Dopamine Transporter Brain Imaging to Assess the Effects of Pramipexole vs Levodopa on Parkinson Disease Progression

PARKINSON DISEASE (PD) is a slow but relentlessly progressive neurodegenerative disorder characterized clinically by bradykinesia, tremor, rigidity, and gait dysfunction. The clinical decline reflects ongoing nigrostriatal dopaminergic degeneration.1-3 Dopaminergic replacement therapy with the precursor levodopa or agonists that stimulate the dopamine receptor is effective in ameliorating many signs and symptoms of early PD. However, progressive neuronal degeneration ultimately results in severe motor, mental, and functional disability.

Increasing evidence from laboratory and animal studies suggests that in addition to their symptomatic effects, levodopa and dopamine receptor agonists may either accelerate or slow the dopaminergic degeneration of PD. Recent data regarding the effects of levodopa have been controversial with in vitro data supporting both a potential toxic and protective effect on dopaminergic neurons.4,5 Studies have demonstrated that dopamine receptor agonists protect cultured dopaminergic neurons from potential levodopa toxicity and may exert direct antioxidant and receptor-mediated antipoptotic effects.6-8 The putative neurotoxic or neuroprotective actions of levodopa or dopamine receptor agonists have provided the rationale for assessing the progression of dopamine neuronal degeneration in patients with PD after treatment with these drugs.

Context Pramipexole and levodopa are effective medications to treat motor symptoms of early Parkinson disease (PD). In vitro and animal studies suggest that pramipexole may protect and that levodopa may either protect or damage dopamine neurons. Neuroimaging offers the potential of an objective biomarker of dopamine neuron degeneration in PD patients.

Objective To compare rates of dopamine neuron degeneration after initial treatment with pramipexole or levodopa in early PD by means of dopamine transporter imaging using single-photon emission computed tomography (SPECT) with 2β-carboxymethoxy-3β(4-iodophenyl)tropane (β-CIT) labeled with iodine 123.

Design Substudy of a parallel-group, double-blind randomized clinical trial.

Setting and Patients Eighty-two patients with early PD who were recruited at 17 clinical sites in the United States and Canada and required dopaminergic therapy to treat emerging disability, enrolled between November 1996 and August 1997.

Interventions Patients were randomly assigned to receive pramipexole, 0.5 mg 3 times per day with levodopa placebo (n=42), or carbidopa/levodopa, 25/100 mg 3 times per day with pramipexole placebo (n=40). For patients with residual disability, the dosage was escalated during the first 10 weeks, and subsequently, open-label levodopa could be added. After 24 months of follow-up, the dosage of study drug could be further modified.

Main Outcome Measures The primary outcome variable was the percentage change from baseline in striatal [123I]β-CIT uptake after 46 months. The percentage changes and absolute changes in striatal, putamen, and caudate [123I]β-CIT uptake after 22 and 34 months were also assessed. Clinical severity of PD was assessed using the Unified Parkinson Disease Rating Scale (UPDRS) 12 hours off anti-PD medications.

Results Sequential SPECT imaging showed a decline in mean (SD) [123I]β-CIT striatal uptake from baseline of 10.3% (9.8%) at 22 months, 15.3% (12.8%) at 34 months, and 20.7% (14.4%) at 46 months—approximately 5.2% per year. The mean (SD) percentage loss in striatal [123I]β-CIT uptake from baseline was significantly reduced in the pramipexole group compared with the levodopa group: 7.1% (9.0%) vs 13.5% (9.6%) at 22 months (P=.004); 10.9% (11.8%) vs 19.6% (12.4%) at 34 months (P=.009); and 16.0% (13.3%) vs 25.5% (14.1%) at 46 months (P=.01). The percentage loss from baseline in striatal [123I]β-CIT uptake was correlated with the change from baseline in UPDRS at the 46-month evaluation (r=−0.40; P=.001).

Conclusions Patients initially treated with pramipexole demonstrated a reduction in loss of striatal [123I]β-CIT uptake, a marker of dopamine neuron degeneration, compared with those initially treated with levodopa, during a 46-month period. These imaging data highlight the need to further compare imaging and clinical end points of PD progression in long-term studies.

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During the past decade, in vivo imaging of the nigrostriatal dopaminergic system has been developed as a research tool to monitor progressive dopaminergic neuron loss in PD. Several reports have demonstrated that at the time of emergence of PD symptoms there is a loss of approximately 40% to 60% of dopaminergic markers in the striatum. In longitudinal studies of PD progression, imaging ligands targeting both dopamine metabolism fluorine 18 fluorodopa (\( ^{18}F \)DOPA) and dopamine transporter density iodine 123 (2-\( \beta \)-carboxymethoxy-3\( \beta \)-iodophenyltropane [\( ^{123}I \)β-CIT]) and fluorine 18 (2-\( \beta \)-carboxymethoxy-3\( \beta \)tropolane [\( ^{18}F \)CFT]) using both positron emission tomography and single-photon emission computed tomography (SPECT) have demonstrated an annualized rate of reduction in striatal \( ^{18}F \)DOPA, \( ^{18}F \)CFT, or [\( ^{123}I \)β-CIT] uptake of approximately 6% to 13% in patients with PD compared with 0% to 2.5% change in healthy controls. In longitudinal studies of PD progression, imaging ligands targeting both dopamine metabolism fluorine 18 fluorodopa (\( ^{18}F \)DOPA) and dopamine transporter density iodine 123 (2-\( \beta \)-carboxymethoxy-3\( \beta \)-iodophenyltropane [\( ^{123}I \)β-CIT]) and fluorine 18 (2-\( \beta \)-carboxymethoxy-3\( \beta \)tropolane [\( ^{18}F \)CFT]) using both positron emission tomography and single-photon emission computed tomography (SPECT) have demonstrated an annualized rate of reduction in striatal \( ^{18}F \)DOPA, \( ^{18}F \)CFT, or [\( ^{123}I \)β-CIT] uptake of approximately 6% to 13% in patients with PD compared with 0% to 2.5% change in healthy controls. These imaging studies are consistent with pathological studies showing that the rate of nigral degeneration in patients with PD was 8- to 10-fold that of healthy, age-matched controls.

We have used in vivo imaging of the dopamine transporter with [\( ^{123}I \)β-CIT] and SPECT to assess the progression of dopaminergic degeneration in a subset of patients with early PD participating in a clinical trial that compared the option of initial treatment with pramipexole with the option of initial treatment with levodopa. The clinical study (called CALM-PD) was a multicenter, parallel-group, double-blind, randomized clinical trial comparing the option of initial treatment with pramipexole or levodopa with regard to the development of dopaminergic motor complications and changes associated with function and quality of life. After 2 years of prospective follow-up, initial treatment with pramipexole delayed the onset of dopaminergic motor complications compared with levodopa therapy but initial levodopa therapy was more effective than pramipexole in ameliorating signs and symptoms of PD. In this report, we present the 4-year follow-up of the subset of study patients who have undergone sequential [\( ^{123}I \)β-CIT] SPECT imaging to compare the rate of loss of the dopamine transporter, a marker for dopaminergic degeneration, between the groups treated initially with pramipexole or levodopa.

**METHODS**

The methods and results of the CALM-PD trial after 2 years of follow-up have been previously reported. With patient informed consent, the trial was extended to a 4-year follow-up with maintenance of the parallel-group, double-blind, randomized design. The methods and outcomes of the imaging substudy, called CALM-PD-CIT, are described herein. The CALM-PD clinical outcomes at 4 years will be reported separately. A total of 82 of the 301 patients in the CALM-PD trial, enrolled between November 1996 and August 1997, participated in the imaging substudy. Research participants in the imaging substudy were recruited at 17 clinical sites (14 in the United States and 3 in Canada) and traveled to the imaging center in New Haven, Conn, for up to 4 imaging assessments. The imaging study was approved by the institutional review board and radiation safety committee. All patients gave written informed consent.

**Study Design**

CALM-PD. Complete eligibility requirements for the trial have been previously detailed. Eligible patients were randomized with equal allocation to each of the 2 treatment groups (pramipexole group or carbidopa/levodopa group) using a computer-generated randomization plan. Participation in the imaging substudy was not considered in the randomization plan. All patients enrolled at sites that chose to participate in the imaging substudy were offered the option, but were not required to participate in the β-CIT SPECT substudy. Baseline imaging was completed prior to randomization.

Patients took study drugs orally 3 times daily, approximately 6 (SD, 2) hours apart, throughout the study. Initially patients entered a 10-week dosage escalation period to reach one of the predetermined dosage levels: 1.5 mg of pramipexole or 75 or 300 mg of carbidopa/levodopa (level 1 dosage); 3.0 mg of pramipexole or 112.5 or 450 mg of carbidopa/levodopa (level 2 dosage); or 4.5 mg of pramipexole or 150 or 600 mg of carbidopa/levodopa (level 3 dosage). Study drug was then maintained at that level until 24 months after baseline, and subsequently the dosage level could be modified during an additional 22- to 36-month evaluation period. Patients with emerging disability posing a threat to ambulation, activities of independent living, or gainful employment were prescribed open-label carbidopa/levodopa as needed.

**CALM-PD-CIT—[\( ^{123}I \)β-CIT] and SPECT Substudy.** All patients in CALM-PD-CIT were evaluated sequentially with imaging studies at baseline and 22, 34, and 46 months after baseline as indicated in Figure 1. Thirteen patients also underwent imaging studies at 10 weeks after baseline to assess short-term effects of study drugs on the imaging outcome.

**Imaging Data Acquisition and Image Analysis**

High specific-activity [\( ^{123}I \)β-CIT] was prepared from the corresponding trimethylstannyl precursor as previously described. Patients were injected with a 6-mCi (222-MBq) dosage of [\( ^{123}I \)β-CIT] after pretreatment with Lugol solution to prevent thyroid uptake of any free \( ^{123}I \). One hundred twenty raw projection images were acquired in a 128 × 128 matrix into a 20% energy window centered on 159 keV at a mean of 24 (SD, 2) hours following injection on a 3-headed detector SPECT system (Picker Prism 3000XP; Marconi Medical, Cleveland, Ohio) fitted with low-energy, high-resolution fan beam collimators.

Projection data were filtered with a standardized 2-dimensional Butterworth filter and reconstructed using a
Outcome Variables
The prespecified primary outcome variable in this study was the percentage change from baseline to month 46 in the specific-nondisplaceable striatal [123I]-β-CIT uptake ratio, a tissue equilibrium distribution volume sampled in regions of caudate and putamen that is linearly related to the density of dopamine transporter binding sites in brain. Specific uptake was determined by subtracting occipital densities (nondisplaceable uptake) from total caudate and/or putamen count densities and dividing by the occipital background region. Striatal uptake was the mean of the caudate and putamen uptake.

Secondary outcome variables included percentage changes from baseline to month 46 in caudate and putamen [123I]-β-CIT uptake ratios and percentage changes from baseline to months 22 and 34 for [123I]-β-CIT uptake.

Clinical Assessment
All study participants were evaluated after 12 hours without study drug and anti-PD medications, the “defined off” state, with Unified Parkinson Disease Rating Scale (UPDRS) and Hoehn and Yahr scores determined at the imaging center before each imaging study. The clinical investigator was blinded to treatment assignment.

PD indicates Parkinson disease; CALM-PD, parallel-group, double-blind comparison study of pramipexole and carbidopa/levodopa in the treatment of PD; CIT, 4-carboxymethoxy-3β-[4-iodophenyl]tropine.
**Table 1. Patient Characteristics at Baseline**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pramipexole (n = 42)</th>
<th>Levodopa  (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61.9 (10.8)</td>
<td>60.1 (11.1)</td>
</tr>
<tr>
<td>Male, %</td>
<td>66</td>
<td>59</td>
</tr>
<tr>
<td>White, %</td>
<td>93</td>
<td>95</td>
</tr>
<tr>
<td>Time since diagnosis, y</td>
<td>1.3 (1.4)</td>
<td>1.6 (1.9)</td>
</tr>
<tr>
<td>UPDRS scores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial total</td>
<td>34.6 (13.1)</td>
<td>30.6 (11.4)</td>
</tr>
<tr>
<td>Initial motor</td>
<td>23.2 (9.7)</td>
<td>21.5 (8.8)</td>
</tr>
<tr>
<td>β-CIT uptake</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Striatum</td>
<td>3.04 (0.72)</td>
<td>2.91 (0.66)</td>
</tr>
<tr>
<td>Caudate</td>
<td>4.07 (0.86)</td>
<td>3.90 (0.83)</td>
</tr>
<tr>
<td>Putamen</td>
<td>2.01 (0.68)</td>
<td>1.93 (0.56)</td>
</tr>
<tr>
<td>Ipsilateral striatum</td>
<td>3.28 (0.75)</td>
<td>3.17 (0.74)</td>
</tr>
<tr>
<td>Contralateral striatum</td>
<td>2.81 (0.75)</td>
<td>2.65 (0.64)</td>
</tr>
</tbody>
</table>

*UPDRS indicates Unified Parkinson Disease Rating Scale; β-CIT, 2β-carboxymethoxy-3β-idropophenylpropene; contralateral, side opposite to initial symptoms; ipsilateral, side of initial symptoms. Data are mean (SD) unless otherwise noted.

The association between change from baseline in UPDRS score (dependent variable) and percentage change from baseline in [123I]β-CIT uptake (independent variable) was examined using a multiple regression model that adjusted for initial treatment (pramipexole, levodopa) and baseline UPDRS score. This analysis was performed separately for each time point (months 22, 34, and 46).

For all analyses, patients were grouped by the intention-to-treat principle according to their original randomized treatment assignment (pramipexole, levodopa) even if they received supplemental levodopa therapy or withdrew from CALM-PD, but continued to be followed up in CALM-PD-CIT. Two separate analyses were performed, one using only available data and another that incorporated imputation of missing follow-up data. Imputation was performed as follows: (1) for patients with complete data at month 22, a regression model was fit with the month 22 value as the dependent variable and the baseline value and treatment group as the independent variables; (2) using this regression model, a missing value at month 22 was imputed given the treatment group and baseline value for a patient with missing data; (3) for patients with complete data at month 34, a regression model was fit with the month 34 value as the dependent variable and the baseline value, month 22 value, and treatment group as the independent variables; and (4) using this regression model, a missing value at month 34 was imputed given the treatment group, baseline value, and month 22 value for a patient with missing data. Steps 3 and 4 were repeated to impute a missing value at month 46 given the treatment group and baseline, month 22, and month 34 values for a patient with missing data. Unless otherwise specified, the analyses reported are those that were performed using only available data. The results obtained using these 2 analysis strategies were similar. All statistical tests were 2-tailed. Statistical analyses were performed using SAS version 8.0 (SAS Institute Inc, Cary, NC) and tested at the .05 level of significance.

**RESULTS**

**Patient Demographics**

The demographic characteristics of the study cohort at baseline are shown in Table 1. The 82 patients participating in the imaging substudy did not differ from the 301 patients in the CALM-PD study.22 The age, sex, and ethnic distributions of patients enrolled in the 2 treatment groups were similar. The patients initially treated with levodopa were slightly less impaired as measured by the baseline UPDRS. There was a similar reduction in striatal β-CIT uptake consistent with early PD in both treatment groups.

During the 46-month evaluation period, 9 patients (21.4%) initially treated with pramipexole and 8 patients (20%) initially treated with levodopa withdrew from the study (Figure 1). For patients who did not complete 46 months of follow-up, the mean (SD) baseline striatal β-CIT uptake was 2.8 (0.9) in the pramipexole group (n=9) and 3.1 (1.1) in the levodopa group (n=8). For patients who completed 46 months of follow-up, the mean (SD) baseline striatal β-CIT uptake was 3.0 (0.7) in the pramipexole group (n=33) vs 2.9 (0.5) in the levodopa group (n=32). One patient in the pramipexole group withdrew because of worsening PD with hallucinations; 1 patient in the pramipexole group and 3 patients in the levodopa group withdrew because of worsening medical illness not related to PD. There were 4 deaths in the pramipexole group and 2 deaths in the levodopa group that were judged to be unrelated to study drug.

**Sequential Imaging Analysis**

Sequential imaging of the entire study cohort showed a mean (SD) decline from baseline in [123I]β-CIT striatal uptake of 0.28 (0.31) at 22 months, 0.42 (0.36) at 34 months, and 0.58 (0.40) at 46 months. The corresponding mean (SD) percentage loss from baseline of striatal β-CIT uptake was 10.3% (9.8%) at 22 months, 15.3% (12.8%) at 34 months, and 20.7% (14.4%) at 46 months, declining approximately 5.2% per year during the 46-month evaluation period (Figure 2). The mean (SD) percentage loss from baseline of [123I]β-CIT uptake at 46 months was greater in the putamen (22.5% [19.5%]) than in the caudate (19.6% [13.6%]). Although there was a greater baseline reduction in the side contralateral to initial symptoms (Table 1), the progressive loss of [123I]β-CIT uptake in each hemisphere did not differ.
Analysis of the treatment groups demonstrated that the rate of decline in striatal $[\text{123I}]\beta$-CIT uptake from baseline was significantly reduced in the group treated initially with pramipexole compared with the group treated initially with levodopa (Figure 3A and Table 2). The mean (SD) percentage loss from baseline of $[\text{123I}]\beta$-CIT striatal uptake in the pramipexole vs levodopa groups was 16.0% (13.3%) vs 25.5% (14.1%) at 46 months ($P = .01$). Similarly, comparison of the percentage loss from baseline of $[\text{123I}]\beta$-CIT uptake from baseline was significantly reduced in the group treated initially with pramipexole compared with the group treated initially with levodopa ($FIGURE 3$ and $TABLE 2$). The mean (SD) percentage loss from baseline of $[\text{123I}]\beta$-CIT striatal uptake in the pramipexole vs levodopa groups was 16.0% (13.3%) vs 25.5% (14.1%) at 46 months ($P = .01$). Similarly, comparison of the percentage loss from baseline in the pramipexole group with the levodopa group was 7.1% (9.0%) vs 13.5% (9.6%) at 22 months ($P = .004$) and 10.9% (11.8%) vs 19.6% (12.4%) at 34 months ($P = .009$). Putamen and caudate $[\text{123I}]\beta$-CIT uptake showed a similar reduction in the rate of decline in the pramipexole group (Figure 3B and C and Table 2). Analyses that incorporated imputation of missing follow-up data revealed similar results (pramipexole vs levodopa at 46 months): striatal $[\text{123I}]\beta$-CIT uptake, 16.6% (12.7%) vs 24.9% (14.0%) ($P = .005$); caudate $[\text{123I}]\beta$-CIT uptake, 15.6% (11.6%) vs 23.7% (12.5%) ($P = .003$); and putamen $[\text{123I}]\beta$-CIT uptake, 18.6% (18.8%) vs 27.2% (19.3%) ($P = .05$).

During the initial 22 months of the study, 19 of 39 patients in the pramipexole group and 22 of 39 patients in the levodopa group were treated with study drug alone without requiring supplemental levodopa. The percentage loss of $[\text{123I}]\beta$-CIT striatal uptake from baseline after 22 months in these
study participants was 6.9% (9.0%) in the pramipexole group compared with 12.0% (11.1%) in the levodopa group (P= .08), a relative decrease in the pramipexole group of 43%. Among study participants who did require supplemental levodopa by 22 months after baseline, the percentage loss of [123I]-β-CIT striatal uptake from baseline after 22 months was 7.3% (9.2%) in the pramipexole group compared with 15.5% (7.0%) in the levodopa group (P=.009), and after 46 months from baseline was 17.2% (15.5%) in the pramipexole group versus 28.9% (16.4%) in the levodopa group (P=.03).

The short-term effect of pramipexole (n=7) and levodopa (n=6) on [123I]-β-CIT uptake was further assessed in the subset of study participants who underwent imaging 10 weeks after initiating treatment. Comparison of [123I]-β-CIT striatal uptake at 10 weeks with baseline showed a decrease of 5.4% (12.2%) in the pramipexole group and 4.6% (4.4%) in the levodopa group.

### Correlation of [123I]β-CIT Uptake and UPDRS Score

The mean total and motor UPDRS scores obtained in the “defined off” state were reduced in the levodopa group at 22 months compared with baseline and the pramipexole group, but were not significantly different from baseline or the pramipexole group by 34 or 46 months (Table 3). There was a correlation of the percentage loss of striatal [123I]-β-CIT uptake from baseline with the change in total UPDRS score from baseline in all patients (r =−0.01, P=.94 at 22 months; r =−0.30, P=.01 at 34 months; and r =−0.40, P=.001 at 46 months from baseline). The percentage loss of putamen and caudate [123I]-β-CIT uptake from baseline showed increasing correlation with the change in UPDRS score from baseline as the duration of assessment increased (putamen: r =−0.03, P=.78 at 22 months; r =−0.39, P=.001 at 34 months; and r =−0.39, P=.001 at 46 months from baseline; caudate: r =0.02, P=.89 at 22 months; r =−0.20, P=.11 at 34 months; and r =−0.35, P=.005 at 46 months from baseline).

### COMMENT

In vivo dopamine transporter imaging with [123I]β-CIT SPECT demonstrated reduced loss of striatal [123I]-β-CIT uptake in patients with PD treated initially with pramipexole compared with those treated initially with levodopa during a 46-month evaluation period. As [123I]β-CIT SPECT is a quantitative biomarker for striatal dopamine neuron terminals, these data indicate that treatment with pramipexole, levodopa, or both may modify the dopaminergic neuronal degeneration of PD.

The identification of disease-modifying therapies for PD is a major unmet need. Studies that evaluate neuroprotective effects of medications have been limited by the lack of a clear end point defining neuroprotection and confounded by potential simultaneous symptomatic and neuroprotective benefit. In vivo imaging offers the potential of an objective method to

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**Table 2. Change in [123I]-β-CIT Uptake in Sequential Scans After Initial Treatment With Pramipexole or Levodopa**

<table>
<thead>
<tr>
<th></th>
<th>Striatum</th>
<th>Putamen</th>
<th>Caudate</th>
<th>Ipsilateral striatum</th>
<th>Contralateral striatum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pramipexole (n = 39)</td>
<td>−7.1 (0.0)</td>
<td>−7.9 (13.7)</td>
<td>−6.4 (8.8)</td>
<td>−7.2 (0.4)</td>
<td>−6.8 (10.1)</td>
</tr>
<tr>
<td>Levodopa (n = 39)</td>
<td>−13.5 (0.6)</td>
<td>−16.9 (12.9)</td>
<td>−11.8 (0.4)</td>
<td>−14.3 (10.9)</td>
<td>−12.6 (10.0)</td>
</tr>
<tr>
<td>% Change From Baseline, Mean (SD)</td>
<td>0.04</td>
<td>0.005</td>
<td>0.02</td>
<td>0.003</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>P Value</strong></td>
<td>.009</td>
<td>.001</td>
<td>.04</td>
<td>.003</td>
<td>.06</td>
</tr>
</tbody>
</table>

**Table 3. Change in UPDRS (“Defined Off”) After Initial Treatment With Pramipexole or Levodopa**

<table>
<thead>
<tr>
<th></th>
<th>22 Months</th>
<th>34 Months</th>
<th>46 Months</th>
</tr>
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<tbody>
<tr>
<td><strong>UPDRS Score (SD)</strong></td>
<td>Pramipexole (n = 39)</td>
<td>Levodopa (n = 38)</td>
<td>P Value</td>
</tr>
<tr>
<td>Total</td>
<td>0.9 (12.2)</td>
<td>−3.3 (8.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Motor</td>
<td>0.0 (8.2)</td>
<td>−2.5 (6.0)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>UPDRS Score (SD)</strong></td>
<td>Pramipexole (n = 35)</td>
<td>Levodopa (n = 36)</td>
<td>P Value</td>
</tr>
<tr>
<td>Total</td>
<td>2.5 (10.7)</td>
<td>0.7 (11.5)</td>
<td>0.40</td>
</tr>
<tr>
<td>Motor</td>
<td>0.2 (8.0)</td>
<td>−0.5 (7.9)</td>
<td>0.57</td>
</tr>
<tr>
<td><strong>UPDRS Score (SD)</strong></td>
<td>Pramipexole (n = 33)</td>
<td>Levodopa (n = 32)</td>
<td>P Value</td>
</tr>
<tr>
<td>Total</td>
<td>4.1 (9.9)</td>
<td>4.0 (8.7)</td>
<td>0.61</td>
</tr>
<tr>
<td>Motor</td>
<td>1.0 (7.4)</td>
<td>2.1 (6.2)</td>
<td>0.84</td>
</tr>
</tbody>
</table>

*β-CIT indicates 2β-carboxy-methoxy-3β-[4-iodophenyl]-tropane; contralateral, side opposite to initial symptoms; ipsilateral, side of initial symptoms.

*UPDRS indicates Unified Parkinson Disease Rating Scale.*
monitor neuronal degeneration unaffected by a short-term symptomatic drug effect.31

Several recent studies have used neuroimaging to investigate the possible neuroprotective effects of dopamine agonists. A preliminary study that assessed the effects of ropinirole hydrochloride did not demonstrate a change in neuronal loss as measured by [18F]DOPA positron emission tomography, but showed a trend toward reduction in the change of [18F]DOPA uptake in the patients treated with the dopamine agonist.34

Initial analysis of our data in the CALM-PD-CIT study after 22 months showed a similar trend toward reduction in the rate of loss of [123I]β-CIT uptake in patients initially treated with pramipexole compared with those treated with levodopa.22 The 22-month data presented in this study differ from the previous study because these data were analyzed using improved reconstruction analysis technology developed during the study and designed to more accurately measure count density in regions with low counts. During the past 2 years, we have both improved our reconstruction analysis technology and extended the duration of the double-blind, parallel-group design, while retaining 79% of enrolled patients at 46 months. We now present data demonstrating a significant and persistent reduction in the rate of loss of [123I]β-CIT uptake in patients with PD initially treated with pramipexole compared with levodopa during the 46-month evaluation period.

Evidence from animal studies, healthy humans, and patients with PD has demonstrated that [123I]β-CIT uptake is a biomarker for striatal dopamine transporter density and also dopamine neuronal terminal integrity.9,25,35,36 Progressive nigrostriatal dopamine neuron loss is the predominant pathologic finding of PD. Therefore, the relative reduction in the rate of loss of [123I]β-CIT uptake in those patients treated with pramipexole compared with levodopa most likely reflects a reduction (by pramipexole) or acceleration (by levodopa) in the progressive loss of striatal dopamine neuronal function. Although it remains possible that the difference in the pramipexole vs levodopa groups is because of an interaction between pramipexole, levodopa, or both and the dopamine transporter, it is likely that such an interaction would be present shortly after initiating therapy. In this study, short-term sequential imaging at 10 weeks did not demonstrate any significant effect of either pramipexole or levodopa on [123I]β-CIT uptake. These data were also consistent with prior studies showing no short-term effects of levodopa, selegiline, or pergolide on [123I]β-CIT uptake.37,38

Approximately 20% of the study cohort withdrew from CALM-PD-CIT before the month 46 visit. However, in both treatment groups, the baseline transporter density measurements in patients who withdrew from the trial were similar to those in patients who completed the trial. The frequency and reasons for withdrawal were also similar in the 2 groups and the treatment effects were reasonably consistent over time, including month 22 in which 95% of the cohort remained. The analyses that incorporated imputation of missing follow-up data yielded results that were similar to those based on only available follow-up data. The regression-based imputation strategy that we used seems reasonable in our setting and more appropriate than an ad-hoc approach such as carrying forward the last available observation.39 For all of these reasons, we do not believe that participant withdrawal had a major impact on the overall results.

Since this study compared 2 active medications without a placebo group, these data cannot directly distinguish whether the difference in the rate of loss of [123I]β-CIT uptake in the treatment groups results from a decrease due to pramipexole, an increase due to levodopa, or both. However, indirect evidence from preclinical studies and prior imaging studies suggests that a decrease in the percentage loss of [123I]β-CIT uptake due to exposure to prami- pexole rather than an increase due to exposure to levodopa is more likely. Preclinical data regarding the effects of levodopa suggest both possible toxic and protective action.4,43 whereas emerging data regarding dopamine agonists have supported a neuroprotective action via antioxidant or antiapoptotic mechanisms.7,8,40

In prior imaging studies, the annual percentage loss of [123I]β-CIT striatal uptake of untreated patients with PD was 6.8%, similar to the levodopa group in this study.9 Furthermore, the percentage loss from baseline of [123I]β-CIT striatal uptake after 46-month follow-up in this study in those patients initially treated with pramipexole who did require supplemental levodopa by 22 months remained reduced compared with those patients initially treated with levodopa also requiring supplemental levodopa by 22 months. These imaging data suggest that treatment with pramipexole may have decreased the rate of loss of [123I]β-CIT uptake despite treatment with levodopa. However, the duration and dose of exposure to supplemental levodopa and the effect of pretreatment with a dopamine agonist on a possible levodopa disease-modifying effect have not been fully evaluated. Studies are under way to directly assess the effect of treatment with levodopa compared with placebo on the rate of loss of [123I]β-CIT uptake in patients with early PD that will further elucidate the relative effects of pramipexole and levodopa on [123I]β-CIT uptake.23

A key therapeutic issue is whether the effects of pramipexole and levodopa on the rate of loss of [123I]β-CIT uptake are associated with a persistent change in clinical function in patients with PD. Several clinical end points for progressive functional decline in PD have been used, including UPDRS in the “defined off” state or after drug washout up to 2 weeks, time to need for dopaminergic therapy, or time to the development of motor fluctuations.5,32,42 These end points reflect the complex clinical progression of PD symptoms and disability. The changes in imag-
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The loss of striatal [123I]β-CIT and imaging outcomes. In this study, minimal. These data suggest that in patients measured by the UPDRS may be
These treatments.43 Second, in early PD the temporal patterns for rate of loss of dopamine transporter and the change in UPDRS score may not be congruent. This is best illustrated by data demonstrating a loss of approximately 40% to 50% of striatal [123I]β-CIT uptake at the time of diagnosis when clinical symptoms measured by the UPDRS may be minimal. These data suggest that in patients with early PD clinical and imaging outcomes provide complementary data and that long-term follow-up will be required to correlate changes in clinical and imaging outcomes. In this study, the loss of striatal [123I]β-CIT uptake from baseline was significantly correlated with the change in UPDRS score from baseline at the 46-month evaluation, suggesting that the correlation between clinical and imaging outcomes will emerge with longer monitoring. We plan to extend the follow-up of this imaging cohort and examine the associations between changes in the loss of striatal [123I]β-CIT uptake and the complete clinical data in the CALM-PD study.

This study demonstrates that [123I]β-CIT SPECT imaging can detect treatment-related changes in the progressive rate of loss of striatal dopamine transporters in patients with early PD. During a 46-month evaluation period, these data show a decrease in the rate of loss of striatal [123I]β-CIT uptake in patients initially treated with pramipexole compared with levodopa. These data highlight the need to compare this imaging marker of dopamine neuronal loss with multiple meaningful clinical end points of disease progression in larger, long-term studies to fully assess its clinical relevance.

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REFERENCES


