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Susan Jeffrey

Susan Jeffrey is the news editor for Medscape Neurology & Neurosurgery. Susan has been writing principally for physician audiences for nearly 20 years. Most recently, she was news editor for thekidney.org and also wrote for theheart.org; both of these Web sites have been acquired by WebMD. Prior to that, she spent 10 years covering neurology topics for a Canadian newspaper for physicians. She can be contacted at SJeffrey@webmd.net.

From Medscape Medical News > Neurology Neurotrophic Factor Promising for PD in Early Phase - Again



Susan Jeffrey

April 26, 2011 (Honolulu, Hawaii) — A change in dosing paradigm has a gene therapy approach to treating Parkinson's disease (PD) back on track to a phase 2b trial.

The therapy injects an adenoassociated virus vector carrying the gene for neurturin, a neurotrophic factor that enhances the function and survival of dopaminergic neurons (*CERE-120*, Ceregene Inc; www.ceregene.com), directly into the brains of PD patients during stereotactic brain surgery. An earlier approach directed injections only to the putamen, which in the end did not sufficiently reduce clinical symptoms, specifically on the primary endpoint of United Parkinson's Disease Rating Scale motor subscore "off of medications," in a [phase 2a](#) trial.

Injection to the putamen in animal studies had shown biological activity, lead study author Joao Siffert, MD, vice president and chief medical officer at Ceregene, told *Medscape Medical News*. However, he said, it came "somewhat as a surprise" that it wasn't enough in patients. The expectation was that the vector and protein would be transported from the putamen into the substantia nigra via the nerve cells, but in fact this wasn't efficient in patients.

"This is more and more acknowledged and reported in the literature — but it's not something that's widespread knowledge — that in fact there is a problem with transport of proteins along the axons in Parkinson's," Dr. Siffert noted.

Now, they are addressing this issue by injecting both the putamen and substantia nigra. However, he added, "In order to ultimately do the testing that we're now conducting, we had to go back and test whether it was feasible and safe in patients, and that's the phase 1 trial I reported."

The new results were presented during a late-breaking science session at the American Academy of Neurology 63rd Annual Meeting.

Open-Label Study

In this open-label study, 2 dose cohorts included 3 patients each; patients all had chronic idiopathic PD and a robust response to levodopa, although with motor complications, such as dyskinesia or severe wearing off.



Dr. Joao Siffert

Both cohorts received injections of 2.0×10^{11} vg into each substantia nigra. The putaminal dose in cohort 1 was 2.7×10^{11} vg, the same dose used in the previous phase 2 study; subjects enrolled in cohort 2 received a much higher dose of 10×10^{11} vg. Patients were dosed once between December 2009 and June 2010.

The primary endpoint was the safety and tolerability of the procedure. Follow-up is now at 9 to 12 months. During that time, there have been no serious adverse events reported in this small number of patients, Dr. Siffert said. There have been no surgical complications or prolonged hospitalizations.

"All the adverse events are mild to moderate and expected, namely, headache and some swelling," he said. "Some patients had transient increase in 'on' state dyskinesias, most of which have resolved."

Importantly, there was no weight loss, he noted. "There were 2 reports in animals, , saying this was risky and could lead to inexorable weight loss, and this has not been shown either in our own animal studies under therapeutic doses or in this clinical study." Magnetic resonance imaging findings have also shown no complications.

"Going forward, we're doing a very rigorous, multicenter, well-controlled trial, comparing CERE-120 delivered through 3 injections in the putamen and 1 into the substantia nigra, on both sides of the brain, with half the patients receiving placebo surgery, Dr. Siffert said in an interview.

Patients will continue taking their usual medications and be evaluated every 3 months.

"We think by the end of the summer we'll complete enrollment, and it will be a year and a half, give or take, until the results," he said. "We're also following patients longer, in part because of the previous study — it may take longer to see an effect and also, I guess, to overcome the period where people are very enthusiastic because the placebo effect can be pretty high in patients with PD."

In the first phase 2 trial, reported at that time by *Medscape Medical News* and published in *The Lancet Neurology* in 2010, they did see "modest but significant" benefits on several endpoints, including the primary outcome in a subgroup of patients assessed at 18 months, suggesting that a longer follow-up might be necessary for the neuritin to provide clinical benefit.

Earlier Intervention

Session comoderator Walter A. Rocca, MD, professor of neurology and epidemiology at the Mayo Clinic, Rochester, Minnesota, asked Dr. Siffert what he sees as the future of this therapy. "Which patient do you think will ever benefit from this and what is your agenda?"

Dr. Siffert said from the ethical standpoint they have had so far to limit their enrollment to those in whom current therapy has failed and are experiencing motor complications, although they are trying to avoid those patients who are so far progressed that a neurotrophic approach would not be expected to make a difference.

"But I don't think it's a far leap to believe that if there's efficacy demonstrated for this in phase 2, and it's replicated in future studies, that ultimately this will be an approach that would be adopted earlier in the disease to really try to preserve the function of these cells before they've further degenerated," he said. "But that's for the future."

The study was supported by Ceregene Inc and the Michael J. Fox Foundation for Parkinson's Research. Dr. Siffert is an employee of Ceregene. Disclosure information for coauthors appear in the abstract. Dr. Rocca has disclosed no relevant financial

relationships.

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