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Zonisamide cotreatment delays striatal dopamine transporter reduction in Parkinson disease: A retrospective, observational cohort study

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ABSTRACT

This study examined whether zonisamide (ZNS) cotreatment delays dopamine transporter (DAT) reduction on SPECT in Parkinson disease (PD) patients. 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; (iv) levodopa administration without a prior history of ZNS use before the first DAT-SPECT (baseline). Attending physicians initially determined whether ZNS (25 mg/day) should be used or not. Levodopa and other anti-PD medications were not restricted. The second DAT-SPECT (endpoint) was conducted 1.2 ± 0.2 years after the first DAT-SPECT. Clinicoradiological changes of HY stage, UPDRS parts II to IV, dyskinesia subscore, and SBR were calculated. Statistical differences were analyzed by Student's *t*-test, ANOVA, or multilogistic analysis. ZNS cotreatment improved wearing off and prevented the development of dyskinesia without additional administration of selegiline, entacapone, and dopamine receptor agonists. The endpoint SBR reduced significantly in the non-ZNS group compared to the baseline ($P < .01$). The SBR decline rate reduced significantly in the ZNS group ($P < .01$). ZNS was an independent preventive factor for SBR reduction. These results suggested a beneficial potential that ZNS preserves striatal presynaptic DAT expression and slows disease progression in early-stage PD.

1. Introduction

Parkinson disease (PD) is a slowly progressive neurodegenerative disease characterized by loss of dopaminergic terminals in the nigrostriatal system. Compared to brain magnetic resonance imaging and cerebral blood flow imaging by single-photon emission computed tomography (SPECT), a more sensitive and useful tool to establish dopaminergic dysfunction is dopamine transporter (DAT)-SPECT using ^{123}I-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane (^{123}I-FP-CIT, ^{123}I-Ioflupane). ^{123}I-FP-CIT binds to the presynaptic DAT, and DAT-SPECT can analyze the integrity of the nigrostriatal projection pathway [1]. This imaging is performed for a differential diagnosis of PD compared to essential tremor, vascular parkinsonism, and drug-induced parkinsonism [2]. Previous postmortem examinations have shown the significant correlation between striatal DAT bindings and substantia nigra cell counts in patients with dopaminergic neurodegeneration [3]. A postmortem study suggested that striatal DAT bindings might reflect axonal dysfunction or DAT expression in PD patients [4]. Longitudinal studies of DAT-SPECT for therapeutic interventions have been reported [5–8]. DAT-SPECT displayed dopamine reduction in asymptomatic *G2019S-LRRK2* mutation carriers; *G2019S-LRRK2* mutation is known as a high risk factor for PD development [9]. An experimental study in an animal model of PD also suggested the relationship between DAT and striatal dopamine contents [10]. Therefore, DAT-SPECT is used as a possible biomarker for progressive evaluation of presynaptic dopaminergic dysfunction in the nigrostriatal pathway of PD patients.

Zonisamide (ZNS), 1,2-benzisoxazole-3-methanesulfonamide, has been used for > 20 years as an anti-epileptic drug in Japan [11]. This drug also improves motor symptoms on the unified Parkinson's disease rating scale (UPDRS) part III in PD patients [12,13]. In 2009, ZNS was approved as an anti-PD drug that was an adjunctive therapy for PD in Japan. ZNS monotherapy ameliorated motor and sleep dysfunction in de novo patients with early-stage PD [14]. Previous experimental studies also revealed that ZNS attenuated loss of dopaminergic neurons in animal models of PD [15–18]. The clinical and experimental evidence prompted us to evaluate whether ZNS administration can delay progression of DAT reduction on DAT-SPECT in PD patients.

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2. Materials and methods

2.1. Enrolled PD patients

All patients were recruited from the Department of Neurology, Toho University Medical Center Omori Hospital, Tokyo, Japan. They were diagnosed according to the UKPD Society Brain Bank criteria [19]. All patients underwent the first DAT-SPECT (baseline) for further differential diagnosis before the entry into this study. The patients selected for the study fulfilled the following criteria: (i) No prior history of ZNS treatment before the first DAT-SPECT; (ii) age ≥ 40 years; (iii) levodopa administration and examination using the Hoehn and Yahr (HY) stage and UPDRS parts II–IV; (iv) HY stage = 2 or 3; and (v) average value of the right and left striatal specific binding ratio (SBR) on DAT-SPECT ≥2.00. Patients meeting the following criteria were excluded: concomitant use of selective serotonin reuptake inhibitors, severe degree of dementia, liver dysfunction, known allergy to iodine, and a prior history of serious cardiac disease. All patients participating in the study were informed of the purpose and the method of the present study, and they all provided written informed consent. The study was approved by the Review Board of the Toho University Medical Center Omori Hospital (M16003).

2.2. ZNS administration

Before initiation of the study, each attending physician freely selected medications of dopamine receptor agonists (DAs: rotigotine, pramipexole, and ropinirole), selegiline, entacapone, and/or ZNS for progression of motor symptoms and wearing off. During the study, the patients were divided into two groups: ZNS group and non-ZNS group. According to ZNS approved usage and dose in Japan, the patients were initially administered the drug at a daily dose of 25 mg (per oral); the dose was increased to 50 mg/day if the higher dose was expected to improve wearing off during the study. Concomitant use of levodopa and other anti-PD medications, including anticholinergics, amantadine, droxidopa, selegiline, entacapone, and DAs, were not restricted. Treatment with or without ZNS was continued for 1.2 ± 0.2 years after the first DAT-SPECT. Patients in the ZNS group who stopped taking ZNS or those in the non-ZNS group who started ZNS were withdrawn from the study.

2.3. Neurological evaluation

Neurological examination was performed every 1 or 2 months. The HY stage and UPDRS parts II–IV were evaluated on time at the baseline and at the endpoint (second DAT-SPECT) by each attending physician. The tremor score and the dyskinesia subscore were measured at the baseline and the endpoint. The tremor score was defined as the sum of UPDRS part II item 16 (self-report), part III item 20 (resting tremor), and part III item 21 (action/positional tremor) [20]. The dyskinesia subscore was defined as the sum of UPDRS part IV items 32–34. The interval between baseline and endpoint was 1.2 ± 0.2 years. Changes in UPDRS parts II–IV were calculated as endpoint score – baseline score.

2.4. DAT-SPECT

Three hours after injection of approximately 167 MBq of ^{123}I-FP-CIT, projection data were obtained for 30 min in a 128 × 128 matrix on a Siemens Symbia T16 equipped with low-to-medium-energy general-purpose collimators. The data were reconstructed by filtered back-projection with a Butterworth filter (order = 8; cut-off = 0.5 cycles/cm) and corrected for attenuation by Chang's method with a uniform attenuation coefficient (0.08/cm). Scatter correction was performed using the triple-energy-window method including a main energy window (159 keV ± 10.5%) and two subwindows (7%).

The striatal SBR was calculated semiquantitatively using DAT VIEW automated analysis software (Nihon Medi-Physics, Tokyo, Japan) based on Tossici–Bolt's method in which the region of interest was placed automatically [21]. As mentioned before, the second DAT-SPECT (endpoint) was conducted 1.2 ± 0.2 years after the first imaging (baseline). The following formulas were used: SBR change = Baseline SBR − Endpoint SBR. Change rate of SBR = (SBR change/Baseline SBR) × 100 (%). To assess the asymmetric degree of the striatal SBR, a striatal asymmetry index (SAI) was calculated as follows [22]: (Right SBR − Left SBR)/(Right SBR + Left SBR) × 2 × 100 (%).

For this study, the normal range of the SBR value was obtained in 10 age-matched control subjects who had neither PD symptoms nor abnormal neurological examination. The SBR range was 4.83–6.61 in controls. The baseline SBR on the first DAT-SPECT ≥2.00 at inclusion criteria was determined as 60% or less reduction of the mean SBR of 5.00 in normal controls.

2.5. Statistical analysis

All data were shown as the mean (standard deviation [SD]). The differences of clinical and SBR data at the baseline or endpoint between the ZNS group and non-ZNS groups were analyzed by unpaired Student's *t*-test. The differences of clinical and SBR data between baseline and endpoint within each group were analyzed by paired Student's *t*-test. The differences of clinicoradiological variables between the ZNS group and non-ZNS groups were analyzed by a two-way repeated-measures analysis of variance (ANOVA). Multiple logistic regression analysis was performed to identify an independent preventive factor for SBR reduction. *P* value of < 0.05 was considered statistically significant. Statistical analyses were performed using PASW Statistics 18.0 (IBM, Chicago, IL, the USA).

3. Results

3.1. Demographic data of participating patients at the baseline

Table 1 lists the demographic data of the patients. The baseline data of age, sex, disease duration, and HY stage did not differ statistically between the ZNS and non-ZNS groups. In addition, there were no significant differences in UPDRS parts II–IV, tremor scores, and dyskinesia subscores at the baseline between the ZNS and non-ZNS groups. The mean dose (SD) of levodopa was 277 (155) mg/day in the ZNS group

Table 1
Clinical background of PD patients at the baseline.

	ZNS group (n = 15)	Non-ZNS group (n = 15)
Men/women	10/5 patients	9/6 patients
Age	73.9 (8.5) years	71.5 (9.9) years
Disease duration	3.5 (1.2) years	3.5 (1.9) years
HY stage	2.3 (0.5)	2.4 (0.5)
UPDRS part II	6.9 (3.2)	6.9 (2.5)
UPDRS part III	13.4 (5.1)	13.1 (6.3)
UPDRS part IV	0.6 (1.0)	0.8 (0.9)
UPDRS parts II–IV	20.9 (8.6)	20.7 (8.2)
Tremor score	2.1 (1.2)	2.2 (1.3)
Dyskinesia subscore	0.1 (0.1)	0.1 (0.2)
Levodopa doses	277 (155) mg/day	290 (114) mg/day
Levodopa user	15 patients (100%)	15 patients (100%)
Amantadine user	1 patient (7%)	0 patient (0%)
Selegiline user	1 patient (7%)	2 patients (13%)
Entacapone user	2 patients (13%)	1 patient (7%)
Rotigotine user	10 patients (67%)	7 patients (47%)
Ropinirole user	0 patient (0%)	1 patient (7%)
Pramipexole user	2 patients (13%)	3 patients (20%)
DAs non-user	3 patients (20%)	4 patients (27%)
Istradefilline user	1 patient (7%)	1 patient (7%)

Data expressed as the mean (SD).
DAs, dopamine receptor agonists; HY, Hoehn and Yale stage; PD, Parkinson disease; UPDRS, unified Parkinson's disease rating scale; ZNS, zonisamide.