Therapeutic effects of drug switching between acetylcholinesterase inhibitors in Alzheimer's disease patients

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Running head: Drug switch between ChEIs in AD

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Abstract

Aim: To evaluate the therapeutic effects of switching from one acetylcholinesterase inhibitor (ChEI), donepezil, galantamine, or rivastigmine, to another in Alzheimer's disease (AD) patients.

Methods: We retrospectively enrolled 171 AD patients, whose ChEI medication was changed. The patients were evaluated on three major aspects of dementia—cognitive, affective, and activities of daily living (ADL) measures—at 6 months (M) before the drug switch, at the time of drug switch (baseline), and at 3M and 6M after the drug switch.

Results: The doses of the three ChEIs were significantly lower at 6M after the switch compared with the pre-switch doses. Improvements in apathy were found at 3M when switching from donepezil to galantamine, but not to rivastigmine, but this switch had adverse effects on ADL. Improvements in cognitive scores at 3M were also found when switching from galantamine to rivastigmine, but not to donepezil. However, both of these changes improved Abe's behavioral and psychological symptoms of dementia (ABS) scores, except ADL. Switching from rivastigmine to donepezil worsened ABS scores at 6M, but preserved cognitive and ADL scores.

Conclusions: This study suggests that despite a relatively lower dose of ChEI after the switch, switching from donepezil or rivastigmine preserved cognitive functions for at least 6M. Switching from galantamine to rivastigmine improved MMSE and ABS at 3M,

but did not improve ADL scores.

Keywords: Alzheimer’s disease, drug switch, donepezil, galantamine, rivastigmine

Introduction

Alzheimer's disease (AD) is a main cause of dementia and mild to moderate cases are usually treated with acetylcholinesterase inhibitors (ChEIs) [1]. In Japan, three ChEIs (donepezil, galantamine, and rivastigmine) are currently available; the efficacy of these in Japanese AD patients has been reported in previous studies [2-5]. However, AD patients sometimes discontinue ChEI therapy or have to switch to another ChEI because of side-effects, a rapid decline in cognitive function or hospitalization unrelated to AD [6].

Previous reports have shown that switching from one ChEI to another is beneficial in improving cognitive and affective functions and activities of daily living (ADL) in AD patients [7-10]. However, most previous reports have focused on the switch from donepezil to galantamine (D→G) or to rivastigmine (D→R) as donepezil was the first ChEI used for the treatment of AD [6-12]. Only one report has investigated the effect of switching from rivastigmine to galantamine (R→G) [9]. Thus the effect of switching between ChEIs has not been fully investigated, particularly from galantamine to donepezil (G→D) or to rivastigmine (G→R), and from rivastigmine to donepezil (R→D).

In this study, we evaluated the therapeutic effects of switching from one ChEI to another (six combinations of drug switch between three ChEIs; galantamine, donepezil, and rivastigmine) on three major aspects of dementia: cognitive and affective functioning,

and ADL.

Methods

The electronic database of Okayama University Hospital, Japan was used for this retrospective clinical cohort study. We enrolled 171 patients with AD who had been treated with one ChEI and then switched to another. AD was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) or the International Classification of Diseases, Tenth Revision (ICD-10) [13].

The 171 patients were divided into three main groups based on the drug treatment prior to the switch: donepezil (Group D), galantamine (Group G) and rivastigmine (Group R). Each main group was further divided into two subgroups based on the drug switched to: 101 patients switched from donepezil to galantamine or rivastigmine (90 D→G, 11 D →R), 49 patients switched from galantamine to donepezil or rivastigmine (17 G→D, 32 G→R), and 21 patients switched from rivastigmine to donepezil or galantamine (9 R→ D, 12 R→G).

All 171 patients were evaluated by six different tests for cognitive, affective and ADL assessments. The mini-mental state examination (MMSE) [14] and Hasegawa dementia rating scale-revised (HDS-R) [15] were used for cognitive assessments. The

geriatric depression scale (GDS) [16], apathy scale (AS) [17] and Abe's behavioral and psychological symptoms of dementia (BPSD) score (ABS) [18] were used for affective assessments (depression, apathy, and BPSD, respectively). The Alzheimer's Disease Co-operative Study – Activities of Daily Living Inventory (ADCS-ADL) [19] was used for assessing ADL.

Medical records were reviewed to evaluate the six different tests at 6 months (M) before the drug switch (pre-switch assessment) to determine the severity of deterioration before switching drugs, at the time of drug switch (baseline assessment), and at 3M and 6M after switching drugs (post-switch assessments) to assess the efficacy of the new drug against further deterioration. The changes between the results of the pre-switch and baseline, and between the baseline and 3M or 6M after drug switch were compared for each score. Clinical demographic data such as age, sex, and educational history were also analyzed.

Comparisons between baseline characteristics (sex, age, and years of education) and the baseline clinical scores of the each of the six subgroups were performed using the Mann–Whitney U test for continuous variables, and Pearson's chi-squared test ($\chi 2$) for comparing proportions. Comparisons between the mean drug doses in each of the different groups and subgroups were performed using the Mann–Whitney U test. Changes

in clinical assessment scores between baseline and 6M pre-switch, and 3M and 6M post-switch were analyzed using the Wilcoxon signed-rank test. All statistical analyses were conducted using SPSS-J for Windows version 21.0 (IBM Corporation, Armonk, NY, USA). A *P* value of less than 0.05 was considered significant.

All of the participants gave written informed consent. This study was approved by the Ethical Committee of Okayama University (approval # 694). This study obtained exempted approval from the institutional review board based on the Okayama University guidelines because of the use of an anonymized and untraceable dataset.

Results

The baseline characteristics of each subgroup at the time of switching are shown in Table 1. No significant differences were found between the subgroups in all three main groups (Groups D, G, and R; switching from donepezil, galantamine, and rivastigmine, respectively) in the six clinical scores measured (MMSE, HDS-R, GDS, AS, ABS, and ADL) as well as sex, age, and years of education (Table 1).

Immediately prior to switching, the ChEIs doses were 5.8 ± 2.7 mg/d for Group D, 13.7 ± 5.4 mg/d for Group G, and 9.7 ± 4.9 mg/d for Group R (the containing dose of transdermal rivastigmine patch). The pre-switch dose of donepezil in the subgroup that

switched to galantamine (D→G) was slightly higher (5.8 ± 2.7 mg/d) than the subgroup that switched to rivastigmine (D→R, 5.3 ± 3.5 mg/d) (*P = 0.020, Fig. 1, left upper panel). There were no significant differences in the doses of galantamine or rivastigmine in Groups G and R (Fig. 1, middle and right upper panels).

At 6M post-switch, the mean doses of ChEIs were 4.8 ± 3.2 mg/d for donepezil, 9.3 ± 3.1 mg/d for galantamine, and 5.0 ± 2.4 mg/d for rivastigmine, which were lower than those before the switch ($^{\dagger\dagger\dagger}P$ = 0.000 for all three ChEIs). However, there were no significant differences between subgroups in the mean doses of donepezil, galantamine, or rivastigmine at 6M post-switch (Fig. 1, lower panels).

The effects of all drug switches as assessed by the six clinical scores (MMSE, HDS-R, GDS, AS, ABS, and ADL) are shown in Fig. 2. Although the cognitive scores (MMSE and HDS-R) had significantly declined pre-switch ($^{\#\#\#}P$ = 0.000), switching from donepezil to galantamine (D→G) stopped any further decline at 3M and 6M (Fig. 2a, b: filled squares), but not significantly. The switch to rivastigmine (D→R) also showed similar amelioration of the deterioration in cognitive scores (Fig. 2a, b: filled triangles). In terms of affective functions, the switch from donepezil to rivastigmine (D→R) showed a significant worsening of AS at 3M post-switch (Fig. 2d; *P = 0.046). Conversely, ADL scores continuously declined when switching from donepezil to galantamine (D→G) at

3M and 6M (Fig. 2f: filled squares; $*P = 0.020$ and 0.042, respectively), but not when switching from donepezil to rivastigmine (D→R, Fig. 2f: filled triangles).

In the Group G, cognitive scores (MMSE and HDS-R) significantly declined pre-switch in subgroup G→D (Fig. 2g, h; $^{\#\#}P = 0.003$ and $^{\#\#}P = 0.005$, respectively) and in subgroup G→R (Fig. 2g; $^{\#\#}P = 0.003$). This was ameliorated at 3M and 6M in subgroup G → D. Although changing from galantamine to rivastigmine (G → R) transiently improved MMSE scores at 3M (Fig. 2g: filled triangles; $*P = 0.023$), a subsequent deterioration of MMSE and HDS-R scores was found at 6M (Fig. 2g, h: filled triangles; $*P = 0.021$ and $**P = 0.010$, respectively). Switching from galantamine to donepezil (G →D) or rivastigmine (G→R) did not affect the affective functions GDS or AS at both follow-up points (Fig. 2i, j). ABS significantly improved in both the galantamine to donepezil (G→D, Fig. 2k: filled circles) and to rivastigmine (G→R, Fig. 2k: filled triangles) subgroups at 3M post-switch ($*P = 0.042$ and 0.035, respectively), but there was no further improvement at 6M (Fig. 2k). ADL scores significantly declined during pre-switch galantamine use but was ameliorated at 3M and 6M after switching to rivastigmine (G→R, Fig. 2l: open square) ($^{\#}P = 0.031$).

In Group R, ABS scores significantly improved before the switch to galantamine (R →G) (Fig. 2q: open triangles; $^{\#}P = 0.048$), stabilizing at 3M and 6M post-switch (Fig. 2q:

filled squares). However, ABS scores significantly worsened at 6M post-switching to donepezil (R→D) (Fig. 2q: filled circles; *P = 0.043). The switch from rivastigmine to donepezil (R→D) or galantamine (R→G) did not affect MMSE, HDS-R, GDS, AS, or ADL scores at both follow up points (Fig. 2m–p, r).

Discussion

In this study, we first investigated the doses of ChEIs before and after switching to another drug. The dose of galantamine was relatively low (13.7 ± 5.4 mg/d) before switching, but the low dose of galantamine is also effective for improving cognitive and affective functions for Japanese [5, 20]. The doses of all three ChEIs were significantly lower at 6M post-switch compared with pre-switch, suggesting that the relatively lower doses of ChEI were effective after switching. Despite the lower doses, switching ChEI resulted in well-preserved cognitive functions in subgroups D→G and G→D, and improved BPSD in subgroups G→D and G→R, but worsened apathy, BPSD, and ADL in subgroups D→R, R→D, and D→G, respectively, at 3M or 6M. Three ChEIs have their own characteristics [8]; Donepezil has a longer half-life compared to others. Galantamine also allosterically modulates neuronal nicotinic receptors [9, 10]. Rivastigmine also inhibits butyrylcholinesterase [3]. Therefore, the switching ChEI could show the different effect

(improvement or worsening), despite the lower doses in this study.

Switching from donepezil to galantamine (D→G) stopped any further decline in cognitive functioning from pre-switch levels. A previous report showed that switching from donepezil to galantamine (D→G) significantly improved MMSE scores at 3M post-switch [10]. Switching from donepezil to rivastigmine (D→R) also ameliorated cognitive deterioration. This supports the findings of previous studies that showed improvements in MMSE scores in 48.9–55.0% patients after switching from donepezil to rivastigmine (D→R) [7, 8, 11]. However, one report failed to show any such benefit [12]. There have been no previous reports of switching from galantamine to another ChEI. In this study, switching from galantamine to donepezil (G→D) stopped the decline that was occurring pre-switch, but switching from galantamine to rivastigmine (G → R) resulted in deterioration of MMSE and HDS-R scores at 6M. Although a previous report showed that switching from rivastigmine to galantamine (R→G) significantly improved MMSE scores [9], switching from rivastigmine to donepezil (R→D) or to galantamine (R→G) did not affect cognitive functioning in the present study.

In terms of affective functions, switching from donepezil to rivastigmine (D→R) resulted in worsened apathy at 3M post-switch, which has not been reported previously [7, 8, 11, 12]. Of interest was that all six combinations of switch had no effect on depression.

This is contrary to a previous report that showed improvements in depression and apathy when switching from donepezil or rivastigmine to galantamine (D→G or R→G) [9]. The present study and previous studies showed no effect on BPSD in switching from donepezil to galantamine or rivastigmine (D→G or D→R) [10, 12]. However, in this study, switching from galantamine to donepezil (G→D) or to rivastigmine (G→R), or from rivastigmine to galantamine (R→G), improved BPSD. Switching from rivastigmine to donepezil (R→D) worsened BPSD, which has not been reported previously.

Switching from donepezil to galantamine (D→G) worsened ADL measures in the present study, which is in contrast with the findings of a previous report [10]. This discrepancy may be related to the dose of galantamine after the switch; that is, a higher dose of galantamine in the previous study (16 or 24 mg/d) [10] compared with the present study (9.4 ± 3.1 mg/d). Although switching from donepezil to rivastigmine (D→R) did not affect ADL in the present study, a previous report showed a benefit of this drug switch in 57.0% of patients [7]. However, another report showed an adverse result [12]. Conversely, in this study the switching from galantamine to rivastigmine (G→R) ameliorated the decline of ADL, but switching from galantamine to donepezil (G→D) did not, which has not been reported previously.

In conclusion, the present study comprehensively examined six combinations of

drug switch between three ChEIs until 6M post-switch and found benefits of the drug switch from galantamine to donepezil (G→D) but not to rivastigmine (G→R) in cognitive functions, and of the switch from rivastigmine to galantamine (R→G), but not to donepezil (R→D), for affective functions. The switch from donepezil to galantamine (D→G), but not to rivastigmine (D→R), was beneficial for affective functioning, but had an adverse effect on ADL. It is possible that if the post-switch doses were higher in the present study, more significant benefits for cognitive and affective functions and ADL may have been seen.

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Koji Abe supervised the project, and made critical adjustments to the manuscript. All authors are in agreement with the content of the manuscript.

Disclosure statement

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Figure Legends

Figure 1 Mean doses of three ChEIs before (upper panels) and 6M (lower panels) after drug switch in Groups D, G, and R, representing the drug switches from donepezil, galantamine, and rivastigmine, respectively. The pre-switch dose of donepezil in the subgroup that changed to galantamine (D→G) was slightly higher than that in the subgroup that switched to rivastigmine (D→R) (*P = 0.020, left upper panel). Note the mean doses of ChEIs at 6M post-switch (lower panels) were generally lower than those pre-switch (upper panels).

Figure 2 Cognitive, affective and ADL assessments of AD patients before (pre) and after (post) drug switch in Groups D, G, and R. The scores are shown at pre-switch, the time of drug switch (baseline), and 3M or 6M after the drug switch (post-switch). $^{\#}P <$ 0.05, $^{\#\#}$ $P < 0.01$, and $^{\#\#\#}$ $P < 0.001$ compared with the baseline (pre-switch assessment). * $P < 0.05$ and ** $P < 0.01$ compared with the baseline (post-switch assessments). Black symbols ($^{\#}$ or *) correspond to black dotted or solid lines (D→G, G→D, and R→D). Gray symbols ($^{\#}$ or *) corresponds to gray-dotted or solid lines (D→R, G→R, and R→G). See the Results section for details.