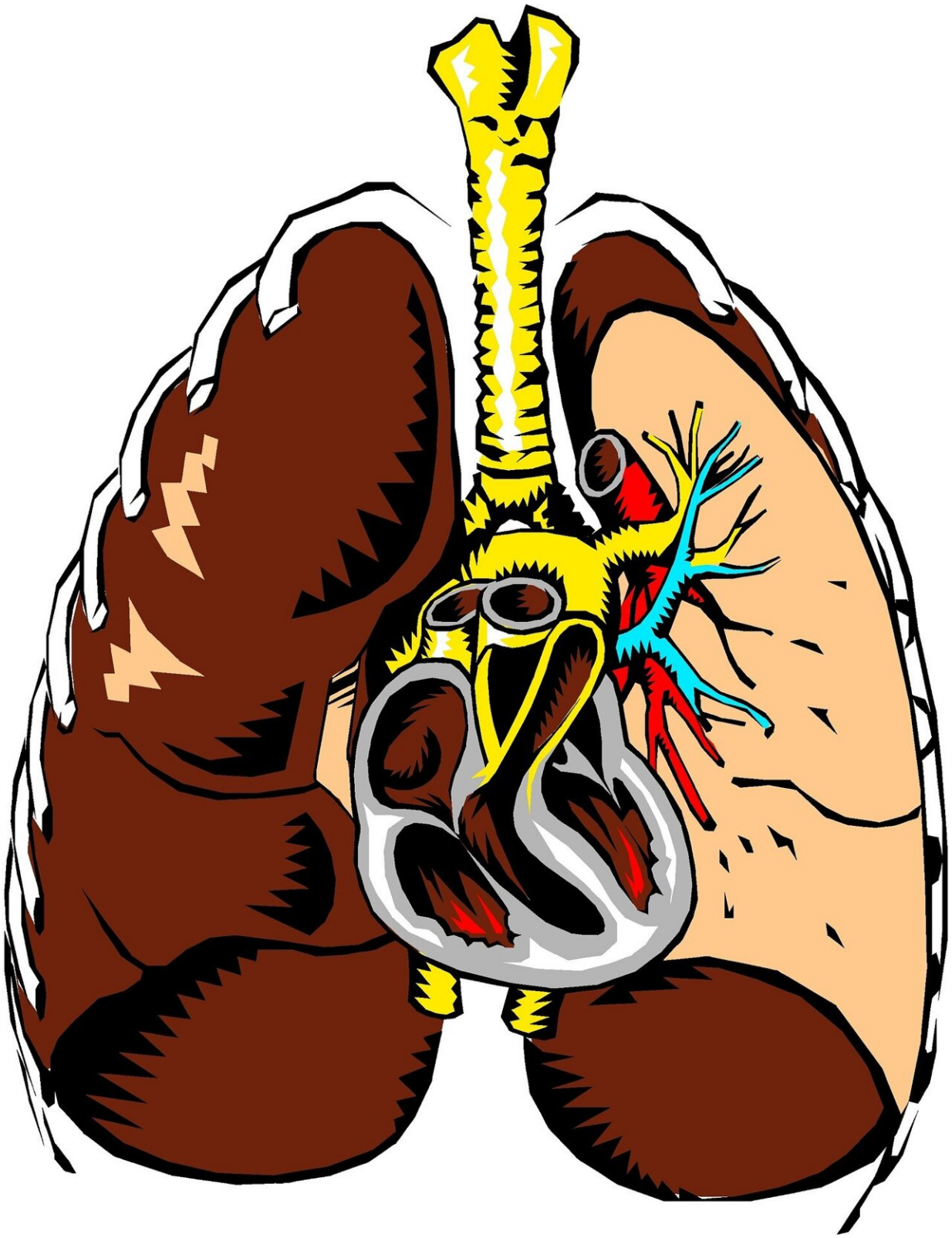

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Patients with pulmonary arterial hypertension (PAH), a severe, progressive condition that affects the heart and lungs, who were treated with the novel first-in-class medication sotatercept on top of existing therapy experienced significant improvements in walking distance via a six-minute walking test—the study's primary endpoint and a validated surrogate for functional improvement and reduced symptom burden. Additionally, participants who received sotatercept also had an 84% lower risk of death or worsening of their condition compared with patients on standard therapy.

The study was presented at the American College of Cardiology's Annual Scientific Session Together With the World Congress of Cardiology. This study was simultaneously published online in the *New England Journal of Medicine* at the time of presentation.

"These results establish the clinical utility of sotatercept as a new approach to the treatment of PAH in combination with existing approved therapies," said Marius M. Hoeper, MD, of Hannover Medical School in Hannover, Germany, and the study's lead author. "It's really a paradigm shift in how we will treat PAH in the future."

PAH is a rare progressive condition caused by narrowing and scarring in the small blood vessels of the lungs that inhibits blood flow from the right side of the heart, which raises blood pressure in the lungs and forces the heart to work harder to pump blood through narrowed arteries. The underlying structural changes in the small pulmonary arteries are caused by imbalances between growth inhibiting and growth promoting mediators, including activins. PAH is often seen in women aged between 30 and 60 years, and about 1 in 5 patients have a family history of the disease. Diagnosis of PAH is frequently delayed because its symptoms—shortness of breath, fatigue, swelling in the feet and legs,

dizziness or fainting spells, chest pain, heart palpitations—resemble those of more common heart and lung diseases.

Globally, more than 10 medications are approved to treat PAH. However, many patients continue to have severe symptoms despite treatment with as many as three medications. The disease can progress rapidly and median survival after diagnosis is about seven years with current therapies, underscoring the need to develop novel therapies, Hoeper said. Sotatercept, a first-in-class activin signaling inhibitor, works by blocking abnormal signaling between cells in the pulmonary blood vessels, which may lead to a partial reversal of the disease process.

The Phase 3 STELLAR trial enrolled 323 patients (median age 48 years, 79% women) with PAH in 20 countries. At enrollment, 60% of the patients had severe symptoms despite maximal therapy with three medications. Many patients had shortness of breath so severe that minimal activity such as taking a few steps or climbing a flight of stairs left them breathless. On average, patients had been living with PAH for almost nine years before enrolling in the trial.

Patients were randomly assigned to receive either sotatercept or a placebo, given as a subcutaneous injection (under the skin) once every three weeks, in addition to their other PAH medications. The trial was double-blinded, meaning that neither patients nor their doctors knew who was receiving sotatercept or the placebo until the trial was over. Patients were followed for a median of 7.5 months.

The trial's primary endpoint was the change in the distance patients could walk in six minutes (known as the six-minute walk distance or 6MWD) at 24 weeks. The average improvement in 6MWD among patients receiving sotatercept was 40.8 meters (134.5 feet, about a half of a typical city block), while patients who received the placebo showed no improvement. The change was statistically significant and exceeded

the minimum of 33 meters (about 108 feet) that, according to earlier research, patients experienced as a noticeable improvement in their walking capacity, Hoeper said.

The study had nine secondary endpoints. Eight of the secondary endpoints were met, including functional class—a measure of impairment due to the disease; proBNP levels, which reflect cardiac strain; and several measures of quality of life. Time to death or the first occurrence of a "clinical worsening" event (defined as a combination of death from any cause, deterioration of exercise capacity or hospitalization for PAH) measured at study completion in August 2022 showed a significant advantage in the sotatercept group.

Nine patients (5.5%) in the sotatercept group died or experienced at least one clinical worsening event, compared with 42 (26.3%) in the placebo group, a risk reduction of 84%. Scores on a validated scale of PAH symptoms showed that patients on sotatercept had statistically significant improvements in symptoms such as shortness of breath and fatigue, as well as in the ability to perform activities such as light household chores, whereas patients on placebo showed no improvements. Scores for cognitive and emotional impacts such as thinking clearly and feeling sad or worried were not significantly different between the two groups.

In addition, the sotatercept group saw a reduction in pulmonary arterial pressure, or blood pressure in the lungs, that was 13.9 mmHg larger than was seen in the placebo group.

"This is the most impressive reduction in the pulmonary arterial pressure that we've ever seen in pretreated patients with PAH," Hoeper said. "For me, it's one of the strongest signals suggesting that we truly achieved some regression of the disease's adverse changes in the pulmonary vessels. However, this remains a hypothesis that we need to explore in future studies."

Overall, the drug was safe and well tolerated. Mild nose bleeds and bleeding of the gums were the most common adverse effects among patients taking sotatercept. More patients on sotatercept also had noticeable dilation, or widening, of the capillaries, called telangiectasias, which appear as red dots on the skin, mostly on the chest and face.

Other adverse effects were increases in hemoglobin levels and lower platelet counts. Platelets are blood cells that help the blood to clot, so a reduction in platelets could leave patients vulnerable to bleeding episodes. These adverse effects were not severe among patients enrolled in the trial, Hoeper said, adding that longer follow-up is needed to assess adverse effects over time.

"With any medication that patients can be expected to take, perhaps for a lifetime, such adverse effects need to be monitored closely," Hoeper said. "Still, what we see in our clinic is fascinating—patients who have been evaluated for lung transplantations coming off the transplant list, patients returning to work, young patients who have been ill for most of their lives starting at their first jobs. [This treatment] opens the door to further research aiming at restoration of a normal pulmonary blood flow."

Most trial participants are now enrolled in a long-term extension study of safety and efficacy in which everyone, including those originally assigned to the placebo group, is being treated with sotatercept. In addition, ongoing phase 3 trials are investigating sotatercept in patients with newly diagnosed PAH and in patients with even more severe PAH than those in the STELLAR trial.

More information: Marius M. Hoeper et al, Phase 3 Trial of Sotatercept for Treatment of Pulmonary Arterial Hypertension, *New England Journal of Medicine* (2023). DOI: 10.1056/NEJMoa2213558

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