EDITORIALS

Focused Ultrasound Ablation of the Globus Pallidus Internus for Parkinson's Disease

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One of the challenges in the management of advanced Parkinson's disease is the occurrence of motor fluctuations and dyskinesias in response to antiparkinsonian medications. The often unpredictable deterioration of motor function in the off-medication state and dyskinesias in the on-medication state can render patients disabled for many hours each day. Deep-brain stimulation of the subthalamic nucleus or the globus pallidus internus is an established treatment for patients with these complications.[1] However, not all patients are eligible for deep-brain stimulation owing to coexisting conditions, and some are unwilling to consider this treatment because it involves invasive placement of electrodes in the brain. It also requires frequent adjustment and expert monitoring of an implanted stimulator, which make it inaccessible for some patients. Ablative radiofrequency surgery, which has been used less frequently since the advent of deep-brain stimulation, is a more invasive and irreversible technique that does not allow for adjustments in response to changes in clinical features.

Focused ultrasound ablation (FUSA), which involves noninvasive, externally applied sonication energy, allows for ablative surgery without the need for craniotomy and is a method for the creation of very focused brain lesions that is potentially safer than radiofrequency surgery. Focused ultrasound lesions of the thalamus have been shown to reduce symptoms of medically refractory essential tremor and tremor-dominant Parkinson's disease,[2] with sustained improvement for several years reported.[3] A small randomized, controlled trial has shown improvement of motor function with unilateral FUSA of the subthalamic nucleus for markedly asymmetric Parkinson's disease; adverse events, including speech and gait disturbances, unilateral weakness, and dyskinesia, were mostly mild and reversible but relatively frequent.[4] Furthermore, open-label studies have indicated that unilateral FUSA targeting the globus pallidus internus for motor complications of Parkinson's disease is associated with clinically meaningful reduction of dyskinesias as well as motor disability in the off-medication state.[5-7]

In this issue of the *Journal*, Krishna et al.[8] report the results of a double-blind, randomized, controlled trial of unilateral FUSA of the globus pallidus internus for Parkinson's disease with motor complications. A total of 94 patients were included, all of whom had at least mild motor fluctuations or dyskinesia; in contrast to a previous feasibility study,[7] the trial did not require patients to have unilateral or markedly asymmetric symptoms. Despite these broad inclusion criteria, the trial showed a significant effect on the primary outcome: at 3 months, 45 of 65 patients (69%) who underwent FUSA (active treatment) were classified as having had a response, showing a reduction in motor impairment in the off-medication state or a reduction in dyskinesias in the on-medication state, as compared with 7 of 22 patients (32%) who underwent a sham procedure (control). In the active-treatment group, reductions were seen in motor impairment in the off-medication state in 29% of the patients, in dyskinesia in the on-medication

state in 12%, and in both in 28%. Furthermore, open-label follow-up indicated that 12 months after the procedure, 30 of 39 patients in the active-treatment group who initially had had a response continued to benefit. At 3 months, adverse events in the active-treatment group included dysarthria, gait disturbance, loss of taste, visual disturbance, and facial weakness. These events were generally mild and reversible, but it is worth emphasizing that despite an incisionless procedure, FUSA of the globus pallidus internus is not risk-free. No explicit quality-of-life measure was included in the trial design, but the change from baseline to 3 months in the score on the Movement Disorders Society–Unified Parkinson's Disease Rating Scale, part II (a measure of motor aspects of daily living and a secondary outcome), did not differ significantly between the two groups.

Where does this trial place FUSA of the globus pallidus internus for treatment of Parkinson's disease? The results confirm that it is effective in reducing motor complications of Parkinson's disease, at least in the short term. However, the degree of improvement was less than suggested by previous open-label studies. Approximately one third of the patients in the FUSA group did not have a response at 3 months, and only one third of the FUSA group had both improved motor function and reduced dyskinesia. It is notable that a third of the patients in the control group were also classified as having had a response, a finding consistent with the high rate of placebo response in Parkinson's disease trials. The reasons for the lower incidence of improvement in this trial than in previous studies may partly lie in the inclusion criteria. Patients in the current trial could have a predominance of motor impairment in the off-medication state with no or little dyskinesia in the on-medication state, as reflected in the low mean scores for dyskinesia at baseline, and there was no requirement for strong asymmetry of motor features for this unilateral procedure. The use of the percentage of patients with a response as the primary outcome measure, rather than the improvement in severity scores, was also perhaps more stringent than previous open-label studies. Nevertheless, the results suggest that not all patients derived a meaningful benefit from the intervention. The supplementary data provide preliminary information indicating that patients who were younger, had lower motor severity scores, or had higher dyskinesia scores were more likely to benefit, but the population most likely to benefit needs to be examined in further studies.

As with other surgical interventions in Parkinson's disease, evaluation of benefit requires longer-term follow-up to establish the overall effect on patients' functioning. The results of this trial are promising, but given the nonreversible nature of the intervention and the progressive nature of the disease, it will be important to establish whether improvements in motor complications are maintained over longer periods and whether treatment results in improved overall functioning and quality of life for patients.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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