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Current Therapy of Drugs in Amyotrophic Lateral Sclerosis

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Abstract: Amyotrophic lateral sclerosis (ALS), commonly termed as motor neuron disease (MND) in UK, is a chronically lethal disorder among the neurodegenerative diseases, meanwhile. ALS is basically irreversible and progressive deterioration of upper and lower motor neurons in the motor cortex, brain stem and medulla spinalis. Riluzole, used for the treatment of ALS, was demonstrated to slightly delay the initiation of respiratory dysfunction and extend the median survival of patients by a few months. In this study, the key biochemical defects were discussed, such as: mutant Cu/Zn superoxide dismutase, mitochondrial protectants, and anti-excitotoxic/ anti-oxidative / anti-inflammatory/ anti-apoptotic agents, so the related drug candidates that have been studied in ALS models would possibly be further used in ALS patients.

Keywords: Amyotrophic lateral sclerosis, motor neuron disease, neurodegenerative disease, SOD1 mutations, riluzole, edaravone, pyrimethamine.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS), also known as "Lou Gehrig's disease", is a chronically lethal neurodegenerative disease first proposed and named by the French neurologist Jean-Martin Charcot [1-3]. The characteristics of ALS are irreversible and progressive deterioration of upper (UMN) and lower (LMN) motor neurons in the motor cortex, brain stem and spinal cord [4, 5]. The prevalence of ALS is 1-2 per 100,000 [6], and the incidence of which is 6-8 per 100,000 people/year [7]. Approximately 90–95 % of ALS is sporadic (sALS) and 5-10% of ALS is inherited (fALS) [7]. Recently, fALS has been further understood by genetic discoveries with identification of nearly 60% responsible mutations [8]. The most studied genetic defect was mutant Cu/Zn superoxide dismutase (SOD1), which comprises approximately 20% of all known inherited mutations [9]. The clinical symptoms of ALS include muscle weakness and atrophy, spasm, poor reflexes, twitching, and speech problems [10]. ALS patients who generally die of respiratory failure have a median survival of months to decades, while the average time of survival has been reported to be 19 months from diagnosis and 30 months from onset [11-13]. Although the precise pathology mechanisms of ALS are still unknown, many pathologic processes have been involved in, such as glutamate toxicity, protein misfolding and aggregation, endoplasmic reticulum (ER) stress, loss of trophic factors, oxidative stress, inflammation, disrupted protein trafficking, and mitochondrial dysfunction [14]. Therapeutic development has been focused on these mechanisms of cellular dysfunction. Until now, riluzole is the only medicine approved by the US Food and Drug Administration (FDA). Riluzole is suggested to possess the ability of anti-glutamate toxicity. Riluzole has been demonstrated to slightly delay the onset of respiratory dysfunction and extend the median survival 2–3 months approximately, thereby increasing 9% survival in the first year [15, 16]. Riluzole partially blocks Na+ currents and affects action potentials but does not prevent firing in human myotubes [17]. Furthermore, riluzole has not proved to ameliorate motor function, myodynamia, tremor or pulmonary capacity; or benefit older and more severe patients [18]. Currently, complementary and alternative medicines for ALS have been extensively studied.

In this review, we will summarize those drugs and the related candidates that have been studied in ALS models and would possibly be further used in ALS patients.

TARGETING SOD1 MUTATIONS

SOD1 mutations as a pathology of ALS lead to cellular death. Mutant G93A SOD1 mice were commonly used as animal models to evaluate the effectiveness of potential therapy for ALS [19, 20]. Delivery of an adeno-associated virus serotype 9 (AAV9) encoding an shRNA to reduce the synthesis of ALS-causing human SOD1 mutants extended survival by delaying both disease onset and slowing down progression in SOD1G93A mice [21, 22]. The molecular chaperone, HSJ1 (DNAJB2), preferentially bound to mutant SOD1, enhanced SOD1 ubiquitylation, reduced SOD1 aggregation and improved motor neuron survival in mutant SOD1 models of ALS. Overexpression of human HSJ1a (hHSJ1a) in motor neurons of SOD1G93A transgenic mice significantly improved muscle force, increased motor unit number and enhanced motor neuron survival [23]. The monoclonal antibody BBS blocks amyloid precursor protein (APP) β-secretase cleavage site, results in reduction of mutant SOD1G93A levels and diminishes inflammation in animal and cellular models of ALS, significantly prolonging life span of SOD1G93A mice [24]. In models of ALS,

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several chemical compounds are able to reduce SOD1 aggregates. 2-[3-iodophenyl]methylsulfanyl]-5pyridin-4-yl-1,3,4-oxadiazole, a known protein kinase inhibitor, decreases G93A-SOD1 expression *in vitro* and *in vivo*, however, it has a biphasic dose response curve and is likely a toxophore which limits its therapy for ALS [25]. The metal complex diacetyl-bis(4-methylthiosemicarbazonato) copperII [CuII (atsm)] and zincII [ZnII(atsm)] treatment in SOD1G37R mice resulted in an improvement in locomotor function and survival [26, 27]. An antisense oligonucleotide, ISIS 333611, decreased SOD1 mRNA and protein levels in spinal cord tissue and prolonged survival in the SOD1G93A rat ALS model. Furthermore, it was well tolerated on intrathecal delivery to subjects with SOD1 familial ALS [28].

Pyrazolone derivatives have previously been found to inhibit Cu/Zn superoxide dismutase 1 (SOD1)-dependent protein aggregation and extend survival of an ALS mouse model [29]. Further investigation about tertiary amine pyrazolones and their salts exhibited numerous benefits both to cellular activity and to center nervous system related drug-like properties *in vitro* and *in vivo*, which indicate that tertiary amine pyrazolones will be drug candidates for ALS [30]. Edaravone, an antioxidant and a free-radical scavenger, was suggested to effectively slow down symptom advancement, weight loss and motor neuron degeneration, and decrease the SOD1 aggregates in mSOD1G93A mice [31]. In a clinic experiment, edaravone administration significantly reduced plasma markers of tissue oxidative damage [32]. Changes in revised ALS functional rating scale (ALSFRS- R) were significantly smaller in edaravone-treated ALS patients than in edaravone-untreated ALS patients [32]. Pyrimethamine was found to reduce SOD1 levels in cultured cells, mice, and ALS patients [33]. However, another experiment was unable to confirm these results [34]. Further studies will be needed to identify the effects of pyrimethamine on SOD1 protein and more importantly, the pathology of ALS [35]. Lithium significantly postponed disease onset and duration, prolonged the lifespan of the G93A mouse, and delayed disease progression in ALS patients with riluzole [36]. However, another report failed to show neuroprotection in G93A mice [37], and two larger multicenter trials failed to certify protective findings [38]. Guanabenz, a centrally acting oral drug approved for hypertension, enhances the PERK pathway by selectively inhibiting GADD34-mediated eIF2α dephosphorylation. Guanabenz-treated G93A mice have less accumulation of mtSOD1 and an enhanced phosphorylation of eIF2α at endstage. Treatment of guanabenz significantly delayed the onset and prolonged the early phase of disease and survival in G93A mtSOD1 transgenic mice [39]. However, another experiment showed that guanabenz treatment accelerated ALS-like disease progression in G93A-SOD1 mice [40].

ANTI-EXCITOTOXIC AGENTS

Glutamate excitotoxicity induced motor neuron death is a pathogenesis of ALS, thus reducing glutamate levels may be potentially therapeutic for ALS patients [35]. Riluzole protects motor neurons against excitotoxicity-induced degeneration by interrupting glutamatergic transmission and decreasing glutamate concentration. Given the metabolism of riluzole is variable in patients, recent studies have focused on inventing riluzole prodrugs that would be more stable *in vivo* [41]. AMPA (alpha-amino-3-hydroxy-5- methyl-4-isoxazole propionic acid) receptors mediate glutamate-induced excitotoxicity in neurodegenerative diseases [42]. Talampanel, non-competitive antagonist of AMPA, was suggested to have beneficial effects on SOD1 mice models when administrated at early stage of the disease [43]. In a phase II study, although without significant differences, ALS Functional Rating Scale, myodynamia, and timed hand movements aggravated at a slower rate in talampanel-treated ALS patients [44]. Moreover, a 150 mg daily dose of talampanel is effective, tolerable and safe when administrated in ALS patients [44]. The cephalosporin antibiotic ceftriaxone, can protect neurons against apoptosis and increase glutamate transporter gene expression, inhibit glutamate neurotoxicity, postpone loss of myodynamia and body weight, and extend survival time [45]. The pharmacokinetics (PK) of ceftriaxone in plasma and cerebrospinal fluid (CSF) were investigated for planning the Phase 3 clinical trial of ceftriaxone in ALS [46]. N-methyl-D-aspartate (NMDA)-mediated cell death and impairment of the glutamate-transport have been suggested to play a key role in ALS pathophysiology [47]. Gacyclidine, a high affinity non-competitive NMDA receptor antagonist, delayed locomotor function impairment, improved survival by 4.3%, partially preserving body weight with a low dose (0.1 mg/kg) [47]. Valproic acid, histone deacetylases (HDAC) inhibitor, protects cultured neurons against glutamate or kainite-induced excitotoxicity [48, 49] and reduces apoptosis [50]. Combination treatment of valproate and lithium postpones disease onset, lessens neurological deficits and extends survival in ALS mice [51]. Moreover, in a clinical experiment, co-treatment of valproate and lithium significantly increased survival and also exerted neuro-protection in sporadic amyotrophic lateral sclerosis patients except for its late adverse events [52]. Vitamin D was proved to protect rodent cortical neurons against glutamate excitotoxicity [53]. Recent studies have demonstrated that high-dose vitamin D3 administration ameliorates paw grip endurance and motor performance in G93A mice [54, 55]. Furthermore, in a recent ALS clinical study, vitamin D3 was proved to reduce the decline in the revised amyotrophic lateral sclerosis functional rating scale (ALSFRS-R) score [56].

MITOCHONDRIAL PROTECTANTS

Mitochondrial dysfunction induces abnormalities of energy production, resulting in generation of reactive oxygen species (ROS). ROS has been detected by increased levels of oxidative stress marker-2,3 DHBA in ALS in *in vitro* and *in vivo* studies [57]. mSOD1 induced defective mitochondria is associated with the pathogenesis of ALS, and mitochondrial swelling and vacuolization are early pathological properties of ALS [19], which prompt the search for neuroprotective agents targeting mitochondria [58]. The over-expression of mitochondria-targeted catalase improved mitochondrial antioxidant defenses and mitochondrial function, reverting the toxicity to co-cultured motor neurons in hSOD1G93A astrocyte cultures [59]. Genetic deletion of a major regulator of the mitochondrial permeability transition pore (mPTP) postpones disease onset and prolongs survival in ALS mice

[60]. Olesoxime directly binding TSPO and VDAC, two proteins of the outer mitochondrial membrane, acts on the mitochondrial mPTP [61, 62]. Olesoxime protects against motor neuron death, delays muscle denervation, astrogliosis, microglial activation, and increases the lifespan of mSOD1G93A mice [62, 63]. In a phase II-III trial, olesoxime was observed to be well tolerated and it did not show a significant beneficial effect in ALS patients treated with riluzole [64]. GNX-4728 inhibited mPTP opening, protected against motor neuron and mitochondrial degeneration, attenuated spinal cord inflammation, and preserved neuromuscular junction (NMJ) innervation in the diaphragm in ALS mice. Furthermore, GNX-4728 slowed disease progression, significantly improved motor function, and extended the lifespan in G37R-human mutant superoxide dismutase-1 (hSOD1) tg mice [65]. MTOR-independent autophagic inducer trehalose can protect mitochondria, inhibit the proapoptotic pathway, reduce skeletal muscle denervation, ubiquitinate protein accumulation and motor neuron loss, decrease SOD1 and SQSTM1/p62 aggregation, improve autophagic flux, significantly delay disease onset, thereby prolonging life span in the spinal cord of sOD1G93A mice [66].

ANTI-APOPTOTIC AGENTS

Apoptosis-related gene c-Abl expression increased 3-fold in postmortem spinal cord tissues from sporadic ALS patients compared with non-ALS patients [67]. Mutation of Cu/Zn-superoxide dismutase-1 (SOD1) upregulated c-Abl and decreased cell viability. Activation of c-Abl was coincident with activated caspase-3 increase in the lumbar spine of G93A-SOD1 transgenic mice. Oral administration of c-Abl inhibitor dasatinib decreased c-Abl phosphorylation, inactivated caspase-3, inhibited cytotoxicity and improved the innervation status of neuromuscular junctions and the survival of G93A mice [67]. The hematopoietic growth factor erythropoietin (EPO) inhibiting apoptotic neuronal changes has been reported to decrease the CSF of ALS patients [68, 69]. EPO was proved to prevent neuronal injury and early motor neuron degeneration and delay the onset of motor deterioration in an ALS model without prolonging survival [70]. There were no serious adverse events and the mean rate of decline in Functional Rating Scale-Revised (ALSFRS-R) score was significantly lower in recombinant human erythropoietin (rhEPO) intravenous treatment in ALS patients [71]. However, in a multicentre randomised double blind placebo controlled phase III study, rhEPO 40 000 IU administrated fortnightly did not change the course of ALS [72].

ANTI-OXIDATIVE AGENTS

Another etiology of ALS is oxidative stress induced motor neurons death [73]. Bromocriptine, a free-radical scavenger, inhibits oxidative stress-induced cell death, sustains motor functions and modestly prolongs survival of ALS-SOD1 transgenic mice after disease onset [74, 75]. Although ceftriaxone, mentioned before, has different mechanisms with bromocriptine for ALS treatment, both drugs display similar core structure- the lactam ring that might be a functional site for ALS therapy [76]. Hydrogen-rich saline significantly suppressed microglial and glial activation, inhibited the release of mitochondrial apoptogenic factors and the subsequent activation of downstream caspase-3, reduced levels of protein carbonyl and 3-nitrotyrosine, suppressed formation of reactive oxygen species (ROS), peroxynitrite and malondialdehyde, preserved mitochondrial function, reduced mitochondrial ROS formation and enhanced mitochondrial adenosine triphosphate synthesis, attenuated loss of motor neurons, delayed disease onset and prolonged survival [77]. Resveratrol was demonstrated to increase expression and activation of Sirtuin 1 and AMPK; consequently it suppressed oxidative stress, downregulated p53 and its related apoptotic pathway, promoted normalization of the autophagic flux, more importantly, increasde mitochondrial biogenesis in the SOD1G93A spinal cord [78, 79]. Furthermore, resveratrol treatment attenuated motor neuron loss, relieved muscle atrophy, and improved mitochondrial function of muscle fibers, thereby significantly delayingthe disease onset and prolonging the lifespan of the ALS mice [78, 79]. In the late-stage ALS mice, 2- [mesityl(methyl) amino]-N-[4-(pyridin-2-yl)-1H-imidazol-2-yl] acetamide trihydrochloride (WN1316) with high blood-brain- barrier permeability and water solubility selectively suppressed oxidative stress-induced cell death and neuronal inflammation [80]. WN1316 was proved to increase both neuronal apoptosis inhibitory protein (NAIP) and NF-E2-related factor 2 (Nrf2), which controlled glutathione (GSH)-related anti-oxidation pathway protecting motor neurons against oxidative injuries[80]. Oral administration of low dose (1–100 mg/kg/day) WN1316 improved motor function and survival rate in ALS(SOD1H46R) and ALS(SOD1G93A) mice [80].

ANTI-INFLAMMATORY AGENTS

Inflammation plays an important role in the pathogenesis of motor neuron death in ALS [81]. Astrocytes derived from fALS and sALS patients are toxic to motor neurons [82]. Activated microglia is involved in the pathogenesis of ALS [83], and T lymphocytes also play a role in mSOD1-caused ALS [84]. Many protective agents targeting inflammatory pathways present some benefit in ALS models. N-acetyl-L-tryptophan, an inhibitor of cytochrome c release and an antagonist of neurokinin 1 receptor (NK-1R), suppressed inflammation, restored NK-1R levels, ameliorated motor neuron loss and gross atrophy, delayed disease onset, extended survival and ameliorated deteriorations in motor performance in mSOD1(G93A) ALS transgenic mice [85]. Erythropoietin mentioned above also significantly decreased the level of pro-inflammatory cytokines and up-regulated the levels of anti-inflammatory cytokines, delayed symptom onset, prolonged time of rotarod failure and preserved motoneurons [86]. NP001, a novel immune regulator of inflammatory monocytes/macrophages, was generally safe and well tolerated; moreover, high-dose of NP001 slowed progression in ALS patients with greater inflammation (wide range C-reactive protein) [87].

TNF-α was suggested to play a critical role in ALS pathogenesis [88]. Thalidomide inhibits TNF-α production, reduces the expression of proinflammatory cytokines, attenuates weight loss and motor neuron death, improves motor performance, and significantly extends survival in

mSOD1G93A mice [89]. However, a phase II open label clinical trial demonstrated that thalidomide cannot effectively modulate the disease progression and causes adverse effects [88]. Glycogen synthase kinase-3 (GSK-3) level is increased in the medulla spinalis of ALS patients [90]. GSK-3 inhibitor VIII decreased caspase-3 and cytosolic cytochrome c, reduced markers of inflammation, delayed symptom onset and increased motor neuron survival in the medulla spinalis of SOD1 G93A mice [91]. Another GSK-3 inhibitor, JGK-263, remarkably improved motor function and prolonged the time until symptom onset, rotarod failure and death in transgenic SOD1-G93A mice [92]. Melittin not only has anti-neuroinflammatory effects in the spinal cord, but also reduced the expression of inflammatory proteins in the lungs and spleen, regulating the immune system in organs affected by ALS. These findings suggest that melittin could be a candidate for ALS therapy [93]. CNS-targeted anti-inflammatory agent 2B3-201 (liposomal methylprednisolone) was proved to reduce activation preferentially in astrocytes compared with microglia, thereby decreasing neuronal loss and vacuolation in brainstem nuclei in the SOD1G93A mouse model of ALS [94]. Janus kinase 2 (JAK2) is one of the key molecules in inflammation. R723, a selective JAK2 inhibitor, significantly reduced the number of Ly6c positive blood monocytes, the expression levels of IFN-γ, nitric oxide synthase 2 and inducible (iNOS) in the spinal cord tissue, but it did not alter disease progression or survival of mSOD1G93A mice [95]. Withaferin A (WA), an inhibitor of nuclear factor-kappa B (NF-κB) activity, attenuated neuroinflammation, decreased levels of misfolded SOD1 species in the spinal cord, reduced loss of motor neurons and denervated neuromuscular junctions in a TDP-43 transgenic mouse model of ALS and in the SOD1G93A mice model [96, 97].

NEUROTROPHIC FACTOR

The loss of neurotrophic factors is one pathological characteristic of ALS. Several neurotrophic factors have been demonstrated to promote neuroprotective and regenerative processes in ALS mouse models, which may be considered as candidate agents for ALS therapy [76]. The expression of GDNF (Glial Cell line-derived Neurotrophic Factor) mediated by AAV-GDNF (adeno-associated virus) prevented motor neuron atrophy, maintained axonal projections, extended lifespan and slowed down the progression of disease in ALS transgenic mice [98, 99]. Selective metabotropic glutamate 3 (mGlu3) receptor agonist LY379268 enhanced GDNF and glutamate transporter GLT-1, and had a beneficial effect on neurological disability in SOD1G93A mice but had no significant effect on the mortality rate of SODG93A [100]. The flavonoid 7,8-dihydroxyflavone as a potent and selective small molecule tyrosine kinase receptor B agonist can mimic the effects of brain-derived neurotrophic factor, significantly improving motor deficits, preserving spinal motor neurons count and dendritic spines in SOD1(G93A) mice [101]. The glycoprotein nonmetastatic melanoma protein B (GPNMB) was substantially expressed in the sera of sporadic ALS patients than that of other diseased patients. As the disease progressed, GPNMB was greatly induced in the spinal cords of ALS patients. Extracellular fragments of GPNMB attenuated the neurotoxicity of SOD1G93A in neural cells [102]. Further investigation showed that the weight and cross-sectional area of the gastrocnemius muscle, number and cross-sectional area of myofibers, and denervation of neuromuscular junctions were ameliorated in SOD1G93A/GPNMB transgenic mice. GPNMB expressed by plasmid increased the numbers of myofibers and prevented myofiber atrophy [103].

CONCLUSION

Many studies about substances mentioned above have demonstrated effective modulations of disease progression and survival in ALS mouse models. Several of them are currently considered as potential agents in ALS treatment [76]. However, seldom of the promising improvements in ALS animal models have shown to be effective in ALS patients. The translational failures might be explained by many reasons, such as: 1) many drugs cannot cross the human blood-brain barrier effectively, 2) positive results are often obtained from drugs administrated before the onset of disease in animal models, 3) as the population of ALS is small and the confirmed pathogenesis of ALS is unknown, clinical effects are regarded as the only end point in present randomized controlled trials (RCTs). RCTs in ALS are hard to get positive results for the rare condition. Further studies should focus on revealing the precise mechanisms underlying ALS pathogenesis, highlighting the biomarkers of this disease and optimizing characteristics of drugs as well.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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