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First successful double-blind trial of gene therapy for advanced Parkinson's disease

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A multi-center gene therapy trial for patients with advanced Parkinson's disease demonstrated reduced symptoms of the progressive movement disorder, according to a new study published in *Lancet Neurology*. The study was designed to deliver the gene for glumatic acid decarboxylase (GAD) packaged in inert viral vectors into an area of the brain called the subthalamic nucleus. GAD makes an important inhibitory chemical called GABA. The subthalamic nucleus is abnormally activated in Parkinson's disease and this activity leads to the debilitating movement problems. The idea of the gene therapy is that the billions of AAV-2 GAD viral vectors delivered into the subthalamic nucleus will increase GABA, thereby quieting this brain region.

The lead investigator of the study was Andrew Feigin, MD, associate professor of neurology and molecular medicine at The Feinstein Institute for Medical Research in Manhasset, NY, and the trial was funded by Neurologix, Inc. Early development of the therapy was done Michael Kaplitt, MD, and Matthew During, MD, co-authors of the current study. The study was conducted at seven US medical centers.

A total of 45 patients were enrolled in the study. Roughly half of the patients (23) were randomized into the sham surgery arm of the study, which meant that they had a surgical procedure that did not penetrate the brain, and received infusions of saline under the skin rather than the active GAD-containing viral vectors. A dose-escalation safety study of the gene therapy technique was published in 2007 and paved the way to this expanded double-blind placebo study to test its effectiveness in

reducing motor symptoms.

Everyone in the study had a positron emission tomography (PET) brain scan before the surgery to confirm the diagnosis of Parkinson's disease. Dr. Feigin and his colleagues found that 11 of 56 patients did not actually have Parkinson's and they were excluded from the study. Everyone was assessed at one month, three months and six months after the genes were infused. Each patient in the active treatment received about a billion viral vectors. It is not clear how long the genes will pump out GAD to make GABA.

The scientists only included patients who got bilateral infusions delivered to the correct area of the brain, the subthalamic nucleus. There were also a few cases where the pumps delivering the treatment (the real and the placebo) malfunctioned during surgery and those cases were taken out of the analysis as well. The final analysis included 16 patients who received active (AAV2-GAD) treatment and 21 who received the sham surgery.

The main outcome measure was a change on a rating scale that assesses motor symptoms. The treated group showed a 23 percent improvement on the United Parkinson's Disease Rating Scale, compared to a 12 percent improvement in those who received sham surgery. Normally over a six-month period patient scores remain stable or worsen. The 12 percent improvement among the sham treated group suggests a placebo response.

"This is a completely novel treatment for advanced Parkinson's disease," said Dr. Feigin. "The treatment was remarkably well tolerated, with mostly only mild adverse events in the AAV2-GAD treated group that were felt to be unrelated to the treatment, and completely resolved," said Dr. Feigin. He added that other secondary clinical assessments also provided evidence for improvements from the gene therapy.