

Real-world Evaluation of Tolerability, Safety and Efficacy of Rivastigmine Oral Solution in Patients with Mild to Moderate Alzheimer's Disease Dementia

Sun-Wung Hsieh^{1,2,3,*}, Jui-Cheng Chen^{4,5,6,*}, Nai-Ching Chen^{7,8}, Kai-Ming Jhang⁹, Wenfu Wang^{9,10}, Yuan-Han Yang^{2,3,11,12,13}

¹Department of Neurology, Kaohsiung Municipal Siao-Gang Hospital, Kaohsiung Medical University, ²Department of Neurology, Kaohsiung Medical University Hospital, Kaohsiung Medical University, ³Neuroscience Research Center, Kaohsiung Medical University, Kaohsiung, ⁴Department of Neurology, China Medical University Hsinchu Hospital, ⁵Department of Neurology, China Medical University Hospital, ⁶School of Medicine, China Medical University, Taichung, ⁷Department of Neurology, Kaohsiung Chang Gung Memorial Hospital, ⁸Department of Neurology, Chang Gung University College of Medicine, Kaohsiung, ⁹Department of Neurology, Changhua Christian Hospital, ¹⁰Department of Holistic Wellness, Ming Dao University, Changhua, ¹¹Department of Neurology, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung Medical University Hospital, ¹²Department of and Master's Program in Neurology, Faculty of Medicine, Kaohsiung Medical University, ¹³Chinese Mentality Protection Association, Kaohsiung, Taiwan

Objective: The purpose of this study is to investigate the safety, tolerability and efficacy of titrating dose of rivastigmine oral solution in patients with mild to moderate Alzheimer's disease (AD) in Taiwan.

Methods: We recruited 108 mild to moderate AD patients with Rivast[®] (rivastigmine oral solution 2 mg/ml) treatment for 52 weeks. We recorded the demographic characteristics, initial cognition by mini-mental state examination (MMSE), initial global status by clinical dementia rating (CDR) with CDR-Sum of Boxes (CDR-SB), initial dose, and titrating dose at each visit. We investigated the adherence, proportion of possible side effects, optimal dose, and time to optimal dose. We demonstrated the proportion of cognitive decline and its possible risk factors.

Results: During the course, 9 patients discontinued the rivastigmine oral solution due to poor compliance or preference. Twelve out of 99 patients (12.1%) reported possible side effects. Among 87 patients, the mean age was 77.2 ± 9.0 years ago with female predominant (65.2%). The optimal dose was 3.6 ± 1.4 ml in average and 4 ml ($n = 31$, 35.6%) in mode. The duration to optimal dose was 12.5 ± 10.2 weeks and 24 weeks ($n = 35$, 40.2%) in mode. It presented 25% with cognitive decline in MMSE, 27% with global function decline in CDR and 63% with global function decline in CDR-SB.

Conclusion: We demonstrated the clinical experience of rivastigmine oral solution in mild to moderate AD patients. It suggested rivastigmine oral solution 4ml is the optimal dose with 24 weeks to the optimal dose for at least one third of patients.

KEY WORDS: Rivastigmine; Alzheimer's disease; Dementia; Mini-mental state examination; Tolerability; Efficacy.

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Address for correspondence: Yuan-Han Yang
Department of Neurology, Kaohsiung Municipal Ta-Tung Hospital, 68 Jhonghua 3rd Road, Cianjin District, Kaohsiung 80145, Taiwan

E-mail: yang1728@yahoo.com

ORCID: <https://orcid.org/0000-0002-1699-4842>

Wenfu Wang

Department of Neurology, Changhua Christian Hospital, 135, Nanxiao St., Changhua 500, Taiwan

E-mail: w4239.tw@gmail.com

ORCID: <https://orcid.org/0000-0002-3963-1649>

*These authors contributed equally to this study as co-first authors.

INTRODUCTION

Alzheimer's disease (AD) is the commonest form of dementia affecting elderly people. The etiology of the disease is not clearly identified, but several mechanisms for the development of AD have been proposed. The cholinergic hypothesis is one of the proposed hypotheses. The deficiency of Acetylcholine (ACh) was found to lead to dysfunctional cholinergic signaling in the cortex and hip-

pocampus, considering as the cause of cognitive impairment. Accordingly, Ach is the primary neurotransmitter facilitating learning and improving attention [1,2]. By far, different types of drugs used for cholinergic neurotransmission modification, and cholinesterase inhibitors remain the mainstay of treatment for mild to moderate AD by inhibiting the breakdown of released acetylcholine and enhancing the cholinergic neurotransmission [3-7].

Rivastigmine is a carbamate-type dual inhibitor of brain cholinesterase, acetyl-cholinesterase (AChE) and butyl-cholinesterase (BuChE). It is characterized by penetrating the blood-brain barrier easily and targeting AChE and BuChE in the brain specifically, particularly in the hippocampus and cortex [8,9]. With the presence of rivastigmine, ACh hydrolysis is inhibited and levels of ACh are elevated in brain synapses. Rivastigmine had shown its efficacy in the symptomatic treatment of improving or maintaining cognitive function, daily living activities, behaviors, and global dementia symptoms in patients with mild to moderate AD and Parkinson's disease dementia [10-12]. The therapeutic dosage of rivastigmine was suggested to titrate from the lower to higher dose for the better clinical response [13]. Due to the cholinergic deficit, tolerability, and treatment response potential, it may be worthwhile keeping high-dose cholinesterase inhibition in reserve [14]. However, considering the anticipation of the gastrointestinal adverse events (nausea, vomiting, diarrhea) associated with cholinesterase inhibitors, it might be dose dependent causing some extent of withdraw medication. Furthermore, the incidence of adverse effects depends on duration of enzyme inhibition and the extent of daily fluctuations in enzyme activity [15]. It is concluded that reducing daily fluctuations in the rivastigmine pharmacokinetic profile contributes decrease in fluctuations in the extent of enzyme inhibition and improvement in overall tolerability. For this reason, Transdermal patches offer many advantages over conventional oral medications.

Oral rivastigmine is available as capsules (1.5, 3.0, 4.5, and 6.0 mg) and a bioequivalent oral solution (2 mg/ml), administered twice daily [16]. Various trials have showed that gastrointestinal adverse events can be tolerated by the slow titration [17,18]. The real-world clinical experience of rivastigmine oral solution is less discussed. Our study predicts that adjusting lower dose to higher dose rivastigmine with oral solution can improve the patient's and caregiver's compliance as well as decrease the medical

discontinue rate. Herein we conducted the observational study investigating the safety, tolerability and efficacy of titrating dose of rivastigmine oral solution in patients with mild to moderate AD in Taiwan.

METHODS

Study Population

We conducted an open label, non-comparative and observational study to investigate the safety, tolerability and efficacy of Rivast[®] (rivastigmine oral solution 2 mg/ml) in mild to moderate AD dementia patients in Taiwan. We recruited patients who met the criteria for AD in neurological out-patient departments in three medical centers in Taiwan (Kaohsiung Chang Gung Memorial Hospital, China Medical University Hospital, and Changhua Christian Hospital). The diagnose of AD was based on the Diagnostic and Statistical Manual of Mental Disorder 4th edition (DSM-IV) criteria and National Institute of Neurological Disorders and Stroke (NINCDS)-Alzheimer's Disease and Related Disorders Association (ADRDA) criteria [19,20]. All the patients underwent a brain imaging survey and a set of blood screening tests, such as complete blood count, renal function, liver function, vitamin B12, folic acid, cortisol level and serologic test of syphilis, to exclude out the possibility of vascular or other type of dementia [21]. Psychometrics were administered for evaluating the global function by Clinical Dementia Rating (CDR) [22] with CDR-Sum of Boxes (CDR-SB) [22], and cognitive function by Mini-Mental State Examination (MMSE) [23]. We recorded the demographic data of the patients, including age, sex, body heights, body weights, body mass index (BMI), education duration, and glomerular filtration rate (GFR). For this study, all practices were carried out in accordance with the Helsinki Declaration, and were approved by Changhua Christian Hospital Institutional Review Board (CCH IRB No. 190501). All participants, or their legal representatives, provided written informed consent before entering the study.

Inclusion and Exclusion Criteria

The inclusion criteria for this study were as follows, (1) Patients having a clinical diagnosis of mild to moderate AD, fulfilling the DSM-IV criteria for dementia and NINCDS-ADRDA diagnostic criteria for probable AD. (2) Cognitive impairment demonstrated by neuropsychiatric tests, with

an MMSE < 27 and CDR \geq 0.5. (3) Generalized normal neurological examinations except impaired cognitive function. (4) No structural brain abnormalities to the diagnosis of AD. (5) The memory and cognitive impairment are not attributable to any medical conditions or medications. (6) Exclusion of other neurodegenerative diseases. (7) The patients or their attorney are able to understand the objectives of the study and signed the informed consent. The exclusion criteria were as follows, (1) Patients with known hypersensitivity to any other cholinesterase inhibitors. (2) Patients with clinical evidence of any medical/neurological/psychiatric disorders which in opinion of investigators are likely to interfere with the study. (3) Patients who have a known or suspected history (within past year) of alcoholism, drug misuse or dementia secondary to alcohol abuse. (4) Cardiac disease potentially resulting in syncope, near syncope or other alterations of mental status. In addition, the following conditions should lead to exclusion: bradycardia less than 50 beats per minute, atrioventricular block. (5) Patients who have received investigational new drug within past three months.

Recommended Rules for Titrating Rivast[®] (Rivastigmine Oral Solution 2 mg/ml)

Titration dose of Rivast[®] (rivastigmine oral solution 2 mg/ml) for AD patients was practiced by neurologists in each visit at 4th, 8th, 12th, 24th week after initial rivastigmine oral solution dose in the Neurological out-patient departments (OPD) following the recommended rules as Table 1. In real clinical practice, the initial dose of rivastigmine oral solution was started by neurologists according to their clinical experiences and the patients' condition. The neurologists adjusted the dose according to the tolerability reported by patients or their family members at each OPD follow-up. The patients reported the prescribed dose of rivastigmine oral solution in each OPD visit at 4th, 8th, 12th, 24th week. The prescribed

dose of rivastigmine oral solution was recorded as optimal dose for the maximal tolerable prescribing dose maintaining for at least 3 months. We recorded the time to optimal dose from the onset time.

Evaluation of Safety, Tolerability and Efficacy of Titrating Dose of Rivast[®] (Rivastigmine Oral Solution 2 mg/ml)

We investigated and reported the adherence, proportion of possible side effects, optimal dose, and time to optimal dose throughout the initial 24 weeks of treating with rivastigmine oral solution at 24 weeks. The observational study will continue to 52 weeks eventually. We investigated the proportion of cognitive decline by MMSE, global function decline by CDR with CDR-SB, and risk factors to cognitive/global function decline. The study procedure and flowchart is demonstrated in Figure 1. The clinicians reported the prescribed dose of rivastigmine oral solution in initial OPD and each OPD visit at 4th, 8th, 12th, and 24th week for the patients. The prescribed dose of rivastigmine oral solution was recorded as optimal dose for the maximal tolerable prescribing dose maintaining for at least 3 months. We recorded the time to optimal dose for patients. Cognitive decline by MMSE was defined as the amount of decreasing MMSE scores \geq 3 in one year. Global function decline by CDR was defined as progression in CDR level in one year. Global function decline by CDR-SB was defined as increasing in CDR-SB scores in one year. We calculated the correlation of optimal dose and time to optimal dose with demographic variables. We demonstrated the proportion of cognitive/global function decline and the possible risk factors.

Statistical Analysis

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS version 19.0; IBM Co., Armonk, NY, USA). We presented the demographic data, including age, sex, body heights, body weights, BMI,

Table 1. Recommended rules for titrating Rivast[®] (rivastigmine oral solution)

Dose	Week											
	Base-line			4th		8th		12th		24th		52nd
AM (ml)	0.5	1	1	1.5	1.5	2	2	2.5	2.5	3	3	3
PM (ml)	1	1	1.5	1.5	2	2	2.5	2.5	3	3	3	3
Daily dose (mg)	3	4	5	6	7	8	9	10	11	12	12	12

1 ml = 2 mg; AM, ante meridiem; PM, post meridiem.

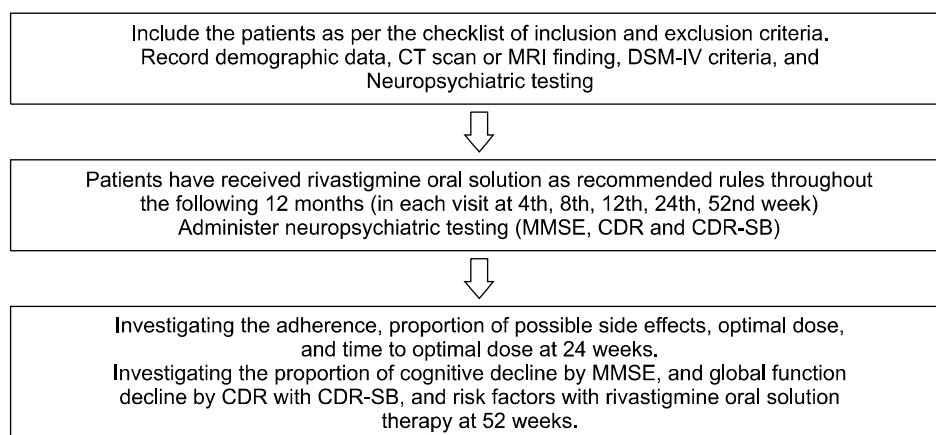


Fig. 1. Study procedure and flowchart.

CT, computed tomography; MRI, magnetic resonance imaging; DSM-IV, Diagnostic and Statistical Manual of Mental Disorder 4th edition; MMSE, mini-mental state examination; CDR, clinical dementia rating; CDR-SB, Clinical Dementia Rating-Sum of Boxes.

education duration and GFR at study onset. Cognitive function by MMSE and global function by CDR with CDR-SB were presented at study onset and after full therapy for 52 weeks. To assess the safety and tolerability of rivastigmine oral solution, we calculated the proportion of patients who did not complete the study for the possible side effects or discontinuation of therapy. We recorded the initial dose, titrating dose at each OPD visit at 4th, 8th, 12th, and 24th week after study onset, optimal dose and duration to optimal dose. The data were presented as maximal value, minimal value, mean (standard deviation), mode (numbers, percentages), and median for continuous variables and numbers (percentages) for categorical variables. We calculated the correlation of optimal dose, time to optimal dose and initial dose with demographic variables using Pearson correlation test. To assess the efficacy of rivastigmine oral solution, cognitive function by MMSE and global function by CDR with CDR-SB were compared before and after rivastigmine oral solution therapy. We determined the significant factors associated with cognitive decline by MMSE and global function decline by CDR with CDR-SB using Student's *t* test. All statistical tests were two-tailed, and a *p* value of 0.05 was considered to show significance with 95% confidence interval.

RESULTS

Description of Studies for Tolerability and Safety

We recruited 108 patients with mild to moderate AD in the study. During the course, there were 9 patients dis-

Table 2. Demographic characteristics (n = 87)

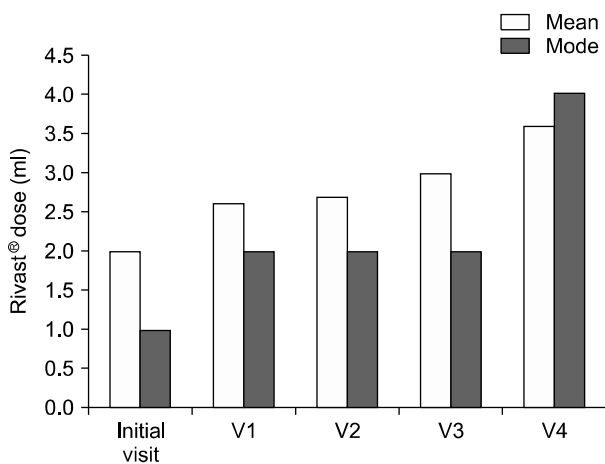
Variable	Min	Max	Value
Age (yr)	55	93	77.2 ± 9.0
Sex, female			57 (65.2)
Education (yr)	0	20	6.5 ± 5.2
Height (cm)	134.6	185	154.8 ± 9.7
Body weight (kg)	41.6	90	57.8 ± 10.7
BMI	16.5	38.8	23.8 ± 4.7
GFR	6.5	152	72.1 ± 29.9
Initial MMSE	10	27	15.0 ± 6.9
Initial CDR-SB	0.5	18	5.7 ± 3.9

Values are presented as mean ± standard deviation or number (%). BMI, body mass index; GFR, glomerular filtration rate; MMSE, mini-mental state examination; CDR-SB, Clinical Dementia Rating-Sum of Boxes.

continued the rivastigmine oral solution due to poor compliance or preference, including 5 for poor compliance and 4 for preference of oral capsule or patch. The rest 99 patients were evaluated for the tolerability, safety and efficacy of rivastigmine oral solution. There were 12 patients reporting the possible side effects and discontinuing the therapy, including 2 for dizziness, 4 for nausea/vomiting, 1 for somnolence, 1 for hallucination, 1 for diarrhea, 1 for hypotension, and 2 for unexpected mortality due to malignancy or bleeding. The proportion of possible side effects was 12.1% (12 out of 99 patients). There were 87 patients having the rivastigmine oral solution therapy for full 52 months, including 4 patients with sinus bradycardia but continuously taking medication. We evaluated the tolerability, safety and efficacy of rivastigmine oral solution therapy. The overall adherence was 80.6% (87 out

Table 3. Dose of each visit, optimal dose and time to optimal dose (n = 87)

Variable	Min	Max	Mean \pm standard deviation	Mode (number, %)	Median
Initial dose (ml)	0.25	6	2.0 \pm 1.4	1 (33, 37.9)	2
V1 dose (ml) (4th week)	0.5	6	2.6 \pm 1.4	2 (37, 42.5)	2
V2 dose (ml) (8th week)	0.5	6	2.7 \pm 1.4	2 (33, 37.9)	2
V3 dose (ml) (12th week)	0.5	6	3.0 \pm 1.4	2 (30, 34.5)	3
V4 dose (ml) (24th week)	0.5	6	3.6 \pm 1.4	4 (31, 35.6)	4
Optimal dose (ml)	0.5	6	3.6 \pm 1.4	4 (31, 35.6)	4
Time to optimal dose (wk)	0	24	12.5 \pm 10.2	24 (35, 40.2)	12

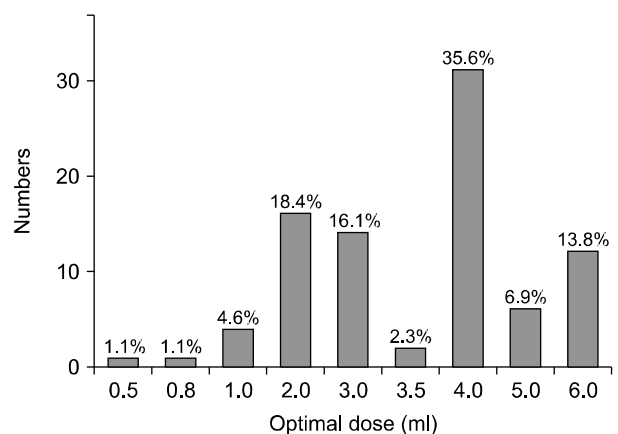
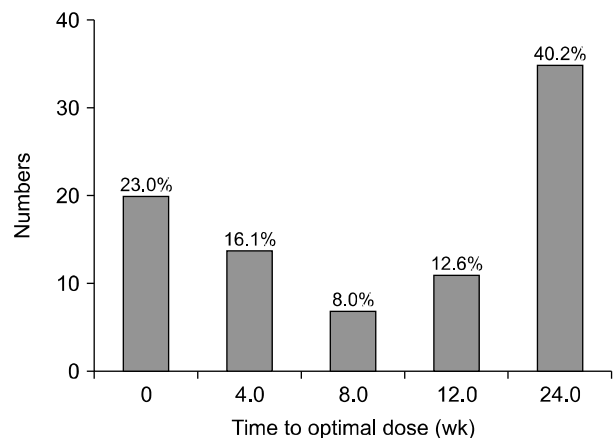
**Fig. 2.** The mean and mode dose during each visit.

of 108 patients) in our study.

The demographic characteristic of our study was demonstrated in Table 2. The mean age in our study was 77.2 ± 9.0 years ago (range 55–93 years old) with female predominant (57 females, 65.2%). The mean education duration was 6.5 ± 5.2 years (range 0–20 years). The mean body weights was 57.8 ± 10.7 kg (range 41.6–90 kg). The mean BMI was 23.8 ± 4.7 (range 16.5–38.8). The mean GFR was 72.1 ± 29.9 (range 6.5–152). The mean initial MMSE was 15.0 ± 6.9 (range 10–27). The mean CDR-SB was 5.7 ± 3.9 (range 0.5–18).

The Optimal Dose and Time to Optimal Dose

The adjusted dose of each visit, optimal dose and time to optimal dose were demonstrated in Table 3 and Figure 2. The initial mean dose was 2.0 ± 1.4 ml (range 0.25–6 ml) and the initial mode dose was 1 ml (n = 33, 37.9%). The mean dose in 24th week was 3.6 ± 1.4 ml (range 0.5–6 ml) and the mode dose in 24th weeks was 4 ml (n = 31, 35.6%). The mean optimal dose was 3.6 ± 1.4 ml (range 0.5–6 ml) and the mode of optimal dose was 4 ml (n =

**Fig. 3.** The distribution of numbers associated with optimal dose.**Fig. 4.** The distribution of numbers associated with time to optimal dose.

31, 35.6%). The mean duration to optimal dose was 12.5 ± 10.2 weeks (range 0–24 weeks) and the mode of duration to optimal dose was 24 weeks (n = 35, 40.2%). The distributions of numbers in associated with optimal dose and time to optimal dose were demonstrated in Figures 3 and 4. The correlation of demographic variables with dose-related variables was shown in Table 4. The age was

Table 4. Correlation of optimal dose, time to optimal dose and initial dose with demographic variables

Variable		Age	Height	BW	BMI	GFR	Initial MMSE	Final MMSE	Initial CDR-SB	Final CDR-SB
Optimal dose (ml)	r	-0.213*	0.012	0.044	0.019	0.025	0.042	0.095	0.006	0.052
	p	0.048	0.915	0.690	0.867	0.818	0.702	0.430	0.954	0.662
Time to optimal dose (wk)	r	-0.138	0.018	0.017	0.013	0.048	0.064	0.106	-0.059	-0.100
	p	0.204	0.873	0.876	0.909	0.656	0.561	0.379	0.587	0.395
Initial dose (ml)	r	-0.040	-0.081	-0.050	-0.008	-0.038	-0.094	-0.064	0.160	0.203
	p	0.714	0.460	0.655	0.945	0.726	0.390	0.594	0.140	0.082

BW, body weights; BMI, body mass index; GFR, glomerular filtration rate; MMSE, mini-mental state examination; CDR-SB, Clinical Dementia Rating-Sum of Boxes; r, correlation coefficient.

* $p < 0.05$, statistic significant.

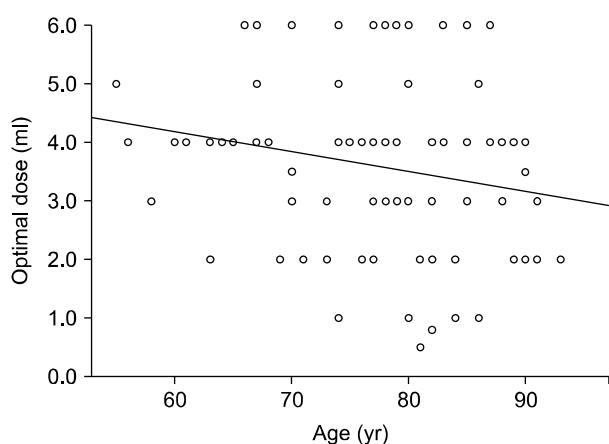


Fig. 5. Correlation of age with optimal dose.
r: -0.213, $p = 0.048$.

negatively correlated with optimal dose ($r = -0.213$, $p = 0.048$) (Fig. 5). Difference of optimal dose, time to optimal dose, and initial dose in sex was shown in Table 5 and it revealed no significant difference.

Efficacy of Rivast[®] (Rivastigmine Oral Solution)

The cognitive function by MMSE and global function by CDR with CDR-SB before and after rivastigmine oral solution therapy was demonstrated in Table 6. The mean initial MMSE was 15.0 ± 6.9 . The mean final MMSE was 14.5 ± 7.8 . There was no significant difference in MMSE before and after rivastigmine oral solution therapy ($p = 0.656$). There were 24 patients (27.6%) with CDR0.5, 45 patients (51.7%) with CDR1 and 18 patients (20.6%) with CDR2. After having rivastigmine oral solution for 52 months, there were 18 patients (20.7%) with CDR0.5, 33 patients (37.9%) with CDR1 and 17 patients (19.5%) with CDR2 and 6 patients (6.9%) with CDR3. There was no significant difference in CDR before and after rivastigmine

Table 5. Difference of optimal dose, time to optimal dose, and initial dose in sex

Variable	Male (n = 30)	Female (n = 57)	p value
Optimal dose (ml)	3.7 ± 1.4	3.5 ± 1.5	0.573
Time to optimal dose (wk)	12.9 ± 9.8	12.2 ± 10.4	0.755
Initial dose (ml)	1.9 ± 1.1	2.1 ± 1.5	0.427

Values are presented as mean \pm standard deviation.

$p < 0.05$, statistic significant.

Table 6. The cognitive function in MMSE, CDR, and CDR-SB in initial visit and after rivastigmine oral solution therapy

Variable	Initial	Final	p value
MMSE	15.0 ± 6.9	14.5 ± 7.8	0.656
CDR	n = 87	n = 74	
CDR0.5	24 (27.6)	18 (20.7)	0.154
CDR1	45 (51.7)	33 (37.9)	
CDR2	18 (20.6)	17 (19.5)	
CDR3	0 (0)	6 (6.9)	
CDR-SB	5.7 ± 3.9	7.1 ± 5.0	0.042*

Values are presented as mean \pm standard deviation or number (%). MMSE, mini-mental state examination; CDR, clinical dementia rating; CDR-SB, Clinical Dementia Rating-Sum of Boxes.

* $p < 0.05$, statistic significant.

oral solution therapy ($p = 0.154$). The mean initial CDR-SB was 5.7 ± 3.9 . The mean final CDR-SB was 7.1 ± 5.0 . There was significant difference in CDR-SB before and after rivastigmine oral solution therapy ($p = 0.042$).

In our study, there were 25% (18 out of 71 with complete MMSE evaluation) patients having cognitive decline in MMSE, 27% (20 out of 73 with complete CDR evaluation) patients having global function decline in CDR and 63% (46 out of 73 with complete CDR-SB evaluation) patients having global function decline in CDR-SB (Table 7–9). The initial dose, optimal dose, and time to optimal dose were not significantly associated with cognitive/global

Table 7. Possible factors associated with cognitive/global function decline by MMSE

Variable	Cognitive decline by MMSE (n = 18)	Cognitive preserved by MMSE (n = 53)	<i>p</i> value
Age (yr)	76.3 ± 9.6	76.6 ± 9.5	0.924
Sex, female	7 (38.9)	37 (69.8)	0.020*
Education (yr)	8.9 ± 6.1	6.4 ± 4.9	0.077
GFR	81.7 ± 31.1	71.9 ± 28.6	0.224
Initial dose (ml)	2.0 ± 0.9	1.7 ± 1.4	0.411
Optimal dose (ml)	3.1 ± 1.3	2.7 ± 1.3	0.221
Time to optimal dose (wk)	5.8 ± 5.4	4.9 ± 4.6	0.508
Initial MMSE	14.5 ± 6.3	16.1 ± 6.8	0.385
Initial CDR-SB	7.4 ± 3.8	4.8 ± 3.7	0.016*

Values are presented as mean ± standard deviation or number (%).

MMSE, mini-mental state examination; CDR, clinical dementia rating; CDR-SB, Clinical Dementia Rating-Sum of Boxes.

**p* < 0.05, statistic significant.

Table 8. Possible factors associated with cognitive/global function decline by CDR

Variable	Global function decline by CDR (n = 20)	Global function preserved by CDR (n = 53)	<i>p</i> value
Age (yr)	79.1 ± 10.2	75.5 ± 9.0	0.181
Sex, female	14 (70.0)	31 (58.5)	0.367
Education (yr)	5.6 ± 5.3	7.4 ± 5.3	0.196
GFR	80.3 ± 28.5	71.4 ± 29.4	0.248
Initial dose (ml)	1.9 ± 1.6	1.8 ± 1.3	0.777
Optimal dose (ml)	3.2 ± 1.5	2.7 ± 1.3	0.215
Time to optimal dose (wk)	4.2 ± 4.6	5.4 ± 4.8	0.328
Initial MMSE	12.1 ± 6.5	16.9 ± 6.3	0.009*
Initial CDR-SB	6.0 ± 3.4	5.4 ± 4.1	0.519

Values are presented as mean ± standard deviation or number (%).

MMSE, mini-mental state examination; CDR, clinical dementia rating; CDR-SB, Clinical Dementia Rating-Sum of Boxes.

**p* < 0.05, statistic significant.

Table 9. Possible factors associated with cognitive/global function decline by CDR-SB

Variable	Global function decline by CDR-SB (n = 46)	Global function preserved by CDR-SB (n = 27)	<i>p</i> value
Age (yr)	78.7 ± 8.8	72.8 ± 9.2	0.008*
Sex, female	28 (60.9)	18 (66.7)	0.769
Education (yr)	7.1 ± 5.6	6.7 ± 4.8	0.737
GFR	75.0 ± 26.6	70.8 ± 33.3	0.548
Initial dose (ml)	1.9 ± 1.3	1.8 ± 1.4	0.820
Optimal dose (ml)	3.5 ± 1.4	3.5 ± 1.4	0.883
Time to optimal dose (wk)	12.3 ± 9.9	14.3 ± 11.0	0.415
Initial MMSE	15.4 ± 6.4	16.0 ± 7.1	0.719
Initial CDR-SB	5.5 ± 3.4	5.7 ± 4.6	0.822

Values are presented as mean ± standard deviation or number (%).

MMSE, mini-mental state examination; CDR, clinical dementia rating; CDR-SB, Clinical Dementia Rating-Sum of Boxes.

**p* < 0.05, statistic significant.

function decline by MMSE, CDR and CDR-SB. Female was associated with less cognitive decline by MMSE (38.9% vs. 69.8%, *p* = 0.02) (Fig. 5). Higher initial CDR-SB was associated with cognitive decline by MMSE

(7.4 ± 3.8 vs. 4.8 ± 3.7, *p* = 0.016) (Table 7). Lower initial MMSE scores was associated with global function decline by CDR (12.1 ± 6.5 vs. 16.9 ± 6.3, *p* = 0.009) (Table 8). Older age was associated with global function decline by

CDR-SB (78.7 ± 8.8 vs. 72.8 ± 9.2 , $p = 0.008$). Initial MMSE and CDR-SB showed no significant difference in determining the global function decline by CDR-SB (Table 9).

DISCUSSION

We demonstrated the real-world clinical experience of rivastigmine oral solution (2 mg/ml) in mild to moderate AD patients in Taiwan. It suggested rivastigmine oral solution 4 ml is the optimal dose with 24 weeks to reach to the optimal dose for at least one third of patients. During the course, 9 patients discontinued the rivastigmine oral solution due to poor compliance or preference. Twelve out of 99 patients (12.1%) reported possible side effects. The overall adherence was 80.6% (87/108) in our study.

This is the first observational study reporting the safety and tolerability of rivastigmine oral solution in mild to moderate AD dementia patients in Asian population. Similar study was conducted in Phoenix, Arizona, USA, comparing the safety and tolerability of novel rivastigmine transdermal patch (a 24-h single application of a 9.5 mg/24-h; 10 cm²; 18 mg dose load) with rivastigmine oral solution (single 3 mg dose) in 30 healthy elderly subjects (MMSE > 27, 13 males, mean 67.7 years old, and mean 73.6 kg in body weights) [16]. Adverse events reported after either patch or oral solution administration were most frequently associated with the gastrointestinal system and nervous system, consistent with the cholinomimetic actions of rivastigmine. The occurrence of gastrointestinal-related adverse events (nausea, vomiting) was lower with the patch (6 subjects, 20%) than with the oral solution (10 subjects, 33%). The occurrence of nervous system-related adverse events (headache and dizziness) was 8 (27%) with the patch and 10 (33%) with the oral treatment. Our study focused on the practicing titrating dose in clinical, showing less reporting adverse events than the previous study. Meanwhile, we concluded that lower optimal dose is considered in AD patients with older age to avoid the possible side events.

There was no difference in cognition function by MMSE and global function decline by CDR before and after rivastigmine oral solution therapy in our study, but it presented 25% with cognitive decline by MMSE, 27% with global function decline by CDR. More than two thirds of patients had cognitive preservation in MMSE or CDR with

rivastigmine oral solution therapy for 1 year. While in CDR-SB, it showed significant change in CDR-SB before and after rivastigmine oral solution therapy and up to 63% of patients with global function decline in CDR-SB. This is because AD is a progressive neurodegenerative disease. MMSE is used extensively in clinical and research settings to measure cognitive impairment as well as cognitive outcomes to cholinesterase inhibitors therapy [24,25]. CDR-SB is a qualitative instrument for assessing the global function and staging the severity of dementia. Studies have adopted this global severity score as therapeutic outcome [26,27]. In spite of the limited case numbers we enrolled in the study, CDR-SB could give a new insight into global function evaluation in AD patients under therapy. In considering the possible risk factors in determining the cognitive/global function decline, we concluded male sex and higher initial CDR-SB are risk factors for cognitive decline by MMSE, lower initial MMSE is the risk factor for global function decline by CDR and older age is the risk factor for global function decline by CDR-SB. Compared to the previous study discussing the efficacy of oral rivastigmine in Taiwan, Chen *et al.* [28] reported 41.3% of AD patients had improvement in cognition by MMSE and 63.5% in global status by CDR-SB. The clinically MMSE improving group had a significantly higher rivastigmine concentration, lower initial MMSE, lower initial CDR-SB scores and presence of APOE $\epsilon 4$ -carriers. Higher education was significantly associated with clinical improvement in global status by CDR-SB. Although therapeutic response rate varies from 20 to 60%, concentrations of rivastigmine may benefit cognitive function of AD patients. In spite of lack rivastigmine concentration in our study, it demonstrated higher proportion of cognitive preservation with rivastigmine oral solution therapy for AD patients, suggesting the oral solution form with the titrating method may benefit in reaching the dose-dependent effect.

Although our study provided the useful information in optimal dose and time to optimal dose of rivastigmine oral solution therapy in real-world practice, there were limitations in our study. Firstly, we did not characterize the plasma pharmacokinetics, bioavailability and metabolite NAP226-90 (inactive pharmacologically) of rivastigmine following oral solution administrations. These profiles might help to understand the fluctuations of the drug concentration in association with the overall tolerability, safety and efficacy. Secondly, Apolipoprotein E gene (ApoE)

was not genotyped in AD patients in our study. Apolipoprotein E4 (ApoE4) is the most prevalent genetic risk factor of AD [29] with its numerous implications in processes of crosstalk with beta-amyloid (A β) and effect on lipid metabolism and inflammation [30-32]. ApoE4 is a promising AD therapeutic target for its role in mediating the processes [33]. Thirdly, we did not enrolled the predictive factors that might have impact on the tolerability, safety and efficacy of rivastigmine in AD patients, such as baseline cardiovascular risk factors, psychological factors, medication, lifestyle, environment [34], diet habit, nutritious status, socio-economic status and family support. Fourthly, we did not enroll the information of behavioral and psychological symptoms of dementia (BPSD). Nearly 90% of AD patients presented with BPSD, leading to independence reduction and incapability of completing daily activities. These might have impacts on medication adherence, tolerability and efficacy [35]. The overall adherence was 80.6% in our study. The frequencies of non-adherence of medication in dementia patients varied considerably across studies in real world [36]. In a cohort study, Stoehr and colleagues [37] concluded the non-adherence rate was 10.7% among cognitive impairment elders aged more than 65 years. The greatest rate of non-adherence was 38% in one prospective cohort study using electronic monitoring [38]. From one case control study, adherence frequencies using 'pill counts' ranged from 17 – 100% among AD patients [39]. The adherence frequencies of oral solution were rarely discussed.

Various neuro-inflammatory processes and cytokines had been proved to have the impact on the pathology of AD [40-42]. Currently, acetylcholinesterase inhibitors are believed to have anti-inflammatory properties [43,44]. Evidences indicated M2b macrophages may have crucial role in improving nerve injuries and brain diseases. The M2b macrophages polarization was gradually used as an inflammatory biomarker in its role of diseases of nervous system and AD [45,46]. Future studies focusing on the macrophage polarization pattern in AD patients with rivastigmine oral solution therapy help to clarify the anti-inflammatory properties of acetylcholinesterase inhibitors and promote the evaluation of therapeutic efficacy more precisely.

The response of rivastigmine to cognitive domains in AD patients, such as memory, language, attention or executive function, vary with study design and the effects re-

main inconclusive [47-49]. It needs further investigations about the efficacy of rivastigmine oral solution in various cognitive domains. In consideration of treating AD, BPSD is an important issue. BPSD lead to poor outcomes, distress among patients and caregivers, earlier placement in nursing homes, long-term hospitalization, misuse of medication, and increased health care costs [35,50]. Whether the oral solution benefits more than the conventional oral capsule in management of BPSD requires further evaluation. Current treatment strategy in AD involves multiple approaches combining pharmacological and non-pharmacological intervention. Making maintenance and establishment of a strong therapeutic alliance to physician, patient, and caregiver is crucial [51]. Accordingly, rivastigmine oral solution in combination with non-pharmacological intervention is encouraging to enhance its efficacy in cognitive improvement and functional abilities.

We demonstrated the clinical experience of rivastigmine oral solution in AD patients. It suggested rivastigmine oral solution 4 ml is the optimal dose with 24 weeks to the optimal dose for at least one third of patients. This study predicts that adjusting treatment dose with rivastigmine oral solution can improve the patient's and caregiver's compliance and decrease medical discontinuation rate.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization: Wenfu Wang. Data acquisition: Jui-Cheng Chen, Nai-Ching Chen, Kai-Ming Jhang. Formal analysis: Yuan-Han Yang. Supervision: Wenfu Wang, Yuan-Han Yang. Writing – original draft, review & editing: Sun-Wung Hsieh.

■ ORCID

Sun-Wung Hsieh	https://orcid.org/0000-0003-3952-7718
Jui-Cheng Chen	https://orcid.org/0000-0003-3987-4816
Nai-Ching Chen	https://orcid.org/0000-0003-2684-0377
Kai-Ming Jhang	https://orcid.org/0000-0001-9525-9944
Wenfu Wang	https://orcid.org/0000-0002-3963-1649
Yuan-Han Yang	https://orcid.org/0000-0002-1699-4842

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