Different clinical effect of 4 anti-dementia drugs

for Alzheimer's patients depending on white matter severity

Yusuke Fukui, Nozomi Hishikawa, Jin Ichinose, Kota Sato, Yumiko Nakano, Ryuta Morihara, Yasuyuki Ohta, Toru Yamashita, and Koji Abe*

Department of Neurology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences,

Okayama University, 2-5-1 Shikatacho, Kitaku, Okayama 700-8558, Japan

*Corresponding author: Prof. Koji Abe

Department of Neurology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences,

Okayama University, 2-5-1 Shikata-cho, Okayama 700-8558, Japan.

Tel.: +81-86-235-7365, Fax: +81-86-235-7368, E-mail: peer1tcc@s.okayama-u.ac.jp

Short running title: Four anti-dementia drugs for AD with WMLs

Abstract

AIM: In order to examine the clinical effect of four anti-dementia drugs (donepezil, galantamine, rivastigmine, and memantine) in Alzheimer's disease (AD) patients who were divided into subgroups based on their periventricular hyperintensity (PVH)-severity.

METHODS: 551 AD patients (201 males and 350 females) were divided into four subgroups based on their PVH-severity (0-III). They received monotherapy for 12 months (M). We compared the clinical effects at the baseline and at 3, 6, and 12 M after initiation.

RESULTS: The baseline age became higher with PVH grades, and the mini-mental state examination (MMSE) and Hasegawa dementia scale-revised (HDS-R) showed a decrease that was dependent on white matter (WM) severity. Although the PVH 0 subgroup showed stable cognitive, affective, and ADL functions until 12 M in all four drug groups, the PVH I subgroup showed an improved apathy scale (AS) from the baseline in response to memantine at 3 and 9 M ($p < 0.05$), and galantamine at 9 M ($p < 0.01$). In the PVH II subgroup, MMSE showed a significant improvement from the baseline in response to galantamine ($p < 0.05$) at 9 M and HDS-R ($p < 0.05$) at 3 M. In the PVH III subgroup, cognitive and affective functions were preserved in all four drug groups until 12 M, but ADL deteriorated in the riverstigmine group at 6 and 12 M ($p < 0.05$).

CONCLUSIONS: The present study demonstrates that these four drugs showed sensitivity dependent on WM severity that clinically affected cognitive, affective and ADL functions.

Keywords: Alzheimer's disease, anti-dementia drug, magnetic resonance imaging, periventricular hyperintensity, white matter lesions

Introduction

As a result of a rapidly aging world population, dementia has become a significant social priority. Alzheimer's disease (AD) is the most common cause of dementia, and is a neurodegenerative disease characterized by the presence of amyloid-beta (Aβ) plaques with neuritic plaques and neurofibrillary tangles that add to the severity of these changes [1].

White matter lesions (WMLs), including periventricular hyperintensity (PVH) and deep white matter hyperintensity (DWMH), are visualized as an increased signal on T2-weighted and fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) sequences [2], and are observed in normal elderly adults as well as in AD patients. In a previous report, WMLs are associated with clinical risk and a symptomatic course of AD [3]. The volume of PVH was also associated with neurofibrillary tangles and the volume of DWMH was associated with diffuse plaques indicating that AD pathology may contribute to the vascular or white matter pathology [4]. Notably, our previous studies demonstrated that the severity of WMLs was closely related to AD pathology, and strongly

influenced the deterioration of cognitive and affective functions in AD patients [5, 6]. Early stage AD patients may be more vulnerable to the cognitive effect of WHLs than cognitively normal elderly adults with a similar burden of WHLs [7].

Although there has been much debate about the relation between AD pathology and WMLs, there is no report on the WML-dependent effectiveness of drugs on AD patients. In the present study, therefore, we examined the clinical effect of four anti-dementia drugs (donepezil, galantamine, rivastigmine, and memantine) in AD patients who were divided into subgroups based on their PVH severity.

Materials and Methods

Participants and study design

This was a retrospective clinical cohort study performed in the outpatient clinic of Okayama University Hospital and affiliated hospitals from June 2011 to March 2016. For the present study, we recruited 551 AD patients (201 males and 350 females; 78.4 ± 7.3 years old, mean ± SD) that were on monotherapy with donepezil, galantamine, rivastigmine, or memantine. All patients are prescribed anti-AD drugs for the first time. Those patients that were receiving combination therapy or

that switched to a combination therapy of cholinesterase inhibitor plus memantine were excluded from

this study. AD patients were diagnosed with probable or possible AD according to the National

Institute of Neurological and Communicative Disorders and Stroke AD and Related Disorders

Association (NINCDS-ADRDA). Magnetic resonance imaging (MRI) was used to estimate changes in

white matter (WM) with PVH using the Fazekas scale [8] on T2 weighted images (T2WI) and fluid

attenuated inversion recovery (FLAIR) images, and were divided into four subgroups according to the

grade of PVH (0-III). Furthermore, parahippocampal gyrus atrophy of each PVH group was evaluated

using Z score of the voxel-based specific regional analysis system for Alzheimer's disease (VSRAD) [9]

which become an indicator reflecting the degree of the entorhinal cortex for diagnosis of early AD [10].

The drug dose was gradually increased as follows: donepezil, from 3 to 5 or 10 mg;

galantamine, from 8 to 16 or 24 mg over 4 or 8 weeks; rivastigmine, from 4.5 to 18 mg over 16 weeks;

memantine, from 5 to 20 mg over 4 weeks. Cognitive functions were assessed using the mini-mental

state examination (MMSE) and Hasegawa dementia scale-revised (HDS-R). The behavioral and

psychological symptoms of dementia (BPSD) were assessed using the 15-item geriatric depression

scale (GDS) for depression, the apathy scale (AS) for apathy, and Abe's BPSD score (ABS) [11]. In

addition, the activities of daily living (ADL) were assessed using the Alzheimer's Disease Cooperative

Study-Activities of Daily Living (ADCS-ADL). These scores were assessed at the baseline and at 3, 6,

and 12 months (M) after initiation (12 M as a whole).

Ethical permission for this study was provided by the Ethics Committee on

Epidemiological Studies of the Okayama University Graduate School of Medicine, Dentistry and

Pharmaceutical Sciences (approval #775), and written informed consent was obtained from all

participants prior to enrollment.

Statistical analysis

Demographic and clinical data are presented as mean ± S.D. in the text and tables.

Statistical analyses were performed using statistical software (SPSS 22.0.0.0; IBM, Armonk, New

York, USA). Differences in the distribution of demographic factors among PVH grades (0 - III) were

analyzed using the χ^2 test and Jonckheere-Terpstra's test. After having checked for normality, baseline

age, Z scores of VSRAD and six clinical scores (i.e., MMSE, HDS-R, GDS, AS, ABS, and

ADCS-ADL) were compared using the Kraskal-Wallis test among PVH grades (0 - III) or

anti-dementia drugs. Similarly, changes from the baseline at each time point were compared using the

Kraskal-Wallis test among anti-dementia drugs. P-values < 0.05 were considered to be significantly

different.

Results

Participants' characteristics

The baseline demographic and clinical features of all AD patients (n=551) and each group

according to the grade of PVH (0-III) are shown in Table 1. The ratio of females among the 551 AD

patients was 63.5 % and the average age of all AD patients was 78.4 ± 7.3 years old (yo, mean $\pm$ SD).

The number of patients in each PVH groups was as follows: PVH 0; n=41, PVH I; n=212, PVH II;

n=179, PVH III; n=119. Although there were no differences in the gender ratio, Z score of VSRAD,

emotional scores (GDS, AS, ABS) or ADL in the four PVH subgroups, the baseline age showed a

WM-severity-dependent increase: 72.2 ± 8.1 yo for PVH 0, 77.5 ± 6.8 yo for PVH I, 79.6 ± 6.7 yo for

PVH II, and 80.5 ± 7.4 yo for PVH III (** $p < 0.01$ vs PVH 0, ## $p < 0.01$ vs PVH I, and p-value for

increasing trend < 0.001). In contrast, cognitive scores showed a WM-severity-dependent decreases in

MMSE (21.1 ± 4.2 for PVH 0, 21.0 ± 4.6 for PVH I, 19.4 ± 5.3 for PVH II, and 19.2 ± 4.6 for PVH

III), and HDS-R (19.2 ± 5.6 for PVH 0, 19.0 ± 5.7 for PVH I, 16.7 ± 6.2 for PVH II, and 16.7 ± 5.3 for

PVH III) (# $p < 0.05$ vs PVH I, ## $p < 0.01$ vs PVH I, and p-value for increasing trend < 0.001).

Table 2 shows the change of each drug dosage (mg/day) from 3 to 12 M, and baseline

PVH-severity-dependent features of AD patients in the four drug subgroups. The average drug dosage

showed a progressive increase from 3 to 12 M in all four drugs (Table 2, top). Finally, 249 patients

dropped out or were lost to follow up, and 302 patients remained. The number of patients in each drug

subgroup was showed in Table 2 (the digit in parentheses shows the number of patients in each term).

In the PVH 0 subgroup (n=41), the rivastigmine group showed a higher baseline ABS (12.3 ± 10.0)

than the donepezil group (2.1 ± 3.1, * $p < 0.05$). In the PVH I subgroup (n=212), the memantine group

showed a higher baseline ABS (9.8 ± 6.9) than the donepezil group (2.8 ± 3.9, * $p < 0.05$) and the

galantamine group (3.2 ± 4.4, # $p < 0.05$). In the PVH II subgroup (n=179), the memantine group

(12.0 ± 9.3) again showed a higher baseline ABS (12.0 ± 9.3) than the donepezil group (3.1 ± 5.4, * p

< 0.05). There were no significant differences in the baseline age and other baseline scores.

Changes from the baseline after the therapy

Fig. 1 - 4 summarize the mean changes of each drug from the baseline (0 M) to 3, 6, 9, and

12 M in PVH 0-III. The data of memantine was omitted from Fig. 1 because there were only two cases

(Table 2). As shown in Fig. 1, the PVH 0 subgroup preserved cognitive MMSE and HDS-R, affective

GDS, AS, ABS, and ADL until 12 M of each drug treatment. An inter-drug comparison showed that

MMSE was better preserved in the galantamine group (1.1 ± 4.0, * $p < 0.05$ vs donepezil) than in the

donepezil group (-1.2 ± 1.9) at 9 M, while GDS was better preserved in the galantamine group ($-0.8 \pm$

3.9) than in the rivastigmine group (1.2 ± 1.6, # $p < 0.05$ vs galantamine) at 9 M.

Fig. 2 also shows the preservation of cognitive MMSE and HDS-R, and affective GDS and ABS until 12 M in the PVH I subgroup. AS showed an improvement from the baseline in the memantine group at 3 M (-9.0 ± 10.8, ¶ $p < 0.05$) and 9 M (-4.2 ± 5.9, ¶ $p < 0.05$) and in the galantamine group at 9 M (-2.5 ± 6.7, §§ $p < 0.01$). The donepezil group worsened in AS at 9 M from the baseline (4.3 ± 10.0, † $p < 0.05$). ADL worsened in the galantamine group (-0.9 ± 4.0, § $p < 0.05$) at 12 M. The inter-drug comparison showed an improvement of ABS in the memantine group (-5.4 ± 4.2, * $p < 0.05$ vs donepezil) than in the donepezil group (0.4 ± 2.6) at 9 M.

Fig. 3 shows well preserved affective GDS, AS, and ABS until 12 M in the PVH II subgroup. MMSE showed a significant improvement from the baseline in the galantamine group (1.5 ± 2.2, § $p < 0.05$) at 9 M and HDS-R (0.4 ± 3.7, § $p < 0.05$) at 3 M. However, the galantamine group showed a significant decline of ADL (-1.8 ± 2.6, § $p < 0.05$) at 12 M. The inter-drug comparison showed better preservation of MMSE in the galantamine group (1.5 ± 2.2, ** $p < 0.01$ vs donepezil) than in the donepezil group (-2.8 ± 2.4) at 9 M.

As shown in Fig. 4, the PVH III subgroup showed well preserved MMSE, HDS-R, GDS, AS, and ABS until 12 M. ADL deteriorated in the riverstigmine group at 6 M (-3.3 ± 2.5, ‡ $p < 0.05$) and 12 M (-3.3 ± 2.7, ‡ $p < 0.05$). The inter-drug comparison showed better preservation of HDS-R in

the rivastigmine group (0.5 ± 4.5, ** p < 0.01 vs donepezil) and the galantamine group (-0.5 ± 5.4, * p

< 0.05 vs donepezil) than in the donepezil group (-4.1 ± 4.6).

Discussion

In the present study, we evaluated the clinical features of AD patients who were divided

into four subgroups according to the PVH grade (0-III). The baseline age became higher with PVH

grades (Table 1), and cognitive scores (MMSE and HDS-R) showed a WM-severity-dependent

decrease (Table 1). The ABS baseline of the rivastigmine group (PVH 0) and the memantine group

(PVH I-II) was significantly higher than that of the donepezil group, while that of the memantine

group was significantly higher than that of the galantamine group (Table 2). However, there were no

significant differences in the baseline age and other baseline scores among the four drug groups (Table

2). The PVH 0 subgroup showed preserved cognitive, affective, and ADL functions until 12 M in all

four drug groups. After treatment with memantine and galantamine, AS improved significantly from

the baseline in the PVH I subgroup while galantamine showed a worse ADL from the baseline (Fig. 2).

In the PVH II subgroup, galantamine showed a significant improvement of cognitive scores (MMSE

and HDS-R) from the baseline but a worse ADL from the baseline (Fig. 3). In the PVH III subgroup,

MMSE, HDS-R, GDS, AS, and ABS were well preserved in all four drug groups until 12 M, but ADL

deteriorated in the riverstigmine group at 6 and 12 M (Fig. 4).

Previous studies indicated that WMLs such as PVH and DWMH reflect demyelination, loss

of ependymal cells, arteriosclerosis, and microinfarcts. PVH was associated with a loss of ventricular

lining, and DWMH with deep WM demyelination [12-14]. The volume of PVH was also associated with

neurofibrillary tangles, indicating that the mechanism of AD may contribute to the vascular or white

matter pathology [4]. Our previous studies demonstrated that the severity of WMLs was closely related

to a deterioration of the cognitive and affective functions in AD patients [5, 6]. Moreover, PVH was

related to a decline in cognitive function [15] and mental processing speed [16]. In the present study,

cognitive scores (MMSE and HDS-R) showed a WM-severity-dependent decrease with aging (Table

1), suggesting that a worse PVH may reflect progression of AD pathology.

The present study first described the clinical effect of four anti-dementia drugs on AD

patients who were divided into four PVH-severity-dependent subgroups. The positive effect of

galantamine in the PVH I-II subgroups may be consistent with a previous report, where galantamine

was effective on cognitive, affective and ADL functions of AD accompanied by cerebrovascular

disease [17] with increasing vascular reactivity [18] and regional cerebral blood flow [19]. We have also

previously reported that galantamine improved frontal lobe cognitive function in elderly AD patients

[20], and maintained or improved cognitive, affective and ADL functions in AD with asymptomatic lacunar infarction [21].

There are several reports that showed that donepezil was effective for both positive and negative affective symptoms [22-24]. However, our present results showed that AS deteriorated at 9 M in the PVH I subgroup (Fig. 2). Similarly, rivastigmine was reported to be effective for cognitive and ADL functions in severe AD patients [25]. However, our present results showed a deterioration of ADL at 6 and 12 M in the PVH III subgroup (Fig. 4). These discrepancies may be due to different severities of AD patients between previous and the present study and our PVH-severity-dependent analysis. Some reports showed significant effects of memantine in cognitive severe impairment battery (SIB) and ADCS-ADL for moderate to severe AD patients [15, 26]. In agreement with our previous results [27, 28], the present study showed a significant improvement from the baseline in AS of the PVH I subgroup at 3 and 9 M (Fig. 2).

There are limitations to our retrospective study, considering nature of AD treatment, outcome of measurements would be evaluated in the longest observation time. In other words, different transient effect in one time point seems to be difficult to evaluate.

In conclusion, the present study demonstrated that cognitive scores (MMSE and HDS-R) showed a WM-severity-dependent decreases with increasing age (Table 1). Moreover, the four drugs

showed WM-severity-dependent sensitivity when assessing the clinical effect of cognitive, affective

and ADL functions.

Conflict of interest

Dr. K. Abe received an honorarium from Takeda Pharmaceutical Company Limited, but

other authors declare no financial or other conflicts of interest.

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Figure legends

Fig. 1)　The mean changes of clinical scores in each drug (donepezil, galantamine, and rivastigmine) from the baseline (0 M) to 3, 6, 9, and 12 M in the PVH 0 subgroup. Cognitive MMSE and HDS-R, affective GDS, AS, ABS, and ADL were well preserved until 12 M of each drug treatment.

Fig. 2) The mean changes of clinical scores in each drug (donepezil, galantamine, rivastigmine, and memantine) from the baseline (0 M) to 3, 6, 9, and 12 M in the PVH I subgroup. AS showed improvements from the baseline in response to memantine at 3 and 9 M (¶ $p < 0.05$) and galantamine at 9 M (§§ $p < 0.01$).

Fig. 3) The mean changes of clinical scores in each drug (donepezil, galantamine, rivastigmine, and memantine) from the baseline (0 M) to 3, 6, 9, and 12 M in the PVH II subgroup. MMSE showed a significant improvement from the baseline in response to galantamine (§ $p < 0.05$) at 9 M and HDS-R (§ $p < 0.05$) at 3 M.

Fig. 4) The mean changes of clinical scores in each drug (donepezil, galantamine, rivastigmine, and memantine) from the baseline (0 M) to 3, 6, 9, and 12 M in the PVH III subgroup. ADL deteriorated in the riverstigmine group at 6 and 12 M (‡ $p < 0.05$).

Fig. 1

PVH 0

donepezil
galantamine
rivastigmine

* p<0.05 vs donepezil
# p<0.05 vs galantamine

Fig. 2

PVH I

Legend:
- —●— donepezil
- ···○··· galantamine
- --■-- rivastigmine
- —△· memantine

† p<0.05 vs baseline donepezil
§ p<0.05 vs baseline galantamine
§§ p<0.01 vs baseline galantamine
¶ p<0.05 vs baseline memantine

* p<0.05 vs donepezil
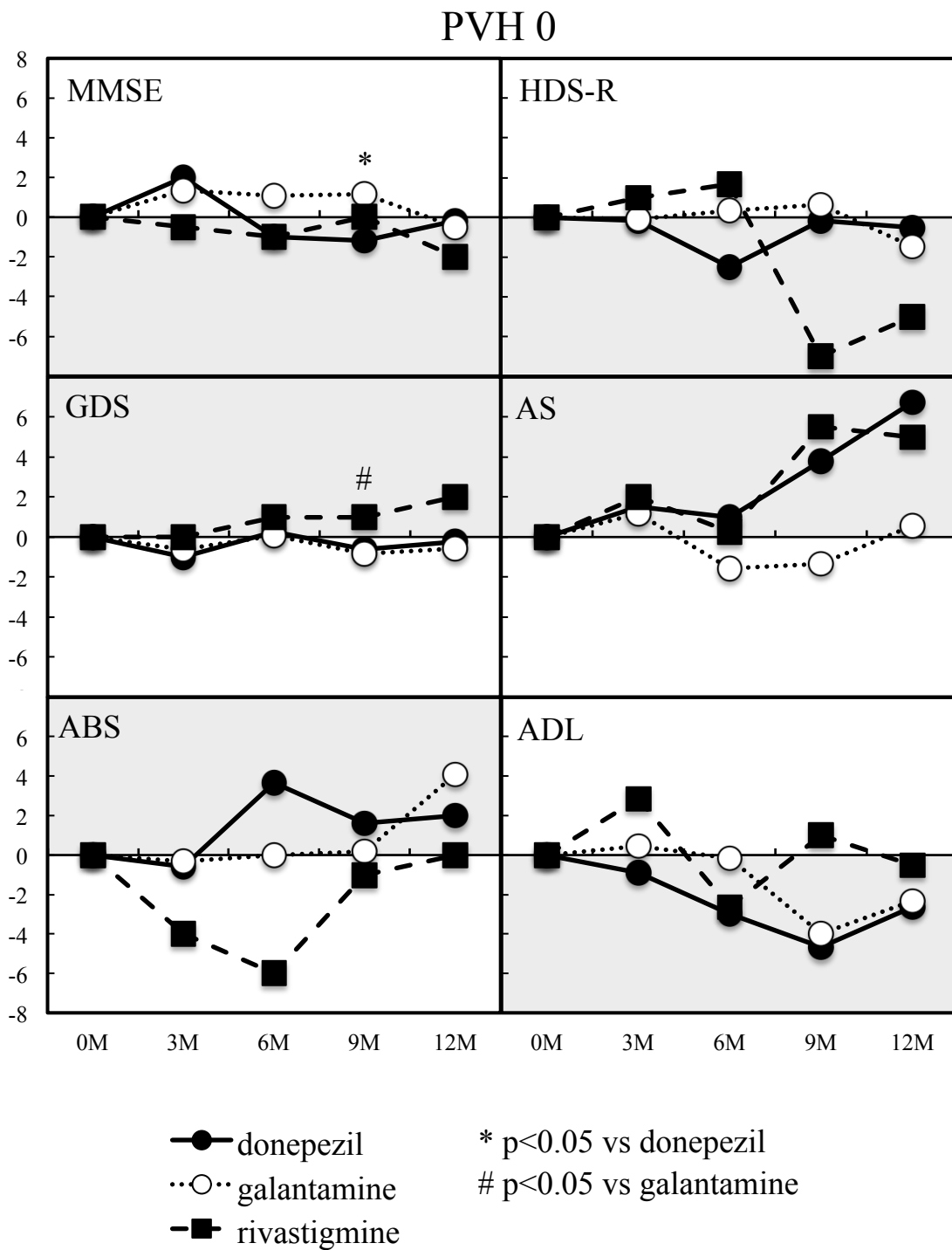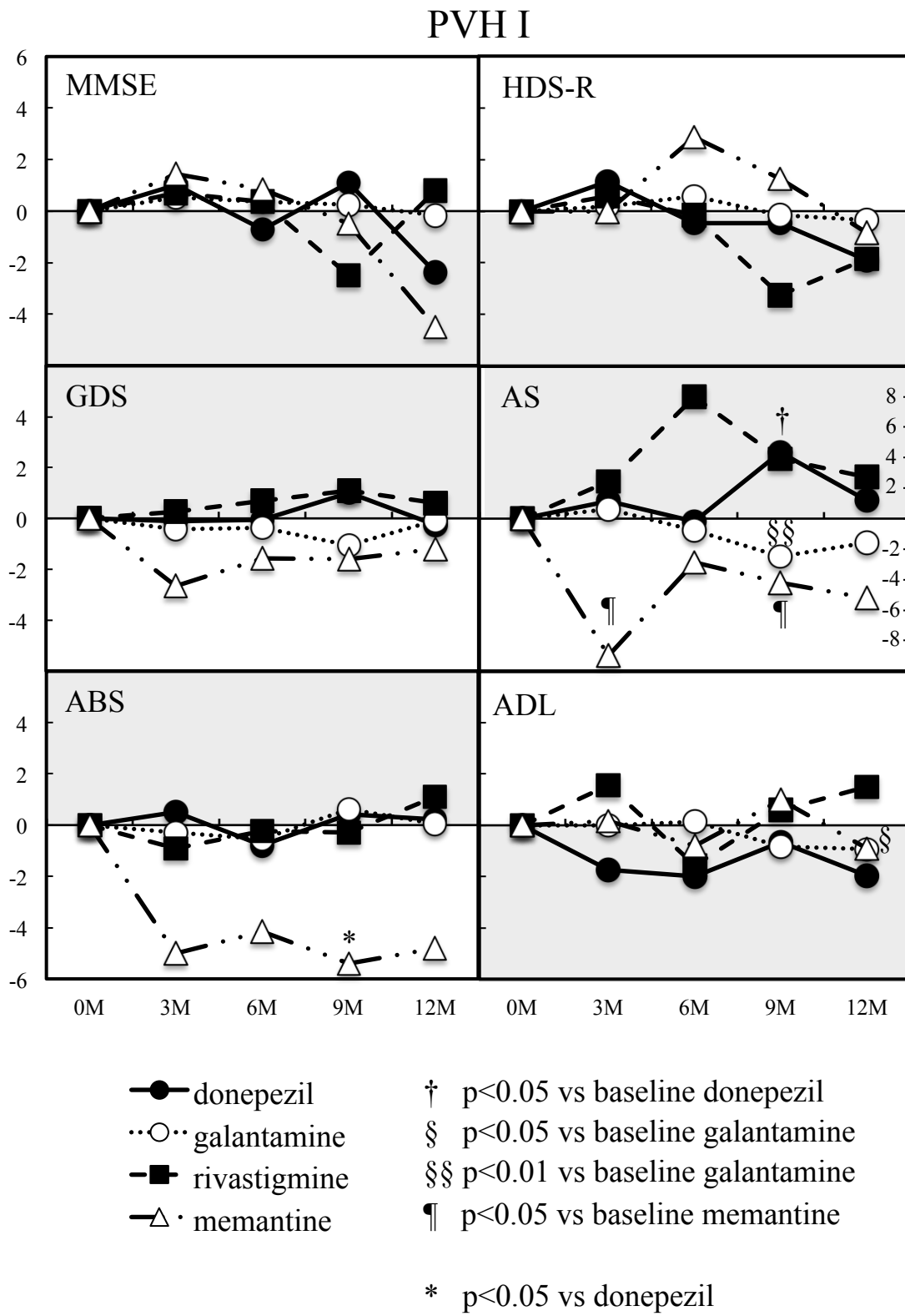
Fig. 3

PVH II

Fig. 4

PVH III

Legend:
- —●— donepezil
- ⋯○⋯ galantamine
- —■— rivastigmine
- —△— memantine

‡ p<0.05 vs baseline rivastigmine

* p<0.05 vs donepezil
** p<0.01 vs donepezil

Table 1

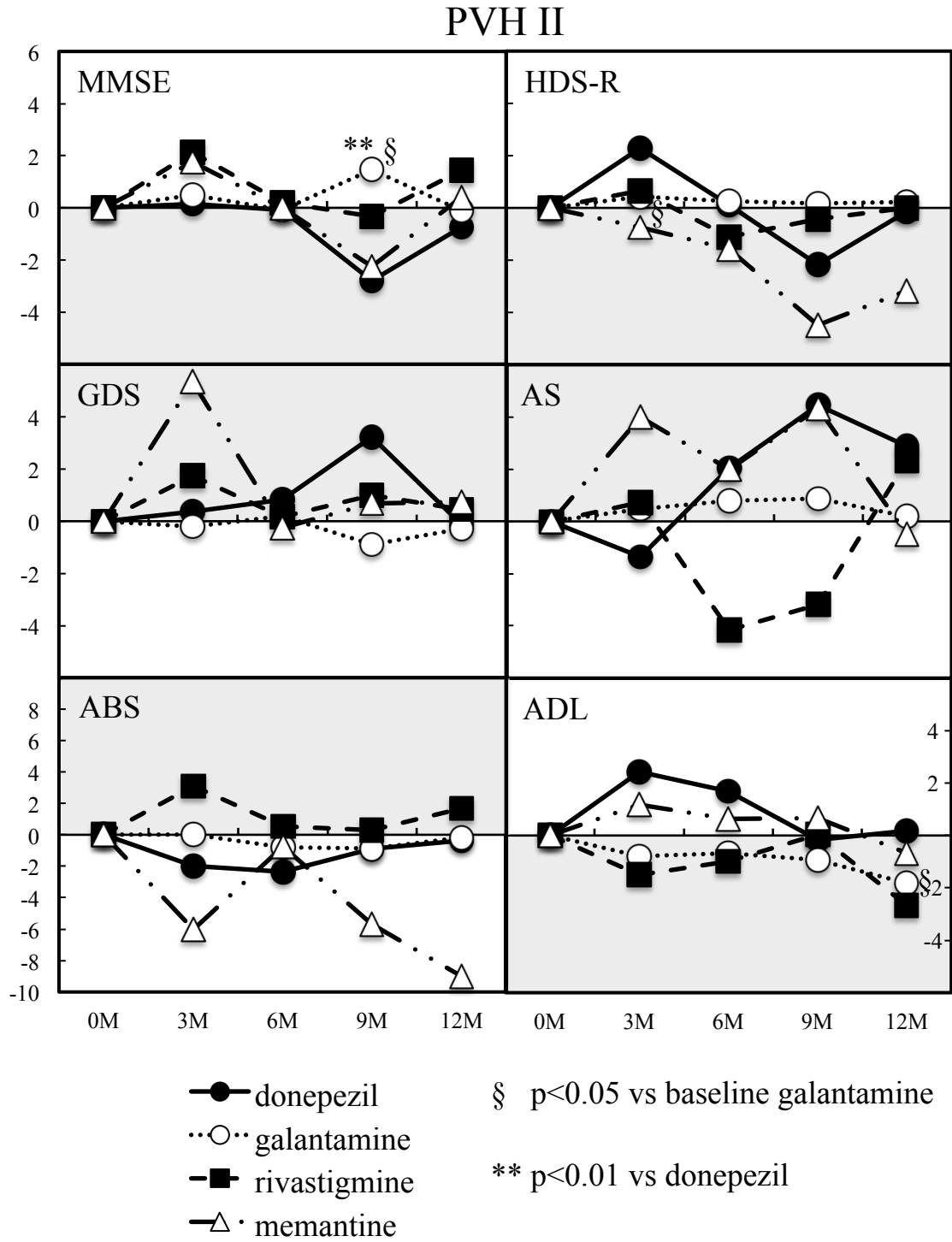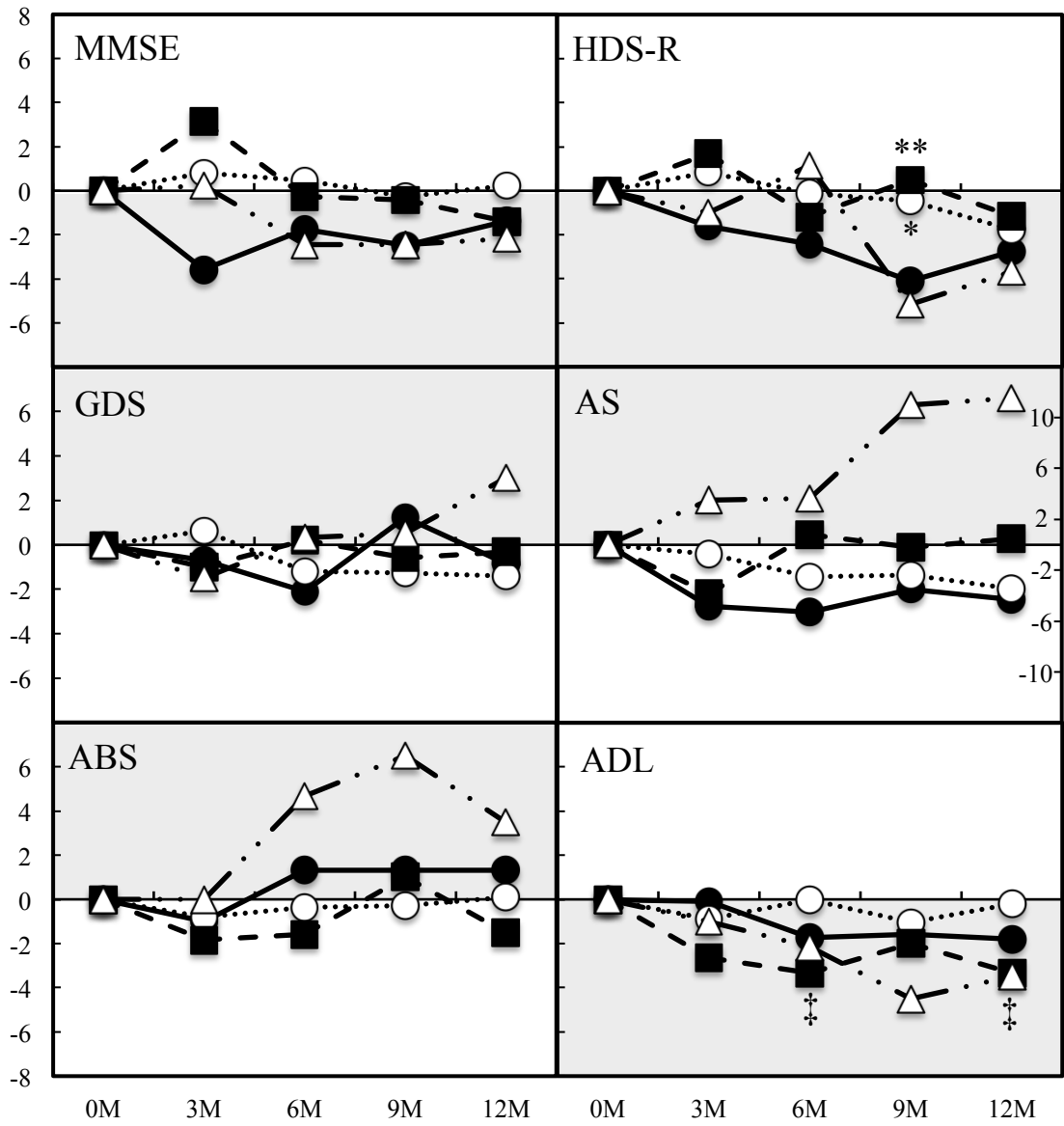Baseline demographic and clinical characteristics of all AD patients and each subgroup according to Fazekas scale

	all AD patients	PVH 0	PVH I		PVH II		PVH III		p-value	p-value for trend
n	551	41	212		179		119			
Gender (male/female)	201/350	18/23	83/129		52/127		48/71			
Female (%)	63.5	56.1	60.8		70.9		59.7		0.084[a]	
Age (years)	78.4 ± 7.3	72.2 ± 8.1	77.5 ± 6.8	**	79.6 ± 6.7	** ##	80.5 ± 7.4	** ##	<0.001[b]	0.001[c]
VSRAD	2.7 ± 1.3	2.6 ± 1.3	2.5 ± 1.1		2.7 ± 1.1		2.9 ± 1.6			
Baseline score										
MMSE	20.1 ± 4.9	21.1 ± 4.2	21.0 ± 4.6		19.4 ± 5.3	#	19.2 ± 4.6	#	0.002[b]	0.001[c]
HDS-R	17.8 ± 5.9	19.2 ± 5.6	19.0 ± 5.7		16.7 ± 6.2	##	16.7 ± 5.3	##	<0.001[b]	0.001[c]
GDS	5.3 ± 3.8	4.6 ± 3.7	5.1 ± 3.7		5.4 ± 3.8		6.0 ± 4.1		0.273[b]	
AS	16.8 ± 9.4	15.1 ± 8.4	16.4 ± 9.7		16.9 ± 9.0		18.5 ± 9.5		0.226[b]	
ABS	4.0 ± 5.5	4.6 ± 6.3	3.8 ± 5.2		3.9 ± 5.7		4.4 ± 5.6		0.706[b]	
ADL	20.9 ± 5.8	21.6 ± 6.3	21.3 ± 5.7		20.4 ± 5.8		20.5 ± 5.9		0.442[b]	

a: χ2 test   ** p<0.01 vs PVH 0 group
b: Kruskal-Wallis test   # p<0.05 vs PVH I group
c: Jonkheere-Terpstra test   ## p<0.01 vs PVH I group

Table 2
Change of drug dosage and baseline demographic and clinical characteristics of AD patients

	donepezil	galantamine	rivastigmine	memantine	p-value
Dosage (mg/day)					
3 months	5.5 ± 2.1	13.7 ± 5.0	10.9 ± 5.1	13.8 ± 5.7	
6 months	6.2 ± 2.3	15.6 ± 5.4	12.3 ± 5.6	16.0 ± 5.1	
9 months	6.4 ± 2.4	16.5 ± 5.4	13.4 ± 5.4	16.3 ± 5.0	
12 months	6.7 ± 2.4	17.2 ± 5.4	13.9 ± 5.3	17.3 ± 4.4	
PVH 0					
n (3M, 6M, 9M, 12M)	11 (11, 10, 6, 5)	24 (24, 23, 22, 19)	4 (4, 3, 2, 2)	2 (2, 2, 2, 2)	
Gender (male/female)	2/9	10/14	3/1	2/0	
Female (%)	81.8	58.3	25.0	0	
Age (years)	69.9 ± 7.7	73.0 ± 8.8	71.3 ± 2.6	78.0	0.618
Baseline score					
MMSE	21.4 ± 4.3	20.4 ± 4.1	21.8 ± 1.3	27.0	0.704
HDS-R	20.3 ± 5.4	18.1 ± 5.6	20.0 ± 4.8	24.0	0.569
GDS	5.3 ± 4.6	5.0 ± 3.3	2.3 ± 2.9	2.0	0.366
AS	16.1 ± 8.9	16.1 ± 8.3	9.8 ± 5.9	9.5	0.519
ABS	2.1 ± 3.1	4.0 ± 15.5	12.3 ± 10.0 *	6.0	<0.05
ADL	24.2 ± 3.8	20.6 ± 7.1	21.6 ± 3.6	23.8	0.589
PVH I					
n (3M, 6M, 9M, 12M)	47 (47, 36, 32, 29)	133 (133, 124, 106, 84)	19 (19, 17 14, 12)	13 (13, 9, 7, 6)	
Gender (male/female)	16/31	52/81	10/9	5/8	
Female (%)	66.0	60.9	47.4	61.5	
Age (years)	77.8 ± 6.5	77.3 ± 7.0	76.8 ± 4.7	78.5 ± 7.7	0.664
Baseline score					
MMSE	21.9 ± 4.3	21.0 ± 4.4	20.3 ± 5.8	18.5 ± 4.8	0.207
HDS-R	19.5 ± 6.4	19.2 ± 5.1	19.3 ± 6.9	16.2 ± 5.9	0.268
GDS	5.0 ± 3.4	5.2 ± 3.9	3.9 ± 2.9	6.1 ± 3.4	0.488
AS	15.2 ± 7.3	16.8 ± 10.1	14.4 ± 7.2	19.0 ± 13.3	0.845
ABS	2.8 ± 3.9	3.2 ± 4.4	5.9 ± 7.6	9.8 ± 6.9 * #	<0.01
ADL	21.4 ± 6.6	21.7 ± 5.5	20.0 ± 5.3	19.6 ± 4.9	
PVH II					
n (3M, 6M, 9M, 12M)	46 (46, 35, 26, 20)	94 (94, 86, 70, 55)	31 (31, 25, 17, 12)	8 (8, 7, 6, 6)	
Gender (male/female)	14/32	31/63	5/26	2/6	
Female (%)	69.6	67.0	83.9	75.0	
Age (years)	78.0 ± 7.5	79.6 ± 6.2	81.5 ± 6.9	81.6 ± 3.6	0.235
Baseline score					
MMSE	19.7 ± 6.0	19.7 ± 4.9	17.3 ± 5.1	21.3 ± 4.0	0.051
HDS-R	16.1 ± 7.2	17.4 ± 5.8	15.0 ± 6.2	17.8 ± 4.6	0.263
GDS	5.4 ± 3.7	5.1 ± 4.1	6.4 ± 3.2	6.5 ± 2.8	0.414
AS	14.5 ± 7.9	16.6 ± 8.9	20.1 ± 8.7	21.5 ± 9.7	0.104
ABS	3.1 ± 5.4	3.5 ± 5.3	4.3 ± 4.2	12.0 ± 9.3 *	<0.05
ADL	19.9 ± 5.3	20.9 ± 6.3	19.4 ± 3.8	19.3 ± 7.0	0.362
PVH III					
n (3M, 6M, 9M, 12M)	22 (22, 18, 15, 8)	69 (69, 58, 51, 30)	19 (19, 15, 12, 6)	9 (9, 9, 7, 6)	
Gender (male/female)	7/15	30/39	8/11	3/6	
Female (%)	68.2	56.5	57.9	66.7	
Age (years)	80.3 ± 5.4	79.7 ± 8.9	82.8 ± 3.4	81.6 ± 4.5	0.283
Baseline score					
MMSE	17.4 ± 5.5	20.0 ± 4.2	18.3 ± 4.7	20.1 ± 3.3	0.235
HDS-R	14.5 ± 5.7	17.7 ± 4.9	15.6 ± 6.0	16.2 ± 3.8	0.196
GDS	6.0 ± 4.4	5.7 ± 3.9	8.9 ± 3.6	5.7 ± 3.7	0.316
AS	18.6 ± 10.2	17.8 ± 9.2	25.9 ± 8.5	13.0 ± 4.3	0.135
ABS	4.8 ± 6.5	3.9 ± 5.2	7.6 ± 6.4	3.3 ± 3.4	0.155
ADL	20.5 ± 5.8	21.1 ± 5.1	18.9 ± 8.1	16.8 ± 7.2	0.770

* p<0.05 vs donepezil
# p<0.05 vs galantamine