Trial Generates Options for DBS in Parkinson's

BY JEFF EVANS

TORONTO — Motor function in Parkinson's disease patients improved by a similar amount after 2 years of bilateral deep brain stimulation of the subthalamic nucleus or globus pallidus in the first blinded, randomized trial to compare outcomes with the two targets.

This result may free clinicians to give greater weight to the effects of deep brain stimulation (DBS) at each site on quality of life, neuropsychiatric symptoms, and medication reduction, Dr. Kenneth A. Follett said at the annual meeting of the American Academy of Neurology.

The subthalamic nucleus (STN) has become the preferred and most common target of deep brain stimulation for Parkinson's disease patients, even though "there really is a lack of high-quality evidence that STN-DBS provides clinical outcomes that are superior to outcomes with GPi [globus pallidus interna]–DBS," said Dr. Follett, professor and chief of neurosurgery at the University of Nebraska Medical Center, Omaha.

GPi-targeted patients completed the trial with slightly better neurocognitive performance in some areas and slightly more "on" stimulation time, but also with significantly greater medication use, compared with STN-targeted patients.

"The bottom line is that given the uniformity of outcomes, clinicians may comfortably take into consideration factors other than just motor function when selecting a target. For example, you may have preferences based on what you perceive is in need of targeting one site or another, the ease of programming one site or another.

"You may decide it's prudent to select one target versus the other based on symptoms. For example, a patient with severe, dose-limiting dyskinesias may be a [slightly] better candidate for GPi. A patient who has medication side effects such as nausea or hallucinations at a low dose may be a better candidate for STN-DBS, knowing that she'll be more likely to reduce medications postoperatively," Dr. Follett said.

Although it is unclear whether medication reduction is necessarily desirable for all patients, it "may play some role ultimately in selection of target," he noted.

During 2002-2008, patients enrolled in the trial and underwent follow-up at 13 VA Parkinson's Disease Research, Education, and Clinical Care Centers and their affiliated universities, Dr. Follett said.

To be enrolled, patients had to be at least moderately disabled off medications (Hoehn and Yahr stage 2 or worse) and be L-dopa responsive with clearly defined "on" periods, and to have a diagnosis of idiopathic Parkinson's disease, persistent disabling symptoms such as dyskinesias, motor fluctuations, and a minimum of 3 hours per day in the "off" state or "on" with dyskinesias.

The investigators excluded patients with "Parkinson's Plus" or secondary or atypical Parkinson's syndromes, previous surgeries for Parkinson's disease, medical contraindications to surgery or stimulation, contraindications to MRI, active alcohol or substance abuse, or a Mini-Mental Status Examination score of 24 or lower or other neuropsychological dysfunction.

VITALS

Major Finding: Scores on the motor subscale of the UPDRS improved from baseline by similar amounts after 2 years of DBS targeting the globus pallidus interna (from 42 to 30) or subthalamic nucleus (from 43 to about 32.5).

Data Source: Randomized, rater-blinded trial of 299 patients with idiopathic Parkinson's disease.

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The randomized DBS trial was embedded within another randomized trial that compared best medical therapy (BMT) with pooled outcomes of DBS. After 6 months, clinical outcomes were examined and BMT patients were randomized to either DBS target.

In an interim analysis of the data when 134 patients had been randomized to BMT and 121 to DBS, the data safety monitoring board decided to stop randomizing patients to BMT because enough data had been gathered to compare the primary outcome.

An additional 61 patients were randomized to only one of the DBS targets, leaving a total of 316 enrolled patients. The investigators conducted follow-up with the patients for 2 years after DBS implantation, meaning that patients who had been initially randomized to BMT received 30 months of follow-up.

A total of 17 BMT patients withdrew from the trial without being randomized to DBS, leaving 152 patients in the GPi group and 147 in the STN group. These patients had a mean age of about 62 years and had been on Parkinson's disease medications for a mean of 11-12 years. Patients and the clinical raters were blinded to the target brain region.

In the "on stimulation, off medication state," scores on the motor subscale (part III) of the United Parkinson's Disease Rating Scale (UPDRS III) at 6 months improved similarly in the GPi (from 42 at baseline to 30) and STN patients (from 43 at baseline to about 32.5). The scores at 2 years—the primary outcome of the trial—were no different. Additional longitudinal analyses with mixed-effect models that used worst-case scenarios for all incomplete data also found no difference between the groups.

"Regardless of how we looked at the data, the result was the same," he said. "This was a very robust finding."

These 25%-30% reductions in UPDRS III scores are not as great as the 40%-50% improvements that have been reported in open-label, uncontrolled studies. This might be a result of having slightly fewer disabled patients in the current study than in studies described in earlier reports, which included patients with UPDRS III scores in the high 40s and low 50s, Dr. Follett said. He noted the possibility of a "floor effect" to DBS, meaning that "you can only improve patients to a certain point, so the lower the UPDRS starting score, the [lower the percentage of] improvement there's going to be."

Data from the patients' motor diaries indicated that at 2 years, GPi patients had about 1 hour more of "on" stimulation time without dyskinesias (from 6.5 to 11.4 hours) than did STN patients (from 7 to 11 hours), although this was not statistically significant.

Quality of life assessments at baseline with the Parkinson's Disease Questionnaire (PDQ-39) indicated that STN-targeted patients had slightly worse scores for emotional well-being, social support, and cognition. Dr. Follett suggested that these "very small point differences" might reflect the fact that the STN arm of the trial included slightly fewer men than women, who "tend to report slightly greater disability in chronic disease compared with men."

At 2 years, there were no differences between the groups on the PDQ-39. With the exception of social support and communication, quality of life improved on each subscale of the PDQ-39. GPi patients reported slightly improved depressive symptoms on the Beck Depression Inventory, compared with slight worsening of symptoms in STN patients. But the difference was not statistically significant.

Baseline assessments of neurocognitive function and mood in category fluency and learning and memory also were slightly worse in STN patients than in GPi patients. After 2 years of DBS, neurocognitive function worsened slightly in both groups. STN patients experienced significantly greater worsening of visuomotor processing speed than did GPi patients, although the change was slight.

No differences between the groups were detected on other UPDRS subscales (I, II, and IV).

Because the trial was not powered to test for differences between secondary outcomes, Dr. Follett noted that further analyses of the data will contend with what to make of very small differences that are detected between groups because of the large sample size.

"The question we need to address is, 'Are those small differences that might be statistically significant [also] clinically significant?' So keep in mind that some of these statistically significant differences are fairly small in terms of points and might not be clinically significant."

Use of Parkinson's disease medications declined by a significantly greater percentage with STN-DBS (30% decrease) than with GPi-DBS (about a 20% decrease).

Similar numbers of serious adverse events occurred in the GPi (77) and STN (83) arms, and there was no difference in the type of events that were seen, such as prolonged or new hospitalization, repeat surgery, morbidity, or death.

"What's going to be much more important is how these folks do 5 years out, 8 years out, 10 years out. Is there a point at which Parkinson's disease progresses or the beneficial effect of DBS will be lost?" he asked. ■

MY TAKE

Nonmotor Effects Rise in Importance

STN has been the most common target of DBS for Parkinson's disease ever since deep brain stimulation pioneer Dr. Alim-Louis Benabid of France suggested in the mid-1990s that it was a better target for DBS than the GPi. Given the similar degree of motor improvement observed with either target in this trial, the choice of stimulation site could now depend on the presence of other factors, such as dyskinesia. (Most clinicians would say that the GPi is a better target than the STN for dyskinesia.)

It will be important to follow up with the patients as planned, but previous reports of DBS with longer than 2 years of follow-up seem to indicate that the effect of stimulation does not decline substantially beyond that. However, there are few reports of more than 5 years of follow-up.

Because the trial was designed nearly 10 years ago, the investigators might not be able to analyze their results for some of the issues that have arisen more recently in Parkinson's disease research, such as the dopamine dysregulation syndrome (including pathological gambling and impulsivity).

It will be important to resolve whether the greater level of depressive symptoms observed in the STN patients is a reflection of their greater reduction in medication use or is a potential effect of stimulating that site. If reducing medications increases depressive symptoms in STN patients, then it could be a reason to not reduce medication use.

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