

Real-world evaluation of compliance and preference in Alzheimer's disease treatment: an observational study in Taiwan

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Purpose: Among the medications approved for Alzheimer's disease (AD), rivastigmine is the only one available as transdermal patch. The aim of this study was to evaluate compliance and caregivers' preference with oral and transdermal (rivastigmine) monotherapy in patients with mild-to-moderate AD from Taiwan.

Methods: Real-world Evaluation of Compliance And Preference in Alzheimer's disease treatment (RECAP) in Taiwan was a prospective, noninterventive, observational study with a 24-week (± 8 weeks) observational period for each participant. Eligible patients were grouped into one of the two treatment cohorts based on the baseline AD therapy: oral (donepezil, galantamine, rivastigmine, or memantine) or transdermal (rivastigmine patch). The primary end points were caregiver preference and caregiver assessment of patients' compliance to the current medication (oral or transdermal medication) at Week 24 (end of the study). Safety was assessed by recording any adverse events.

Results: A total of 301 patients (age: 77.6 ± 7.19 years) were enrolled from nine centers in Taiwan, of whom 138 (45.8%) patients were in the transdermal monotherapy cohort. Caregivers of patients who were exposed to both forms of therapies demonstrated a higher preference for transdermal rivastigmine monotherapy than the oral monotherapy (82.4% [$n=61$] versus 17.6% [$n=13$], $P < 0.0001$); for patients treated with only one therapy, the caregivers' preference was significantly in favor of the treatment to which the patient was exposed (both $P < 0.0001$). In both cohorts, patients showed good compliance, with an overall score of 8.65 ± 1.38 on an 11-point scale. Of 301 enrolled patients, 102 (33.9%) reported at least one adverse event during the study (51 patients each in the two cohorts).

Conclusion: With the higher caregiver preference and a good patient compliance, the transdermal rivastigmine patch is a suitable treatment choice for patients with mild-to-moderate AD, especially for patients intolerant to oral therapies.

Keywords: Alzheimer's disease, caregiver preference, cholinesterase inhibitors, patient compliance, observational study, rivastigmine

Introduction

Alzheimer's disease (AD), a progressive neurodegenerative condition, is the most common cause of dementia that accounted for 35.6 million (dementia) cases worldwide in 2010.¹ The prevalence of AD steadily increases with the aging population, and the risk for developing AD is higher in women than in men.^{2,3} Taiwan is among the countries with the highest prevalence of aged populations ≥ 65 years (12.0% in the year 2014).⁴ AD imposes severe social and economic burden to patients as well as their family members, caregivers of patients, and the society; moreover, the costs

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involved in caring for patients with AD further increase with the aging population adding to the burden.⁵

As the disease progresses, patients with AD require increasing levels of care. Family members play an important role as caregivers for individuals with AD and administer most of the treatments.^{6,7} The choice of treatments among the available options is influenced by caregiver preference, and their preference in choosing a therapy for the patient, which is easy to administer and use, would improve patient compliance to medication.⁷

Currently, approved treatment options for AD in Taiwan are rivastigmine, donepezil, and galantamine (cholinesterase inhibitors), as well as memantine (*N*-methyl-D-aspartate receptor antagonist).^{8,9} Of these, rivastigmine is the only medication also available as transdermal patch. The once-daily transdermal formulation provides smooth and continuous delivery over 24 hours with fewer side effects compared with the twice-daily oral (rivastigmine) formulation.^{8,10} The transdermal rivastigmine (patch) has been associated with higher satisfaction and preference than the oral formulation as indicated by caregivers of patients with AD in a preference substudy of the Investigation of transDermal Exelon in Alzheimer's disease (IDEAL) trial.^{11,12} However, there is a lack of real-world clinical setting data, and no such study is available in patients from Taiwan. The Real-world Evaluation of Compliance And Preference in Alzheimer's disease treatment (RECAP) study is a noninterventional, observational study that evaluated caregiver preference, compliance, safety, and effectiveness in patients with AD treated with either oral or transdermal monotherapy.¹³ The study was conducted in Taiwan, India, Egypt, South Korea, Lebanon, and Singapore.

In this study, we have reported the real-world evaluation of compliance and caregiver preference with oral (donepezil, galantamine, rivastigmine, or memantine) and transdermal (rivastigmine) monotherapy in patients with mild-to-moderate AD from Taiwan only.

Methods

Study design

The RECAP study in Taiwan was a 24-week, prospective, noninterventional, observational study conducted across nine centers between July 27, 2011 and March 19, 2013 (Figure 1). Data were collected at the entry (baseline), Week 12±4 weeks (optional), and at the end of the study (Week 24±8 weeks). All individual patients who were prescribed a capsule or a transdermal patch therapy by their treating physician for AD were invited to participate in the study. Eligible patients were grouped into one of the two

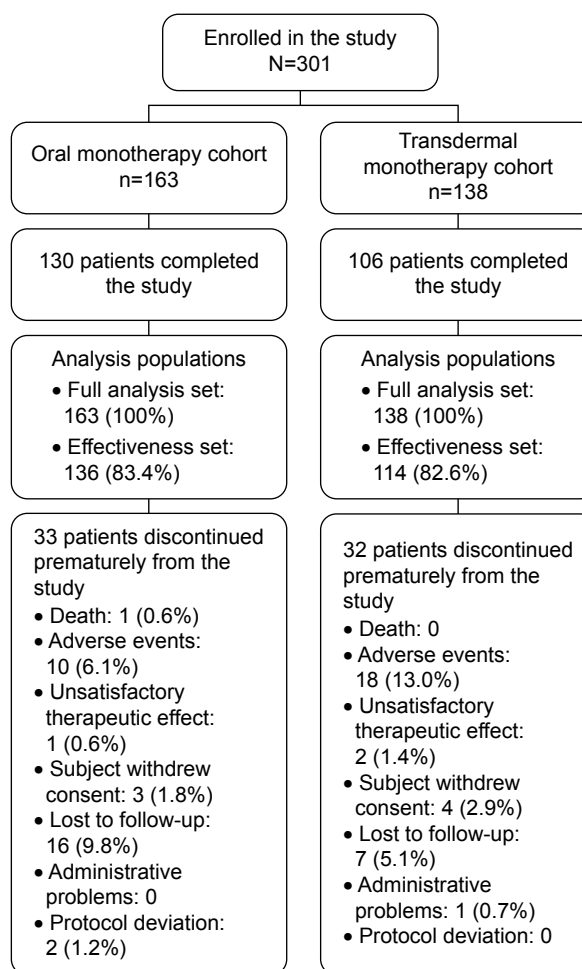


Figure 1 Patient disposition.

treatment cohorts based on the baseline AD therapy: oral (rivastigmine, donepezil, galantamine, or memantine) or transdermal (rivastigmine patch).

The RECAP study was conducted according to the definition of noninterventional trials.¹⁴ In accordance with this definition, the medication was prescribed as per the marketing authorization; the assignment of the patient to the therapy was decided within current practice and the medical indication and was clearly separated from the decision to include the patient in the study. No diagnostic or monitoring procedures additional to the standard care and routine practice were performed. Patient treatment, visits, and assessments were independent of this study, and they were at the discretion of the treating physician following local standard medical practice and local prescribing information (PI; local approved product label).

The study was approved by the Joint Institutional Review Board, Taiwan and also by the Institutional Review Board of each participating sites and was conducted according to the Guidelines for Good Pharmacoepidemiology Practice¹⁵

as well as ethical principles of the Declaration of Helsinki. The reporting of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.¹⁶ Written informed consent was obtained from all patients or through their caregivers before any data were collected. Patients were free to withdraw their consent at any time during the study.

Patients' eligibility criteria

Inclusion criteria were male and female outpatients (aged ≥ 50 years) diagnosed with mild-to-moderate AD, patients prescribed oral (cholinesterase inhibitors or memantine) or transdermal monotherapy (rivastigmine) in adherence with the local PI, and patients having a caregiver willing and able to answer the Caregiver Medication Questionnaire (CMQ). The questions in the CMQ were derived from the AD Caregiver Preference Questionnaire that was developed for use in the IDEAL study.^{12,17,18} Patients were excluded according to the contraindications mentioned in the local PI of the treatment used.

Study end points and assessments

The primary end points were to assess "caregiver preference" for oral medication or transdermal medication and caregiver assessment of "patient compliance" as evaluated using the CMQ at Week 24. The CMQ comprised the following questions to be answered by the caregiver: questions on patient compliance and satisfaction with treatment, general preference for oral or transdermal medication, and top three reasons for medication preference. Caregivers of patients with exposure to only one form of medication for the treatment of AD compared the current medication available during the study with a hypothetical situation in which their patient could have received the alternative form of therapy. The patient compliance to the treatment was rated on an 11-point scale (from 0= "patient never took the medication as prescribed" to a value of 10= "patient always took the medication as prescribed").

Secondary end points assessed at Week 24 included concomitant use of psychotropic medication (yes/no) and the number of psychotropic medications used (1, 2, 3, or >3) per patient, physicians' preference for treatment (including top three reasons for preference) as evaluated using the short questionnaire, and the total daily dosage reached (percentage of patients on which dosage). Questions were asked to each prescribing physician at the end of the patient treatment period of the study. A short physician preference assessment questionnaire was used to assess physicians' preference

for treatment. Safety assessment included the incidence of adverse events (AEs) and serious AEs during the study.

AEs were coded using the Medical Dictionary for Regulatory Activities (Version 16.0). The mean Mini-Mental State Examination (MMSE) scores at the baseline, Week 12, and Week 24 were also recorded.

In this study, a subanalysis was performed to address the following: 1) proportion of patients who were exposed to both oral and transdermal medications and switched from oral to transdermal patch because of intolerability to oral medication and 2) the difference in the amount of the use of concomitant medication at baseline between oral and transdermal monotherapy cohorts.

Statistical methods

Two analysis sets were defined in this study: 1) full analysis set (FAS) consisted of all patients who provided informed consent and received at least one dose of the medication under observation during this study and 2) effectiveness set excluded patients without any post-baseline effectiveness assessment or data collected after the time of treatment switch. The effectiveness set was used to conduct effectiveness analysis, and all other analyses were performed on the FAS.

The study was planned to include ~300 patients in Taiwan, and compiled into the global RECAP study for the final analyses. The details of the statistical power associated with sample size were described elsewhere.¹³ Summary statistics for continuous variables were presented as number of observations (*n*), arithmetic mean, and standard deviation (SD), and categorical variables were presented as absolute and relative frequencies. In addition, two-sided 95% confidence intervals (CIs) as well as *P*-values were presented for the caregiver preferences for the oral or transdermal patch. The differences in the assessment of compliance between the two cohorts were tested using the Student's *t*-test. The two-sided significance level was set at $P < 0.05$.

The SAS statistical package Version 9.2 was used to perform all statistical analyses.

Results

Study population

A total of 302 patients from Taiwan were enrolled, but only 301 patients were analyzed. One patient was excluded from the FAS as the patient was not prescribed any medication due to administrative reasons. Of the 301 enrolled patients, 163 (54.2%) were in the oral monotherapy cohort and 138 (45.8%) patients were in the transdermal monotherapy

cohort. The majority of patients ($n=236$; 78.4%) completed the study: 130 in the oral monotherapy cohort and 106 in the transdermal monotherapy cohort. The remaining 65 patients (21.6%) discontinued the study prematurely, and the primary reasons for discontinuation were AEs ($n=28$; 9.3%) and patient lost to follow-up ($n=23$; 7.6%) followed by the withdrawal of informed consent ($n=7$; 2.3%).

The baseline and demographic characteristics were comparable between the two treatment cohorts (Table 1). The mean age (SD) was 77.6 (7.19) years, the mean (SD) duration of AD was 1.0 (1.54) year, and a total of 31 patients (10.3%) had a family history of AD. Female sex is associated with increased risks of AD in part because women live longer; similar to a previous study,³ we observed, in our study, that the majority of 63.8% patients were women. The majority of patients ($n=287$; 95.3%) were living with caregivers or other individuals. Depression ($n=78$; 25.9%), insomnia ($n=63$; 20.9%), sleep disorder ($n=48$; 15.9%), anxiety ($n=46$; 15.3%), delusion ($n=41$; 13.6%), agitation ($n=17$; 5.6%), and neurosis ($n=2$; 0.7%) were the psychiatric disorders reported at baseline. There were 127 (42.2%) patients who received prior treatment for AD, and among them, the most common reason for changing treatment upon entering the study was

“previous treatment was not well tolerated” ($n=46$; 15.3%) and “optimal dose on previous treatment was not reached” ($n=30$; 10.0%).

Primary assessments

For patients with exposure only to oral or transdermal monotherapy, the caregivers' preference was significantly in favor of the treatment to which the patient was exposed at Week 24 (both P -values <0.0001); however, caregivers of patients exposed to both forms of therapies demonstrated higher preference for transdermal than oral monotherapy at Week 24 ($P<0.0001$; Figure 2). Patients in both cohorts showed good compliance, with the overall mean (SD) score of 8.65 (1.38). At Week 24, the mean (SD) scores for compliance were 8.77 (1.33) (95% CI: 8.54–9.00) and 8.50 (1.43) (95% CI: 8.23–8.77) in the oral and transdermal monotherapy cohorts, respectively. The patient compliance in two treatment cohorts was not significantly different ($P=0.1238$).

Secondary assessments

Overall, 76 (46.6%) patients in the oral monotherapy cohort and 72 (52.2%) patients in the transdermal monotherapy cohort took concomitant psychotropic medications during the

Table 1 Patient demographics and baseline characteristics

	Oral monotherapy cohort ($n=163$)	Transdermal monotherapy cohort ($n=138$)	Total ($n=301$)
Age, years	77.3 (7.63)	77.9 (6.65)	77.6 (7.19)
Female, n (%)	101 (62.0)	91 (65.9)	192 (63.8)
Education, years	6.1 (4.92)	5.7 (5.08)	5.9 (4.99)
MMSE score ^a	18.6 (4.76)	17.8 (5.20)	18.2 (4.96)
Duration of AD, years	0.8 (1.35)	1.3 (1.71)	1.0 (1.54)
Prior treatment for AD	46 (28.2)	81 (58.7)	127 (42.2)
Prior concomitant psychotropic medication ^b	71 (43.6)	69 (50.0)	140 (46.5)
Any family history of AD, n (%)	16 (9.8)	15 (10.9)	31 (10.3)
Current smokers, n (%)	11 (6.7)	3 (2.2)	14 (4.7)
Alcohol history, n (%)			
<1 drink per day	160 (98.2)	137 (99.3)	297 (98.7)
1–2 drinks per day	2 (1.2)	1 (0.7)	3 (1.0)
≥ 3 drinks per day	1 (0.6)	0	1 (0.3)
Current living situation, n (%)			
Living alone	2 (1.2)	6 (4.3)	8 (2.7)
Living with caregiver or other individual	157 (96.3)	130 (94.2)	287 (95.3)
Assisted living/group home	4 (2.5)	2 (1.4)	6 (2.0)
Mean concomitant medications per patient	0.6 (0.90)	0.8 (1.00)	–
0	96 (58.9%)	75 (54.3%)	–
1	37 (22.7%)	25 (18.1%)	–
2	23 (14.1%)	28 (20.3%)	–
3	6 (3.7%)	10 (7.2%)	–
4	1 (0.6%)	0	–

Notes: Full analysis set comprised all patients who provided informed consent and received at least one dose of the medication during the study. ^aMMSE score at baseline was available for 243 out of 250 patients (oral: 135 patients; transdermal: 108 patients) belonging to the effectiveness set. ^bInformation about prior psychotropic concomitant medication was missing for one patient in the transdermal monotherapy cohort. Data are shown as mean (standard deviation) unless otherwise stated.

Abbreviations: AD, Alzheimer's disease; MMSE, Mini-Mental State Examination.

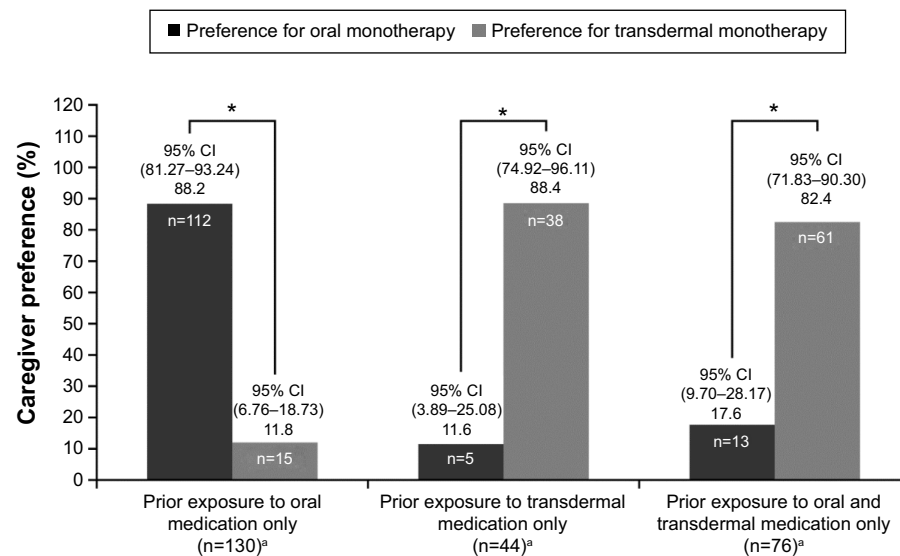


Figure 2 Caregivers' preference for the oral or transdermal medication at Week 24, by their patient's prior exposure.

Notes: Caregivers indicated preference by comparing their experience with the current medication available in oral (administered twice daily) and transdermal patch (administered once a day) during the study to a hypothetical situation where their patient could have received the medication in the alternative form. Effectiveness set excluded patients without any post-baseline effectiveness assessment or data collected after the time of treatment switch. Effectiveness set comprised 250 (83.1%) patients from the full analysis set. Two-sided 95% CIs as well as *P*-values were presented for the caregivers' preferences for the oral or transdermal patch. The 95% CIs were calculated as exact binomial CIs. ^aPatients in the effectiveness set with missing caregiver preference assessment (oral: 3; transdermal: 1; oral and transdermal: 2) were not included in the calculations. *P*-value is based on a binomial test statistic to compare two proportions. A *P*-value <0.05 indicates a statistically significant difference in proportions between the two cohorts. **P*<0.0001.

Abbreviation: CIs, confidence intervals.

observational period. There were 54 (17.9%), 59 (19.6%), 27 (9.0%), and 8 (2.7%) patients in the total study population who took one, two, three, and more than three psychotropic medications, respectively. The use of concomitant psychotropic medication and the number of different psychotropic medications per patient were comparable between the two treatment cohorts (Table 1).

Of the nine participating physicians, five indicated preference for oral monotherapy and four preferred transdermal monotherapy at Week 24. The most important reason (preference rank 1) for oral medication preference was "easier to comply and better acceptance by the patient" as indicated by five (100%) physicians. The most important reason for medication preference, however, varied among the physicians preferring the transdermal monotherapy. The most important reason (preference rank 1) for transdermal medication preference was "more convenient and fits better into daily life" as indicated by two (50%) physicians followed by "easier to use" and "easier to comply/better acceptance by the patient" as indicated by one physician each for one reason.

The most common medications used by patients in the oral monotherapy cohort (n=163) at the end of the study were rivastigmine (oral) at 3 mg for 50 patients and donepezil at 5 mg and 10 mg for 33 and 27 patients, respectively,

whereas in the transdermal monotherapy cohort most of the patients (n=134) were on the 4.6 mg rivastigmine (patch; Figure 3). The data on change in the MMSE score from the baseline at Week 24 were obtained from 195 of the 250 patients in the effectiveness set. The mean (SD) MMSE scores at Week 24 (199/250 patients) were 18.6 (4.76) and 17.8 (5.91) in the oral and transdermal monotherapy cohorts, respectively. At Week 24, there was no change in the MMSE score (195/250 patients) as shown by the median change of zero.

Results of the subanalysis showed that a very small number of patients (n=4; 4.3%) switched from oral to patch formulation due to intolerability at baseline. At baseline, 22.7% patients in the oral monotherapy cohort received at least one concomitant medication compared with 18.1% in the transdermal monotherapy cohort (Table 1).

Safety

During the study, a total of 102 (33.9%) patients reported at least one AE, and the proportion of patients who reported AEs was comparable between the two cohorts (oral: n=51 [31.3%]; transdermal: n=51 [37.0%]). The most frequent AEs in the oral monotherapy cohort were nausea (n=9; 5.5%), dizziness (n=8; 4.9%), decreased appetite (n=7; 4.3%), vomiting (n=7; 4.3%), and insomnia (n=5; 3.1%),

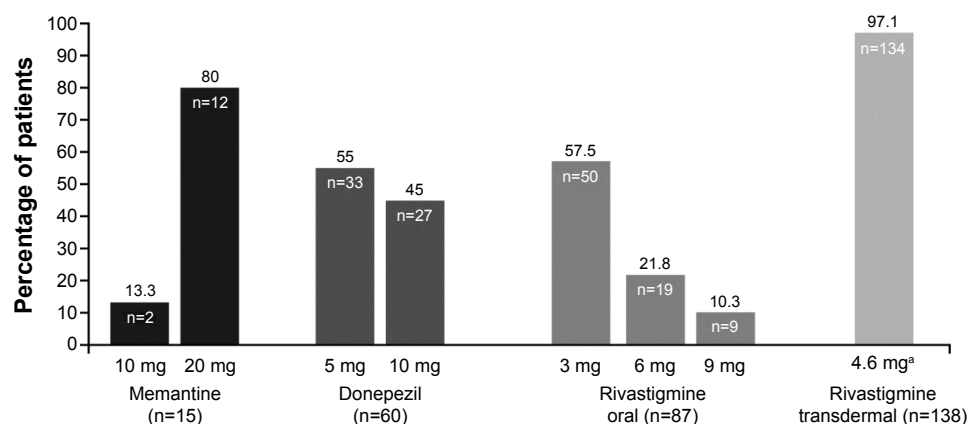


Figure 3 Drug regimens among patients on cholinesterase inhibitors and memantine at Week 24.

Notes: For patients who switch therapy during the study, the last monotherapy dosing is used. ^aThis group includes transdermal treatment with rivastigmine where dosages were recorded as 5 mg/24 h or 4.6 mg/24 h (5 cm² transdermal patch). Only one patient was in the galantamine group who was on the 8 mg/24 h dose at Week 24. Two and six patients were in the rivastigmine oral group who were on 1.5 mg/24 h and 4.5 mg/24 h dose, respectively, at Week 24. Three patients were in the rivastigmine transdermal group who were on 4.5 mg/24 h dose at Week 24. Data for other individual doses that are not available were not included.

whereas in the transdermal monotherapy cohort they were pruritus (n=11; 8.0%), dizziness (n=7; 5.1%), and rash (n=7; 5.1%).

Of the 301 enrolled patients, 27 (9.0%) discontinued prematurely from the study because of AEs (oral: 11 [6.7%]; transdermal: 16 [11.6%]). The most common AEs leading to discontinuation were skin and subcutaneous tissue disorders (oral: 0; transdermal: 14 [10.1%]), gastrointestinal disorders (oral: 8 [4.9%]; transdermal: 0 [0.0%]), and metabolism and nutrition disorders (oral: 3 [1.8%]; transdermal: 0). There was one death reported in the oral monotherapy cohort and was not considered to be related to the study medication as assessed by the investigator.

Discussion

RECAP in Taiwan was the first study regarding compliance and caregiver satisfaction with transdermal rivastigmine in a real-world clinical setting. The results of the current study showed higher caregivers' preference (82.4%) to rivastigmine transdermal patch for patients exposed to both forms of medication, and the findings were consistent with previous studies.^{12,19} The current study, however, did not show a clear preference of caregivers for either oral or transdermal treatment, which was due to the prior exposure to particular form of therapy influencing the caregivers' preference.

Previously, the IDEAL,¹² Alzheimer disease: eXamination of patiEnt compliance and caregiver satisfacTion (AXEPT),²⁰ Effective Management of Alzheimer's Disease By TReating pAtients and relieving Caregivers with Exelon Patch (EMBRACE),¹⁹ ENTERPRISE,²¹ global RECAP

study,¹³ and an observational clinical study²² have assessed the caregiver preference and/or satisfaction for the treatment of AD. IDEAL was the first pivotal trial^{17,23} to demonstrate the non-inferiority of the rivastigmine transdermal patch over oral capsules; the study¹² also showed higher caregivers' preference (72%) for the rivastigmine transdermal patch compared with oral capsules. Moreover, the results from the EMBRACE study¹⁹ showed 88.2% caregivers of patients with AD preferred rivastigmine transdermal patch over other oral medication.

The overall patient compliance in the current study was good in both the treatment cohorts, unlike other studies including AXEPT²⁰ and global RECAP¹³ that showed greater patient compliance with rivastigmine transdermal patch over other oral medications as indicated by the caregivers of patients with AD. Results from the ENTERPRISE study²¹ also showed high compliance rates (60.5%) with transdermal rivastigmine patch compared with the oral formulation. A decrease in caregiver burden is associated with the use of rivastigmine patch, and patch contributes to improved patient compliance.²⁴

The MMSE score in the current study was comparable in both the treatment cohorts, and the median change of zero in the MMSE score indicates neither improvement nor deterioration, unlike other studies where improvement in the MMSE score was observed.²⁵ In the current study, there were no patients with serious AEs of skin and subcutaneous tissue disorder, yet the number of patients who discontinued due to AEs of skin and subcutaneous tissue disorder is high (14 patients, 10.1%), implying more education/information should be provided to optimize skin tolerability. Higher

gastrointestinal AEs were noted in the oral monotherapy cohort compared with the transdermal monotherapy cohort (n=21 [12.9%] versus n=7 [5.1%], respectively), as observed in a previously reported study.¹³

This study has limitations. First, it was a nonrandomized open-label study with inherent potential for bias. Second, only 30% of patients from whom the caregiver preference was available were exposed to both forms of therapy and were able to provide a comparative preference. The remainder had the preferences for the oral or the transdermal treatment clearly related to the prior exposure to one or other form of treatment. Third, there was a slight imbalance in patients assigned to the oral therapy (n=163; 54.2%) and those assigned to the transdermal therapy (n=138; 45.8%) and the imbalance in the use of the drug therapy for AD prior to enrollment in this study (46 [28.2%] patients to whom oral treatment was prescribed versus 81 [58.7%] to whom transdermal treatment was prescribed).

Conclusion

The RECAP study showed good patient compliance for both oral and transdermal treatments and higher caregiver preference with the rivastigmine transdermal monotherapy, suggesting rivastigmine transdermal monotherapy as a suitable treatment choice for patients with mild-to-moderate AD in Taiwan.

Acknowledgments

The authors thank K Ananda Krishna from Novartis Healthcare Pvt Ltd, Hyderabad, India, for medical writing assistance and incorporating subsequent revisions. This study was funded by Novartis Pharma AG, Basel, Switzerland. The study results were presented as a poster presentation at the First International Taiwanese Congress of Neurology and 2015 Annual Meeting of Taiwan Neurological Society, Taipei, Taiwan, May 7–10, 2015.

Author contributions

All authors were involved in data collection, analysis, and/or interpretation of the results and critical revision and approval of the article.

Disclosure

The authors report no conflicts of interest in this work.

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