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Long-term donepezil use for dementia with Lewy bodies: results from an open-label extension of Phase III trial

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Abstract

Introduction: The long-term efficacy and safety of donepezil 10 mg in patients with dementia with Lewy bodies (DLB) were investigated in a 52-week Phase 3 trial.

Methods: This 52-week study consisted of 16-week randomized placebo-controlled (RCT) and 36-week open-label extension phases. Of 142 DLB patients enrolled in the RCT phase (three arms: placebo, 5 mg, and 10 mg), 110 entered the extension phase. The placebo group of the RCT phase initiated active treatment at week 16, and the active groups maintained allocated treatment and dosages until week 24. After week 24, all patients received 10 mg. Dose reduction to 5 mg for safety concerns was allowed. Efficacy measures included Mini-Mental State Examination (MMSE) for cognitive function and Neuropsychiatric Inventory (NPI) for behavioral symptoms. Safety evaluations included adverse events (AEs) and the unified Parkinson disease rating scale.

Results: In total, 100 subjects completed the study. Cognitive function improvement was sustained for 52 weeks (MMSE at week 52 in 10 mg: 2.8 ± 3.5 (mean \pm standard deviation); $P < 0.001$, Student-paired t test). Those who received placebo in the RCT phase showed an improvement after starting active treatment. NPI improved in all the groups throughout the study, including the placebo period. In the subgroup of the 5 mg group without remarkable cognitive or behavioral improvement at week 24, further improvement was observed after a dose increase to 10 mg. After week 24, 21 patients experienced dose reduction. The incidence of any AEs did not increase over time.

Conclusions: The long-term administration of donepezil at 10 mg/day improved cognitive function for up to 52 weeks in patients with DLB without increasing the risk of clinically significant safety events.

Trial registration: NCT01278407. Trial registration date: January 14, 2011.

Introduction

Dementia with Lewy bodies (DLB) is a common form of dementia in the elderly, and constitutes the second largest group of patients with dementia, following Alzheimer disease (AD) [1]. The core clinical features of DLB include neuropsychiatric symptoms and parkinsonism, as well as cognitive impairment characterized by deficits of attention, executive function, and visual perception [2]. The progression of cognitive impairment is faster than or similar to that in AD [3-6]. Patients with DLB have a higher risk for falls [7,8], higher risk of admission [9],

lower activities of daily living, lower quality of life, and a heavier caregiver burden [10-13], compared with those with AD.

Cholinergic neurotransmission is more defective in patients with DLB than in those with AD [14]. Although cholinergic losses in DLB affect both brainstem and basal forebrain presynaptic nuclei, postsynaptic cortical muscarinic and nicotinic receptors are preserved [15]. For these reasons, cholinesterase inhibitors (ChEIs) may be effective for treating DLB, and several clinical trials have demonstrated favorable potential of ChEIs such as galantamine, rivastigmine, and donepezil for DLB [16-22].

The previous Phase 2, 12-week, randomized double-blind placebo-controlled trial of three different doses of donepezil in patients with DLB [22] demonstrated that

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donepezil significantly improved all of the efficacy endpoints of cognitive impairment, behavioral and psychiatric symptoms, global clinical symptoms, and caregiver burden, compared with placebo, and the open-label 1-year extension study of donepezil at 5 mg/day [23] showed that the major concerns about the safety of long-term administration of 5 mg donepezil, including parkinsonism and cardiovascular events, were minimal, and that the mild improvement of cognitive impairment and psychiatric symptoms was sustained for up to 52 weeks.

Based on these results, a Phase 3 study, which integrated a randomized placebo-controlled, double-blind comparative study (RCT phase) and an open-label extension study (extension phase), was conducted in patients with DLB to confirm the superiority of donepezil at 5 and 10 mg/day for 12 weeks over placebo and to evaluate the safety and efficacy of long-term administration of 10 mg/day. The RCT phase yielded the efficacy of donepezil on cognitive impairment with significant improvement in MMSE compared with placebo in the 10 mg group (mean \pm standard deviation (SD): 0.6 ± 3.0 and 2.2 ± 2.9 in the placebo and 10 mg group, respectively; $P = 0.016$, analysis of covariance (ANCOVA)), although a significant difference was not detected on the behavioral and neuropsychiatric measures (change in Neuropsychiatric Inventory-2 (NPI-2) (mean \pm SD): -2.0 ± 4.2 and -2.9 ± 4.7 in the placebo and 10 mg group, respectively; $P = 0.391$, ANCOVA), falling short of confirming the pre-defined superiority of donepezil compared with placebo at either dose (5 or 10 mg/day). With detailed information of the results reported elsewhere [24], this report describes the results obtained through long-term administration of the higher dose of donepezil in DLB.

Methods

Patients

Patients diagnosed as probable DLB, according to the consensus diagnostic criteria [2], were recruited from 72 psychiatric or neurologic specialty centers throughout Japan from February 2011 to March 2012. Eligible patients were outpatients aged ≥ 50 years with mild to moderately severe dementia (10 to 26 on the MMSE and Clinical Dementia Rating ≥ 0.5) and behavioral and psychiatric symptoms NPI-plus ≥ 8 and NPI-2 ≥ 1). NPI-plus consisted of 12 items: original 10 items [25,26], sleep, and cognitive fluctuation, which was reported as Cognitive Fluctuation Inventory [27]. NPI-2 consisted of hallucinations and cognitive fluctuation [22]. Caregivers of the eligible patients had to stay with them routinely at least 3 days per week and 4 hours per day, provide information for this study, assist with the compliance with treatment, and escort them to required visits. The evidence or rationale for the presence of the core features, on which

each diagnosis of DLB was based, was provided and examined by the review board (Mori, Ikeda, and Kosaka) to assure the validity of the diagnosis.

Exclusion criteria included Parkinson disease diagnosed at least 1 year prior to the onset of dementia; focal vascular lesions on MRI or CT that might cause cognitive impairment (for example, infarcts/hemorrhages affecting the thalamus, caudate nucleus, or globus pallidus, single infarct of diameter ≥ 1.5 cm or multiple infarcts in any other regions, and moderate or severe white matter changes); other neurologic or psychiatric diseases; clinically significant systemic disease; complications or history of severe gastrointestinal ulcer, severe asthma or obstructive pulmonary disease; systolic hypotension (< 90 mm Hg); bradycardia (< 50 m^{-1}); sick sinus syndrome; atrial or atrioventricular conduction block; QT-interval prolongation (≥ 450 ms); hypersensitivity to donepezil or piperidine derivatives; severe parkinsonism (Hoehn and Yahr score \geq IV) [28]; and treatment with ChEIs or any investigational drug within 3 months before screening. ChEIs, antipsychotics, and anti-Parkinson drugs other than L-dopa or dopamine agonists were not allowed during the study.

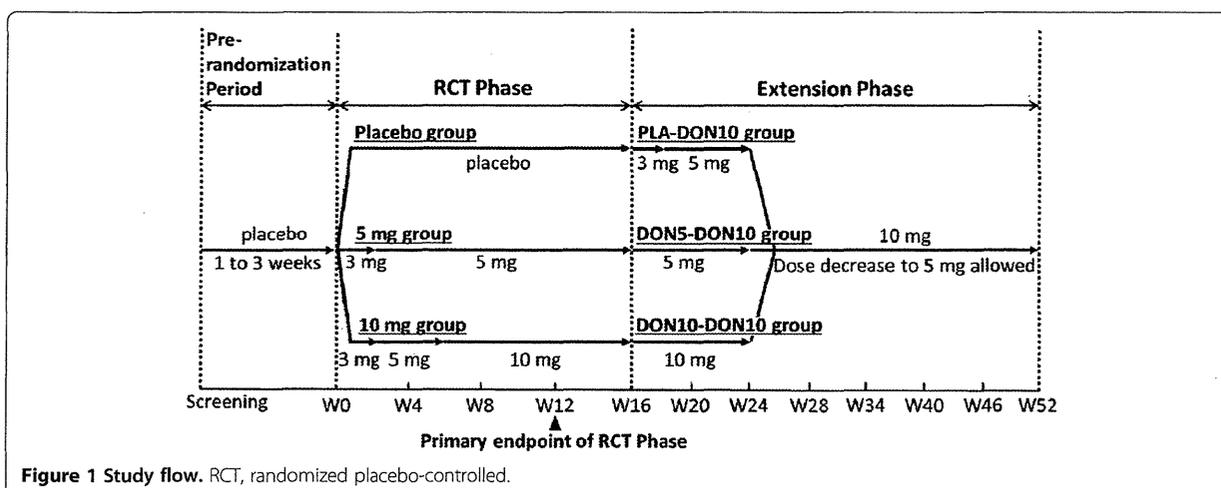
Procedures

This was a 52-week, multicenter, Phase 3 study consisting of a 16-week, randomized, double-blind, placebo-controlled phase (referred as RCT phase) and the subsequent 36-week, open-label extension phase (referred as extension phase) (Figure 1).

After a 2-week prerandomization period with placebo administration, the patients were randomly assigned in a 1:1:1 ratio to placebo or 5 mg or 10 mg of donepezil in the RCT phase. Treatment began with 3 mg and was then titrated. After the RCT phase (ended before Week 16), the dose was maintained until Week 52 in the 10 mg group of the RCT phase (referred to as DON10-DON10). In the 5 mg group of the RCT phase, the dose was increased to 10 mg/day at Week 24 (referred to as DON5-DON10). The placebo group started active treatment with 3 mg at the beginning of the extension phase (at Week 16), and the dose was then increased to 5 mg at Week 18 and to 10 mg at Week 24 (referred to as PLA-DON10). After Week 24, dose reduction to 5 mg was allowed if continuation at 10 mg caused any safety concerns.

The randomization code was broken in August 2012 after all data of the RCT phase were fixed before the end of the extension phase (March 2013). The physicians and patients were kept blinded to the treatment allocation until the extension phase completion by blinded titration by using a similar placebo.

Written informed consent was obtained from the patient (if at all possible) and his/her primary caregiving family member before initiating the study procedures. The study was conducted in accordance with the principles of



the Declaration of Helsinki. The protocol was approved by the institutional review board at each center (see Additional file 1).

Outcome measures

Cognitive function was assessed by using the MMSE [29]. Behavioral and psychiatric symptoms were assessed by using the NPI-2 [22] and NPI-10 [25,27]. NPI-2 was calculated as the sum of the scores for hallucinations and cognitive fluctuation [26], which correspond to the core features of DLB in the consensus criteria. These measures were assessed at Weeks 0, 4, 8, 12, 16, 20, 24, 28, 34, 40, 46, and 52. Caregiver burden was assessed by using the Zarit Caregiver Burden Interview (ZBI) [30], which evaluates the physical, psychological, and social consequences of caring activities. The ZBI contains 22 items scored from 0 (best) to 4 (worst), from which a total score of 0 to 88 is calculated. The ZBI was assessed at 0, 12, 24, 40, and 52 weeks.

Safety was assessed based on the adverse events (AEs), vital signs, electrocardiogram, and laboratory tests. All AEs were classified and coded according to Medical Dictionary for Regulatory Activities (MedDRA) terms. Gastrointestinal symptoms, parkinsonian symptoms, psychiatric symptoms, and arrhythmia were assessed as AEs of interest. Motor function was assessed as a safety measure by using the Unified Parkinson's Disease Rating Scale (UPDRS) part III [31].

Statistical analyses

Sample-size calculation is reported elsewhere [24]. The safety analysis set (SAS) comprised all patients who received at least one dose of donepezil and had safety-assessment data. The incidence of AEs was summarized based on the treatment period with the active drug; safety analysis in the DON5-DON10, DON10-DON10 groups, and the combined group of them (referred to

as DON-DON10) encompasses the entire study period, including the RCT phase (52 weeks), and that in the PLA-DON10 group covers the extension phase alone (36 weeks). Laboratory parameters and vital signs were summarized by descriptive statistics. Scores or their changes in UPDRS part III from the baseline in each of the DON5-DON10 and DON10-DON10 groups or in the DON-DON10 group were analyzed by using Student paired *t* test.

Efficacy was analyzed in the full analysis set (FAS), including the randomized patients who received the study drug at least once and had valid efficacy assessment data at more than one point. Exploratory analyses were performed as appropriate to compare scores at every evaluation point in each of the three groups with the baseline (Week 0) by paired *t* tests, and in the DON5-DON10 group, also to compare scores at every evaluation point with Week 24 to evaluate the effect of dose increment by paired *t* tests and mixed-effect model for repeated measures (MMRMs). The parameters included in the model were the Observed value at week 24 as a covariate, and Subgroup stratified according to the degree of improvement, Visit, and Interaction as factors. Values at the final evaluation were imputed by using a last observation carried forward (LOCF) method.

P values were not adjusted for multiplicity. All statistical tests were two-tailed, and $P < 0.05$ was considered to indicate statistical significance. All analyses were made on SAS versions 9.1 and 9.2 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics

Of 161 patients enrolled in the pre-randomization period, 142 were enrolled in the RCT phase and randomized to the placebo, 5 mg, and 10 mg groups (46, 47, and 49 patients, respectively). During the RCT phase (by Week 16), 32 patients were discontinued (9, 17, and 6 patients in the

placebo, 5 mg, and 10 mg groups, respectively). The reasons for the discontinuations were AEs (17 patients), patient's request (11 patients), and other reasons (4 patients). In the placebo group, 37 patients started active treatment at Week 16. During the extension phase, 10 patients were discontinued (3, 4, and 3 patients in the PLA-DON10, DON5-DON10, and DON10-DON10 groups, respectively) because of AEs (6 patients) and patient's request (4 patients) (Figure 2).

Demographic and baseline characteristics of the FAS are summarized in Table 1. No characteristic differences occurred between the three groups. Females accounted for 58.0%. The mean age was 77.9 (range, 57 to 95) years; all but 2 patients were 65 years or older. Dementia medication had previously been used by only 5.8% of the patients. The mean score of the MMSE at baseline was 20.4 points.

Cognitive function

Changes in MMSE are shown in Figure 3. Significant improvement compared with baseline was observed from Weeks 8 to 52 in the DON5-DON10 group, and from Week 4 to 52 in the DON10-DON10 group. The mean changes (mean \pm SD, Student paired *t* test) at Week 52 and at the final evaluation (LOCF) from baseline were 2.5 ± 3.1 ($P < 0.001$) and 1.3 ± 3.6 ($P = 0.018$) in the

DON5-DON10 group, 2.8 ± 3.5 and 2.4 ± 3.7 ($P < 0.001$ each) in the DON10-DON10 group, respectively.

In the DON5-DON10 group, MMSE increased by 0.4 to 1.1 points at Week 28 to 52 compared with that before the dose increase at Week 24, although it was not significant (Student paired *t* test). For further exploration of this result, changes in MMSE by the subgroups with and without MMSE improvement of 3 points or more from baseline at Week 24 (cognitively improved and less improved by 5 mg) were calculated (Figure 4). Using MMRM for the observed value at or after Week 24, the effect of dose increment was found significant (subgroup, visit, and interaction were $P = 0.018$, $P = 0.328$, and $P = 0.047$, respectively). In the subgroup of less-improved, MMSE significantly increased after dose increment (mean changes from Week 24 with SD (Student paired *t* test) at Weeks 28, 34, 46, and 52: 2.2 ± 3.1 ($P = 0.019$), 2.6 ± 3.2 ($P = 0.011$), 2.0 ± 2.4 ($P = 0.013$), and 1.8 ± 2.2 ($P = 0.019$), respectively).

The PLA-DON10 group showed significant improvement from the baseline (Week 0) through the period after starting active drug at Week 16; the mean changes at Week 28 or later were similar to those in the DON5-DON10 and DON10-DON10 groups, in which treatment with active drugs was started earlier.

In 18 patients whose dose was reduced from 10 mg to 5 mg because of adverse events (9, 4, and 5 patients in

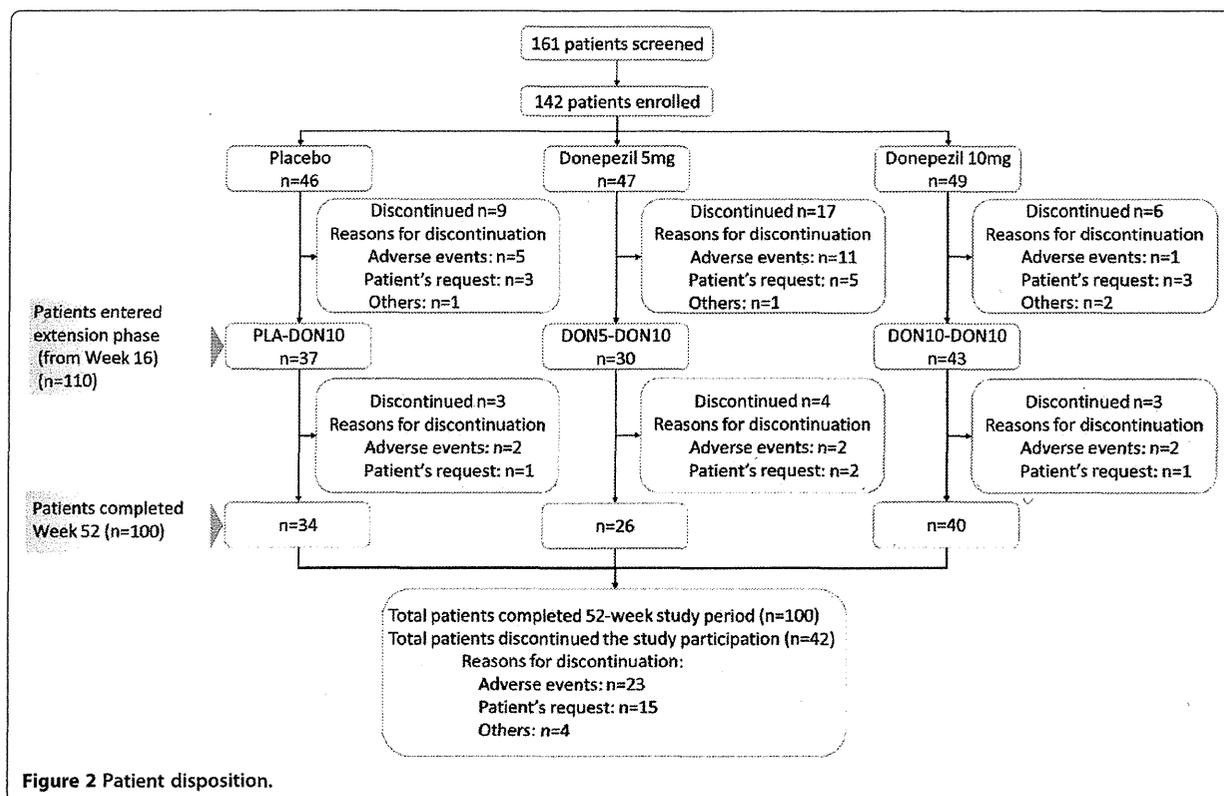
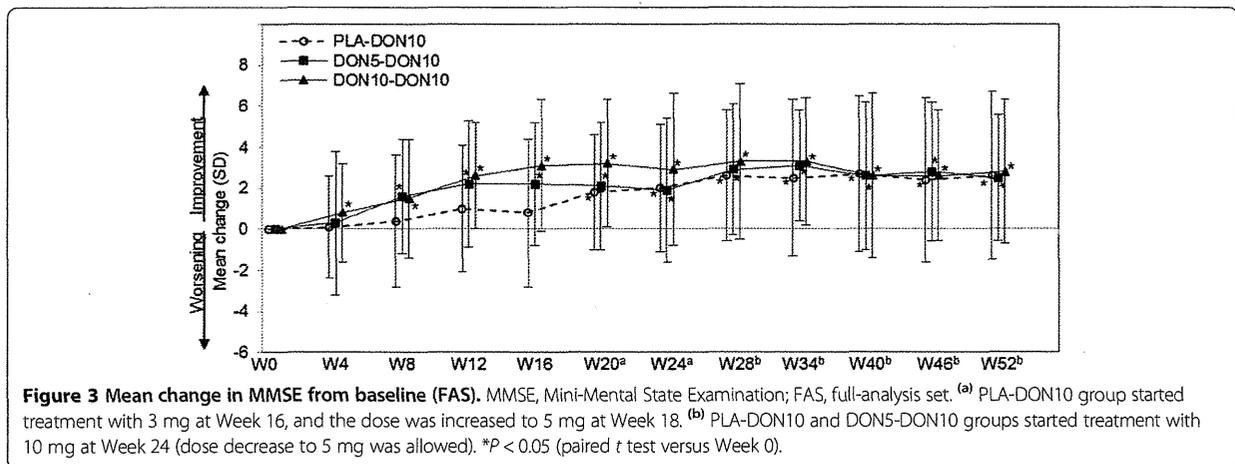
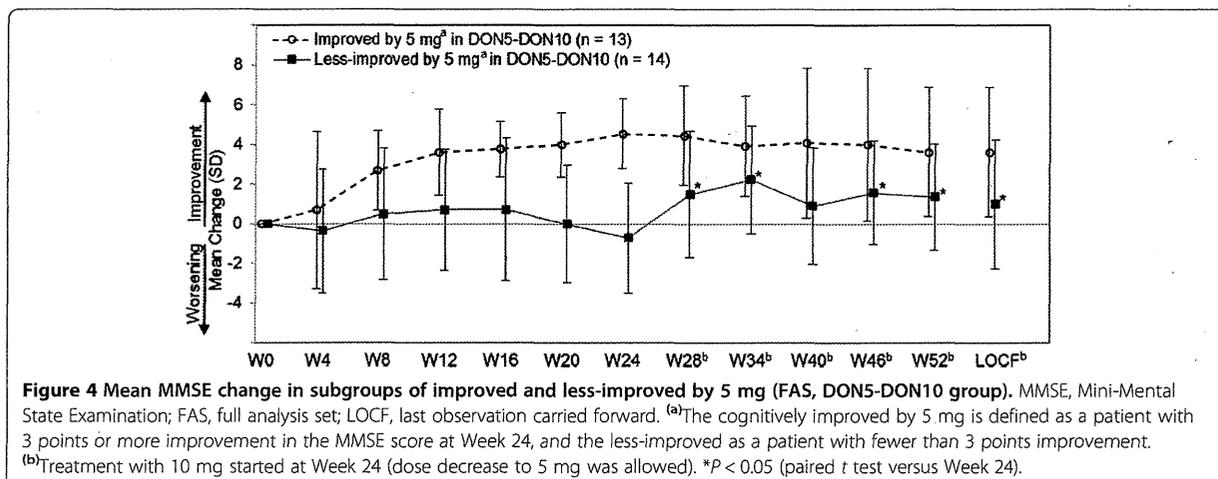


Table 1 Patient demographics and baseline characteristics (FAS)

	PLA-DON10 (n = 37)	DON5-DON10 (n = 45)	DON10-DON10 (n = 49)	DON-DON10 (n = 94)
Sex, number (%)				
Male	14 (37.8)	20 (44.4)	21 (42.9)	41 (43.6)
Female	23 (62.2)	25 (55.6)	28 (57.1)	53 (56.4)
Age, years	76.7 ± 6.0	78.8 ± 5.1	77.7 ± 6.8	78.2 ± 6.1
Weight, kg	51.52 ± 10.68	50.68 ± 9.24	51.72 ± 9.89	51.22 ± 9.55
Duration of dementia, years	2.1 ± 2.4	2.7 ± 1.8	2.3 ± 1.9	2.5 ± 1.9
History of antedementia medication, number (%)				
Yes	1 (2.7)	3 (6.7)	4 (8.2)	7 (7.4)
No	36 (97.3)	42 (93.3)	45 (91.8)	87 (92.6)
Visual hallucinations, number (%)				
Yes	37 (100.0)	39 (86.7)	39 (79.6)	78 (83.0)
No	0	6 (13.3)	10 (20.4)	16 (17.0)
Cognitive fluctuation, number (%)				
Yes	34 (91.9)	41 (91.1)	46 (93.9)	87 (92.6)
No	3 (8.1)	4 (8.9)	3 (6.1)	7 (7.4)
Parkinsonism, number (%)				
Yes	32 (86.5)	39 (86.7)	44 (89.8)	83 (88.3)
No	5 (13.5)	6 (13.3)	5 (10.2)	11 (11.7)
Hoehn & Yahr, number (%)				
I	4 (10.8)	8 (17.8)	7 (14.3)	15 (16.0)
II	15 (40.5)	17 (37.8)	19 (38.8)	36 (38.3)
III	13 (35.1)	14 (31.1)	18 (36.7)	32 (34.0)
MMSE	20.2 ± 4.3	20.6 ± 4.1	20.3 ± 4.8	20.4 ± 4.4
NPI-2	6.9 ± 3.9	6.9 ± 4.5	7.3 ± 4.7	7.1 ± 4.6
NPI-10	19.1 ± 13.5	18.9 ± 15.3	16.6 ± 11.7	17.7 ± 13.5
ZBI	26.0 ± 15.4	28.3 ± 18.5	31.4 ± 17.8	29.9 ± 18.1

FAS, full analysis set, MMSE, Mini-Mental State Examination, NPI: Neuropsychiatric Inventory, ZBI: Zarit Caregiver Burden Interview. Values are expressed as mean ± SD, unless otherwise specified.





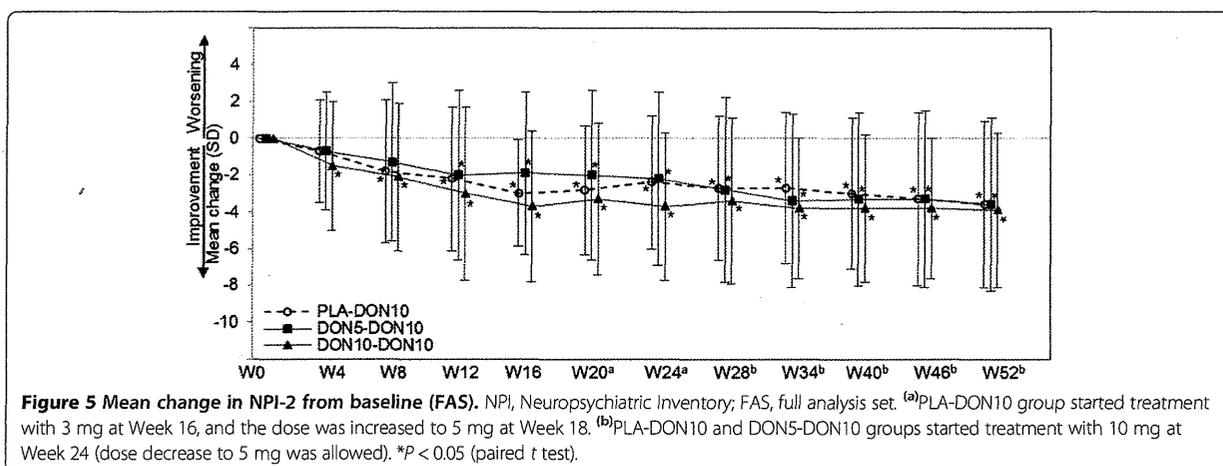
the PLA-DON10, DON5-DON10, and DON10-DON10 groups), the change in MMSE from the last administration of the 10 mg was calculated. The changes (mean ± SD) at 6, 12, 18, and 24 weeks after the dose reduction were 0.7 ± 3.0, 0.5 ± 3.5, -0.5 ± 3.6, and -0.7 ± 3.9, respectively; the score was still above the baseline at 24 weeks after the dose reduction (mean change from the baseline, 1.0 ± 3.8).

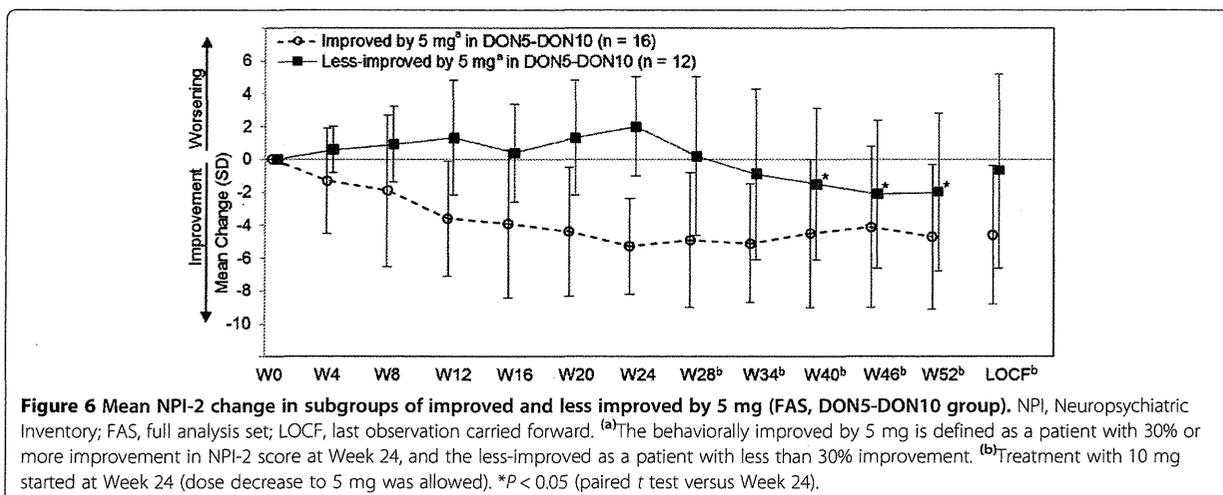
Behavioral and neuropsychiatric symptoms

NPI-2 significantly improved compared with baseline from Weeks 12 to 52 in the DON5-DON10, and from Weeks 4 to 52 in the DON10-DON10 groups (Figure 5). The mean changes (mean ± SD, Student paired *t* test) at Week 52 and at the final evaluation (LOCF) from baseline were -3.6 ± 4.7 (*P* < 0.001) and -2.1 ± 4.8 (*P* = 0.005) in the DON5-DON10 group, and -3.9 ± 4.2 and -3.4 ± 4.4 (*P* < 0.001 each) in the DON10-DON10 group, respectively. The PLA-DON10 group also showed a

sustained reduction in the score from the RCT phase under placebo administration through the extension phase.

In the DON5-DON10 group, NPI-2 decreased by 0.6 to 1.0 points at Weeks 28 to 52 compared with that before the dose increase at Week 24, although it was not significant (Student paired *t* test). Changes in NPI-2 by the subgroups with and without NPI-2 improvement of 30% or more from baseline at Week 24 (behaviorally improved and less improved by 5 mg) are shown in Figure 6. As the result of an MMRM for observed value at or after Week 24 with observed value at week 24 as a covariate, and with subgroup, visit and interaction as factors, the factor of interaction were significant (*P* < 0.001) and the factors of subgroup and visit were not significant (*P* = 0.282, *P* = 0.199). In the subgroups of less-improved, NPI-2 significantly decreased after dose increment (mean changes from Week 24 with SD (Student paired *t* test) at Weeks 40, 46, and 52: -3.2 ± 4.0 (*P* = 0.033), -3.8 ± 4.9 (*P* = 0.035), and -3.7 ± 4.9 (*P* = 0.042), respectively).





Significant improvement in NPI-10 compared with baseline was observed from Weeks 34 to 52 in the DON5-DON10 group, and from Weeks 4 to 52 in the DON10-DON10 group, with the largest changes (mean ± SD) at Week 40 (−8.8 ± 14.9) in the DON5-DON10 group, and Week 16 (−7.3 ± 7.2) in the DON10-DON10 group. The PLA-DON10 group also showed a sustained score decrease from baseline for 52 weeks.

Caregiver burden

Changes in ZBI scores from baseline in each of the PLA-DON10, DON5-DON10, and DON10-DON10 groups are shown in Figure 7. The improvement was significant at Week 40 in the DON5-DON10 group, but not at any points in the PLA-DON10 and DON10-DON10 groups.

Safety

AEs were reported by 93.8% (90 of 96) in the DON-DON10 group throughout the 52-week study period and by 89.2% (33 of 37) in the PLA-DON10 group during 36

weeks of the extension phase. Sixteen patients reported 23 serious AEs. Of these, 2 patients died because of asphyxia (PLA-DON10) or pneumonia (DON5-DON10) while receiving 10 mg, but a causal relation with the study drug was ruled out.

The incidence of AEs reported by more than 5% of the DON-DON10 group is shown in Table 2 (by 12-week intervals and total period). Major AEs with high incidence were nasopharyngitis (17.7% (17 of 96)) and parkinsonism (12.5% (12 of 96)). Treatment-related AE reported by more than 5% was only parkinsonism (10.4% (10 of 96)). All the treatment-related AEs were mild or moderate, except for 5 events (insomnia, visual hallucinations, irritability, agitation, and paranoia) reported by 2 patients in the DON5-DON10 group. The incidence of no AEs increased over time. AEs reported by the PLA-DON10 group showed a similar trend as the DON-DON10 group (Table 3).

Gastrointestinal events were reported by 31.3% (30 of 96) in the DON-DON10 group. The events reported by more

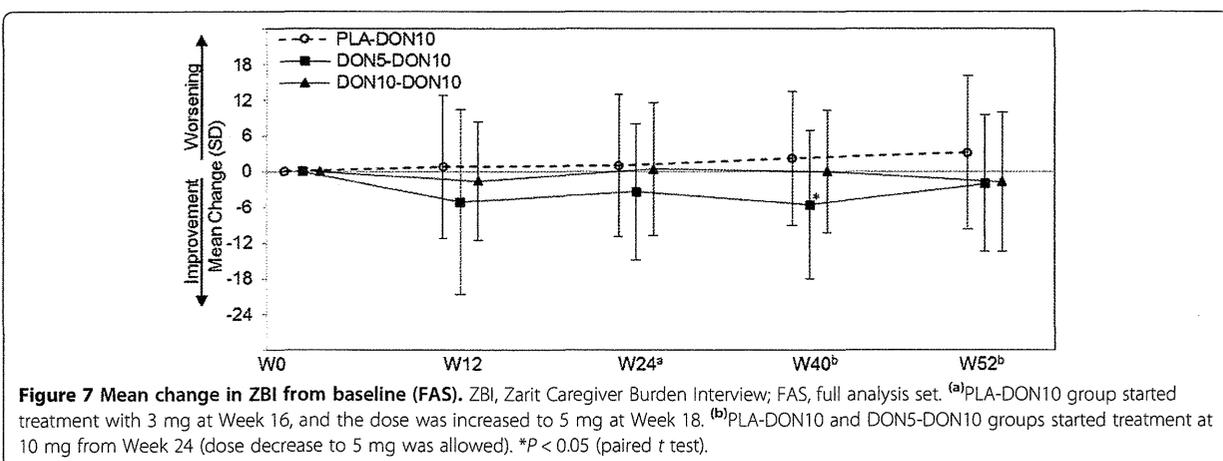


Table 2 Incidence of adverse events reported by more than 5% in the DON-DON10 group over time (SAS)

AE	DON-DON10 group (DON5-DON10 ^a and DON10-DON10)					Treatment-related AE ^b
	AE					
	Week 1–12 (n = 96)	>Week 12–24 (n = 75)	>Week 24–36 (n = 72)	>Week 36 (n = 69)	52 weeks (n = 96) n (%)	52 weeks (n = 96) n (%)
Total number of incidents	65	15	7	3	90 (93.8)	46 (47.9)
Constipation	0	2	0	3	5 (5.2)	2 (2.1)
Diarrhea	2	1	1	2	6 (6.3)	1 (1.0)
Nausea	4	1	0	0	5 (5.2)	3 (3.1)
Nasopharyngitis	6	4	4	3	17 (17.7)	0
Contusion	1	2	1	3	7 (7.3)	0
Blood creatine phosphokinase increased	2	1	0	2	5 (5.2)	0
Glucose urine present	2	2	1	0	5 (5.2)	0
Decreased appetite	5	1	0	0	6 (6.3)	4 (4.2)
Muscle spasms	3	2	0	0	5 (5.2)	1 (1.0)
Parkinsonism	6	1	3	2	12 (12.5)	10 (10.4)
Insomnia	2	2	2	0	6 (6.3)	4 (4.2)

SAS, safety analysis set; AE, adverse event.

^aTreatment with 10 mg started from Week 24.^bAEs for which a causal relation with the study drug was considered possible or probable.

than 5% were diarrhea, decreased appetite (6.3% (6 of 96) each), constipation, and nausea (5.2% (5 of 96) each). All the gastrointestinal events but ileus in 1 patient (DON5-DON10, while receiving 10 mg) were mild or moderate (Table 4). In the PLA-DON10, the incidence rate was 32.4% (12 of 37). Constipation, diarrhea (8.1% (3 of 37) each), abdominal pain upper, dyspepsia, gastritis, nausea, and decreased appetite (all 5.4% (2 of 37) each) were reported by more than 5%. All these events were mild or moderate. Analyzed by 2-week intervals, the incidence rate was the highest (22.2% (8 of 36)) in the interval from Weeks 24 to 26 subsequent to the dose increase to 10 mg.

Parkinsonian symptoms were reported by 12.5% (12 of 96) in the DON-DON10 group; parkinsonism (12.5% (12 of 96)) and camptocormia (1.0% (1 of 96)) were reported (Table 5). In the PLA-DON10 group (13.5% (5 of 37)), parkinsonism (8.1% (3 of 37)), akinesia, and tremor (2.7% (1 of 37) each) were reported. None of the reported parkinsonian symptoms were severe or serious. Six events led to discontinuation or dose reduction in these patients, but all of them were recovered or relieved. UPDRS part III did not significantly increase from the baseline in any groups (Table 6). In the DON5-DON10 group, the score significantly improved throughout the study.

Table 3 Incidence of adverse events reported by more than 3 patients in the PLA-DON10 group over time (SAS)

AE	PLA-DON10 group ^a				Treatment-related AE ^b
	AE				
	Week 16–28 (n = 37)	Week 28–40 (n = 36)	Week >40 (n = 34)	36 weeks (n = 37) n (%)	36 weeks (n = 37) n (%)
Total number of incidents	26	7	0	33 (89.2)	22 (59.5)
Constipation	3	0	0	3 (8.1)	1 (2.7)
Diarrhea	3	0	0	3 (8.1)	2 (5.4)
Nasopharyngitis	6	3	4	13 (35.1)	0
Dizziness	3	0	0	3 (8.1)	2 (5.4)
Parkinsonism	2	1	0	3 (8.1)	3 (8.1)

SAS, safety analysis set; AE, adverse event.

^aTreatment with 3 mg started at Week 16, and the dose was increased to 5 mg at Week 18 and to 10 mg at Week 24.^bAEs for which a causal relation with the study drug was considered possible or probable.

Table 4 Incidence of gastrointestinal events^a (SAS)

AE ^a	PLA-DON10 (n =37)	DON5-DON10 (n =47)	DON10-DON10 (n =49)	DON-DON10 ^b (n =96)
Subjects with any gastrointestinal events, number (%)	12 (32.4)	15 (31.9)	15 (30.6)	30 (31.3)
Abdominal discomfort	0	1 (2.1)	1 (2.0)	2 (2.1)
Abdominal pain	0	2 (4.3)	0	2 (2.1)
Abdominal pain upper	2 (5.4)	0	0	0
Constipation	3 (8.1)	1 (2.1)	4 (8.2)	5 (5.2)
Diarrhea	3 (8.1)	2 (4.3)	4 (8.2)	6 (6.3)
Dyspepsia	2 (5.4)	0	0	0
Epigastric discomfort	1 (2.7)	0	0	0
Fecal incontinence	0	1 (2.1)	0	1 (1.0)
Functional gastrointestinal disorder	0	0	1 (2.0)	1 (1.0)
Gastric ulcer	0	0	1 (2.0)	1 (1.0)
Gastritis	2 (5.4)	1 (2.1)	0	1 (1.0)
Gastrointestinal disorder	0	0	1 (2.0)	1 (1.0)
Gastroesophageal reflux disease	0	2 (4.3)	1 (2.0)	3 (3.1)
Intestinal obstruction	0	1 (2.1)	0	1 (1.0)
Nausea	2 (5.4)	3 (6.4)	2 (4.1)	5 (5.2)
Proctalgia	0	1 (2.1)	0	1 (1.0)
Vomiting	1 (2.7)	1 (2.1)	1 (2.0)	2 (2.1)
Gastroenteritis	0	1 (2.1)	0	1 (1.0)
Decreased appetite	2 (5.4)	3 (6.4)	3 (6.1)	6 (6.3)

SAS, safety analysis set; AE, adverse events. ^aGastrointestinal events^a included Preferred Terms (PTs) classified by the SOCs of "gastrointestinal disorders" (except for "dry mouth," "inguinal hernia," "dysphagia," "toothache," "food poisoning," "dental caries," "periodontal disease," "salivary hypersecretion," and "oral ulceration") as well as "decreased appetite" and "gastroenteritis."

^bDON5-DON10 and DON10-DON10 groups.

Psychiatric events were reported by 18.8% (18 of 96) in the DON-DON10 group. Only insomnia was reported by more than 5% (6.3% (6 of 96)) (Table 7). Ten severe psychiatric events (visual hallucinations, 3; insomnia, 2; paranoia, 2; agitation, irritability, and hallucinations, 1 each) were reported by 5 patients. In the PLA-DON10 group, these events were also reported by 16.2% (6 of 37); all events were mild or moderate.

Arrhythmic events were reported by 9.4% (9 of 96) in the DON-DON10 group, each of which was reported by less than 5% (Table 8). All the events were mild or

moderate, except for loss of consciousness in 1 patient (DON10-DON10, while receiving 5 mg). In the PLA-DON10 group, 8.1% (3 of 37) of the patients reported arrhythmic events. Only loss of consciousness was reported by more than 5% (5.4% (2 of 37)). All events were mild or moderate. Four events led to discontinuation or dose reduction in these patients, but 3 of them recovered or were relieved.

Excessive decrease of systolic and diastolic blood pressure was reported by 8.4% (11 of 131) and 10.7% (14 of 131) of all the subjects, respectively. Excessive increase of

Table 5 Incidence of parkinsonian events (SAS)

AE	PLA-DON10 (n =37)	DON5-DON10 (n =47)	DON10-DON10 (n =49)	DON-DON10 ^a (n =96)
Subjects with any parkinsonian events, n (%)	5 (13.5)	3 (6.4)	9 (18.4)	12 (12.5)
Camptocormia	0	0	1 (2.0)	1 (1.0)
Akinesia	1 (2.7)	0	0	0
Parkinsonism	3 (8.1)	3 (6.4)	9 (18.4)	12 (12.5)
Tremor	1 (2.7)	0	0	0

SAS, safety analysis set; AE, adverse event.

^aDON5-DON10 and DON10-DON10 groups.

Table 6 Change in UPDRS part III score from baseline (SAS)

Evaluation points	PLA-DON10				DON5-DON10				DON10-DON10			
	<i>n</i>	Score	Change ^a	<i>P</i> value ^b	<i>n</i>	Score	Change ^a	<i>P</i> value ^b	<i>n</i>	Score	Change ^a	<i>P</i> value ^b
Screening	46	21.4 ± 12.5	-	-	47	20.6 ± 11.9	-	-	49	19.3 ± 12.3	-	-
Week 12	37	20.1 ± 13.2	-1.1 ± 4.7	<i>P</i> = 0.184	32	17.0 ± 11.9	-3.0 ± 7.6	<i>P</i> = 0.032*	44	19.6 ± 13.2	0.3 ± 5.3	<i>P</i> = 0.711
Week 24	36	19.1 ± 12.0	-1.8 ± 4.6	<i>P</i> = 0.023*	29	17.0 ± 11.5	-3.5 ± 8.3	<i>P</i> = 0.029*	43	19.4 ± 14.7	-0.2 ± 8.6	<i>P</i> = 0.873
Week 40	33	19.9 ± 13.8	-2.0 ± 6.9	<i>P</i> = 0.106	25	16.1 ± 12.6	-5.0 ± 9.5	<i>P</i> = 0.014*	42	20.6 ± 15.7	0.6 ± 10.0	<i>P</i> = 0.680
Week 52	34	20.6 ± 16.0	-0.7 ± 9.4	<i>P</i> = 0.677	26	16.1 ± 13.2	-4.8 ± 10.2	<i>P</i> = 0.023*	40	21.1 ± 16.2	0.9 ± 10.0	<i>P</i> = 0.584
Week 52 (LOCF)	42	20.6 ± 14.9	-1.1 ± 8.9	<i>P</i> = 0.431	44	19.2 ± 13.9	-1.8 ± 9.6	<i>P</i> = 0.211	48	20.1 ± 15.5	1.0 ± 9.4	<i>P</i> = 0.474

UPDRS, Unified Parkinson's Disease Rating Scale; SAS, safety analysis set; LOCF, last observation carried forward.

Bolds indicate the period when the patients in each group took placebo.

Italics indicate the period when the PLA-DON10 and DON5-DON10 patients took 5 mg study drug (the PLA-DON10 and DON5-DON10 groups took 3 mg from Week 16 to 18 and Week 0 to 2, respectively).

The rest indicates the period when the patients took 10 mg (the DON10-DON10 group took 3 mg from Weeks 0 to 2, and 5 mg from Weeks 2 to 6).

^aA positive value of the UPDRS part III change indicates deterioration in motor function.

^bStudent paired *t* test.

**P* < 0.05.

blood pressure was reported by 2.3% (3 of 131) each. Abnormal change in pulse rate was reported by 3.1% (4 of 131), none of which led to any related serious AEs. Weight was decreased by 7% or more in 31.3% (41 of 131) of all the patients; only 4 of them were reported as AEs. None of the changes were reported as serious AEs.

Discussion

The DON5-DON10 and DON10-DON10 groups showed a significant improvement on the MMSE compared with baseline for 52 weeks. The previous long-term study presented a similar treatment effect of 5 mg donepezil over 52 weeks [23]. These results suggest that improvement of

Table 7 Incidence of psychiatric events^a (SAS)

AE ^a	PLA-DON10 (<i>n</i> = 37)	DON5-DON10 (<i>n</i> = 47)	DON10-DON10 (<i>n</i> = 49)	DON-DON10 ^b (<i>n</i> = 96)
Subjects with any psychiatric events, <i>n</i> (%)	6 (16.2)	9 (19.1)	9 (18.4)	18 (18.8)
Irritability	1 (2.7)	2 (4.3)	0	2 (2.1)
Cognitive disorder	0	1 (2.1)	0	1 (1.0)
Somnolence	2 (5.4)	0	0	0
Affect lability	1 (2.7)	0	0	0
Aggression	0	0	1 (2.0)	1 (1.0)
Agitation	1 (2.7)	3 (6.4)	0	3 (3.1)
Anxiety	0	1 (2.1)	0	1 (1.0)
Apathy	0	1 (2.1)	0	1 (1.0)
Delirium	0	0	1 (2.0)	1 (1.0)
Depression	0	1 (2.1)	1 (2.0)	2 (2.1)
Disinhibition	0	1 (2.1)	1 (2.0)	2 (2.1)
Disturbance in sexual arousal	0	0	1 (2.0)	1 (1.0)
Eating disorder	0	1 (2.1)	0	1 (1.0)
Hallucination	0	1 (2.1)	2 (4.1)	3 (3.1)
Hallucination, visual	0	3 (6.4)	0	3 (3.1)
Insomnia	0	4 (8.5)	2 (4.1)	6 (6.3)
Paranoia	0	1 (2.1)	1 (2.0)	2 (2.1)
Sleep disorder	1 (2.7)	1 (2.1)	0	1 (1.0)

SAS, safety analysis set; AE, adverse event.

^a"Psychiatric events" included Preferred Terms (PTs) classified as the SOC "Psychiatric disorders" as well as "irritability," "cognitive disorder," and "somnolence."

^bDON5-DON10 and DON10-DON10 groups.

Table 8 Incidence of arrhythmic events (SAS)

AE	PLA-DON10 (n =37)	DON5-DON10 (n =47)	DON10-DON10 (n =49)	DON-DON10 ^a (n =96)
Subjects with any arrhythmic events, n (%)	3 (8.1)	4 (8.5)	5 (10.2)	9 (9.4)
Atrioventricular block	0	0	2 (4.1)	2 (2.1)
Palpitations	0	1 (2.1)	0	1 (1.0)
Sinus bradycardia	0	1 (2.1)	1 (2.0)	2 (2.1)
Supraventricular extrasystoles	0	1 (2.1)	0	1 (1.0)
Ventricular extrasystoles	0	0	1 (2.0)	1 (1.0)
Electrocardiogram QT prolonged	0	1 (2.1)	0	1 (1.0)
Loss of consciousness	2 (5.4)	0	1 (2.0)	1 (1.0)
Syncope	1 (2.7)	0	0	0

SAS, safety analysis set; AE, adverse event.
^aDON5-DON10 and DON10-DON10 groups.

cognitive impairment by donepezil at 5 mg and 10 mg is sustainable for at least 1 year in patients with DLB. In an open-label long-term study of donepezil in patients with mild to moderate AD, the improvement in MMSE was maintained until 24 weeks after administration start, and gradually waned and deteriorated afterward [32]. Considering this result in the context of a similar or faster progression in cognitive impairment in DLB than in AD [3-6], the duration during which the cognitive improvement induced by donepezil persists in patients with DLB may surpass those with AD. Although learning effects due to repeated tests possibly contributed to the improvement in the extension phase, a 1-year lasting effect of cognitive impairment is of clinical significance.

For behavioral and psychiatric symptoms, donepezil administration at any dose (5 or 10 mg) reduced the NPI-2 and NPI-10 over 52 weeks. However, similar improvement seen in the PLA-DON10 group, even from the RCT phase, makes it difficult to attribute the improvement to the study drug. It is conceivable that caregiver education about the disease and instructions on coping, which were likely given at the beginning of and during the study, affected the behavioral and psychiatric symptoms. However, because it is unlikely to last long, such an effect on the symptom improvement may be replaced or enhanced by donepezil after treatment initiation and may lead to a 1-year lasting improvement, even in the PLA-DON10 group.

With regard to the effect of dose increment in the DON5-DON10 group, although no significant improvement due to the dose increment was detected either in MMSE score or in NPI-2 score as a whole, the subgroup either with an MMSE change of <3 points or with a NPI-2 change of <30% from the baseline at Week 24 showed an improvement after the dose increment. There may be a range of doses at which the maximum improvement can be obtained, and 5 mg can provide a sufficient effect to some patients. The expected further

improvement by increasing to 10 mg may allow recommendation for a dose increase to 10 mg based on the individual safety when 5 mg is insufficient.

After Week 24, 18 patients experienced a dose reduction from 10 mg to 5 mg. Because MMSE scores remained above the baseline at all times, without deterioration of more than 0.7 points, the effects can be maintained even with a reduction to 5 mg. When intolerable at 10 mg, treatment could effectively be continued by dose reduction to 5 mg.

No great difference was observed in the occurrence of AEs due to the length of the administration period. Thus, the possibility of delayed onset of AEs with long-term treatment seems low. Most of the treatment-related AEs were mild or moderate, and only parkinsonism had an incidence of 5% or more. Of the 107 patients who continued the treatment beyond Week 24, dosage was reduced in 21 (19.6%) of patients. The main adverse events leading to dose reduction were gastrointestinal, psychiatric, and parkinsonian symptoms. All of these resolved or were relieved after dose reduction, and did not lead to discontinuation after the reduction. Gastrointestinal events are well-known adverse events of ChEIs. Gastrointestinal events most frequently reported by the patients who received 10 mg of donepezil in the 52-week study in AD patients were diarrhea (12.7%), nausea (12.2%), and vomiting (10.1%) [33]; the equivalent incidences of these in the present study in patients with DLB were lower. A slight increase in the incidence after a dose increase from 5 to 10 mg suggests the need to pay attention to the occurrence of gastrointestinal events on dose increase. However, this comparison, the present result of mostly mild to moderate severity and the absence of an increasing trend in the incidence over time support a low risk for clinically significant gastrointestinal symptoms.

Another AE of specific concern is parkinsonism; donepezil may induce or exacerbate extrapyramidal symptoms, which are threatening for DLB patients in whom

parkinsonism occurs frequently. However, none of the reported parkinsonian symptoms was severe or serious. Neither the incidence nor UPDRS part III scores were inclined to increase over time, representing no notable deterioration over time. Psychiatric events were not considered to be notable safety concerns, according to their incidence (including lower rate in 10 mg group in the RCT). Arrhythmic events require particular attention, based on the incidence of 9.0% (12 of 133) of all the included patients and 3 cases of loss of consciousness, one of which was severe. In the RCT phase, the incidence of arrhythmic events did not clearly tend to increase in the active groups (placebo, 5, and 10 mg: 4.3%, 4.3%, and 6.1%, respectively). In the extension phase, the incidence by 12-week intervals did not exceed the incidence in the placebo group during the RCT phase. As loss of consciousness reported by 1 patient in the placebo group during the RCT phase is certainly attributed to the disease itself, those reported in patients who received donepezil might not be necessarily attributed to donepezil.

Another safety event to be noted is abnormal weight loss, which was reported in a substantial proportion of patients. However, it was mostly self-limited and not serious, as it was rarely recognized to be an adverse event.

The findings suggest that no major concerns exist regarding the safety or tolerability profile of long-term administration of donepezil at up to 10 mg. Safe and tolerable treatment can be assured by alerting the patients and their caregivers about the occurrence of parkinsonism and gastrointestinal or arrhythmic symptoms and managing the risks for such events by reducing the dose.

The major limitations include the short duration (12 week) of the RCT phase and the open-label design of the extension phase as well as the small sample size. Because of the progressive nature of this disease and the increasing caregiver stress, it would be difficult to enroll patients with DLB in a long-term placebo-controlled trial. For these reasons, the long-term efficacy and safety of 10 mg of donepezil over 5 mg or placebo cannot be stated assertively.

Conclusions

The open-label long-term administration of donepezil at 10 mg/day improved impaired cognitive function for up to 52 weeks in patients with DLB without increasing the risk of clinically significant safety events.

Additional file

Additional file 1: List of all institutional review board.

Abbreviations

AD: Alzheimer disease; AE: adverse event; ANCOVA: analysis of covariance; ChAT: choline acetyltransferase; ChEI: cholinesterase inhibitor; DLB: dementia with Lewy bodies; FAS: full analysis set; LOCF: last observation carried forward; MMRM: mixed-effect model for repeated measures; MMSE: Mini-Mental

State Examination; NPI: neuropsychiatric Inventory; PPS: per protocol set; RCT: randomized, double-blind, placebo-controlled; SAS: safety analysis set; SD: standard deviation; UPDRS: Unified Parkinson's Disease Rating Scale; ZBI: Zarit Caregiver Burden Interview.

Competing interests

EM received personal fees from Eisai during the conduct of the study; grants and personal fees from Eisai, Janssen, Daiichi Sankyo, Nihon Medi-Physics, and FUJIFILM RI; personal fees from Johnson & Johnson, Lundbeck, Novartis, Ono, and Medtronic outside the submitted work. All grants were for his department, and he received them as the director of the department. MI received personal fees from Eisai during the conduct of the study; grants and personal fees from Daiichi Sankyo, Eisai, FUJIFILM RI, Janssen, Nihon Medi-Physics, Novartis, Pfizer, Takeda, and Tsumura; and personal fees from MSD, and Ono Pharmaceutical outside the submitted work. All grants were for his department, and he received them as the director of the department. RM, KM, and MN are employees of Eisai. KK received personal fees from Eisai during the conduct of the study; and personal fees from Tsumura, Eisai, Janssen, FUJIFILM RI, Novartis, Nihon Medi-Physics, Daiichi Sankyo, Ono, Otsuka, and Dainippon Sumitomo outside the submitted work.

Authors' contributions

EM and MI designed the study, analyzed the data, and wrote the manuscript. RN and KM designed the study and analyzed the data. MN designed and conducted the study. KK designed and supervised the study. All the authors reviewed the manuscript and made final approval of the version to be published.

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原著

本邦における FTD に対する off-label 処方の実態について

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要 旨

全国4施設の専門外来をFTD圏の診断名で紹介された連続例87例の背景因子、紹介医の診療科および認知症症状に対する処方の内容などを調査した。紹介医は精神科医が6割で、ほか神経内科医、一般内科医、脳神経外科医などであった。約半数の例に認知症症状に対する薬剤が用いられ、コリンエステラーゼ阻害剤は様々な診療科から2割の患者に処方されていた。向精神薬は精神科医によって1/3以上の患者に処方され、抗うつ薬、抗精神病薬の処方が多かった。前頭側頭葉変性症や運動ニューロン疾患と診断されていた例には処方はなされてい

なかった。他の背景因子は薬剤使用には影響を与えなかった。FTDへの薬物療法ガイドラインの作成が望まれる。

キーワード：前頭側頭型認知症，off-label 処方，コリンエステラーゼ阻害剤，向精神薬，薬物療法

1. はじめに

前頭側頭型認知症 (frontotemporal dementia : FTD) は前頭葉や側頭葉前方部に変性の中心がある変性性認知症群であり、初老期に発症する変性性認知症の中では、アルツハイマー病 (Alzheimer's disease : AD) に次いで多いとされる (Ratnavalli et al., 2002)。FTDの患者は病初期から前頭葉機能の障害に伴う社会行動の変化や人格の変化を呈することが特徴であり、臨床診断基準においても、脱抑制や無為、共感性の欠如、常同行動、食行動異常といった行動変化が主要な項目として述べられている (Rascovsky et al., 2011)。これらの特徴的な行動変化から病初期から介護者の負担が大きく (Mioshi et al., 2013)、一方で精神疾患や他の認知症性疾患に誤診されていることも多いため (Woolley et al., 2011)、医療現場においても対象に苦慮することが多い疾患群である。

現時点では、本邦においても、また主要な欧米諸

Off-label medication for frontotemporal dementia in Japan
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国においてもFTDに保険適応のある薬剤はない (Boxer et al., 2012b). アルツハイマー病 (Alzheimer's disease: AD) に対して用いられるコリンエステラーゼ阻害剤 (Cholinesterase inhibitor: ChEI) がFTDに用いられている例も臨床場面ではみとめられるが、これらの薬剤はFTDの行動障害を悪化させることが報告されている (Mendez et al., 2007). また行動障害を抑える目的で抗精神病薬が用いられることも多いが、FTDの患者は抗精神病薬に対して錐体外路症状などの危険性が高いことも報告されている (Kerssens et al., 2008). このような疾患であるFTDに対して、本邦における適応外処方の実態はこれまで明らかになっていない。

本研究の目的は専門医以外によってFTDと診断を受けた場合、1) どのような処方がなされるのか、2) 処方の内容に影響を与えるような因子があるのか、を明らかにすることである。

2. 対象と方法

2008年1月から2010年12月の期間に全国4施設 (公益財団法人浅香山病院, 愛媛大学医学部附属病院精神科神経科, 熊本大学医学部附属病院神経精神科, 東京慈恵大学医学部附属病院精神神経科) の認知症専門外来を受診した連続例から、紹介医でFTDないしはそれに類する診断名 (ピック病, 疑い病名を含む) で紹介された患者を抽出した。そのうえで、それらの患者の年齢, 性別, 教育歴, 罹病期間, Mini mental state examination: MMSE得点 (Folstein et al., 1975) といった背景因子, 前医の診療科, 前医における認知症症状に対する処方 (ChEI, 他の認知機能障害に対する薬剤, 抗精神病薬, 抗うつ薬, 抗不安薬, 気分調整薬, 漢方薬など) の有無とその内容, 介護保険取得状況, 専門医の最終診断などを各施設の認知症データベースより調査した。ただし、本報告は2010年末までの集計であり、ChEIとして処方されたのはDonepezilのみである。診療科別の処方割合や紹介医の診断別の処方割合については χ^2 検定およびFisherの正確検定にて検定を行い、薬剤の使用に影響を与える背景因子を検討

するための2群比較においては、 t 検定あるいは χ^2 検定およびFisherの正確検定にて検討を行った。

専門医の最終診断にあたっては、各施設に認知症学会及び老年精神医学会の専門医がおり、画像診断および共通した認知機能バッテリーを用いて、血液検査などで共通のプロトコールに則って除外診断を行い、各疾患の診断基準に基づいて診断を行っている。

本研究はデータベースを用いた調査であり介入研究ではない。患者の匿名性に関しては十分な配慮がなされており、データベースを用いる研究を行うことに関しては、各施設の倫理委員会の承認を各々得ている。

3. 結果

3.1. 患者および紹介医の背景

今回対象となった患者87例の背景を表1に示す。男女比はほぼ同等で、平均年齢が66.9歳、平均の初診時MMSE得点は18.4であった。

紹介医の診断はFTDおよび疑い、前頭側頭葉変性症 (Frontotemporal lobar degeneration: FTLD) および疑い、側頭葉優位型圏内、ピック病および疑い、運動ニューロン疾患 (Frontotemporal dementia with motor neuron disease: FTD-MND) 圏内などであり、FTDの診断が6割以上を占めた。紹介医の属性は精神科, 神経内科, 内科, 脳神経外科, その他であり、精神科が6割以上を占めた。

3.2. 認知症に対する薬剤を使用していた例

87例のうち、何らかの認知症に対する薬剤の使用を用いていた例はほぼ半数の49.4% (43例) であった。認知機能に対する薬剤を用いていたのは23% (20例) であり、ChEIは20.7% (18例) に用いられていた。脳代謝改善薬は2.3% (2例) に用いられていた。一方で精神症状に対する薬剤 (以下向精神薬とする: 抗精神病薬, 抗うつ薬, 抗不安薬, 気分調整薬, 特定の漢方薬を含む) は35.6% (31例) に用いられていた (ChEIとの重複や、向精神薬同士での重複を含む)。抗うつ薬が16.1% (14例) に、漢方薬 (全て抑肝散) が11.5% (10例) に、抗精

表 1. demographic data of patients and referring physicians

Sex (Male : Female)	42 : 45
Age	66.9 (11.6)
education (year)	11.3 (2.9)
disease duration (year)	3.0 (2.1)
MMSE score	18.4 (9.5)
Referring physicians' diagnosis (FTD/FTLD/temporal variant/Pick's disease/FTD-MND)	55/5/9/11/7
Referring physicians' background (psychiatrist/neurologist/general physician/neurosurgeon/others)	53/17/9/6/2

MMSE : Mini-Mental State Examination
 FTD : Frontotemporal dementia
 FTLD : Frontotemporal Lobar Degeneration
 FTD-MND : FTD with motor neuron disease
 mean (SD) for Age, education, disease duration, and MMSE score

神病薬が 10.3% (9 例) に、抗不安薬が 9.2% (8 例) に、気分調整薬が 1.1% (1 例) に用いられていた。

3.3. 診療科別の処方

診療科によって処方の傾向が異なるかどうかを検討した。まず ChEI の診療科別の処方率であるが、精神科では 13/53 (24.5%)、神経内科では 2/17 (11.8%)、内科では 2/9 (22.2%)、その他は 1/8 (12.5%) であった。 χ^2 検定 (Fisher の正確検定) にて有意差は認められなかった。一方で向精神薬は精神科では 26/53 (49.1%) に処方されていたのに対し、神経内科では 1/17 (5.9%)、内科では 2/9 (22.2%)、その他は 2/8 (25.0%) と χ^2 検定 (Fisher の正確検定) にて有意 ($P=0.003$) に精神科で多く処方されていた。抗精神病薬が処方されていた 9 例のうち 8 例は精神科での処方であり、抗うつ薬は 14 例全例が精神科での処方であった。漢方薬 (抑肝散) は 10 例中 8 例が精神科での処方であった。向精神薬については、どの種類の薬剤でも精神科での処方が多いという結果であった。

3.4. 紹介医の診断別の処方

紹介医の診断名による処方割合についても検討した。まず、ChEI が処方されていた 18 例では FTD および疑いという診断が 11 例 (61.1%) で最も多く、FTLD および疑い、FTD-MND 圏内と診断された例には ChEI は処方されていない。向精神薬が処方されていた 31 例でも FTD および疑いが 21 例

(67.7%) ともっと多く、FTLD および疑い、FTD-MND 圏内と診断された例には向精神薬は処方されていたなかった。

3.5. 専門医の診断と紹介医の処方

専門医の診断は必ずしも紹介医の診断と一致しない。紹介医の過小診断や過剰診断に基づく処方も問題になりうる。そこで、専門医の診断と紹介医の処方割合についても検討した。ChEI が処方されていた 18 例のうち、専門医によって FTD と診断された例は 4 例 (28.6%) であったが、ChEI が処方されていない 69 例のうち、専門医によって FTD と診断された例は 20 例 (29.0%) であった。ほぼ類似した値であり、 χ^2 検定と Fisher の正確検定によって有意差は認められなかった。向精神薬が処方されていた 31 例のうち、専門医によって FTD と診断された例は 5 例 (16.1%) であった。一方で向精神薬が処方されていない 56 例のうち、専門医によって FTD と診断された例は 19 例 (33.9%) であり、向精神薬が処方されていない例の方が専門医によって FTD と診断される割合が高い傾向にあった。しかし χ^2 検定と Fisher の正確検定によって有意差は認められなかった。

3.6. 薬剤の使用に影響を与える背景因子

ChEI の使用に影響を与えるような背景因子があるかどうか、ChEI の使用の有無によって 2 群に分け、比較を行った (表 2)。しかしながら、性別、

表 2. Factors associated with ChEI use

	No ChEI use (n=69)	ChEI use (n=18)	
Sex (Male : Female)	33 : 36	9 : 9	n.s
Age	65.7 (12.1)	71.4 (8.0)	n.s
education (year)	11.3 (3.0)	11.5 (2.8)	n.s
disease duration (year)	2.8 (2.1)	3.7 (1.8)	n.s
MMSE score	19.0 (9.5)	16.0 (9.2)	n.s
care insurance use (yes : no)	20 : 49	5 : 13	n.s

ChEI : Cholinesterase Inhibitor

MMSE : Mini-Mental State Examination

mean (standard deviation) for Age, education, disease duration, and MMSE score

表 3. Factors associated with psychotropic drug use

	No psychotropic drug use (n=56)	psychotropic drug use (n=31)	
Sex (Male : Female)	26 : 30	16 : 15	n.s
Age	67.6 (11.4)	65.7 (12.0)	n.s
education (year)	11.5 (2.8)	11.1 (3.2)	n.s
disease duration (year)	2.9 (2.1)	3.0 (2.2)	n.s
MMSE score	17.7 (9.2)	19.6 (10.0)	n.s
care insurance use (yes : no)	19 : 37	6 : 25	n.s

MMSE : Mini-Mental State Examination

mean (standard deviation) for Age, education, disease duration, and MMSE score

年齢、教育年数、罹病期間、MMSE 得点、介護保険の取得状況などいずれも 2 群間の有意差はなかった。

同様に、向精神薬の使用に影響を与えるような背景因子があるかどうか、向精神薬の使用の有無によって 2 群に分け、比較を行った (表 3)。しかしながら、性別、年齢、教育年数、罹病期間、MMSE 得点、介護保険の取得状況などいずれも 2 群間の有意差はなかった。

4. 考 察

本検討は本邦で最初の FTD に対する off-label 処方の実態調査である。その結果、約半数の例に何らかの認知症症状に対する薬剤が用いられ、ChEI は 2 割の例に処方されていることが明らかになった。

向精神薬は 1/3 以上に処方されており、中では抗うつ薬の処方が多かった。ChEI はさまざまな診療科の医師に処方されているが、向精神薬は主に精神科医によって処方されていた。

FTD に対する不適切な治療に関してはいくつかの問題がある。まず、FTD が他の疾患に誤診され、間違った治療を受けている可能性である。FTD は精神疾患や他の認知症性疾患に誤診されることも多く (Woolley et al., 2011)、そのために不適切な治療を受ける可能性がある。しかしながら、今回の対象は、紹介医によって FTD 及び類する疾患の診断がなされている例である。その例に対して 2 割に ChEI が、1/3 以上に向精神薬が処方されていた。

この本報告の ChEI の処方率の 2 割という割合を多いと判断するか、少ないと判断するかは、意見の分かれる点と思われる。例えば、他の変性疾患によ

る認知症の例では、レビー小体型認知症 (Dementia with Lewy bodies: DLB) に対してのChEIの使用は数多くの論文で有用性が示され、本邦のMoriらの多施設共同RCTにおいても、認知機能、全般機能、そして精神症状も改善したと報告された (Mori et al., 2012)。実臨床においても、ChEIは多くの例に用いられていると推測される。

その一方でFTDに対するChEIの投与の報告は多くはない (Kertesz et al., 2008; Mendez et al., 2007)。そしてほとんどで、有効性は認められなかったと報告され、また脱抑制と衝動性の悪化が認められたとの報告もある (Mendez et al., 2007)。筆者らもFTDの精神症状がChEIで悪化した例を報告している (品川ら, 2009)。本報告でChEIが処方された2割のFTD例は、他に選択肢がなくChEIを使用していると推測されるが、これはなるべく避けるべきであり、今後さらなる啓発が必要と思われる。

ChEIが処方されていた18例においても、ChEIが処方されていなかった69例においても、専門医によってFTDと診断された例は3割弱であった。これはつまり、例えば行動・心理症状 (Behavioral and psychological symptoms of dementia: BPSD) を伴うADのような例が紹介医によって多くFTDと誤診され、ChEIが処方されているわけではないことを意味する。さらにChEIが用いられている対象と、そうでない対象との間には背景因子に有意差のある項目はなく、ChEIが用いられる対象の一定の傾向は認められなかった。

本報告は2010年末までの集計であり、2011年に本邦で発売された、GalantamineやRivastagmine、Memantineは今回の検討には含まれていない。Memantineは認知機能改善目的以外にもBPSDに対して有用との報告があり (Gauthier et al., 2008)、BPSDのある対象に比較的多く用いられ、Memantineが今回の調査の対象に含まれていたならば、その頻度は高かったかもしれない。しかしながら、Memantineは近年米国において大規模な無作為化試験が行われたが、プラセボに比して有意な結果を得ることはできなかった (Boxer et al., 2012a)。実際にはMemantineの投与も有用でない可能性が高い。

一方で35%という向精神薬の処方割合についてはどう考えるべきであろうか？ 2012年の「かかりつけ医による認知症者に対する向精神薬の使用実態調査に関する研究事業報告書」によれば、認知症患者に対する向精神薬の服用は95%とかなり高率であった (認知症ケア学会, 2012)。ただしこの数字は医師が複数の患者に対してひとりでも向精神薬を使用している割合であり、単純な比較はできない。また2006年の報告で、精神科医が診ている認知症患者の62%にBPSDが認められ、そのうち93%が薬物療法を受け、そのうち81%に抗精神病薬が用いられていた (すなわち、精神科医が診ている認知症患者の47%に抗精神病薬が用いられていた) という報告もある (本間, 2006)。それらに比べると本報告の数字は低い。他の疾患より行動症状が目立ち、それに伴う介護負担も大きいはずのFTDにおいて、何故向精神薬の処方割合が低いのであろうか？ これにはいくつかの理由があると考えられる。まず、他の認知症と異なり、FTDと診断された場合、不用意に向精神薬を処方せず、専門医への紹介を優先させている可能性がある。また、本研究の例は入院例を含まない外来例であることや、処方医の診療科の比率が前述の調査と異なるため、それが処方割合に影響している可能性もある。いずれにせよ、安易な向精神薬の処方を行っていないという点では、好ましいことと思われる。

向精神薬のなかで、抗うつ薬の使用が最も頻度が高かったのは興味深い。選択的セロトニン再取り込み阻害薬 (selective serotonin reuptake inhibitor: SSRI) の強迫性障害や神経性大食症に対する有効性を背景として、最初にSwartzらがFTD患者に対するSSRIの使用を報告して以降 (Swartz et al., 1997)、フルボキサミンやパロキセチン、セルトラリンの有用性の報告がなされている (Ikeda et al., 2003; Mendez et al., 2005; Moretti et al., 2002)。SSRIではないが、間接的セロトニン再取り込み阻害薬であるトラドゾンを用い、興奮、焦燥、うつなどの症状に改善がみられたという報告もあり (Lebert et al., 2004)。抗うつ薬はFTDの常同行動や食行動異常に対して有用である可能性が高い。その抗うつ薬が抗