学位論文

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Preliminary evidence that rivastigmine-induced inhibition of serum butyrylcholinesterase activity improves behavioral symptoms in Japanese patients with Alzheimer's disease

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Running title: Inhibiting BuChE improves AD behavior

Abstract

Aim: To investigate whether the inhibitory rate of serum butyrylcholinesterase (BuChE) activity in Japanese patients with Alzheimer's disease (AD) is correlated with cognitive function, behavioral symptoms, and caregiver burden.

Methods: Sixty-one patients with mild to moderately-severe AD who were not undergoing cholinesterase enzyme inhibitor/memantine combinatorial treatment received a rivastigmine (18 mg) patch for 24 weeks. The rate of inhibition of BuChE was correlated with scores obtained on cognitive [MMSE], behavioral [the Japanese version of modified Crichton Geriatric Behavioral Rating Scale (CGBRS) and Vitality Index (VI)], and burden [the Japanese version of Zarit Burden Inventory (ZBI)] scales; and the Clinical Global Impression of Change scale (CGIC).

Results: The serum BuChE activity showed a significant decrease after 24 weeks compared with baseline ($p<0.001$). Overall, significant effects were found on MMSE score, VI score, and modified CGBRS score. We then divided patient groups into a high inhibitory rate (≥40%) [HIR] group and a low inhibitory rate (<40%) [LIR] group; there were significant improvements on MMSE score, VI score, and modified CGBRS score in both groups. However, favorable results were seen in cooperation, restlessness, and leisure on modified CGBRS subscales in the HIR group ($p<0.001$, $p=0.007$, $p<0.001$, respectively), and rehabilitation and other activities on VI subscales in the HIR group

(p=0.005) compared with those in the LIR group.

Conclusions: Demonstrable significant improvements in behavioral symptoms like low cooperation, restlessness, or low activities in patients with AD were achieved upon inhibition of BuChE at a rate of 40% or more.

Keywords: Alzheimer disease, rivastigmine, cholinesterase inhibitors, butyrylcholinesterase, behavioral symptoms

Introduction

Rivastigmine (transdermal formulation) is distinct from other available cholinesterase inhibitors (donepezil and galantamine) in that it is a pseudo-irreversible inhibitor of both acetylcholinesterase (AChE) and butyrylcolinesterase (BuChE).[1] It has demonstrated benefits across the spectrum of Alzheimer's disease (AD) severity, as well as across its cognitive, functional, and behavioral domains of AD.[2] Moreover, a close relationship was found between the concentration of rivastigmine and inhibition of AChE and BuChE in plasma and brain tissues, especially in the hippocampus and cerebral cortex in rats.[3] In addition, the percentage reductions of specific activities of plasma AChE and BuChE were highly correlated with those in the cerebrospinal fluid (CSF) of patients with mild AD following 12 months of rivastigmine treatment.[4]

To the best of our knowledge, few studies have focused on the relationship between the inhibitory rate of BuChE activity and clinical efficacy in patients with AD.[5-9] In particular, no data are available on the effects the inhibitory rate of serum BuChE activity on neuropsychiatric symptoms in Japanese patients with AD, with one report being the exception.[6] This report indicated that more than 40% inhibition of plasma BuChE activity showed significant correlations with efficacy in relation to both cognitive function and the memory domain.

If the therapeutic efficacy can indeed be predicted by measuring convenient and cheap serum BuChE over time, the inhibitory rate of BuChE shows potential as a predictive biomarker in patients with AD who undergo rivastigmine therapy. In this study, we aimed to evaluate whether the inhibitory rate of serum BuChE activity following rivastigmine patch treatment in Japanese patients with AD is correlated with cognitive function, behavioral symptoms, and caregiver burden.

Materials and Methods

Subjects

Our study was planned as a 24-week, prospective, single cohort, observational, and open-label study. The study was conducted according to the Declaration of Helsinki, and was approved by the Ethics Committee of Kaisei General Hospital, Japan (2014-13).

Patients enrolled in this study were from the outpatient unit of the Department of Psychiatry, Kaisei General Hospital, Kagawa, Japan. Subjects included outpatients diagnosed with AD who lived with or had regular daily visits from a responsible caregiver. Dose titrations of rivastigmine patches were performed every 4 weeks using 4.5 mg/day increments, from 4.5 mg/day to 18 mg/day. Data were gathered from all

subjects receiving the maximum dosage (18 mg) of rivastigmine patch for AD between February of 2015 and January of 2016.

The concomitant use of cholinomimetic drugs or cholinergic antagonists was not permitted during the study, and patients who had received any cholinergic or cognitive-enhancing drugs during the last 3 months were excluded. Patients were also excluded if they had evidence of severe or unstable physical illness, including acute or severe asthmatic conditions, severe or unstable cardiovascular disorders, active peptic ulcer disease, clinically significant laboratory abnormalities, or any medical condition that could prohibit them from completing the clinical trial. All patients were nonsmokers and at least 50 years old.

We initially enrolled and screened 90 patients in this study. The patients who experienced cholinesterase inhibitor-related, intolerable side effects (n=14), or were lost during follow-up (n=15), were excluded. In particular, 6 (6.7%) had cutaneous reactions, 2 (2.2%) had gastrointestinal disorders, and 1 (1.1%) had hypertension. Overall, 61 patients completed all of the study evaluations, and their data were considered in the final analysis.

Comorbid medical illnesses were present in about 67% of the whole patient population. The most frequent comorbid illnesses were hypertension (n=23, 38%), dyslipidemia

(n=12, 20%) and non-complicated diabetes (n=12, 20%); other concomitant stable illnesses, such as gastrointestinal, renal, pulmonary, and metabolic diseases, accounted for less than 5% of patients.

All patients had baseline Mini-Mental State Examination (MMSE)[10] scores of 10-24 inclusive, indicating mild to moderately-severe dementia, as defined by a dementia of the Alzheimer type according to *The Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revision (DSM-IV-TR; APA 2000) criteria; and probable AD according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA).[11] They were required to have contact with a responsible caregiver at least once a day. All patients and their responsible caregivers provided written informed consent to participate in the study. In case of a patient's inability to consent due to progressed dementia, his/her legal representative was asked to do so.

To evaluate BuChE activity levels in the serum, blood was taken from all patients at baseline (day 0) and after 24 weeks of treatment. After centrifugation, the activity was measured using spectrophotometric measurement of the decrease of NADPH (nicotinamide adenine dinucleotide phosphate) with commercially available automated kits.[12]

Neuropsychological assessments

To evaluate the effects of rivastigmine treatment on the cognitive abilities of patients with AD, the MMSE, the Japanese version of the modified Crichton Geriatric Behavioral Rating Scale (CGBRS),[13] the Vitality Index (VI),[14] and the Japanese version of the Zarit Burden Interview (ZBI)[15] were administered at baseline and week 24. Trained psychologists performed all evaluations.

The modified CGBRS includes a total of 7 items (comprehension of time and place, carrying out conversation, cooperation, restlessness, dressing, social activities, and leisure) evaluated in 8 grades that assess basic activities of daily living, communication functions, psychiatric symptoms, and quality of life, and was made to evaluate self-care and other adaptive skills.[13]

The Vitality Index (VI) was used to assess daily activities of the patients. This index was established and validated by Toba et al.[14] It is comprised of 5 items (Waking pattern, Communication, Feeding, On and off toilet, Rehabilitation, and other activities) each assessed according to 3 ratings. The severity of each symptom was scored based on structured questions administered to the caregivers.

The Zarit Burden Interview (ZBI) is useful not only for identifying caregiver burden, but also for predicting main caregiver collapse, and has been developed to measure

subjective burden among caregivers of adults with dementia.[15] Items were generated based on clinical experience with caregivers and prior studies, resulting in a 22-item self-report inventory that examines burden associated with functional/behavioral impairments and the home care situation. The items are worded subjectively, focusing on the affective response of the caregiver. The ZBI is scored on a 5-point Likert scale ranging from "never" to "nearly always present" for each question. Total scores range from 0 (low burden) to 88 (high burden).

Treatment responses and grouping

Treatment response was measured at week 24 by the Clinical Global Impression of Change scale (CGIC), which was rated based on a clinical interview with the patient and his/her caregiver. CGIC is a categorical scale ranging from 1 to 7, with a low score indicating clinical improvement.[16] The patients and their caregivers are interviewed by the clinician. Based upon the clinician's total experience with this population, the rater makes an assessment of the patient's cognition, behavior, and functional ability scored as a single evaluation score. Patients were grouped as responders or non-responders, such that patients with CGIC 1–4 were considered responders, and CGIC 5–7 were non-responders.

Follow-up examinations

All patients underwent clinical examinations to assess side effects and dosage appropriateness. The MMSE, CGBRS, VI, and ZBI were also performed. Blood was taken from all patients at the 24-week follow-up, and glutamate-oxaloacetate transaminase (GOT), glutamate pyruvate transaminase (GPT), and serum BuChE activity were measured.

Statistical analysis

All data were summarized using Microsoft Excel software ver. 2013, and analyzed using Statistical Package for Social Sciences (SPSS) version 18 for Windows (SPSS Japan, Tokyo, Japan).

With respect to patient demographics, a chi-squared test was used for enumerated data with no ordered relation. A Mann-Whitney U-test was used for ordered data and measured data, and a lack of equilibrium between the groups was studied. Comparisons between the baseline and week 24 were performed using a Wilcoxon signed-rank test. We considered findings of a p-value less than 0.05 to indicate statistical significance.

Results

Patient characteristics at baseline

In the final sample of 61 patients, 49% were female. The mean age ± standard

deviation (SD) was 79.3 ± 7.2 years and the mean body weight ± SD was 54.2 ± 13.4 kg. The mean length of education ± SD was 11.1 ± 2.2 years and the mean duration of disease ± SD was 2.1 ± 2.1 years.

Comparisons between the baseline and week 24

The differences in GOT levels and GPT levels were not statistically significant (p=0.17, P=0.73, respectively). The activity of serum BuChE showed a significant decrease (p<0.001, the mean inhibitory rate of serum BuChE activity=41.6%) (Table 1). Significant changes were seen in the MMSE score, VI score, and modified CGBRS score. Among the modified CGBRS subscales, significant decreases were seen in all terms. Significant increases were seen in terms of communication, on and off toilet, and rehabilitation and other activities among the VI subscales. The ZBI score difference did not reach statistical significance (p=0.74). Based on CGIC, 54 (89%) of the 61 patients were responders and 7 were non-responders.

Comparisons between low inhibitory rate and high inhibitory rate groups

Because previous studies have indicated that rivastigmine displays a dose-dependent activity that is clinically efficacious at 40% or higher inhibition of BuChE,[6,9] we divided each group based on that threshold of serum BuChE inhibition. The clinician performing the assessments did not know which group the patient being assessed

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belonged to. Demographic data for patients grouped into the low inhibitory rate (<40%) [LIR] group (mean inhibitory rate = 20.1%) and the high inhibitory rate (≥40%) [HIR] group (mean inhibitory rate = 56.8%) are shown in Table 2. No statistically significant differences were observed between the LIR and HIR groups with respect to the sex ratio, age, body weight, length of education, duration of disease, and neuropsychological assessments except for ZBI scores. At week 24, the mean CGIC score was 3.0 and 3.2 for the LIR and HIR groups, respectively. No significant decline from baseline (i.e., improvement or no change in their condition [CGIC rating score ≤4]) was seen in 23 (88.4%) patients in LIR group and 31 (88.6%) patients in HIR group.

Serum BuChE activity showed significant decreases in both groups (LIR group, HIR group; $p<0.001$, $p<0.001$) (Table 3). Both groups showed significant increases in MMSE scores (LIR group, HIR group; $p=0.031$, $p=0.035$) and VI scores (LIR group, HIR group; $p=0.006$, $p=0.015$), and a significant decrease on the modified CGBRS score (LIR group, HIR group; $p=0.003$, $p<0.001$). However, scores for cooperation (LIR group, HIR group; $p=0.187$, $p<0.001$), restlessness (LIR group, HIR group; $p=0.183$, $p=0.007$), and leisure (LIR group, HIR group; $p=0.068$, $p<0.001$) on modified CGBRS subscales in HIR group showed significant decreases, and scores for rehabilitation and other activities (LIR group, HIR group; $p=0.070$, $p=0.005$) on VI subscales in the HIR

group showed significant increases compared with those in the LIR group. Communication (LIR group, HIR group; p=0.038, p=0.487) on VI subscales in the LIR group showed significant improvement compared with that in the HIR group. A tendency towards decreased ZBI scores in the LIR group was seen, whereas a tendency towards increased ZBI score in the HIR group was seen, albeit with no significant differences for either group (LIR group, HIR group; p=0.28, p=0.24).

Discussion

The results of the present open-label observational study demonstrated that serum BuChE activity showed a significant decrease, while the differences in GOT and GPT activities were not statistically significant. Because serum BuChE activity is a marker of liver damage or nutritional status,[17] the decreased activity noted in our patient groups, who were in generally good physical condition, was considered to be due to the pharmacological action of rivastigmine therapy.

Interestingly, higher rates of BuChE inhibition (above 40%; the HIR group) were related to improvements in rehabilitation and other activities (LIR group, p=0.070; HIR group, p=0.005) in the VI, cooperation (LIR group, p=0.187; HIR group, p<0.001), restlessness (LIR group, p=0.183; HIR group, p=0.007), and leisure (LIR group,

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p=0.068; HIR group, p<0.001) scales in the modified CGBRS in the HIR group. Unfortunately, CSF was not taken in this study. However, considering that the percentage reductions of specific activities of plasma AChE and BuChE were found to be highly correlated with those in CSF,[4] we believe it likely that the HIR group would demonstrate similarly high inhibitory rates in CSF. Previous studies have shown weak or absent correlations between changes in cognitive performance and inhibition of plasma BuChE.[7,8] However, the lack of association might be related to the limitations of the specific studies, such as a small sample size (n=3 or 16)[7] or relatively low doses.[8] In this study, both the LIR and HIR groups showed significant improvements in the MMSE score, VI score, and modified CGBRS score, as well as either improvement or no change in their condition [CGIC rating score ≤4]). In fact, these encouraging results were seen in 88.4% of patients in the LIR group and 88.6% of patients in the HIR group. Therefore, though some clinical improvements were associated with less than 40% inhibition of serum BuChE activity, our data indicate that further improvements could be achieved with higher (above 40%) inhibition of serum BuChE activity.

With all of these considerations in mind, we propose that serum BuChE activity, which can be measured easily and at a low cost, may be used as a predictive biomarker in patients with AD who undergo rivastigmine treatment. Moreover, periodic measurement

of serum BuChE activity might be useful for (i) evaluating therapeutic resistance to rivastigmine, (ii) titrating pharmacological interventions to optimal levels (e.g., over 40% inhibition of serum BuChE activity), and (iii) observing medication adherence. However, more work is needed to validate these preliminary data.

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Rivastigmine was recently indicated to have a possible positive effect on AD with comorbid apathy or depressive symptoms in a placebo-controlled study.[18,19] Some patients in this study responded well to low-dose rivastigmine (4.5 mg/day or 9 mg/day) with regard to their depressive state and apathy, loss of appetite, and low vitality. Thus, it is possible that our favorable results in the MMSE and other assessment scores might be related to improvement of depressive phenomenology, but this point will need further validation. In patients with cognitive dysfunction, decreased activities of daily living, abnormal behavior, and depression are reported to be predictive factors for mortality, and a low VI score is a good predictor of the progression of functional decline.[14] In this study, VI scores after treatment were significantly greater than the baseline values for both the LIR and HIR groups. Though it remains unclear why communication in the VI subscales in the LIR group produced a favorable result relative to the HIR group, these findings suggest that rivastigmine might improve mood or vitality even though the inhibitory rate of BuChE is lower.

One of the aims of pharmacological interventions for the treatment of AD is to reduce caregiver burden. Unfortunately, when assessed by the ZBI score, neither group demonstrated significantly reduced caregiver burden. In this study, though, the degree of caregiver burden based on the ZBI score[20] was moderate or lower the majority of the time [little or no burden (0-20); 65.2%, mild to moderate burden (21-40); 20.0%, moderate to severe burden (41-60); 11.5%, severe burden (61-88); 3.3%]. Also, a cut-off score ranging from 24–26 was reported to have significant predictive validity for identifying caregivers at risk for depression,[21] and the percentage of caregivers who were above this ZBI cut-off score was relatively low (29.5%). However, somewhat surprisingly, burden was not associated with changes in clinical improvements in this study. Some possible explanations for this lack of association may be overly positive expectations of caregivers for rivastigmine therapy, aging of caregivers, and caregiver distress due to behavioral and psychological symptoms of dementia. More research is needed to determine what kind of intervention is most effective in reducing the caregivers' burdens.

The results of this study must be viewed in light of its several critical limitations. First, the CGIC is subjective – it is the clinician's impression of change in a patient's condition. Second, the number of patients enrolled was relatively small. Third, this

study was conducted according to an open-label design. Finally, this study did not include an untreated control group that would have allowed us to better quantify the extent of the improvements observed with the treatments under study. Nevertheless, the aim of the study was to assess the real-life effectiveness of the inhibitory rate of serum BuChE activity in treatment-naïve patients. The limitations inherent in this study do not marginalize the importance of the information collected from the patients in a clinical setting without experimental intervention.

In conclusion, serum BuChE activity might be a cheaply and rapidly measured value with potential for use as a biomarker for rivastigmine treatment effectiveness in patients with AD, although further studies are needed to confirm our findings.

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No potential conflicts of interest were disclosed in this study.

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Table 1. Comparisons of serum BuChE, MMSE, modified CGBRS domains, VI domains and ZBI at baseline and week 24 (values are mean ± SD)

	Baseline (N =61)	Week 24 (N =61)	P-value
Serum BuChE (U/L)	271.6±80.8	158.5±69.1	<0.001***
MMSE score	19.3±4.1	20.6±5.3	0.003**
Modified CGBRS score	16.0±12.3	10.5±9.6	<0.001***
Comprehension to time and place	2.9±2.4	2.0±2.0	0.001**
Carrying out conversation	2.3±1.9	1.4±1.5	<0.001***
Cooperation	2.6±2.3	2.0±2.0	0.001**

Restlessness	0.7±1.5	0.2±0.6	0.002**
Dressing	2.2±2.6	1.4±2.0	<0.001***
Social activities	2.9±2.7	2.1±2.6	<0.001***
Leisure	2.3±2.5	1.4±1.9	<0.001***
VI score	8.2±1.8	9.0±1.4	<0.001***
Waking pattern	1.7±0.6	1.8±0.4	0.127
Communication	1.6±0.6	1.7±0.5	0.039*
Feeding	1.9±0.4	1.9±0.3	0.209
On and off toilet	1.7±0.5	1.8±0.4	0.035*
Rehabilitation and other activities	1.3±0.8	1.7±0.6	0.001**

ZBI score	20.6±17.0	20.0±15.4	0.740

*p<0.05; **p<0.01; ***p<0.001

BuChE=butyrylcholinesterase; MMSE=Mini-Mental State Examination; CGBRS=Crichton Geriatric Behavioral Rating Scale; VI=Vitality Index; ZBI=Zarit Burden Inventory; SD=Standard Deviation

Table 2. Demographic and clinical characteristics of patients at baseline

	Low inhibitory rate of BuChE activity (N =27)	High inhibitory rate of BuChE activity (N =34)	P-value
Females, n (%)	10 (33.3%)	20 (66.7%)	0.091
Males, n (%)	17 (54.8%)	14 (45.2%)	
Mean age, y (mean ± SD)	77.5±8.0	80.7±6.4	0.142
Mean weight, Kg (mean ± SD)	57.1±14.2	52.1±12.5	0.152
Mean length of education, y (mean ± SD)	11.0±2.2	11.2±2.2	0.740
Mean duration of disease, y (mean ± SD)	1.6±1.5	2.6±2.4	0.086

MMSE score (mean ± SD/total)	20.0±4.2/30	18.8±4.0/30	0.266
Modified CGBRS score (mean ± SD/total)	13.0±11.7/56	18.1±12.4/56	0.106
VI score (mean ± SD/total)	8.3±2.0/10	8.2±1.8/10	0.840
ZBI score (mean ± SD/total)	14.1±11.7/88	25.4±18.8/88	0.008**
CGIC score (mean ± SD)	3.0±1.1	3.2±1.2	0.590

**p<0.01

BuChE= butyrylcolinesterase; SD=Standard Deviation; MMSE=Mini-Mental State Examination; CGBRS=Crichton Geriatric Behavioral Rating Scale; VI=Vitality Index; ZBI=Zarit Burden Inventory; CGIC=Clinical Global Impression of Change

Table 3. Comparisons between the low inhibitory rate (LIR) and the high inhibitory rate (HIR) groups at baseline and week 24 (values are mean ± SD)

	LIR (N =27)		P-value	HIR (N =34)		P-value
	Baseline	Week 24		Baseline	Week 24	
Serum BuChE (U/L)	262.9±71.8	210±57.7	<0.001***	278.1±87.3	120.1±49.1	<0.001***
MMSE score	20.0±4.2	21.4±4.8	0.031*	18.8±4.0	19.9±5.7	0.035*
Modified CGBRS score	13.0±11.7	8.7±9.1	0.003**	18.1±12.4	11.9±9.9	<0.001***
Comprehension to time and place	2.6±2.2	1.7±1.8	0.015*	3.1±2.5	2.3±2.1	0.018*
Carrying out conversation	1.7±1.6	1.0±1.3	0.007**	2.8±2.0	1.7±1.6	<0.001***
Cooperation	2.2±2.4	1.8±2.3	0.187	2.9±2.1	2.1±1.9	<0.001***

Restlessness	0.5±1.3	0.2±0.6	0.183	0.9±1.7	0.2±0.5	0.007**
Dressing	2.2±2.7	1.5±2.2	0.048*	2.3±2.6	1.3±1.9	0.004**
Social activities	2.4±2.6	1.7±2.2	0.024*	3.2±2.7	2.5±2.8	0.003**
Leisure	1.5±2.1	0.7±1.0	0.068	2.9±2.6	1.9±2.2	<0.001***
VI score	8.3±2.0	9.2±1.6	0.006**	8.2±1.8	8.9±1.3	0.015*
Waking pattern	1.7±0.6	1.8±0.5	0.376	1.7±0.6	1.8±0.4	0.211
Communication	1.5±0.8	1.8±0.5	0.038*	1.6±0.5	1.7±0.5	0.487
Feeding	1.8±0.4	1.9±0.3	0.161	1.9±0.4	1.9±0.2	0.487
On and off toilet	1.7±0.5	1.9±0.3	0.103	1.7±0.6	1.8±0.5	0.184
Rehabilitation and other activities	1.5±0.8	1.8±0.5	0.070	1.2±0.8	1.6±0.6	0.005**

ZBI score	14.1±11.7	16.4±9.8	0.282	25.4±18.8	22.7±18.2	0.236

*p<0.05; **p<0.01; ***p<0.001

SD=Standard Deviation; BuChE=butyrylcholinesterase; MMSE=Mini-Mental State Examination; CGBRS=Crichton Geriatric Behavioral Rating Scale; VI=Vitality Index; ZBI=Zarit Burden Inventory