

# Efficacy and safety of sodium oligomannate in the treatment of Alzheimer's disease

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**Abstract:** To evaluate the efficacy and safety of sodium oligomannate in the treatment of Alzheimer's disease. Patients with mild-to-moderate AD were randomly divided into three groups, the scores of ADAS-Cog, ADL, CIBIC-plus, NPI and CSDD were evaluated at the 0<sup>th</sup>, 12<sup>th</sup>, 24<sup>th</sup>, 36<sup>th</sup> and 48<sup>th</sup> weeks of medication. Comparing the mean scores of each scale in each cycle of each group. Using SPSS21.0 software for measurement data using t test, Chi-square test was used for counting data. A total of 72 patients with AD were included. The difference of CIBIC-plus score at week 12(P=0.007) and 24(P=0.005), ADAS-Cog scores (P=0.01) at week 24 in GV-971 group was statistically significant compared with that in the control group. The CIBIC-plus score at week 24(P=0.01) and week 48 (P=0.04), CSDD scores at week 48(P=0.02) of GV-971 group was statistically significant compared with that of donepezil group. There were 2 cases of adverse reaction of increased stool frequency in GV-971 (5.67%), and 2 cases of adverse reaction of nausea in donepezil group (8.33%), the difference was statistically significant. GV-971 is as effective as donepezil in the treatment of Alzheimer's disease, and may even be better. It has good safety.

**Keywords:** Alzheimer's disease, donepezil, GV-971, sodium oligomannate.

## INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease, Main clinical features include memory impairment, aphasia, apraxia, agnosia, visual spatial ability impairment, abstract thinking and calculation impairment, personality and behavior changes (Jia J.P. *et al.*, 2018). AD is the most common disease that causes loss of the ability to perform daily activities in the elderly and is the fifth leading cause of death in the elderly. AD not only brings great pain to patients, but also brings heavy spiritual and economic burden as well as medical and nursing burden to families and society. Globally, the incidence of AD doubles every five years among people over 65 years old; As the average age of the population increases, the number of AD cases is expected to more than triple. By 2050, there will be 115 million AD patients (Lancet, 2014). Society's direct spending on Alzheimer's is second only to cancer treatment. In the United States alone, it is estimated that \$172 billion is spent annually on health care for AD (Reitz *et al.*, 2014). With the development of health care and the improvement of people's living conditions and health awareness, the increase of life expectancy will lead to the increase of AD prevalence rate (Imtiaz *et al.*, 2018). Therefore, AD has become a major issue affecting global public health and social sustainable development (Jia *et al.*, 2018).

The pathogenesis of AD is not yet clear. According to the prevailing amyloid hypothesis, the abnormal deposition of A $\beta$  protein due to the imbalance between the production of A $\beta$  protein and the clearance of A $\beta$  protein is the main

pathogenesis of the sequential cleavage of the amyloid precursor protein by the  $\beta$  and  $\gamma$  secretases enzymes in the brain (Lane *et al.*, 2018).

For AD, there is no effective treatment at present, high quality of meta analysis (Cui *et al.*, 2019) shows that, donepezil is effective in improving the light moderately severe cognitive dysfunction in patients with AD, it is better than that of other dementia drugs (memantine, huperzine A, galantamine, etc.), Has failed to prevent the continued progress of AD patients. A new drug, sodium oligomannate (GV-971) (Meiyu Gen, 2017), developed in Shanghai Institute of Materia Medica, Chinese Academy of Sciences in 2019, can inhibit A $\beta$  aggregation and promote the depolymerization of A $\beta$  that has been aggregated, while inhibiting the neurotoxicity of A $\beta$ . To improve and perhaps even reverse cognitive function in patients with AD. This study selected patients with mild-to-moderate AD, Who were living longterm in Fujian Putian and visited the hospital from July 2019 to December 2020. The aim of this study was to provide an alternate treatment option for clinically treating AD.

## MATERIALS AND METHODS

### General information

Followed up AD patient who visited our hospital from in July 2019 to December 2020 took sodium oligomannate (GV-971, manufacturers: Green Valley Pharmaceutical Co. Ltd., approval number: H20190031, specification: 150mg/tablet), or donepezil (Eisai (China) Pharmaceutical Co. Ltd., approval number: H20050978, specifications: 5 mg/tablet) or placebo pills made of starch. 72 cases of patients with Alzheimer's disease diagnosis were included

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in the study, all the three groups will be evaluated for their efficacy and safety. (1) Inclusion criteria: 1) Male or female, age >18 years old; 2) Meet the AD diagnostic criteria of National Stroke Institute for Neurological Speech Disorders (NINCDS-ADRDA) (Dubois *et al.*, 2007) ;3) Mild to moderate cognitive impairment ( $10 \leq$  MMSE score < 27).(2) Exclusion criteria: 1)Patients with severe physical diseases; 2) Patients with mental illness; 3) Complicated with meningitis or other brain organic lesions or braintraumatism; 4) Patients with severe infection or immune system diseases;5)Allergic or intolerant to the drugs used in this study.

### **Methods**

This study was a prospective study. The subjects were divided into 3 groups by computer random number method, and the patient data were sealed in an opaque envelope. Neither the researchers nor the subjects were clear about the grouping information. GV-971 group received sodium oligomannate 450mg bid, donepezil group received donepezil 5mg qd, and placebo group received starch tablet 1 pill qd, it was recommended for at least 48 weeks. This study was approved by the ethics committee of the hospital and all patients and their families agreed and signed the informed consent.

### **Observation Indicators**

Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) (Rosen *et al.*, 1984), Activities of Daily Living (ADL) (Collin *et al.*, 1988), Clinician's Interview-based Impression of Change Plus Caregiver Input (CIBIC-Plus) (Boothby *et al.*, 1995), Neuropsychiatric Inventory (NPI) (Cummings *et al.*, 1994) and Cornell Scale for Depression in Dementia (CSDD) (Alexopoulos *et al.*, 1988) were selected as the main observation indicators. The main outcome indicators were the scores of patients (ADAS-Cog, ADL, CIBIC-plus, NPI and CSDD score) at week 0, 12, 24, 36 and 48 of the treatment cycle for each group, and the scores of each scale in each period were recorded for each patient. The scale was evaluated by the same person from beginning to end.

### **STATISTICAL ANALYSIS**

SPSS 21.0 software was used for statistical analysis of the obtained data. Continuous variables in line with normal distribution were represented by mean  $\pm$ SD, and those not in line with normal distribution were represented by median (range). T-test was used for comparison. Categorical variables were represented by frequency and % and  $\chi^2$  test was used for comparison.  $P < 0.05$  was considered statistically significant.

### **RESULTS**

#### **General data**

A total of 72 AD patients who met the inclusion criteria were included, including 36 males and 36 females.

Among them, 36 patients took sodium oligomannate, including 16 males and 20 females. Their ages ranged from 62 to 74 years old, with an average age of  $67.67 \pm 4.92$  years old. 24 patients were treated with donepezil, including 16 males and 8 females. Their age ranged from 64 to 76 years, with an average age of  $70 \pm 6$  years. 12 patients, including 4 male and 8 females, took placebo. Their ages ranged from 54 to 72 years old, with a mean age of  $64.33 \pm 7.59$  years old. There were not statistically significant in age, MMSE, ADAS-Cog, ADL, CIBIC-plus, NPI and CSDD scores between each group ( $P > 0.05$ )(table 1).

### **Outcomes**

#### **GV-971 group vs Placebo group**

GV-971 vs placebo-12w By comparing the changes of scores from baseline between the GV-971 group and the placebo group at the 12<sup>th</sup> week of treatment, there were no statistically significant differences in ADAS-Cog score ( $P=0.74$ ), ADL score ( $P=0.54$ ), NPI score ( $P=0.14$ ), and CSDD score ( $P=0.79$ ). There was a significant difference in CIBIC-plus score ( $P=0.007$ ).

GV971 vs placebo-24w By comparing the changes of scores from baseline between the GV971 group and the placebo group at the 24<sup>th</sup> week of treatment, there were no statistically significant differences in ADL score ( $P=0.22$ ), NPI score ( $P=0.10$ ) and CSDD score ( $P=0.36$ ). There were significant differences in ADAS-Cog score ( $P=0.01$ ) and CIBIC-plus score ( $P=0.005$ ).

GV-971 vs placebo-36w By comparing the changes of scores from baseline between the GV-971 group and the control group at the 36<sup>th</sup> week of treatment, there was no statistical significance in ADAS-Cog score ( $P=0.12$ ), ADL score ( $P=0.50$ ), CIBIC-plus score ( $P=0.42$ ), NPI score ( $P=0.07$ ) and CSDD score ( $P=0.27$ ) at the 36<sup>th</sup> week of treatment.

GV-971 vs placebo-48w By comparing the changes of scores from baseline between the GV-971 group and the placebo group at the 48<sup>th</sup> week of treatment, there were statistically significant differences in ADAS-Cog score ( $P=0.01$ ) and CIBIC-plus score ( $P=0.05$ ), while there were no statistically significant differences in ADL score ( $P=0.27$ ), NPI score ( $P=0.14$ ), and CSDD score ( $P=0.36$ ).

#### **GV-971 group vs Donepezil group**

GV-971 vs donepezil-12w By comparing the changes of scores from baseline between the GV-971 group and donepezil group at the 12<sup>th</sup> week of treatment, there were no statistically significant differences in ADAS-Cog score ( $P=0.98$ ), ADL score ( $P=0.20$ ), CIBIC-plus score ( $P=0.408$ ), NPI score ( $P=0.22$ ) and CSDD score ( $P=0.81$ ).

GV-971 vs donepezil-24w By comparing the changes of scores from baseline between the GV-971 group and the

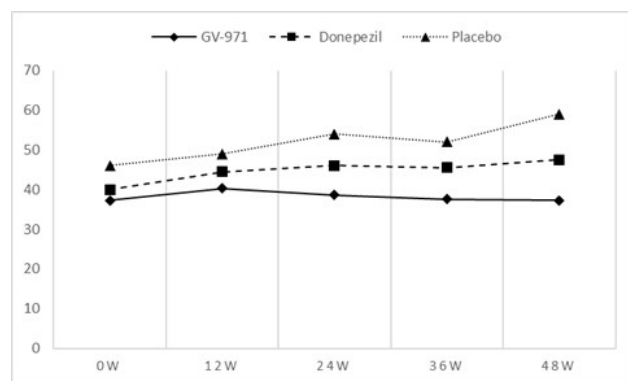
donepezil group at the 24<sup>th</sup> week of treatment, there were no statistically significant differences in ADAS-Cog score (P=0.29), ADL score (P=0.56), NPI score (P=0.13) and CSDD score (P=0.16). There was significant difference in CIBIC-plus score (P=0.01).

GV-971 vs donepezil-36w By comparing the changes of scores from baseline between the GV-971 group and the donepezil group at the 36<sup>th</sup> week of treatment, there were no statistically significant differences in ADAS-Cog score (P=0.35), ADL score (P=0.47), CIBIC-plus score (P=0.25), NPI score (P=0.32) and CSDD score (P=0.21).

GV-971 vs donepezil group-48w By comparing the changes of scores from baseline between the GV-971 group and the donepezil group at the 48<sup>th</sup> week of treatment, there were no statistically significant differences in ADAS-Cog score (P=0.07), ADL score (P=0.36) and NPI score (P=0.22), while there were statistically significant differences in CIBIC-plus score (P=0.04) and CSDD score (P=0.02).

#### Adverse reactions

There were no serious adverse reactions during the study, but 2 cases of GV-971 group had adverse reactions of increased stool frequency. There was 2 case of nausea adverse reaction in the donepezil group. There was no adverse reaction in the placebo group. And there were statistically significant (P=0.01) differences in adverse reaction rate in the GV-971 group (5.67%) and donepezil group (8.33%). It can be considered that the adverse reaction rate of GV-971 group was lower than that of donepezil group and it was easier to tolerate. None of the 72 subjects showed drug withdrawal due to adverse reactions.



**Fig. 1:** Line chart of ADAS-Cog score changes in each treatment period of each experimental group

## DISCUSSION

Pathological features of brain biopsy in patients with AD are neuronal death, and common neuropathological changes include acetylcholine deficiency, glutamate excitatory toxication, extracellular deposition of  $\beta$ -

amyloid ( $A\beta$  plaques) (Hata *et al.*, 2019; Bassil *et al.*, 2019). Formation of intracellular neurofibrillary tangles, hyperphosphorylated tau protein deposition, neuro-inflammation, and extensive neuronal loss (Justyna *et al.*, 2016, Graham *et al.*, 2017) etc. Shanghai Institute of Materia Medica, Chinese Academy of Sciences published an article (Wang *et al.*, 2019) in Cell Research on 6 September 2019, which proposed a new pathogenesis theory of AD: The dysregulation of gut microbiota is closely related to the development of AD disease, ecological disruption of gut microbiota is essential for a variety of peripheral immune cells infiltrating the brain, the changes of gut microbiota caused the accumulation of phenylalanine and isoleucine in peripheral blood and its stimulus Th1 differentiation and proliferation, With invasion in the brain and activating the brain M1 microglia, leading to the nerve inflammation, eventually producing cognitive dysfunction. Their new drugs sodium oligomannate (GV-971) is a marine algae-derived oral oligosaccharide, which can therapeutically repair the gut microbiota and reduced the concentration of phenylalanine and isoleucine in the blood and the feces, and reduced the neuro inflammation related Th1 cells in the brain, then removed the  $\beta$ -amyloid deposition and hyperphosphorylated tau protein, thus improving cognitive function in AD patients.

From the results of this study, it can be seen that the improvement in the Clinician's interview based impression of change (CIBIC-plus score) was seen early (12<sup>th</sup> week) in the GV-971 group compared with the placebo group. At the 24<sup>th</sup> week and 48<sup>th</sup> week of treatment, not only did the improvement in the CIBIC-plus was seen in the GV-971 group compared with the placebo group. There was also an improvement in Alzheimer's Disease Assessment Scale-cognitive section (ADAS-Cog) scores. It suggests that GV-971 is effective in the treatment of mild to moderate Alzheimer's disease, and the overall clinical impression can be improved in the early stage. However, long-term continuous use of GV-971 is needed to effectively improve the cognitive function of patients. The GV-971 group showed better improvement in the Clinician's interview based impression of change (CIBIC-plus score) than the donepezil group at 24<sup>th</sup> week after treatment. The improvement in the Clinician's interview based impression of change (CIBIC-Plus score) and the Cornell scale for depression in dementia (CSDD score) was also better than that in the donepezil group at the later stage (48<sup>th</sup> week). But no difference was found in other scales. These results indicated that GV-971 was better than donepezil in improving the overall clinical impression and depressive symptoms of AD patients, but the efficacy of GV-971 was comparable to donepezil group in improving the cognitive function, self-care ability and mental symptoms of AD patients. As can be intuitively seen from fig. 1, the ADAS-Cog score of the placebo group

**Table 1:** Baseline characteristics of the subjects and baseline scores of each scale

	GV-971 (N=36)	Placebo (n=12)	Donepezil (n=24)
Male/ female	16/20	4/8	16/8
Age	67.67±4.92 (62-74)	64.33±7.59 (54-72)	70±6 (64-76)
Disease time	3.67±1.55	1.25±0.75	3.5±2.5
MMSE	16±3.27	16±1	14.5±0.5
ADAS-Cog	37.22±11.96	40±10	46±6
ADL	90±7.07	85±15	62.5±22.5
CIBIC-PLUS	19.67±6.60	9±1	17.5±0.5
NPI	11.67±4.78	3.5±0.5	13±3
CSDD	6±2.94	5.5±0.5	11±8

Notes: all data have no \* P>0.05 means no statistical difference

**Table 2:** Changes of scores from baseline of each scale in each period

Groups	ADAS-Cog	ADL	CIBIC-plus	NPI	CSDD
GV971					
0w	37.22±11.96	90±7.07	19.67±6.60	11.67±4.78	6±2.94
12w	3.11±3.62	3.33±2.36	4.00±0.00	7.00±1.41	-0.67±2.36
24w	1.33±0.47	-1.67±2.36	-2.33±0.94	-4.33±5.56	-2.33±2.62
36w	0.33±2.62	-1.67±2.36	-1.00±5.66	-1.67±3.30	-1.33±2.62
48w	0.00±1.41	0.00±0.00	-2.33±3.40	-1.67±4.64	-1.67±1.70
Placebo					
0w	40±10	85±15	9±1	3.5±0.5	5.5±0.5
12w	4.50±2.50	7.50±7.50	6.50±0.50*	4.00±1.00	0.00±1.00
24w	6.00±1.00**	5.00±5.00	6.00±1.00**	8.00±1.00	0.50±1.50
36w	5.50±0.50	0.00±0.00	4.00±2.00	6.50±0.50	2.00±1.00
48w	7.50±0.50**	2.50±2.50	7.00±2.00*	7.00±1.00	0.00±0.00
Donepezil					
0w	46±6	62.5±22.5	17.5±0.5	13±3	11±8
12w	3.00±5.00	-12.50±12.50	6.50±3.50	3.50±2.50	0.00±2.00
24w	8.00±7.00	-12.50±22.50	10.0±3.00**	8.00±4.00	2.50±1.50
36w	6.00±6.00	-12.50±17.50	7.00±3.00	6.50±8.50	2.50±0.50
48w	13.00±6.00	-20.00±25.00	9.50±2.50*	7.00±5.00	5.50±0.50*

Notes: \*P<0.05 means significant difference, \*\*P<0.01 means extremely significant difference

**Table 3:** Adverse reactions in each group

Adverse groups	GV-971	Donepezil	Placebo
Increased stool frequency	2	0	0
Nausea	0	2	0
Total	2	2	0
rate	5.67%	8.33%	0

increased gradually over time, and the disease became worse day by day. The donepezil group had a tendency to increase, but not as significantly as the placebo group. GV-971 group did not increase, but showed a downward trend, which further indicated that GV-971 may reverse the condition of AD patients and make their condition improve day by day, but further evidence is required long-term follow-up observation.

During the whole research process no serious adverse reactions were observed. The number of stools in patients in the GV-971 group increased, which may be related to

the effect of the drug itself by improving intestinal flora. In addition, no other adverse reactions were observed in the GV-971 group. The adverse reaction rate of GV-971 group was lower than that of donepezil group, indicating that GV-971 group had higher safety than donepezil.

### CONCLUSION

In conclusion, GV-971 is as effective as donepezil in treating Alzheimer's disease, maybe even better. It has good safety and should be good for clinical application. This study is a single-center study with small sample size

and short follow-up period and the results obtained are subject to certain risk of bias. For stronger evidence further studies are required with larger sample size.

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## REFERENCES

- Alexopoulos GS, Abrams RC, Young RC, Shamoian CA (1988). Cornell scale for depression in dementia. *Biol. Psychiatry*, **23**(3): 271-284.
- Bassil F, Brown HJ, Pattabhiraman S, Iwasyk JE, Maghames CM, Meymand ES, Cox TO, Riddle DM, Zhang B, Trojanowski JQ and Lee VMY (2020). Amyloid-Beta (Abeta) plaques promote seeding and spreading of alpha-synuclein and tau in a mouse model of lewy body disorders with abeta pathology. *Neuron*, **105**(2): 260-275.
- Boothby HMA and Barker A (1995). Factors determining inter rater agreement with rating global change in dementia: The cubic-plus. *Int. J. Geriatr Psychiatry*, **10**(10): 1037-1045.
- Collin C, Wade DT, Davies S and Horne V (1988). The Barthel ADL Index: A reliability study. *Int. Disabil Stud.*, **10**(2): 61-63.
- Cui CC, Sun Y, Wang XY, Zhang Y and Xing Y (2019). The effect of anti-dementia drugs on Alzheimer disease-induced cognitive impairment: A network meta-analysis. *Medicine (Baltimore)*, **98**(27): e16091.
- Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA and Gornbein J (1994). The neuropsychiatric inventory: Comprehensive assessment of psychopathology in dementia. *Neurology*, **44**(12): 2308-2314.
- Dubois B, Feldman H, Jacova C, Hampel H, Molinuevo JL, Blennow K., T DeKosky ST, Gauthier S, Selkoe D, Bateman R, Cappa S, Crutch S, Engelborghs S, Frisoni GB, Fox NC, Galasko D, Habert MO, Jicha GA, Nordberg A, Pasquier F, Rabinovici G, Robert P, Rowe C, Salloway S, Sarazin M, Epelbaum S, Souza LC, Vellas B, Visser PJ, Schneider L, Stern Y, Scheltens P and Cummings JL (2014). Advancing research diagnostic criteria for Alzheimer's disease: The IWG-2 criteria. *Lancet Neurol.*, **13**(6): 614-629.
- Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, Delacourte A, Galasko D, Gauthier S, Jicha G, Meguro K, O'Brien J, Pasquier F, Robert P, Rossor M, Salloway S, Stern Y, Visser PJ and Scheltens P (2007). Research criteria for the diagnosis of Alzheimer's disease: Revising the NINCDS-ADRDA criteria. *Lancet Neurol.*, **6**(8):734-746.
- Graham WV, Bonito-oliva A and Sakmar TP (2017). Update on Alzheimer's disease therapy and prevention strategies. *Annu. Rev. Medicine*, **68**(14): 413-430.
- Hata S, Omori C, Kimura A, Saito H, Kimura N, Gupta V, Pedrini S, Hone E, Chatterjee P, Taddei K, Kasuga K, Ikeuchi T, Waragai M, Nishimura M, Hu A, Nakaya T, Meijer L, Maeda M, Yamamoto T, Masters CL, Rowe CC, Ames D, Yamamoto K, Martins RN, Gandy S and Suzuki T (2019). Decrease in p3-Alc-beta37 and p3-Alc-beta40, products of Alc-beta generated by gamma-secretase cleavages, in aged monkeys and patients with Alzheimer's disease. *Alzheimers Dement (NY)*, **5**(7): 740-750.
- Imtiaz D, Khan A and Seelye A (2018). A mobile multimedia reminiscence therapy application to reduce behavioral and psychological symptoms in persons with Alzheimer's. *J. Healthc. Eng.*, 1536316.
- Jia JP and Chen SD (2018). *Neurology*, 8th ed. People's Sanitary Publishing Press, pp.265-270.
- Justyna G, Jakub J, Dawid P and Barbara M (2016). Therapeutic strategies for Alzheimer's disease in clinical trials. *Pharmacol. Rep.*, **68**(1): 127-138.
- Lane CA, Hardy J and Schott JM (2018). Alzheimer's disease. *Eur. J. Neurol.*, **25**(1): 59-70.
- Meiyu G (2017). A novel anti-Alzheimer's disease drug, mannoooligosaccharide diacid. *Chin J. Pharmacol. Toxicol.*, **31**(5): 459-460.
- Reitz C and Mayeux R (2014). Alzheimer disease: Epidemiology, diagnostic criteria, risk factors and biomarkers. *Biochem. Pharmacol.*, **88**(4): 640-651.
- Rosen WG, Mohs RC and Davis KL (1984). A new rating scale for Alzheimer's disease. *The American journal of psychiatry*. *Am. J. Psychiatry.*, **141**(11): 1356-1364.
- Wang X, Sun G, Feng T, Zhang J, Huang X, Wang T, Xie Z, Chu X, Yang J, Wang H, Chang S, Gong Y, Ruan L, Zhang G, Yan S, Lian W, Du C, Yang D, Zhang Q, Lin F, Liu J, Zhang H, Ge C, Xiao S, Ding J and Geng M (2019). Sodium oligomannate therapeutically remodels gut microbiota and suppresses gut bacterial amino acids-shaped neuro inflammation to inhibit Alzheimer's disease progression. *Cell Res.*, **29**(10): 787-803.