PARKINSON DISEASE

Gene therapy for Parkinson disease shows promise in phase II trial

Delivery of the gene encoding glutamic acid decarboxylase (GAD) improves motor symptoms of Parkinson disease (PD), according to a double-blind, randomized, sham-surgery-controlled phase II study recently reported in *The Lancet Neurology*. The motor symptoms of PD—a condition that is caused by basal ganglia dysfunction resulting from dopaminergic imbalances—can be managed during the early stages by pharmacotherapy. However, as the disease progresses, this strategy becomes inadequate and motor complications can arise, leading to a need for new approaches to disease management.

In the current study (registered with ClinicalTrials.gov, NCT00643890), Andrew Feigin and colleagues delivered the gene encoding GAD—the rate-limiting enzyme in the production of γ -aminobutyric acid (GABA)—to the subthalamic nucleus (STN) of patients with PD. “The idea for this approach stems from the observation that in PD there is a loss of GABAergic input to the STN, leaving this structure abnormally

regulated, and this leads to some of the symptoms of PD,” explains Feigin, who is based at The Feinstein Institute for Medical Research in Manhasset, New York, USA. “By introducing the gene for GAD, the goal is to restore GABAergic tone to the STN.” The team used an adeno-associated viral vector—AAV2—to deliver the GAD gene. “We took this approach because it looked promising from preclinical work and in our phase I study,” adds Feigin.

45 patients with idiopathic PD, which was identified on the basis of strict clinical criteria and ^{18}F -fluorodeoxyglucose PET imaging, were enrolled in the study across seven centers in the USA. The patients had all experienced the disease for at least 5 years and scored an overnight off-medication unified Parkinson’s Disease Rating Scale (UPDRS) motor rating of 25 points or more.

The patients were randomly assigned to receive either gene therapy, delivered via a catheter inserted into the STN, or sham surgery, which consisted of the generation of partial-thickness burr holes into which saline was infused from an external catheter. Patients who did not successfully receive the allocated intervention—owing to infusion failure, for example—were excluded from the study, leaving 16 patients in the gene therapy group (designated AAV2–GAD) and 21 patients in the sham-surgery group for inclusion in the analysis. Patients were then assessed during a follow-up period of 6 months.

Importantly, the off-medication-state UPDRS motor score decreased by 8.1 points in the AAV2–GAD group at 6 months, compared with only 4.7 points in the sham-treated group. Thus, gene therapy improved the primary measure of motor function by 23.1% from baseline, compared with only a 12.7% improvement in the control group (thought to be a placebo effect of surgery).

Some secondary end points such as freezing of gait and consistency of medication effects, which were assessed on the basis of patient reports, also suggested improvements in the AAV2–GAD group compared with the sham-treated group. These changes could represent an advantage of gene delivery over deep brain stimulation to the STN, which is used to treat motor symptoms in the later stages of PD but does not treat all parkinsonian features. However, the changes in the secondary end points were not statistically analyzed, so further work is needed to assess their clinical importance. “From my perspective, the most significant findings were that the procedure was generally very safe and well-tolerated, and that the results are the first to demonstrate efficacy for a gene therapy in a neurological disease in a double-blind, sham-surgery-controlled study,” says Feigin.

Previous efforts to apply gene therapy to the treatment of PD involved the delivery of the genes encoding glial cell-derived neurotrophic factor and its structural and functional analog neurturin to the putamen. Although preclinical studies and open-label trials showed encouraging results, beneficial effects were not observed in larger trials.

The results from Feigin and colleagues, therefore, represent an important step forward. Studies involving more patients and longer follow-up times are needed to address issues such as the duration of the benefits associated with gene delivery and possible off-target transduction or adverse effects of the viral vector.

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