ORIGINAL ARTICLE

Disease state changes and safety of long-term donepezil hydrochloride administration in patients with Alzheimer’s disease: interim results from the long-term, large-scale J-GOLD study in Japan

Heii ARAI,1 Kenta SUMITOMO,2 Yukinori SAKATA,2 Kasumi DAIDOJI,2 Takao TAKASE2 and Tetsumi TOYODA3

1Department of Psychiatry and Behavioral Science, Juntendo University Graduate School of Medicine, 2Eisai Co., Ltd., Tokyo, and 3Clinical Study Support Inc., Nagoya, Japan

Correspondence: Dr Heii Arai MD PhD, Department of Psychiatry and Behavioral Science, Juntendo University Graduate School of Medicine, Hongo 2-1-1, Bunkyo-ku, Tokyo 113-0033, Japan. Email: heii@juntendo.ac.jp

Received 12 December 2014; revision received 6 February 2015; accepted 27 March 2015.

Abstract

Background: There have been very few long-term studies involving a large study population; existing studies usually have no more than a few hundred patients with Alzheimer’s disease. For these reasons, there are no detailed investigations regarding changes in activities of daily living evaluated by the Functional Assessment Staging Test (FAST).

Methods: A long-term, large-scale observational study of donepezil hydrochloride (Aricept®; Eisai Co., Ltd, Tokyo, Japan) is currently in progress. Its objective is to investigate disease state changes associated with the long-term administration of this drug and its safety in patients with Alzheimer’s disease. In this report, data collected over a maximum of 24 months were compiled. Efficacy was assessed using FAST and a cognitive function test (Mini-Mental State Examination or the Hasegawa’s Dementia Scale-Revised).

Results: The percentages of patients whose FAST stage improved or remained the same compared to at the start of donepezil hydrochloride administration (baseline) were 91.1% at 6 months, 83.0% at 12 months, 79.5% at 18 months, and 74.8% at 24 months. Multivariate logistic regression analysis was conducted to investigate factors that affect the improvement and maintenance or exacerbation of FAST at 24 months. ‘Independence level in the daily life of elderly with dementia’ and ‘duration of illness’ were identified as variables that affected the improvement and maintenance or exacerbation of FAST.

Cognitive function improved significantly at 12 weeks and at 6 months compared to baseline, maintained baseline levels at 12 months and at 18 months, and decreased significantly at 24 months compared to baseline.

Conclusions: This is the largest prospective study involving Alzheimer’s disease patients in Japan, and we believe it is an important study that shows the reality of daily clinical practice.

Key words: Alzheimer’s disease, donepezil, Functional Assessment Staging Test, Hasegawa’s Dementia Scale-Revised, large-scale, long-term, Mini-Mental State Examination.

INTRODUCTION

The number of patients suffering from dementia is estimated to be approximately 44 million worldwide, with 4 million in Japan, and further increases in this number are predicted. Alzheimer’s disease (AD) accounts for the greatest proportion of dementia cases.1,2 Donepezil hydrochloride (Aricept®; Eisai Co., Ltd, Tokyo, Japan; referred to as donepezil in this manuscript) was approved in October 1999 as the first AD treatment drug in Japan with the ability to ‘suppress the progression of dementia symptoms in mild and moderate grades of AD’. Furthermore, its admin-
istration at 10 mg/day was approved in severe AD in August 2007, and donepezil consequently became available for the treatment of all stages of AD. However, there have been very few long-term studies on donepezil that included a large study population; existing studies usually involve no more than a few hundred patients. For these reasons, there are no detailed investigations regarding changes in activities of daily living evaluated with Functional Assessment Staging Test (FAST). For these reasons, there are no detailed investigations regarding changes in activities of daily living evaluated with Functional Assessment Staging Test (FAST).

Large-scale data on disease state changes primarily assessed by FAST and the safety of long-term administration of donepezil in AD patients may become extremely important not only for patients, but also for their families, caregivers, and physicians. By providing specific information on disease state, physicians are able to provide appropriate treatment and guidance to patients’ families and caregivers. Furthermore, by imagining a situation that may occur in the future, patients’ families and caregivers are better able to mentally prepare or take countermeasures when dealing with patients’ symptom progression.

To obtain data, a long-term, large-scale study of 10,000 patients who were newly or continuously treated with donepezil was initiated in 2010 with a follow-up period of 48 months. This study is still in progress at the present time. The interim analysis results of data regarding disease state changes and safety in AD patients who were newly treated with donepezil over a maximum 24-month period are reported.

**METHODS**

**Subjects**
The study investigated patients who were diagnosed with AD based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, classification and who had mild or moderately severe dementia according to FAST (FAST4 and FAST5, respectively).

**Study method**
The investigating physicians conducted patient enrolment, and the start date of donepezil administration was considered the study start date in newly treated patients.

The dose and schedule of donepezil administration were defined according to its prescribing information. In general, for adults, 3 mg was administered once a day for the first 1 to 2 weeks. Subsequently, the dose was increased to 5 mg. For patients with severe AD, after 5 mg was administered for more than 4 weeks, the daily dose was increased to 10 mg. The dose was adjusted according to the symptoms. However, there were no restrictions on changing the dose or administration schedule; physicians could make changes at their discretion because this study was conducted as part of daily clinical practice.

The follow-up period for each patient was 48 months from the start date of donepezil administration. If donepezil administration was temporarily stopped for ≥3 weeks at a time or discontinued completely, the patient was withdrawn from the study. Patient data were collected using electronic data capture, and they were compiled and analyzed independently by EPS Corporation (Tokyo, Japan) and CLINICAL STUDY SUPPORT Inc. (Nagoya, Japan).

The scientific and ethical validity of the study design were discussed at Eisai Co., Ltd, and the observational study Japan – Great Outcome of Long-Term Trial with Donepezil (J-GOLD) was conducted. This study has been conducted in accordance with Good Post-marketing Study Practice, which is an authorized standard for appropriate post-marketing surveillance to assure the safety and efficacy of a pharmaceutical product after its marketing by manufacturing distributors. In addition, management of personal information related to this study was conducted in accordance with privacy protection laws.

**Study items**

**Patient characteristics**

For patient condition, time of AD onset, complications, concomitant drugs, use of home services, and Category of Condition of Need for Long-Term Care were assessed.

**Efficacy**

Efficacy was assessed by FAST and a cognitive function test (Mini-Mental State Examination (MMSE) or the Hasegawa’s Dementia Scale-Revised (HDS-R)).

**Safety**

All undesirable or unintended diseases, symptoms, and signs of such diseases, as well as abnormal changes in clinical examination parameters, that developed in patients who received donepezil were considered to be adverse events, and the occur-
rences of such adverse events were investigated. However, because AD is a progressive disease, spontaneous exacerbation diagnosed by the study physician (such as decreased cognitive function or worsened FAST stage) and exacerbation of the Category of Condition of Need for Long-Term Care were not considered to be adverse events. Adverse events in which attribution to donepezil could not be ruled out were considered adverse drug reactions (ADR).

**Study and evaluation time points**

Time points of FAST evaluation were baseline, 6, 12, 18, 24, 30, 36, 42, and 48 months (or at the time of discontinuation) after the start of donepezil administration.

Examinations of cognitive function were conducted at 12 weeks after the start of the study as an early evaluation after donepezil administration in addition to the same evaluation time points as FAST. If examinations were conducted between time points, the results were included in the study.

**Statistical analysis**

Adverse events and ADR were compiled with the Japanese version of the Medical Dictionary for Regulatory Activities (v16.0) (https://www.jmo.gr.jp/jmo/servlet/mdrLoginTop), and the number of patients who developed these conditions, the incidence rates, and the number of patients (cases) and incidence rates by system organ class and preferred term were determined. For the FAST evaluation, the number and percentage of patients at each evaluation time point are shown by severity. The number and percentage of patients whose severity either improved or remained the same in comparison to baseline (i.e. patients whose FAST stage did not deteriorate) were determined, and paired t-tests were performed.

When test statistics were used, the two-tailed significance level was set at 5%. For variable selection in multivariate logistic regression analysis, a two-tailed significance level of 30% was used. Statistical analysis was conducted independently by EPS Corporation and Clinical Study Support, Inc. under contract with Eisai Co., Ltd.

**RESULTS**

**Patient composition**

Patients were enrolled at 1798 centres, most of which were the clinics of primary care doctors. Data were compiled from 3964 case report forms (CRF) of patients newly treated with donepezil at 6 months after the start of donepezil administration and were collected until September 2013. Approximately 40% of patients discontinued or dropped out of the study, and the dataset included 2965 CRF at 12 months, 2465 CRF at 18 months, and 1427 CRF at 24 months. From these 3964 patients, a total of 103 patients (with duplicates) were excluded, resulting in an inclusion of 3861 patients in the safety dataset. Those excluded were patients without safety data due to failure to follow up (n = 100), those who did not meet the enrolment criteria (n = 4), and those who were ineligible for safety evaluation (n = 3). Furthermore, 681 patients who were missing efficacy data were excluded as were 6 patients who used donepezil to treat excluded conditions (with duplicates). Therefore, 3176 patients were included in the efficacy dataset for the data analysis (Fig. 1).

**Patient characteristics**

Table 1 shows the background characteristics of the 3176 patients who were the target population for the efficacy dataset. There were more women than men (67.0% vs 33.0%), and the mean age was 80.2 years. In terms of the severity of dementia, 71.3% had FAST4 severity and 28.7% had FAST5 severity.

**Efficacy**

*Changes in severity of dementia (FAST)*

The distributions of FAST stages up to 24 months are shown in Figure 2. The percentages of patients whose FAST stage improved compared to baseline were 14.3% at 6 months, 18.5% at 12 months, 19.1% at 18 months, and 19.4% at 24 months.

The percentages of patients whose FAST stage worsened compared to baseline were 8.9% at 6 months, 17.0% at 12 months, 20.5% at 18 months, and 25.2% at 24 months.

The percentages of patients whose FAST stage either improved or remained the same in comparison to baseline (i.e. patients whose FAST stage did not deteriorate) were 91.1% at 6 months, 83.0% at 12...
months, 79.5% at 18 months, and 74.8% at 24 months (Table 2).

Factors that affect the FAST
Multivariate logistic regression analysis was conducted to identify factors that affected improvement and maintenance or exacerbation of FAST at 24 months. Through a stepwise method, ‘independence level in the daily life of elderly with dementia’ ($P < 0.001$), ‘duration of illness’ ($P = 0.059$), and ‘Category of Condition of Need for Long-Term Care’ ($P = 0.144$) were identified as variables affecting improvement and maintenance or exacerbation of FAST. However, ‘Category of Condition of Need for Long-Term Care’ was not used as a factor because it had a $P$-value that exceeded 0.1 and was similar to ‘independence level in the daily life of elderly with dementia’.

In addition to the aforementioned variables that were identified with the stepwise method, ‘sex’, ‘age at onset’, ‘presence of complications (hypertension)’, ‘presence of complications (abnormal lipid metabolism (hyperlipidaemia))’, and ‘presence of complications (diabetes)’, which were clinically considered to possibly affect FAST (although these were not identified as significant factors), were included in the model for multivariate logistic regression analysis, and the adjusted odds ratios were calculated (Fig. 3). Consequently, ‘independence level in the daily life of elderly with dementia’ ($P = 0.001$) and ‘duration of illness’ ($P = 0.005$) were identified as variables affecting improvement and maintenance or exacerbation of FAST.

Changes in cognitive function
MMSE and HDS-R scores improved significantly compared to baseline at 12 weeks and at 6 months, maintained baseline levels at 12 months and at 18 months, and decreased significantly at 24 months (Figs 4, 5).

Safety
Adverse events in which attribution to donepezil could not be ruled out were classified as ADR. The occurrences of ADR in 3861 patients who were included in the safety data analysis are shown in Table 3. Major ADR were decreased appetite, nausea, agitation, diarrhoea, vomiting, and dizziness.

DISCUSSION
In AD patients who are not taking donepezil, it has been reported that the time it takes for FAST scores to worsen from mild (FAST4) to moderate (FAST5) is 24 months and from moderate (FAST5) to moderately severe (FAST6) is 18 months. Because patients who were not treated with donepezil (an untreated group) were not included in the present study, a direct comparison between the donepezil-treated group and an untreated group cannot be made. However, because approximately 75% of the patients maintained or

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**Table 2**

| Number of patients with available CRFs | n=3964 |
| Number of patients included in the safety analysis | n=3861 |
| Number of patients excluded from the safety analysis | n=103 |
| Reasons for exclusion (includes duplicates) | |
| Lost to follow-up (did not visit hospital after start of administration) | n=100 |
| Enrollment exclusion† | n=4 |
| Ineligible for safety evaluation†† | n=3 |

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**Table 3**

| Number of patients included in the efficacy analysis | n=3176 |
| Number of patients excluded from the efficacy analysis | n=685 |
| Reasons for exclusion (includes duplicates) | |
| Missing efficacy data††† | n=681 |
| Drug used for other (excluded) diseases | n=6 |
showed improved FAST stages during the first 24 months after donepezil administration, it appears that donepezil treatment is useful given that AD is a progressive disease. These results could become valuable information on changes in FAST in Japan, especially as it has been over 10 years since the above report on worsening FAST scores was published.

Independence level in the daily life of elderly with dementia at the start of administration

| Independence level | Number of patients |
|--------------------|--------------------|
| I                  | 576                |
| IIA                | 1070               |
| IIb                | 880                |
| IIla               | 385                |
| IIb                | 100                |
| IV                 | 63                 |
| M                  | 20                 |
| Unknown            | 82                 |

†There are duplicate data included in complications. HDS-R, Hasegawa’s Dementia Scale-Revised; MMSE, Mini-Mental State Examination.

It has been reported that cognitive function improves temporarily at 12 weeks after donepezil
administration but then gradually declines.\textsuperscript{13} Because this study did not include an untreated group, a direct comparison in terms of donepezil’s efficacy cannot be made. However, according to a meta-analysis from overseas on changes in MMSE in AD patients, the MMSE change in untreated AD patients is reported to be approximately −3 points/year.\textsuperscript{14} In the present study, this MMSE change was −0.4 points/year, a smaller change than that in the untreated patients in the previous study.

Table 2 Percentage of patients whose FAST stage improved or deteriorated (compared to the start of administration)

| Evaluation time point | Number of patients | FAST stage improvement | FAST stage exacerbation | FAST stage improvement or maintenance |
|-----------------------|--------------------|------------------------|------------------------|---------------------------------------|
|                       | Number of patients | Number of patients | Percentage (%) | Number of patients | Percentage (%) | Number of patients | Percentage (%) |
| At 6 months           | 2747               | 394                   | 14.3                 | 245                  | 8.9               | 2502                 | 91.1            |
| At 12 months          | 2292               | 424                   | 18.5                 | 389                  | 17.0              | 1903                 | 83.0            |
| At 18 months          | 1829               | 349                   | 19.1                 | 375                  | 20.5              | 1454                 | 79.5            |
| At 24 months          | 1136               | 220                   | 19.4                 | 286                  | 25.2              | 850                  | 74.8            |

Figure 2 Changes in FAST scores. FAST, Functional Assessment Staging Test.

Figure 3 Factors that affect the FAST at 24 months. FAST, Functional Assessment Staging Test.
In terms of safety, the incidence rate of ADR up to the 24-month time point was 7.5% (288/3861 patients). This rate was lower than that reported in a 24-week, double-blind, placebo-controlled study in Japan that investigated mild and moderate AD at the time of donepezil’s development (10.3% (14/136 patients)), \(^{13}\) in a 52-week, continuous, long-term administration study (27.3% (71/260 patients)), \(^{15}\) and in post-marketing surveillance conducted after donepezil’s approval (10.7% (346/3240 patients)). The efficacy of donepezil measured by FAST and cognitive function and the incidence rate of ADR resulted in clinically favourable outcomes in the present study compared to data from the clinical trial in Japan. However, the clinical trial was performed over 10 years ago. Advances in our understanding of AD and donepezil, medical and nursing care, and non-medical therapy may have contributed to the achievement of favourable results.

There are several limitations to this study because it was an investigation conducted in daily clinical practice. These limitations include the exclusion of patients from analysis because they did not visit the hospital after the start of donepezil administration; the
analysis’s inclusion of patients who discontinued the study after switching to a generic drug during the study period; the presence of a considerable number of patients who did not undergo examinations of cognitive function; and the difficulty in confirming medication adherence.

This is the largest prospective study involving AD patients in Japan, and it shows the reality of daily clinical practice. The present report is an interim outcome at the 2-year time point after starting the study, and we plan to continue data collection and report the results of the analysis at the 4-year time point.

ACKNOWLEDGMENTS

The authors would like to thank the participating medical institutions and their staff members for their cooperation in this study.

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Table 3 Occurrence of ADR

| Items                              | Total | Serious | Non-serious |
|------------------------------------|-------|---------|-------------|
| Number of study centres            | 1114  | –       | –           |
| Number of study patients           | 3861  | –       | –           |
| Number of patients who developed ADR | 288   | 28      | 261         |
| Cases of ADR                       | 366   | 40      | 326         |
| Incidence of ADR (percentage of patients) | 7.6%   | 0.7%    | 6.8%        |
| Type of ADR†                       | Cases of ADR by type (and percentage %) |
| Metabolism and nutrition disorders |       |         |             |
| Decreased appetite                 | 55 (1.4) | 3 (0.1) | 52 (1.3)    |
| Psychiatric disorders              | 34 (0.9) | –       | 34 (0.9)    |
| Nervous system disorders           | 10 (0.3) | –       | 10 (0.3)    |
| Gastrointestinal disorders         | 27 (0.7) | –       | 27 (0.7)    |
| Nausea                             | 50 (1.3) | 5 (0.1) | 45 (1.2)    |
| Vomiting                           | 20 (0.5) | 2 (0.1) | 18 (0.5)    |

†Only ADR with ≥10 cases are listed in the table. ADR, adverse drug reaction.
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**APPENDIX**

The independence level in daily life of elderly with dementia

| Ranking | Criteria | Examples of observed symptoms and behaviours |
|---------|----------|---------------------------------------------|
| I       | Person has some sort of dementia, but is almost completely independent in daily domestic and social activities. |  |
| II      | Symptoms, behaviour, or communication difficulties that interfere with the person’s daily life are observed to some degree, but the person can live independently if someone is there to look after him/her. | Person frequently gets lost and makes noticeable mistakes in activities he/she was able to do previously such as shopping, administrative work, and money management. |
| IIa     | Conditions listed in II are observed outside of the home. | Person cannot manage medications and cannot stay at home alone (i.e. cannot answer phone calls or visitors). |
| IIb     | Conditions listed in II are also observed at home. |  |
| III     | Symptoms, behaviour, or communication difficulties that interfere with the person’s daily life are observed once in a while and require care. | Person has difficulty (cannot perform well or requires a lot of time) in changing clothes, eating meals, defecating, and urinating. |
| IIIa    | Conditions listed in III are observed primarily during the day. | Person frequently places objects in mouth, gathers and collects items, wanders, is incontinent, raises his/her voice or makes strange noises, does not take care after using fire (e.g. for cooking), presents unclean behaviour or abnormal sexual behaviour, etc. |
| IIIb    | Conditions listed in III are observed primarily at night-time. | Same as Rank IIIa. |
| IV      | Symptoms, behaviour, or communication difficulties that interfere with the person’s daily life are observed frequently and require constant care. | Same as Rank III. |
| M       | Significant psychotic manifestations, problem behaviour, or severe physical diseases are observed and require specialized medical care. | Person has condition in which there are continual psychiatric symptoms such as delirium, delusion, excitement, and harm to self or others as well as problematic behaviours caused by such psychiatric symptoms. |

Translated from the Ministry of Health, Labour and Welfare home page.