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ORIGINAL RESEARCH

A 48-Week, Multicenter, Open-Label, Observational Study Evaluating Oral Rivastigmine in Patients with Mild-to-Moderate Alzheimer's Disease in Taiwan

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ABSTRACT

Introduction: Rivastigmine is a cholinesterase inhibitor, approved for the treatment of mild-to-moderate dementia of Alzheimer's type. This study assessed the short- and long-term effectiveness and safety of rivastigmine in patients with mild-to-moderate Alzheimer's disease (AD) in a real-world clinical setting in Taiwan.

Methods: This was a 48-week, single-arm, open-label, prospective, observational, post-marketing surveillance, multicenter study. The primary outcomes were change from baseline to week 48 in the Mini-Mental State Examination (MMSE) and Clinical Dementia Rating (CDR) scores. One-year persistence to treatment, effect on activities of daily living, and incidence of adverse events (AEs) were also assessed.

Results: Overall, 151 patients were enrolled in the study, of which 91 (60.26%) completed this study. At the end of the study, the mean rivastigmine dose received by the patients was 6.59 mg/day. At week 48, the changes in mean [standard deviation (SD)] MMSE and CDR scores in the intent-to-treat (ITT) population from baseline were − 1.00 (3.8; $p = 0.0344$) and 0.07 (0.29; $p = 0.0403$), respectively. The most frequently reported AEs by preferred term were dizziness (12.58%) and nausea (9.27%). No new or unexpected AEs were observed, and 30 (20.13%) patients in the ITT population were on rivastigmine therapy for 1 year without treatment discontinuation.

Conclusion: Despite the low 1-year persistence rate, rivastigmine showed a stabilizing effect on declining cognition in patients with mild-to-

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moderate AD in a real-world scenario. Rivastigmine is well tolerated at 6.0–9.0 mg/day with no unexpected safety concerns.
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Keywords: Alzheimer's disease; Cognition; Dementia; Neurology; Rivastigmine; Treatment persistence

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and functional impairment [1]. The proportion of individuals aged ≥ 65 years in Taiwan has increased from 4.1% in 1980 to 10.7% in 2010 [2–4], and this increase in the aging population has led to an increase in the prevalence of age-related AD [2]. In a nationwide survey conducted in Taiwan, the age-adjusted prevalence of all-cause dementia was 8.04% [5], and this number is projected to increase up to 0.21 million by 2020 [6].

The drugs available for treatment of AD in Taiwan include rivastigmine, donepezil, galantamine [cholinesterase inhibitors (ChEIs)], and memantine (*N*-methyl-D-aspartate receptor antagonist) [7]. Rivastigmine is a reversible (pseudo-irreversible) ChEI that targets both acetyl cholinesterase and butyryl cholinesterase [8]. Rivastigmine capsules were approved for the treatment of mild-to-moderate AD in the US and Taiwan in 2000 [9].

To date, limited information is available on the average dose or treatment persistence rate in patients with newly diagnosed AD in the Asian population [10]. Hence, it is worthwhile to assess the effectiveness of rivastigmine in the real-world setting. We report a real-world, observational study in rivastigmine-naïve Taiwanese patients with newly diagnosed mild-to-moderate AD. This study was designed to assess the effects of oral rivastigmine on cognition [Mini-Mental State Examination (MMSE)] and dementia [Clinical Dementia Rating (CDR)]. In addition, 1-year persistence to rivastigmine therapy and safety were assessed.

METHODS

Study Design

This was a 48-week, single-arm, open-label, multicenter, prospective, observational, post-marketing surveillance study conducted across four centers in Taiwan between 2 September 2010 and 2 August 2012. Patients were followed up at outpatient clinics for 1 year to observe the real-world usage of rivastigmine capsules. Effectiveness and safety assessments were conducted at 24 and 48 weeks after the first prescription. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the following institutional review boards: the institutional review board of Tri-Service General Hospital, Chang Gung Medical Foundation Institutional Review Board, the Institutional Review Board of the Kaohsiung Medical University Hospital, and the Institutional Review Board of Chung Shan Medical University Hospital. All patients provided written informed consent before enrollment.

Patient Eligibility Criteria

The study population comprised male and female outpatients aged 50–85 years, diagnosed with mild-to-moderate dementia of the Alzheimer's type, who received a new prescription of rivastigmine by the treating physician in adherence with the local prescribing information and provided informed consent. The diagnosis of AD was based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition [11] and the probable AD criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association [12]. Based on the National Health Insurance reimbursement in Taiwan, treatment with ChEIs in patients diagnosed with mild-to-moderate AD should follow the reimbursement criteria to receive approval for rivastigmine capsule treatment (Exelon®, Novartis Pharmaceuticals, Taiwan). The National Health Insurance reimbursement criteria included (1) clinical

diagnosis of AD; (2) an MMSE score of 10–26 or CDR score of 1–2; (3) computed tomography or magnetic resonance imaging report suggestive of AD; (4) normal blood profiles of liver and renal vitamin B_{12} and folate levels.

The patients were excluded if they had previously received rivastigmine, other concomitant ChEIs, or any other investigational product within 4 weeks before enrollment. Women who were pregnant or intended to become pregnant were excluded.

Study End Points and Assessments

The primary end points were changes in MMSE and CDR scores from baseline to week 48.

Secondary end points included change from baseline to week 24 in MMSE and CDR scores, 1-year persistence rate of rivastigmine therapy, and safety profile of rivastigmine, as assessed by incidence of adverse events (AEs). The 1-year persistence rate, defined as patients with no treatment interruptions for > 14 consecutive days, and safety were assessed by the incidence of AEs. In addition, patients were given an option to provide data on Instrumental Activities of Daily Living (IADL) scores at week 48.

Statistical Analysis

Effectiveness was analyzed in the intent-to-treat (ITT) and per-protocol (PP) populations. The ITT population comprised all enrolled patients who received at least one dose of study medication. Patients who did not have any protocol violations and completed baseline and week 24 and 48 visits were included in the PP population. A paired *t* test was used to calculate the changes from baseline in MMSE scores at weeks 24 and 48. Changes in CDR scores were measured as counts and percentages. The last observation carried forward (LOCF) method was used to estimate the missing primary effectiveness variables. The persistence rate was summarized using descriptive analysis, including counts, percentages, and 95% confidence intervals (CIs). Safety analyses were performed in the safety population and included safety variables, such as incidence of AEs/serious AEs (SAEs). A paired *t* test was used to analyze the change in IADL scores from baseline to week 48.

RESULTS

Study Population

Of the 151 enrolled patients, 91 (60.26%) completed this study, and 60 (39.74%) discontinued primarily because of AEs or any change in health status ($n = 26$, 43.33%), followed by consent withdrawal ($n = 22$, 36.67%). Three patients were excluded from the total enrolled population because of protocol violations (Fig. 1). The baseline demographics and disease characteristics of 148 patients are presented in Table 1.

All the enrolled patients who received at least one dose of study medication were included in the ITT and safety populations. The PP population comprised 66 (43.71%) patients. The mean [standard deviation (SD)] duration of study medication was 37.65 (20.72) weeks (range 0.43–85.14; 95% CI 34.30–41.01) and 50.42 (5.98) weeks (range 40.43–82.86; 95% CI 48.95–51.89) for the ITT and PP populations, respectively.

At the end of the study, the mean rivastigmine dose received by patients was 6.59 mg/day. Forty (26.5%) patients received a mean rivastigmine dose of ≤ 3 mg/day, 37 (24.5%) $>$ 3.0–6.0 mg/day, 72 (47.7%) $>$ 6.0–9.0 mg/day, and 2 (1.32%) $>$ 9.0 mg/day.

Primary and Secondary Assessments

MMSE scores at baseline, weeks 24 and 48 are presented in Fig. 2. The change in the mean (SD) MMSE score from baseline at week 24 was 0.30 (3.26) in the ITT population ($p = 0.34$) and 0.58 (3.16) in the PP population ($p = 0.14$). The change in the mean (SD) MMSE score from baseline at week 48 was $-$ 1.00 (3.80) in the ITT population ($p = 0.0344$) and $-$ 1.02 (3.82) in the PP population ($p = 0.0344$). Based on the LOCF analysis, the change in the mean (SD) MMSE score at week 48 was $-$ 0.55 (3.69) in the ITT population ($p = 0.125$).

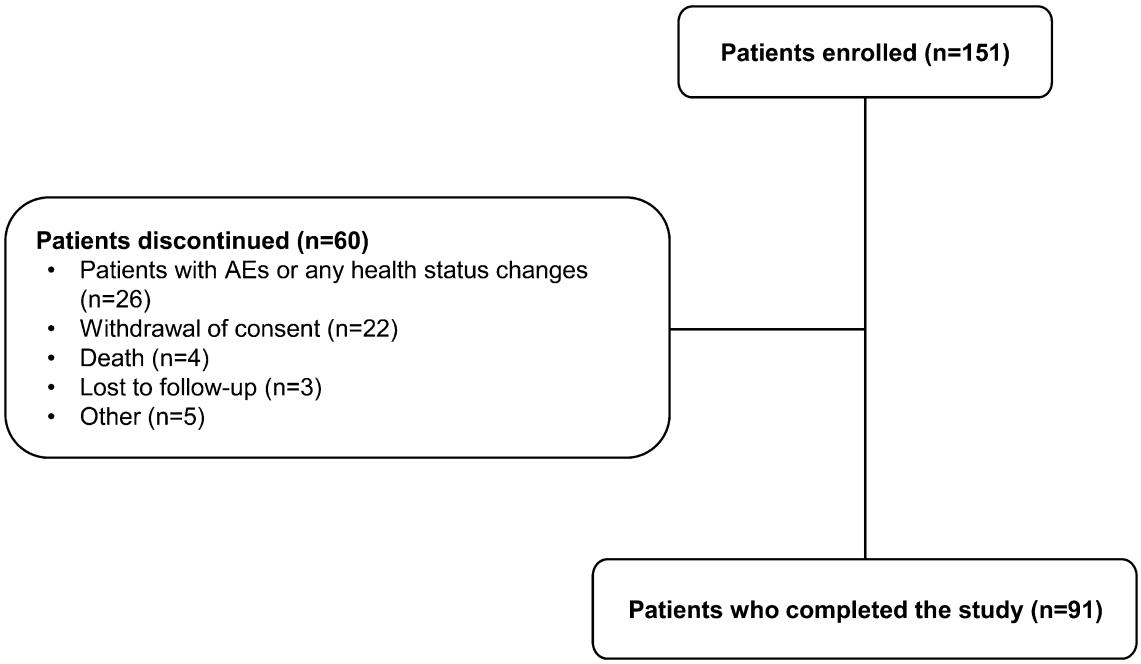

Fig. 1 Patient disposition in the study

The mean (SD) CDR scores at baseline, weeks 24 and 48 are presented in Fig. 3. The change in mean (SD) CDR scores from baseline at week 24 was 0.06 (0.35) and 0.02 (0.21) in the ITT and PP populations, respectively (both $p = 0.061$). The mean (SD) change in the CDR score from baseline at week 48 was 0.07 (0.29) in the ITT population ($p = 0.0403$) and 0.08 (0.29) in the PP population ($p = 0.0403$). Based on the ITT-LOCF analysis, the change in mean (SD) CDR score at week 48 from baseline was 0.10 (0.38; $p = 0.0071$).

Only 30 (20.13%) patients in the ITT population and 17 (25.76%) in the PP population were on rivastigmine therapy for 1 year without treatment discontinuation.

The IADL scores were collected from 80 patients. The mean (SD) IADL score at baseline and week 48 was 9.93 (6.75) and 9.06 (6.61), respectively. The change in the mean (SD) IADL total score from baseline to week 48 was 1.39 (3.45; $p = 0.0417$).

Safety

A total of 287 AEs were reported in 105 (69.54%) patients; of these, 86 events reported in 56 (37.09%) patients were considered drug related, as assessed by the investigator. The most frequently reported AEs were dizziness (12.58%), nausea (9.27%), abdominal discomfort (8.61%), decreased appetite (6.62%), and vomiting (6.62%; Table 2). For the drug-related AEs, 27.15% were mild, 8.61% moderate, and 1.32% severe in severity. Most commonly reported AEs leading to discontinuation of study drug included gastrointestinal symptoms ($n = 15$) such as vomiting and gastrointestinal upset. SAEs were reported in 12 (7.95%) patients. A total of six SAEs resulted in the death of five patients; however, these SAEs were not considered to be drug-related, as assessed by the investigator. One SAE (falling with abdominal trauma) was suspected to be related to the study drug; however, the patient recovered completely in 12 days.

DISCUSSION

This was an observational study conducted in rivastigmine-naïve patients newly diagnosed with mild-to-moderate AD over 48 weeks. At an average final dose of 6.59 mg/day, oral

Table 1 Patient demographics and baseline characteristics

Parameters	Total (n = 148)[a]
Age, years	74.4 ± 7.7
Gender, n (%)	
Female	95 (64.2)
Male	53 (35.8)
Time since AD diagnosis, years	0.3 ± 1.2
Prior treatment with ChEIs, n (%)	
Donepezil	5 (3.4)
None	143 (96.6)
Family history of AD, n (%)	14 (9.5)
MMSE score[b]	18.0 ± 5.3
CDR score	0.9 ± 0.5

Data are presented as mean ± SD unless otherwise indicated

AD Alzheimer's disease, *ChEIs* cholinesterase inhibitors, *CDR* Clinical Dementia Rating, *MMSE* Mini-Mental State Examination, *SD* standard deviation

[a] Three patients were excluded from the analyses because of protocol violation. These protocol violations included treatment discontinuation in two subjects along with violation of inclusion criterion 1 (subject aged 86 years not 50–85 years) in one and violation of exclusion criterion 2 (subject took rivastigmine prior to study entry) in the other subject

[b] The baseline MMSE score was not available for one patient

rivastigmine therapy had at least a stabilizing effect on patients with AD. Our study had three key findings: (1) in the Asian population, the escalation and maintenance dose can be tolerably reached to > 6 mg/day in 49.02% patients, with 37.09% patients showing AEs possibly related to study drugs; (2) a low persistence rate of oral rivastigmine capsules is noted in patients with AD, despite considerable therapeutic effects on the MMSE and CDR scores; (3) the longitudinal follow-up in the ITT group showed a significant decline in the MMSE, CDR, or IADL scores in AD after treatment at 48 weeks after the initial dose.

Short-Term (24-Week) Longitudinal Analysis

While the annual decline in the MMSE score varies from 1–5 points per year in patients with AD who receive placebo or no treatment [13], results from the pivotal phase III studies [9, 14] and the recently reported Cochrane review suggested the therapeutic benefits of rivastigmine capsules with respect to cognitive outcomes in patients with mild-to-moderate AD [15]. The meta-analysis suggested that the use of rivastigmine was associated with better outcomes for MMSE after the 26-week treatment, with a mean difference of 0.74 (95% CI 0.52–0.97; n = 3205; 5 studies) compared with placebo [15]. Rivastigmine capsules (3–12 mg/day) in a placebo-controlled trial showed significant improvement in mean (SD) MMSE scores (0.8 [3.2]; p = 0.002) at week 24 compared with baseline, and the differences were also significantly better than those of the placebo group [14]. In contrast to other placebo-controlled studies, our study reports the longitudinal differences compared with baseline. In the present study, an increase in MMSE score at week 24 was observed in both the ITT and PP populations, which was contradictory to the results of the previously reported post-marketing surveillance study in Taiwan that showed a decrease in mean (SD) MMSE scores [1.23 (0.63)] after 6-month rivastigmine therapy [10]. Although this increase in the MMSE score did not reach statistical significance, our real-world observation suggested that rivastigmine therapy improves or at least stabilizes cognition progression in patients with AD within the initial 24 weeks.

Long-Term (48-week) Longitudinal Analysis

In this study, the MMSE score decreased by 1–1.02 points over a period of 48 weeks in both the ITT and PP populations, and the decline showed an SD of 3.80–3.82 points. The use of ChEIs requires annual renewal in Taiwan, and only AD patients with an annual MMSE score decline of ≤ 1 received approval for follow-up

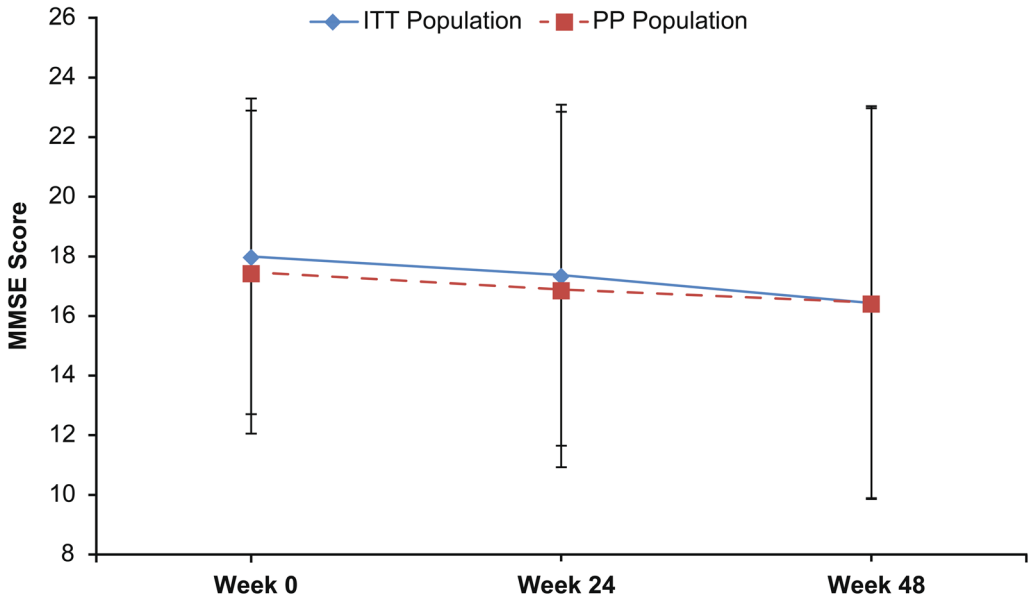

Fig. 2 Mean MMSE score at each visit (ITT and PP populations). The baseline MMSE score was not available for one patient. A total of 107 patients had MMSE scores recorded at either week 24 or week 48. MMSE scores at week 48 were available for 65 patients. The LOCF procedure was used to impute the missing values. *LOCF* last observation carried forward, *ITT* intent to treat, *MMSE* Mini-Mental State Examination, *PP* per protocol

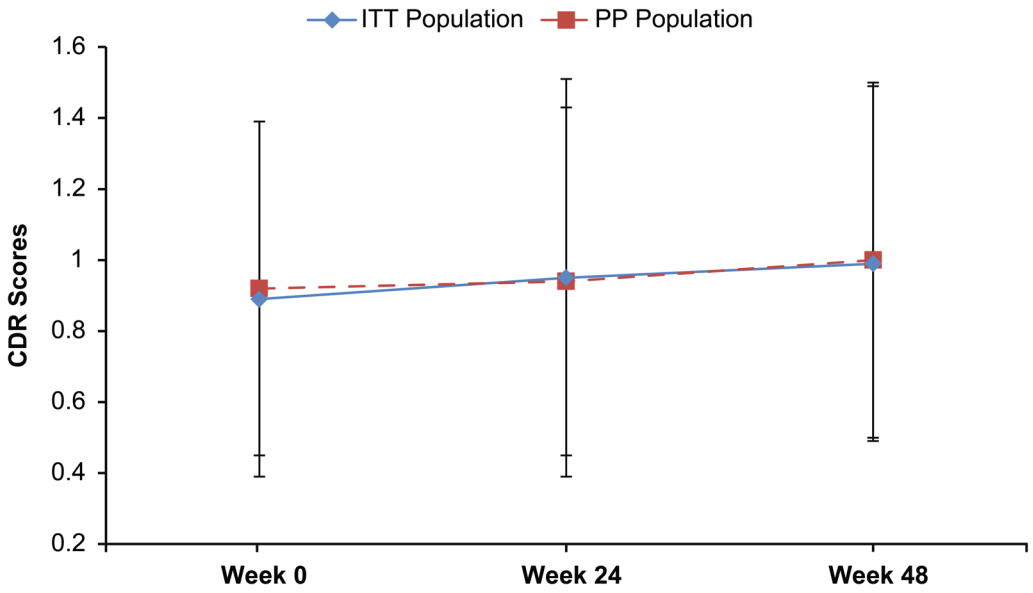

Fig. 3 Mean CDR score at each visit (ITT and PP populations). The CDR scores at week 48 were available for 65 patients. The LOCF procedure was used to impute the missing values; 109 patients had CDR scores recorded at week 24 or week 48. *CDR* Clinical Dementia Rating, *LOCF* last observation carried forward, *ITT* intent to treat, *MMSE* Mini-Mental State Examination *PP* per protocol

ChEI insurance reimbursement. The treatment regulation concerning the medical-ethical-economic aspects has been greatly debated. Our study showed that despite disease stabilization, the regulation might restrict some patients from ChEI treatment. Reports on long-term

Table 2 Adverse events ($\geq$ 2%)

AEs	*n* (%)
Patients with AE	105 (69.54)
AE possibly related to study drugs	56 (37.09)
Dizziness	19 (12.58)
Nausea	14 (9.27)
Abdominal discomfort	13 (8.61)
Vomiting	10 (6.62)
Decreased appetite	10 (6.62)
Gastritis	7 (4.64)
Diarrhea	6 (3.97)
Constipation	6 (3.97)
Insomnia	6 (3.97)
Hypertension	6 (3.97)
Death[a]	5 (3.31)
Headache	4 (2.65)

[a] There were no drug-related deaths
AE adverse event

treatment with rivastigmine capsules were limited. The single-center double-blinded, placebo-controlled, parallel-group, randomized, controlled trial of rivastigmine showed cognitive improvement and good tolerability after 52 weeks of treatment in advanced moderate-stage patients with AD [16]. The decline of mean (SD) MMSE scores in the aforementioned study was 0.2 (0.1), which might be attributed to the differences in disease stages and treatment responses.

The mean (SD) CDR score at baseline [ITT: 0.89 (0.50); PP: 0.92 (0.47)] indicated that patients had "very mild" to "mild dementia" [17] in this study, whereas similar scores were observed after the 48-week rivastigmine treatment [ITT: 0.99 (0.50); PP: 1.00 (0.50)]; this observation indicates stabilization in functional capacity within the initial 48 weeks. A numerical increase of 0.07 points was observed in CDR scores, and this change may not be clinically meaningful. These results are consistent with the findings of a previously reported observational study conducted in Taiwan [10].

In the present study, patients (n = 80) showed a significant improvement in IADL scores at week 48 (p = 0.0417). Patients with AD generally present with deterioration in activities of daily living (ADL), which, if improved, would be beneficial in improving patients' quality of life and caregivers' burden [18]. Improvement in IADL scores observed in the present study indicates a beneficial effect, although the numerical difference might not be clinically relevant.

Dosage and Persistence Rate

Results of the previously reported observational study in Taiwan showed that 6-month rivastigmine therapy at a lower dose (< 6 mg/day) shows a stabilizing effect on the MMSE score (change from baseline MMSE score, p = 0.0537). However, significant improvements in MMSE scores were achieved with a higher dose of rivastigmine after the 6-month treatment [10]. In the phase III IDEAL study, an average final dose of 9.7 mg/day showed significant improvements in MMSE scores (relative to placebo at week 24; $p \leq 0.05$) after 24-week rivastigmine therapy [14]. In the present study, the average final dose of 6.59 mg/day might suggest an insufficient dosage for the optimal clinical benefit. However, the 1-year persistence rate observed in our ITT and PP populations was only 20.13–25.76%, which may also be considered a clinical situation in which patients with AD may not continue treatment for 1 year. Treatment persistence is known to be associated with long-term effects in improving cognition [19]. Another observational study showed a 1-year persistence rate of 55.87% with mild-to-moderate AD in Taiwan [20]; however, the present study included only rivastigmine-naïve AD patients with an average diagnosis of 0.3 years. The low persistence rate observed in the present study may have limited our ability to observe the effectiveness of rivastigmine in patients with AD. In addition, it also raised concern regarding the clinical significance of higher drug discontinuations in drug-naïve AD

patients compared with those on the medication for a long period [20]. The cognitive benefits and persistence to the treatment have been reported to be higher with rivastigmine transdermal formulation [19]. Previously, the observational Real-world Evaluation of Compliance And Preference (RECAP) study conducted in Taiwan reported greater preference for the rivastigmine patch compared with the oral formulation as assessed by a caregiver medication questionnaire [21]. Determining whether this favorable preference leads to longer and better treatment compliance still requires more evidence.

Safety

No new or unexpected AEs were observed. Most commonly observed AEs (> 5%) were related to dizziness and gastrointestinal symptoms. The most commonly reported AEs leading to discontinuation of study drug included gastrointestinal symptoms, similar to the previously reported studies. In this study, the incidence of the most commonly observed AEs was slightly lower than that in the 6-month multinational IDEAL study [14]. The lower incidence of AEs could be related to the lower dosage used in the current study population. However, the lower 1-year persistence rate and higher subject discontinuation due to AEs (17.21%), compared with 8.5% in the IDEAL study, might reflect the unique clinical differences in the Asian population.

Study Limitations

The selection of disease staging and drug-naive populations may limit the generalization of the study results to all patients using rivastigmine. The population in this study is a sample of patients with AD, with more females (64.19%) than males (35.81%), and most patients were newly diagnosed with AD and were in the mild stage. Results of this study might be extendable only to a population with similar characteristics. Decline in the MMSE scores is reported as one of the predictors of study discontinuations [22]; however, no analysis was performed in this study to establish a link between MMSE scores at baseline and discontinuations. There were some data anomalies, which are not unusual in observational studies and are described in the study report wherever relevant. However, none of the inconsistencies affected the overall results or integrity of the data.

CONCLUSION

The rivastigmine capsule showed a stabilizing effect on declining cognition and functions in patients with mild-to-moderate AD in this real-world study. Rivastigmine is well tolerated at a dose of 6.0–9.0 mg/day, with no new or unexpected safety concerns in the long term. The 1-year persistence rate was low in the treatment-naïve Asian AD population.

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Authorship. All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

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Compliance with Ethics Guidelines. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the following institutional review boards: the institutional review board of Tri-Service General Hospital, Chang Gung Medical Foundation Institutional Review Board, the Institutional Review Board of the Kaohsiung Medical University Hospital, and the Institutional Review Board of Chung Shan Medical University Hospital. All patients provided written informed consent before enrollment.

Data Availability. The data sets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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