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# Advancements In Treatment Of Amyotrophic Lateral Sclerosis (ALS) – symptoms, causes, gene theraphy. Literature review

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**Abstract:**

**Introduction and Objective:** Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease characterized by the loss of motor neurons. Each year, amyotrophic lateral sclerosis is diagnosed in 4-5 people per 100,000 population. The disease is commonly known as Lou-Gehrig's disease after the famous American baseball player who died two years after receiving the diagnosis at the age of 39. The etiology of the disease is not fully understood, but gene mutations that contribute to the development of ALS have been identified. Such mutations include the gene encoding superoxide dismutase type 1 (SOD1), C9orf72, TBK1 and FUS125, among others. Since the first SOD1 mutation was identified as the genetic cause of SLA, there has been a significant milestone in clinical research aimed at finding a cure for this terminal and dreaded disease. In this article, we will discuss the early symptoms of ALS, factors that increase the risk of developing the disease and, most important, the knowledge and latest treatments, such as the use of antisense oligonucleotides (ASOs).

**Aim of Study**: This article presents up-to-date treatments for the neurodegenerative disease amyotrophic lateral sclerosis, focusing on recent clinical trials and their potential therapeutic targets. We will also review interdisciplinary treatments such as mechanical ventilation and pain management. We will also discuss factors that increase the risk of developing this incurable disease.

**Materials and methods:**

For this review article, databases such as PubMed and Google Scholar were searched. The search terms used to find relevant scientific articles included: Amyotrophic Lateral Sclerosis, ALS treatment, Tofersen, Riluzole. Ultimately, 35 research articles were cited.

**Keywords:** Amyotrophic Lateral Sclerosis, El escorial scale, Tofersen, Riluzole, SOD1

## Introduction:

Amyotrophic lateral sclerosis (ALS) is a terminal neurological disease characterized by degeneration of motor neurons in the brain and spinal cord. The first symptoms of ALS include muscle atrophy and weakness. This is followed by paralysis of voluntary muscles, including respiratory muscles in the final stage. Damage to motor neurons leads to symptoms such as spasticity, exaggerated reflexes, clonus movements and fasciculations. There are currently two forms of the disease - the limb-on-set form (about 3/4 of SLA cases) and the bulbar-on-set form (about 1/4 of SLA cases)[1]. It is estimated that about 50% of ALS patients die within 30 months of the onset of symptoms, mostly due to respiratory failure [2]. The average age of onset is rated at 43 to 52 years, compared to 58 to 63 years for sporadic forms of the disease. The familial amyotrophic lateral sclerosis (FALS) form of ALS affects 5-10% of all patients [1]. An interesting fact noted by neuropathologist Harry Zimmerman is the remarkable-higher prevalence of ALS, parkinsonism and dementia on Guam. Epidemiological studies showed that the number of ALS patients on the island were 50 times higher than anywhere else in the world. [3]

To evaluate symptoms and disease progression, the Amyotrophic Lateral Sclerosis Functional Rating Scale and its revised version (ALSFRS-R) were developed in the 1990s. This scale has become a key main endpoint in ALS clinical trials to evaluate functional disability and it is currently considered the gold standard for ALS patients[4]. The ALSFRS-R consists of 12 components that assess various aspects of a patient's functional abilities. The main components include: speech, salivation, swallowing, handwriting, cutting food and handling utensils, dressing and hygiene, turning in bed, walking, climbing stairs, dyspnea, orthopnea, and respiratory function. Each item is scored on a scale from 0 to 4, with higher scores

indicating better functional ability. The total score ranges from 0 to 48, with lower scores indicating increased disability and the necessity for enhanced patient care [5].

**First symptoms, El Escorial scale**

ALS gained grim notoriety in 1941, when American baseball player Henry Louis Gehrig (commonly known by his nickname Iron Horse) died - to this day, we can often see ALS described as Lou Gehrig's disease. ALS is characterized by variation regarding clinical features - both upper and lower motor neuron symptoms are present. Upper motor neuron (UMN) symptoms include hyperreflexia, lack of coordination, increased spasticity and clonus movements. Typical LMN symptoms include dysarthria and dysphagia, muscle weakness, muscle atrophy and fasciculations. Most patients initially present with weakness in the hand, shoulder girdle or complain of a drooping foot that makes it difficult for them to move. An uncommon symptom, seen in a minority of patients in the early stages of the disease, is weakness of the respiratory muscles or general weakness combined with weakness of the muscles of the bulbar (difficult swallowing, unclear speech). In the later stages of the disease, cognitive impairment may occur - problems with memory, thinking or emotions. Other behavioral changes include disinhibition, perseverative behavior or pathological crying and laughing (emotional lability)[9] [24]. Diagnosis of the disease is based on the El Escorial criteria. This is the most important scale used to diagnose ALS. According to the criteria, diagnosis requires: confirmation of lower motor neuron damage by clinical, EMG or histological examination, confirmation of upper motor neuron damage by clinical examination, demonstration of progression of motor abnormalities in one area or their appearance in subsequent topographic areas by history or clinical examination, exclusion by EMG or histological examination of other diseases that may explain the symptoms of upper or lower motor neuron damage, exclusion by neuroimaging studies (CT, MR) of other diseases that may explain the observed clinical and electrophysiological EMG abnormalities. The diagnosis of ALS is divided into four categories based on specific criteria. Certain ALS is identified by the presence of UMN and LMN damage in at least three anatomical areas. Clinically probable ALS occurs when UMN and LMN symptoms are present in at least two regions, and at least some UMN damage symptoms come from areas higher than those from which LMN damage symptoms come. Probable ALS, which is laboratory-confirmed, includes the presence of UMN and LMN symptoms in one region with electromyographic (EMG) evidence of LMN involvement in another region. Possible ALS is characterized by the presence of UMN and LMN symptoms in one region or UMN symptoms in two or three regions, which can include conditions such as monomelic ALS, progressive paralysis and primary lateral sclerosis. It takes about 10-16 months from the onset of the first symptom to a proper diagnosis. ALS is a difficult disease to diagnose due to the lack of a characteristic ALS marker, the plurality of symptoms also present in other neurodegenerative diseases, which often results in the diagnosis of ALS being made by excluding other diseases. [6] [7] [8] Laboratory tests that should be done to diagnose ALS include: ESR, CRP, serum and urine protein electrophoresis, thyroid function tests, calcium-phosphate balance testing and cerebrospinal fluid analysis. Testing for heavy metals is indicated in patients with a history of metal exposure. In Ashkenazi Jews, it may be indicated to test the activity of the alpha and beta subunits of hexaminidase B (hexaminidase deficiency can mimic the symptoms of ALS - in fact, it is Tay-Sachs disease). It is important to do imaging tests - the most common is magnetic resonance imaging of the brain and spinal cord (often to eliminate other diseases

from the differential diagnosis). On histological examination, characteristic features that can be observed include loss of myelin fibers, loss of axons and regeneration [10][22] A pathological sign of ALS is ubiquitinated cytoplasmic inclusions consisting of Tar-DNA binding protein.[11] Research is currently underway to find a useful marker in the differential diagnosis of ALS and in predicting disease progression. Blood neurofilament light chain can be used as a biomarker with prognostic value for ALS. In ALS patients, serum NfL value correlates with disease progression; higher NfL levels indicate shorter survival. Studies have shown that NfL levels in the blood of ALS patients are about four times higher than in controls, which represents great potential for NfL as a biomarker in the future. [12]

**Risk factors**

There are many risk factors that can increase the possibility of developing ALS. First of these is the significant association between ALS and active sports participation. A cohort study of Italian soccer players revealed a major increase in the prevalence of this neurodegenerative disease. Analysis of the study proved an association between head injuries in football players (odds ratio [OR] = 3.2; 95% CI = 1.2-8.1). A special terminology has been defined - chronic post-traumatic encephalopathy, which is the result of repeated head injuries observed among professional athletes and war veterans. Long-term exposure to head trauma can lead to neurodegenerative changes and the subsequent onset of ALS. Studies in the nutrition area have noted that consuming large amounts of glutamate can have adverse effects on ALS patients. When glutamate receptors are over-stimulated, intracellular calcium levels increase, which can cause neuronal death. On the other hand, omega-3 fatty acids, vitamin E and dietary fiber may have a protective effect, because of their anti-inflammatory properties. It has been proven that omega-3 fatty acids combined with vitamin E reduce the risk of ALS by up to 60%. [10] Another potential risk factor developing ALS are lithium and manganese. A case-control study revealed that blood lead levels were higher among newly diagnosed ALS cases compared to controls, even after careful adjustment for bone turnover status and polymorphism. In addition, as for manganese, it penetrates the barriers of the choroid plexus system and accumulates in the central nervous system. Medical work has proven that manganese concentrations were elevated in cerebrospinal fluid samples from ALS patients. Pesticides (particularly chlorinated compounds, pyrethroids, herbicides and fumigants) are another potential etiological factor. Meta-analyses have identified a significant correlation between pesticide use and a higher risk of SLA. The coincidence of exposure to β-methylamino-L-alanine (BMAA) and the incidence of amyotrophic lateral sclerosis is an interesting aspect. This association may explain the mystery of the higher incidence of ALS on Guam and in the Western Pacific. [2] An important lifestyle-related determinant is smoking. Smoking may be an important risk factor in women, especially those after menopause.

**Familial amyotrophic lateral sclerosis (FALS)** - the genes responsible for the development of the disease. It is estimated that the familial form of ALS accounts for about 5-10% of all cases. The most common mutation (about 25-40% of FALS cases) is caused by an expansion of intron hexanucleotide repeats in the gene encoding open reading frame 72 (C9ORF72) of chromosome 9. Another 12-20% of FALS cases are caused by mutations in the SOD1 gene. [13] [14] TARDBP, FUS ALS2, SETX, VAPB, DCNT1, FIG4 are also known mutations involved in ALS pathogenesis[15]. In addition, studies confirm the simultaneous occurrence of some genes together with frontotemporal dementia, demonstrating a molecular link

between those diseases. [16] The familial form of ALS is characterized primarily by cognitive and neurobehavioral impairment - patients often have speech and swallowing disorders ( bulbar dysfunction) as the first symptom [9].

**Medications used in ALS.**

**Riluzole** is an organic chemical compound benzothiazole derivative, a glutamate antagonist. In the pathogenesis of ALS, elevated levels of glutamate in the cerebrospinal fluid have been proven to be detected in about 40% of patients and correlated with more severe spinal symptoms. Concentrated liquid and oral forms of riluzole were developed and approved by the FDA in 2018 and 2019, respectively. A dose of 100 mg per day has been shown to improve survival by 15% and prolong overall survival by nearly 3 months after 18 months of treatment. This is especially important in patients with mild to moderate disease, as it significantly enhances long-term. It is now accepted that riluzole therapy should be continued regardless of its cost [1] [17] The main goal of riluzole therapy is to reduce excitotoxicity, especially of glutamate, due to the fact that riluzole is a glutamate antagonist. In addition, riluzole acts as a sodium channel blocker in presynaptic neurons, which reduces the release of glutamate into the synaptic gap. It also inhibits AMPA and N-methyl-D-aspartate (NMDA) receptors on postsynaptic neurons. Another effect of riluzole is to reduce gamma-aminobutyric acid (GABA) reuptake and enhance the GABA receptor.[9] Another mediacation uses in ALS patients is Edaravone. **Edaravone** is a well-known drug in Japan - it has been used to treat acute stroke for more than two decades. In a phase II study, 20 patients with SLA received 30 or 60 mg of edaravone, and a significant improvement was achieved in ALSFRS score (ALSFRS-R) was observed over the 6-month treatment period. [12] Edarvone was approved by the FDA in 2017. It function as a free radical scavenger, reduces oxidative stress, inhibits the formation of hydroxyl and peroxynitrite radicals, and protects neurons, slowing disease progression in ALS patients. [9][18] However, the mechanism of action of edarvone is not fully explained- it has been proven that action on oxidative stress helps to inhibit the progression of the disease . Tauro-ursodeoxycholic acid (TUDCA), which is mainly used to treat cholestasis and in the treatment of gallstones, crosses the blood-brain barrier. This feature can be used to treat ALS. Studies have found that TUDCA has neuroprotective effects and is able to inhibit apoptosis by interfering with the mitochondrial cell death pathway. Consequently, this inhibits oxygen radical production and reduces endoplasmic reticulum stress. Two Phase II studies have demonstrated promising results in ALS, justifying the initiation of a Phase III trial. [18] A retrospective study showed that patients who took 1,000 mg or more of TUDCA daily lived longer [Phase II study]. Research is currently ongoing on the role and validity of ursodeoxycholic acid in the treatment of neurodegenerative diseases such as just ALS, but also other diseases such as Alzheimer's and Parkinson's disease. Pain treatment is an important issue in ALS patients, mainly to improve quality of life. Therapy may be started with paracetamol and non-steroidal anti-inflammatory drugs. If pain control is unsatisfactory, opioids should be included in treatment. If dyspnea is present, the drug of choice is morphine. Morphine can be used either orally, subcutaneously , or through a gastrostomy. The initial dose of morphine is 1 mg orally (every 4-6 hours). The morphine dose should be titrated until the patient achieves target symptom control. In patients in the final stage of the disease and with severe uncontrollable dyspnea, short-acting nondiazepines can be added to morphine. An important element in the interdisciplinary perspective is the prevention of bedsores - providing the patient with

changes in position. During painful muscle spasms, topical warming devices can be used, as well as massage. An important part in the treatment of muscle pain are drugs from the gabapentinoid group (gabapentin, pregabalin). The integration of myorelaxant drugs (baclofen) into the treatment, should be properly analyzed, because the addition of their positive effect, they may carry with them an aggravation of respiratory failure. [19] A fundamental issue in the treatment of ALS is also the proper rehabilitation of the patient - the patient should be equipped with adequate orthopedic equipment, such as orthopedic collars, orthoses, an appropriate decubitus mattress, a wheelchair - depending on the stage of the disease and the patient's symptoms. Regular exercise has been shown to improve and slightly slow the progression of the disease, in addition, ALSFRS-R scores decrease by 0.13 [20][21] It is important that rehabilitation training be sustainable so as not to overload the muscles. Recent studies have shown that people who train twice a week have better results than those who train five times a week. It is also important to choose the right exercises - moderate intensity exercises, such as swimming, for example, are most preferable. It has been proven that there is a correlation between patients who did moderate exercise and a higher density of motor neurons in the ventral horn of the spinal cord, which led to slower muscle atrophy. Therefore, the use of physiotherapy to improve physical fitness is very important, as there is a strengthening of muscle cells that haven't yet been damaged. [21] Taking a multidisciplinary view, is recommended to implement therapeutic exercises before and during the onset of the disease. Analysis has shown that submaximal aerobic activity has a positive effect on slowing the patient's respiratory muscle deterioration (slowing the rate of FVC decline from 15-25% of spirometric values to 7-15%)[20]. Exercise can slow the degeneration of motor neurons, minimize the load on fast twitch muscle fibers, reduce spasticity, strengthen weakened muscles, inhibit fatigue, increase musculoskeletal endurance and improve cardiorespiratory function. Further high-quality studies are needed to best determine recommendations for patients with ALS (appropriate frequency, type, duration) [21]. Swallowing disorders and drooling are other symptoms present in this disease unit. These disorders often occur simultaneously with choking when consuming drinks or food. Small doses of amitriptyline (from 10 to 50-75 mg per night) should be used for such complaints. In later stages of the disease, hyoscine butylbromide, which has a spasmolytic effect, can be used. In cases of severe dysphagia and aphagia, endoscopic gastrostomy (PEG) should be considered. A precondition for PEG insertion is that the patient has at least 50 percent respiratory failure (due to the risk of respiratory arrest during endoscope insertion). Weight loss is often observed in ALS as the disease progresses and is multifactorial-it occurs through a mechanism of muscle tissue loss, hypermetabolism, difficulty eating (swallowing or dyspnea, or decreased appetite). Guidelines recommend that patients have a gastrostomy to allow enteral feeding, and thus maintain adequate nutrition and medications, when weight loss of more than 10% occurs. However, recent studies suggest that insertion of a gastrostomy tube is most effective at an earlier stage (weight loss of 5%). Use of NIV at night (and during the day, if necessary) is associated with a 7-month increase in median survival, as well as improved quality of life. The results of a cohort study of 929 patients suggest that NIV has a beneficial effect on survival in patients with bulbar onset and that a trial of NIV treatment should be offered to all patients, even though it may be poorly tolerated [19][20] A serious problem that troubles patients is the presence of constipation - usually due to reduced physical activity, complete loss of mobility, use of opioids or other medications that slow bowel peristalsis. The basis is constipation prevention - dietary fiber, preparations such as lactulose,

macrogols or glycerin suppositories. Massage of the abdominal lining and rehabilitation exercises to stimulate peristalsis can also be used. In patients, due to weakened respiratory muscles, evacuation of secretions from the airways is very difficult. This leads to a backlog of viscous secretions. This creates a risk of exacerbation of respiratory failure or development of pneumonia. For such problems, the use of mucolytic drugs (such as acetylcysteine) is effective, along with chest patting. If expectoration is not possible, positioning drainage or the previously mentioned use of amitriptyline and hyoscine butylbromide can be used. [19] Another drug that may have an impact on the progression of the disease is Nuedexta. This drug is a combination of chondroitin sulphate and dextromethorphan bromide - it regulates neurotransmission in the nervous system and has been found to have a positive effect on bulbar function[20]. Another perspective in the treatment of ALS that could potentially benefit is neuromodulatory interventions, which use electrical, magnetic and photon stimulation, to modulate neuronal activity and induce a therapeutic response. These procedures are generally adjustable, reversible and have proven some efficacy in the treatment of ALS.[21] In addition, cervical transcutaneous spinal stimulation (cTSS) can be used to improve the patient's condition. It is a non-invasive technique that applies electrical stimulation to the cervical spinal cord through the skin. Studies have shown that when applied to patients, the technique activates motor function by triggering afferent sensory circuits. TES can be applied using electrodes placed on the skin, and the electrical currents delivered are adjusted to achieve therapeutic effects - pain relief, muscle strengthening or neural modulation. TES can lead to increased muscle density in people diagnosed with ALS, both in terms of clinical status and intracortical neuronal responses.[23] Di Lazzaro and other authors proposed that low-frequency rTMS decreases motor cortex excitability, potentially moderating glutamate receptor overactivation, thus reducing the glutamatergic excitotoxicity observed in ALS patients. Studies show that mitochondrial dysfunction appears to be a major mediator of neurodegenerative disease pathogenesis and progression. To delay neuronal damage, photobiomodulation (PBM) appears to be a non-pharmacological therapeutic approach that involves the use of red or near-infrared light (650-1200 nm). This light is absorbed by chromophores present in cells. PBM therapy has the unusual ability to stimulate neurons to produce essential neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF). Electrical stimulation can have both efferent (on alpha motor neurons) and afferent (on afferent nerves) effects, which can result in improved muscle strength and reduced spasticity [23**]** Pramipexole and dexpramipexole, are dopamine receptor agonists used in Parkinson's disease. The drugs have neuroprotective effects and reduce oxidative stress. In a randomized, double-blind phase III trial in SLA, dexpramipexole was generally well tolerated, but no favorable results were found, despite significant benefits in a phase II study involving SLA patients [24]. Calcium channel blockers may be effective in the treatment of ALS, as they reduce the further effects of glutamate excitotoxicity by stopping calcium inflow, leading to reduced excitability of motor neurons in the cerebral cortex and spinal cord. However, a randomized trial showed that nimodipine was ineffective in slowing the progression of ALS. Further studies are needed to determine the role of calcium channel blockers in slowing disease progression. There are reports of neuroprotective benefits of methylcobalamin (a vitamin B12 analog) at ultra- high doses. A long-term randomized controlled phase II/III trial involving 373 patients with ALS showed a lower decrease in ALSFRS-R score along with low treatment-related adverse events. High-dose methylcobalamin treatment may reduce symptom progression if it is

implemented early enough [24]. Another compound that researchers are interested in is the antimalarial drug - pyrimethamine. Studies have found that patients taking pyrimethamine had reduced levels of SOD1 in the cerebrospinal fluid of SLA patients. In cell culture systems, pyrimethamine reduces SOD1 levels. In patients with ALS caused by SOD1 mutations, pyrimethamine can significantly reduce the total SOD1 protein content in CSF. [24] Another potential drug that can inhibit the progression of ALS symptoms is the combination of nebivolol and donepezil. The results showed that nebivolol-donepezil significantly reduced cytokine levels in microglia cell lines, inhibited nuclear translocation of nuclear factor κB in HeLa cells, which protects against neuronal loss and promotes differentiation of neuronal precursor cells into motor neurons. PXT864, a low-dose combination of acamprosate and baclofen, has shown the ability to protect neuromuscular connections and maintain the integrity of motor neurons in glutamatergic-damaged primary neuron and muscle models, suggesting that it may be a promising therapeutic strategy for ALS. [9] Iron is essential for all mammalian cells due to the element's role in many cellular processes. It's been documented that dysfunction of motor neurons in the spinal cord can affect cellular iron homeostasis and enhance oxidative stress. Iron accumulation in the body may play an important role in the pathogenesis of ALS. A mouse model of ALS was used to confirm the role of iron in the pathogenesis of the disease. Studies have shown that impaired iron homeostasis in the central nervous system contributes to disease progression in a mouse model of ALS. It has been reported that administration of Jaeumganghwa-Tang (JGT) delays damage to motor function in hSOD1G93A transgenic mice (human transgenic mice with SOD1 mutation). JGT can reduce the expression of Toll-like receptor 4 (TLR4)-related signaling proteins and improve iron homeostasis in the spinal cord. In addition, the imbalance in ROS production in ALS patients, which can be directly caused by mutant SOD1, can induce Fe-S cluster damage or lead to an iron-responsive regulatory protein (IRE-IRP) mechanism and inactivation of mitochondrial enzymes. Various iron chelators are currently being investigated as potentially promising therapeutic agents. [12] Masitinib is a tyrosine kinase inhibitor. When taken orally, it can reduce microgliosis and motor neuron pathology and prolong survival after paralysis in SOD1G93A mice. In phase 2/3 and 3 clinical trials, masitinib showed efficacy-the risk of death after the drug was reduced by 47%. Masitinib has received orphan drug status from the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). Fasudil is a strong rho kinase (ROCK) inhibitor that slows disease progression in SOD1G93A mice, prolongs survival and reduces motor neuron loss. Fasudil also attenuates the increase in ROCK activity and phosphorylated phosphatase and tensin homolog deleted on chromosome 10 (PTEN). [12] To achieve optimal treatment of ALS, it is important to have the cooperation provided by a multidisciplinary team that includes physiotherapists, occupational therapists, speech therapists, pulmonologists, dieticians, gastroenterologists, social workers, family physicians, neurologists and rehabilitation physicians. Gene therapy in ALS: Gene therapy for amyotrophic lateral sclerosis (ALS) is an experimental treatment that involves inserting genetic material into a patient's cells. A chance to stop the progression of the disease, delaying progression in patients with mutations in genes (SOD1, C9orf72, TARDBP and FUS) is therapy using antisense oligonucleotides targeting specific mutations. Antisense oligonucleotides (ASOs) enable precise modulation of gene expression without altering host DNA. They modify protein expression, thus acting directly on target RNA. Clinical trials of antisense oligonucleotides (ASOs) are currently underway in ALS patients with SOD1, C9orf72, ATXN2 and FUS mutations. In recent years, gene therapy targeting the SOD1 gene

has made significant progress in animal experiments. For example, clustered regularly interspaced short palindromic repeats (CRISPR) / CRISPR-related (Cas9) / sgRNA delivered by the adenovirus (AAV) system can be used to edit the genome. Intravenous injection of AAV9-SACas9 SgrNA into newborn mice with the SOD1-G93A mutation can delete the SOD1 gene. The survival rate of the mice improved by 54.6%, and physiological functions also improved. [25] Another clinical study showed that AAV encoding microRNAs (miRNAs) targeting SOD1 can inhibit mutant gene expression in patients with FALS and SOD1 mutation. [5] A strategy using stable isotope labeling and mass spectrometry has been demonstrated in SOD1 transgenic mice treated with SOD1-degrading ASO. After 30 days of intravenous injection, SOD1 levels in cerebrospinal fluid were minimally reduced, but a >50% reduction in newly synthesized 13C6-leucine-labeled SOD1 could be detected as early as 10 days after the dose. Tofersen (Qalsody) was registered in the European Union on May 29, 2024. In the United States, it was approved by the FDA in April 2023. It is the first registered therapy targeting the genetic cause of ALS - it reduces the expression of the SOD1 gene. The drug is administered intrathecally. [26][5] Initiation of Tofersen treatment has been demonstrated to reduce neurofilament axon damage, reduce neurodegeneration and improve disease outcomes[27]. Another important mutation found in people with ALS is the C9orf72 gene mutation. Although the exact mechanisms are unknown, studies suggest an important role for gain-of-function mediated in part by RNA G4C2 repeats and in part by dipeptide repeat proteins. The first ASO-based strategies focused on reducing toxicity in induced pluripotent stem cells (iPSCs) derived from humans with C9orf72 expansion. Three such studies published simultaneously showed that ASO-mediated reduction of the C9orf72 transcript led to a reduction in nuclear RNA foci in C9orf72-associated ALS. FUS is the most common gene in juvenile and childhood ALS, a mutation that causes a particularly aggressive and early form. In 2019. Ionis Pharmaceutical, in collaboration with Columbia Medical Center, developed an ASO targeting this mutation through delivery and received FDA approval for experimental use in a young woman, after whom the therapy was named Jacifusen. [11] [17] With advances in stem cell technology, stem cell therapy has been proposed as a new treatment for SLA. Stem cells (SCs) have the potential to act on several putative mechanisms involved in disease onset and progression. SC cells may act in neurodegenerative diseases to replace dead cells, but may also restore function through other mechanisms. Motor neurons can be generated in vitro from stem cells derived from a variety of sources, including embryonic stem cells (ESCs), induced pluripotent stem cells (iPS) and nervous system stem cells (NSCs). Moreover, astrocytes clearly play a role in the pathogenesis of SLA, and impaired astrocyte function clearly promotes neurodegeneration. Recent studies suggest that even during normal aging, astrocytes become less supportive of motor neurons, suggesting a role for aging in significant astrocyte-associated motor neuron death in a rodent model.[28][29] Astrocyte precursors or astrocytes derived from stem cells promote axonal growth, support mechanisms involved in oligodendrocyte myelination, are also able to modulate the host immune response, deliver neurotrophic factors and provide protective molecules against oxidative or excitotoxic damage. Studies in chimeric mice have shown that administration of wild-type glial cells in a model of ALS can improve the disease phenotype. In the event of injury, stress or CNS damage, astrocytes enter a reactive state characterized by changes in their morphology and gene expression profile. Depending on the signal, astrocytes can transform into reactive neurotoxic A1-type astrocytes or neuroprotective A2-type astrocytes. [28][30] Astrocytes in ALS patients show A1-type

characteristics. Toxicity to motor neurons has been demonstrated after co-culture of direct conversion of ALS patients' fibroblasts with SOD1 or C9orf72 mutations to induced neural progenitor cells (iNSCs) and subsequent differentiation into astrocytes (i-astrocytes. [31][32] This toxicity may be mediated by extracellular vesicles secreted by astrocytes containing miRNAs such as miR-494-3p or proteins such as SOD1, phospho-TDP-43 and FUS**.** [33] [34]. Some of the best studied factors secreted by astrocytes are neurotrophins, which induce neuronal development and function. These include brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), vascular endothelial growth factor (VEGF), neurotrophin-3 (NT-3), ciliary neurotrophic factor (CNTF), glial-derived neurotrophic factor (GDNF) and neurturin (NRTN). Lower levels of neurotrophins were found in the cerebrospinal fluid of ALS patients, and their supplementation protected against delaying disease progression. Astrocytes also release extracellular vesicles (with the presence of neuroglobin) that can target close or distant sites with neuronal selective potential and act as neuroprotection against cell damage [34] [35]. These findings support the effectiveness of therapies based on astrocyte replacement in SLA to alleviate overall astrocyte dysfunction, delivering neurotrophic factors to degenerative spinal cord tissue. In conclusion, astrocytes play a key role in ALS and other neurodegenerative diseases. Targeting astrocyte functionality using a variety of therapeutic approaches can provide significant benefits to ALS patients. Step by step, astrocytes are becoming an important component and are showing great potential in the treatment of ALS, based on preclinical studies and preliminary results from clinical trials.Stem cells are a huge hope in the treatment of ALS, so research in this area is intense [28].

In summary, our knowledge of the genetics of ALS has changed significantly over the past 20 years. Scientists have discovered that both familial and sporadic SLA have a genetic basis, and the number of confirmed gene cases is constantly growing. These discoveries are largely due to the desire to study ALS. The observation that genes largely play a prominent role in SLA has led to much research into gene therapy to stop the symptoms of the disease, or even cure it. However, there are still many other genetic “hotspots” that could be therapeutic targets and in the future become a treatment for ALS. Thanks to ongoing research, we can understand the pathogenesis of this neurodegenerative disease, discovering important new pathways relevant to the onset and progression of the disease. Currently, there is no drug to stop the progression of this terminal disease, but with studies and multidisciplinary care, its progression can be delayed and patients can have a better quality of life.

**Conclusions:** The results indicate that association therapies can help decelerate the progression of ALS, improve patients' quality of life and prolong their life expectancy, making them highly promising treatment options. Our knowledge of the genetics of ALS has changed significantly over the past 20 years. Researchers have discovered that both familial and sporadic forms of ALS have a genetic basis, and the number of confirmed gene cases is steadily increasing. The discovery that genes largely play a major role in ALS has led to numerous studies of gene therapy to stop the symptoms of the disease and even cure it. The first drug approved by the FDA was Tofersen. Currently, there is no drug that will stop the progression of this deadly disease, but with research and multidisciplinary care, it is possible to delay its progression, and give patients a better quality of life than 20 years ago.

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