Unilateral intraputaminal glial cell line–derived neurotrophic factor in patients with Parkinson disease: response to 1 year each of treatment and withdrawal

JOHN T. SLEVIN, M.D., DON M. GASH, PH.D., CHARLES D. SMITH, M.D., GREG A. GERHARDT, PH.D., RICHARD KRYSCIO, PH.D., HIMACHANDRA CHEBROLU, M.S., ASHLEY WALTON, B.S., RENEE WAGNER, R.N., AND A. BYRON YOUNG, M.D.

Departments of Anatomy and Neurobiology, Neurology, Statistics and Public Health, and Neurosurgery, the Morris K. Udall Parkinson’s Disease Research Center of Excellence, and the Magnetic Resonance Imaging and Spectroscopy Center, Chandler Medical Center, University of Kentucky; and Neurology Service, Veterans Affairs Medical Center, Lexington, Kentucky

Object. Glial cell line–derived neurotrophic factor (GDNF) infused unilaterally into the putamen for 6 months was previously shown to improve motor functions and quality of life measures significantly in 10 patients with Parkinson disease (PD) in a Phase I trial. In this study the authors report the safety and efficacy of continuous treatment for 1 year or more. After the trial was halted by the sponsor, the patients were monitored for an additional year to evaluate the effects of drug withdrawal.

Methods. During the extended study, patients received unilateral intraputaminal infusion of 30 µg/day GDNF at a basal infusion rate supplemented with pulsed boluses every 6 hours at a convection-enhanced delivery rate to increase tissue penetration of the protein. When the study was stopped, the delivery system was reprogrammed to deliver sterile saline at the basal infusion rate of 2 µl/hour.

The Unified PD Rating Scale (UPDRS) total scores after 1 year of therapy were improved by 42 and 38%, respectively, in the “off” and “on” states. Motor UPDRS scores were also improved: 45 and 39% in the off and on conditions, respectively. Benefits from treatment were lost by 9 to 12 months after GDNF infusion was halted. At that time, the patients had returned to their baseline UPDRS scores and required higher levels of conventional antiparkinsonian drugs to treat symptoms. After 11 months of treatment, the delivery system had to be removed in one patient because of the risk of infection. In seven patients antibodies to GDNF developed, with no evidence of clinical sequelae. There was also no evidence of GDNF-induced cerebellar toxicity, as evaluated using magnetic resonance imaging analysis and clinical testing.

Conclusions. Unilateral administration of GDNF results in significant, sustained bilateral benefits. These improvements are lost within 9 months after drug withdrawal. Safety concerns with GDNF therapy can be closely monitored and managed.

KEY WORDS • glial cell line–derived neurotrophic factor • striatum • Unified Parkinson’s Disease Rating Scale • Core Assessment Program for Surgical Intervventional Therapies • magnetic resonance imaging

We report the results of unilateral GDNF therapy that was continued for 1 year for the treatment of PD, and we also detail the patient responses during the 1st year of drug withdrawal. The responses of the 10 patients to 6 months of therapy in this Phase I trial have already been published. Although GDNF has been repeatedly demonstrated to promote neural restoration and functional recovery in animal models of PD, the results from clinical trials have been mixed. All patients in two Phase I trials who received intraputaminaly infused GDNF through implanted programmable pumps and catheters improved significantly. In both trials, total and Part III (motor) UPDRS scores were improved at 6 months by approximately 30% whether patients were “off” or “on” conventional medication. However, investigators in a recent multicenter Phase II trial of intraputaminal GDNF infusion did not achieve the primary end point of significant improvement in the UPDRS motor off score after 6 months of therapy. Differences in dose, catheter design, and delivery protocols may explain the discrepancy between the Phase I and II studies.

On September 1, 2004, the sponsor halted the extended
study and required that all patients have the drug removed from their pumps within a 10-day period. The failure of the Phase II trial to achieve the primary end point along with two safety concerns were cited as the reasons for discontinuing this and two other ongoing clinical trials.16 One safety issue was the detection of antibodies to GDNF in blood samples obtained in some patients. The other concern was the presence of cerebellar lesions in four rhesus monkeys that were receiving high doses of GDNF in a toxicology study. The patients in our trial discontinued GDNF therapy, but elected to retain their delivery systems. Because entry into the Kentucky trial was staggered, the duration of GDNF therapy ranged from 8 to 26 months. Eight patients were able to complete 1 year of therapy before the drug was withdrawn. One year of GDNF washout data was obtained in all 10 patients.

Clinical Material and Methods

We obtained informed consent for procedures from all patients in accordance with US Food and Drug Administration and University of Kentucky Medical Center Internal Review Board regulations and guidelines. Eight men and two women whose ages ranged from 47 to 70 years and who had moderate to advanced idiopathic PD (Hoehn and Yahr Stage III or IV) composed the study population (Table 1). Patients underwent stereotactic surgery for implantation of a catheter in their putamen, and the device was then connected to a SynchroMed pump (Medtronic, Inc., Minneapolis, MN), which was subcutaneously implanted in the abdominal wall. The 40-port catheters (model 10532; Medtronic) were unilaterally implanted into the posterior to midputamen, contralateral to the most affected side. Details on the surgery, the drug delivery system, and the response of the patients to the first 6 months of GDNF therapy have been described previously.19 In this study we report the effects of intraputaminal GDNF infusion in patients who underwent this therapy until the trial was halted by the sponsor (end of therapy). We also report on patient response to 12 months of withdrawal from the drug.

Treatment With GDNF and its Withdrawal

We used recombinant methionyl human GDNF (Amgen, Thousand Oaks, CA) produced in Escherichia coli for the infusions. After the pumps were implanted, vehicle (10 mM citrate and 150 mM sodium chloride, pH 5) was delivered for 1 month. An infusion protocol was used in which a steady, low rate was interspersed with brief bursts of infusion at a convection-enhanced delivery rate to promote bulk flow of GDNF into the surrounding brain parenchyma, theoretically increasing its volume of distribution in the putamen. The infusion pumps were programmed to maintain a basal infusion rate of 2 μl/hour (which is required to keep the pumps operating properly), supplemented every 6 hours with a bolus delivered at a much faster rate (21.3 μl infused in 117 seconds). This infusion protocol was used throughout the therapy phase of the study, delivering 133 μl/day of solution into the putamen. The GDNF infusion began 4 weeks after surgery and the dose was then escalated every 8 weeks (first 3 μg/day, then 10 μg/day, and finally 30 μg/day). At the end of the 24-week GDNF treatment period, all patients underwent a 5-week drug washout test.19 All 10 patients elected to reinstate treatment in an extended study and all were subsequently treated with the highest dose level tolerated (30 μg/day).

When the sponsor terminated the trial, GDNF was withdrawn from the pumps. The devices were refilled with saline and programmed to deliver fluid at the basal infusion rate of 2 μl/hour. All changes in protocols, including termination of GDNF treatment with subsequent laboratory and clinical monitoring, were approved by the Internal Review Board, and informed consent was obtained from all patients at the time of the changes.

Clinical Testing and Follow Up

Clinical evaluations included UPDRS total on and off scores, UPDRS motor on and off scores, and CAPSIT-PD times.4 Testing was scheduled every 3 months during extended treatment and the first 12 months of GDNF withdrawal. The MR imaging studies of the brain were obtained at baseline, after 1 year of treatment (the formal study plus 6 months of extended treatment), and 1 year after drug withdrawal. For MR imaging assessment of possible cerebellar injury, magnetization-prepared rapid acquisition gradient echo imaging data sets were evaluated to detect differences at the voxel level within patients between baseline treatment and 12 months after withdrawal.3 After drug withdrawal, blood samples were collected monthly for analysis of GDNF antibody titers (in vitro determination of binding and neutralizing antibody levels; Amgen, Inc.).

Statistical Analysis

For the UPDRS end points, the comparison of mean responses across time was based on a linear mixed model with post hoc comparison of means based on the Fisher protected least significant differences procedure. Confidence intervals for the percent change from baseline were obtained by the delta method and are based on a t-distribution with 9 degrees of freedom. For the CAPSIT-PD end points, some patients were unable to complete some tasks; when this was the case, a score of 90 seconds was assigned to the stand-walk-sit task and 30 seconds was assigned to the hand-arm movement test. Comparison of the distribution of responses was based on the Friedman chi-square statistic with post hoc comparison of means, which was conducted using the Fisher protected least significant differences procedure applied to the ranks across time, determined on a patient-by-patient basis. Control of the Type I error rate for testing each week of follow up and comparing it with the baseline week was obtained by applying the Bonferroni–Holm procedure.10 Statistical significance was determined at the 0.05 level for probability values.

Results

Effects of GDNF on Levodopa Treatment, UPDRS Scores, and CAPSIT-PD Measures

Conventional antiparkinsonian medication levels were not changed while the patients received GDNF treatment (Table 1). Although levodopa-equivalent levels remained constant, patients attained significant improvement after 1 year of treatment (Table 2). In the off medication state, total and motor UPDRS scores improved by 42 and 45%, re-
Unilateral intraputaminal GDNF in patients with PD

TABLE 1

Patient data, side effects, and safety issues in 10 patients with PD who underwent therapy with GDNF *

<table>
<thead>
<tr>
<th>Characteristic†</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>age at baseline (yrs)</td>
<td>70</td>
<td>54</td>
<td>49</td>
<td>61</td>
<td>48</td>
<td>50</td>
<td>63</td>
<td>69</td>
<td>68</td>
<td>47</td>
</tr>
<tr>
<td>duration of PD at baseline (yrs)</td>
<td>5.6</td>
<td>5.2</td>
<td>11.4</td>
<td>15.4</td>
<td>7.9</td>
<td>4.8</td>
<td>6.2</td>
<td>12.2</td>
<td>11.8</td>
<td>6.8</td>
</tr>
<tr>
<td>levodopa equivalents/day</td>
<td>baseline</td>
<td>450</td>
<td>300</td>
<td>1275</td>
<td>902</td>
<td>750</td>
<td>700</td>
<td>1775</td>
<td>1200</td>
<td>1167</td>
</tr>
<tr>
<td>end of therapy</td>
<td>450</td>
<td>300</td>
<td>1275</td>
<td>902</td>
<td>750</td>
<td>700</td>
<td>1775</td>
<td>1200</td>
<td>1167</td>
<td>500</td>
</tr>
<tr>
<td>sx during withdrawal</td>
<td>850</td>
<td>500</td>
<td>&gt;1334</td>
<td>&gt;1090</td>
<td>&gt;750</td>
<td>&gt;1050</td>
<td>&gt;2633</td>
<td>&gt;800</td>
<td>1383</td>
<td>1238</td>
</tr>
</tbody>
</table>

| sx during withdrawal increase in hypomimia (off) | 0 | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 0 |
| increase in hypophonia (off/on) | 1/1 | 1/2 | 0/0 | 2 | 2/1 | 1/1 | 1/2 | 0/0 | 0/0 |
| decline in postural stability (off) | 1 | 1 | 0 | 1 | 2 | 8 | 1 | 1 | 1 |
| increase in end-of-dose fluctuations | 0 | 0 | 0 | 2 | 0 | 2 | 2 | 0 | 0 |
| increase in dyskinesia | 0 | 0 | 2 | –1 | 0 | 0 | 0 | 1 | –1 |
| increase in hallucinations | no | no | yes | yes | yes | no | yes | yes | yes |
| device-related SAEs | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 |
| antibodies to GDNF (B &/or N) yes (B) yes (B) yes (B) yes (B&N) yes (B) yes (B) yes (B) yes (B) no no |

* B = binding antibody; N = neutralizing antibody; SAE = severe adverse events; sx = symptoms.
† Duration of disease was counted from the onset of symptoms to the week prior to surgery.
‡ Values for 1-year treatment compared with baseline.
†† Probability value for comparing response across time. The rest are probability values for post hoc comparisons.

respectively (see videos of one patient walking while off antiparkinsonian medications before [Clip 1] and 24 weeks after [Clip 2] treatment with GDNF). In the on condition, total and motor UPDRS scores showed improvement in the same range (38 and 39%, respectively). Improvements in the UPDRS scores at 1 year did not differ significantly from ratings at the end of therapy (Table 2), where the duration of GDNF therapy was as long as 26 months, depending on the date of entry into the trial.

Videos 1 and 2: Video clips of one patient walking while off antiparkinsonian medications before (Video 1) and 24 weeks after (Video 2) treatment with GDNF. In the off medication state, total and motor UPDRS scores improved by 42 and 45%, respectively, after 1 year of treatment. Click here to view Video 1 with Windows Media Player and a broadband connection, or here to view with RealPlayer. Click here to view Video 2 with Windows Media Player and a broadband connection, or here to view with RealPlayer.

TABLE 2

Extended treatment with GDNF in patients with PD: UPDRS and CAPSIT measures obtained after 1-year withdrawal*

| Test | Baseline | p Value† | 1-Yr GDNF Tx | p Value‡ | End of GDNF Tx | p Value§ | 1-Yr GDNF Withdrawal | p Value|| |
|------|----------|----------|--------------|----------|----------------|----------|----------------------|--------|
| total UPDRS score | 64 ± 5 | 0.0001 | 37 ± 3 (–42) | 0.0001 | 44 ± 3 (–31) | 0.19 | 63 ± 3 (–2) | 0.0001 |
| on | 47 ± 3 | 0.0001 | 29 ± 3 (–38) | 0.0001 | 30 ± 3 (–36) | 0.46 | 43 ± 3 (–9) | 0.0002 |
| motor UPDRS score | 40 ± 4 | 0.0001 | 22 ± 2 (–45) | 0.0001 | 26 ± 3 (–35) | 0.32 | 39 ± 3 (–2) | 0.0001 |
| on | 23 ± 2 | 0.0006 | 14 ± 3 (–39) | 0.0004 | 13 ± 3 (–43) | 0.77 | 19 ± 3 (–17) | 0.025 |
| CAPSIT stand-walk-sit | 39.0 ± 8.2 | 0.12 | 28.4 ± 9.4 (–27) | 0.12 | 33.1 ± 9.9 (–15) | 0.75 | 37.9 ± 10.3 (–3) | 0.063 |
| on | 21.7 ± 5 | 0.052 | 14.6 ± 1.4 (–33) | 0.18 | 13.4 ± 1.3 (–38) | 0.19 | 22.3 ± 7.9 (3) | 0.390 |
| CAPSIT hand-arm contralat | 18.3 ± 2.2 | 0.0006 | 9.3 ± 1.5 (–49) | 0.0001 | 9.3 ± 1.3 (–49) | 0.96 | 11.4 ± 2.4 (–38) | 0.11 |
| off | 13.4 ± 2.2 | 0.0001 | 8.7 ± 1.9 (–35) | 0.0001 | 7.3 ± 1.3 (–46) | 0.007 | 7.9 ± 1.5 (–41) | 0.06 |
| ipsilat | 15.1 ± 1.6 | 0.0009 | 7.9 ± 1.2 (–48) | 0.0001 | 7.9 ± 1.1 (–48) | 0.88 | 8.9 ± 1.2 (–41) | 0.74 |
| on | 11.7 ± 1.5 | 0.0002 | 7.2 ± 1.3 (–38) | 0.0001 | 6.5 ± 1 (–44) | 0.46 | 7.2 ± 1.2 (–38) | 0.015 |

* Baseline UPDRS scores for each patient are the means of three determinations made at 1 week before and 1 and 4 weeks after catheter implantation (before administration of GDNF). The UPDRS measures are given as the mean score ± SEM, and CAPSIT measures are in seconds ± SEM (the percentage decrease in scores is given in parentheses). Abbreviations: SEM = standard error of the mean; Tx = treatment.
† Probability value for comparing response across time. The rest are probability values for post hoc comparisons.
‡ Values for 1-year treatment compared with baseline.
§ Values for 1-year treatment compared with end of GDNF therapy.
|| Values for end of GDNF therapy compared with 1-year withdrawal.
At 1 year of treatment, CAPSIT-PD times were significantly improved bilaterally for arm and hand movements in both on and off testing (see videos of arm-hand movements obtained in one patient who was off antiparkinsonian medications before [Clip 3] and 24 weeks after [Clip 4] treatment with GDNF). As with UPDRS scores, there were no significant differences compared with end-of-therapy measures. However, CAPSIT-PD stand-walk-sit times did not improve significantly during the study. Although the mean times in this walking task were faster at 1 year and at the end of therapy for patients while on and off medication, variability on task performance was high.

Videos 3 and 4: Video clips of arm-hand movements obtained in one patient who was off antiparkinsonian medications before (Video 3) and 24 weeks after (Video 4) treatment with GDNF. At 1 year of treatment, CAPSIT-PD times were significantly improved bilaterally for arm and hand movements in both on and off testing. Click here to view Video 3 with Windows Media Player and a broadband connection. or here to view with RealPlayer. Click here to view Video 4 with Windows Media Player and a broadband connection, or here to view with RealPlayer.

Effects of GDNF Withdrawal on Levodopa Treatment, UPDRS Scores, and CAPSIT-PD Measures

There was a steady deterioration of motor function and quality of life measures over the first 9 months after GDNF withdrawal. By 9 to 12 months off GDNF, all improvements that had occurred while the patient was receiving therapy were lost (Fig. 1, Table 2). Total UPDRS scores off and on conventional medication were significantly worse than end-of-therapy scores (p < 0.0001 and p < 0.0002, respectively; Table 2). Motor UPDRS scores similarly declined. The difference in motor off scores between the end of therapy and 1 year after withdrawal was highly significant (p < 0.0001). Although there was more variability in motor on scores, the difference was also significant (p < 0.025).

Conventional antiparkinsonian medications, measured as levodopa equivalents, were increased to treat the functional declines of the patients (Table 1). Medication increases appeared to mitigate the progressive functional declines by 9 to 12 months after GDNF withdrawal (Fig. 1). Predictably, as medication levels increased so did side effects, thus limiting effective treatment doses. In several patients, medication-induced side effects following GDNF withdrawal precluded a sustained increase, and in one instance (Case 8), medication had to be reduced.

Changes in CAPSIT-PD times after GDNF withdrawal were more complex (Table 2). The stand-walk-sit times were close to baseline measures. Contralateral and ipsilateral arm movement times were, on average, 38 to 41% faster than baseline measures, but 5 to 11% slower than at the end of therapy (statistically significant for the on time).

Safety and Side Effects

The patient in Case 4 experienced a series of problems related to the delivery system. At the end of the initial 6-month study, an excoriation of the scalp developed in the region overlying the site where the tubing from the pump was connected to the base of the indwelling intraputaminal catheter. After hospitalization, surgical revision, and recovery, GDNF therapy resumed. Five weeks later, the patient was readmitted because an MR image indicated increased edema associated with the catheter track in the putamen. Her GDNF dose was reduced to 10 μg/day, and then increased to 30 μg/day, which was tolerated. Finally, the excoriation redeveloped 4 months into the extended treatment, and because of the risk of infection, the entire delivery system (pump, tubing, and catheter) was surgically removed. A small hole in the tubing leading from the pump was found near the connection to the base of the catheter, perhaps caused by a suture needle. This patient had detectable titers of binding and neutralizing antibodies to GDNF (Table 1) that were not associated with evident clinical sequelae. Other than in this patient, no other serious adverse events were encountered with the delivery device.

Binding antibodies to GDNF were identified in the plasma of another six patients (Table 1). The GDNF antibodies have continued to be detected for at least 9 months following trophic factor withdrawal. As with the patient in Case 4, the presence of antibodies has not been accompanied by evident clinical symptoms. The serum albumin/globulin ratio was measured at baseline, at the end of therapy, and 3 months after the end of therapy, with testing randomly distributed among patients and time points (range 1.06–1.92). Furthermore, at 3 months after the end of therapy, the erythrocyte sedimentation rate, C-reactive protein levels, antinuclear antibody, antimitochondrial antibody, antismooth–muscle antibody, and rheumatoid factor were normal or negative in all patients except for the rheumatoid factor in the patient in Case 1 (weakly reactive at 1:80; clinically asymptomatic). The absence of clinical symptoms and laboratory markers of overt inflammation argue against a harmful immune response in association with GDNF antibodies.

The other safety concern arose from a toxicology study conducted in rhesus monkeys in which high doses of GDNF that were intraputaminally infused for 6 months were associated with cerebellar lesions. Because three of the four monkeys with lesions were in the 3-month washout group, drug withdrawal may have been a contribut- ing factor. High-resolution, voxel-by-voxel comparisons of brain MR imaging studies capable of detecting volumetric changes of ± 0.5% obtained in patients 1 year after GDNF withdrawal did not reveal changes from baseline (methods reported in Chebrolu, et al.18). This suggests that lesions resulting from GDNF therapy or withdrawal of therapy, if present, are below the resolution of our MR imaging techniques.

Features of PD that improved in some of the patients during the first 6 months of GDNF therapy worsened during the year after withdrawal of the drug (Table 1). Four of the patients experienced hallucinations, in some cases requiring hospitalization. The pattern of increased medications and increased side effects was typical of progressive PD in the moderate to advanced stages.

Discussion

Assessment of safety is the primary end point in Phase
I trials. The fundamental medical problem experienced by all patients in the present study was progression of PD when GDNF was withdrawn. Conventional antiparkinsonian drug treatment had to be increased, with resultant increases in side effects. Serious complications related to the delivery system developed in one patient, and these events necessitated removal of the system, which resolved the problem. No evident clinical manifestations related to the safety concerns about GDNF cerebellar toxicity in nonhuman primates and GDNF antibodies were observed in the 10 patients of this study.

The GDNF-binding antibodies were detected in seven of the 10 patients; the immune response in one of them progressed to production of neutralizing antibody. In this patient, there was evidence of subcutaneous extravasation of GDNF beneath the scalp where the base of the catheter was anchored to the skull, which may have contributed to the immune reaction by exposing the vascular tissues to GDNF. Neutralizing antibodies pose a hypothetical risk because they may bind to endogenous GDNF molecules, attenuating the normal actions of the trophic factor. Risk assessment is difficult for a number of reasons. The neutralizing activity was measured in an in vitro system whose capacity to predict in vivo activity is not clear. The functions of GDNF in middle-aged and elderly adults are not well understood, so effects from autoimmunity are also difficult to predict. The antibodies were generated against an exogenous GDNF protein produced in bacteria, which differs in several ways from endogenous GDNF. The latter is glycosylated and folded as it is processed through the endoplasmic reticulum and Golgi apparatus. It is not known whether antibodies generated against chemically folded, weakly glycosylated E. coli–produced GDNF also neutralize endogenous GDNF activity. To date, clinical sequelae from GDNF autoimmunity have not been evident, and results of clinical tests to detect active immune responses have been negative. It also remains to be seen if the experience with neutralizing antibodies to GDNF will parallel the experience with IFN-β, where neutralizing antibodies reduce the efficacy of drug treatment and can be associated with disease progression.

Segmental cerebellar lesions have been observed in rhesus monkeys receiving high doses of GDNF infused into the putamen. Although this remains a concern and the mechanisms of action are not known, there was no evidence of cerebellar injury in repeated clinical evaluations or on MR imaging studies in this treatment group after up to 26 months of GDNF therapy and 12 months of GDNF washout. Results of an earlier MR imaging volumetric and intensity analysis conducted in the same group after 1 year of GDNF administration were also negative. Definite characterization of cerebellar pathological features requires postmortem histopathological evaluation. Such an assessment has been conducted in one patient in the Bristol Phase 1 trial, who died from an unrelated myocardial infarct 3 months after GDNF withdrawal. In this individual, there was a single, small cerebellar infarct, typical of the

---

**Fig. 1.** Graphs showing UPDRS scores with 95% confidence intervals for total and Part III (motor) evaluations. The baseline is the mean score of three separate evaluations conducted prior to the start of intraputaminal GDNF infusion. Tx = treatment.
occasional ischemic lesions found in the cerebella of elderly individuals with vascular disease. In addition, we have completed a histopathological analysis of cerebellar tissue obtained in rhesus monkeys receiving intracerebral GDNF infusions in the dose range of the Kentucky Phase I study. The cerebella of GDNF recipients in the rhesus monkey study did not differ from the age- and sex-matched controls. The best evidence to date supports the suggestion that cerebellar lesions caused by GDNF are related to continuous dosing at levels well above the therapeutic range used in the current study. Although indications of efficacy are secondary in Phase I trials, the data obtained can be useful in evaluating the methodology and in designing subsequent Phase II studies. In our trial, PD features as measured by the UPDRS scores were decreased by 38 to 45% after 1 year of treatment, indicating that the benefits seen at 6 months were maintained and tended to increase with continued treatment. At the same time, disease progression may be slowed because conventional symptomatic antiparkinsonian medications were unchanged during this period. Our results are consistent with the other Phase I trial, in which the five patients showed improvements in the course of the first 12 months that were maintained over the next year of treatment.

Nevertheless, our results differ from the inconclusive ones in a recent Phase II study, in which a 10% improvement in UPDRS motor off scores was found in 17 patients receiving intraputaminal GDNF compared with a 4.5% improvement in 17 patients receiving placebo (vehicle) infusions. Differences in drug delivery and dosing may account for differences in results. Optimizing trophic factor distribution in target tissue is critical for efficacy. Parkinsonian rhesus monkeys, the volume of infused GDNF distribution in the brain was at least fourfold greater using a multiport catheter (a smaller version of the one used in the Kentucky Phase I trial) compared with the distribution achieved with the Phase II catheter. Dose is another critical variable. Both Phase I studies, in which 30 to 45% improvements in UPDRS motor off scores were seen, used doses up to two or three times greater than the Phase II trial.

The long-term effects of GDNF withdrawal have not been systematically studied. The 10 patients in the extended trial underwent a 5-week withdrawal as part of the formal dose escalation study without a significant decline in functional effects. The pattern seen in our extended study is one of a precipitous deterioration in movement functions by 3 months after discontinuation of treatment. Most benefits from GDNF therapy were lost by 9 to 12 months after withdrawal. The exception was CAPSIT upper-extremity motor function compared with baseline. The faster times in both on and off states may reflect either practice effects on these specific arm movement tasks or a residual effect of GDNF.

Conclusions

The results from 1-year intraputaminal GDNF infusion in our study are consistent with extensive animal data and the Bristol Phase I trial results, in which it has been stated that trophic factor treatment can be both protective and restorative. The recent inconclusive Phase II results may be the result of differences in GDNF dosing and delivery protocols. The two safety issues with GDNF—development of antibodies to exogenous GDNF and possible toxic injury to the cerebellum in nonhuman primates—require further study. In this patient group, however, neither clinical manifestations in response to GDNF antibodies nor clinical or imaging evidence of cerebellar lesions were evident. Given the following three considerations: 1) that advanced PD is profoundly debilitating and life-threatening; 2) that the known safety concerns can be closely monitored and medically managed; and 3) that the methodology used in the two Phase I trials shows strong indications of efficacy, we believe that additional Phase II clinical trials are warranted to continue developing the approach featuring intraputaminal delivery of trophic factors for treating PD.

Acknowledgments

We thank Avalon Sandoval for assistance with the manuscript. We also thank Dr. Robert Coffey, Medtronic, Inc., for his comments on the manuscript.

References

Unilateral intraputaminal GDNF in patients with PD

16. Peck P: Amgen decision to halt GDNF clinical trials and withdraw the drug triggers protest from researchers and patients. *Neurology Today* 5:4, 7, 24, 2005

Manuscript received March 15, 2006.
Accepted in final form April 4, 2006.
This work was supported by the Consolidated Anti-Aging Foundation; Medtronic, Inc.; and Amgen, Inc.

*Address reprint requests to:* John T. Slevin, M.D., Department of Neurology, University of Kentucky Medical Center, KY Clinic (Wing D)-L445, Lexington, Kentucky 40536-0284. jslevin@uky.edu.