Biomarkers Show Improvements

Parkinson's *from page 1*

ulating the neuronal network that regulates movement by delivery of the glutamic acid decarboxylase (GAD) gene into neurons of the subthalamic nucleus, where it catalyzes synthesis of the inhibitory neurotransmitter γ-aminobutyric acid (GABA).

By leading to effects similar to those caused by deep brain stimulation (DBS), this approach aims to suppress the excessive activity of the subthalamic nucleus that is characteristic of advanced PD, though without the potential hazards of deep brain stimulation.

"DBS is a very effective treatment for patients with Parkinson's disease, but it comes with considerable risk and an adverse event rate exceeding 30%," said Dr. Matthew J. During, who is professor of molecular virology, immunology, and medical genetics at Ohio State University, Columbus.

"We felt that if we could at least match DBS and potentially improve on it, plus reduce the risk using local anesthetic, it would be a significant advance in the field. That's what we attempted to do," Dr. During said in an interview.

The trial included 11 men and 1 woman, whose mean age was 58 years and whose disease duration exceeded 5 years. All had scores of 30 or higher on the Unified Parkinson's Disease Rating Scale (UPDRS) and had previously responded to levodopa.

The vector used for gene delivery was adeno-associated virus (AAV), serotype 2. Three doses (low, medium, and high) were given, each to four patients. Only the side of the brain contralateral to the most affected side of the body was treated, to maintain at least one intact hemisphere should unexpected problems ensue and to act as control to the treated hemisphere.

PET scanning with ^{18}fluorodeoxyglucose was done before the treatment and at 12 months to evaluate biochemical changes resulting from the treatment.

Significant clinical improvements of 25%-30% on UPDRS were seen at both 6 and 12 months on the contralateral side of the body. There also was a strong trend toward improvement in activities of daily living, even though only one side had been treated.

Most important, these clinical improvements correlated very strongly with reductions in thalamic metabolism shown on the PET imaging, Dr. During said. "We had a correlation coefficient of about 0.82, which is very high, suggesting that we had a strong biochemical marker of the clinical improvement," he said. There were no adverse events associated with the surgery, and some patients now have been followed beyond 4 years. No deaths have occurred.

The next step will be a blinded, sham surgery–controlled phase II study to be carried out at six centers throughout the United States. This is expected to begin in the next several months, and will involve bilateral treatment, according to Dr. During, who is a founder and consultant to Neurologix Inc., the study sponsor.

"We are very encouraged. At least in terms of our study, we think the field shows enormous promise. These are patients who essentially had come to the end of their medical treatment and whose only real therapeutic option was DBS, which is a complicated, expensive surgery performed on only about 5,000-7,000 of the 150,000 patients in this country each year who could benefit from it," Dr. During said.

In discussing the benefits of gene therapy versus DBS, Dr. During and colleagues wrote, "Although deep brain stimulation of the subthalamic nucleus uses a fixed voltage to regulate the activity of this area locally, AAV-GAD gene therapy might make the motor network function return to normal through activity-dependent release of GABA both locally within the subthalamic nucleus and throughout the network via connections to other hyperactive areas" (Lancet 2007;369:2097-105).

Another reassuring finding from the study was that, although two patients at baseline had substantial anti-AAV2 immunity, no new cases of elevated titers were seen during the study. There had been concern about cell-mediated and humoral immunity developing against the viral capsid proteins (Exp. Neurol. 2008;209:51-7).

A second trial sought to restore normal levels of the enzyme aromatic-L-amino-acid decarboxylase (AADC) in the striatum of patients with PD with the goal of enhancing the brain's response to levodopa and minimizing side effects. "This approach is not meant to cure the disease, but rather to help patients function better," said Dr. Krystof Bankiewicz, who is principal investigator, Brain Tumor Research Center, University of California, San Francisco. Dr. Bankiewicz holds the patent for the technology used in the study and in the past has had a consulting agreement with Genzyme, the sponsor of the study.

The trial included 12 patients with advanced PD. Unlike in the AAV-GAD trial, treatment was bilateral, with patients receiving infusions into the postcommissural putamen. Bilateral treatment was considered necessary with this approach, because altering the levodopa response in only one hemisphere could pose difficulties in management, according to Dr. Bankiewicz.

The same viral vector was used, and patients in this trial also underwent PET scanning to quantify AADC expression and correlate this with improvement in levodopa response.

"The results have been quite striking in terms of neuroimaging and clinical response, with all patients showing some degree of response," Dr. Bankiewicz said in an interview. "We don't have a placebo control group yet, but the whole team here at UCSF is extremely excited about this," he said.

A third approach involves the use of neurotrophic factors that can enhance neuronal function and protect neurons from degeneration. The first member of this family to be identified, in 1993, was glial cell line–derived neurotrophic factor (GDNF), which fosters the growth of dopamine-generating neurons.

GDNF was evaluated in various animal models and seemed promising, showing reduction in parkinsonian symptoms and increases in numbers of neurons. When GDNF was tested in human trials, however, results were disappointing; safety concerns arose, including loss of neurons in the cerebellum; and the trials were stopped. This action, and Amgen Inc.'s subsequent unwillingness to permit further investigation or compassionate use of the drug, generated considerable controversy, particularly among some scientists and patient advocacy groups. Some of the clinical trial participants, who felt the drug had been beneficial, brought lawsuits against Amgen, but judges ruled against them.

Subsequently, a related ligand known as neurturin (CERE-120) underwent preclinical testing and has now been tested in a phase I trial that included 12 patients with advanced disease. This trial was described by Dr. Jeffrey Kordower at a meeting sponsored by the Parkinson's Disease Foundation.

The GDNF homologue, a survival factor for dopaminergic neurons, was given in one of two doses via stereotactic neurosurgery under general anesthesia, with deposits being placed throughout the putamen. Among patients who received the low dose, after 9-12 months of follow-up there was a 35% improvement on UPDRS, and among those who received the higher dose, after 6-9 months of follow-up there was a 40% mean improvement, Dr. Kordower said.

"On patient motor diaries, there was an approximate doubling of mean duration of 'on time without dyskinesias,' and approximately a halving of off time," said Dr. Kordower, who is the Jean Schweppe-Armour Professor of Neurological Sciences at Rush University Medical Center, Chicago. He is also a founder and consultant to Ceregene Inc., manufacturer of the GDNF homologue, and cosponsor of the study with the Michael J. Fox Foundation for Parkinson's Research.

The cohort has continued to be followed, and most recently, the eight evaluable responders showed a 52% mean improvement in symptoms and a statistically significant reduction in UPDRS score, according to a press release posted on the Ceregene Web site.

"It's comforting that it looks good, but these are open data and are prone to placebo effects and experimenter bias," Dr. Kordower cautioned. A double-blind, phase II trial recently completed enrollment of 58 patients from nine medical centers in the United States, with results expected to be available late in 2008.

"The most important piece of data from the phase I trial was that there were no issues of safety related to the gene therapy approach," Dr. Kordower said. "That's true for all these clinical trials. These appear to be very safe procedures that may have striking, long-lasting benefits for patients with Parkinson's disease. The once-futuristic concept of changing the genes and repairing the brains of Parkinson's patients is now here," he said. ■

Gene Sequence Variant Linked to Restless Legs Syndrome

BY MARY ANN MOON
Contributing Writer

A newly discovered gene sequence variant is strongly associated with periodic limb movements in sleep, a component of restless legs syndrome, reported Dr. Hreinn Stefansson of deCODE Genetics, Reykjavik, Iceland, and associates.

Even though the authenticity of restless legs syndrome (RLS) has been called into question, "our study provides evidence that periodic limb movements in sleep is a genuine syndrome with an ascertainable phenotype and a genetic basis," the researchers said.

Restless legs syndrome is characterized by uncomfortable and distressing sensory urges to move the legs during rest or inactivity. The condition often but not always involves involuntary, highly stereotypical, regularly occurring foot and leg movements in sleep.

The pathogenesis of the disorder is unclear, but it has been linked to low iron levels and has "a substantial" genetic component, according to the researchers.

Dr. Stefansson and associates genotyped 306 case subjects who had periodic limb movements in sleep, most of whom also had restless legs syndrome, as well as 15,664 control subjects from the general Icelandic population.

Overall, the researchers were able to assess more than 300,000 single nucleotide polymorphism (SNP) markers distributed across the human genome.

The researchers found a strong link between the disorder and allele A of rs3923809 on chromosome 6p.

To validate these results, they then conducted replication studies in an additional Icelandic cohort that included 123 case subjects and 1,233 control subjects, and in a U.S. cohort of 188 case subjects recruited from a sleep disorders center and 662 control subjects.

The association was evident in each study population, and it was highly significant when all three of the samples were combined, the investigators said (N. Engl. J. Med. 2007;357:639-47).

Subjects who carried the gene sequence variant also had higher ferritin indexes, a measure inversely related to bodily iron stores, as well as decreased serum ferritin levels. This correlation "is consistent with the suspected involvement of iron depletion in the pathogenesis" of RLS, Dr. Stefansson and his associates added.

In an editorial accompanying the study, Dr. John W. Winkelman of, Brigham and Women's Hospital and Harvard Medical School, Boston, said the results offer "hope to patients with periodic limb movements in sleep and RLS that the syndrome's pathophysiology will be understood, and that such knowledge will lead to additional effective and durable treatments" (N. Engl. J. Med. 2007;357:703-5). ■