

## Gene therapy for beta-thalassemia safe, effective in people

## April 18 2018

In a powerful example of bench-to-bedside science showing how observations made in the lab can spark life-altering therapies in clinic, an international team of clinician-investigators has announced that gene therapy for patients with a severe form of the blood disorder betathalassemia can be safe and effective.

Led by study director Philippe Leboulch, MD, a sponsored collaborator in Brigham and Women's Hospital's Division of Genetics and lecturer in medicine at Harvard Medical School, the research team reports that a one-time treatment with the gene therapy known as LentiGlobin BB305 vector reduced or eliminated the need for <u>blood</u> transfusions in 22 <u>patients</u> with severe beta-thalassemia. The team's results are published in the April 19 issue of *The New England Journal of Medicine*.

"It was always our hope to bring our research findings to patients," said co-corresponding author Leboulch, whose primary appointment has transitioned to the University of Paris as a Professor of medicine and Institute Director. "We have taken our work from the lab, through preclinical models, and past the proof-of-principle stage, and are now able to gauge its effectiveness in patients with this disease. It is immensely gratifying."

Beta-thalassemia is a genetic disorder that impairs the body's ability to produce a key component of hemoglobin, a critical protein in <u>red blood</u> <u>cells</u> that carries oxygen to organs and tissue. Beta-thalassemia and sickle-cell disease are related disorders - both hamper hemoglobin production



and can have lifelong repercussions. From toddlerhood on, people with the most severe forms of beta-thalassemia require monthly blood transfusions to replenish their red blood cell supplies along with iron chelation to remove extra iron from the body.

As a postdoctoral fellow at MIT, Leboulch began researching a therapeutic approach to compensate for the genetic mutations that lead to both sickle-cell disease and beta-thalassemia. Leboulch joined the Brigham's Division of Genetics in 1996, where he continued his work as an HMS associate professor in medicine to develop a viral carrier, or vector, that could insert genetic instructions into a patient's own blood stem cells and restore hemoglobin production. Leboulch and colleagues hoped that re-introducing the altered cells back into people would allow them to make enough hemoglobin, eliminating the need for blood transfusions. At the Brigham and HMS, Leboulch and colleagues studied the vector, known as "LentiGlobin," in pre-clinical models, publishing results from mouse studies in Science. In 2010, Leboulch and his collaborator, Marina Cavazzana of University Paris-Descartes, published a paper in Nature detailing the success of using Leboulch's LentiGlobin to genetically correct cells and transplant them back into a single betathalassemia patient. Last year, they published in the NEJM on a successful gene therapy of the first sickle-cell anemia patient using the same vector.

In the newly published NEJM study, Leboulch, Cavazzana and their colleagues teamed up with a second group of U.S. and international clinical investigators in Australia and Thailand to share data and results from their respective phase II clinical trials. In total, the two teams treated 22 patients at six different sites around the world. Among nine patients with the most severe form of beta-thalassemia, the one-time treatment reduced the need for red-blood cell transfusions by 73 percent. Three of the nine subsequently discontinued transfusions altogether. Twelve of the 13 patients with a slightly less severe form of the disease



no longer needed any blood transfusions after treatment. The team reports no safety concerns - treatment-related adverse effects were typical of those seen in patients who receive cell transplants of their own stem cells.

"When you have an anecdote of a single patient, you never know if it will be confirmed. Here, with a multi-center trial in a larger number of patients, we see a convergence of results, and we can measure the magnitude of the therapeutic effect," said Leboulch. "There is room for improvement, as we'd like to see the elimination of dependency on transfusion even for patients with the most severe form of the disease; but there is also hope with protocol modifications we have introduced in our phase III trials."

Based on these results, two pre-drug marketing phase III clinical trials have begun.

**More information:** *New England Journal of Medicine* (2018). <u>DOI:</u> <u>10.1056/NEJMoa1705342</u>

## Provided by Brigham and Women's Hospital

Citation: Gene therapy for beta-thalassemia safe, effective in people (2018, April 18) retrieved 2 May 2024 from <u>https://medicalxpress.com/news/2018-04-gene-therapy-beta-thalassemia-safe-effective.html</u>

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