Dopamine Transporter Imaging in Parkinson Disease: Progressive Changes and Therapeutic Modification after Anti-parkinsonian Medications

Ken Ikeda, Junya Ebina, Kiyokazu Kawabe and Yasuo Iwasaki

Abstract:
Parkinson disease (PD) is a slowly progressive neurodegenerative disease characterized by the loss of dopaminergic neurons and terminals in the nigrostriatal system. Dopamine transporter (DAT) imaging is widely performed for the differential diagnosis of PD and other degenerative parkinsonism from essential tremor, vascular parkinsonism, and drug-induced parkinsonism. DAT is the plasma membrane carrier specific to dopamine neurons that are responsible for re-uptaking dopamine from the synaptic cleft back into the nerve ending. DAT binding might reflect striatal presynaptic dysfunction or DAT expression in PD patients. Longitudinal studies of DAT imaging have reported progressive changes from early PD patients. This imaging may be used as a progressive biomarker. Follow-up DAT imaging for therapeutic interventions has been applied for several anti-parkinsonian drugs. We herein review the progressive changes and therapeutic modification of DAT binding by anti-PD medications in early PD patients.

Key words: Parkinson disease, dopamine transporter, dopamine transporter imaging, progressive change, anti-PD medication, therapeutic modification

Clinical Role of Dopamine Transporter Imaging

Parkinson disease (PD) is a progressive neurodegenerative disease characterized by clinical signs of bradykinesia, tremor, rigidity, and gait disturbance. The neuropathological profile reveals a loss of dopaminergic neurons and nerve terminals in the nigrostriatal system.

Dopamine transporter (DAT) is a membrane protein expressed in dopaminergic cells. DAT is the most important mechanism for the re-uptake of extracellular dopamine into presynaptic terminals, and regulates the amount of dopamine available for dopamine receptor stimulation after its release from the presynaptic terminal. Previous pathological studies disclosed a severe depletion of DAT in the striatum of PD patients (1, 2). Measurement of DAT was correlated with striatal dopamine levels in PD patients (3).

Many kinds of DAT radiotracers for positron emission tomography (PET) and single-photon emission computed tomography (SPECT) are known, and [123I], [11F], or [11C] linked 2β-carbomethoxy-3β(4-iodo-phenyl)tropane (β-CIT) and N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane (FP-CIT) are used commonly. These tracers are analogs of cocaine that bind reversibly with high affinity to the DAT protein, a marker for presynaptic terminals in dopaminergic nigrostriatal neurons. Those are suitable for the in vivo quantification of DAT binding. [123I]FP-CIT SPECT is used widely for the differential diagnosis of PD and other neurodegenerative parkinsonism from essential tremor, drug-induced parkinsonism, or other neurological diseases that do not involve the nigrostriatal dopaminergic system (4, 5). A previous postmortem examination showed the significant correlation between striatal DAT binding and nigral neuron counts in patients with dopaminergic neurodegeneration, including PD, dementia with Lewy body (DLB), multiple systemic atrophy (MSA), and corticobasal degeneration (CBD) (6). Otherwise, a recent postmortem study...
has pointed out that DAT binding was not associated with dopamine neuron counts in the substantia nigra in PD patients. Striatal DAT binding could contribute to axonal dysfunction or DAT expression in the nigrostriatal pathway of PD patients (7). A number of longitudinal DAT imaging studies have described progressive changes in PD patients (8-27). Therapeutic effects of anti-PD medications on DAT binding have also been reported in early PD patients (14, 20, 28-33). The present review highlights the progressive changes and therapeutic modification of DAT binding after the administration of anti-parkinsonian drugs in early PD patients.

**Initial and Progressive Changes of DAT Binding in PD Patients**

The first positron emission tomography (PET) examination using 

\[ ^{11}C\]RTI-32, a selective and specific DAT ligand, was performed in levodopa-naive patients with very early PD (n=11). Compared to healthy controls (n = 10), DAT binding was reduced in the contralateral posterior putamen (-56%) and anterior putamen (-28%). The result highlighted an important possibility that the threshold for clinical parkinsonism may be approximately 50% loss of dopaminergic innervation in the putamen (34).

Progressive changes of DAT binding are summarized in Table 1. Longitudinal DAT imaging studies have been reported from 2000 to 2018 (8-27). Those clinical findings show the mean PD duration of 0.5-9.0 years and the Unified PD Rating Scale (UPDRS) motor score of 9-28. The annual decline rate of DAT binding in the striatum was 4.6%-11.9% compared to baseline. The temporal decline of DAT binding was divided into two patterns: a linear decrease (12-14, 16, 22) and an exponential negative reduction (9, 15, 19, 23, 24, 26, 27). Recently, the Parkinson’s Progression Markers Initiative (PPMI), a longitudinal cohort study of early PD, was published in 2018, enrolling newly diagnosed de novo PD patients (n=423). Most patients (99.5%) had Hoehn and Yahr (HY) stage of 1-2 at baseline. At year 1, 162 participants (41%) had no medication, and 165 participants (42%) had dopaminergic therapy (DT), defined as levodopa and/or dopamine agonists. The remaining 66 participants (17%) had non-DT medications, including monoamine oxidase type B (MAO-B) inhibitors, anticholinergics, and amantadine. At year 2, levodopa was treated in approximately 50% of participants, and increased to 83% at year 5. About 40% of participants received dopamine agonists by year 5. A total of 358 patients remained in the study at year 5. DAT SPECT using \[^{11}I\]β-CIT SPECT was used to examine DAT binding in 8 patients with HY stage of 1-3. The short-term administration of levodopa/carbidopa (600/150 mg/day for 4-6 weeks) had no significant effects on its striatal uptake compared to baseline and 1-week withdrawal (28).

A comparative study of PET using \[^{11}C\]RTI-32 was performed in 2 groups of levodopa- and placebo-treated PD patients (n=10/group). Short-term therapy (6 weeks) with levodopa/carbidopa (300/75 mg/day) modestly decreased striatal DAT binding compared to placebo (31). The possible mechanism striatal DAT binding after levodopa treatment revealed that this drug could induce down-regulation in DAT expression or affinity.

Regarding the effects of long-term treatment with levodopa on DAT binding, \[^{18}F\]CFT PET was performed in 7 de novo PD patients (HY stage of 2) before and after 3-month medication of levodopa/carbidopa or levodopa/benserazide (200-400 mg/day). Levodopa therapy did not significantly influence the \[^{18}F\]CFT uptake in the striatum compared to baseline (30). In the CALM-PD-CIT study, the longer administration of levodopa/carbidopa (375-750 mg/day for 46 months) revealed a marked decrease of DAT binding from baseline. The decline rate was -13.5% at 22 months, -19.6% at 34 months, and -25.5% at 46 months (14). In the ELLDOPA study, early PD patients receive placebo or carbidopa/levodopa at a daily dose of 37.5/150 mg, 75/300 mg, and 150/600 mg for 40 weeks. \[^{11}I\]β-CIT SPECT was performed in 142 patients at baseline and at week 40. Nineteen patients without dopaminergic deficits at baseline were excluded from the analysis of DAT binding. In the subgroup of 116 patients, the mean decline rate was -6% in 28 patients with levodopa (150 mg/day), -4% in 34 patients with levodopa (300 mg/day), -7.2% in 28 patients with levodopa (600 mg/day), and -1.4% in 26 patients with placebo. The

**DAT Binding Modulation after Anti-PD Medications**

Previous studies described therapeutic effects of several anti-PD drugs on DAT binding in early PD patients (14, 20, 28-33). Changes of DAT binding before and after anti-parkinsonian medication of levodopa, dopamine agonists or zonisamide (ZNS) are summarized in Table 2.

1. **Levodopa**

Previous studies of DAT imaging were reported in early PD patients treated with levodopa compared to baseline or placebo.

\[^{11}I\]β-CIT SPECT was used to examine DAT binding in 8 patients with HY stage of 1-3. The short-term administration of levodopa/carbidopa (600/150 mg/day for 4-6 weeks) had no significant effects on its striatal uptake compared to baseline and 1-week withdrawal (28).

A comparative study of PET using \[^{11}C\]RTI-32 was performed in 2 groups of levodopa- and placebo-treated PD patients (n=10/group). Short-term therapy (6 weeks) with levodopa/carbidopa (300/75 mg/day) modestly decreased striatal DAT binding compared to placebo (31). The possible mechanism striatal DAT binding after levodopa treatment revealed that this drug could induce down-regulation in DAT expression or affinity.

Regarding the effects of long-term treatment with levodopa on DAT binding, \[^{18}F\]CFT PET was performed in 7 de novo PD patients (HY stage of 2) before and after 3-month medication of levodopa/carbidopa or levodopa/benserazide (200-400 mg/day). Levodopa therapy did not significantly influence the \[^{18}F\]CFT uptake in the striatum compared to baseline (30). In the CALM-PD-CIT study, the longer administration of levodopa/carbidopa (375-750 mg/day for 46 months) revealed a marked decrease of DAT binding from baseline. The decline rate was -13.5% at 22 months, -19.6% at 34 months, and -25.5% at 46 months (14). In the ELLDOPA study, early PD patients receive placebo or carbidopa/levodopa at a daily dose of 37.5/150 mg, 75/300 mg, and 150/600 mg for 40 weeks. \[^{11}I\]β-CIT SPECT was performed in 142 patients at baseline and at week 40. Nineteen patients without dopaminergic deficits at baseline were excluded from the analysis of DAT binding. In the subgroup of 116 patients, the mean decline rate was -6% in 28 patients with levodopa (150 mg/day), -4% in 34 patients with levodopa (300 mg/day), -7.2% in 28 patients with levodopa (600 mg/day), and -1.4% in 26 patients with placebo. The
Table 1. Previous Longitudinal Studies of DAT Imaging in PD Patients.

<table>
<thead>
<tr>
<th>Study and/or author name</th>
<th>Reported year</th>
<th>DAT imaging</th>
<th>Patient number</th>
<th>Mean PD duration (years) at baseline</th>
<th>Mean UPDRS motor score at baseline</th>
<th>Scan number</th>
<th>Mean interval of DAT scan</th>
<th>Mean annual rate of decline in striatal DAT binding</th>
<th>Decline pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staffen et al. [9]</td>
<td>2000</td>
<td>[123I]β-CIT SPECT</td>
<td>15</td>
<td>Not reported</td>
<td>Not described</td>
<td>2</td>
<td>1.3 years</td>
<td>7.3%</td>
<td>Exponential **</td>
</tr>
<tr>
<td>Numri et al. [10]</td>
<td>2000</td>
<td>[18F]CFT PET</td>
<td>8</td>
<td>2.1</td>
<td>20.5</td>
<td>2</td>
<td>2 years</td>
<td>13.1% in putamen 12.5% in caudate</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Winogrodzka et al. [11]</td>
<td>2001</td>
<td>[123I]FP-CIT SPECT</td>
<td>20</td>
<td>2.5</td>
<td>16.5</td>
<td>2</td>
<td>1.0 year</td>
<td>8.1%</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Chouker et al. [12]</td>
<td>2001</td>
<td>[123I]β-CIT SPECT</td>
<td>8</td>
<td>3.6</td>
<td>Not described</td>
<td>3</td>
<td>1.0 year</td>
<td>5.8%</td>
<td>Linear</td>
</tr>
<tr>
<td>Marek et al. [13]</td>
<td>2001</td>
<td>[123I]β-CIT SPECT</td>
<td>15</td>
<td>2.5</td>
<td>18.2</td>
<td>2</td>
<td>2.3 years</td>
<td>11.2%</td>
<td>Linear</td>
</tr>
<tr>
<td>CALM-PD-CIT</td>
<td>2002</td>
<td>[123I]β-CIT SPECT</td>
<td>65</td>
<td>1.5</td>
<td>22.4</td>
<td>4</td>
<td>22, 34 and 46 weeks</td>
<td>5.2%</td>
<td>Linear</td>
</tr>
<tr>
<td>Parkinson Study Group [14]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pirker et al. [15]</td>
<td>2002</td>
<td>[123I]β-CIT SPECT</td>
<td>36</td>
<td>2.4 and 9.2</td>
<td>18.4 and 23.3</td>
<td>2</td>
<td>2.2 years</td>
<td>6.8% and 4.1%</td>
<td>Exponential *</td>
</tr>
<tr>
<td>Pirker et al. [16]</td>
<td>2003</td>
<td>[123I]β-CIT SPECT</td>
<td>21</td>
<td>2.4</td>
<td>19.0</td>
<td>3</td>
<td>2.2 and 3.2 years</td>
<td>5.8%</td>
<td>Linear</td>
</tr>
<tr>
<td>Winogrodzka et al. [17]</td>
<td>2003</td>
<td>[123I]β-CIT SPECT</td>
<td>50</td>
<td>2.7</td>
<td>19.2</td>
<td>2</td>
<td>1.0 year</td>
<td>7.6%</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Numri et al. [18]</td>
<td>2003</td>
<td>[18F]CFT PET</td>
<td>12</td>
<td>1.7</td>
<td>26.8</td>
<td>2</td>
<td>2.2 years</td>
<td>11.9% in anterior putamen</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Schwarz et al. [19]</td>
<td>2004</td>
<td>[123I]β-CIT SPECT</td>
<td>6</td>
<td>3.2</td>
<td>Not described</td>
<td>4</td>
<td>1 and 5.5 years</td>
<td>7.2%</td>
<td>Exponential **</td>
</tr>
<tr>
<td>ELDOPA</td>
<td>2004</td>
<td>[123I]β-CIT SPECT</td>
<td>29</td>
<td>0.4</td>
<td>7.8</td>
<td>2</td>
<td>40 weeks</td>
<td>1.8%</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Fahn et al. [20]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colloby et al. [21]</td>
<td>2005</td>
<td>[123I]FP-CIT SPECT</td>
<td>20</td>
<td>4.5</td>
<td>24.5</td>
<td>2</td>
<td>1.0 year</td>
<td>5.2% in anterior putamen</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Huang et al. [22]</td>
<td>2007</td>
<td>[18F]FP-CIT PET</td>
<td>10</td>
<td>&lt;2.0</td>
<td>9.5</td>
<td>3</td>
<td>2.0 and 2.0 years</td>
<td>6.7% in putamen</td>
<td>Linear</td>
</tr>
<tr>
<td>Nandhagopal et al. [23]</td>
<td>2009</td>
<td>[11C]MP PET</td>
<td>19</td>
<td>7.6</td>
<td>27.4</td>
<td>3</td>
<td>4.0 and 4.0</td>
<td>Not reported</td>
<td>Exponential</td>
</tr>
<tr>
<td>Jakobson et al. [24]</td>
<td>2013</td>
<td>[123I]FP-CIT SPECT</td>
<td>22</td>
<td>1.5</td>
<td>27.0</td>
<td>3</td>
<td>1.0 and 2.0 years</td>
<td>4.2%</td>
<td>Exponential **</td>
</tr>
<tr>
<td>PRECEPT</td>
<td>2014</td>
<td>[123I]β-CIT SPECT</td>
<td>629</td>
<td>0.8</td>
<td>18.4</td>
<td>2</td>
<td>1.8 years</td>
<td>4.6%</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Marek et al. [25]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPMI</td>
<td>2015</td>
<td>[123I]FP-CIT SPECT</td>
<td>241</td>
<td>0.6</td>
<td>21.5</td>
<td>3</td>
<td>12 and 24 weeks</td>
<td>7.9%</td>
<td>Exponential **</td>
</tr>
<tr>
<td>Seibyl et al. [26]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPMI</td>
<td>2018</td>
<td>[123I]FP-CIT SPECT</td>
<td>423</td>
<td>0.6</td>
<td>32</td>
<td>3</td>
<td>12, 24 and 48 weeks</td>
<td>5-11%</td>
<td>Exponential *</td>
</tr>
</tbody>
</table>

*Greater decline in patients with shorter or less severe disease duration.
**Greater decline at the first year of the follow-up compared to subsequent 2-4 years.
Greater decline in patients with shorter or less severe disease duration.
**Greater decline at the first year of the follow-up compared to subsequent 2-4 years.
### Table 2. Previous Studies of DAT Binding Changes after Anti-PD Medications.

<table>
<thead>
<tr>
<th>Author name</th>
<th>Reported year</th>
<th>DAT imaging</th>
<th>Anti-PD drug (daily dose)</th>
<th>Patient number</th>
<th>Mean age (SD) years</th>
<th>Treatment duration</th>
<th>Mean disease duration (SD)</th>
<th>HY stage</th>
<th>Mead (SD) of total UPDRS</th>
<th>Change rate of DAT binding from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innis et al. 1999</td>
<td>[28]</td>
<td>[123I]</td>
<td>Levodopa/carbidopa (600/150 mg)</td>
<td>8</td>
<td>65 (10)</td>
<td>4-6 weeks</td>
<td>2.4 years</td>
<td>1-3</td>
<td>28 (10)</td>
<td>-3%</td>
</tr>
<tr>
<td>Numui et al. 2000</td>
<td>[30]</td>
<td>[18F]</td>
<td>Levodopa/carbidopa or levodopa/benserazide (200-400 mg)</td>
<td>7</td>
<td>66.6 (8.5)</td>
<td>3 months</td>
<td>31.2 (20) months</td>
<td>Not described</td>
<td>31 (5) (UPDRS motor score)</td>
<td>-4.1% (anterior putamen) -1.9% (posterior putamen) -4.0% (caudate) -16 to -22% *</td>
</tr>
<tr>
<td>Gutman et al. 2001</td>
<td>[31]</td>
<td>[11C]</td>
<td>Levodopa/carbidopa (300/75 mg)</td>
<td>10</td>
<td>60.7 (10)</td>
<td>6 weeks</td>
<td>22.8 (19) months</td>
<td>Not described</td>
<td>23.9 (6.0)</td>
<td>-</td>
</tr>
<tr>
<td>Parkinson Study Group 2001</td>
<td>[14]</td>
<td>[123I]</td>
<td>Levodopa/carbidopa (300/75,450/112.5, 600/150 mg)</td>
<td>40</td>
<td>60.1 (11.1)</td>
<td>22, 34, 46 months</td>
<td>1.6 (1.9) years</td>
<td>Not described</td>
<td>30.6 (11.4)</td>
<td>-13.5% at 22 months -19.6% at 34 months -25.5% at 46 months</td>
</tr>
<tr>
<td>Fahn et al. 2004</td>
<td>[20]</td>
<td>[123I]</td>
<td>Levodopa/carbidopa (150, 300, 600 mg)</td>
<td>33 at 150 mg/day 37 at 300 mg/day 36 at 600 mg/day</td>
<td>64.5 (11.8) at 150 mg/day 63.1 (10.2) at 300 mg/day 62.3 (9.8) at 600 mg/day</td>
<td>40 weeks</td>
<td>6.2 (6.6) months at 150 mg/day 6.6 (6.4) months at 300 mg/day 6.9 (5.9) months at 600 mg/day</td>
<td>1-3</td>
<td>27.8 (1.3) at 150 mg/day 26.3 (10.3) at 300 mg/day 31.7 (13.4) at 600 mg/day</td>
<td>-6.0% at 150 mg/day † † -4.0% at 300 mg/day † † -7.2% at 600 mg/day † †</td>
</tr>
<tr>
<td>Innis et al. 1999</td>
<td>[28]</td>
<td>[123I]</td>
<td>Selegiline (10 mg)</td>
<td>8</td>
<td>63 (6)</td>
<td>4-6 weeks</td>
<td>5.1 years</td>
<td>1-3</td>
<td>35 (14)</td>
<td>-4%</td>
</tr>
<tr>
<td>Ahskog et al. 1999</td>
<td>[29]</td>
<td>[123I]</td>
<td>Pergolide (1.5-3.0 mg) **</td>
<td>12</td>
<td>65.8 (7.3)</td>
<td>6 weeks</td>
<td>9.1 (4.8) years</td>
<td>2-3</td>
<td>22.9 (13.8) at UPDRS motor score</td>
<td>+8% (striatum) +1% (caudate)</td>
</tr>
<tr>
<td>Parkinson Study Group 2001</td>
<td>[14]</td>
<td>[123I]</td>
<td>Pramipexole (1.5-4.5 mg)</td>
<td>42</td>
<td>61.9 (10.8)</td>
<td>22, 34, 46 months</td>
<td>1.3 (1.4) years</td>
<td>Not described</td>
<td>34.6 (13.1)</td>
<td>-7.1% at 22 months † † † -10.9% at 34 months † † † -16.0% at 46 months † † † -3 to -20% *, †</td>
</tr>
<tr>
<td>Gutman et al. 2001</td>
<td>[31]</td>
<td>[123I]</td>
<td>Pramipexole (1.5 mg)</td>
<td>10</td>
<td>56.0 (7)</td>
<td>6 weeks</td>
<td>22.8 (19) months</td>
<td>Not described</td>
<td>29.8 (9.8)</td>
<td>-3 to -20% *, †</td>
</tr>
<tr>
<td>Rossi et al. 2017</td>
<td>[32]</td>
<td>[123I]</td>
<td>Rotigotine (optimal doses)</td>
<td>8</td>
<td>59.2 (6.2)</td>
<td>12 weeks</td>
<td>15.0 (4.0) months</td>
<td>1-2</td>
<td>11.9 (2.6) **</td>
<td>+17% (putamen) † † † +13% (caudate) † † †</td>
</tr>
<tr>
<td>Ikeda et al. 2018</td>
<td>[33]</td>
<td>[123I]</td>
<td>Zonisamide (25-50 mg)</td>
<td>15</td>
<td>73.9 (8.5)</td>
<td>1.0-1.2 years</td>
<td>3.5 (1.2)</td>
<td>2-3</td>
<td>21 (9)</td>
<td>-1.8%</td>
</tr>
</tbody>
</table>

*Significant decrease compared to placebo.

** Pergolide add-on under chronic levodopa/carbidopa treatment.

*** Significant reduction of DAT binding change compared to the levodopa group.

**** Significant increase compared to baseline.

† Lesser decline compared to the levodopa/carbidopa group.

†† Nineteen patients without dopaminergic deficits on the baseline scans were excluded from the analysis.
decline of the [123I]β-CIT uptake was significantly greater in the levodopa group than in the placebo group. Levodopa treatment accelerated the loss of DAT binding compared to placebo (20).

Levodopa treatment significantly decreased DAT binding compared to placebo (20, 31) whereas there were no significant effects of levodopa compared to baseline (28, 30). Previous PET and SPECT studies provided that different study designs might cause contradictory results of levodopa effects on DAT binding.

2. Selegiline

Selegiline, an irreversible inhibitor of MAO-B, is an analog of amphetamine and is metabolized to L-amphetamine and L-methamphetamine. These metabolites have a low affinity for DAT ligand. A previous study examined whether selegiline medication could affect the DAT binding in PD patients. Eight patients (HY stage of 1-3) who received a steady dose of levodopa with wearing off participated in the study. [123I]β-CIT SPECT was performed 3 times: at baseline, on medication (10 mg/day for 4-6 weeks), and after 9-week withdrawal. Selegiline treatment did not cause significant changes of DAT binding compared to baseline and washout (28). How long-term effects of selegiline treatment remains unknown in this short-term study. Further studies are therefore needed to determine whether long-term administration of selegiline can maintain DAT binding in early PD patients.

3. Dopamine agonists

Several DAT imaging studies have shown how three dopamine agonists pergolide (29), pramipexole (14, 31), and rotigotine (32) could influence DAT binding.

3.1. Pergolide

A total of 12 levodopa-responsive PD patients (HY stage of 2-3) receiving chronic levodopa/carbidopa therapy (mean administration duration of 5.8 years) were enrolled in the pergolide add-on study. [123I]β-CIT SPECT was performed 3 times: at baseline, 6 weeks after pergolide on medication, and 4 weeks after pergolide washout. During pergolide treatment, the striatal and putamen [123I]β-CIT uptake ratio were tended to increase at 8% (p=0.105). The caudate [123I]β-CIT uptake was 11% higher after 6 weeks’ administration of pergolide (p = 0.042), but not significant by multiple comparisons (p=0.126). After pergolide washout, the striatal, putamen, and caudate uptake ratios did not differ from baseline statistically. Thus, additional therapy with pergolide had a slight increased tendency of striatal DAT binding in levodopa-treated patients (29).

3.2 Pramipexole

Two previous studies of DAT binding were before and after pramipexole treatment. DAT binding using [11C]RTI-32 PET was compared in three groups (levodopa, pramipexole, and placebo treatment; n=10/group). Short-term therapy (6 weeks) with pramipexole significantly decreased the DAT binding in the contralateral caudate (-15%), ipsilateral anterior putamen (-14%), and posterior putamen (-20%) compared to placebo. These decline rates of striatal DAT binding were lower than those with levodopa therapy (31).

Another study of CALM-PD-CIT examined longitudinal changes of DAT binding in early PD patients who received initial monotherapy of pramipexole or levodopa. Patients were randomly assigned to receive pramipexole (1.5 mg/day, n=42) or carbidopa/levodopa (75/300 mg/day, n=40). For patients with residual disability, the dosage was escalated during the first 10 weeks, and open-label levodopa could be added subsequently. After 24 months of follow-up, the dosage of both drugs could be further modified. [123I]β-CIT SPECT was performed at baseline (n=82), 22 months (n=78), 34 months (n=71), and 46 months (n=65) after the initial treatment. The mean decline (SD) of [123I]β-CIT uptake from baseline was 10.3% (9.8%) at 22 months, 15.3% (12.8%) at 34 months, and 20.7% (14.4%) at 46 months in the striatum. The annual decline rate was approximately 5.2%/year. The mean decrease rate (SD) of striatal [123I]β-CIT uptake was significantly inhibited in the pramipexole group compared to the levodopa group: 7.1% (9.0%) vs. 13.5% (9.6%) at 22 months (p=0.004); 10.9% (11.8%) vs. 19.6% (12.4%) at 34 months (p=0.009); and 16.0% (13.3%) vs. 25.5% (14.1%) at 46 months (p=0.01). The loss of striatal [123I]β-CIT uptake was correlated with the change of the UPDRS score at 46 months (r=-0.40; P=0.001). Initially treatment with pramipexole delayed a reduction of striatal [123I]β-CIT uptake for 46 months compared to initial treatment with levodopa (14). The CALM-PD-CIT study concluded that the initial medication influenced the progressive decline of striatal DAT binding in early PD patients.

3.3. Rotigotine

Rotigotine, (6S)-6-[(propyl (2-(2-thienyl) ethyl) amino]-5,6,7,8-tetrahydro-1-naphthalenol, is a non-ergot dopamine D3/D2/D1 receptor agonist. SPECT using [123I]FP-CIT was performed at baseline and three months after the optimal dose of rotigotine monotherapy in 8 de novo PD patients (HY stage 1-2). The mean dose (SD) of rotigotine was 7.75 (1.98) mg/day. Rotigotine treatment increased the [123I]FP-CIT uptake significantly in the striatum. The mean increase rate was 13% in the caudate nucleus and 17% in the putamen (32). Rotigotine may up-regulate presynaptic DAT binding in the striatum by compensatory reactions, and DAT normalization can prompt dopamine turnover and stabilization of the dopamine levels in the synaptic cleft, leading to the suppression of dyskinesia development. How longer administration of this drug alters striatal DAT binding remains unclear.

4. ZNS

ZNS, 1,2-benzisoxazole-3-methanesulfonamide, has been used for more than 20 years as an anti-epileptic drug in Japan (35). This medication was reported to ameliorate motor symptoms on UPDRS part III in PD patients (36-38). In 2009, ZNS was approved as an adjunctive therapy for Japanese PD patients. The pharmacological mechanism of this
drug seems to reveal the activation of dopamine synthesis, suppression of MAO-B, prevention of dopamine quinone formation, blockage of T-type calcium currents, and potentiation of sodium channel inactivation (39-44). A recent study examined whether long-term adjunctive therapy of ZNS can maintain DAT binding (33). The study participants met the following criteria: (i) age ≥40 years, (ii) HY stage 2 or 3, (iii) average specific binding ratio (SBR) ≥2.00 on [123I]FP-CIT SPECT at baseline, (iv) chronic administration of levodopa. Attending physicians initially determined whether ZNS (25 mg/day) should be used or not. The patients were divided into the ZNS group (n=15) and the non-ZNS group (n=15). Levodopa and other anti-PD medications were not restricted during the study. The second scan was conducted 1.0-1.2 years after the first imaging. Clinicoradiological changes of HY stage, UPDRS parts II to IV, dyskinesia subscore, and DAT binding (SBR) were calculated. ZNS co-treatment shortened wearing off time and prevented the development of dyskinesia without the additional administration of selegiline, entacapone, and dopamine agonists (rotigotine, pramipexole, and ropinirole). The decline rate of DAT binding was significantly lower in the ZNS group (mean ± SD: -1.8%±3.6%) than in the non-ZNS group (mean ± SD: -18.7%±14.1%). ZNS was an independent preventive factor for DAT binding reduction (odds ratio=0.913; 95% confidence interval [CI]=0.847-0.984; p=0.0168). After the end of the study, ZNS washout was performed for two weeks in four patients of the ZNS group. Temporary cessation of the drug did not influence the striatal DAT binding.

A previous [123I]FP-CIT PET study suggested that a decrease in putaminal DAT activities played a role in the levodopa-induced dyskinesia in de novo PD patients (45). Preservation of striatal DAT binding may contribute to a low frequency of dyskinesia and wearing off in ZNS-treated patients. This study indicated a beneficial potential that ZNS preserves striatal presynaptic DAT expression and can slow disease progression in early PD patients.

**Conclusion**

DAT imaging is a useful diagnostic and progressive biomarker in early PD patients. Previous longitudinal studies of DAT images revealed a linear or an exponential decline of DAT binding (9, 12-16, 19, 22-24, 27). Annual decline rates were approximately 4%-15%. The PPMI study has showed that the annual decline rate of striatal DAT binding was -11% at 1 year after the diagnosis in early PD patients (HY stage of 1-2) and -5% to -6%/year from years 1 to 4 (27). This exponential decline suggested a floor effect of DAT binding along with disease progression.

Second, the present review explored whether anti-PD medications could influence DAT binding. Follow-up DAT imaging was conducted in early PD patients treated with levodopa, selegiline, pergolide, pramipexole, rotigotine, or zonisamide. After the short-term administration of levodopa (4-6 weeks), DAT binding was not significantly changed compared to baseline and washout (28). The long-term administration of levodopa (3 months) also did not significantly influence DAT binding in the putamen or caudate nucleus compared to baseline (30). Furthermore, two other placebo-controlled studies revealed a significant decline of DAT binding after short- or long-term treatment with levodopa (20, 31). Short-term medication of levodopa (6 weeks) significantly reduced DAT binding (31). The ELLDOPA study demonstrated that the long-term administration of levodopa (40 weeks) significantly reduced prompted decline of DAT binding significantly compared to placebo (20). Another longitudinal study of levodopa (46 months) decreased DAT binding at the mean rate of -25.5% from baseline (14). MAO-B inhibitor therapy of selegiline (4-6 weeks) had no significant effects on DAT binding compared to baseline and washout (28).

With respect to dopamine agonists of pergolide, pramipexole, and rotigotine, follow-up DAT imaging was performed in early PD patients. Pergolide add-on therapy (6 weeks) tended to increase striatal DAT binding slightly in patients who had chronic administration of levodopa compared to baseline (29). The CALM-PD-CIT study reported that initial treatment with pramipexole delayed reduction of DAT binding significantly at 24, 34, and 46 months from baseline compared to initially levodopa-treated patients (14). Another study also suggested lesser reduction of DAT binding after short-term medication of pramipexole (6 weeks) compared to levodopa (31).

Rotigotine monotherapy (12 weeks at the optimal doses) increased DAT binding significantly at 17% in the putamen and 13% in the caudate nucleus in de novo patients with HY stage 1-2 (32). Long-term adjunctive therapy of ZNS (1-1.2 years) inhibited decline of striatal DAT binding significantly in levodopa-treated patients compared to patients without ZNS treatment (33). There are limited data on the sensitivity of DAT binding to longitudinal change. The decline rates of DAT binding become small gradually from the early stage to the advanced stage in PD patients. The first comparative study between DAT imaging and nigral pathology was reported in patients with dopaminergic neurodegeneration, including PD, DLB, MSA, CBD, and atypical parkinsonism. The mean interval from DAT imaging to death was 29.3 months. The number of dopamine neurons was highly correlated with DAT binding (6). Recently another postmortem study has demonstrated no association between DAT binding and dopamine neuron counting in the substantia nigra in PD patients. However, the study limitation included the mean time interval (SD) between [123I]FP-CIT SPECT and death of 5.2 (2.7) years (7), and did not reveal total number of nigral cells. No relationship has been reported between DAT imaging and neuromelanin imaging on 7-tesla MRI.

DAT imaging could not reflect nigral neurodegeneration adequately in some PD patients. DAT imaging is limited for its applicability to PD clinical trials. This imaging should be
used to assess presynaptic dysfunction or axonal denervation in the nigrostrial system. Further novel and non-invasive biomarkers for degeneration of nigral dopamine neurons are needed to evaluate the neurodegenerative progression and therapeutic neuroprotection in PD patients.

The authors state that they have no Conflict of Interest (COI).

References


The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).