New drug targeting genetic variant in Parkinson's disease found to be ineffective in clinical trial

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An experimental drug targeting a genetic variant linked to Parkinson's disease had no effect on patients, according to the results of a new clinical trial published in *The Lancet Neurology*.

Parkinson's disease, a brain disorder that causes uncontrollable movements such as shaking, stiffness and difficulty with balance, affects nearly one million people in the U.S., according to the Parkinson's Foundation.

A subset of Parkinson's disease has been linked to mutations in the gene GBA1, but exactly how the mutation leads to Parkinson's is still not fully known.

Patients with GBA1 mutations may have a more aggressive course of Parkinson's disease. GBA1 is known to control the production of glucocerebrosidase, an enzyme essential for lysosomal function, i.e., breaking down large molecules and clearing them out of the body. Glucocerebrosidase deficiency may lead to accumulation of glucosylceramide, one of the enzyme substrates, thereby leading to lysosomal dysfunction. Preclinical data supported the positive effect of reducing glucosylceramide levels on disease biology.

In the study, investigators sought to understand if the experimental drug venglustat, which inhibits glucosylceramide synthesis, would have any effect on patients with GBA1-related Parkinson's disease.

"Parkinson's is not a single-gene disease. However, there are a number of genetic variants that are clearly associated with an increased risk of Parkinson's disease, and GBA1 is very high on the list," said Tanya Simuni, MD, the Arthur C. Nielsen, Jr., Research Professor of Parkinson's Disease and Movement Disorders, director of the Parkinson's Disease and Movement Disorders Center, and a co-author of the study. "This study was the first genetically targeted therapeutic study for Parkinson's disease utilizing a truly personalized therapeutic intervention."

As part of the study, more than 200 people at 52 different medical

centers throughout the world with GBA1-associated Parkinson's disease were given either venglustat or a placebo once a week for a year. While venglustat was deemed safe with only minor side effects, it had no beneficial effects, according to the findings.

"Despite the fact that, biologically, the drug did what it was supposed to do and reduced the level targeted enzyme, the findings of the study were negative," Simuni said. "The study was very well designed and executed, and the result gives us confidence to say that the drug did not work because this particular way of modifying the GBA1 pathway does not work, unequivocally."

The results do not negate the proven association between GBA1 variants and Parkinson's disease, Simuni said, and future research will focus on targeting the gene in different ways.

"This study was a success in that it was the first of its kind and also recruited a large number of Parkinson's patients with this gene variant, which is noteworthy because genetic testing is not standard-of-care for Parkinson's," Simuni said. "Negative studies are frustrating, but we learn a lot from them."

More information: Nir Giladi et al, Safety and efficacy of venglustat in GBA1-associated Parkinson's disease: an international, multicentre, double-blind, randomised, placebo-controlled, phase 2 trial, *The Lancet Neurology* (2023). DOI: 10.1016/S1474-4422(23)00205-3

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