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ORIGINAL RESEARCH

Effectiveness of the 10 cm^2 Rivastigmine Patch in Taiwanese Patients with Mild-to-Moderate Alzheimer's Dementia: A 48-Week Real-World Observational Study

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ABSTRACT

Introduction: The current study aimed to provide data on the effectiveness of the 10 cm^2 rivastigmine patch in patients with Alzheimer's disease (AD) in a real-world setting in Taiwan.
Methods: This was a 48-week, single-arm, open-label, observational, and post-marketing study conducted across seven centers in Taiwan between May 5, 2016 and July 10, 2017. Eligible patients (aged 55–95 years) treated with the 10 cm^2rivastigmine patch were enrolled based on physicians' judgment and according to the Taiwan reimbursement criteria of the drug. Data were prospectively collected at Week 0 (baseline), Week 24, and Week 48. The primary endpoint was the change in the cognitive assessment screening instrument (CASI) scores at Week 48 versus baseline. The changes from baseline in clinical dementia rating (CDR), mini-mental state examination (MMSE), and neuropsychiatric inventory (NPI) scores were evaluated, as were treatment persistence and the safety profile.
Results: Of the 285 eligible patients [full analysis set (FAS)], 216 (75.8%) completed the study protocol while 180 (63.2%) persisted on the 10 cm^2 rivastigmine patch for the full 48 weeks.

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At baseline, 89.8% of patients had a CDR score of 0.5 or 1, while the change in CDR score at Week 48 was not significant. In the FAS, both the CASI and MMSE scores had numerical improvement at Week 24 but declined by 2.1 and 0.4 points, respectively, at Week 48 ($p = 0.005$ and $p = 0.022$). The increment in NPI scores was not significant. The most common drug-related adverse events (AEs) were pruritus (11.2%), nausea (3.5%), rash (3.2%), and vomiting (2.8%). ***Conclusions***: The use of the 10 cm^2 rivastigmine patch in the mild stage of AD maintained cognitive function at Week 24 and neuropsychiatric function at Week 48. The treatment persistency and safety profile support the clinical tolerability of the rivastigmine patch in the management of mild-to-moderate AD in Taiwan.

Keywords: Alzheimer's disease; Cognitive function; Rivastigmine patch

Key Summary Points

Taiwan has one of the fastest growing aging populations in the world, and the number of people with dementia was projected to increase to up to 210,000 by 2020.

The 10 cm^2 rivastigmine patch was approved in 2013 in Taiwan, yet its real-world treatment efficacy in Alzheimer's disease (AD) patients from Taiwan is still limited.

The current study aimed to provide additional efficacy and safety data of the 10 cm^2 rivastigmine patch in a real-world setting by primarily assessing cognitive assessment screening instrument score.

Treatment with the 10 cm^2 rivastigmine patch was well tolerated and improved cognitive functioning, neuropsychiatric functioning, and treatment persistence in patients with mild-to-moderate AD.

The prospective study suggests that the 10 cm^2 rivastigmine patch is a convenient treatment option in the management of mild-to-moderate AD in Taiwan.

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by a steady decline in the patient's cognition, function, and behavior. The World Alzheimer's Report in 2019 estimated that there are over 50 million people living with dementia, and that this is set to increase to 152 million by 2050 [1]. Taiwan has one of the fastest growing aging populations in the world, and the percentage of people aged ≥ 65 years increased from 4.1% in 1980 to 10.7% in 2010 [2]. In a nationwide survey conducted from 2011 to 2012 in Taiwan, the prevalence of all-cause dementia in patients aged ≥ 65 years was 8.04% [3], and the number of people with dementia was projected to increase to up to 210,000 by 2020 [4].

Rivastigmine is a reversible cholinesterase inhibitor (ChEI), originally developed as an oral capsule and liquid formulation. In the United States, rivastigmine is indicated for the treatment of all stages of AD and mild-to-moderate Parkinson's disease.

In a large, 24-week, randomized, multicenter, placebo-controlled, double-blind study (IDEAL; Investigation of transDermal Exelon in ALzheimer's disease), the 10 cm^2 rivastigmine patch was shown to have comparable efficacy and improved tolerability than the 12 mg/day rivastigmine capsules. The patch also had fewer withdrawals due to gastrointestinal adverse events (AEs) and three-fold lower incidences of nausea and vomiting, allowing most patients to achieve the optimal dose compared to the 12 mg/day rivastigmine capsules (95.9% vs. 64.4%, respectively). The IDEAL study therefore established the 10 cm^2 rivastigmine patch as the currently recommended target maintenance dose in the treatment of patients with mild-to-moderate AD [5, 6]. This patch, containing 18 mg of rivastigmine in line with a dosage of 9.5 mg/24 h, was approved in Taiwan in 2013.

Various structured neuropsychological tools have been used in AD clinical trials for different purposes [7, 8]. In Taiwan, annual cognitive changes are generally measured simultaneously by the mini-mental state examination (MMSE), cognitive assessment screening instrument

(CASI) [9], and clinical dementia rating (CDR) [10].

Oral acetylcholinesterase inhibitors (AchEIs) have demonstrated efficacy in treating patients with AD [11]; however, many patients adhere to their treatment for a relatively short duration [12]. A number of factors may contribute to the non-adherence in AD. Decline in cognitive or functional abilities is inevitable in AD, and the non-adherence may be related to dissatisfaction of the treatment outcome. However, a greater proportion of non-adherence is related to AEs of AchEIs or forgetfulness about medication. Non-compliance with oral agents has been a common problem for the treatment of AD, mostly due to the gastrointestinal side effects associated with large fluctuations in acetylcholine levels [12]. The patch formulation allows smooth and continuous drug delivery. In addition, its favorable tolerability, efficacy, and convenience of use may increase treatment compliance.

The overall persistence and adherence to rivastigmine (oral and the 5 cm^2 patch) versus donepezil in the Taiwanese population was recently reported using the national health dataset [13]. The real-world treatment efficacy of the 10 cm^2 rivastigmine patch in patients with AD has still not been extensively reported. To our knowledge, the present study is the first prospective large-scale observational study of this patch in Taiwan. Here, we report the efficacy and safety results of a 48-week, observational study of the 10 cm^2 rivastigmine patch. The study also evaluated the results of adherence to this patch and the most commonly accepted dosing regimen in Taiwan.

METHODS

Study Design

This was a 48-week, single-arm, open-label, multicenter, prospective, non-interventional, observational, and post-marketing study of the 10 cm^2 rivastigmine patch conducted in Taiwan between May 5, 2016 and July 10, 2017. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The Independent Ethics Committee or Institutional Review Board reviewed the study protocol for each center (information provided within the supplementary material). All patients provided written informed consent before enrollment.

Study Workflow

Patients initiating treatment with the 10 cm^2 rivastigmine patch were enrolled based on the physicians' judgment and the Taiwan reimbursement criteria of rivastigmine.

The assignment of the patient to the rivastigmine patch was decided within the current practice and the medical indication. Patients were followed-up at outpatient clinics for 48 weeks to observe usage of the rivastigmine patch.

After informed consent, the study included one screening phase (Week 0) and two follow-up phases (Weeks 24 and 48). In the screening phase at baseline (Week 0), the inclusion and exclusion criteria were checked and the demographics data were collected. We also collected the neurobehavioral assessment data at baseline. At Week 24, there was a follow-up neurobehavioral assessment, which included collection of CASI, MMSE, CDR, and neuropsychiatric inventory (NPI) scores. AEs were also recorded and treatment persistency was calculated. At the second follow-up at Week 48, all effectiveness and safety assessments were performed and the persistency data were collected.

Eligibility Criteria

Patients aged 55–95 years with a diagnosis of mild-to-moderate AD based on the core clinical criteria proposed by the National Institute on Aging/Alzheimer's Association workgroup were included in the study [14]. Eligible patients had to have received a new prescription of the 10 cm^2 rivastigmine patch at the screening phase and had to provide a written informed consent. The prior treatments of eligible patients were the 5 cm^2 rivastigmine patch, and oral rivastigmine 9 mg/day and oral rivastigmine 3 mg/day.

Patients were excluded if they had previously exhibited contraindications to rivastigmine or had contraindications to the rivastigmine as described on the drug label.

Study Endpoints and Assessments

The primary endpoint of the study was the change in the CASI scores [9] between baseline and Week 48. The CASI is used as a screening instrument for dementia, to monitor disease progression, and to provide a profile of impairment among various cognitive domains [9]. The maximum score of the CASI is 100, with higher scores indicating better cognitive ability.

Secondary endpoints were the changes in MMSE, CDR, and NPI scores from baseline to Week 48. The NPI is a questionnaire administrated to caregivers of AD patients to assess the 12 subdomains of neuropsychiatric behavioral symptoms in AD (including delusions, hallucinations, depression, anxiety, euphoria, and anomalous behavior) over the previous months by rating the frequency of the symptoms on a 4-point scale and their severity on a 3-point scale. NPI is quantified by calculation of the product of frequency (0–4 points) and severity (0–3 points) of each subdomain. A maximum score of 12 is given to each symptom, with an overall scale of 0–144 points; a higher score indicates more serious neuropsychiatric behavioral symptoms. The safety profile of rivastigmine patch was also assessed in this study.

We also calculated treatment persistency, which was the proportion of patients who continued using the 10 cm^2 rivastigmine patch to the end of the study. The calculation was based on the following equation:

$$\text{Treatment persistency}\,(\%) = (\text{full analysis set [FAS]} - \text{number of withdrawals})/(\text{FAS} \times 100).$$

Statistical Analysis

In this study, there were two analysis sets: the full analysis set (FAS) and the per-protocol (PP) population. The FAS included all enrolled patients who met the eligibility criteria of the protocol. The PP population included patients who completed the 10 cm^2 rivastigmine patch treatment for 48 weeks. Data collection from the patients was missed at certain time points. Hence, there was a difference in the number of patients analyzed from week to week.

The primary and secondary endpoints were presented as descriptive statistics for both absolute values and the change from baseline. A paired *t* test or a Wilcoxon signed rank test was performed, as appropriate, in calculating longitudinal changes. Summary statistics for continuous variables included number, mean, standard deviation (SD), minimum, median, maximum, and the 95% confidence interval. For discrete variables, summary statistics were presented in contingency tables with absolute and relative frequencies. If not otherwise specified, *p* values were presented as two-sided and the significance level was set at 0.05. AEs were coded using the Medical Dictionary for Regulatory Activities (v.21.1). The occurrence of each AE was counted and reported as a relative percentage.

RESULTS

Between May 5, 2016 and July 10, 2017, 285 patients were enrolled across seven sites. Of the 285 patients (FAS), 181 (63.5%) were titrated from the 5 cm^2 rivastigmine patch, and the rest were switched/titrated from various doses of the rivastigmine capsule. In total, 216 (75.8%) patients completed the study (patients were not considered as dropped out if they switched to another form/dose of rivastigmine after the 10 cm^2 rivastigmine patch) and 180 (63.2%) patients remained on the patch for 48 weeks. The mean (SD) duration of the patch treatment was 284.3 (143.3) days (range 1.0–1161.0). Sixty-nine patients (24.2%) discontinued the study, due to AEs (26.1%, 18/69), withdrawal of consent (27.5%, 19/69), lost to follow-up (15.9%, 11/69), and death (15.9%, 11/69) (Fig. 1). None of the deaths were considered related to usage of the rivastigmine patch.

Baseline demographics and disease characteristics are summarized in Table 1. Female

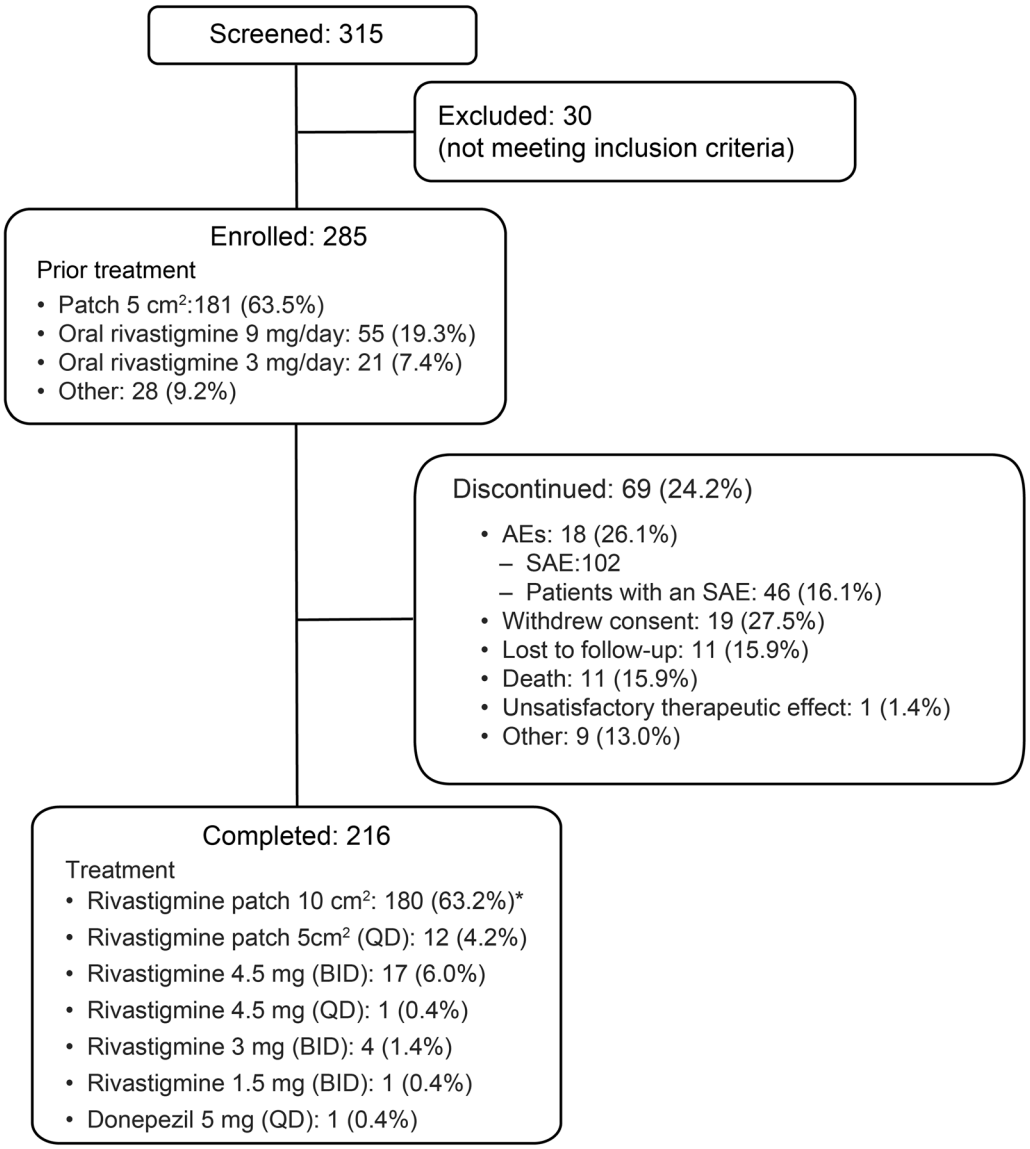

Fig. 1 Patient flow chart. *180 patients persisted on the 10 cm^2 rivastigmine patch for 48 weeks. *AE* adverse events, *BID* twice a day, *QD* once a day, *SAE* serious AE

patients accounted for 57.2% of the FAS population. At baseline, the mean (SD) age of the FAS population was 78.1 (7.7) years and the mean (SD) body weight was 58.3 (10.8) kg. The majority of patients ($n = 254$; 89.8%) were diagnosed with mild AD with a CDR score of 0.5 or 1 at baseline. Most of the patients ($n = 276$; 96.8%) lived with family or caregivers.

The primary endpoint was the change in CASI score after the 48-week treatment period. After 48 weeks of treatment, the CASI score (mean [SD]) was significantly reduced by 2.1 (9.3) points ($p = 0.005$) in the FAS population (Fig. 2). The reduction was from a baseline score of 64.1 (17.2) to a score of 62.5 (18.8) at Week 48 (Fig. 2).

The FAS population showed stable MMSE scores with small mean (SD) changes from baseline of 0.2 (2.7) at Week 24 and − 0.4 (2.8) at Week 48 (Fig. 3). CDR scores were well

Table 1 Baseline demographics and disease characteristics of the FAS population

Particulars		**10 cm^2rivastigmine patch $n = 285$**
Age	Mean ± SD	78.1 (7.7)
Female	*n* (%)	163 (57.2)
Body weight (kg)	Mean ± SD	58.3 (10.8)
Diagnosed with mild AD	*n* (%)	254 (89.8)
Patients living with family or a caregiver	*n* (%)	276 (96.8)
Baseline MMSE score	Number of patients	284
	Mean ± SD	18.9 ± 5.4
	95% CI	18.3, 19.6
Baseline CDR score, *n* (%)	Patient number	283
	0.5	145 (51.2)
	1 (mild)	109 (38.5)
	2 (moderate)	29 (10.2)
Baseline CASI score	Patient number	268
	Mean ± SD	64.1 ± 17.2
	95% CI	62.1, 66.2
Baseline NPI score	Patient number	167
	Mean ± SD	7.7 ± 11.9
	95% CI	5.9, 9.5

AD Alzheimer's disease, *CASI* cognitive assessment screening instrument, *CDR* clinical dementia rating, *CI* confidence interval, *FAS* full analysis set, *MMSE* mini-mental state examination, *NPI* neuropsychiatric inventory, *SD* standard deviation

sustained over the 48-week treatment period (Table 2). The proportion of patients from the FAS population with CDR score ≤ 1 at baseline dropped from 89.7 to 84.6% at Week 48. Most patients (78.6%) had no change or improvement in CDR score at Week 48. The FAS showed numerically stable NPI scores with small mean (SD) changes of 0.9 (12.4) at Week 24 and 0.4 (11.0) at Week 48 for the total score. Changes from baseline in scores of single NPI domains, including delusions, hallucinations, apathy, and depression, were also limited to between − 0.2 and 0.5 points at Week 48 (Table 2).

The overall treatment persistency was 63.2%. Treatment persistency was also calculated for patients based on their prior treatment. It was observed that the majority of patients in the study had used either oral rivastigmine 3 mg/day ($n = 21$, 7.4%), oral rivastigmine 9 mg/day ($n = 55$, 19.3%) or the 5 cm^2 rivastigmine patch ($n = 181$, 63.5%) as the prior treatment. Treatment persistency over a 1-year period was similar in patients irrespective of prior treatment (oral rivastigmine 3 mg vs. oral rivastigmine 9 mg vs. 5 cm^2 rivastigmine patch: 66.7% vs. 65.5% vs. 66.3%). Effects of persistency on CASI, MMSE, and CDR scores were also investigated. We observed that CASI score

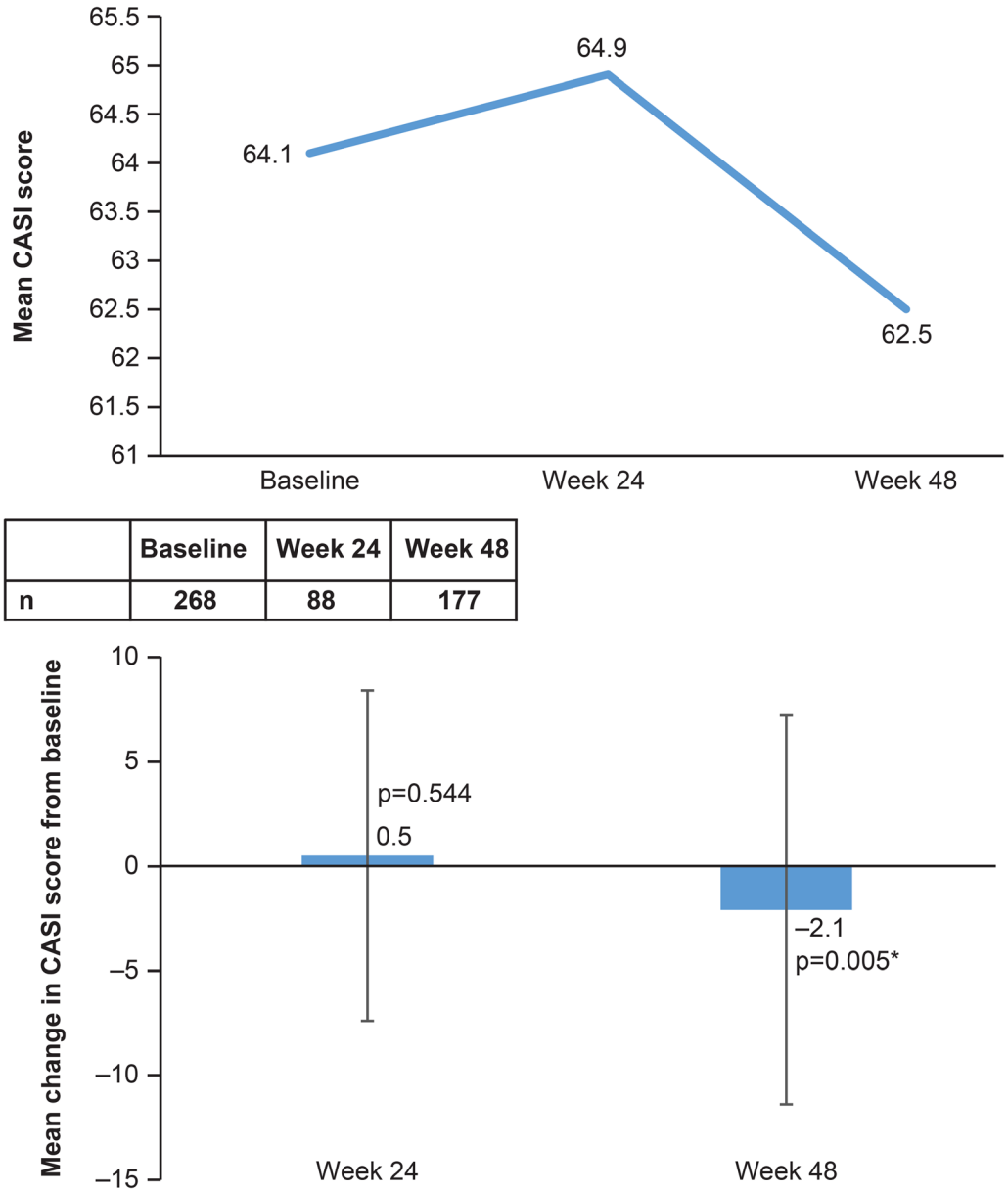

Fig. 2 Change in the CASI score. *Significant *p* value. *CASI* cognitive assessment screening instrument. *n* number of patients analyzed

[mean (SD)] was reduced by 2.0 (9.3) ($p = 0.010$) in patients who persisted on the 10 cm^2 rivastigmine patch treatment for 48 weeks (Table 3). The reduction was from a baseline score of 64.4 (16.3) to a score of 63.1 (17.9) at Week 48. MMSE scores were stable with small mean (SD) changes from baseline of 0.1 (2.6) at Week 24 and − 0.3 (2.7) at Week 48 (Table 3). CDR scores were well sustained over the 48-week treatment period. Most patients (79.2%) had no change or an improvement in CDR score at Week 48 (Table 3). Over the study period, 523 AEs were reported by 158 (55.4%) patients; among these, 102 were serious AEs (SAEs) occurring in 46 (16.1%) patients. The most common drug-related AEs were pruritus

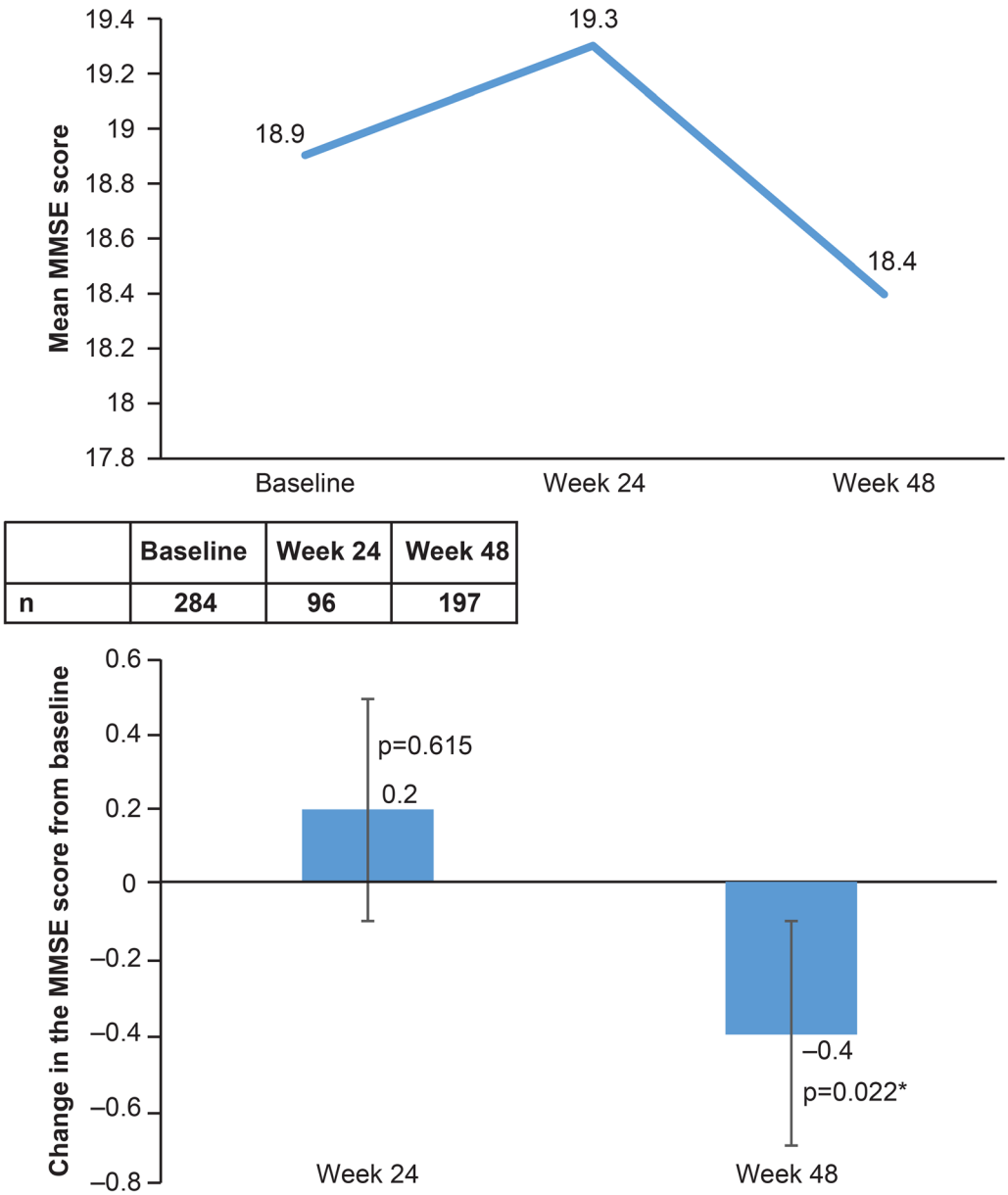

Fig. 3 Change in the MMSE score. *Significant *p* value. *MMSE* mini-mental state examination

(11.2%), nausea (3.5%), rash (3.2%), and vomiting (2.8%) (Table 4). Forty-eight (16.8%) patients discontinued the 10 cm^2 rivastigmine patch due to AEs, and these were most commonly pruritus (4.9%) or rash (2.1%). Most AEs were managed by symptomatic treatments (39.3%). The most common SAE (≥ 5.0%) was infection and infestations [*n* (%); 21 (7.4%)], of which pneumonia [11 (3.9%)] and urinary tract infection [7 (2.5%)] occurred in ≥ 2% patients. Although 58 of the 102 SAEs were graded as severe [occurring in 29 (10.2%) patients], eight as life threatening [3 (1.1%) patients], and seven as fatal in severity [7 (2.5%) patients], none were suspected to be related to the 10 cm^2 rivastigmine patch. Of these SAEs, 53 were resolved in

Table 2 Secondary endpoints in the FAS population

		10 cm^2rivastigmine patch $n = 285$
Summary of changes in the CDR score[a]		
Week 24, *n* (%)	− 1 stage	5 (5.3)
	No change	78 (82.1)
	+ 1 stage	12 (12.6)
	+ 2 stages	0
Week 48, *n* (%)	− 1 stage	6 (3.2)
	No change	147 (78.6)
	+ 1 stage	32 (17.1)
	+ 2 stages	2 (1.1)
Changes in NPI score		
Total score		
Week 24 ($n = 39$)	Mean ± SD	8.6 ± 10.3
	Change from baseline	0.9 ± 12.4
	p value	0.671
Week 48 ($n = 115$)	Mean ± SD	6.5 ± 10.7
	Change from baseline	0.4 ± 11.0
	p value	0.994
Delusions		
Week 24 ($n = 38$)	Mean ± SD	0.6 ± 1.5
	Change from baseline	0.3 ± 1.5
	p value	0.211
Week 48 ($n = 115$)	Mean ± SD	0.7 ± 2.1
	Change from baseline	0.3 ± 2.0
	p value	0.236
Hallucinations		
Week 24 ($n = 38$)	Mean ± SD	0.5 ± 2.0
	Change from baseline	− 0.4 ± 1.5
	p value	0.188
Week 48 ($n = 115$)	Mean ± SD	0.1 ± 0.4
	Change from baseline	− 0.2 ± 1.3
	p value	0.073

Table 2 continued

		10 cm^2rivastigmine patch*n* = 285
Apathy		
Week 24 ($n = 38$)	Mean ± SD	1.4 ± 2.4
	Change from baseline	0.6 ± 2.5
	p value	0.159
Week 48 ($n = 115$)	Mean ± SD	1.0 ± 2.2
	Change from baseline	0.3 ± 2.6
	p value	0.176
Depression		
Week 24 ($n = 38$)	Mean ± SD	0.7 ± 1.7
	Change from baseline	0.0 ± 2.1
	p value	0.951
Week 48 ($n = 115$)	Mean ± SD	0.7 ± 2.0
	Change from baseline	0.0 ± 2.2
	p value	0.978

CDR clinical dementia rating, *FAS* full analysis set, *NPI* neuropsychiatric inventory, *SD* standard deviation
[a] A decrease in the stage suggests improvement of the status, and vice versa

30 (10.5%) patients. However, 11 SAEs caused 7 (2.5%) patients to discontinue the rivastigmine patch and 22 SAEs caused the death of 11 (3.9%) patients. However, none of the deaths were related to use of the rivastigmine patch. The cause of death included metastases to lung/colon cancer, septic shock, cardiac failure, metastases to liver, necrosis, renal failure, respiratory failure, colon cancer stage IV/hepatic cirrhosis, acute kidney injury, pneumonia, hemophagocytic lymphohistiocytosis, multiple organ dysfunction syndrome, cardiac arrest, sepsis, urinary tract infection, fall, and myocardial infraction.

DISCUSSION

Our results demonstrated that the 10 cm^2 rivastigmine patch provides clinical benefit in patients with mild-to-moderate AD. Over 80% of patients maintained a CDR score ≤ 1 in the 48 weeks of treatment with the patch. We observed a decrease of < 3 points in the CASI score, especially in patients with mild-to-moderate dementia at baseline, which was lower than that in previous research [9].

To the best of our knowledge, this is the first study to evaluate CASI outcomes after treatment with the 10 cm^2 rivastigmine patch in a real-world setting. Our study demonstrated an increase of 0.5 points in CASI score at Week 24 compared with baseline, which compares favorably with the decrease of 1.5 points in CASI score in the 6-month pilot study of rivastigmine 4.5 mg capsules [15]. The disparity in this result could be due to varying disease severity and the distinct dose and drug formulation. Patients in the pilot study had a lower mean CASI score at baseline (47.5 vs. 64.1 in the

Table 3 Effect of persistency on CASI, MMSE, and CDR scores

Score	Persistency	
	Yes $n = 180$	No $n = 105$
Change from baseline in CASI score		
Week 24		
Number	67	15
Mean ± SD	0.7 ± 7.93	− 0.2 ± 7.92
p value	0.333	0.911
Week 48		
Number	143	25
Mean ± SD	− 2.0 ± 9.33	− 2.3 ± 8.98
p value	0.010*	0.210
Change from baseline in MMSE score		
Week 24		
Number	76	20
Mean ± SD	0.1 ± 2.63	0.6 ± 3.08
p value	0.855	0.395
Week 48		
Number	159	38
Mean ± SD	− 0.3 ± 2.66	− 1.1 ± 3.06
p value	0.124	0.041*
Summary of changes in the CDR score		
Week 24, *n* (%)		
− 1 stage	3 (4.0)	2 (10.0)
No change	63 (84.0)	15 (75.0)
+ 1 stage	9 (12.0)	3 (15.0)
+ 2 stages	0 (0.0)	0 (0.0)
Week 48, n (%)		
− 1 stage	6 (4.0)	0 (0.0)
No change	118 (79.2)	29 (76.3)
+ 1 stage	25 (16.8)	7 (18.4)
+ 2 stages	0 (0.0)	2 (5.3)

CASI cognitive assessment screening instrument, *CDR* clinical dementia rating, *MMSE* mini-mental state examination, *SD* standard deviation
*Statistical significance

present study), representing a population with a more advanced disease stage. Again, the 10 cm^2 rivastigmine patch provides similar exposure to rivastigmine as the capsule, although the dose of rivastigmine in the capsule formulation is slightly higher (12 mg/day vs. 9.5 mg/day) than that in the patch [16]. Finally, unlike capsules, the patch formulation allows continuous and steady delivery of rivastigmine through the skin, thus avoiding the first-pass effects after oral administration [17]. This could mean that titrating to a higher dose earlier may allow patients to achieve an optimal therapeutic dose and also benefit from a longer duration of treatment. However, findings suggest that further research is required to determine which population of patients may benefit from titrating to a high dose [16, 17]. Clinical adherence of the 5 cm^2 rivastigmine patch has been explored and the results have shown a significant negative correlation between subscapular skin fold thickness and serum metabolite levels [18].

A decline of 2.3 points per year in MMSE scores has been observed in those who progressed to dementia without treatment [19]. Per the National Health Insurance regulations in Taiwan, patients with AD using reimbursed rivastigmine should switch to another treatment if the MMSE score decreases by more than two points [13]. During the follow-up period, patients treated with the 10 cm^2 rivastigmine patch maintained cognitive performance, and only one patient had to withdraw from the study due to a failure in re-submission for health insurance reimbursement; however, the

Table 4 Drug-related adverse events

Adverse event, *n* (%)	**10 cm^2rivastigmine patch *n* = 285**
Skin and subcutaneous tissue disorders	53 (18.6)
Pruritus	32 (11.2)
Rash	9 (3.2)
Erythema	5 (1.8)
Gastrointestinal disorders	17 (6.0)
Nausea	10 (3.5)
Vomiting	8 (2.8)
Nervous system disorders	8 (2.8)
General disorders and administration site conditions	5 (1.8)
Decreased appetite	5 (1.8)
Ear and labyrinth disorders	3 (1.1)
Cardiac disorders	2 (0.7)
Psychiatric disorders	2 (0.7)
Weight decreased	1 (0.4)
Renal and urinary disorders	1 (0.4)

reason for the failure was not specified. The results were as expected, supporting the beneficial role of the 10 cm^2 rivastigmine patch in the maintenance of global cognition and disease severity. Based on the results for the CASI total score, MMSE scores, and CDR scores, we observed that a higher persistency rate with the 10 cm^2 rivastigmine patch is associated with numerically better clinical outcomes. Moreover, even though the overall treatment persistency was 63.2%, the remaining ~ 37% of patients still adhered to the treatment for 274 days. Our effectiveness data were also comparable to prior observational studies. An 18-month observational Canadian study comprising of patients treated with the 5 or 10 cm^2 rivastigmine patches showed a mean change in MMSE score of 0.5 at 6 months and 0.2 at 12 months [20]. In an observational study conducted by Minthon et al., the change in the MMSE score was 0.11 at 6 months and − 0.62 at 12 months [21]. A 6-month, observational study of switching from donepezil or rivastigmine capsules to the 5 or 10 cm^2 rivastigmine transdermal patches also reported a stable MMSE outcome, with a minimal change of − 0.5 [22].

There are a number of AchEIs used in real-world practice for AD patients. From a statistical perspective, oral rivastigmine 3 mg/day, oral rivastigmine 9 mg/day, and the 5 cm^2 rivastigmine patch are comparable in bridging to the 10 cm^2 rivastigmine patch when the persistency rate for the 10 cm^2 rivastigmine patch serves as the major clinical outcome. These results may indicate the relatively applicable usage of either 3-transformation formula, i.e., switching from either of the three doses of rivastigmine (oral rivastigmine 3 mg or 9 mg and the 5 cm^2 rivastigmine patch) to the 10 cm^2 rivastigmine patch is feasible. Of particular note is that the shift from oral rivastigmine 3 mg/day to the 5 cm^2 rivastigmine patch is tolerable in the Taiwanese population [23].

In our study, the majority of AEs were mild, local skin tolerability was good, discontinuations due to drug-related AEs occurred in less than a fifth of the patients, and no unexpected safety issues arose. The IDEAL study [5] demonstrated that the 10 cm^2 rivastigmine patch provided similar efficacy as the rivastigmine capsule (12 mg/day), but with a superior tolerability profile due to lower incidences of vomiting (6.2%) and nausea (7.2%) over 6 months; however, in our study, such incidences occurred in only 1.4% patients, each over a longer observational period of 48 weeks. In the current study, 63.2% of patients continued on the 10 cm^2 rivastigmine patch treatment at Week 48, which was in line with the 55–65% of patients observed with earlier studies at Week 24 with an equivalent oral dose (obtained with 12 mg/day rivastigmine capsules) [21, 24, 25]. These findings were comparable to those in an open-label study, which reported a study completion rate of 74.5% after 24 weeks of treatment with the 10 cm^2 rivastigmine patch, and the 6-month IDEAL study where 83.8% of participants stayed on the 10 cm^2 rivastigmine patch for at least 8 weeks [25]. The results from

the Real-world Evaluation of Compliance And Preference in Alzheimer's disease treatment (RECAP) [23] and Exploring and Managing Dementia in Black African and Caribbean Elders (EMBRACE) [20] studies also showed that 82.4% and 88.2% of caregivers of patients with AD preferred the rivastigmine transdermal patch over oral medication. Therefore, the 10 cm^2 rivastigmine patch may allow patients easier access to higher doses compared with the 12 mg/day rivastigmine capsule, thereby enabling patients to stay on and benefit from long-term effective treatment.

The safety data in our study were also comparable to prior observational studies. In a Canadian study with the 5 or 10 cm^2 rivastigmine patches, 18.3% of patients discontinued due to an AE, with pruritus (4.0%), erythema (2.9%), nausea (2.5%), rash (1.9%), skin reaction (1.7%), application site erythema (1.6%), vomiting (1.3%), decreased appetite (1.1%), and dizziness (1.0%) being the most common [20]. Similarly, in a 6-month observational study of switching from donepezil or rivastigmine capsules to the 5 or 10 cm^2 rivastigmine patches, discontinuation due to AEs occurred in 18% of patients, with skin reactions and gastrointestinal disorders causing 9% and 3% of patients, respectively, to stop the treatment [22].

All AchEIs require titration from a low dose and the complex dosing regimen [26] may affect drug adherence and, therefore, the outcome. Rivastigmine is administered in four oral formulations (doses of 1.5 mg, 3 mg, 4.5 mg, and 6 mg) and two transdermal patch formulations (5 cm^2 and 10 cm^2) [27, 28]. Consequently, the dosing regimen may vary widely among practicing physicians as observed in this study and hence might interfere with compliance. The other two approved AchEIs in Taiwan are galantamine and donepezil, which are administered in two oral doses, and the dosing regimens are titrated if an AE occurs. In clinical practice, AD patients also fail to adhere to AchEI treatment due to a lack of efficacy. When one AchEI may fail to reach the therapeutic expectation and the dosing strategy may not improve efficacy, the physician may consider switching to another AchEI [29], using an add-on of memantine, or discontinuing the AchEI altogether [26, 30].

The efficacy and safety of the rivastigmine patch has been validated in patients with AD who failed to benefit from treatment with donepezil [31], and the switch from donepezil to the (5 cm^2) rivastigmine patch and the gradual switch or a cross-tapering strategy both showed a high rate of adherence and low incidences of side effects [22, 32, 33]. The favorable safety and tolerability profile reported with the 10 cm^2 rivastigmine patch and increased ease of use than an oral formulation may increase adherence to a higher dose therapy. This could encourage patients with AD to stay on treatment for a longer period, offering the possibility of enhanced outcomes in clinical practice. Although the transdermal patch may cause skin reactions, these events were manageable. In line with prior studies [5], erythema/rash and pruritus were the most commonly reported reactions in our study; however, importantly, no patient experienced a skin reaction that was reported as an SAE. Our data support a favorable skin tolerability profile for the 10 cm^2 rivastigmine patch and therefore further reinforce the fact that its benefits should not be dismissed due to skin irritation problems.

Limitations

The open-label and real-life observational design of our study has some limitations. As there was no placebo or parallel control group, outcomes in the absence of the 10 cm^2 rivastigmine patch are unknown. It is suggested that researchers in this field should consider including a control group in future studies. Physicians were not blinded to study treatment and were able to adjust the dosage freely as needed within the study, such as temporarily switching to the other formulation (i.e., rivastigmine capsule) or a lower dose (i.e., the 5 cm^2 rivastigmine patch). These adjustments could be influential to treatment response. Therefore, the clinical outcome might not entirely represent the effects of the continuous 10 cm^2 rivastigmine patch treatment. Also, it is important to note that randomized controlled

trials, despite being conducted in a controlled setting, are associated with several limitations including incomplete understanding of AD pathophysiology that might have led to selection of the wrong targets, inappropriate patient selection, variable rates of progression, suboptimal dosing, drug exposure and/or target engagement, inappropriate time of intervention, inappropriate outcome measures, and low sensitivity of clinical scales. These variables are even more difficult to control in a real-world study.

The results may not be generalized to the entire Taiwan population because, in the real world, patients face the issue of failing the re-application of drug reimbursement and the effect of this situation is not captured in our study. However, the present study offers real-world insights into the persistency, treatment outcomes and unique treatment pattern in Taiwan.

CONCLUSIONS

The use of the 10 cm^2 rivastigmine patch in a real-life setting was efficacious for patients with mild-to-moderate AD and was not associated with any significant safety concerns. Thus, the 10 cm^2 rivastigmine patch represents an efficacious, tolerable, and convenient treatment option in the management of mild-to-moderate AD in Taiwan.

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Compliance with Ethical Guidelines. Participants provided written informed consent prior to participation. The Independent Ethics Committee or Institutional Review Board reviewed the study protocol for each study center (information provided within supplementary material). The study was conducted according to the Guidelines for Good Clinical Practice that have their origin in the Declaration of Helsinki.

Data Availability. The datasets used and/or analyzed during the study are available from the corresponding author on reasonable request.

REFERENCES

1. World Alzheimer Report 2019. Alzheimer's disease international: attitudes to dementia. https://www.alz.co.uk/research/WorldAlzheimerReport2019.pdf. Accessed 16 Dec 2019.

2. Wang WF, Chiu PY, Lin YT, Hu CJ, Fuh JL, Yang YH. Registration of Alzheimer's disease in Taiwan: patient and informant. Am J Alzheimers Dis Other Demen. 2014;29:18–22.

3. Fan LY, Sun Y, Lee HJ, Yang SC, Chen TF, Lin KN, et al. Marital status, lifestyle and dementia: a nationwide survey in Taiwan. PLoS ONE. 2015;10:e0139154.

4. Chang CC, Peng GS, Lai TJ, Li CH, Liu CK. A 48-week, multicenter, open-label, observational study evaluating oral rivastigmine in patients with mild-to-moderate Alzheimer's disease in Taiwan. Adv Ther. 2019;36:1455–64.

5. Winblad B, Grossberg G, Frölich L, Farlow M, Zechner S, Nagel J, et al. IDEAL: a 6-month, double-blind, placebo controlled study of the first skin patch for Alzheimer disease. Neurology. 2007;69(4 Suppl 1):S14-22.

6. Sadowsky CH, Micca JL, Grossberg GT, Velting DM. Rivastigmine from capsules to patch: Therapeutic advances in the management of Alzheimer's disease and Parkinson's disease dementia. Prim Care Companion CNS Disord. 2014. https://doi.org/10.4088/PCC.14r01654.

7. Gauthier S, Juby A, Dalziel W, Réhel B. Schecter R and on behalf of the EXPLORE investigators. Effects of rivastigmine on common symptomatology of Alzheimer's disease (EXPLORE). Curr Med Res Opin. 2010;26:1149–60.

8. Sabbagh MN, Malek-Ahmadia M, Kataria R, Beldena CM, Connor DJ, Pearson C, et al. The Alzheimer's questionnaire: a proof of concept study for a new informant-based dementia assessment. J Alzheimers Dis. 2010;22:1015–21.

9. Teng EL, Hasegawa K, Homma A, Imai Y, Larson E, Graves A, et al. The cognitive abilities screening instrument (CASI): a practical test for cross-cultural epidemiological studies of dementia. Int Psychogeriatr. 1994;6:45–58.

10. Yang YH, Wu MN, Chou PS, Su HC, Lin SH, Sung PS. Longitudinal neuropsychological outcome in Taiwanese Alzheimer's disease patients treated with medication. Curr Alzheimer Res. 2018;15:474–81.

11. Geldmacher DS. Treatment guidelines for Alzheimer's disease: redefining perceptions in primary care. Prim Care Companion J Clin Psychiatry. 2007;9:113–21.

12. Small G, Dubois B. A review of compliance to treatment in Alzheimer's disease: potential benefits of a transdermal patch. Curr Med Res Opin. 2007;23:2705–13.

13. Chang CJ, Chou TC, Chang CC, Chen TF, Hu CJ, Fuh JL, et al. Persistence and adherence to rivastigmine in patients with dementia: results from a noninterventional, retrospective study using the National Health Insurance research database of Taiwan. Alzheimers Dement (N Y). 2019;5:46–51.

14. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7:263–9.

15. Chou MC, Chen CH, Liu CK, Chen SH, Wu SJ, Yang YH. Concentrations of rivastigmine and NAP 226–90 and the cognitive response in Taiwanese Alzheimer's disease patients. J Alzheimers Dis. 2012;31:857–64.

16. Winbald B, Cummings J, Andreasen N, Grossberg G, Onofrj M, Sadowsky C, et al. A six-month double-blind, randomized, placebo-controlled study of a transdermal patch in Alzheimer's

disease—rivastigmine patch versus capsule. Int J Geriatr Psychiatry. 2007;22:456–67.

17. Kurz A, Farlow M, Lefe'vre G. Pharmacokinetics of a novel transdermal rivastigmine patch for the treatment of Alzheimer's disease: a review. Int J Clin Pract. 2009;63:799–805.

18. Chou PS, Jhang KM, Huang LC, Wang WF, Yang YH. Skinfold thickness for rivastigmine patch application in Alzheimer's disease. Psychopharmacology. 2019;236:1255–60.

19. Aevarsson O, Skoog I. A longitudinal population study of the mini-mental state examination in the very old: relation to dementia and education. Dement Geriatr Cogn Disord. 2000;11:166–75.

20. Gauthier S, Robillard A, Cohen S, Black S, Sampalis J, Colizza D, et al. Real-life effectiveness and tolerability of the rivastigmine transdermal patch in patients with mild-to-moderate Alzheimer's disease: the EMBRACE study. Curr Med Res Opin. 2013;29:989–1000.

21. Minthon L, Wallin AK, Eriksson S, Wattmo C, Andreasen N. Long-term rivastigmine treatment in a routine clinical setting. Acta Neurol Scand. 2009;119:180–5.

22. Cagnin A, Cester A, Costa B, Ermani M, Gabelli C, Gambina G, et al. Effectiveness of switching to the rivastigmine transdermal patch from oral cholinesterase inhibitors: a naturalistic prospective study in Alzheimer's disease. Neurol Sci. 2015;36:457–63.

23. Lai TH, Wang WF, Yip BS, Yang YW, Peng GS, Tsai SJ, et al. Real-world evaluation of compliance and preference in Alzheimer's disease treatment: an observational study in Taiwan. Patient Prefer Adherence. 2016;10:383–90.

24. Rösler M, Anand R, Cicin-Sain A, Gauthier S, Agid Y, Dal-Bianco P, et al. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. BMJ. 1999;318:633–8.

25. Articus K, Baier M, Tracik F, Kühn F, Preuß UW, Kurz A. A 24-week, multicentre, open evaluation of the clinical effectiveness of the rivastigmine patch in patients with probable Alzheimer's disease. Int J Clin Pract. 2011;65:790–6.

26. Gauthier S, Emre M, Farlow MR, Bullock R, Grossberg GT, Potkin SG. Strategies for continued successful treatment of Alzheimer's disease: switching cholinesterase inhibitors. Curr Med Res Opin. 2003;19:707–14.

27. Exelon patch®. US prescribing information. http://www.pharma.us.novartis.com/product/pi/pdf/exelonpatch.pdf. Accessed 30 Oct 2019.

28. Exelon® for oral use. US prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020823s036,021025s024lbl.pdf. Accessed 30 Aug 2021.

29. Ryan AA. Medication compliance and older people: a review of the literature. Int J Nurs Stud. 1999;36:153–62.

30. Dantoine T, Auriacombe S, Sarazin M, Becker H, Pere JJ, Bourdeix I. Rivastigmine monotherapy and combination therapy with memantine in patients with moderately severe Alzheimer's disease who failed to benefit from previous cholinesterase inhibitor treatment. Int J Clin Pract. 2006;60:110–8.

31. Auriacombe S, Pere JJ, Loria-Kanza Y, Vellas B. Efficacy and safety of Rivastigmine in patients with Alzheimer's disease who failed to benefit from treatment with donepezil. Curr Med Res Opin. 2002;18:129–38.

32. Sadowsky CH, Dengiz A, Olin JT, Koumaras B, Meng X, Brannan S. Switching from donepezil tablets to rivastigmine transdermal patch in Alzheimer's disease. Am J Alzheimers Dis Other Demen. 2009;24:267–75.

33. Sadowsky CH, Dengiz A, Meng X, Olin JT. Switching from oral donepezil to rivastigmine transdermal patch in Alzheimer's disease: 20-week extension phase results. Prim Care Companion J Clin Psychiatry. 2010;12:PCC.09m00852.