PRESS RELEASE
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A promising new approach to the treatment of pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a rare and serious disease for which curative treatment is not currently available. By identifying a therapeutic target based on an in-depth understanding of the heritable forms of the disease, researchers from the Hôpital Bicêtre AP-HP, Université Paris-Saclay and the French National Institute of Health and Medical Research (INSERM) have made major progress in developing a new treatment to complement standard of care therapies. Their work was published in the *New England Journal of Medicine* on 1 April 2021 by Marc Humbert, professor at Université Paris-Saclay and head of the Pulmonology Department at the Hôpital Bicêtre AP-HP, and his colleagues from the international PULSAR study.

Pulmonary arterial hypertension (PAH) is a rare lung disease that is characterised by increased blood pressure in the arteries from the right side of the heart to the lungs. Over time, small pulmonary arteries of less than 0.5 mm in diameter become thick and blocked due to a gradual accumulation of cells in the vessel wall; a process called vascular remodelling. Remodelling obstructs blood flow in the lung vessels, increasing pulmonary arterial pressure. This resistance also puts strain on the heart, which can eventually lead to heart failure. Without effective treatment, this results in gradual shortness of breath during exercise, but also when resting, and syncope. PAH is a serious, life-threatening illness in the short or medium term.

Current treatments consist mainly of vasodilators which improve exercise capacity and the quality of life for patients, slow disease progression and prolong survival. However, none of these treatments cure the disease. Half of patients die within seven years following diagnosis, despite the combination of two or three vasodilator drugs which target the prostacyclin, endothelin-1 and nitric oxide pathways. In the past two decades, key progress has been made in understanding the cellular and molecular mechanisms of PAH and in proposing therapeutic innovations that target pulmonary vascular proliferation to complement vasodilator treatments.

In light of this, the discovery of mutations in the gene encoding for BMPR-II as one of the main causes of heritable forms of PAH has played a key role in the field. BMPR-II is a type II receptor and member of the transforming growth factor-beta (TGF-β) superfamily, which can limit cellular proliferation and consequently, the accumulation of vascular cells in the pulmonary arterial walls. A defect in this signalling pathway removes a physiological “brake”, disrupting lung vessel homeostasis. It has recently been proven that ligands of the activin receptor type IIA (ActRIIA) are responsible for this surge in cell proliferation when BMPR-II is dysfunctional. Similar mechanisms are also linked to non-heritable forms of PAH.

With this in-depth understanding of the disease, the researchers decided to explore the therapeutic potential of sotatercept, a fusion protein developed by the Acceleron laboratory (Cambridge, MA, USA). Sotatercept is composed of the extracellular domain of the ActRIIA receptor fused to the Fc domain of the human IgG1 antibody. It acts as a trap for the ActRIIA ligands, preventing the excessive onset of vascular proliferation pathways released by the BMPR-II brake. The objective of this approach is to re-establish pulmonary vascular homeostasis.

During a multicentre, 24-week, phase 2 trial, researchers selected 106 adults, who were already receiving background therapy for PAH (two or three vasodilators for the majority of patients), who subcutaneously received sotatercept at a dose of 0.3 mg per kilogramme of body weight every three weeks, or 0.7 mg per kilogramme every three weeks, or a placebo (PULSAR trial, NCT03496207). The results were conclusive and demonstrated that sotatercept reduces pulmonary vascular resistance, measured objectively by cardiac catheterisation. Furthermore, improvements were also noted in patients' exercise capacity, measured by a six-minute walk, as well as in various biomarkers and cardiac function. The treatment proved to be relatively safe and well tolerated.

Patients are currently participating in an extension period to assess the safety and efficacy of sotatercept in the long-term. Phase 3 trials are ongoing or have been planned in order to assess this biotherapy rigorously. This work is already a sign of promising progress for the treatment of this serious illness and a beacon of hope for those who suffer from it.

This innovative therapeutic work to combat a rare lung disease is aligned with the priorities of the pulmonary hypertension reference centre (PulmoTension), the Université Paris-Saclay/Inserm UMR_S 999 joint research unit, the Graduate Schools and Interdisciplinary Projects in Health at Université Paris-Saclay (HeaDS, LHS et HEALTHI), the French Healthcare sector and the European Reference Network for Rare Respiratory Diseases (RespiFIL and ERNLUNG).

References

Sotatercept for the Treatment of Pulmonary Arterial Hypertension

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Targeting transforming growth factor beta receptors in pulmonary hypertension

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