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Review

Clinical Research on Traditional Chinese Medicine compounds and their preparations for Amyotrophic Lateral Sclerosis

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ABSTRACT

Purpose: Amyotrophic lateral sclerosis (ALS) is a chronic, fatal neurodegenerative disease which leads to progressive muscle atrophy and paralysis. In order to summarize the characteristics of Traditional Chinese Medicine compounds and their preparations in the prevention and treatment of ALS through analyzing the mechanism, action site, and symptoms according to effective clinical research.

Methods: We searched ALS, motor neuron disease, chemical drugs, herbal medicine, Chinese medicine, Traditional Chinese Medicine (TCM), and various combinations of these terms in databases including the PudMed, Springer, Ovid, Google, China National Knowledge Infrastructure, and Wanfang databases.

Result: It was found that the chemical drugs almost had not sufficient evidence to show their effectiveness in the treatment of ALS, except RILUZOLE. According to the characteristics of clinical symptoms of ALS, Chinese medicine practitioners believe that this disease belongs to the category of "atrophic disease". In clinical research, many Chinese herbal formulas had good clinical efficacies in the treatment of ALS with multiple targets, multiple links, and few side effects. And four kinds of dialectical treatment had been developed based on Clinical data analysis and the use of dialectical therapy: Benefiting the kidney; Declaring the lungs; Enhancing the Qi; and Dredging the meridian.

Conclusion: In this review, we provide an overview of chemical drugs and Traditional Chinese Medicine compound and its preparations in therapy of ALS as well as how they may contribute to the ALS pathogenesis, thereby offering some clues for further studies.

1. Introduction

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a chronic, fatal neurodegenerative disease which makes a severe pain on patient's life. It affects both upper and lower motor neurons in the brain and in the spinal cord, which results in progressive degeneration and death of upper and lower motor neurons, severe muscle atrophy, and respiratory insufficiency [1]. With an incidence of 2.16 per 100,000 person-years and a median survival time of 3–5 years, the peaking age is between 70 and 80 years, and the incidence are lower in women than man. ALS clinical registry data and more recent meta-analysis based on prospective population based registries suggest that up to 10% of ALS patients have a family history of ALS in a first- or second-degree relative, generally classified as familial ALS (FALS) [2]. The remaining 90% of patients with no evident family history of ALS are designated as sporadic ALS (SALS).

It has been suggested that glutamate-induced excitotoxicity plays a central role in the development of ALS. RILUZOLE is the only FDA approved drug for the treatment of ALS, whose initial protective effect is to reduce glutamatergic neurotransmission [3]. However, the effectiveness is questionable not only extends life expectancy for only 2 to 4 months, but the little effect on survival of the short-term use [4]. And Li et al. found that there was no difference in clinical disease onset or survival between treated and untreated groups [5]. In addition, Kakuta reported the first report of RILUZOLE-induced lung injury in ALS patients [6]. It is certain that there are also many other anti-excitotoxic

Abbreviations: ALS, Amyotrophic lateral sclerosis; Bcl, 2 B-cell lymphoma-2; COX-2, cyclooxygenase-2; DHYZ, DihuangYinziFang; DPPH, 2,2-diphenyl-1-picrylhydrazyl; FALS, familial Amyotrophic lateral sclerosis; FasL, Fas ligand; FDA, Food and Drug Administration; IFN, Interferon; iNOS, inducible nitric oxide synthase; JWL, JiWeiLing injection; JWSJZ, Jiawei Sijunzi decoction; MDA, Malondialdehyde; NFATC, Nuclear factor of activated T-cells cytoplasmic; PEG2, Prostaglandin E2; RAM, *Rhizoma Atractylodis Macrocephalae*; ROS, reactive oxygen species; SALS, sporadic Amyotrophic lateral sclerosis; SJZT, Sijunzi decoction; SOD, Superoxide Dismutase; TCM, Traditional Chinese Medicine; TNF-α, tumor necrosis factor-α; TNFR1, tumor necrosis factor receptor1

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agents, such as penicillin and its derivatives and cephalosporin; Ceftriaxone [7]; the kainate receptors inhibition [8,9] Talampanel, but a phase II study demonstrated that the neuroprotective effects of Talampanel were only present during the early stage of the disease [10–12]. Although ALS usually develops sporadically, 5%–10% of cases are familial, and over 100 genes are potentially responsible for FALS [13]. Protein aggregation is one of the important causes of ALS, including SOD1, TDB-43 and C9orf72. Among these, the mutation in SOD1 gene is responsible for 20% of FALS [14]. On the basis of activity, several cyclohexane-1,3-dione derivatives, including Fasudil [15,16], 4-aminopyridine derivative Y-27632 [17], methylene blue and mexiletine, and spermidine [18], were reported because of the protective effect against protein aggregation induced toxicity in cells [19]. Similarly, a 1,3-diphenylurea derivative or multikinase inhibitor to treat ALS by reducing the amount of SOD1 gene expression was applied [20]. But it was found to have only poor activity in primary cortical neurons, indicating that it could not treat directly on the ALS [21]. While free radicals and inflammation constitute major routes of neuronal injury occurred in ALS, neither antioxidants nor non-steroidal anti-inflammatory drugs have shown significant efficacy in clinical trials, such as 2-hydroxy-5-[2-(4-trifluoromethylphenyl)-ethylaminobenzoic acid] [22] and Nimesulide (which may be more suitable for prevention) [23]. The pathogenesis of ALS is also linked with SOD1 aggregation in the defective mitochondria due to the toxic function of SOD1, which prompts the search for neuroprotective agents targeting mitochondria [24], such as Cyclosporine A, Ru360, and Dexpramipexole [25,26]. Additionally, the occurrence of cellular oxidative stress due to mitochondrial dysfunction is another proposed mechanism responsible for motor neuron degeneration in ALS. For example, Bromocriptine mesylate [3] could delay the disease progression of ALS mouse [27]. In addition, heat shock protein 70 [28,29], arimoclomol [30,31], rosmarinic acid [32,33], and tauroursodeoxycholic acid [34] all showed the potential neuroprotective activityfor ALS.

To our knowledge, except that the recent small trial has been shown to display protection in mutant SOD1 mice in laboratories, there are not enough tests in clinical trials [35]. It is clear that the chemical drugs mentioned above all have not sufficient evidence to show their effectiveness in the treatment of ALS, except RILUZOLE. But the average medical expenditure per ALS patient was 16-fold greater than the general population of Taiwan. And the cost compared with of other diseases was 120-fold greater than hematophili, 31-fold ventilator-dependent patients, 26-fold dialysis and 6-fold cancer [36]. With the high cost, side effects and uncertain efficiency, it's a huge obstacle to many patients to trust RILUZOLE. It has also urged researchers to look for more effective pharmacological treatments for ALS. At this time, TCM for ALS deeply attracted our attention because of the unique targeted therapy and effective treatment. ALS is diagnosed as "flaccidity syndrome" by traditional Chinese theory based on the weakness and atrophy of limbs and body, the difficulty with chewing, swallowing, and breathing, which ultimately leads to progressive weight loss and increases risk of choking and aspiration pneumonia. And "flaccidity syndrome" is classified as the nervous system diseases including myelitis, myasthenia gravis, muscle dystrophy, multiple neuritis, multiple sclerosis and ALS in Western medicine. And TCM is frequently used in the clinical treatment of ALS. The clinical studies showed that TCM had a great potential for the treatment of ALS, with neuroprotective function against excitatory amino acid toxicity, oxidative stress, and neuro inflammation [37]. Different combinations of drugs having different effects can improve the different clinical symptoms, extend the survival period, reduce the course of each of the targeted symptoms, reduce the side effects, and enhance medicinal efficacy. Although there is no unified understanding of clinical opinions, the traditional Chinese doctors, based on cluster analysis and the use of dialectical therapy, developed four kinds of Dialectical Treatment for ALS, which are benefiting the kidney; declaring the lungs, enhancing the Qi, and dredging the meridian.

At present, there are some articles about the contribution of chemical drugs [38], a class of drugs [39,40], and TCM single compound [37] on the treatment of ALS, but few, if any, of TCM compounds and its preparations. From the clinical point of view, many Chinese herbal formulas had good clinical efficacies in the treatment of ALS. The mechanism of TCM and chemical drugs in prevention and treatment of ALS is the same way; however, TCM has multiple targets, good efficacy, low adverse reactions, low cost, and other advantages in the treatment of ALS. Based on the latest literatures from 1985 to now (32 years), this paper reviewed the countermeasures of prevention and treatment of ALS by TCM on the basis of analyzing the mechanism of ALS. The aim of this study was to summarize the characteristics of TCM and its preparations in the prevention and treatment of ALS based on analyzing the action site, action mechanism, and symptoms, thereby providing an informative reference for the prevention and treatment of ALS and offering some clues for further in-depth studies.

2. The pathogenesis of ALS

In ALS, protein aggregation is one of the important causes, including SOD1, TDB-43, and C9orf72, which are closely linked to astrocytes. In FALS, more than 90 mutations are found in Superoxide dismutase [Cu-Zn] also known as superoxide dismutase 1 or SOD1 [14], and 15–20% of FALS are associated with mutations in the gene SOD1 [28], which is the first causative gene identified for ALS [41]. It is hence generally accepted that mutations in SOD1 are involved in the disease through a gain of toxicities but not a loss of its physiological functions. Also, the disruption of metal homeostasis has long been debated as a possible pathomechanism of SOD1-ALS because of the metalloprotein binding function of copper and zinc ions [42]. In addition, Rojas et al. showed that exposing primary rat spinal cord cultures express human $SOD1^{G93A}$ quickly enhanced Nav channel-mediated excitability and calcium influx, generated intracellular reactive oxygen species (ROS). Meanwhlie, astrocytes expressed mutant SOD1 and TDP43 lead to death of moto neurons within days [18]. And available evidence suggested that the dysregulation of gene expression, including RNA splicing attributed to pathogenic TARDPB variants and the toxic gain-of-function of mutant TDP-43 protein, contributed to neurodegeneration but the causal mechanism is not established [43,44]. Recently, Sasaguri et al. provided further evidence confirming the critical role of the extreme N-terminus of TDP-43 in regulating protein structure as well as mediating toxicity associated with its aggregation [45]. While SOD1 variants linked to disease are found in about 12% and TARDPB variants account for a few percent each, the C9orf72hexanucleotide repeat expansion accounts for approximately 40% of FALS [46]. The massive expansion of a GGGGCC repeat upstream of the coding region of C9orf72 is the most common ALS causing mutation [12,47], and other less common or rare gene variants are found in the remainder (Fig. 1).

Despite the pathogen of ALS has been well studied, the understanding of its mechanism is still incomplete. For now glutamate-induced excitotoxicity is a major contributor to motor neuron degeneration in the pathogenesis of ALS. Glutamate is the primary excitatory neurotransmitter in the mammalian central nervous system. When excess extracellular glutamate aggregates, neuronal degeneration can be induced *in vivo and in vitro*. That's why we call it glutamate 'excitotoxicity' [48]. The glutamate transporter GLT-1 is the most important transporter involved in keeping extracellular glutamate concentration below neurotoxic levels. Cristina Vanoni et al. indicated that a cell-autonomous toxic effect of $SOD1^{G93A}$ could cause a specific post-translational downregulation of GLT-1 which makes glutamate aggregation [49]. And the glial glutamate transporter EAAT2 is primarily responsible for clearance of glutamate from the synaptic cleft, so the loss of functional EAAT2 could lead to the accumulation of extracellular glutamate, resulting in cell death known as excitotoxicity. Guo et al. showed that the amount of EAAT2 protein and the associated Na +-dependent glutamate uptake were increased about 2-fold in EAAT2