DRUG UPDATE

Sodium Oligomannate: a Promising Hope in Treatment of Alzheimer's Disease Through Suppression of Gut Dysbiosis

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INTRODUCTION

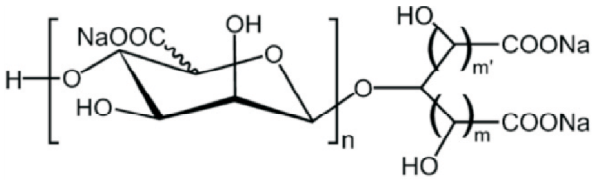
Sodium oligomannate, Is seaweed-based cocktail of linear oligosaccharides (ranging from dimers to decamers) derived from marine (brown) algae and an orally administered drug for Alzheimer's disease (AD).

Marine algae can source some distinctive metabolites which have varied health benefits. Their pharmacological characteristics, namelyanti-inflammatory, anti-oxidant, protein clearance and anti-amyloidogenic potentials, protect against neuroinflammation, oxidative stress, and deregulated proteostasis in neurodegenerative disorders. Alzheimer's disease involves two proteins: amyloid-βand tau, wheneither reaches abnormal levels in the brain, it leads to the formation of plaque, which gets deposited between neurons, damaging nerve cells[1].

Recently, many studies show the interaction between gut microbiota and host immune system[2,3]. The dysbiosis in gut flora may disturb host immune system and induce inflammation[4]. There is a growing evidence that gut microbiota is correlated with the incidence of Alzheimer's disease, Parkinson's disease, depression, and other central nervous system disorders. During the preclinical studies, the drug has shown to improve cognitive function by restructuring the balance of gut microbiota, inhibiting the anomalous increase of specific metabolites of this microbiota, reducing central and peripheral inflammation, amyloid-β deposition and hyper phosphorylation of Tau protein in AD[5].

In November 2019, after 22 years of research, this drug finally got conditional approval from China's National Medical Products Administration (NMPA) for treatment of mild to moderate Alzheimer's disease[6]. It is developed and manufactured by Shanghai Green Valley Pharmaceuticals, Ocean University and Shanghai Institute of Materia Medica. A**lternative names of** Sodium oligomannateare*GV-971, Hamput Sodium, Mannut Sodium, Oligomannate, Sodium oligomannurarate, Nine Phase One,* Sodium oligo-β-1 → 4-D-mannuronic acid-*O*-dicarboxylic acid.

CHEMICALSTRUCTURAL



Chemical structure of sodium oligomannate. n = 1~9; m = 0, 1, 2; m′ = 0, 1

Chemical Name: Sodium oligo-β-1 → 4-D-mannuronic acid-*O*-dicarboxylic acid

ATC code (WHO)- N06D (Anti-Dementia Drugs)

MECHANISM OFACTION

Sodium oligomannate can penetrate the blood brain barrier (BBB) through glucose transporter 1 (GLUT1) and inhibit amyloid-βfibril formation and destabilizing the fibrils into nontoxic monomers. Although the absolute mechanism of action remains unclear, sodium oligomannate controls neuroinflammation and decreases memory impairment by suppressing gut dysbiosis and the associated phenylalanine/isoleucine accumulation (Figure.1). Significant changes seen in regulation in amino acid related metabolic pathway and enzymes especially phenylalanine related pathway in GV-971 treated Tg Mice and inhibition of neuroinflammationalso seen. Microglial activation, brain cytokine level, Aβ plaque

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deposition and tau protein phosphorylation reduced in GV-971 treated Tg mice. Th1 cells in brain of recipient C57BL/6 WT mice decreased after Feces transplantation from GV-971 treated Tg mice[1].

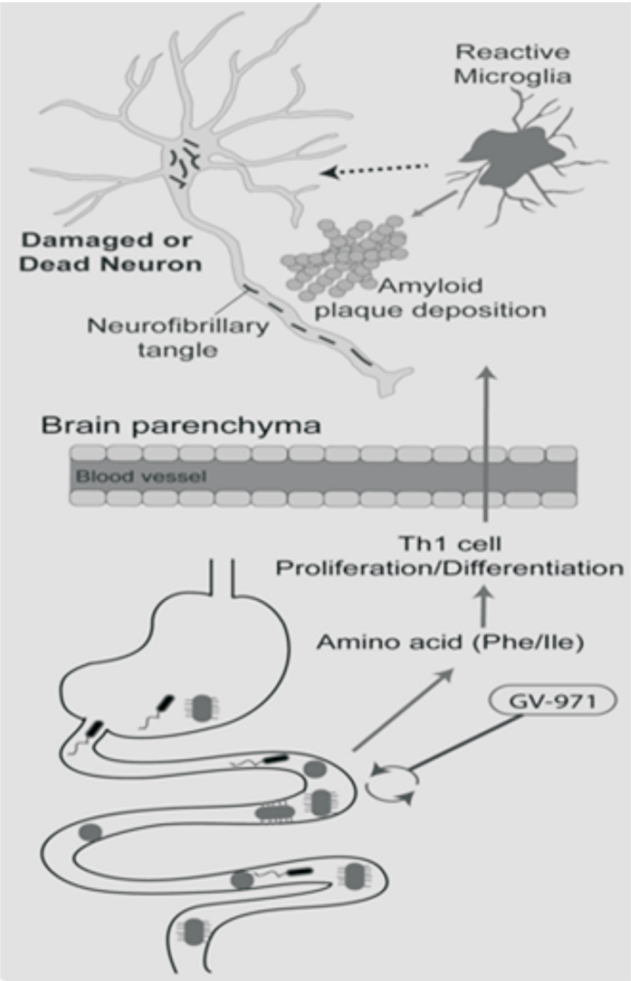

Figure 1: Mechanism of action: sodium oligomannate

In a phase II pilot study, in patients with Alzheimer's disease, there was an elevation of amyloid-β levels in the cerebrospinal fluid (CSF) following sodium oligomannate treatment, suggesting an important role in amyloid-β clearance into CSF[7]. There was a differential reduction in the cerebral glucose metabolic rate by sodium oligomannate. While in the phase II trial, the cerebral glucose metabolic rate in left orbito-frontal gyrus and precuneus &right posterior cingulate gyrus, and hippocampus were low, in the phase III trial, the lower rate was found in superior and inferior parietal gyrus, angular gyrus, and the anterior wedge in the brain[8].

PHARMACOKINETICS

Sodium oligomannate has low oral absorption and peak plasma concentration achieved at 5.4 hours. The apparent volume of distribution is 9608.7 L after 600 or 750 mg single oral dose. Plasma half-life ranges from 11-22 hours. The study data about metabolism and excretion of sodium oligomannate is not available. After twice daily dosing for five days, the apparent clearance was found 117.4-158 Liter/hr[9].

SIDE EFFECTS AND TOLERABILITY

Sodium oligomannate was well tolerated in clinical trial phase- II and III with minimal side effects[7,10]. The most common adverse drug reaction (ADR) in sodium oligomannate group was dry mouth, hematuria and elevated ALT and AST, bilirubin and low density lipoprotein level. Severe ADR (pneumonia) was found in one patient (0.2%). One patient with dizziness, one with seizures and one with gastritis have suspended the treatment while another seven patients left the treatment due to ADR[9].

DOSE

Sodium oligomannate is available in oral dosage form as capsule in the strength of 150 mg. The dose of this drug in Alzheimer's disease is 450 mg twice daily.

Cost: A prescription of 42 capsules of sodium oligomannate costs 895 Yuan (Approx. INR 10000)

RESULTS OF CLINICALTRIAL

In CT-phase II (NCT01453569), (n=255) received sodium oligomannate or placebo for 24 weeks in the dose of 600 mg/900 mg per day. The parameter of disease was accessed by Alzheimer's Disease Assessment Scale (ADAS-cog12) and Clinician's Interview- Based Impression of Change-Plus (CIBIC+). ADAS-cog12 score was not significantly different from baseline to 24 weeks treatment in the treatment group of 600mg and 900 mg vs placebo groups. CIBIC+ score was significantly improved at 24 weeks treatment with 900 mg/day vs placebo[7].In CT phase III (NCT02293915), (n=818) received sodium oligomannate 450mg twice a day or placebo for 36 weeks. At the 4 weeks onward, the ADAS-cog12 score was significantly improved in treatment group as compared to placebo group. But CIBIC+ score was not significantly improved[9,10].

CURRENT STATUS

02nd November 2019: The China National Medical Product Administration (NMPA) provisionally permits the use of sodium oligomannate to treat individuals with mild to moderate Alzheimer's disease.

03rd April 2020: The FDA approves IND (Investigational New Drug) application for sodium oligomannate in Alzheimer's disease.

27th April 2020: Shanghai Green Valley Pharmaceuticals plans to submit a New Drug Application (NDA) to the FDA for Alzheimer's disease by 2025.

27th Oct 2020: Shanghai Green Valley Pharmaceutical starts the phase-III GREEN MEMORY trial for Alzheimer's Disease in United States.

Till now, there is no cure for Alzheimer's disease, the medications only help control the symptoms and/ delay the progression of the disease. With the recent approval of Sodium oligomannate, a fresh ray of hope has emerged among the people affected with this disease.

However, sodium oligomannate lacks the global data of effectiveness and therefore requires large scale global trials before it can receive approval from the (FDA).

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