A comparative trial of selegiline and zonisamide for disease modifying effects on DAT-SPECT in patients with Parkinson's disease: study protocol for a prospective multicenter randomized study (DATSZ-PD study)

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Study protocol

Keywords: Disease modifying therapy, dopamine transporter scintigraphy, monoamine oxidase-B inhibitor, Parkinson's disease, randomized controlled trial, study protocol, zonisamide, selegiline

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Abstract

Background: Therapeutic strategies to prevent degeneration of dopaminergic neurons in Parkinson's disease have not been developed to date. Although previous non-clinical and clinical studies have shown that selegiline and zonisamide can protect dopamine neurons, their protective action has been clinically evaluated in few studies. In this study, we will compare levodopa/decarboxylase inhibitor (DCI) alone with the combination of levodopa/DCI and selegiline or zonisamide to investigate whether degeneration of dopaminergic neurons could be prevented by the combination therapy in patients with early Parkinson's disease.

Methods: This multicenter, open-label, randomized controlled study will enroll 180 patients. Sixty patients will be randomly assigned to receive levodopa/DCI alone, 60 patients will be assigned to receive levodopa/DCI and selegiline, and 60 patients will be assigned to receive levodopa/DCI and zonisamide, and followed-up for 1 year. The primary endpoint is the percent change of specific binding ratio (SBR; Southampton's method) of 123Iodine-labelled N-(3-fluoropropyl) -2β-carbomethoxy-3β-(4-iodophenyl) nortropane ([123I]FP-CIT) single-photon emission computed tomography (SPECT) (dopamine transporter SPECT, DAT-SPECT) from baseline to the end of one-year follow-up. The secondary endpoints are the percent change of Unified Parkinson's Disease Rating Scale (Part II and Part III) scores and Parkinson's Disease Questionnaire -39 scores from baseline to post-treatment.

Discussion: This multicenter, randomized controlled study will evaluate the disease-modifying effect of selegiline and zonisamide on degeneration of nigrostriatal dopaminergic neurons in patients with Parkinson's disease based on the percent change of SBR of DAT-SPECT (primary endpoint). If our study findings suggest that selegiline or zonisamide has a disease-modifying effect from the clinical aspect, the long-term efficacy should be evaluated in a larger-scale phase III study. T

Trial Registration: University hospital medical information network (UMIN): UMIN000022533. Registered 30 May 2016, https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000025960

Background

Parkinson's disease is a progressive neurodegenerative disorder characterized by the degeneration of dopaminergic neurons in the substantia nigra. However, no curative treatment to prevent this clinico-pathological progression has been developed to date. Only symptomatic therapy represented by dopamine replacement is available at present. Drug therapy or surgery is selected as appropriate according to the severity and the type of symptoms. The most effective anti-Parkinsonian drug for symptomatic treatment is levodopa. However, because long-term, high dose treatment with levodopa is associated with motor complications, approaches to avoid such complications in early stage and to decrease complications in the advanced stage are recommended [1]. Meanwhile, negative effects of inappropriately delaying levodopa therapy have been noted [2, 3].

Although various clinical studies to prevent degeneration of dopaminergic neurons have been conducted, no drug with a proven protective action on dopamine neurons is currently available [4]. Existing monoamine oxidase-B (MAO-B) inhibitors such as selegiline were shown to have a potential disease-modifying effect in some clinical studies; [5-8] however, adequate evidence is not available.

Some *in vivo* and *in vitro* studies suggested that MAO-B inhibitors may reduce oxidative stress caused by aging and environmental neurotoxins and they may be involved in the induction of neurotrophic factors and in the regulation of anti-apoptotic factor expression [9-11]. Zonisamide has been shown to improve motor function in Parkinson's disease [12]. It is also a candidate drug for disease-modifying therapy because of its protective action on dopamine neurons shown in non-clinical studies [13-18].

Unified Parkinson's Disease Rating Scale (UPDRS), which is the validation tool for activities of daily living (ADL) and motor dysfunction, has been used for efficacy evaluation of anti-Parkinson drugs in previous studies. Progress of dopaminergic neuronal degeneration, the underlying cause of Parkinson's disease, has been used as a primary endpoint in few studies. We planned a multicenter, open-label, randomized controlled study to examine whether levodopa/decarboxylase inhibitor (DCI) combined with selegiline or zonisamide prevents dopaminergic neuronal degeneration more effectively in patients with early Parkinson's disease than levodopa/DCI alone. Specific binding ratio (SBR) of ^{123}Iodine-labelled N-(3-fluoropropyl) -2β-carbomethoxy-3β-(4-iodophenyl) nortropane ([^{123}I] FP-CIT) single-photon emission computed tomography (SPECT) (dopamine transporter SPECT, DAT-SPECT) was used as an indicator of dopaminergic neuron degeneration [19, 20].

Methods

Study objectives

Disease-modifying effect, effect on motor symptoms, and safety of levodopa/DCI in combination with selegiline or zonisamide will be evaluated in patients with Parkinson's disease who are currently treated with levodopa/DCI.

Study setting

Multicenter, prospective, randomized, parallel-group, open-label study.

Endpoints

The primary endpoint is the percent change of SBR of DAT-SPECT from the first evaluation to the final evaluation at 1 year. The first DAT-SPECT will be conducted between 14 and 42 days after randomization, and the second will be conducted between 365 and 393 days (Figure 1).

The method of SBR measurement is as follows: (1) [^{123}I] FP-CIT 167MBq (DaTSCAN; Nihon Medi-Physics, Tokyo, Japan) will be intravenously administered under a resting state with patient's eyes closed. (2) Continuous repetitive rotation acquisition will be performed for 20 to 30 min after 180 min of [^{123}I] FP-CIT administration. The scan range will be adjusted to cover the entire brain, including the vertex and cerebellum. (3) Reconstruction of DAT-SPECT will be performed in accordance with the method used by the institution. (4) Neither scatter correction nor attenuation correction will be performed. (5) SBR, the specific binding capacity of striatum, will be calculated using the SBR analysis software DaTView (Aze corporation, Kanagawa, Japan) [19, 20].

Secondary endpoints are the percent change of UPDRS Part II and Part III scores and Parkinson's Disease Questionnaire (PDQ)-39 scores from baseline to post-treatment. UPDRS is a widely-used standard for comprehensive evaluation of severity of Parkinson's disease. Assessment of mental state, ADL, motor function, and treatment-related complications is made on a scale of 5. UPDRS Part II and Part III will be used in this study. PDQ-39 is a Parkinson's disease-specific tool for quality of life assessment based on 8 aspects (mobility, ADL, emotional well-being, stigma, social support, cognitions, communication, and bodily discomfort).

Sample size

The primary objective of this study is to select a candidate arm to elucidate the additive effect of selegiline or zonisamide to levodopa/DCI. A screening design will therefore be used. When this study is conducted as a phase II randomized controlled study using a significance level α of 0.20 (one sided) to take into account indeterminate results, Bonferroni's multiple comparison adjustment will provide a p-value of 0.10 (0.20/2) in 2 inter-group comparisons with levodopa/DCI. By using the reported minimum SBR reduction rate in DAT-SPECT for levodopa/DCI alone (4%) [21], the reported maximum SBR reduction rate in combination therapy (7.5%), and standard deviation of 10% (common value), the minimum required sample size to make the power (1-β) 0.70 or higher will be 54. Expecting around 10% of participants to be ineligible or withdraw from the study, one treatment arm should include 60 patients (180 in total).

Eligibility criteria

Patients with early stage of Parkinson's disease (within 3 years of onset) will be eligible to participate in the study. Participants will be recruited from the Neurology experts of 13 general hospitals specialized in Parkinson's disease treatment.

Inclusion criteria

Patients with Parkinson's disease diagnosed based on the UK Brain Bank criteria and treated with levodopa/DCI at the participating institutions at the time of registration and those who fulfil the following inclusion criteria will be included in the study:

(1) Aged ≥55 and <80 at the time of registration

(2) Within 3 years of onset of motor symptoms

(3) Within 3 months after starting levodopa/DCI and having been treated with levodopa/DCI alone for at least 28 days immediately before starting the study treatment

(4) Receiving levodopa/DCI at a daily dose between 150 and 300 mg

(5) Mini-Mental State Examination score of 24 or higher

(6) Eligibility determined by the physician

(7) Capable of providing written consent to participate in this study

Exclusion criteria

Patients who meet any of the following criteria will be excluded from this study:

(1) Treated with drugs other than levodopa/DCI for Parkinson's disease for 1 month or longer

(2) Confirmed or possible pregnancy, breastfeeding

(3) Currently being treated with antidepressant(s) or antipsychotic(s)

(4) Past or current infarction or cerebrovascular disease in the basal ganglia

(not including asymptomatic lacunar infarction)

(5) History of epilepsy or currently under treatment for epilepsy

(6) Under treatment for alcohol poisoning

(7) Serious complication(s) (e.g., hepatic damage, renal damage, endocrine disease)

(8) Family history of Parkinson's disease

(9) Hypersensitivity to ^{123}I-ioflupane

Sampling and recruitment strategies

Potential study participants who consulted the participating institutions will be continuously sampled. The target sample size will be achieved because many patients with Parkinson's disease are treated at the participating institutions. The cost of DAT-SPECT is covered by research funds.

Randomization

Eligible patients with Parkinson's disease will be randomly assigned to three arms; (1) levodopa/DCI alone, (2) levodopa/DCI + selegiline, or (3) levodopa/DCI + zonisamide. The minimization method will be used for randomization. Institution and age will be the adjustment factors for medication assignment. The study dose will be levodopa/DCI 150–300 mg/day, selegiline 5 mg/day, and zonisamide 25 mg/day.

Data collection

The investigators will screen potential participants, provide information on this study to eligible patients based on the information documents, obtain written consent from them, and interview them to obtain demographic and background information. All primary and secondary outcome data will be collected at baseline and 1 year. All evaluations will be made when the motor symptoms are in "on" state. The participating patients will be instructed to avoid taking anti-Parkinson drugs other than the study drugs, and all the drugs known to affect DAT-SPECT (Figure 2). The subject will be withdrawn from the study when there is (1) the subject's request, (2) occurrence of severe adverse events, (3) worsening of the subject's medical condition, and (4) eligibility criteria violation. The Data Center (Clinical Study Support Center, Wakayama Medical University) is responsible for data management, central monitoring, and statistical analysis. The audit will be conducted by quality assurance room (Clinical Study Support Center, Wakayama Medical University) independently from investigators and the sponsor.

Statistics

Primary analysis and evaluation criteria

Percent change of SBR [(SBRpre – SBRpost)/SBRpre] will be calculated based on SBR of DAT-SPECT for the initial evaluation (SBRpre) and SBR at the time of final evaluation at 1 year (SBRpost) for each patient in the full analysis set. The one-sided alternative hypothesis "the reduction rate in the levodopa/DCI alone arm is higher than that in the levodopa/DCI + selegiline arm or the levodopa/DCI + zonisamide arm" will be tested against the null hypothesis "the mean reduction rate is comparable between the levodopa/DCI alone arm and levodopa/DCI + selegiline arm and between the levodopa/DCI alone arm and the levodopa/DCI + zonisamide arm" using the two-sample *t*-test. The Bonferroni adjustment will be used

while considering multiple comparisons. The combination therapy will be considered more effective than levodopa/DCI alone if p-value from the test is less than 0.10 and the reduction rate in the combination therapy arm is lower than that in the levodopa/DCI alone arm. If levodopa/DCI + selegiline and levodopa/DCI + zonisamide are both effective, the treatment arm with lower SBR reduction rate will be considered a candidate treatment.

Evaluation of primary endpoint

In addition to evaluation based on the primary analysis and evaluation criteria, 95% confidence interval (CI) for the sample mean of percent change of SBR and population mean will be calculated for each arm. Two-sample *t*-test will be performed for the mean percent change of SBR in the levodopa/DCI + selegiline arm and levodopa/DCI + zonisamide arm. A subgroup analysis will be performed to compare the patient background and adjustment factors for treatment assignment among the treatment arms. If a bias is found in the adjustment factors for treatment assignment or patient background ($p = 0.20$), a multiple regression analysis will be performed using the biased factor and the treatment arm (the levodopa/DCI alone group as control) as independent variables.

Evaluation of secondary efficacy endpoints

UPDRS scores and PDQ-39 scores will be compared between the levodopa/DCI alone arm and levodopa/DCI + selegiline arm and between the levodopa/DCI alone arm and levodopa/DCI + zonisamide arm using two-sample *t*-test with Bonferroni adjustment. 95% CI will be calculated for sample mean and population mean in each treatment arm.

Ethical consideration

autonomy, privacy, and confidentiality

The protocol of this study was approved by the Ethical Review Board of Wakayama Medical University in January 2016 and registered at the University Hospital Medical Information Network (UMIN) clinical trials registry in May 2016 (UMIN000022533). Potential participants will be provided thorough information on this study based on the information document to help them for making a decision about their participation in this study. Voluntary written consent for study participation will be obtained from them. Request for withdrawal of consent from participants will be accepted anytime. If any matters affecting the decision of participants to continue their participation in this study arise, the information document will be revised, the study participants will be provided study information based on the revised information document, and written consent to continue their participation will be obtained. Personal information will

be anonymized and maintained in a securely locked database. The protocol of this study will be carried out in accordance with the Declaration of Helsinki.

Risks and safety

Levodopa/DCI, selegiline, zonisamide, and ^{123}I-ioflupane to be used in this study are already in clinical use. The study dosage will be within the scope of the approved clinical dosage; therefore, the treatment will be highly safe. However, the participants will be exposed to low-dose radiation more frequently than regular clinical practice because of DAT-SPECT that will be performed twice within a year. The candidate participants will be thoroughly informed of the additional irradiation.

Discussion

This will be the first randomized controlled study to examine whether selegiline or zonisamide has a disease-modifying effect in patients with Parkinson's disease as the primary endpoint. If the drug(s) is/are shown to have a disease-modifying effect in clinical and neuroradiological aspects, this study will provide significant evidence that selegiline and zonisamide can delay clinical course of Parkinson's disease. Specifically, the use of the above drug(s) in patients with early Parkinson's disease may be recommended to increase treatment options. A larger-scale phase III study and a study on long-term prevention of progression of clinical symptoms may be conducted using either of the drugs with a higher disease-modifying effect and the same methods as those in this study.

One of the limitations of this study will be the short observation period of 1 year that may not allow detection of disease-modifying effect or long-term efficacy even if a disease-modifying effect is detected. A separate larger-scale, longer clinical trial or extension study will be necessary. Another limitation will be the inclusion of patients with motor symptoms that initially occurred in past 3 years to ensure an adequate sample size, because enrollment of a relatively large number of patients will be necessary to reproduce the results of SPECT imaging. In Parkinson's disease, more than a half of dopaminergic neurons in the substantia nigra are already degenerated at the onset of motor symptoms, and the rate of cell loss may become lower as the disease progresses [22]. Therefore, the detection of intergroup differences may be difficult. The study participants should be in early stage of Parkinson's disease to increase the detection rate for demonstrating the disease-modifying effect. An interventional study at an earlier stage may be possible if Parkinson's disease can be diagnosed at the prodromal phase in the future. Lastly, there may be data variations because of different imaging devices used for DAT-SPECT at multiple institutions participating in this study. However, it may not be a significant problem because each patient will undergo DAT-SPECT under the same condition at the same institution before and after taking the study drugs to evaluate the percentage reduction of SBR.

Abbreviations

ADL: activities of daily living

CI: confidence interval

DAT: dopamine transporter

DCI: decarboxylase inhibitor

MAO-B: monoamine oxidase-B

PDQ: Parkinson's Disease Questionnaire

SBR: Specific binding ratio

SPECT: single-photon emission computed tomography

UPDRS: Unified Parkinson’s Disease Rating Scale

Declarations

- Trial Status

The latest protocol is version 4.1 revised on April 5th, 2018.

The patient registration started in June 2016. The recruitment will be completed by December 31th, 2019. This study will be completed in December 2020.

*Ethics approval and consent to participate

The protocol of this study was approved by the Ethical Review Board of Wakayama Medical University in January 2016. Protocol amendments will be also approved by the Ethical Review Board of Wakayama Medical University, and notify to each facility as soon as possible.

The study has gained ethical approval at both central and local levels. Central ethical approval has been confirmed from the Ethical Review Board of Wakayama Medical University (ref approval no. 1731) and we will not begin recruiting at other centers in the trial until local ethical approval has been obtained.

Informed consent will be obtained from all study participants.

- Consent for publication

Potential participants will be provided thorough information on this study based on the information document to help them take a decision about their participation in this study. Voluntary written consent for study participation will be obtained from them. Request for withdrawal of consent from participants will be accepted anytime. If any matters affecting the decision of participants to continue their participation in this study arise, the information document will be revised, the study participants will be provided study information based on the revised information document, and written consent to continue their participation will be obtained.

- Availability of data and material

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

- Competing interests

The authors declare that they have no competing interests.

- Funding

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- Authors' contributions

MT devised the study. HI and MT designed and supervise all aspects of the study implementation. HI, JK, TS, TH, YKto, SK, RK, KN, AO, TS, TT, and MT conceived the study design. JK, TH, YKto, SK, YKya, RK, KN, AO, HS, TS, HY, MI, TT, and MT collected clinical data. Statistical analysis was performed by TS. HI, JK, TS and MT wrote the manuscript. All authors made contributions in revising the content, read, and approved the final manuscript. The results of this study will be published in peer-reviewed journals. Authorship eligibility guidelines will be adhering the International Committee of Medical Journal Editors (ICMJE) guidelines.

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Figures

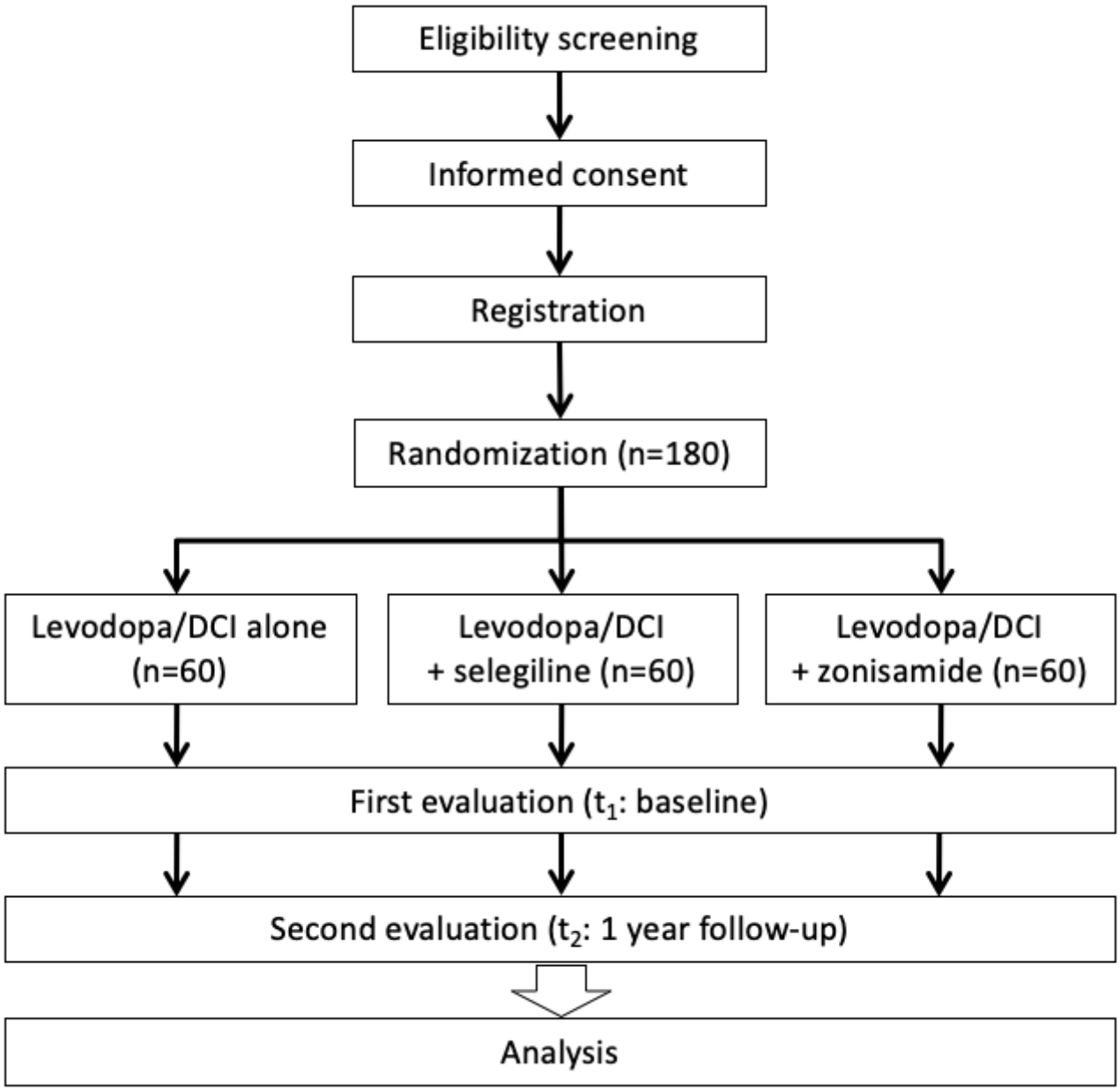

Figure 1

Trial flow diagram.

	STUDY PERIOD				
	Enrollment	Allocation	Post-allocation		Close-out
TIMEPOINT*	***Day -42 to 0***	**0**	t_1	t_2	t_x
ENROLLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS:					
Levodopa/DCI alone		◆—	—	—◆	
Levodopa/DCI +selegiline		◆—	—	—◆	
Levodopa/DCI +zonisamide		◆—	—	—◆	
ASSESSMENTS:					
Demographics**	X				
DAT-SPECT†			X	X	
UPDRS†			X	X	
PDQ-39†			X	X	
Adverse events‡		◆—	—	—	—◆

Figure 2

Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline * t1: first evaluation (day 14 to 42); t2: second evaluation (day 365 to 393). **Demographics includes age, height, weight, past disorders, and complications. †UPDRS and PDQ-39 assessment should be performed within 7 days before or after DAT-SPECT. DAT-SPECT, UPDRS and PDQ-39 assessment should be performed within 14 days of withdrawal to the extent possible. ‡Information on adverse events that occurred within

7 days after DAT-SPECT should be collected. DAT: dopamine transporter, SPECT: single-photon emission computed tomography, PDQ: Parkinson's Disease Questionnaire, UPDRS: Unified Parkinson's Disease Rating Scale.

Supplementary Files

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- supplement1.doc