DOI: 10.1111/ggi.13644

ORIGINAL ARTICLE

EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Efficacy of rivastigmine transdermal therapy on low food intake in patients with Alzheimer's disease: The Attitude Towards Food Consumption in Alzheimer's Disease Patients Revive with Rivastigmine Effects study

Norifumi Tsuno,[1] Takahiro Mori,[1] Ichiro Ishikawa,[1] Nobuyasu Bando,[2] Haeyoung Park,[3] Yoshito Matsumoto,[4] Itsuko Mori,[5] Mariko Tanaka,[6] Takayuki Hirano[7] and Yu Nakamura[1]

[1]Department of Neuropsychiatry, Faculty of Medicine, Kagawa University, Miki-cho, Japan
[2]Department of Mental Health, Kaisei General Hospital, Sakaide, Japan
[3]Harukaze Clinic, Chiba, Japan
[4]Nishitakamatsu Neurosurgery and Internal Medicine Clinic, Takamatsu, Japan
[5]Medical Juridical Person Eisei Hospital, Nakatado, Japan
[6]Mino Tanaka Hospital, Miyoshi, Japan
[7]Zikeikai-Aoimori Hospital, Aomori, Japan

Correspondence
Dr Norifumi Tsuno MD PHD, Department of Neuropsychiatry, Faculty of Medicine, Kagawa University, 1750-1, Ikenobe, Miki-cho, Kita-gun, Kagawa, 761-0793, Japan.
Email: tsuno@med.kagawa-u.ac.jp

Received: 20 November 2018
Revised: 24 January 2019
Accepted: 3 February 2019

Aim: Most patients with Alzheimer's disease (AD) experience poor food intake and/or loss of appetite, which accelerates cognitive impairment. Several reports have shown that rivastigmine improves appetite in AD patients. The present study investigated the efficacy of a rivastigmine transdermal patch for the treatment of low food intake in AD patients.

Methods: AD patients, recruited through the Attitude Towards Food Consumption in Alzheimer's Disease Patients Revive with Rivastigmine Effects study, were recognized as experiencing either a loss of appetite or poor food intake. A rivastigmine transdermal patch was administered to study participants for 16 weeks. Patients' food intake, bodyweight, Mini-Mental State Examination scores and any adverse events were recorded.

Results: A total of 38 patients with AD (age 86.2 ± 5.4 years) were examined. Their mean Mini-Mental State Examination score was 10.1 ± 7.0 at baseline. A significant increase in food intake amount (54.9 ± 98.0 g, $P < 0.01$) and food intake ratio (9.3% ± 17.6%, $P < 0.01$) was observed by week 1, improvements that were maintained throughout the study duration. A multiple linear regression analysis showed that no independent variables were significantly associated with changes in food intake amount or ratio. Patients in the higher Mini-Mental State Examination subgroup showed a trend change in food intake amount, although this did not reach statistical significance ($P = 0.07$).

Conclusions: The present study suggests that a rivastigmine transdermal patch might improve poor food intake or loss of appetite in patients with AD. **Geriatr Gerontol Int 2019; 19: 571–576.**

Keywords: Alzheimer's disease, appetite, rivastigmine, transdermal patch.

Introduction

Worldwide, nearly 47 million people have Alzheimer's disease (AD) or a related dementia, which is the leading cause of disability in later life.[1] More than 80% of patients with AD manifest poor food intake or loss of appetite, which might increase their risk of further cognitive impairments, neuropsychiatric symptoms and malnutrition.[2] As a result, a vicious cycle decreases the functionality and quality of life in patients with AD.

Cholinesterase inhibitors (ChEI), namely donepezil, galantamine and rivastigmine, are first-line drugs and are used globally for the treatment of mild-to-moderate AD. ChEI function by inhibiting the breakdown of acetylcholine, an important neurotransmitter associated with memory, by the enzyme cholinesterase.[3] While donepezil and galantamine specifically inhibit acetylcholine esterase (AChE), rivastigmine inhibits both AChE and butyrylcholine esterase (BuChE), both of which act to hydrolyze intracerebral acetylcholine. BuChE is also known to degrade ghrelin,[4] a gastrointestinal tract hormone[5] that serves to increase appetite.[6,7] Some clinical reports have shown that rivastigmine therapy in AD patients has beneficial effects on appetite.[8–10] Loss of appetite in AD patients is thought to occur not only because of AD-associated cognitive impairments, but also because of additional comorbidities including depression, anxiety, gastrointestinal symptoms that accompany physical complications and disrupted swallowing caused by cerebrovascular complications. Rivastigmine was also reported to have beneficial effects on these symptoms.[9,11–13]

Although ChEI can have adverse effects on various cholinergic tissues, including both central and peripheral organs, these adverse effects are most evident in the gastrointestinal tract, where they result in symptoms such as nausea, vomiting or diarrhea.[14] Rivastigmine is currently the only approved drug for transdermal patch administration for the treatment of AD symptoms. Transdermal administration provides for continuous drug delivery and reduced plasma level fluctuations.[15] As such, the administration of rivastigmine through a transdermal patch makes it easier to achieve

optimal dosing, and might further offer improved tolerability and therapeutic advantages over other methods of administration. Considering these advantages and the problem of poor food intake among individuals with AD, the primary aim of the present study was to investigate the efficacy of a rivastigmine transdermal patch in the treatment of poor food intake in patients with AD.

Methods

Study design

The Attitude Towards Food Consumption in Alzheimer's Disease Patients Revive with Rivastigmine Effects (FOOD-ARRIVE) study was designed as a multicenter, prospective, observational, single-arm trial. This study was registered at the University Hospital Medical Information Network Clinical Trial Registry (UMIN000018172), a non-profit organization in Japan that meets the requirements of the International Committee of Medical Journal Editors. The study protocol was approved by the ethics review board at each participating institution. The present study was carried out according to the Declaration of Helsinki and all current legal regulations in Japan. Data collection and management were carried out by a third-party contract research organization to avoid any possible bias.

Study population

The present study was carried out at 17 clinical sites across Japan. Inpatients with AD at the study sites were approached to participate in this study from May 2015 to August 2016. Participant inclusion criteria were as follows: (i) a diagnosis of AD per the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition criteria; (ii) recently commenced regular use of rivastigmine transdermal patch therapy, as provisioned by individual health insurance; (iii) a clinically-recognized loss of appetite or poor food intake necessitating nursing care for mealtime support; and (iv) written informed consent for study participation provided by patients themselves or by a family member proxy. The use of other ChEI (donepezil or galantamine) was prohibited during the study period, but patients who had already used donepezil or galantamine, but agreed to switch to rivastigmine transdermal patch therapy, were also included. The use of other agents for AD treatment (such as memantine, yokukansan and psychotropic agents) was allowed if they had been used before the study, but dose change or withdrawal of these agents were prohibited during the study period. Participant exclusion criteria were as follows: (i) a history of hypersensitivity to rivastigmine, any components of rivastigmine or carbamate derivatives; (ii) a movement disorder that might affect food intake; (iii) a serious disease, such as malignant neoplasm or pneumonia, that might increase mortality; (iv) a functional gastrointestinal transit disorder; and (v) active physician concern about being otherwise unsuitable for participation. All participants were required to reside in an inpatient care facility for the duration of the study.

Rivastigmine administration

A rivastigmine transdermal patch was administered once daily to participants who met inclusion and exclusion criteria guidelines, as described above. In general, rivastigmine doses were sequentially increased by 4.5 mg every 4 weeks, starting at 4.5 mg. When a maximal daily dose of 18 mg was reached, this maximal dosing was maintained to week 16. Physicians were allowed to titrate rivastigmine dosing according to the patients' condition.

Observation period data

Participant data were recorded throughout a 16-week observation period. Data on participant food intake amount, food intake ratio, time spent eating lunch, bodyweight and study drug dosage were collected at baseline, and at weeks 1, 2, 3, 4, 6, 8, 12 and 16. Food intake amount (g) was measured by subtracting the after-meal total meal weight, including eating utensils, from that before meal. Similarly, a provided meal amount (g) was measured by subtracting the weight of eating utensils from the total meal weight (including eating utensils) before the meal. The food intake ratio was defined as the ratio of food intake amount to the provided meal amount. Food intake amount was measured at every mealtime of each time point, and mean food intake amount and food intake ratio of the day were calculated at each time point. Cognitive or neuropsychiatric function were assessed using the Neuropsychiatric Inventory-Nursing Home Version (NPI-NH)[16,17] (at baseline, and weeks 4, 8 and 16) and the Mini-Mental State Examination (MMSE)[18] (at baseline and week 16), respectively. All adverse events that occurred during the study observation period were recorded and reported.

Study outcomes

The primary end-points in the present study were changes to the mean food intake amount and ratio per day due to rivastigmine transdermal patch therapy. Secondary end-points were changes to the following outcomes: (i) time spent eating lunch; (ii) bodyweight; (iii) NPI-NH score; and (iv) MMSE score. Stratified analysis of the primary end-points by MMSE score was further carried out.

Statistical analysis

One-sample *t*-tests or Wilcoxon signed-rank tests were applied to continuous variables for detecting significant changes from baseline. A two-sample Student's *t*-test was applied to all continuous variables for two-group comparisons. A multiple linear regression analysis was carried out, with changes in food intake as dependent variables, and age, bodyweight, MMSE score, use of psychotropic drugs at baseline and physical complications as independent variables. First, by using univariate linear regression analysis, we detected variables having a P-value <0.1. By using these factors as independent variables, multiple linear regression analysis was carried out. Anonymized data management and statistical analyses were outsourced to a third-party contract research organization to ensure impartiality (Soiken, Osaka, Japan). All statistical analyses were carried out using SAS software version 9.3 (SAS Institute, Cary, NC, USA).

Results

Participant recruitment and clinical characteristics

A total of 38 patients with AD were enrolled at 17 clinical sites during the study period. One patient was excluded for violation of inclusion criteria (use of prohibited concomitant drug). The study participants were 10 men (27%) and 27 women (73%), aged 86.2 ± 5.4 years (mean ± SD). The mean time since first AD diagnosis was 46.7 ± 46.2 months, and the mean MMSE score was 10.1 ± 7.0. Nine patients (24.3%) had a history of psychotropic drug use. One patient used memantine. A total of 18 patients dropped out of the study. This attrition was due to the occurrence of adverse events ($n = 6$), discharge from hospital or care facility ($n = 9$) and transfer to another hospital ($n = 3$). Most reasons for discharge or transfer to another hospital were clinical improvement of symptoms (e.g. neuropsychiatric symptom). A total of 19 patients completed the 16-week observation period. The mean dose of rivastigmine was 4.7 ± 1.0 mg at baseline and 14.8 ± 3.8 mg at week 16 (Table 1).

Effect of rivastigmine through a transdermal patch on food intake

Figure 1 shows changes in food intake amount and ratio from baseline. Both food intake amount (192.0 ± 139.5 g and

Table 1 Characteristics of patients at baseline

Characteristics	
Sex (male/female)	10 (27.0)/27 (73.0)
Age (years)	86.2 ± 5.4
Bodyweight (kg)	39.6 ± 5.9
Elapsed time since Alzheimer's diagnosis (months)	46.7 ± 46.2
Psychotropic drug use history	9 (24.3)
MMSE score	10.1 ± 7.0

Total $n = 37$. Data are presented as number (%) or mean ± standard deviation. MMSE, Mini-Mental State Examination.

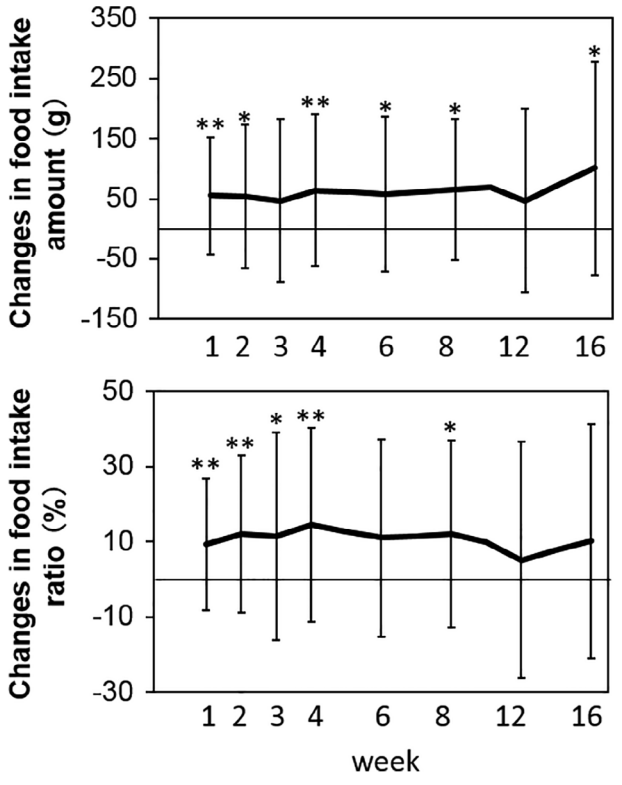

Figure 1 Changes in food intake after initiation of rivastigmine transdermal patch therapy. *$P < 0.05$, **$P < 0.01$ by one-sample *t*-test.

246 ± 160.4 g at baseline and week 1, respectively; change 54.9 ± 98.0 g, $P < 0.01$) and food intake ratio (40.5 ± 26.9% and 49.5 ± 28.6% at baseline and week 1, respectively; change 9.3 ± 17.6%, $P < 0.01$) significantly increased from baseline to week 1, increases that tended to be maintained throughout the study. A significant change in food intake amount from baseline was detected at weeks 1, 2, 4, 6, 8 and 16 ($P < 0.01$ at weeks 1 and 4, $P < 0.05$ at weeks 2, 6, 8 and 16), and in food intake ratio at weeks 1, 2, 3, 4 and 8 ($P < 0.01$ at weeks 1, 2, and 4, and $P < 0.05$ at weeks 3 and 8). No statistically significant change was detected in time spent eating lunch, bodyweight or NPI-NH or MMSE scores, except for NPI-NH score at week 4 (change from baseline −3.8 ± 9.9, $P = 0.039$; Table 2).

Change in food intake amount from baseline to week 16 was further analyzed between higher MMSE (MMSE ≥10, $n = 11$) and lower MMSE score (MMSE <10, $n = 6$; Fig. 2) patient subgroups. The higher MMSE score subgroup showed a significant improvement of food intake amount with the rivastigmine transdermal patch therapy (change 152.3 ± 189.9%, $P = 0.024$), whereas the lower MMSE subgroup did not (change 7.8 ± 110.9%, $P = 0.87$). The higher MMSE score subgroup also showed a non-significant trend towards a larger change in food intake amount than the lower MMSE subgroup ($P = 0.07$).

A multiple linear regression analysis was carried out to explore the variables that might predict changes to food intake after rivastigmine treatment through a transdermal patch at week 16, including age, bodyweight, MMSE score, use of psychotropic drugs at baseline and any physical complications (Table 3). No independent variables were significantly associated with changes to food intake amount or ratio.

Adverse events

Events were reported in 16 of the total 38 study participants (42.1%). The most common adverse event was application site erythema ($n = 5$, 13.2%), followed by aspiration pneumonia ($n = 3$, 7.9%), contact dermatitis ($n = 2$, 5.3%), urinary tract infection ($n = 2$, 5.3%), behavioral and psychological symptoms of dementia ($n = 2$, 5.3%), and pneumonia ($n = 2$, 5.3%). Serious adverse events were reported in two patients (2 aspiration pneumonia 5.3%, and 1 emphysema 2.6%).

Discussion

The present study shows that rivastigmine transdermal patch therapy increased the dietary food intake amount in AD patients experiencing loss of appetite symptomatology. Previous work has shown that a majority of AD patients experience a problematic loss of appetite.[2] These eating problems occur even in mild AD,[2] and represent one of the greatest sources of complications and mortality in advanced AD patients.[19] AD patients who had a clinically-recognized loss of appetite or poor food intake, and who required nursing care, were enrolled in the present study. The mean MMSE score of enrolled participants was 10.1 ± 7.0, representing moderate-to-severe AD. Although the food intake amount significantly improved in the higher MMSE subgroup (MMSE ≥10), it did not in the lower MMSE subgroup (MMSE <10), and the difference in food intake amount between the MMSE severity subgroups did not reach statistical significance (Fig. 2). This suggests that the rivastigmine transdermal patch therapy might be more effective in mild AD than in moderate or severe AD for the treatment of appetite deficits. As the loss of appetite and weight loss have been shown to hasten the onset of AD and progression of cognitive impairments, we suggest that rivastigmine transdermal patch therapy should be administered to dementia patients who present with abnormal eating behaviors, a loss of appetite or significant weight loss.[20–22] The present results showed that the food intake ratio is likely to improve at the beginning of the study period, particularly at weeks 1, 2, 3, 4 and 8 (Fig. 1). This raises the possibility that the rivastigmine transdermal patch might be more effective for poor appetite in lower doses. In contrast, a significant improvement of food intake amount tended to be maintained throughout the observation period. Although the present study did not detect the correlation between the dose of rivastigmine and improvement of poor appetite, further study might be required to ascertain this relationship.

Several reports have shown that rivastigmine bolsters appetite in AD patients.[8–10] The present study further shows that the rivastigmine transdermal patch, when used in AD patients with a loss of appetite, significantly increased patient food intake amount and ratio (Fig. 1; Table 2). One potential underlying mechanism for this might be that rivastigmine suppresses the degradation of plasma ghrelin by inhibiting plasma BuChE.[23] Ghrelin is a gastrointestinal tract hormone[5] known to increase appetite.[6,7] Further potential mechanisms for this improvement of appetite in patients with AD might be both the inflammatory effects of ChEI in cholinergic pathways, and their ability to improve smell and taste perception by increasing the acetylcholine concentration in olfactory mucosa and taste buds, respectively.[24,25] In addition to rivastigmine's inhibition of ChE, it might further contribute to improved swallowing by inhibiting BuChE.[9] All of these potential mechanisms serve as targets for illumination by future studies.

Table 2 Changes in study parameters

Variable	baseline	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 12	Week 16
Food intake amount (g)	192.0 ± 139.5 (37)	246.0 ± 160.4 (34)	247.3 ± 136.4 (30)	239.9 ± 143.5 (30)	255.5 ± 143.6 (30)	254.1 ± 145.3 (24)	258.9 ± 148.8 (23)	256.8 ± 160.5 (18)	304.3 ± 155.8 (17)
Change	–	54.9 ± 98.0 (34)	54.0 ± 118.7 (30)	46.6 ± 135.8 (30)	63.9 ± 125.7 (30)	57.4 ± 128.8 (24)	65.9 ± 117.7 (23)	47.2 ± 153.4 (18)	101.3 ± 177.3 (17)
P-value	–	0.003	0.019	0.07	0.009	0.039	0.014	0.21	0.032
Food intake ratio (%)	40.5 ± 26.9 (36)	49.5 ± 28.6 (33)	51.1 ± 27.3 (30)	50.4 ± 30.2 (30)	53.7 ± 29.9 (30)	50.8 ± 28.6 (24)	50.8 ± 28.2 (23)	50.6 ± 30.1 (18)	55.2 ± 24.5 (17)
Change	–	9.3 ± 17.6 (33)	12.1 ± 20.9 (30)	11.4 ± 27.7 (30)	14.6 ± 25.8 (30)	11.0 ± 26.4 (24)	12.1 ± 25.0 (23)	5.2 ± 31.5 (18)	10.2 ± 31.1 (17)
P-value	–	0.005	0.004	0.032	0.004	0.05	0.030	0.50	0.19
time spent eating lunch (min)	27.4 ± 16.0 (33)	28.7 ± 15.6 (31)	31.2 ± 15.7 (28)	28.9 ± 14.0 (26)	27.1 ± 15.9 (26)	28.5 ± 15.6 (23)	30.6 ± 17.7 (21)	33.0 ± 18.3 (18)	33.4 ± 19.2 (17)
Change	–	0.6 ± 13.2 (29)	2.3 ± 12.1 (26)	−1.7 ± 12.9 (25)	−1.8 ± 14.2 (25)	−2.5 ± 13.2 (20)	−0.9 ± 11.7 (18)	−2.5 ± 11.6 (15)	−4.3 ± 17.5 (15)
P-value	–	0.82	0.34	0.52	0.54	0.42	0.75	0.42	0.36
Bodyweight (kg)	39.6 ± 5.9 (33)	39.5 ± 5.8 (31)	39.4 ± 5.5 (28)	39.4 ± 5.4 (28)	39.4 ± 4.6 (29)	39.9 ± 4.5 (20)	38.9 ± 4.5 (21)	38.5 ± 4.7 (18)	39.2 ± 3.9 (16)
Change	–	−0.1 ± 1.2 (30)	−0.1 ± 1.6 (27)	−0.2 ± 2.0 (27)	−0.5 ± 2.6 (27)	−0.2 ± 2.0 (17)	−0.4 ± 2.0 (18)	0.9 ± 3.2 (15)	0.2 ± 2.5 (13)
P-value	–	0.52	0.64	0.66	0.37	0.67	0.41	0.30	0.74
NPI-NH score	13.4 ± 16.1 (36)	–	–	–	10.3 ± 11.3 (31)	–	10.9 ± 14.4 (22)	–	7.8 ± 8.1 (17)
Change	–	–	–	–	−3.8 ± 9.9 (31)	–	−4.2 ± 15.1 (22)	–	−4.9 ± 13.8 (17)
P-value	–	–	–	–	0.039	–	0.20	–	0.16
Caregiver burden	4.9 ± 6.5 (36)	–	–	–	4.1 ± 5.0 (31)	–	3.8 ± 5.3 (22)	–	3.2 ± 4.6 (17)
Change	–	–	–	–	−1.2 ± 4.0 (31)	–	−1.7 ± 4.7 (22)	–	−2.1 ± 5.7 (17)
P value	–	–	–	–	0.12	–	0.10	–	0.16
MMSE score	10.1 ± 7.0 (36)	–	–	–	–	–	–	–	11.9 ± 8.2 (19)
Change	–	–	–	–	–	–	–	–	0.1 ± 3.6 (19)
P value	–	–	–	–	–	–	–	–	0.90

Data are presented as mean ± standard deviation (n). *P* -values show results of statistical tests for changes by one sample t-test. *MMSE*, Mini-Mental State Examination; *NPI-NH*, Neuropsychiatric Inventory in Nursing Home version.

Table 3 Multiple linear regression for changes in food intake amount and ratio at week 16

Independent variable	Food intake amount (g)		Food intake ratio (%)	
	Regression coefficient (SE)	*P*-value	Regression coefficient (SE)	*P*-value
Age (years)	−4.86 (14.42)	0.74	0.68 (2.54)	0.79
Baseline weight (kg)	4.51 (10.90)	0.69	0.16 (1.99)	0.94
Baseline MMSE score	6.62 (5.92)	0.28	0.12 (1.08)	0.92
Baseline psychotropic drug use	−70.90 (95.75)	0.47	−10.54 (16.91)	0.54
Complications/comorbidity				
Constipation	20.85 (92.79)	0.83	−8.20 (16.19)	0.62
Hypertension	−59.66 (103.58)	0.57	−0.35 (18.39)	0.98
Reflux esophagitis	−86.58 (136.04)	0.53	−14.92 (23.91)	0.54
Osteoporosis	137.11 (133.24)	0.32	29.52 (22.99)	0.22
Chronic gastritis	77.34 (136.41)	0.58	13.97 (23.95)	0.57
Heart failure	−136.55 (111.06)	0.24	−14.88 (20.10)	0.47
Gastric ulcer	−29.02 (137.66)	0.84	8.88 (24.11)	0.72
Overactive bladder	−25.51 (137.71)	0.86	3.85 (24.20)	0.88
Asthma	−36.01 (188.55)	0.85	10.04 (33.06)	0.77
Hypothyrosis	0.00 (–)	-	0.00 (–)	-
Hyperuricemia	−275.07 (174.91)	0.14	−41.83 (31.35)	0.20
Prostatomegaly	0.00 (–)	-	0.00 (–)	-
Diabetes	0.00 (–)	-	0.00 (–)	-
Cerebrovascular disease	−69.52 (88.45)	0.44	−6.10 (15.78)	0.70
Psychiatric disorder	33.15 (89.85)	0.72	6.56 (15.76)	0.68

MMSE, Mini-Mental State Examination.

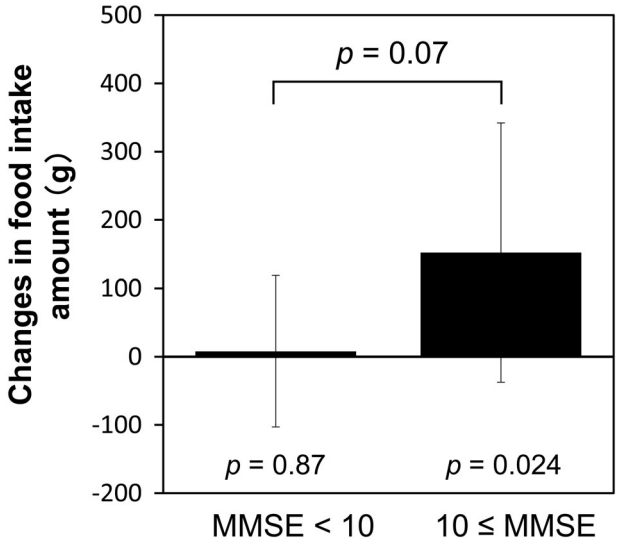

Figure 2 Changes in food intake amount from baseline to week 16 in lower and higher Mini-Mental State Examination (MMSE) severity subgroups. *P*-values show results of statistical tests for intragroup comparison by one-sample *t*-test or for intergroup comparison by two-sample *t*-test.

Unlike changes to appetite, we did not find differences in bodyweight, NPI-NH or MMSE scores with rivastigmine transdermal patch therapy in the present study. Multiple linear regression analyses also showed that baseline age, bodyweight, MMSE score, use of psychotropic drugs and physical complications during the study were not significantly associated with changed food intake (Table 3). These results suggest that the increased food intake participants in the present study showed was directly related to rivastigmine action on appetitive drive and not by changes to bodyweight or cognitive function. Nevertheless, other confounders could not be entirely eliminated from the present study. Further large-scale randomized controlled trials are required to have significant statistical power to evaluate the influence of other factors on the improvement of food intake during rivastigmine transdermal patch therapy.

Rivastigmine is generally well tolerated and effective in benefitting a number of symptom domains, including cognition, global functioning and performance of activities of daily living, in patients with mild-to-moderate AD.[26] However, high doses of rivastigmine are associated with an increased incidence of gastrointestinal adverse events, such as nausea, vomiting and diarrhea.[14,27] It was reported that a rapid increase in maximum rivastigmine concentration was associated with these adverse gastrointestinal events.[28] Compared with oral dosing, transdermal delivery reduces maximum rivastigmine concentration and prolongs the time to maximum rivastigmine concentration for an equivalent dose.[15] In addition, transdermal delivery reduces plasma drug level fluctuations and allows for more continuous drug delivery. This prolonged time to maximum rivastigmine concentration might improve the gastrointestinal tolerability of rivastigmine.[27–29] Indeed, although adverse events were reported in >40% of the present study participants, no adverse gastrointestinal events (e.g. nausea, vomiting and diarrhea) were reported during the 16-week study period.

The present study had several limitations. First, a relatively small number of study participants were included in this study. Because of this small sample size and attrition of some participants (3 men and 14 women by week 16), biases in our data should be carefully considered. An additional limitation was the study's single-arm, observational design, which did not include a placebo or competitor drug control group. A final limitation was that rivastigmine was only administered for 16 weeks. Despite these limitations, the present study provides some novel insights into treatment of appetitive suppression in AD. Direct comparisons among ChEI in clinical studies have not suggested any significant differences of the effect on cognitive impairments in AD patients, suggesting that the mechanism by which rivastigmine acts is more central to hunger.[30] The present findings might aid clinicians and others in the selection of ChEI for the treatment of patients with AD. Further investigation might be required to confirm the present findings in large-scale and long-term trials, also to directly compare rivastigmine transdermal patch therapy with other ChEI treatment.

Acknowledgements

This study was supported by Ono Pharmaceutical. The authors thank Shoji Kikui, Mitsuhiro Nishigawa, Hiromichi Taniuchi,

Yoshimasa Takase and Harutaka Yamada for their participation in and contribution to this study.

Disclosure statement

Norifumi Tsuno has received research funds from Daiichi Sankyo, Novartis Pharma and Mitsubishi Tanabe Pharma. Haeyoung Park has received a lecture fee from Otsuka Pharmaceutical. Takayuki Hirano has received lecture fees from Daiichi Sankyo, Eisai Co, MSD, Otsuka Pharmaceutical, Janssen Pharmaceutical, Novartis Pharma, Ono Pharmaceutical, Yoshitomiyakuhin Corporation, Mochida Pharmaceutical, Takeda Pharmaceutical, Ono Pharmaceutical, Eli Lilly and Company, and Meiji; travel fees for attending lecture meetings from Otsuka Pharmaceutical, Janssen Pharmaceutical, Eli Lilly and Company, Tsumura & Co., and Sumitomo Dainippon Pharma; and research funds from Daiichi Sankyo, Eli Lilly and Company, and Ono Pharmaceutical. Yu Nakamura has received a lecture fee from Otsuka Pharmaceutical, Daiichi Sankyo, Eisai, MSD, Novartis Pharma, Ono Pharmaceutical, Mochida Pharmaceutical, Takeda Pharmaceutical, Eli Lilly and Company, Janssen Pharmaceutical, Sumitomo Dainippon Pharma, Biogen Japan Co, Pfizer, Boehringer Ingelheim, GE Health Care Japan, Astellas Pharma, Toyama Chemical, and Meiji. Takahiro Mori, Ichiro Ishikawa, Nobuyasu Bando, Yoshito Matsumoto, Itsuko Mori and Mariko Tanaka declare no conflict of interest.

References

1 Prince M, Comas-Herrera A, Knapp M, Guerchet M, Karaglannidou M. *World Alzheimer Report 2016*. London: Alzheimer's Disease International, 2016.
2 Kai K, Hashimoto M, Amano K, Tanaka H, Fukuhara R, Ikeda M. Relationship between eating disturbance and dementia severity in patients with Alzheimer's disease. *PLoS One* 2015; **10**: e0133666.
3 Grossberg GT. Cholinesterase inhibitors for the treatment of Alzheimer's disease: getting on and staying on. *Curr Ther Res Clin Exp* 2003; **64**: 216–235.
4 De Vriese C, Gregoire F, Lema-Kisoka R, Waelbroeck M, Robberecht P, Delporte C. Ghrelin degradation by serum and tissue homogenates: identification of the cleavage sites. *Endocrinology* 2004; **145**: 4997–5005.
5 Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature* 1999; **402**: 656–660.
6 Kojima M, Kangawa K. Ghrelin: structure and function. *Physiol Rev* 2005; **85**: 495–522.
7 Muller TD, Nogueiras R, Andermann ML *et al*. Ghrelin. *Mol Metab* 2015; **4**: 437–460.
8 Bullock R, Bergman H, Touchon J *et al*. Effect of age on response to rivastigmine or donepezil in patients with Alzheimer's disease. *Curr Med Res Opin* 2006; **22**: 483–494.
9 Uwano C, Suzuki M, Aikawa T *et al*. Rivastigmine dermal patch solves eating problems in an individual with advanced Alzheimer's disease. *J Am Geriatr Soc* 2012; **60**: 1979–1980.
10 Soysal P, Isik AT. Effects of acetylcholinesterase inhibitors on nutritional status in elderly patients with dementia: a 6-month follow-up study. *J Nutr Health Aging* 2016; **20**: 398–403.
11 McKeith I, Del Ser T, Spano P *et al*. Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. *Lancet* 2000; **356**: 2031–2036.
12 Winblad B, Cummings J, Andreasen N *et al*. A six-month double-blind, randomized, placebo-controlled study of a transdermal patch in Alzheimer's disease--rivastigmine patch versus capsule. *Int J Geriatr Psychiatry* 2007; **22**: 456–467.
13 Nakamura Y, Imai Y, Shigeta M *et al*. A 24-week, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety and tolerability of the rivastigmine patch in Japanese patients with Alzheimer's disease. *Dement Geriatr Cogn Dis Extra* 2011; **1**: 163–179.
14 Ali TB, Schleret TR, Reilly BM, Chen WY, Abagyan R. Adverse effects of cholinesterase inhibitors in dementia, according to the pharmacovigilance databases of the United-States and Canada. *PLoS One* 2015; **10**: e0144337.
15 Kurz A, Farlow M, Lefevre G. Pharmacokinetics of a novel transdermal rivastigmine patch for the treatment of Alzheimer's disease: a review. *Int J Clin Pract* 2009; **63**: 799–805.
16 Wood S, Cummings JL, Hsu MA *et al*. The use of the neuropsychiatric inventory in nursing home residents. Characterization and measurement. *Am J Geriatr Psychiatry* 2000; **8**: 75–83.
17 Shigenobu K, Hirono S, Tabushi K, Ikeda M. Validity and reliability of the Japanese version of the Neuropsychiatric Inventory-Nursing Home Version (NPI-NH). *Brain Nerve* 2008; **60**: 1463–1469.
18 Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; **12**: 189–198.
19 Mitchell SL, Teno JM, Kiely DK *et al*. The clinical course of advanced dementia. *N Engl J Med* 2009; **361**: 1529–1538.
20 Stewart R, Masaki K, Xue QL *et al*. A 32-year prospective study of change in body weight and incident dementia: the Honolulu-Asia Aging Study. *Arch Neurol* 2005; **62**: 55–60.
21 Johnson DK, Wilkins CH, Morris JC. Accelerated weight loss may precede diagnosis in Alzheimer disease. *Arch Neurol* 2006; **63**: 1312–1317.
22 Cova I, Clerici F, Rossi A *et al*. Weight loss predicts progression of mild cognitive impairment to Alzheimer's disease. *PLoS One* 2016; **11**: e0151710.
23 Kuroda A, Setoguchi M, Uchino Y, Nagata K, Hokonohara D. Effect of rivastigmine on plasma butyrylcholine esterase activity and plasma ghrelin levels in patients with dementia in Alzheimer's disease. *Geriatr Gerontol Int* 2018; **18**: 886–891.
24 Dando R, Roper SD. Acetylcholine is released from taste cells, enhancing taste signalling. *J Physiol* 2012; **590**: 3009–3017.
25 Schofield PW, Finnie S, Yong YM. The role of olfactory challenge tests in incipient dementia and clinical trial design. *Curr Neurol Neurosci Rep* 2014; **14**: 479.
26 Rosler M, Anand R, Cicin-Sain A *et al*. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. *BMJ* 1999; **318**: 633–638.
27 Sadowsky CH, Micca JL, Grossberg GT, Velting DM. Rivastigmine from capsules to patch: therapeutic advances in the management of Alzheimer's disease and Parkinson's disease dementia. *Prim Care Companion CNS Disord* 2014; **16**. https://doi.org/10.4088/PCC.14r01654.
28 Lefevre G, Sedek G, Jhee SS *et al*. Pharmacokinetics and pharmacodynamics of the novel daily rivastigmine transdermal patch compared with twice-daily capsules in Alzheimer's disease patients. *Clin Pharmacol Ther* 2008; **83**: 106–114.
29 Cummings J, Winblad B. A rivastigmine patch for the treatment of Alzheimer's disease and Parkinson's disease dementia. *Expert Rev Neurother* 2007; **7**: 1457–1463.
30 Tsuno N. Donepezil in the treatment of patients with Alzheimer's disease. *Expert Rev Neurother* 2009; **9**: 591–598.

How to cite this article: Tsuno N, Mori T, Ishikawa I, et al. Efficacy of rivastigmine transdermal therapy on low food intake in patients with Alzheimer's disease: The Attitude Towards Food Consumption in Alzheimer's Disease Patients Revive with Rivastigmine Effects study. Geriatr. Gerontol. Int. 2019;19:571–576. https://doi.org/10.1111/ggi.13644