JCN Open Access ORIGINAL ARTICLE

pISSN 1738-6586 / eISSN 2005-5013 / J Clin Neurol 2021;17(3):376-384 / https://doi.org/10.3988/jcn.2021.17.3.376

Discontinuation Rate of Newly Prescribed Donepezil in Alzheimer's Disease Patients in Asia

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Received December 22, 2020
Revised April 15, 2021
Accepted April 15, 2021

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Background and Purpose The rate of donepezil discontinuation and the underlying reasons for discontinuation in Asian patients with Alzheimer's disease (AD) are currently unknown. We aimed to determine the treatment discontinuation rates in AD patients who had newly been prescribed donepezil in routine clinical practice in Asia.

Methods This 1-year observational study involved 38 institutions in seven Asian countries, and it evaluated 398 participants aged 50–90 years with a diagnosis of probable AD and on newly prescribed donepezil monotherapy. The primary endpoint was the rate of donepezil discontinuation over 1 year. Secondary endpoints included the reason for discontinuation,

treatment duration, changes in cognitive function over the 1-year study period, and compliance as assessed using a clinician rating scale (CRS) and visual analog scale (VAS).

Results Donepezil was discontinued in 83 (20.9%) patients, most commonly due to an adverse event (43.4%). The mean treatment duration was 103.67 days in patients who discontinued. Among patients whose cognitive function was assessed at baseline and 1 year, there were no significant changes in scores on the Mini-Mental State Examination, Montreal Cognitive Assessment, and Trail-Making Test–Black and White scores, whereas the Clinical Dementia Rating score increased significantly (p<0.001). Treatment compliance at 1 year was 96.8% (306/316) on the CRS and 92.6±14.1% (mean±standard deviation) on the VAS.

Conclusions In patients on newly prescribed donepezil, the primary reason for discontinuation was an adverse event. Cognitive assessments revealed no significant worsening at 1 year, indicating that continuous donepezil treatment contributes to the maintenance of cognitive function.

Key Words Alzheimer's disease, Asia, cognition, donepezil.

INTRODUCTION

The life expectancy of humans is steadily increasing, with the average lifespan projected to exceed 90 years by 2030.[1] One of the main challenges of an aging population is the expected increase in the prevalence of dementia. According to the World Health Organization, nearly 50 million people worldwide have dementia,[2] and this number is projected to increase to 135 million by 2050.[3] Furthermore, approximately 23 million people in the Asia-Pacific region reportedly suffered from dementia in 2015, and this was estimated to reach 71 million by 2050, which would equate to more than 50% of all dementia patients worldwide.[4] Therefore, research focusing on dementia patients in the Asia-Pacific region is of paramount importance. This is especially relevant for Alzheimer's disease (AD), which constitutes 60−70% of dementia cases.[3] Despite significant efforts to develop disease-modifying drugs, there is no cure for AD, and so only symptomatic treatments such as acetylcholine esterase inhibitors (AChEIs) and memantine are currently used.

Based on data from multiple randomized clinical trials, donepezil is a safe and effective treatment option that is widely used in most countries to treat AD.[5-9] Donepezil hydrochloride is an AChEI that selectively and reversibly blocks the activity of acetylcholinesterase.[10] The consequent increase in the acetylcholine concentration produces improvements in the cognitive capability and quality of daily life in patients with AD and vascular dementia.[5-8,10,11] In addition, donepezil has been shown to have neuroprotective effects in both animal and human studies, which supports its use as an early treatment option.[12-15] In terms of the treatment efficacy of donepezil, there is evidence of a clinical improvement in the short to medium term, as well as evidence that donepezil treatment maintains global benefits and stabilizes cognition and function in the long term.[16-21] If medication is discontinued, donepezil-related benefits only persist if treatment is reinitiated within 3 weeks, with these benefits not necessarily being fully regained if treatment is reinitiated after 6 weeks.[22,23] Therefore, continuation of donepezil is necessary for maintaining its treatment benefits.

Discontinuation rates have been reported to be higher in community-based clinical studies than in clinical trials, which may be due to concerns about the safety profile and cost-effectiveness of administering donepezil in clinical practice.[24] Recent studies have evaluated the rate of treatment discontinuation among patients with AD,[21,25] and the persistence and adherence to long-term AchEI treatments;[26-28] however, these studies did not include Asian populations. There are limited data on the rate of donepezil discontinuation and the reasons for discontinuation in Asian patients with AD.[29,30]

The present study aimed to determine the rate of treatment discontinuation over 1 year in Asian patients with AD who had newly been prescribed donepezil (Aricept®, Eisai, Tokyo, Japan). We also investigated the reasons for discontinuation, the person who made the decision to discontinue, the duration of treatment, the changes in treatment regimen, the effects of continuous treatment on the patient's cognitive function and disease severity, and compliance with treatment in routine clinical practice in Asia.

METHODS

Study design

This was an observational, multicenter study with a 1-year observation/follow-up period involving routine clinical practice at 38 institutions across seven Asian countries: Korea, China, Taiwan, Singapore, the Philippines, Hong Kong, and Thailand. All institutions were tertiary hospitals. This study

was approved by the institutional review boards of all participating centers, and all patients provided written informed consent to participate. The trial was registered at clinicaltrials.gov (NCT02262975).

Given the noninterventional nature of this study, the method and duration of newly prescribed donepezil monotherapy were determined at the discretion of the treating physician. Data were collected at five visits: Visit 1, baseline (day 0); Visit 2, 1 month; Visit 3, 3 months; Visit 4, 6 months; and Visit 5, end of study (1 year). Patients were followed up for 1 year even when donepezil treatment had been discontinued.

Patients

The inclusion criteria were as follows: aged 50–90 years, diagnosis of probable AD based on criteria of the Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association,[31] newly being prescribed donepezil monotherapy, and both the patient and caregiver being able to visit the hospital. Patients with a history of memantine or AChEI treatment prior to participating in this study were excluded. Participants who withdrew consent, were lost to follow-up, or were judged by the investigators as being unable to continue the study were excluded from the analysis.

Patients who did not attend a subsequent visit after the first visit were considered to have dropped out from the study or to have discontinued treatment. Patients who were lost to follow-up after the second visit were considered to have discontinued treatment at the last visit and were analyzed as patients who dropped out.

Study endpoints

The primary endpoint was the rate of discontinuation of donepezil treatment after the 1-year follow-up period. The secondary endpoints included the reasons for treatment discontinuation; the person who made the decision to discontinue; the duration of donepezil treatment; the changes in treatment regimen; disease progression as assessed by changes in scores on cognitive function tests [Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA)], Trail-Making Test–Black and White (TMT-B&W) Parts A and B, and Clinical Dementia Rating (CDR); and compliance as assessed using a clinician rating scale (CRS) and visual analog scale (VAS).

The cognitive function tests (MMSE and MoCA), TMT-B&W, and CDR were applied at baseline and at Visits 4 and 5. Compliance assessments (CRS and VAS) were performed at Visits 2, 3, 4, and 5. When compliance was analyzed using the CRS, scores of $\geq$5 and $\leq$4 points were defined as compliance and noncompliance, respectively. Compliance was also assessed for each visit using the VAS, where 0% was defined as 'the subject has taken no medication' and 100% was defined as 'the subject has taken all prescribed medication.'

Statistical analyses

The required sample size was not calculated since this was an exploratory observational study. The analysis set comprised all enrolled patients who 1) met the inclusion criteria, 2) were assessed for the primary endpoint after treatment, and 3) completed the 1-year observation period.

Baseline characteristics were assessed using descriptive statistics. For continuous data, the mean$\pm$standard-deviation, median, and range were used, while frequency and percentage according to category were used for categorical data. For continuous data, inter- and intragroup comparisons were made using a Student's t-test or Wilcoxon's rank-sum test. For categorical data, intergroup comparisons were conducted using the chi-square test or Fisher's exact test. All statistical analyses were performed using SAS (version 9.3; SAS Institute, Cary, NC, USA).

RESULTS

Patient characteristics

A flow chart of patient inclusion is shown in Fig. 1. The study recruited 537 patients from 38 institutions in seven Asian countries, of which 529 were enrolled. A further 12 patients were excluded since they did not meet the study criteria. Therefore, 517 patients were initially included, among whom 119 prematurely dropped out of the study for the following reasons: withdrawal of consent (n=63, 52.9%), loss to follow-up after the first visit (n=36, 30.3%), investigator's decision (n=4, 3.4%), or another reason (n=16, 13.4%). Thus, 398 patients were finally evaluated.

The 398 analyzed patients, who included 41.2% (n=164) males, were aged 75.46$\pm$7.10 years and had an education duration of 7.35$\pm$5.23 years. The sex distribution and the baseline CDR score differed significantly between patients who did and did not discontinue treatment (Table 1). Furthermore, sex was the only factor that significantly influenced donepezil discontinuation (Supplementary Table 1 in the online-only Data Supplement).

Rate of donepezil treatment discontinuation

The overall discontinuation rate of donepezil treatment during the 1-year study period was 20.9% (83/398) (Table 2). The discontinuation rates stratified by country was 50.0% (4/8) in Hong Kong, 41.9% (26/62) in China, 38.3% (18/47) in Singapore, 16.9% (10/59) in Taiwan, 16.7% (1/6) in Thailand, 12.1% (24/198) in Korea, and 0.0% (0/18) in the Philip-

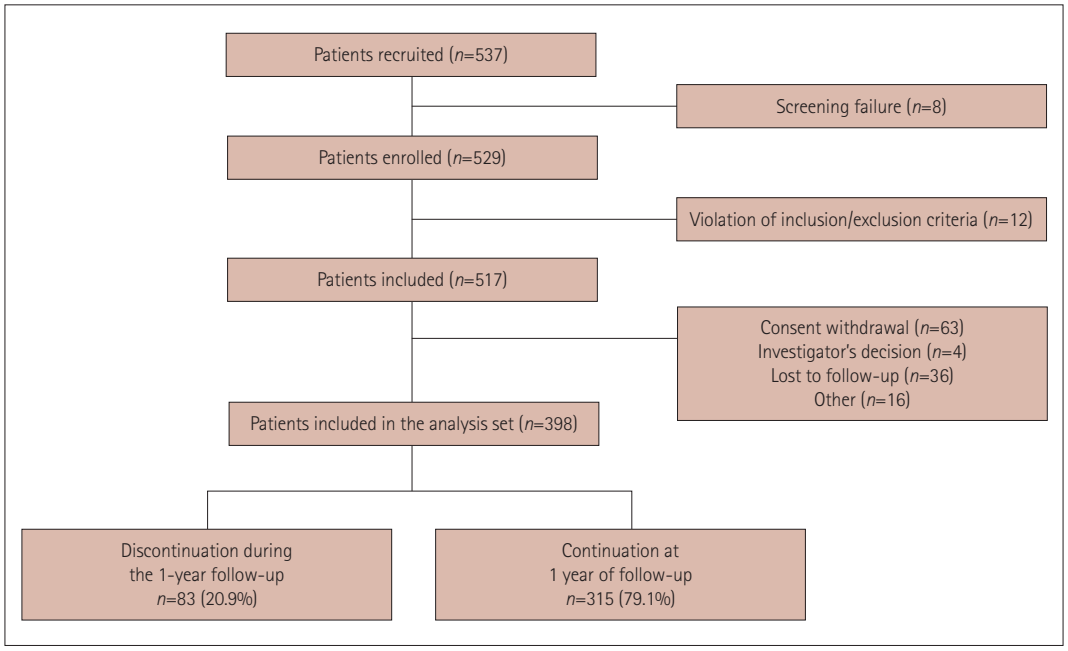

Fig. 1. Flow chart of Alzheimer's disease patient who newly being prescribed donepezil monotherapy.

Table 1. Baseline demographic and clinical characteristics of patients

	Total (*n*=398)	Discontinuation group (*n*=83)	Continuation group (*n*=315)	*p*
Sex, male	164 (41.21)	20 (24.10)	144 (45.71)	<0.001*
Age, years	75.46±7.10	75.81±7.74	75.37±6.94	0.475†
Education duration, years	7.35±5.23	6.77±4.99	7.51±5.29	0.315†
BMI, kg/m^2	*n*=362 23.09±3.19	*n*=76 23.15±3.72	*n*=286 23.07±3.04	0.865†
MMSE score	*n*=382 18.93±5.30	*n*=76 18.21±5.26	*n*=306 19.11±5.31	0.133†
MoCA score	*n*=79 16.19±6.07	*n*=9 13.44±6.82	*n*=70 16.54±5.92	0.159†
CDR (sum of boxes) score	*n*=397 5.13±3.00	*n*=82 5.50±3.72	*n*=315 5.03±2.78	0.579†
CDR (global) score	*n*=394	*n*=82	*n*=313	0.032§
0.5	162 (40.81)	36 (43.90)	126 (40.00)	
1	188 (47.36)	32 (39.02)	156 (49.52)	
2	43 (10.83)	11 (13.41)	32 (10.16)	
3	4 (1.01)	3 (3.66)	1 (0.32)	
TMT-B&W (Part A: time to completion), seconds	*n*=375 174.63±88.43	*n*=74 186.31±89.65	*n*=301 171.76±88.05	0.202†
TMT-B&W (Part A: no. of errors)	*n*=375 1.76±3.85	*n*=74 1.74±3.53	*n*=301 1.77±3.93	0.610†
TMT-B&W (Part B: time to completion), seconds	*n*=364 269.49±59.06	*n*=71 277.43±46.67	*n*=293 267.57±61.61	0.377†
TMT-B&W (Part B: no. of errors)	*n*=364 3.37±5.57	*n*=71 3.32±5.06	*n*=293 3.38±5.70	0.489†

Data are mean±standard-deviation or *n* (%) values.
*Pearson's chi-square test, †Wilcoxon's rank-sum test, ‡Two-sample *t*-test, §Fisher's exact test.
BMI: body mass index, CDR: Clinical Dementia Rating, MMSE: Mini-Mental State Examination, MoCA: Montreal Cognitive Assessment, TMT-B&W: Trail-Making Test–Black and White.

Table 2. Reasons for donepezil discontinuation and subject who made the choice

Reason for donepezil discontinuation	Total (*n*=83)	Physician (*n*=17)	Patient (*n*=34)	Caregiver (*n*=19)
Occurrence of an AE	36 (43.4)	10 (58.8)	16 (47.1)	10 (52.6)
Lost to follow-up	13 (15.7)	-	-	-
Concerns about AE	5 (6.0)	-	3 (8.8)	2 (10.5)
Symptoms unchanged	7 (8.4)	1 (5.9)	1 (2.9)	5 (26.3)
Poor disease and treatment awareness	4 (4.8)	-	3 (8.8)	1 (5.3)
Other	3 (3.6)	-	3 (8.8)	-
Concomitant disease aggravated	5 (6.0)	2 (11.7)	2 (5.9)	1 (5.3)
Symptoms aggravated	5 (6.0)	2 (11.7)	3 (8.8)	-
Financial	2 (2.4)	-	2 (5.9)	-
Inconvenience of administration	2 (2.4)	2 (11.7)	-	-
Symptoms improved	1 (1.2)	-	1 (2.9)	-

Data are *n* (%) values.
AE: adverse event.

Table 3. Rate of discontinuation of donepezil treatment by country

	Total (*n*=398)	Korea (*n*=198)	China (*n*=62)	Taiwan (*n*=59)	Singapore (*n*=47)	Philippines (*n*=18)	Hong Kong (*n*=8)	Thailand (*n*=6)
Discontinuation of donepezil	83 (20.9)*	24 (12.1)	26 (41.9)	10 (16.9)	18 (38.3)	0	4 (50.0)	1 (16.7)
Reasons for discontinuation								
Physician's choice	17 (20.5)	9	0	2	5	0	1	0
Patient's choice	34 (50.0)	5	16	8	4	0	0	1
Caregiver's choice	19 (22.9)	1	6	0	9	0	3	0
Patient's choice+caregiver's choice	53 (63.9)	6	22	8	13	0	3	1

Data are *n* or *n* (%) values.
*Of the 83 patients who discontinued treatment, 13 were lost to follow-up.

pines (Table 3).

Reasons for the discontinuation of donepezil treatment

The most common reason for discontinuation was the occurrence of an adverse event (AE) (36/83, 43.4%). Other reasons for discontinuation included follow-up failure (15.7%), symptoms unchanged (8.4%), and concerns about AEs, aggravation of concomitant disease, and aggravation of symptoms (6.0% each) (Table 2). The 83 patients who discontinued treatment included 20.5%, 50.0%, and 22.9% that were choices of the treating physician, patient, and caregiver, respectively (Table 3). The decision to discontinue donepezil treatment was predominantly made by the patient or caregiver in most countries (Table 3).

Treatment duration and changes to treatment regimen

The treatment duration was 321.99±102.48 days overall during the 1-year observation period, and 103.67±94.95 days in the discontinuation group (Supplementary Table 2 in the online-only Data Supplement). Of the 83 patients who discontinued treatment, 51.8% discontinued treatment within 90 days of initiating donepezil treatment (Supplementary Table 2 in the online-only Data Supplement). The proportions of patients who discontinued treatment due to the occurrence of an AE were 53.5% and 32.5% in those with treatment durations of ≤90 and >90 days, respectively (p=0.054) (Supplementary Table 3 in the online-only Data Supplement). The doses of donepezil administered in the patients who discontinued and continued treatment during the 1-year follow-up are listed in Supplementary Table 4 in the online-only Data Supplement. The time to increase the dose from 5 to 10 mg was 40.80±28.36 days in the discontinuation group (20 of 83 patients evaluated) and 77.03±75.56 days in the continuation group (115 of 313 patients evaluated) (p=0.045 in Wilcoxon's rank-sum test).

There were 304 instances of a change to the treatment regimen, with 244 dose increases, 32 dose reductions, and 31 treatment switches. Of the 31 patients who switched treatment, 25 (80.7%) patients switched to rivastigmine and 6 (19.4%) switched to memantine (Supplementary Table 5 in the online-only Data Supplement). Of the 315 patients who continued treatment, 163 (51.7%) remained on their initial dose with no dose changes during the 1-year observational period (Supplementary Table 6 in the online-only Data Supplement).

Table 4. Changes in scores on the cognitive function tests (MMSE and MoCA), TMT-B&W, and CDR

Test	Baseline	1 Year	Change	*p**
MMSE score (*n*=331)	18.84±5.35	18.57±6.34	-0.27±3.54	0.198
MoCA score (*n*=71)	16.25±6.02	16.35±6.22	0.10±2.19	0.491
TMT-B&W, seconds				
Part A: time to completion (*n*=318)	172.54±86.25	172.04±89.04	-0.51±54.83	0.323
Part B: time to completion) (*n*=307)	269.67±58.52	273.32±51.67	3.65±51.96	0.630
CDR (global) score (*n*=346)	0.94±0.48	1.05±0.59	0.11±0.37	<0.001
CDR (sum of boxes) score (*n*=346)	5.23±2.98	5.91±3.47	0.68±1.98	<0.001

Data are mean±standard-deviation values. This analysis only included patients whose cognitive function was assessed both at baseline and 1 year.
*Wilcoxon's signed-rank test.
CDR: Clinical Dementia Rating, MMSE: Mini-Mental State Examination, MoCA: Montreal Cognitive Assessment, TMT-B&W: Trail-Making Test–Black and White.

Changes in cognitive function

The changes in the scores on the cognitive function tests from baseline to 1 year in patients who continued or discontinued treatment are presented in Table 4. There were no statistically significant changes from baseline to the final visit in cognitive function as measured by MMSE (-0.27±3.54, p=0.198) and MoCA (0.10±2.19, p=0.491) scores. However, the test completion time and the number of errors on the TMT-B&W decreased from baseline to final visit, although these changes were also not statistically significant [Part A: time to completion, decrease of 0.51±54.83 (p=0.323); Part B: time to completion, 3.65±51.96 (p=0.630)]. However, the CDR scores increased significantly from baseline to the final visit [sum of boxes: 0.68±1.98 (p<0.001); global: 0.11±0.37 (p<0.001)].

Compliance at 1 year

Compliance with donepezil treatment was 96.8% (306 of 316 patients) at 1 year, as assessed using the CRS (≥5 points). Kaplan–Meier analysis revealed a significant difference (p< 0.0001) between compliant (CRS ≥5 points) and noncompliant (CRS <5 points) patients who were treated with donepezil (Supplementary Fig. 1 in the online-only Data Supplement). Compliance with donepezil treatment as measured using the VAS was 92.6±14.1% after 1 year of treatment. Education was found to be a factor associated with CRS score in univariate repeated-measures analysis of variance (p<0.001).

DISCUSSION

This multinational and prospective observational study assessed the rate of treatment discontinuation in patients with AD from Korea, China, Taiwan, Singapore, the Philippines, Hong Kong, and Thailand who had newly been prescribed donepezil. During the 1-year observational period, 20.9% of patients discontinued donepezil treatment, which was predominantly due to the occurrence of an AE, consistent with the findings of previous clinical studies.[5-8,11] The rate of treatment discontinuation in this study was consistent with that found in a previous open-label extension of 2 phase 3 studies that investigated the safety and efficacy of donepezil in 763 patients with moderately severe AD.[22] That study found that the incidence of discontinuations related to an AE was 17% (n= 128). A Finnish study similarly found that 20% of patients discontinued AChEI treatment during the first year due to an AE.[25] However, other studies have found much higher rates of donepezil discontinuation after 1 year, with New Zealand and Canadian reports of discontinuation rates of 49%[26] and 66.4%,[32] respectively. We speculate that these discrepancies in discontinuation rates could be due to differences in cultural backgrounds as well as differences in financial reimbursement systems between countries.

The rate of discontinuation in the present study (20.9%) was also notably lower than those found in previous studies involving Asian patients with AD: 53.1% in a Japanese study[29] and 50% in a Korean study.[30] We speculate that differences in study designs may have contributed to these differences. The present study had a prospective study design, and so the patients included had agreed to participate and were aware that treatment discontinuation was being assessed. In contrast, those two previous studies had retrospective designs in which data were obtained from chart reviews[29] or a review of a health insurance database.[30] The willingness to participate can differ between retrospective and prospective studies. Furthermore, other differences in patient characteristics between the studies, including in the mean age, sex, and education duration, may have also contributed to interstudy differences in discontinuation rates. The Korean study was based on health insurance data, which include data from the entire healthcare system, whereas the present study was conducted in tertiary hospitals only. This disparity in addition to potentially different prescription methods may have also contributed to differences in the characteristics of patients and caregivers between the studies.

This study found that the only factor that significantly influenced discontinuation of donepezil treatment was sex. In

the previous Japanese study, patients with more severe cognitive impairment (CDR score=3) discontinued donepezil earlier and more frequently.[29] In the Finnish study, being older and female were also found to be increase the probability of AChEI treatment discontinuation.[25] Overall, being female, being older, having a lower body weight, and receiving higher doses of donepezil increased the probability of experiencing AEs.[33]

Unlike previous studies, the present study also investigated who made the decision to discontinue donepezil treatment. Categorizing the decision into the choice of the physician, patient, or caregiver revealed that discontinuation was predominantly decided by the patients, followed by caregivers and then physicians. Although an AE was the main reason for a patient choosing to discontinue treatment, in cases where this was the caregiver's choice, it was unchanged symptoms and poor disease and treatment awareness that accounted for 31.6% of treatment discontinuations. Therefore, it may be possible to substantially reduce the rate of treatment discontinuation by educating caregivers and patients about treatments and the disease course.

The present study found that the rate of donepezil treatment discontinuation varied widely by country, from 0% to 50%. The physician's choice was the strongest factor influencing treatment discontinuation in Korea, while the choices of the patient and caregiver were the most important factors in China and Singapore. This difference may be due to cultural factors. For example, Korean patients may tend to rely more on the opinions of physicians, whereas Chinese patients and their caregivers may be more willing to try alternative medicines. Another possible reason for this difference is treatment reimbursement, which may have resulted in a greater number of discontinuations by caregivers and patients in countries other than Korea. Differences in the insurance coverage between countries may have also contributed to the wide range of donepezil treatment discontinuation rates.

During the 1-year observation period, 212 (53.3%) of the 398 patients who were treated with donepezil monotherapy maintained their initial dose: 10 (4.7%), 183 (86.3%), and 19 (9.0%) of those receiving 2.5, 5, and 10 mg, respectively. The other 186 (46.7%) patients changed their dose during the observation period: 241 (60.6%) increased their donepezil dosage, while only 32 (8.0%) underwent a dose reduction, which suggests that donepezil treatment was well tolerated. The mean time to increase the dose from 5 to 10 mg was significantly longer in the continuation group than in the discontinuation group (77.03 vs. 40.80 days, p=0.045). This finding suggests that a slow titration contributes to decreasing the treatment discontinuation rate.

The results obtained in the present assessments of cognitive function (global cognition and frontal executive function) did not change significantly from baseline when using the MMSE, MoCA, or TMT-B&W. This suggests that donepezil treatment contributed to maintaining cognitive function from baseline to 1 year, and is consistent with previous reports.[18-20,34] However, it is possible that no significant change in cognitive function was found using the MMSE because this test is less effective than other neuropsychological assessment tests in detecting frontal lobe functioning.[35] Although the CDR score significantly increased after 1 year, it does not mean that there was no benefit of donepezil in terms of CDR score when comparing the continuation and discontinuation groups. Given that CDR assesses both cognitive function and activities of daily living, this overall increase in CDR score may be attributable to its functional component that evaluates additional items such as community involvement, home life and hobbies, and personal care. Nonetheless, this finding contrasts with a previous report of a slowing of functional decline after donepezil treatment compared with placebo.[9] It has been suggested that the donepezil-induced improvement in cognitive function is associated with its combined effects on the right gyrus rectus, the right precentral gyrus, and the left superior temporal gyrus.[36] Despite previous studies showing that donepezil was associated with a 38% reduction in the risk of functional decline,[37] it is possible that the functional components of CDR did not adequately reflect the improvement in the activities of daily living. However, if patients with AD have not been treated previously with donepezil, it is possible that their clinical decline in functional domains would progressively worsen over time in comparison with patients who have been previously treated with donepezil.[9,38] As such, previous research has shown that if treatment is discontinued for longer than 3 weeks at any time point, the functional benefits of long-term donepezil treatment are unlikely to be recoverable after treatment is reinitiated due to the ongoing disease progression.[22,23] Therefore, cognitive function as measured using CDR would irrevocably worsen if donepezil treatment was discontinued at any time point. In addition, the high proportion of the total patient population in this study with moderate-to-severe AD (CDR score of 2 or 3) in the discontinuation group may have affected the data, owing to the presence of ongoing cognitive decline after treatment discontinuation. They comprised 11.84% of the patients, and it is possible that the rate of decline is greater in patients with higher CDR scores because they were not treated with high-dose donepezil (23 mg/day).

This study had some limitations. First, it was limited by the number of enrolled patients differing between the included countries, which restricted the comparisons that could be made between discontinuation rates in different countries. However, since this is the first multinational observational study of Asian patients with AD, the obtained data are clinically

meaningful for the Asian population. Second, it is possible that some patients who discontinued the study did so due to the occurrence of an AE, but this could not be confirmed. Despite this, we consider that our estimations were accurate for the following reasons: 1) if a patient experienced an AE, they would have reported this to the attending physician at the subsequent visit, and 2) if a patient considered that the treatment was needed despite the occurrence of an AE, they would have visited the attending physician to consult about the issue. Therefore, we assumed that if a patient did not attend a subsequent visit after the first visit, this was due to the patient refusing treatment rather than the occurrence of an AE. Finally, since the main analysis population included patients who completed 1 year of follow-up, completer bias may have been present.

In conclusion, this study found that the rate of discontinuation of donepezil treatment in Asia was slightly lower than that observed in Western countries, although the occurrence rate of AEs as the primary reason for discontinuation was the same. In terms of cognitive function, our data indicate no significant worsening after 1 year of donepezil treatment, which supports the continuous use of donepezil for maintaining cognitive function.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2021.17.3.376.

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Conflicts of Interest

All authors received investigator fees for conducting the study from Eisai Korea Inc. Quimin Qu, Huali Wang, and Yun Xu also received personal fees from Eisai Korea Inc.

Acknowledgements

We thank Jin Ran Kim of MSL, Eisai Korea for consultation and medical writing support. We thank Keyra Martinez Dunn, MD, Michelle Belanger, MD, and James Graham, PhD, of Edanz Pharma for providing medical writing support, which was funded by Eisai Korea Inc.

The authors would also like to thank all of the participating centers in this study: Seoul National University Bundang Hospital, Republic of Korea; Bucheon St. Mary's Hospital, Republic of Korea; Gachon Gil Medical Center, Republic of Korea; Hanyang University Seoul Hospital, Republic of Korea; Korea University Anam Hospital, Republic of Korea; Pusan National University Hospital, Republic of Korea; Eulji University Hospital, Republic of Korea; Ewha Womans University Medical Center, Republic of Korea; Inha University Hospital, Republic of Korea; Chonbuk National University Hospital, Republic of Korea; Kyungpook National University Medical Center, Republic of Korea; VHS Medical Center, Republic of Korea; Hallym University Medical Center, Kangnam Sacred Heart Hospital, Republic of Korea; Kangwon National University Hospital, Republic of Korea; First Affiliated Hospital of Medical College of Xi'an Jiaotong University, China; Shanghai Huashan Hospital, affiliated to Fudan University, China; Peking Union Medical College Hospital, China; Peking University Sixth Hospital, China; Renji Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, China; Nanjing Drum Tower Hospital, China; Peking University Third Hospital, China; Changhua Christian Hospital, Taiwan; Chi Mei Hospital, Liouying, Taiwan; Kaohsiung Medical University Chung-Ho Memorial Hospital, Taiwan; Kaohsiung Veterans General Hospital, Taiwan; Taipei Medical University Shuang-Ho Hospital, Taiwan; Chi Mei Medical Center, Taiwan; Shin Kong Wu Ho-Su Memorial Hospital, Taiwan; King Chulalongkorn Memorial Hospital (KCMH), Thailand; Phramongkutklao Hospital, Thailand; Ramathibodi Hospital, Thailand; Siriraj Hospital, Thailand; National University Hospital, Singapore; National Neuroscience Institute, Singapore; St. Luke's Medical Center, Philippines; Queen Mary Hospital, Hong Kong.

This study was funded by Eisai Korea Inc. This was a sponsor-initiated study, but the sponsor had no role in the data collection, data analysis, or the decision to publish.

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