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Original Article

Safety and efficacy of rivastigmine and memantine combined for treatment of patients with Alzheimer's disease: a retrospective study

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Abstract: Objective: To assess the effects and safety of combining rivastigmine hydrogen tartrate capsules with memantine tablets for Alzheimer's disease (AD). Methods: A retrospective study was conducted on AD patients admitted to The Third People's Hospital of Yongkang from November 2021 to June 2023. There were two groups: a single drug group (n=21) given only memantine tablets, and a combination group (n=39) treated with both rivastigmine hydrogen tartrate capsules and memantine tablets. Data were collected, including age, gender, education, overall response rate, adverse reaction rate, mini-mental state examination (MMSE), activity of daily living (ADL), behavioral pathology in Alzheimer's disease scale (BEHAVE-AD), serum tumor necrosis factor-α (TNF-α), serum interleukin-6 (IL-6) and serum Tau at baseline and at week 12. Results: In both groups, compared to baseline, at week 12, MMSE increased, while ADL, BEHAVE-AD, serum TNF-α, IL-6, and Tau decreased (all $P<0.05$). After treatment, compared with the single drug group at week 12, the combination group had a higher MMSE ($t=2.519$, $P=0.015$), better effectiveness ($\chi^2=4.331$, $P=0.037$), and lower ADL ($t=2.418$, $P=0.019$), BEHAVE-AD ($t=3.231$, $P=0.002$), TNF-α ($t=3.496$, $P=0.001$), IL-6 ($t=2.513$, $P=0.015$) and Tau ($t=2.290$, $P=0.026$) levels. Conclusion: The combination of the two drugs was more effective in alleviating AD symptoms with comparable safety. It also showed an edge in suppressing pro-inflammatory cytokines and Tau in AD.

Keywords: Alzheimer's disease, rivastigmine, memantine, effectiveness and safety

Introduction

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease among the elderly, characterized by Tau aggregate deposition and synapse loss [1-3]. It impairs various brain functions, including memory, comprehension, language, attention, and judgment [4]. AD is progressive, typically advancing from mild cognitive impairment to dementia [5, 6]. Currently, nearly 50 million people are affected by AD, and it is projected that the global prevalence could triple by 2050 [7, 8]. Notably, from 1990 to 2019, both the incidence and mortality of AD exhibited an upward trend, imposing a substantial burden on society and individuals [9]. Despite advancements in AD prevention and mitigation, effective treatments remain scarce [10]. Hence, exploring efficacious therapies remains a key focus in AD research.

The N-Methyl D-aspartate (NMDA) receptor is involved in synaptic transmission and plasticity by mediating Ca^{2+} influx into neurons [11]. In AD pathology, alterations in NMDA receptor activation leads to synaptic loss and cognitive impairment [12]. Memantine, an approved partial NMDA antagonist for AD treatment, can block the NMDA receptor and prevent Ca^{2+} accumulation in neurons. Growing evidence supports its neuroprotective role in AD. In AD mouse models, memantine can suppress AD-like behaviors by modulating amyloid precursor protein and presenilin 2. It can also curtail mitochondrial reactive oxygen species in microglia via regulating Ca^{2+} influx, thereby alleviating microglia-related neuroinflammation and neuronal death [13]. Prophylactic use of memantine has been shown to enhance cognitive and behavioral functions in AD patients [14, 15]. Thus, memantine plays a central therapeutic role in clinical AD management.

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Interestingly, the combination of oral memantine and cholinesterase inhibitors has demonstrated excellent efficacy and tolerability in mild to severe AD. Rivastigmine, a cholinesterase inhibitor, inactivates acetylcholinesterase and butyrylcholinesterase, which are crucial in AD pathogenesis [16]. Moreover, it can upregulate α-secretase, interrupting the production of toxic Aβ in AD [17]. A 12-week pilot study indicated that the combination of rivastigmine and memantine led to significant reductions in the Alzheimer's disease assessment scale-cognitive section (ADAS-cog) and mini-mental state examination (MMSE) scores of AD patients [18]. A meta-analysis concluded that the combination of memantine and rivastigmine conferred an advantage over monotherapy in improving the mental status of AD patients [19]. Overall, the combination of rivastigmine and memantine holds promise for AD treatment.

Nevertheless, while prior studies have established the general effectiveness of the combined rivastigmine and memantine therapy, certain aspects remain unaddressed. Notably, the impact of this combination on inflammatory biomarkers such as TNF-α and IL-6 and its correlation with cognitive outcomes have not been thoroughly elucidated. Additionally, real-world evidence of its efficacy in Chinese populations is limited. Therefore, our study aimed to fill these knowledge gaps by evaluating the effectiveness and safety of the combination of rivastigmine hydrogen tartrate capsules and memantine tablets in AD. We assessed changes in overall response rate, adverse reaction occurrence rate, MMSE, activity of daily living (ADL), behavioral pathology in Alzheimer's disease scale (BEHAVE-AD), serum tumor necrosis factor-α (TNF-α), serum interleukin-6 (IL-6) and serum Tau.

Materials and methods

Study design

This retrospective study analyzed data from AD patients admitted to The Third People's Hospital of Yongkang during the period from November 2021 to June 2023. Serum TNF-α and IL-6 measurements were collected as part of the hospital's research project during the initial patient assessment, with proper patient consent obtained. The study comprised two groups: a single drug group, where patients received only memantine tablets, and a combination group, in which patients were administered a combination of rivastigmine hydrogen tartrate capsules and memantine tablets.

Inclusion criteria were as follows: Patients had to be diagnosed with AD according to the DSM-5 and National Institute on Aging-Alzheimer's Association (NIA-AA) guidelines. Disease severity was categorized as mild (MMSE score 21-26, with mild memory loss), moderate (MMSE score 10-20, with significant memory impairment), or severe (MMSE score <10, with severe cognitive decline). Patients were required to be aged between 55 and 95 years old. Complete documentation was mandatory, including: baseline assessments (comprehensive neurological examination, cognitive scores of MMSE, ADL, and BEHAVE-AD, serum TNF-α, IL-6, and Tau levels), treatment records (medication prescriptions, compliance documentation, adverse event monitoring), and 12-week follow-up data (cognitive reassessment, laboratory tests, adverse events documentation). Only patients who completed the prescribed treatment regimen and all necessary evaluations were included.

Exclusion criteria were applied to rule out patients who had participated in other studies prior to this one, those suffering from other neurologic or psychiatric illnesses, patients with infections, cerebral infarctions, or brain tumors. Initially, 392 AD patients were screened for eligibility. Among them, 267 patients were excluded based on the following reasons: not meeting AD diagnostic criteria (n=82), presence of other neurologic or psychiatric illnesses (n=45), active infection (n=38), having had a cerebral infarction within 6 months (n=35), brain tumor (n=22), participation in other clinical studies (n=25), and incomplete baseline data (n=20). Of the remaining 125 cases, 65 were further excluded due to: loss to follow-up at week 12 (n=25), withdrawal of consent (n=20), and incomplete outcome evaluations (n=20). The final analysis included 60 patients, with 21 cases in the single drug group and 39 cases in the combination group (**Figure 1**).

Ethics statement

The retrospective analysis was approved by the Ethics Committee of The Third People's Hospital of Yongkang.

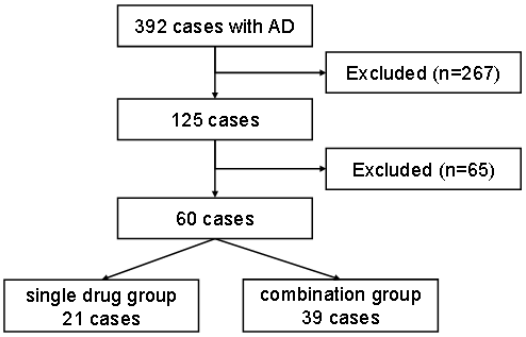

Figure 1. Flow chart. Note: AD, Alzheimer's disease.

Data extraction

By querying electronic medical records, data on patients' age, gender, education, overall response rate, adverse reaction rate, MMSE, ADL, behavioral pathology in Alzheimer's disease scale (BEHAVE-AD), TNF-α, IL-6 and serum Tau at baseline (pre-hospitalization) and at the 12-week visit after diagnosis and treatment were collected.

Outcome measures

Major outcome: (1) A comparison was made in terms of the treatment outcomes between the single drug group and combination group were compared. (2) The adverse reactions in both groups, including headache, dizziness, limb swelling, sleep disorders, limb tremors, and depressed mood, were compared.

Secondary outcome: (1) TNF-α and IL-6 levels at baseline and 12 weeks after treatment were compared between the single drug and combination groups. (2) Serum Tau levels at baseline and 12 weeks after treatment were contrasted between the two groups. (3) The BEHAVE-AD scores of patients in both groups at baseline and 12 weeks after treatment were evaluated and compared. (4) MMSE and ADL scores between the single drug and combination groups at baseline and 12 weeks after treatment were also compared.

Statistical analysis

Statistical analysis was carried out using SPSS 23.0 software. Measurement data were presented as mean ± SD, and enumeration data as n (%). Enumeration data were analyzed with the Chi-square test. For between-group comparisons of measurement data, the independent sample t-test was employed. For intra-group before-after comparisons of measurement data, the paired sample t test was used. All statistical analyses were two-sided tests, and a significant change was considered when $P<0.05$.

Results

Comparison of baseline data

As shown in **Table 1**, there were no statistically significant differences in baseline age ($t=0.644$, $P=0.522$), gender distribution ($\chi^2=0.110$, $P=0.740$), education level ($\chi^2=0.691$, $P=0.708$), MMSE scores ($t=1.363$, $P=0.178$), ADL scores ($t=0.684$, $P=0.497$), BEHAVE-AD scores ($t=0.297$, $P=0.768$), serum TNF-α levels ($t=0.153$, $P=0.878$), serum IL-6 levels ($t=0.889$, $P=0.378$) and serum Tau levels ($t=1.263$, $P=0.212$) between the two groups.

Comparison of treatment outcomes between the single drug and combination group

As presented in **Table 2**, in the single drug group, 5 cases had a markedly effective treatment outcome, 7 were effective, and 9 were ineffective. In the combination group, 14 cases were markedly effective, 18 were effective, and 7 were ineffective. There was a significant difference in treatment effectiveness between the two groups (single drug group vs combination group: 57.14% vs 82.05%, $\chi^2=4.331$, $P=0.037$).

Comparison of safety analysis

In the single drug group, 1 patient had a headache and 1 had a sleep disorder. In the combination group, 1 patient had a headache, 1 had dizziness, and 1 had limb tremors. There was no statistically significant difference in the adverse reaction rate between the two groups ($\chi^2=0.060$, $P=0.807$) (**Table 3**).

Comparison of MMSE and ADL

Figure 2 depicts the MMSE and ADL values in both groups at baseline and 12 weeks after treatment. In comparison to the baseline, the MMSE scores at week 12 post-treatment exhib-

Table 1. Baseline of patients with AD in the single drug and combination group

	Single drug group (n=21)	Combination group (n=39)	χ^2/t	P
Age	67.81±7.50	69.26±8.68	0.644	0.522
Gender			0.110	0.740
Male	9 (42.86)	15 (38.46)		
Female	12 (57.14)	24 (61.54)		
Education			0.691	0.708
Primary school and below	29 (48.33)	31 (51.67)		
Middle school	19 (31.67)	15 (25.00)		
Over middle school	12 (20.00)	14 (23.33)		
MMSE	13.62±3.15	12.46±3.13	1.363	0.178
ADL	29.67±3.97	28.97±3.62	0.684	0.497
BEHAVE-AD	16.24±3.37	16.51±3.45	0.297	0.768
Serum TNF-α	7.10±1.03	7.02±0.98	0.153	0.878
Serum IL-6	147.52±12.69	143.90±16.14	0.889	0.378
Serum Tau	215.25±15.93	219.83±11.85	1.263	0.212

Note: AD, Alzheimer's Disease; MMSE, Mini-Mental State Examination; ADL, Activities of Daily Living; BEHAVE-AD, Behavioral Pathology in Alzheimer's Disease Rating Scale.

Table 2. The treatment outcomes in patients with AD between the single drug and combination group

	Single drug group (n=21)	Combination group (n=39)	χ^2	P
Markedly effective	5 (23.81)	14 (35.90)	1.138	0.286
Effective	7 (33.33)	18 (46.15)	0.923	0.337
Ineffective	9 (42.86)	7 (17.95)	4.331	0.037
Effectiveness	12 (57.14)	32 (82.05)	4.331	0.037

Note: AD, Alzheimer's Disease.

Table 3. The adverse events in patients with AD between the single drug and combination group

	Single drug group (n=21)	Combination group (n=39)	χ^2	P
Headache	1 (4.76)	1 (2.56)	0.205	0.651
Dizziness	0 (0.00)	1 (2.56)	0.522	0.470
Swollen limbs	0 (0.00)	0 (0.00)	-	-
Sleep disorder	1 (4.76)	0 (0.00)	1.889	0.169
Tremors in limbs	0 (0.00)	1 (2.56)	0.547	0.459
Depressed mood	0 (0.00)	0 (0.00)	-	-
In total	2 (9.52)	3 (7.69)	0.060	0.807

Note: AD, Alzheimer's Disease.

ited a significant increase in both the single drug group (t=3.875, P=0.001) and the combination group (t=9.626, P=0.000). Concurrently, the ADL scores at week 12 of treatment demonstrated a significant decrease in both groups (single drug group: t=5.430, P=0.000; combination group: t=9.928, P=0.000). At week 12 after treatment, the combination group displayed a higher MMSE score (t=2.519, P=0.015) and a lower ADL score (t=2.418, P=0.019) when contrasted with the single drug group.

Comparison of BEHAVE-AD

As illustrated in **Figure 3**, the BEHAVE-AD scores at week 12 were lower than those at baseline in both the single drug (t=4.393, P=0.000) and combination (t=8.827, P=0.000) groups. After 12 weeks of treatment, the

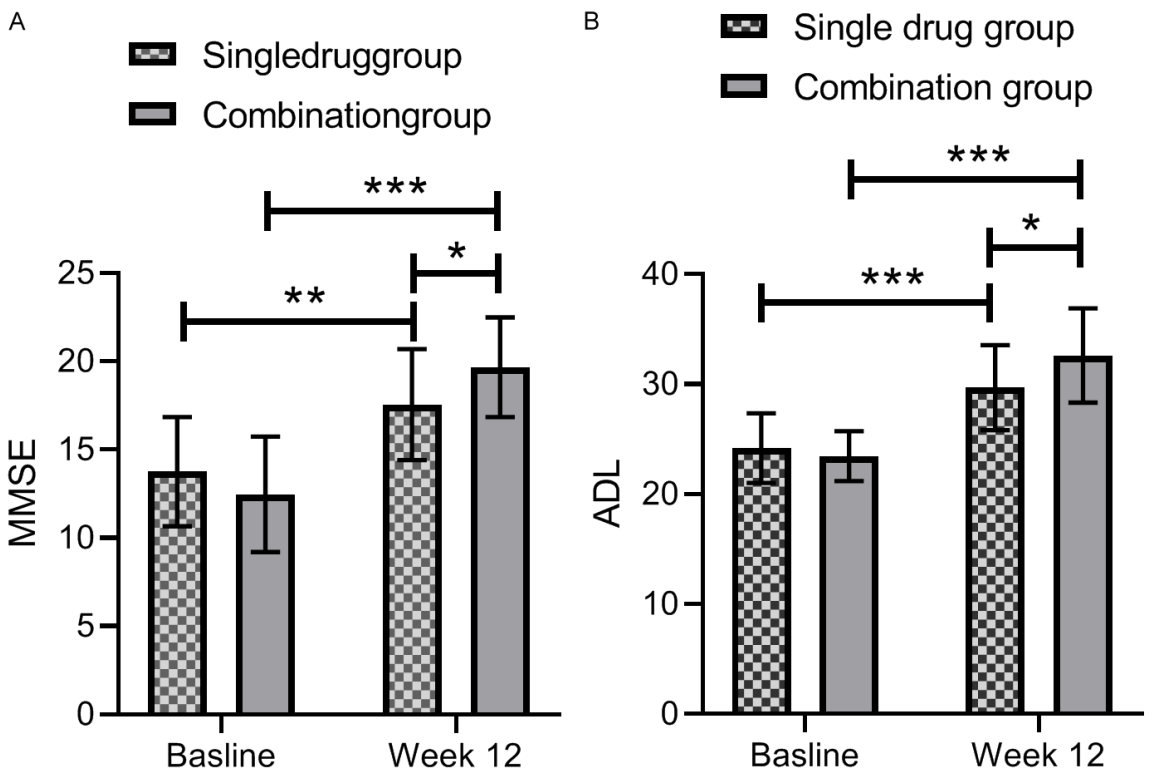

Figure 2. Comparison of MMSE and ADL of patients in the single drug and combination groups at baseline and week 12 after treatment. A: MMSE of patients in the single drug and combination group at baseline and week 12 after treatment; B: ADL of patients in the single drug and combination group at baseline and week 12 after treatment; *P<0.05, **P<0.01, ***P<0.001. Note: MMSE, Mini-Mental State Examination; ADL, Activities of Daily Living.

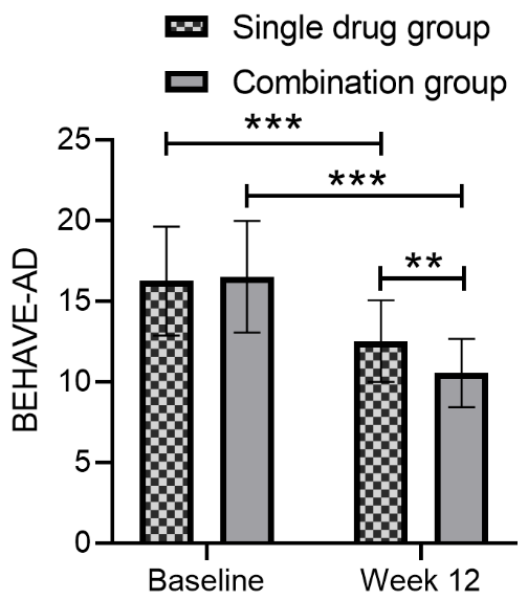

Figure 3. Comparison of BEHAVE-AD between the single drug and combination groups at baseline and week 12 after treatment (**P<0.01, ***P<0.001). Note: BEHAVE-AD, Behavioral Pathology in Alzheimer's Disease Rating Scale.

BEHAVE-AD score in the combination group was further reduced compared to that in the single drug group (t=3.231, P=0.002).

Comparison of serum Tau between the single drug and combination group

As shown in **Figure 4**, the serum Tau level at week 12 was lower than that at baseline in both the single drug (t=5.940, P=0.000) and combination (t=15.273, P=0.000) groups. At week 12 after treatment, the serum Tau level in the combination group was also lower than that in the single drug group (t=2.290, P=0.026).

Comparison of TNF-α and IL-6

Compared to the baseline levels of TNF-α and IL-6, both TNF-α (t=5.057, P=0.000; t=8.855, P=0.000) and IL-6 (t=2.345, P=0.029; t=4.067, P=0.000) levels at week 12 after treatment were significantly reduced in both groups (**Figure 4**). At week 12, the TNF-α (t=3.496, P=0.001) and IL-6 (t=2.513, P=0.015) levels in

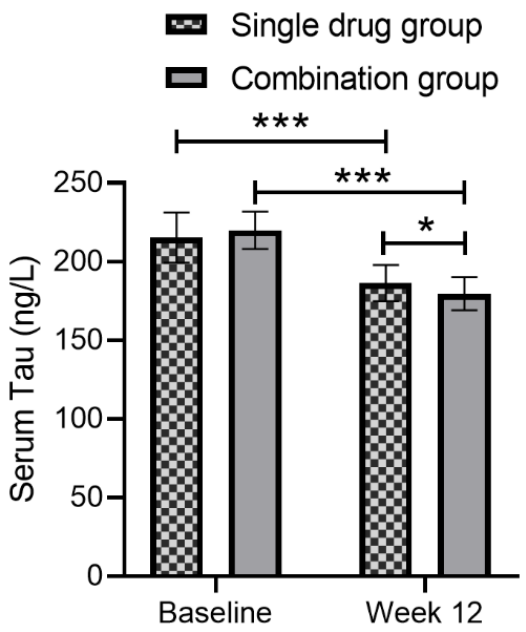

Figure 4. Comparison of serum Tau between the single drug and combination groups at baseline and week 12 after treatment (*P<0.05, ***P<0.001).

the combination group were lower than those in the single drug group (**Figure 5**).

Discussion

Memantine has been recognized as a beneficial drug with potential in AD treatment. It functions as an excitatory amino acid receptor antagonist and is utilized for the treatment of moderately severe to severe Alzheimer's type dementia. Recent investigations have also attested to its efficacy in mild to severe AD. However, the sole administration of memantine might be insufficient to rectify the complex neurotransmitter dysfunction in AD [20]. Advances in the combination of memantine and rivastigmine have been noted in AD treatment [21]. Yanev et al. demonstrated that the combination of memantine and rivastigmine enhanced the learning and memory functions in mice with cognitive impairment [22]. A 26-week prospective trial established that the combination of memantine and rivastigmine was both safe and tolerable in patients with moderate AD [23]. In line with these prior studies, we have shown that the combination of rivastigmine hydrogen tartrate capsules and memantine tablets ameliorated the symptoms of AD patients.

Multiple clinical studies support our findings regarding the augmented efficacy of combination therapy. A meta-analysis by Chen et al. examined the treatment effects of monotherapy versus combination therapy and discovered that patients receiving donepezil in combination with memantine exhibited significant improvements in cognitive functions, behavioral and psychological symptoms in dementia, and global functions compared to those receiving donepezil alone [24]. These results are particularly noteworthy as they display consistency across multiple outcome measures. Additionally, a comprehensive review by Kabir et al. underlined that combination therapy is more efficacious than monotherapy, especially when initiated early in the disease course. They pointed out that since AD pathogenesis is multifactorial, a multimodal therapeutic intervention targeting several molecular entities appears to be the most pragmatic approach to modify disease progression [25]. This observation concurs with the current understanding of AD as a complex ailment necessitating multifaceted treatment strategies. The enhanced effectiveness of the combination administration in our study, compared to single administration, aligns with previous findings and suggests that the combination of rivastigmine tartrate capsules and memantine tablets could be a more judicious choice in AD therapy.

The synergistic effect of combination therapy can be elucidated by their complementary mechanisms of action. Memantine modulates glutamatergic transmission via NMDA receptor regulation, while rivastigmine boosts cholinergic function by inhibiting both acetylcholinesterase and butyrylcholinesterase. Given the intricate nature of AD pathophysiology, this dual mechanism holds particular significance. Recent research has centered on devising diverse therapeutic approaches that target different pathological processes in AD [25]. The combination approach is potentially highly beneficial as it concurrently tackles multiple facets of the disease process. Martinez et al. have emphasized the importance of targeting specific pathways in AD treatment, with a particular focus on developing disease-modifying therapeutic agents [26]. Their work implies that the most efficacious treatments will likely be those capable of addressing multiple pathological

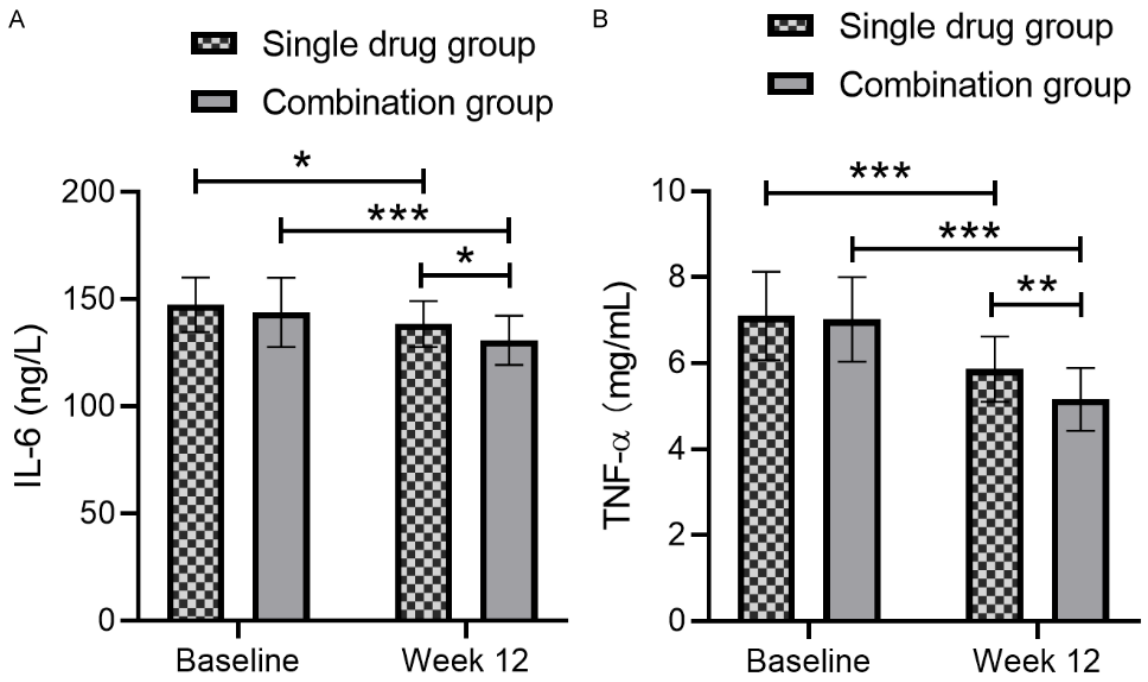

Figure 5. Comparison of TNF-α and IL-6 between the single drug and combination groups at baseline and week 12 after treatment. A: Serum IL-6 in the single drug and combination group at baseline and week 12 after treatment; B: Serum TNF-α in the single drug and combination group at baseline and week 12 after treatment; *P<0.05, **P<0.01, ***P<0.001.

processes simultaneously. Notably, despite the dual mechanism, the combination administration in our study exhibited a similar occurrence rate of adverse reactions to that of the single administration. This indicates that the combination approach has comparable safety to single-drug treatment, which is especially crucial for elderly patients who are more prone to adverse drug reactions.

Tau accumulation is a hallmark of AD. In AD, the pathological state leads to the formation of paired neurofibrillary tangles by tau aggregates, contributing to synaptic loss and neuronal death [27]. Elevated serum Tau levels have been detected in AD patients [28-30], suggesting that serum Tau can serve as a biomarker for AD progression. Understanding the connection between Tau pathology and clinical symptoms has become progressively more critical in AD research. Moreover, AD is accompanied by inflammation, characterized by increased pro-inflammatory cytokines and inflammasome activation [31, 32]. This inflammatory aspect represents a key component of AD pathogenesis and could be a target for therapeutic interventions. Serum TNF-α has been associated with apathy symptoms and cognitive impairment in AD patients [33]. The DELCODE study concluded that serum IL-6 was negatively correlated with structural measures of Braak regions in AD patients [34]. These findings underscore the crucial roles of inflammatory markers as both therapeutic targets and potential biomarkers. Recent neuroimaging studies have further revealed that elevated inflammatory markers correlate with accelerated brain atrophy and faster cognitive decline [35]. This correlation indicates that controlling inflammation might be vital for decelerating disease progression. Evidently, TNF-α and IL-6 in the serum also function as potential biomarkers for AD progression.

Consequently, we were equally intrigued by the impact of the combined medication on Tau, TNF α and IL-6. We observed that Tau, TNF-α and IL-6 levels in the serum were significantly decreased in both groups. Furthermore, compared to the single drug group at week 12 after treatment, the combination group demonstrated greater reductions in serum Tau, TNF-α, and IL-6. The changes in Tau and the cytokines suggest a potential intervention effect of the two

therapy strategies beyond symptom management. This finding is especially significant as it suggests that combination therapy might possess disease-modifying effects in addition to symptom relief. Importantly, compared to single administration, the combination administration exhibited an advantage in suppressing the pro-inflammatory cytokines and Tau in AD. This superior impact on multiple pathological markers indicates a broader therapeutic reach. Additionally, the alterations in Tau, TNF-α and IL-6 hint at their potential value for evaluating the treatment effectiveness of the combination of rivastigmine tartrate capsules. These biomarkers could potentially serve as objective gauges of treatment response in future clinical practice.

The limitations of this study are as follows: Firstly, it is a single-center study, which likely led to a restricted sample size. Secondly, the short study duration potentially restricted the comprehensive evaluation of the effectiveness and safety of the combination administration in AD. Thirdly, the findings from this retrospective study necessitate validation by a subsequent prospective study. Fourthly, the absence of standardized protocols for biomarker measurements might have introduced variability into our results. Fifthly, the potential confounding effects of comorbidities and concomitant medications were not fully accounted for in our analysis. Moreover, due to the retrospective nature of the study, some potential confounding factors might not have been adequately controlled, and the selection of patients for combination therapy versus monotherapy might have been influenced by clinical factors that were not captured in our analysis.

In summary, we established that the combination of rivastigmine hydrogen tartrate capsules and memantine tablets was more effective in alleviating AD symptoms and had comparable safety for AD patients. Significantly, we discovered that, compared to the single administration of memantine tablets, the combination of rivastigmine hydrogen tartrate capsules and memantine tablets demonstrated an edge in inhibiting the pro-inflammatory cytokines and Tau in AD patients. These findings add to the mounting evidence supporting combination therapy as a promising avenue for AD treatment.

Disclosure of conflict of interest

None.

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