Mashhad University of Medical Sciences (MUMS)

Reviews in Clinical Medicine

Clinical Research Development Center Ghaem Hospital

A comprehensive Review of Amyotrophic Lateral Sclerosis Including: Prevalence, Pathogenesis, Biomarkers Diagnosis, and Current Treatment Options

Najmeh Malekzadeh Gonabadi (MD)

Faculty of science, Department of biology, Sistan and Baluchestan university,Zahedan,Iran.

ARTICLE INFO

Article type
Review article

Article history
Received: 21 Apr 2021
Revised: 12 Jun 2021
Accepted: 21 Dec 2021

Keywords
ALS
Diagnosis
Treatment

ABSTRACT

Amyotrophic lateral sclerosis (ALS) also known as motor neuron disease is a destroying neurodegenerative disease that mainly affects the upper and lower motor neurons. It is now believed that primary diagnosis and treatment are essential and useful. Early diagnosis with newer methods prevents the progression of the disease and allows you to choose the right treatment at a more appropriate time. Earlier and more efficient treatment becomes visible to significantly improve the prognosis of this disease. In this article, we define the disease and the methods of diagnosing it, Then the mechanisms of the disease and treatment options based on these are described. ultimately the old and new methods for treatment ALS were reviewed. These methods include: small molecule, nanotechnology, protein therapy, gene therapy, bone marrow transplantation, stem cell therapy, miRNA therapy and gene editing. The purpose of this review article is to help diagnose and select a suitable treatment and improve patients more effectively.

Please cite this paper as:
Malekzadeh Gonabadi N. A comprehensive Review of Amyotrophic Lateral Sclerosis Including: Prevalence, Pathogenesis, Biomarkers Diagnosis, and Current Treatment Options. Rev Clin Med. 2021;8(4):166-171.

Introduction

ALS is a complex multifactorial disease with numerous intrinsic and extrinsic factors underlying disease pathogenesis such as glutamate excite toxicity, mitochondrial dysfunction, oxidative stress, altered glial cell function, disabled axonal transport, protein aggregations, immune reactivity, neurotrophic factor loss and neuro inflammation. These several reasons and the diffuse motor neuron degeneration in ALS caused problems to treatment development for this disease (1) Patients with ALS become progressively weaker over months to years, until death from neuromuscular respiratory failure, typically 2–5 years after the first symptoms. ALS is sometimes seen in conjunction with another neurodegenerative disease, frontotemporal dementia (FTD), in which behavioral, language and executive impairments can occur. Most of sick people are 70 years old . Its estimated that the risk of ALS is ~1 in 300 and the incidence is 1–2 per 100,000 persons. The point prevalence, how¬ever, is only 5 per 100,000 persons because of the very poor prognosis. Non-genetic risk fac-tors include: Age and male sex that patient populations have a 3:2 males: female ratio. This sex difference, depends to structure of the studied group, as men predominate in younger groups of patients (2). Here, we review

***Corresponding author:** Najmeh Malekzadeh Gonabadi, Faculty of science , Department of biology, Sistan and Baluchestan,university,Zahedan,Iran.*
***E-mail:** najmehmalekzadeh@yahoo.com*
***Tel:** 09153209644*

present and future clinical methods for ALS therapy.

Literature review

1.Diagnosis

1.1Magnetic resonance imaging (MRI)

techniques, Diffusion tensor imaging (DTI), Fractional aniso tropy (FA), Tractography analyses, Proton magnetic resonance spectroscopy (1H-MRS). these techniques have been applied to increase our understanding of changes in different brain regions in ALS. For recognizing the prognosis and clinical decisions, Neuroimaging technique is used. Measuring lower FA by Using DTI, in the cortico spinal tract (CST) and hypermetabolic patients with ALS have a shorter life (3,4).Preconditioning (PC) is a phenomenon where in a moderate factor induces resistance to a later, severe injury. The cycad neurotoxin beta-methylamino-Lalanine (L-BMAA) is able to prevent of ALS progression in SOD1 G93A mice and a membrane transporter that named NCX3, is able to control the deregulation of ionic homeostasis occurring during ALS, its estimated that it can take part in this neuro protective effect. A sub toxic dosage of L-BMAA is used as preconditioning stimulus and because of this protective effect of NCX3 it can be used as a new therapeutic target (5).

More importantly, IL-6 protein levels of ALS M1 macrophages positively correlated with disease burden, a positive marker for disease progression rates is TNFα protein levels of ALS M1 macrophages. It shows that monocytes from ALS patients are more readily activated and differentiated to a pro-inflammatory M1 phenotype, and represent a potential target for immune modulatory therapy (6). Finally, iron is considered as a biomarker. It has been demonstrated that the excess ferritin level can worsen muscle degeneration and shorten patients' (7).

2.Pathogenesis mechanism

2.1ER pathway

Signaling between the endoplasmic reticulum (ER) and mitochondria has important function in ALS and some problems in mitophagy causes damages in organelles. Finally, there are inflammatory responses with the presence of inflammatory mediators and cytokines in ALS. So one method for treatment is anti-inflammatory agents. The biological conundrum is; how so many apparently disparate physiological processes are damaged collectively? The therapeutic challenge is deciding which of these different processes are prior for drug discovery (8). Unfolded protein response (UPR), which is strongly activated in most neurodegenerative disorders in the endoplasmic reticulum (ER) has great function in keeping proteostasis. When UPR signaling pathways activated,response (UPR), which is strongly activated in most neurodegenerative disorders in the endoplasmic reticulum (ER) has great function in keeping proteostasis. When UPR signaling pathways activated, transcription factors can change the expression of genes involved in protein folding and degradation with pro-survival effects. Studies show that IRE1α- XBP1 and ATF6 pathways are strongly activated in ALS. Some gene like a DNAJB9, SEL1L and OS9 that have a role in chaperone activity and ER-associated degradation (ERAD) confirm the function of XBP1 and ATF6 gene in ALS; therefore, known to be new therapeutic strategies (8,9).

2.2 The kynurenine pathway (KP)

basic route for tryptophan (TRP) catabolism and causes ALS. The intermediates generated by this pathway significantly increase in ALS motor cortex and spinal cord (10). lipid patterns in the CSF could be predict the clinical evolution of ALS patients. So we can find pathologic mechanisms associated with the deregulation of lipid metabolism and signaling Lipid profiles (11).

2.3 Purinergic receptor pathway

P2X4 and P2X7 receptors that belong to purinergic system contribute in microglia reactivity and astrogliosis, so these receptor has an important role in ALS pathogenesis. Also Adenosine A2A receptor has some effects on disease depending on the disease state. During the early phase of ALS, mediates excite toxicity effects on neuromuscular. Caffeine has an effect on the life length of the ALS patient because it decreases A2AR levels in the spinal cord (12,13).

3. Treatment for ALS

3.1 DRUGs

HLSJ is a Traditional Chinese medicine formula which has indicated that HLSJ may have therapeutic effects in ALS patients. Additionally, HLSJ moderate the atrophy of the gastrocnemius muscles and reduce the cell program death and inflammatory levels in the spinal cords of SOD1G93A mice. HLSJ has been made of six herbs could delay the disease progression (14).

3.2 Gene and protein therapies

NRG1 gene therapy activated the survival pathways in muscle and spinal cord, increasing the number of surviving motoneurons (MNs) and neuromuscular junctions and reducing the astroglial reactivity in the spinal cord of the treated SOD1G93A mice. Furthermore, NRG1-I overexpression preserved motor function and delayed the onset of clinical disease (15).

VEGF protein family have a role in angiogenesis and lymph angiogenesis, moreover they have neurotropic effects. VEGF-A, B functions as a survival or

protection neurons factors. There is a clear potential for VEGF therapy in ALS patient. VEGF-A165 protein is tolerated and safe and there are positive effects such as delayed loss of motor function and increasing the quality of life (16).

3.3 Small molecule therapy

C9ORF72 interacted with endosomes and was required for normal vesicle trafficking and lysosomal biogenesis in motor neurons is the most common cause of amyotrophic lateral sclerosis (ALS). Repeating expansion reduces C9ORF72 expression, results in neurodegeneration, cooperativity between gain- and loss-of-function mechanisms.

Restoring C9ORF72 levels or augmenting its function with constitutively active RAB5 or chemical modulators of RAB5 effectors rescued patient neuron survival and ameliorated neurodegenerative processes in both gain- and loss-of-function C9ORF72 mouse models. So Small molecule and genetic regulators of endosomal trafficking can be a target therapy for ALS (17,18).

3.4 miRNA therapy

There are two models of miRNA-based therapeutics. miRNA antagonists inhibit endogenous miRNAs that have a toxic gain-of-function in diseased tissues, and involve the use of an anti-miR—a chemically modified antisense RNA—to knockdown miRNA. Another miRNA therapeutics include miRNA mimics and miRNA replacement therapies, which can reintroduce miRNAs into cells that decreases miRNA and reactivate key pathways (19). An antisense oligonucleotide (ISIS 333611) that targets SOD1 mRNA to halt the production of the mutant protein has been proved to be effective and safe when deliv¬ered to the CSF of patients with SOD1-related familial ALS (20). Increasing of MIR208B and MIR499 levels in the muscles of ALS patients with a slower disease progression is recognized. Some molecular signaling that have a role in muscle regeneration is blocked during the disease, so we could design new treatment protocol for this factors (19,21).

3.5 Epigenetic therapy

Dysregulation in acetylation homeostasis has been implicated in the pathogenesis of the amyotrophic lateral sclerosis. Epigenetic drugs, modulating the enzymatic activity of histone deacetylases (HDACs) and histones acetyl transferases (HATs) have emerged as a potential tool to cure neurodegenerative diseases In ALS patients there are an unbalance of HATs and HDACs activity. increased levels of HDAC4, during the progression of the disease were also observed. So miRNA for these could be a new target therapy. Another study shows restoration of the acetylation state of RelA in the spinal cord, delaying the onset and increasing the lifespan of SOD1(G93A) mice (22).

3.6 Gene Editing

The most common reason of ALS is Hexanucleotide-repeating expansions in the C9ORF72 gene. The nucleotide-repeating expansions are translated into dipeptide-repeat (DPR) proteins, which are aggregation prone and may contribute to neuro degeneration. Modifier can change the protein and help the treatment. For example TMX2, regulated the ER-stress signature created by C9ORF72 DPRs in neurons and improved survival of human induced motor neurons of the patients with C9ORF72 ALS. Gene editing technique such as the CRISPR–Cas9 system can use to perform genome-wide gene-knockout screens for suppressors and enhancers of C9ORF72 DPR toxicity in human cells (23,24).

3.7 Bone marrow transplantation

Bone marrow-derived hematopoietic stem cells into ALS mice leads to improvements disease and enhanced motor neuron survival by two pathways: Transplanted cells differentiate into endothelial cells and with placement into capillary walls in the spinal cord and causing the BSCB restoration. Second, transplanted cells potentially regulate the inflammatory microenvironment in the spinal cord (1).

3.8 Stem cell therapy

Stem cell therapy is promising in the treatment of ALS since stem cells have the potential to be grown to slow the progression of motor neuron disease or even replace motor neurons. Mesenchymal stem cells (MSCs) are bone marrow (BM) cells that are differentiated into mesodermal cell derivatives. It has been indicated that MSCs to delay disease progression. A clinical trial in the IV administration of MSCs in ALS patients was shown to be safe and induced immediate immune modulatory activity. In addition to BM, adipose-derived MSC (ASC) has been utilized too. ASC was found to migrate into damaged tissues and exert immune modulatory activity by inhibiting both in vitro and in vivo T cell proliferation (25).

Cell-based clinical trials demonstrate the safety of both neural stem cells and mesenchymals stem cells but lack definitive evidence of efficacy in ALS patients. The protocols for cellular expansion in most clinical studies are not reported or are suboptimal. In vivo molecular imaging, advances in tissue engineering and the use of Nano materials are promising technologies for improving future clinical trials (26).

3.9 Nano therapy

A challenge for ALS treatment is the delivery of different drugs, trophic factors and bio macromolecules across the BBB/BSCB to CNS.

Nanotechnologies offers potential solutions for these limitations. Nano materials may be designed for:Glutamate inhibitor, anti-oxidant, anti-inflammatory therapeutic agents, iron chelators, SOD1-loaded poly (lactic-co-glycolic acid) (PLGA), to deliver novel DNA, antisense oligonucleotides (ASOs) and RNA for gene therapy (27).

Neurotrophic proteins or drug compounds that promote neuronal survival and regeneration, HDAC6 inhibitor-encapsulated nanoparticles, stem cell delivery. A variety of new approaches have been applied to the problem of penetrating the BBB to increase the therapeutic index of a variety of therapeutics: Glycosylated nano carrier, Virus mimic nanomaterials, Exosomes (28).

3.10 Biological drugs for ALS

The antisense drug and monoclonal antibody Drug repurposing: Finding new uses for existing drugs that called drug repurposing strategy is a fruitful method to discover and develop new drugs for rare diseases. Several approved drugs for many different medical needs are currently in clinical development for ALS.

Triumeq an antiretroviral, an HIV medication, is now investigated in a Phase IIa open-label study to determine its safety and tolerability in Motor Neuron Disease (MND)/ALS patients, sponsored by Neuroscience Trials Australia (29).

FDA-Approved Treatments for ALS (30).

Name of Drug	Mechanism of function
Riluzole	glutamate antagonist
Edaravone	antioxidant and free radical scavenger that has been shown to reduce excess oxidative stress and cell death
Four compounds ready for phase 3 clinical trial investigation	
Masitinib	The oral tyrosine kinase inhibitor masitinib targets microglia, macrophage, and mast cell activity in the central and peripheral nervous systems to provide a neuroprotective effect
Tofersen	an antisense oligonucleotide being investigated for treatment of ALS caused by mutations in the SOD1 gene
Ravulizumab-cwvz	long-acting humanized monoclonal antibody that blocks terminal complement C5 activation
Mesenchymal stem cell (MSC)-neurotrophic factor (NTF) cells	autologous bone marrow-derived MSC platform that expands and induces the cells to secrete high levels of NTFs (MSC-NTF) to promote the growth of nerve tissue and improve neuroprotective function. The compound is delivered via intramuscular or intrathecal injection

Example of Clinical trial phase 3 for ALS (31)

Drug	Title study
MT-1186	Safety Extension Study of Oral Edaravone
Tauroursodeoxycholic Acid	Safety and Efficacy of Tauroursodeoxycholic (TUDCA) as add-on Treatment
MediCabilis CBD Oil	Efficacy of Cannabinoids in Amyotrophic Lateral Sclerosis or Motor Neurone Disease
MN-166	Evaluation of MN-166 (Ibudilast) for 12 Months Followed by an Open-label Extension for 6 Months in Patients With ALS (COMBAT-ALS)
Zilucoplan ,Verdiperstat ,CNM-Au8 ,Pridopidine	HEALEY ALS Platform Trial - Master Protocol

Conclusion

ALS is a complex genetic disease that with the identification of different pathogens and the identification of genes involved in causing the disease, now a great step has been taken to treat it. With the emergence of different methods of diagnosis and finding the gene involved in the disease, the appropriate treatment method can be selected. Today, there are various treatments such as biological drugs, miRNA therapy, cell therapy, etc. To overcome the limitations of these methods, better delivery methods of these drugs are used, such as nanotechnology, which has led to more effective improvement and slowing down the progression of the disease. Also, the existence of model animals has provided the possibility of simultaneous testing of several treatment methods and the possibility of optimizing different treatments and achieving appropriate cell therapy protocols.

The choices of several simultaneous methods for complex diseases such as cancer, etc. are used today. Therefore, the selection of a suitable combination treatment protocol for these patients should be done. The choice of treatment is made by patients according to the individual's understanding of his position and the role of culture and value system, Age, education, phonemic fluency, etc. Therefore, educational systems must also provide the necessary training programs for the patients.

Conflict of interest

There is no any kind of conflict of interest in this article.

References

1. Garbuzova-Davis S, Kurien C, Thomson A, et al. Endothelial and Astrocytic Support by Human Bone Marrow Stem Cell Grafts into Symptomatic ALS Mice towards Blood-Spinal Cord Barrier Repair. Sci Rep. 2017;7:884.
2. Al-Chalabi A, LH van den Berg, Veldink J. Gene discovery in amyotrophic lateral sclerosis: implications for clinical management. Nat Rev Neurol. 2017;13:96-104.
3. Montibeller L, Belleroche J De. Amyotrophic lateral sclerosis (ALS) and Alzheimer's disease (AD) are characterised by differential activation of ER stress pathways: focus on UPR target genes. Cell Stress Chaperones. 2018;23:897-912.
4. Foerster BR, Welsh RC, Feldman EL. 25 years of neuroimaging in amyotrophic lateral sclerosis. Nat Rev Neurol. 2013;9:513-524.
5. Steyn FJ, Ioannides ZA, Eijk RPAV, et al. Hypermetabolism in ALS is associated with greater functional decline and shorter survival. J Neurol Neurosurg Psychiatry. 2018;89:1016-1023.
6. Anzilotti S, Brancaccio P, Simeone G, et al. Preconditioning, induced by sub-toxic dose of the neurotoxin L-BMAA, delays ALS progression in mice and prevents Na(+)/Ca(2+) exchanger 3 downregulation. Cell Death Dis.2018;9:206.
7. Sheykhansari S, Kozielski K, Bill J, et al. Redox metals homeostasis in multiple sclerosis and amyotrophic lateral sclerosis: a review. Cell Death Dis. 2018;9:348.
8. Du Y, Zhao W, Thonhoff 2 JR, et al. Increased activation ability of monocytes from ALS patients. Exp Neurol. 2020;328:113259.
9. Lau D, Hartopp N, Welsh NJ, et al. Disruption of ER-mitochondria signalling in fronto-temporal dementia and related amyotrophic lateral sclerosis. Cell Death Dis. 2018;9:327.
10. Chen Y, Stankovic R, Cullen KM, et al. The kynurenine pathway and inflammation in amyotrophic lateral sclerosis. Neurotox Res. 2010;18:132-142.
11. Blasco H, Veyrat-Durebex C, Bocca C, et al. Lipidomics Reveals Cerebrospinal-Fluid Signatures of ALS. Sci Rep. 2017;7:17652.
12. Sebastião AM, Rei N, Ribeiro JA. Amyotrophic Lateral Sclerosis (ALS) and Adenosine Receptors. Front Pharmacol. 2018;9:267.
13. Oliveira-Giacomelli A, Naaldijk Y, Sardá-Arroyo L, et al. Purinergic Receptors in Neurological Diseases With Motor Symptoms: Targets for Therapy. Front Pharmacol. 2018;9:325.
14. Zhou Q, Wang Y, Zhang J, et al. Fingerprint analysis of Huolingshengji Formula and its neuroprotective effects in SOD1(-G93A) mouse model of amyotrophic lateral sclerosis. Sci Rep. 2018;8:1668.
15. Mòdol-Caballero G, Herrando-Grabulosa M, Verdés S, et al. Verdés Gene therapy for overexpressing Neuregulin 1 type I in skeletal muscles promotes functional improvement in the SOD1(G93A) ALS mice. Front Neurol. 2021;12:693309.
16. Keifer OP Jr, DM O'Connor, Boulis MN. Gene and protein therapies utilizing VEGF for ALS. Pharmacol Ther. 2014;141:261-271.
17. Shi Y, Lin S, Staats KA, et al. Haploinsufficiency leads to neurodegeneration in C9ORF72 ALS/FTD human induced motor neurons. Nat Med. 2018;24:313-325.
18. Mathew B, Ruiz P, Pathak V, et al. Development of novel small molecules for the treatment of ALS. Bioorg Med Chem Lett. 2020;30:126950.
19. Pietro LD, Baranzini M, Berardinelli MG, et al. Potential therapeutic targets for ALS: MIR206, MIR208b and MIR499 are modulated during disease progression in the skeletal muscle of patients. Sci Rep. 2017;7:9538.
20. Paez-Colasante X, Figueroa-Romero C, Sakowski SA, et al. Amyotrophic lateral sclerosis: mechanisms and therapeutics in the epigenomic era. Nat Rev Neurol. 2015;11:266-279.
21. Kovanda A, Leonardis L, Zidar J, et al. Differential expression of microRNAs and other small RNAs in muscle tissue of patients with ALS and healthy age-matched controls. Sci Rep. 2018;8:5609.
22. Schiaffino L, Bonafede R, Scambi I, et al. Acetylation state of RelA modulated by epigenetic drugs prolongs survival and induces a neuroprotective effect on ALS murine model. Sci Rep.2018;8:12875.
23. Lim CKW, Gapinske M, Brooks AK, et al. Treatment of a Mouse Model of ALS by In Vivo Base Editing. Mol Ther. 2020;28:1177-1189.
24. Kramer NJ, Haney MS, Morgens DW, et al. CRISPR-Cas9 screens in human cells and primary neurons identify modifiers of C9ORF72 dipeptide-repeat-protein toxicity. Nat Genet. 2018;50:603-612.
25. Yacila G, Sari S. Potential therapeutic drugs and methods for the treatment of amyotrophic lateral sclerosis. Curr Med Chem.2014;21:3583-3593.
26. Mazzini L, Ferrari D, Andjus PR, et al. Advances in stem cell therapy for amyotrophic lateral sclerosis. Expert Opin Biol Ther. 2018;18:865-881.
27. Tamaki Y, Shodai A, Morimura T, et al. Elimination of TDP-43 inclusions linked to amyotrophic lateral sclerosis by a misfolding-specific intrabody with dual proteolytic signals. Sci Rep. 2018;8:6030.
28. Wang GY, Rayner SL, Chung R, et al. Advances in nanotechnology-based strategies for the treatments of amyotrophic lateral sclerosis. Mater Today Bio. 2020;6:100055.
29. Martinez A, Palomo Ruiz MD, Perez DI, et al. Drugs in clinical development for the treatment of amyotrophic lateral sclerosis. Expert Opin Investig Drugs. 2017;26:403-414.
30. Chen, JJ. Overview of current and emerging therapies for amytrophic lateral sclerosis. Am J Manag Care. 2020;26:S191-S197.
31. Filipi T, Hermanova Z, Tureckova J, et al. Glial Cells-The Strategic Targets in Amyotrophic Lateral Sclerosis Treatment. J Clin Med. 2020;9:261.