【 REVIEW ARTICLE 】

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 C (1, 2). Measurement of DAT was correlated with striatal dopamine levels in PD patients (3).

Many kinds of DAT radiotracers for positron emission to- mography (PET) and single-photon emission computed to- mography (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, dug-induced parkinsonism, or other neurological dis- eases that do not involve the nigrostriatal dopaminergic sys- tem (4, 5). A previous postmortem examination showed the significant correlation between striatal DAT binding and ni- gral neuron counts in patients with dopaminergic neurode- generation, including PD, dementia with Lewy body (DLB), multiple systemic atrophy (MSA), and corticobasal degen- eration (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 [^{123}I]FP-CIT was performed at baseline and years 1, 2, and 4. There was a significant longitudinal change of DAT binding in all striatal regions. During the 4-year assessment interval, the decrease of DAT binding was found in the putamen. The mean reduction of putaminal DAT binding was -13% at year 1, -19% at year 2, and -11% at year 4. The annual decline rate was calculated as -13%/year at the first year, and -5% to -6%/year

at the subsequent 3 years (years 2 and 4). Therefore, the change of DAT binding was greatest at year 1 compared to years 2 and 4. The decline pattern might show a floor effect on striatal DAT binding. There was a significant but weak correlation between the Movement Disorders Society UPDRS (MDS-UPDRS) and DAT binding at baseline and years 1, 2, and 4. However, no correlation was found between the change rates of the two variables (27).

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.

[^{123}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. [^{123}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.

Reference no.	Reported year	DAT imaging	Patient number	Mean PD duration (years) at baseline	Mean UPDRS motor score at baseline	Scan number	Mean interval of DAT scan	Mean annual rate of decline in striatal DAT binding	Decline pattern
[9]	2000	[123I]β-CIT SPECT	15	Not reported	Not described	2	1.3 years	7.3%	Exponential **
[10]	2000	[18F]CFT PET	8	2.1	20.5	2	2 years	13.1% in putamen 12.5% in caudate	Not applicable
[11]	2001	[123I]FP-CIT SPECT	20	2.5	16.5	2	1.0 year	8.1%	Not applicable
[12]	2001	[123I]β-CIT SPECT	8	3.6	Not described	3	1.0 year	5.8%	Linear
[13]	2001	[123I]β-CIT SPECT	15	2.5	18.2	2	2.3 years	11.2%	Linear
[14]	2002	[123I]β-CIT SPECT	65	1.5	22.4	4	22, 34 and 46 weeks	5.2%	Linear
[15]	2002	[123I]β-CIT SPECT	36	2.4 and 9.2	18.4 and 23.3	2	2.2 years	6.8% and 4.1%	Exponential *
[16]	2003	[123I]β-CIT SPECT	21	2.4	19.0	3	2.2 and 3.2 years	5.8%	Linear
[17]	2003	[123I]β-CIT SPECT	50	2.7	19.2	2	1.0 year	7.6%	Not applicable
[18]	2003	[18F]CFT PET	12	1.7	26.8	2	2.2 years	11.9% in anterior putamen	Not applicable
[19]	2004	[123I]β-CIT SPECT	6	3.2	Not described	4	1 and 5.5 years	7.2%	Exponential **
[20]	2004	[123I]β-CIT SPECT	29	0.4	7.8	2	40 weeks	1.8%	Not applicable
[21]	2005	[123I]FP-CIT SPECT	20	4.5	24.5	2	1.0 year	5.2% in anterior putamen	Not applicable
[22]	2007	[18F]FP-CIT PET	10	<2.0	9.5	3	2.0 and 2.0 years	6.7% in putamen	Linear
[23]	2009	[11C]MP PET	19	7.6	27.4	3	4.0 and 4.0	Not reported	Exponential
[24]	2013	[123I]FP-CIT SPECT	22	1.5	27.0	3	1.0 and 2.0 years	4.2%	Exponential **
[25]	2014	[123I]β-CIT SPECT	629	0.8	18.4	2	1.8 years	4.6%	Not applicable
[26]	2015	[123I]FP-CIT SPECT	241	0.6	21.5 (MDS-UPDRS)	3	12 and 24 weeks	7.9%	Exponential **
[27]	2018	[123I]FP-CIT SPECT	423	0.6	32 (MDS-UPDRS)	3	12, 24 and 48 weeks	5-11%	Exponential *

*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.

Reference no.	DAT imaging	Anti-PD drug (daily dose)	Patient number	Mean age (SD) years	Treatment duration	Mean disease duration (SD)	HY stage	Mead (SD) of total UPDRS	Change rate of DAT binding from baseline
[28]	$[^{123}I]$ FP-CIT SPECT	Levodopa/carbidopa (600/150 mg)	8	65 (10)	4-6 weeks	2.4 years	1-3	28(10)	-3%
[30]	$[^{18}F]$ CFT PET	Levodopa/carbidopa or levodopa/benserazide (200-400 mg)	7	66.6 (8.5)	3 months	31.2 (20) months	Not described	31 (5) (UPDRS motor score)	-4.1% (anterior putamen) -1.9% (posterior putamen) -4.0% (caudate)
[31]	$[^{11}C]$ RTI-32 PET	Levodopa/carbidopa (300/75 mg)	10	60.7(10)	6 weeks	22.8 (19) months	Not described	23.9 (6.0)	-16 to -22% *
[14]	$[^{123}I]$ FP-CIT SPECT	Levodopa/carbidopa (300/75,450/112.5, 600/150 mg)	40	60.1 (11.1)	22, 34, 46 months	1.6 (1.9) years	Not described	30.6 (11.4)	-13.5% at 22 months -19.6% at 34 months -25.5% at 46 months
[20]	$[^{123}I]$ β-CIT SPECT	Levodopa/carbidopa (150, 300, 600 mg)	33 at 150 mg/day 37 at 300 mg/day 36 at 600 mg/day	64.5 (11.8) at 150 mg/day 63.1 (10.2) at 300 mg/day 62.3 (9.8) at 600 mg/day	40 weeks	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	1-3	27.8 (13.1) at 150 mg/day 26.3 (10.3) at 300 mg/day 31.7 (13.4) at 600 mg/day	-6.0% at 150 mg/day†† -4.0% at 300 mg/day†† -7.2% at 600 mg/day††
[28]	$[^{123}I]$ FP-CIT SPECT	Selegiline (10 mg)	8	63 (6)	4-6 weeks	5.1 years	1-3	35(14)	-4%
[29]	$[^{123}I]$ FP-CIT SPECT	Pergolide (1.5-3.0 mg) **	12	65.8 (7.3)	6 weeks	9.1 (4.8) years	2-3	22.9 (13.8) at UPDRS motor score	+8% (striatum) +11% (caudate)
[14]	$[^{123}I]$ FP-CIT SPECT	Pramipexole (1.5-4.5 mg)	42	61.9 (10.8)	22, 34, 46 months	1.3 (1.4) years	Not described	34.6 (13.1)	-7.1% at 22 months *** -10.9% at 34 months *** -16.0% at 46 months ***
[31]	$[^{11}C]$ RTI-32 PET	Pramipexole (1.5 mg)	10	56.0(7)	6 weeks	22.8 (19) months	Not described	29.8 (9.8)	-3 to -20% *, †
[32]	$[^{123}I]$ FP-CIT SPECT	Rotigotine (optimal doses)	8	59.2 (6.2)	12 weeks	15.0 (4.0) months	1-2	11.9 (2.6) **	+17% (putamen) **** +13% (caudate) ****
[33]	$[^{123}I]$ FP-CIT SPECT	Zonisamide (25-50 mg)	15	73.9 (8.5)	1.0-1.2 years	3.5 (1.2)	2-3	21 (9)	-1.8%

*Significant decrease compared to placebo.

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

*** Significant reduction of DAT binding decline 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 [^{123}I]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. [^{123}I]β-CIT SPECT was performed 3 times: at baseline, on medication of selegiline (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. [^{123}I]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 [^{123}I]β-CIT uptake ratio were tended to increase at 8% (p=0.105). The caudate [^{123}I]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 [^{11}C]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 ante-

rior 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. [^{123}I]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 [^{123}I]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 [^{123}I]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 [^{123}I]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 [^{123}I]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 [^{123}I]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 [^{123}I]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 longstanding therapy 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 nigrostriatal 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

1. Kaufman MJ, Madras BK. Severe depletion of cocaine recognition sites associated with the dopamine transporter is decreased in the caudate nucleus in Parkinson's disease. Synapse **9**: 43-49, 1991.
2. Niznik HB, Fogel EF, Fassos EF, Seeman P. The dopamine transporter is absent in Parkinsonian putamen and reduced in the caudate nucleus. J Neurochem **56**: 192-198, 1991.
3. Wilson JM, Levey AI, Rajput A, et al. Differential changes in neurochemical markers of striatal dopamine nerve terminals in idiopathic Parkinson's disease. Neurology **47**: 718-726, 1996.
4. Tatsch K, Poepperl G. Nigrostriatal dopamine terminal imaging with dopamine transporter SPECT: an update. J Nucl Med **54**: 1331-1338, 2013.
5. Bajaj N, Hauser RA, Grachev ID. Clinical utility of dopamine transporter single photon emission CT (DaT-SPECT) with (123I) ioflupane in diagnosis of parkinsonian syndromes. J Neurol Neurosurg Psychiatry **84**: 1288-1295, 2013.
6. Kraemmer J, Kovacs GG, Perju-Dumbrava L, Pirker S, Traub-Weidinger T, Pirker W. Correlation of striatal dopamine transporter imaging with post mortem substantia nigra cell counts. Mov Disord **29**: 1767-1773, 2014.
7. Saari L, Kivinen K, Gardberg M, Joutsa J, Noponen T, Kaasinen V. Dopamine transporter imaging does not predict the number of nigral neurons in Parkinson disease. Neurology **88**: 1461-1467, 2017.
8. Kaasinen V, Vahlberg T. Striatal dopamine in Parkinson Disease: a meta-analysis of imaging studies. Ann Neurol **82**: 873-882, 2017.
9. Staffen W, Mair A, Unterrainer J, Trinka E, Ladurner G. Measuring the progression of idiopathic Parkinson's disease with [^{123}I] beta-CIT SPECT. J Neural Transm (Vienna) **107**: 543-552, 2000.
10. Nurmi E, Ruottinen HM, Kaasinen V, et al. Progression in Parkinson's disease: a positron emission tomography study with a dopamine transporter ligand [18F]CFT. Ann Neurol **47**: 804-808, 2000.
11. Winogrodzka A, Bergmans P, Booij J, van Royen EA, Janssen AG, Wolters EC. [123I]FP-CIT SPECT is a useful method to monitor the rate of dopaminergic degeneration in early-stage Parkinson's disease. J Neural Transm (Vienna) **108**: 1011-1019, 2001.
12. Chouker M, Tatsch K, Linke R, Pogarell O, Hahn K, Schwarz J. Striatal dopamine transporter binding in early to moderately advanced Parkinson's disease: monitoring of disease progression over 2 years. Nucl Med Commun **22**: 721-725, 2001.
13. Marek K, Innis R, van Dyck C, et al. [123I]beta-CIT SPECT imaging assessment of the rate of Parkinson's disease progression. Neurology **57**: 2089-2094, 2001.
14. Parkinson Study Group. Dopamine transporter brain imaging to assess the effects of pramipexole vs. levodopa on Parkinson disease progression. JAMA **287**: 1653-1661, 2002.
15. Pirker W, Djamshidian S, Asenbaum S, et al. Progression of dopaminergic degeneration in Parkinson's disease and atypical parkinsonism: a longitudinal beta-CIT SPECT study. Mov Disord **17**: 45-53, 2002.
16. Pirker W, Holler I, Gerschlager W, Asenbaum S, Zettinig G, Brücke T. Measuring the rate of progression of Parkinson's disease over a 5-year period with beta-CIT SPECT. Mov Disord **18**: 1266-1272, 2003.
17. Winogrodzka A, Bergmans P, Booij J, van Royen EA, Stoof JC, Wolters EC. [(123)I]beta-CIT SPECT is a useful method for monitoring dopaminergic degeneration in early stage Parkinson's disease. J Neurol Neurosurg Psychiatry **74**: 294-298, 2003.
18. Nurmi E, Bergman J, Eskola O, et al. Progression of dopaminergic hypofunction in striatal subregions in Parkinson's disease using [18F]CFT PET. Synapse **48**: 109-115, 2003.
19. Schwarz J, Storch A, Koch W, Pogarell O, Radau PE, Tatsch K. Loss of dopamine transporter binding in Parkinson's disease follows a single exponential rather than linear decline. J Nucl Med **45**: 1694-1697, 2004.
20. Fahn S, Oakes D, Shoulson I, et al.; Parkinson Study Group. Levodopa and the progression of Parkinson's disease. N Engl J Med **351**: 2498-2508, 2004.
21. Colloby SJ, Williams ED, Burn DJ, Lloyd JJ, McKeith IG, O'Brien JT. Progression of dopaminergic degeneration in dementia with Lewy bodies and Parkinson's disease with and without dementia assessed using 123I-FP-CIT SPECT. Eur J Nucl Med Mol Imaging **32**: 1176-1185, 2005.
22. Huang C, Tang C, Feigin A, et al. Changes in network activity with the progression of Parkinson's disease. Brain **130**: 1834-1846, 2007.
23. Nandhagopal R, Kuramoto L, Schulzer M, et al. Longitudinal progression of sporadic Parkinson's disease: a multi-tracer positron emission tomography study. Brain **132**: 2970-2979, 2009.
24. Jakobson Mo S, Linder J, Forsgren L, Holmberg H, Larsson A, Riklund K. Pre- and postsynaptic dopamine SPECT in idiopathic Parkinsonian diseases: a follow-up study. Biomed Res Int **2013**: 143532, 2013.
25. Marek K, Seibyl J, Eberly S, et al.; Parkinson Study Group PRECEPT Investigators. Longitudinal follow-up of SWEDD subjects in the PRECEPT Study. Neurology **82**: 1791-1797, 2014.
26. Seibyl J, Jennings D, Marek K. Assessment of Parkinson disease progression using 123-I-Ioflupane SPECT: update from Parkinson Progression Marker Initiative Trial (S40.003). Neurology **84** (14 Suppl): 2015.
27. Simuni T, Siderowf A, Lasch S, et al.; Parkinson's Progression Marker Initiative. Longitudinal change of clinical and biological measures in early Parkinson's disease: Parkinson's Progression Markers Initiative Cohort. Mov Disord **33**: 771-782, 2018.
28. Innis RB, Marek KL, Sheff K, et al. Effect of treatment with L-dopa/carbidopa or L-selegiline on striatal dopamine transporter SPECT imaging with [123I]beta-CIT. Mov Disord **14**: 436-442, 1999.
29. Ahlskog JE, Uitti RJ, O'Connor MK, et al. The effect of dopamine agonist therapy on dopamine transporter imaging in Parkinson's disease. Mov Disord **14**: 940-946, 1999.
30. Nurmi E, Bergman J, Eskola O, et al. Reproducibility and effect of levodopa on dopamine transporter function measurements: a [18F]CFT PET study. J Cereb Blood Flow Metab **20**: 1604-1609, 2000.
31. Guttman M, Stewart D, Hussey D, Wilson A, Houle S, Kish S. Influence of L-dopa and pramipexole on striatal dopamine transporter in early PD. Neurology **56**: 1559-1564, 2001.
32. Rossi C, Genovesi D, Marzullo P, et al. Striatal dopamine transporter modulation after rotigotine: results from a pilot single-photon emission computed tomography study in a group of early stage Parkinson disease patients. Clin Neuropharmacol **40**: 34-36, 2017.
33. Ikeda K, Yanagihashi M, Miura K, et al. Zonisamide cotreatment delays striatal dopamine transporter reduction in Parkinson disease: a retrospective, observational cohort study. J Neurol Sci1 **391**: 5-9, 2018.
34. Guttman M, Burkholder J, Kish SJ, et al. [11C]RTI-32 PET stud-

ies of the dopamine transporter in early dopa-naive Parkinson's disease: implications for the symptomatic threshold. Neurology **48**: 1578-1583, 1997.

35. Uno H, Kurokawa M, Masuda Y, Nishimura H. Studies on 3-substituted 1.2-benzisoxazole derivatives 6: syntheses of 3- (sulfamoylmethyl)-1,2- benzisoxazole derivatives and their anticonvulsant activities. J Med Chem **22**: 180-183, 1979.

36. Murata M, Horiuchi E, Kanazawa I. Zonisamide has beneficial effects on Parkinson's disease patients. Neurosci Res **41**: 397-399, 2001.

37. Murata M, Hasegawa K, Kanazawa I. The Japan Zonisamide on PD Study Group. Zonisamide improves motor function in Parkinson disease: a randomized, double-blind study. Neurology **68**: 45-50, 2007.

38. Ikeda K, Hanashiro S, Sawada M, Iwasaki Y. Preliminary study of zonisamide monotherapy in *de novo* patients with early Parkinson's disease. Neurol Clin Neurosci **3**: 163-166, 2015.

39. Asanuma M, Miyazaki I, Diaz-Corrales FJ, Miyoshi K, Ogawa N, Murata NM. Preventing effects of a novel anti-parkinsonian agent zonisamide on dopamine quinone formation. Neurosci. Res **60**: 106-113, 2008.

40. Murata M. Novel therapeutic effects of the anti-convulsant, zonisamide, on Parkinson's disease. Curr. Pharm. Des **10**: 687-693, 2004.

41. Rock DM, Macdonald RL, Taylor CP. Blockade of sustained repetitive action potentials in cultured spinal cord neurons by zonisamide (AD 810, CI 912), a novel anticonvulsant. Epilepsy Res **3**: 138-143, 1989.

42. Schauf CL. Zonisamide enhances slow sodium inactivation in Myxicola. Brain Res **413**: 185-188, 1987.

43. Suzuki S, Kawakami K, Nishimura S, et al. Zonisamide blocks T-type calcium channel in cultured neurons of rat cerebral cortex. Epilepsy Res **12**: 21-27, 1992.

44. Kito M, Maehara M, Watanabe K. Mechanisms of T-type calcium channel blockade by zonisamide. Seizure **5**: 115-119, 1996.

45. Hong JY, Oh JS, Lee I, et al. Presynaptic dopamine depletion predicts levodopa-induced dyskinesia in *de novo* Parkinson disease. Neurology **82**: 1597-1604, 2014.