Gene Therapy Helps Parkinson's in Phase I Trial

BY JONATHAN GARDNER
London Bureau

Gene therapy for Parkinson's disease was safe and well tolerated by 11 patients, who also showed significant improvement in motor function at 1-year follow-up in an open-label phase I trial .

The 11 patients were treated at New York–Presbyterian Hospital, New York, with a therapy aimed at inhibiting the neurologic stimulation that causes motor dysfunction in Parkinson's disease patients. To accomplish this goal, surgeons delivered the glutamic acid decarboxylase gene to the neurons of the subthalamic nucleus using adeno-associated virus (AAV); no adverse events occurred.

At 1 year after treatment, the researchers found a statistically significant improvement in scores on the 56-point motor component of the Unified Parkinson's Disease Rating Scale (UPDRS)—by 24% when patients were tested 12 hours after withdrawal of medication, and by 27% an hour after patients had taken medication. Statistically significant improvements in scores were also recorded at 3 and 6 months (Lancet 2007;369:2097-105).

"Our results show that AAV-mediated gene transfer can be done safely in the human brain, with no evidence of substantial toxic effects or adverse events in the perioperative period" and for at least 1 year after treatment, wrote the researchers, led by Dr. Michael G. Kaplitt of Cornell University, New York. This open label, nonrandomized phase I study "was not designed to assess the effectiveness of the intervention. Nonetheless, the clinical outcomes were encouraging."

Should further research support this treatment for Parkinson's, it would have an advantage over deep-brain stimulation, which is being used to improve motor function, the researchers wrote.

"The absence of indwelling hardware reduces the risk of infection, and some patients with Parkinson's disease simply prefer not to have an implanted device," they wrote. "Additionally, frequent visits for deep brain stimulation adjustments are not needed" with the investigational approach.

In an accompanying commentary, Dr. A. Jon Stoessl, of the Pacific Parkinson's Research Centre at the University of British Columbia, Vancouver, questioned whether the development of a gene-therapy approach would be superior to deep-brain stimulation.

At 1 year after treatment, improvement was found in scores on the 56-point motor component of the Unified Parkinson's Disease Rating Scale.

"Apart from the avoidance of stimulator adjustments and potential hardware problems, what is the real advantage of this approach?" Dr. Stoessl wrote. He cautioned that the research did not study the long-term effect of changing the neurologic pathways. But he praised the study and wrote that the approach should be subjected to further randomized, double-blind evaluation.

Because of ethical concerns, the researchers were restricted to using the treatment in only the more symptomatic hemisphere of the brain. They recorded greater improvements in motor function in the contralateral side of the body, compared with the untreated side, on the UPDRS.

In addition, although they did not record any improvements in the activities of daily living scores during the course of the study, at 12 months they measured a trend toward improvement in the off-medication state.

The researchers performed PET scans on the patients at 12 months, and found substantial reductions in glucose metabolism in the thalamus and overall in the operated hemisphere, a change that they did not detect on the untreated side. ■