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First clinical study of new gene therapy shows promise for reducing motor symptoms of Parkinson's disease

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A new triple gene therapy called ProSavin might safely improve motor function in Parkinson's patients by reprogramming brain cells to produce dopamine—a chemical essential for the proper control of movement—according to a phase 1/2 trial published in *The Lancet*.

"Lack of dopamine results in the tremors, limb stiffness, and loss of balance that characterise Parkinson's", explains study leader Professor Stéphane Palfi from AP-HP, Groupe Henri-Mondor Albert-Chenevier in Créteil, France.

"ProSavin uses an inert virus to deliver three dopamine-making genes directly into the striatum region of the brain that controls movement, with the aim of converting non dopamine-producing striatal neurons [nerve cells] into dopamine-producing factories to replace the constant source of dopamine that is lost in Parkinson's disease."

Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's, affecting around 5 million people worldwide. The symptoms of Parkinson's are due to loss of dopamine-producing nerve cells in the part of the brain responsible for controlling movement.

The most widely used treatment is the drug levodopa, a precursor of dopamine that can cross the blood-brain barrier. However, over time cell death is so great that effectiveness lessens and patients can develop

involuntary muscle spasms (dyskinesias) and other side effects.

The current study tested the safety, tolerability, and efficacy of three different doses of ProSavin in 15 individuals aged 48 to 65 years with advanced Parkinson's disease who were no longer responding well to other treatments.

Patients were rated on a Parkinson's disease scale of motor functions that includes speech, tremors, rigidity, finger taps, posture, gait, and bradykinesia (slow movement). The lower the rating, the better the function.

All patients injected with ProSavin had only mild to moderate side-effects related to the treatment; the most common being on-medication dyskinesias (20 events, 11 patients) and on-off phenomena (12 events, nine patients).

Significant improvements in motor scores were seen in all patients in the off-medication state (when patients had been off their medications for 12 hours) at both 6 months (38 vs 26) and 12 months (38 vs 27) after surgery.

However, the authors warn, "Although the efficacy findings show promise, the magnitude of effects are within the placebo range reported in other clinical trials for Parkinson's disease using surgical techniques, and must be interpreted with caution."

They conclude, "[Our findings suggest that this] therapeutic approach that provides continuous and stable dopamine replacement, restricted to the dopamine-depleted striatum, might provide an effective long-term treatment without the onset of behavioural complications."

Writing in a linked Comment, A Jon Stoessl from the University of

British Columbia, Vancouver, Canada says, "The approach taken by Palfi and colleagues is novel in that it is the first time that lentiviral vectors have been successfully applied to the treatment of neurological disease in humans and does not depend on survival of dopaminergic neurons, but rather assumes that transfected striatal neurons preserved in Parkinson's disease will develop the capacity to synthesise dopamine."

However, he adds, "Despite numerous imperfections, we have reasonably good treatments for the motor manifestations of Parkinson's disease in the form of levodopa, infusion therapies, and deep brain stimulation. The challenge of Parkinson's disease is the management of nonmotor problems, many of which have a non-dopamine basis. The therapy described here will not address these issues, but the safety of the approach could be seen as a proof of principle for future studies focused on rigorous assessment of efficacy as well as targeting these devastating problems."

More information: www.thelancet.com/journals/lan … (13)61939-X/abstract

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