Disease state changes and safety of long-term donepezil hydrochloride administration in patients with Alzheimer’s disease: Japan-Great Outcome of Long-term trial with Donepezil (J-GOLD)

Heii ARAI,1 Naoyuki HASHIMOTO,2 Kenta SUMITOMO,2 Takao TAKASE2 and Mika ISHII2

1Department of Psychiatry and Behavioral Science, Juntendo University Graduate School of Medicine and 2Eisai Co., Ltd., Tokyo, Japan
Correspondence: Dr Heii Arai MD. PhD, Department of Psychiatry and Behavioral Science, Juntendo University Graduate School of Medicine. Hongo 3-1-3, Bunkyo-ku, Tokyo 113-8431, Japan. Email: heii@juntendo.ac.jp
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Abstract

Background: A long-term, large-scale study of donepezil hydrochloride in patients with Alzheimer’s disease (AD) was conducted. Previously, two interim reports were published during this study. We have now completed the study and herein present our analysis of the final results.

Methods: The subjects of this study included AD patients who received the drug for the first time (newly treated patients), as well as AD patients who were already receiving the drug at the start of the study (continuously treated patients). The observation period was 48 months. Changes in cognitive function and severity of dementia associated with the drug administration and its safety were assessed.

Results: Cognitive function decreased significantly after 24 months in newly treated patients and after 6 months in continuously treated patients, compared with baseline. The percentages of patients whose dementia severity improved or remained the same compared with baseline were 59.27% at 48 months in the newly treated patients and 57.09% at 48 months in the continuously treated patients. There were no major safety problems with the drug.

Conclusions: We conducted a large-scale study of AD patients in Japan. Here, we present our analysis of the final results and describe current clinical practice with the drug, changes in cognitive function and dementia severity associated with long-term administration of the drug, and the drug’s safety.

INTRODUCTION

The Japan–Great Outcome of Long-term Trial with Donepezil, also known as J-GOLD—a long-term, large-scale prospective study of donepezil hydrochloride (Aricept®; Eisai Co., Ltd., Tokyo, Japan) in Alzheimer’s disease (AD) patients—was initiated in 2010. Two interim reports were published during the course of this study. The first interim report presented an analysis of the data at 12 months and described the effects of the drug on cognitive function (Hasegawa’s Dementia Scale-Revised (HDS-R) and Mini-Mental State Examination (MMSE)) and dementia severity (Functional Assessment Staging (FAST)) in newly treated and continuously treated patients.1 The second interim report presented an analysis of the data of newly treated patients at 24 months and indicated that the duration of AD and independence levels in the daily lives of elderly patients with dementia were identified as variables that affected the improvement and maintenance of dementia severity (according to FAST).2

Here, we report the final results of the long-term, large-scale study involving 10 000 patients over a period of 48 months.
METHODS

Subjects

The study investigated patients who were diagnosed with AD based on the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, criteria and who had mild or moderately severe dementia according to the FAST (FAST-4 and FAST-5, respectively). Patients were enrolled at 1787 centres, most of which were the clinics of primary care doctors. The number of enrolled patients was 10,238. Data were compiled from 9,753 case report forms. A total of 174 patients were excluded from the safety analysis, leaving 9,579 patients in the safety data set. Furthermore, 1,119 patients were excluded from the efficacy analysis, leaving 8,460 patients in the efficacy data set (Fig. 1). The reasons for exclusion (with duplicates) are shown in the figure describing patient composition. The study population included both newly treated patients and continuously treated patients. Table 1 summarizes the demographic information of the newly treated and continuously treated patients included in the efficacy analysis. The duration of drug exposure (mean ± SD) before the start of the study in the continuously treated patients was 18.55 ± 18.58 months (median: 12.54 months). The durations of AD were 1.20 ± 1.43 years (median: 0.69 years) in the newly treated patients and 2.67 ± 2.05 years (median: 2.21 years) in the continuously treated patients.

Study method

The investigating physicians conducted patient enrolment. For newly treated patients, the study start date was defined as the start date of donepezil administration. For continuously treated patients, the study start date was defined as the first visit with an investigating physician during the study period. The follow-up period for each patient was 48 months from the study start date. If donepezil administration was temporarily stopped ≥ 3 weeks at a time or discontinued completely, the patient was withdrawn from the study. Patient data were collected using electronic data capture.

The scientific and ethical validity of the study design was discussed at Eisai Co., Ltd., and the study was conducted as ‘the special drug use surveillance of Aricept: Japan—Great Outcome of Long-term trial with Donepezil (J-GOLD)’. This study was conducted in accordance with the Good Post-marketing Study Practice, which is an authorized...
standard for appropriate post-marketing surveillance to ensure the safety and efficacy of a pharmaceutical product after its marketing by manufacturing distributors. In addition, personal information related to this study was managed in accordance with privacy protection laws.
Study items

Patient characteristics
The time of AD onset, complications, concomitant drugs, use of home care services, and Category of Condition of Need for Long-Term Care were assessed.

Changes in disease state
Changes in disease state were assessed using cognitive function tests (i.e. HDS-R or MMSE) and FAST (for dementia severity).

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, the occurrence of which were investigated. However, because AD is a progressive disease, spontaneous exacerbation of AD diagnosed by the study physician and exacerbation of the Category of Condition of Need for Long-Term Care were not considered to be adverse events. Adverse events for which attribution to donepezil could not be ruled out were considered to be adverse drug reactions (ADR).

Evaluation time points
Cognitive function was examined at 12 weeks and at 6, 12, 18, 24, 30, 36, 42, and 48 months after the start of the study (or at the time of discontinuation). If the examinations were conducted between these time points, the results were included in the study. Time points of FAST evaluation were 6, 12, 18, 24, 30, 36, 42, and 48 months after the start of the study (or at the time of discontinuation).

Analysis
Adverse events and ADR complied with Japanese version 18.1 of the Medical Dictionary for Regulatory Activities. The number of patients who developed these conditions, the incidence proportion, and the number of patients (cases) and incidence proportion according to system organ class and preferred term were determined. The incidence proportion of ADR was also calculated according to the time of onset.

For examinations of cognitive function and for each type of examination conducted, summary statistics regarding changes between baseline and each evaluation time point were determined, and paired t-tests were performed.

For the FAST evaluation, the number and percentage of patients at each evaluation time point according to severity were reported. The number and percentage of patients whose severity either improved or worsened from baseline were also reported. In addition, a multivariate logistic regression analysis was performed to measure the improvement and maintenance or exacerbation of FAST at 48 months in the newly treated patients.

The results were primarily summarized using descriptive statistics. All statistical tests were two-tailed unless otherwise specified, and the significance level was set at 5%. For variable selection in multivariate logistic regression analysis, a two-tailed significance level of 30% was used. All analyses were conducted using SAS release 9.3 (SAS Institute, Inc. Cary, NC, USA) and were performed independently by the EPS Corporation (Tokyo, Japan) under contract with Eisai Co., Ltd.

RESULTS

Changes in disease state

Changes in cognitive function
Changes in cognitive function were evaluated by the HDS-R or MMSE, with the two tests showing similar patterns of change. In the newly treated patients, cognitive function improved significantly at 12 weeks and 6 months compared with baseline, maintained baseline levels at 12 months and 18 months, and decreased after 24 months. In the continuously treated patients, cognitive function was maintained up to 12 weeks and significantly decreased after 6 months (Figs 2,3).

Changes in the severity of dementia (FAST)
The distribution of FAST stages in the newly treated patients and the continuously treated patients are shown in Figures 4 and 5, respectively. The percentages of patients whose FAST stage improved and worsened compared with baseline are shown Table 2. The percentages of patients whose FAST stage improved compared with baseline or was maintained at 48 months compared with baseline were 59.27% (588/992 cases) in the newly treated
patients and 57.09% (910/1594 cases) in the continuously treated patients.

Factors affecting the severity of dementia (FAST)
Multivariate logistic regression analysis was conducted to identify factors that affected improvement and maintenance or exacerbation of FAST at 48 months. Through a stepwise method, baseline age, severity of dementia at the start of the study (FAST), duration of AD, presence of abnormal lipid metabolism (hyperlipidaemia), use of home care service at the start of the study, and independence level in the daily life of elderly with dementia at the start of the study were identified as relevant variables. In addition, sex, the presence of hypertension, and the presence of diabetes mellitus were included in the model for multivariate regression analysis because they were clinically considered to possibly affect FAST, and the adjusted odds ratios (OR) were calculated (Fig 6). Consequently, severity of dementia at the start of the study (FAST) (OR of FAST-5 vs FAST-4 = 1.698), presence of abnormal lipid metabolism (hyperlipidaemia) (OR of presence vs absence of complication = 1.507), independence level in the daily life of elderly with dementia at the start of the study were identified as relevant variables. In addition, sex, the presence of hypertension, and the presence of diabetes mellitus were included in the model for multivariate regression analysis because they were clinically considered to possibly affect FAST, and the adjusted odds ratios (OR) were calculated (Fig 6). Consequently, severity of dementia at the start of the study (FAST) (OR of FAST-5 vs FAST-4 = 1.698), presence of abnormal lipid metabolism (hyperlipidaemia) (OR of presence vs absence of complication = 1.507), independence level in the daily life of elderly with dementia at the start of the study were identified as relevant variables. In addition, sex, the presence of hypertension, and the presence of diabetes mellitus were included in the model for multivariate regression analysis because they were clinically considered to possibly affect FAST, and the adjusted odds ratios (OR) were calculated (Fig 6). Consequently, severity of dementia at the start of the study (FAST) (OR of FAST-5 vs FAST-4 = 1.698), presence of abnormal lipid metabolism (hyperlipidaemia) (OR of presence vs absence of complication = 1.507), independence level in the...
Figure 4 Changes in Functional Assessment Staging Test (FAST) score of newly treated patients.

Figure 5 Changes in Functional Assessment Staging Test (FAST) score of continuously treated patients.

Table 2 Percentages of patients in whom the Functional Assessment Staging Test stage improved or worsened (compared with baseline)

| Evaluation time point | Newly treated patients | Continuous treated patients |
|-----------------------|------------------------|-----------------------------|
|                       | Total n     | Improved n | %   | Worsened n | %   | Total n     | Improved n | %   | Worsened n | %   |
| At 6 months           | 2738        | 392        | 14.32 | 244        | 8.91 | 4555        | 431        | 9.46 | 559        | 12.27 |
| At 12 months          | 2289        | 423        | 18.48 | 389        | 16.99 | 3796        | 522        | 13.75 | 782        | 20.60 |
| At 18 months          | 1867        | 354        | 18.96 | 383        | 20.51 | 3162        | 437        | 13.82 | 827        | 29.69 |
| At 24 months          | 1686        | 314        | 18.62 | 444        | 26.33 | 2711        | 368        | 13.57 | 805        | 29.69 |
| At 30 months          | 1398        | 267        | 19.10 | 419        | 29.97 | 2309        | 310        | 13.43 | 774        | 33.52 |
| At 36 months          | 1215        | 227        | 18.68 | 404        | 33.25 | 2018        | 242        | 11.99 | 768        | 38.06 |
| At 42 months          | 1091        | 209        | 19.16 | 403        | 36.94 | 1785        | 196        | 10.98 | 732        | 41.01 |
| At 48 months          | 992         | 192        | 19.35 | 404        | 40.73 | 1594        | 168        | 10.54 | 684        | 42.91 |
| Last observation      | 3039        | 446        | 14.68 | 1079       | 35.51 | 5003        | 509        | 10.17 | 1978       | 39.54 |

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daily life of elderly with dementia at the start of the study (OR of IIIa – IV + M vs I – IIb = 0.718), and duration of AD (OR ≥ 6 months vs < 6 months = 0.661) were identified as variables affecting improvement or exacerbation of FAST.

**Safety**

**Occurrence of ADR**

Adverse events for which attribution to donepezil could not be ruled out were classified as ADR. The occurrence of ADR in the newly treated patients and the continuously treated patients are shown in Table 3. Major ADR (occurring in ≥ 0.2% of patients) in the newly treated patients were decreased appetite (1.43%), nausea (1.35%), diarrhoea (0.76%), agitation (0.65%), vomiting (0.55%), anger (0.50%), dizziness (0.29%), aggression (0.26%), constipation (0.23%), delusion (0.21%), insomnia (0.21%), restlessness (0.21%). Major ADR in the continuously treated patients were decreased appetite (0.64%), anger (0.55%), agitation (0.43%), diarrhoea (0.39%), nausea (0.30%), aggression (0.27%), constipation (0.23%), bradycardia (0.23%), and vomiting (0.21%). There were no major safety problems with the drug.

**Timing of occurrence of ADR**

The proportion of patients in whom ADR occurred in each period in the newly treated patients and continuously treated patients are shown in Figure 7. During the first 4 weeks, ADR occurred in 3.47% (133/3838) of cases. The major ADR (occurring in ≥ 0.1% of patients) were nausea (0.68%), decreased appetite (0.60%), diarrhoea (0.42%), vomiting (0.34%), agitation (0.23%), anger (0.21%), dizziness (0.13%), headache (0.13%), and abdominal pain (0.10%).

**DISCUSSION**

The interim reports already indicated that cognitive function in the continuously treated patients decreased after the start of the study, whereas cognitive function in the newly treated patients improved significantly but temporarily after donepezil administration and then declined. In the present study with a longer follow-up period, cognitive function in the continuously treated patients decreased significantly after 6 months compared with baseline and that in the newly treated patients decreased significantly after 24 months compared with baseline.

In the present study, the changes in cognitive function in the newly treated patients after 24 months were −0.63 points/year for the MMSE and −0.94 points/year for the HDS-R. Although the subjects were restricted to those who were able to be followed up, the change was less than 1 point/year even after 24 months, confirming the significance of long-term administration of the drug. We believe that this large-scale, long-term study provides valuable clinical information about changes in cognitive function.

Regarding changes in dementia severity, the proportion of patients whose FAST stages maintained or
improved was &gt;70% during the first 24 months and nearly 60% during the first 48 months, suggesting the significance of long-term administration of the drug. (If it is assumed that all patients who discontinued the study treatment were exacerbated, the proportion of patients whose FAST stages maintained or improved was nearly 40% during the first 24 months and nearly 20% during the first 48 months.)

In the second interim report of the present study, independence level in the daily life of elderly with dementia at the start of the study and duration of AD were factors that significantly affected the

Table 3 Occurrence of adverse drug reactions (ADR)

| Item                      | Newly treated patients               | Continuously treated patients         |
|---------------------------|--------------------------------------|---------------------------------------|
|                           | All ADR | Serious | Non-serious | All ADR | Serious | Non-serious |
| Patients surveyed (n)     | 3838     |         |             | 5636     |         |             |
| Patients with ADR (n)    | 329      | 52      | 292         | 262      | 45      | 221         |
| ADR (n)                   | 417      | 52      | 265         | 338      | 50      | 288         |
| Incidence of ADR          | 8.57%    | 0.99%   | 7.61%       | 4.65%    | 0.80%   | 3.92%       |
| Type of ADR               | n %      | n %      | n %         | n %      | n %      | n %         |
| Metabolism and nutrition disorders |         |         |             |         |         |             |
| Decreased appetite        | 55 1.43  | 3 0.08   | 52 1.35     | 36 0.64  | 2 0.04   | 34 0.60     |
| Psychiatric disorders     |         |         |             |         |         |             |
| Aggression                | 10 0.26  | 1 0.03   | 9 0.23      | 15 0.27  | —        | 15 0.27     |
| Agitation                 | 25 0.65  | 1 0.03   | 24 0.63     | 24 0.43  | —        | 24 0.43     |
| Anger                     | 19 0.50  | 1 0.03   | 18 0.47     | 31 0.55  | 1 0.02   | 30 0.53     |
| Delirium                  | 4 0.10   | —        | 4 0.10      | 7 0.12   | 2 0.04   | 5 0.09      |
| Insomnia                  | 8 0.21   | —        | 8 0.21      | 5 0.09   | —        | 5 0.09      |
| Irritability              | 6 0.16   | 1 0.03   | 5 0.13      | 5 0.09   | —        | 5 0.09      |
| Restlessness              | 8 0.21   | 1 0.03   | 7 0.18      | 7 0.12   | —        | 7 0.12      |
| Nervous system disorders  |         |         |             |         |         |             |
| Dizziness                 | 11 0.29  | —        | 11 0.29     | 4 0.07   | —        | 4 0.07      |
| Somnolence                | 5 0.13   | —        | 5 0.13      | 7 0.12   | —        | 7 0.12      |
| Cardiac disorders         |         |         |             |         |         |             |
| Bradycardia               | 3 0.08   | 1 0.03   | 2 0.05      | 13 0.23  | 4 0.07   | 9 0.16      |
| Gastrointestinal disorders|         |         |             |         |         |             |
| Constipation              | 9 0.23   | —        | 9 0.23      | 13 0.23  | —        | 13 0.23     |
| Diarrhoea                 | 29 0.76  | —        | 29 0.76     | 22 0.39  | 1 0.02   | 21 0.37     |
| Nausea                    | 52 1.35  | 6 0.16   | 46 1.20     | 17 0.30  | —        | 17 0.30     |
| Vomiting                  | 21 0.55  | 2 0.05   | 19 0.50     | 12 0.21  | 2 0.04   | 10 0.18     |

ADR with an overall incidence of ≥0.10% are listed.

Figure 7 Percentage of patients in whom adverse drug reactions occurred during each period. M, months; W, weeks.
improvement and maintenance or exacerbation of FAST at 24 months. In the present analysis, based on the data at 48 months, the severity of dementia (FAST) at the start of the study and the presence of abnormal lipid metabolism (hyperlipidaemia) were newly identified as also affecting the improvement and maintenance or exacerbation of FAST.

Among the variables that have a greater influence on clinical condition, hypertension and diabetes mellitus were not identified as significant factors in the present analysis or in the interim report. However, abnormal lipid metabolism (hyperlipidaemia) was newly identified in the present study, suggesting that patients with abnormal lipid metabolism (hyperlipidaemia) are more likely to improve or maintain FAST stages. This result contradicts the previous study. It is possible that concomitant drugs, such as statin, had some impact; a report indicated that AD progression was slower in AD patients with early statin use than those without. However, we cannot explain the reason because we did not investigate the use of concomitant drugs in detail.

The results also showed that patients with moderate AD (FAST-5) at the start of the study showed more improvement and maintenance of FAST stages than those with mild AD (FAST-4) at the start of the study. Because this was not observed in the interim report at 24 months, we considered the possibility that dropout cases at 24 months or later might have influenced the results. To clarify this point, we performed an analysis using the data at the end of assessment including those who had dropped out. Consequently, the OR decreased to 1.411 but remained statistically significant ($P = 0.003$). We also examined the effect of the daily donepezil dose but did not find any differences. An integrated analysis of six double-blind comparative studies showed that the effect of the drug on activities of daily living was not different from that of placebo in mild AD, but it was effective in improving or maintaining some activities of daily living in moderate AD. This result supports our findings because the assessment of FAST is based on changes in activities of daily living. It suggests that long-term donepezil administration can suppress the progression of AD to moderately severe disease. In addition, AD patients with a disease duration <6 months and elderly patients with dementia with a higher independence level in their daily lives showed improvement and maintenance of FAST stages in the present study, as well as in the interim report. It is, therefore, believed that early diagnosis and treatment with donepezil can suppress disease severity.

In terms of safety, the incidence proportion of ADR was higher in newly treated patients than in continuously treated patients. In the interim report, the incidence proportion of ADR in the newly treated patients in the first 24 months was 7.46% (288/3861 patients). In the present study, the incidence proportion of ADR in the newly treated patients during 48 months was 8.57% (329/3838 patients), but as in the interim report, there were no particular safety issues.

This study is distinguished by the inclusion not only of newly treated patients but also of continuously treated patients. The mean ± SD drug administration period before the start of the study in the continuously treated patients was 18.55 ± 18.58 months (median: 12.54 months). The changes in cognitive function and the incidence proportion of ADR for each period in the continuously treated patients were similar to those in the newly treated patients during the period starting at 12–18 months; that is, the data from the continuously treated patients were assumed to be similar to those from newly treated patients after the treatment period equivalent to what the continuously treated patients had before the start of the study. Based on this assumption, the data from the continuously treated patients at 36 months is considered to be similar to the data from newly treated patients at 48 months. It is, thereby, possible to obtain more data from the long-term study conducted in daily clinical practice by including continuously treated patients.

There were several limitations to this study because it was conducted during daily clinical practice. These limitations include the exclusion of a certain number of patients from analysis because they did not visit the hospital after the start of the study or they switched to a generic drug during the study period. Additionally, some patients did not undergo examination to assess cognitive function. Nevertheless, this was one of the largest prospective studies of AD patients in Japan. This study described current clinical practice with donepezil, the changes in cognitive function and dementia severity associated with
the long-term administration of the drug, and its safety.

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