WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Drugs Used in the Treatment of Amyotrophic Lateral Sclerosis Disease

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ABSTRACT:

ALS, also known as amyotrophic lateral sclerosis, is a neurodegenerative disease that primarily affects the motor system but also manifests in extra-motor areas. Progressive

muscle weakness and wasting result from the loss of upper and lower motor neurons in the motor cortex, the brain stem nuclei, and the anterior horn of the spinal cord. The loss of respiratory muscles often restricts survival to 2–5 years following disease onset in ALS, which frequently has a localised onset before spreading to various body parts. In preclinical animal models of amyotrophic lateral sclerosis (ALS), a plethora of investigational medications have been found to slow disease development; however, these drugs either failed to show efficacy in human clinical trials or are currently awaiting approval under Phase I-III trials. The only medication with minor advantages on survival that has been approved by the US Food and Drug Administration for the treatment of ALS is riluzole, a glutamatergic neurotransmission inhibitor. Recent research has shown that the antioxidant medication edaravone, created by Mitsubishi Tanabe Pharma, can effectively arrest the course of ALS in its early stages. A force multiplier for the treatment of ALS is the recently approved medication edaravone.

Keywords: Amyotrophic lateral sclerosis, riluzole, edaravone.

Introduction-

It is thought that amyotrophic lateral sclerosis (ALS), often known as Lou Gehrig's disease or motor neurone disease (MND), is at play. The other 5% to 10% of cases are referred to as genetic ALS because they have a genetic aetiology, which is frequently connected to a family history of the disease. One of two particular genes has disease-causing variations in almost half of these hereditary cases. a neurodegenerative condition where the motor neurons that regulate voluntary muscles gradually disappear. The most prevalent motor neuron disease is ALS. The majority of ALS cases (about 90% to 95%), also referred to as sporadic ALS, have no recognised cause. However, there are environmental and genetic influences. A person's signs and symptoms are used to make the diagnosis, and testing is done to rule out any other probable reasons. A specific form of motor neuron disease is ALS. Motor neurons deteriorate and die, and as a result, they stop communicating with the muscles. This results in the muscles becoming weaker, beginning to twitch (fasciculations), and atrophying (wasting away). The capacity of the brain to initiate and regulate voluntary motions eventually declines. Although it can happen earlier, ALS most frequently strikes persons between the ages of 40 and 70, regardless of race or ethnicity. The nerve cells that regulate voluntary muscular movements like walking and talking are impacted by ALS. Motor neurons are the name for these nerve cells. Motor neurons are divided into two groups. The first group includes the brain, spinal cord, and all of the body's muscles. Upper motor neurons are what we refer to them as. The second group includes all of the body's muscles, starting at the spinal cord. Lower motor neurons are the name given to them.

Both motor neuron populations steadily degrade and eventually die as a result of ALS. Motor neurons stop communicating with the muscles when they are destroyed. Therefore, the muscles are unable to work.

It is possible to pinpoint a genetic aetiology for 10% of ALS patients. The reason of the remaining cases is unknown.

Pathophysiology

Loss of motor neurons in the majority of brainstem motor nuclei, the motor cortex, and the spinal ventral horns are all symptoms of ALS disease. Lower motor neurons have histologically ubiquinated inclusions and axonal swellings that are hypothesised to hold disorganised neurofilaments. Although the precise mechanism causing selective motor neuron degeneration is unknown, there is evidence to suggest that a number of potential causes, including oxidative damage, excitotoxicity, apoptosis, abnormal neurofilament function, deficiencies in axonal transport, aberrant protein processing and degradation, elevated inflammation, and mitochondrial dysfunction, may be involved.

Studying the genes that, when mutated, might cause ALS points to a number of pathways that result from improper protein interactions. These abnormal interactions not only cause the proteins to lose function but, more critically, to gain function, such as a toxic effect on neurons. Potential susceptibility

genes for sporadic ALS are emerging, and it is likely that a complex interplay between genetic and environmental variables is responsible in the majority of cases.

Neuropathology

Skeletal muscle atrophy, motor cortex atrophy, sclerosis of the corticospinal and corticobulbar tracts, thinning of the hypoglossal nerves (which control the tongue), and thinning of the anterior roots of the spinal cord are all symptoms of the disease that are visible to the naked eye when an autopsy is performed. Other than the loss of motor neurons, the majority of ALS variants share two other traits: focal initial pathology, which means that symptoms initially only affect one area of the spinal cord, and progressive continuous spread, which means that symptoms gradually affect more areas of the spinal cord.

Biochemistry-

Although the cause of ALS-related neurodegeneration is still not fully known, it is believed to involve a wide range of cellular and molecular mechanisms. Based on how they normally function, the genes known to play a role in ALS can be divided into three broad categories: those that affect protein breakdown, the cytoskeleton, and those that affect RNA processing. Intracellular aggregations of mutant SOD1 protein prevent protein breakdown. In sporadic ALS, the wild-type (normal) SOD1 protein frequently aggregates in the cytoplasm.

According to theory, mutant SOD1 that has misfolded can aggregate and misfold wild-type SOD1 in nearby neurons in a prion-like way. VCP, OPTN, TBK1, and SQSTM1 are other protein degradation genes that, when defective, can result in ALS. DCTN1, PFN1, and TUBA4A are three genes associated with ALS that are crucial for cytoskeleton upkeep and axonal transport.

ALS genes that code for RNA-binding proteins are many. The nuclear protein TDP-43, which collects in the cytoplasm of motor neurons in almost all instances of ALS, was the first to be identified. Mutations in TARDBP, the gene that codes for TDP-43, are an uncommon cause of ALS, though. Another RNA-binding protein with a similar function to TDP-43, which when altered can result in ALS, is encoded by the FUS gene.

Diagnosis-

ALS, also known as amyotrophic lateral sclerosis, can be challenging to identify in its early stages since its symptoms often resemble those of other illnesses. Tests to rule out other diseases or assist in the diagnosis of ALS may include-

Electromyogram (EMG)-

Multiple muscles are penetrated with a needle via the skin. During the test, the electrical activity of the muscles both during contractions and at rest is recorded. This might reveal whether there is a muscle or nerve issue.

Nerve conduction study-

The capacity of your nerves to activate muscles in various parts of the body is measured in this study. If you have nerve damage, this test can reveal it. Nearly all EMG and nerve conduction investigations are performed in tandem.

MRI-

A high magnetic field and radio waves are used in an MRI to provide precise images of the brain and spinal cord. An MRI can detect tumours in the spinal cord, herniated neck discs, and other diseases that may be the source of your symptoms. Sometimes, the highest- resolution cameras can view ALS changes for themselves.

Blood and urine tests-

The elimination of other potential causes of your symptoms may be aided by having samples of your blood and urine examined in a lab. Typically, individuals with ALS have elevated serum neurofilament light levels, as determined by blood samples. Early in the disease's course, the test may aid in a diagnosis.

Spinal tap, known as a lumbar puncture-

This entails taking a spinal fluid sample for analysis in the lab. A tiny needle is placed between two lower back bones to drain spinal fluid. Although the spinal fluid in ALS patients appears normal, further investigation may reveal another cause of symptoms.

Muscle biopsy-

If your medical professional believes you may have an illness affecting your muscles rather than ALS, you can be given a muscle biopsy. While you are unconscious and being brought to a lab for analysis, a small portion of your muscle is removed.

Nerve biopsy-

A nerve biopsy may be performed if your doctor suspects that you may have a disease of the nerves rather than ALS. You have local anaesthetic, then a small portion of your nerve is removed and sent to a lab for examination.

Symptoms-

Different symptoms are experienced by ALS patients. Which symptoms are present depends on the health of the nerve cells. Typically, muscle weakness is the first sign of ALS, and it grows worse over time. Some indications include:

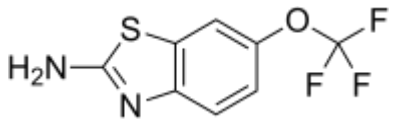
- Difficulty walking or performing daily tasks.
- Falling and tripping.
- Ankle, foot, and leg weakness.
- Hand clumsiness or weakness.
- Speech slurring or swallowing issues.
- Arm, shoulder, and tongue twitching and weakness brought on by cramping.
- Frequent yawning, laughing, or weeping.
- Modifications in thought or behaviour.

ALS frequently starts in the hands, feet, arms, or legs. Later, it spreads to many body parts. Muscles get weaker due to the loss of nerve cells. Eventually, this affects how you breathe, speak, chew, and swallow.

Drug used in the treatment of ALS

- Riluzole
- Rilutek
- Edaravone
- Radicava
- Tiglutik
- Exservan
- Radicava ORS
- Relyvrio
- Qalsody
- Sodium phenylbutyrate/ taurursodiol

Riluzole:



- IUPAC name- 6-(trifluoromethoxy)benzothiazol-2-amine
- Trade names-Rilutek, Tiglutik, Exservan,
- Formula -C8H5F3N2OS
- Molar mass -234.20 g·mol−1

The drug riluzole is used to treat motor neuron illnesses including amyotrophic lateral sclerosis. Riluzole may extend survival by two to three months and delay the start of

tracheostomy or ventilator reliance in some patients. There are pill and liquid forms of riluzole. The U.S. Food and Drug Administration (FDA) authorised riluzole for the treatment of ALS in the country in 1995.

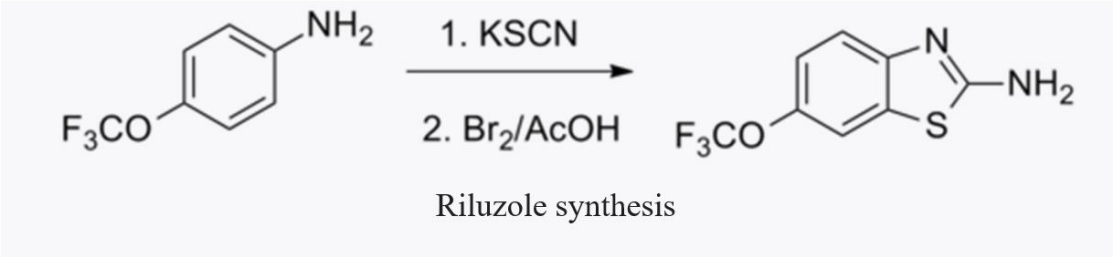
Mechanism of action-

TTX-sensitive sodium channels, which are connected to injured neurons, are preferentially blocked by riluzole.Additionally, kainate and NMDA receptors have been observed to be directly inhibited by riluzole.Additionally, it has been demonstrated that the medication potentiates postsynaptically GABAA receptors by attaching to an allosteric location.

Riluzole's effect on glutamate receptors, however, has generated debate because no evidence of the drug's binding to any identified locations for them has been provided. It is also unclear if it functions in this manner because its antiglutamatergic action can still be felt in the presence of sodium channel blockers. Rather, many of its actions appear to be mediated by its capacity to promote glutamate absorption. Riluzole may inhibit glutamate release from presynaptic terminals in addition to its function in hastening glutamate clearance from the synapse. Since TDP-43 proteinopathy, a pathogenic feature of ALS, is caused in part by CK1, understanding how drugs work might be made easier.

Synthesis

Riluzole can be prepared beginning with the reaction of 4-(trifluoromethoxy)aniline with potassium thiocyanate followed by reaction with bromine, forming the thiazole ring.



Riluzole synthesis

Side effects-

Riluzole may cause side effects. Tell your doctor if any of these symptoms are severe or do not go away:

- Weakness
- Dizziness
- Dry mouth
- Mouth numbness
- Difficulty falling asleep or staying asleep
- Drowsiness
- Swelling of the hands, feet, ankles, or lower legs
- Fast heart rate

Some side effects can be serious. If you experience any of these symptoms, call your doctor immediately or get emergency medical treatment:

- Hives
- Rash
- Itching
- Difficulty breathing or swallowing
- Dry cough
- Nausea
- Stomach pain
- Vomiting
- Extreme tiredness
- Unusual bleeding or bruising
- Loss of appetite
- Pain in the upper right part of the stomach
- Yellowing of the skin or eyes

- Dark urine
- Fever, chills, cough, or other signs of infection
- Muscle or joint pain
- Headache

Qalsody:

The drug tofersen, marketed under the trade name Qalsody, is used to treat amyotrophic lateral sclerosis (ALS). Tofersen is an antisense oligonucleotide that aims to prevent the

enzyme superoxide dismutase 1, whose mutant form is frequently linked to ALS, from being produced. It is injected intrathecally into the spinal cord over the course of three initial "loading doses" spaced by 14 days, followed by a "maintenance" dose given every 28 days.

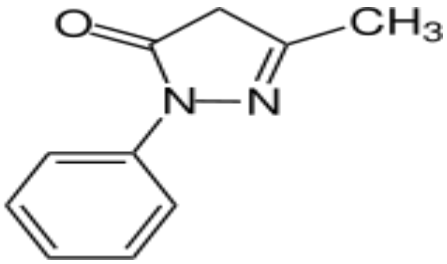
Mechanism of Action-

Antisense oligonucleotide (ASO) Qalsody (tofersen) is intended to bind to SOD1 mRNA and inhibit the generation of SOD1 protein. By binding to SOD1 mRNA, Tofersen causes SOD1 mRNA to degrade, which lowers the production of SOD1 protein.

Side effects-

- pain
- fatigue
- joint pain
- increased cerebrospinal fluid white blood cells and
- muscle pain
- Serious eye symptoms such as sudden vision loss, blurred vision, tunnel vision, eye pain or swelling, or seeing halos around lights;
- Serious heart symptoms such as fast, irregular, or pounding heartbeats; fluttering in your chest; shortness of breath; and sudden dizziness, light headedness, or passing out;
- Severe headache, confusion, slurred speech, arm or leg weakness, trouble walking, loss of coordination, feeling unsteady, very stiff muscles, high fever, profuse sweating, or tremors.

Edaravone (Radicava):



- IUPAC name- 5-methyl-2-phenyl-4H-pyrazol-3-one
- Trade names -Radicava
- Formula-C10H10N2O
- Molar mass-174.203 g·mol−1

Edaravone is a drug used to treat ALS and amyotrophic lateral sclerosis (ALS), among other conditions. It is marketed under the trade names Radicava and other names. It is administered orally and intravenously.

The most frequent adverse effects are headaches, gait difficulties, and bruising (contusions).

Edaravone's potential method of action is uncertain. Since oxidative stress has been hypothesised to play a role in the process that causes neurons to die in ALS patients, the drug is known to be an antioxidant.

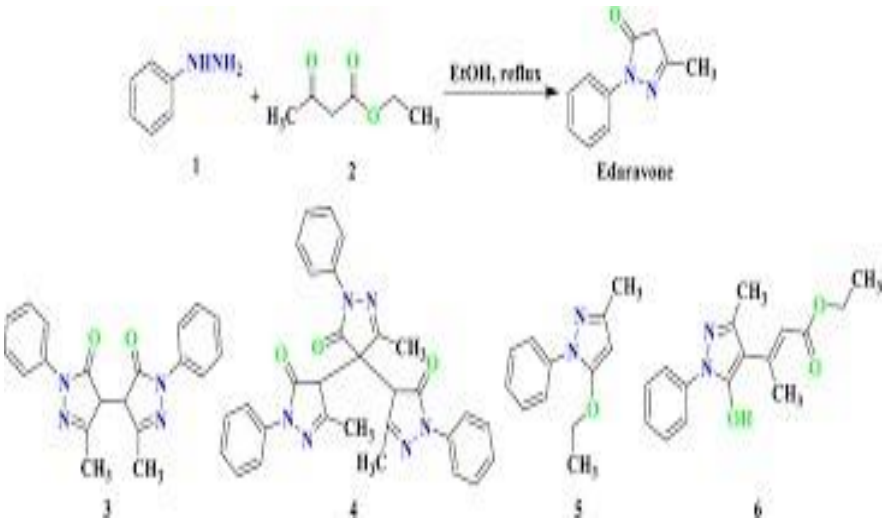
The rate of deterioration in everyday functioning can be slowed down by this medication. It is administered either orally as a drink or by a vein in your arm. Its impact on life expectancy is still unknown. Bruising, headaches, and problems walking are examples of possible side effects. This medicine is given daily for two weeks each month.

Pharmacology-

We don't know how edaravone works to treat ALS, but it may. Since oxidative stress has been hypothesised to play a role in the process that causes neurons to die in ALS patients, the drug is known to be an antioxidant.

Edaravone has a half-life of 4.5 to 6 hours, and its metabolites have a half-life of 2 to 3 hours. It is converted into two inactive compounds, a sulphate conjugate and a glucuronide conjugate. It is mainly eliminated in urine in the form of the glucuronide conjugate.

Synthesis-

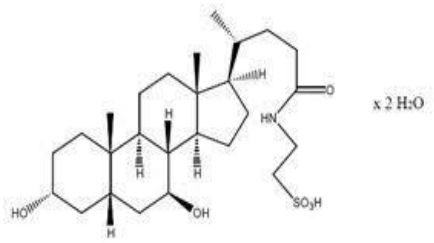


Synthesis of edaravone

Side effects-

- Blistering, crusting, irritation, itching, or reddening of the skin
- blue lips, fingernails, or skin
- chest pain or tightness
- change in walking and balance
- clumsiness or unsteadiness
- cough
- confusion
- cracked, dry, scaly skin
- difficult or troubled breathing
- dizziness
- fast heartbeat
- hives, itching, rash, or swelling
- irregular, fast or slow, or shallow breathing
- skin rash, encrusted, scaly and oozing
- unusual bruising
- weakness
- Sugar in the urine

Sodium phenylbutyrate-taurursodiol (Relyvrio):



- IUPAC Name- sodium;2-[[(4*R*)-4-[(3*R*,5*S*,7*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-3,7-dihydroxy-10,13-dimethyl-2,3,4,5,6,7,8,9,11,12,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl]pentanoyl]amino]ethanesulfonic acid;4- phenylbutanoate
- Trade name- Albrioza, Relyvrio
- Formula-C36H56NNaO8S
- Molar mass- 186.18 g/mol

A fixed-dose combination drug used to treat amyotrophic lateral sclerosis (ALS) is sodium phenylbutyrate/ursodoxicoltaurine, also known as sodium phenylbutyrate/taurursodiol and marketed under the brand name Albrioza among others. It contains ursodoxicoltaurine (taurursodiol) and sodium phenylbutyrate.

The most frequent side effects of sodium phenylbutyrate/ursodoxicoltaurine include upper respiratory tract infections, diarrhoea, and abdominal pain.

The endoplasmic reticulum and mitochondrial cell death pathways are blocked by sodium phenylbutyrate/ursodoxicoltaurine. Chemical chaperone sodium phenylbutyrate assists proteins in maintaining their regular shape, preventing aggregation that can cause cell death. The generation of mitochondrial energy is enhanced by ursodoxicoltaurine.

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This drug, which the FDA authorised in 2022, can reduce the rate of functional deterioration in ALS patients by roughly 25%. Additionally, it might extend the lives of ALS patients by around six months. This medication is a powder that is dissolved in warm water. Diarrhoea, abdominal pain, nausea, and upper respiratory infection are possible adverse effects. If you take this medication and have a bile acid circulation issue, your diarrhoea can develop worse. The flavour of the medication is disagreeable.

Mechanism of action-

The drug's exact mode of action is not entirely understood, but it is generally anticipated that its two components would combine to prevent nerve cell death by blocking stress signals in two cellular compartments, specifically the endoplasmic reticulum and mitochondria.

Relyvrio was created to concurrently address the harmful systems. While sodium phenylbutyrate enhances endoplasmic reticulum stress through the overexpression of chaperone proteins, taurursodiol enhances the generation of mitochondrial energy.

In order to prevent the creation of protein clumps that lead to the death of nerve cells, phenylbutyrate aids proteins in taking on their normal shape.

Side effects-

- Diarrhea
- Stomach pain
- Nausea
- Runny nose, sore throat, and other symptoms of an upper respiratory tract infection
- Feeling tired

- Drooling a lot
- Dizziness

Therapies used in ALS-

When ALS affects your ability to breathe, speak and move, therapies and other forms of support can help.

Breathing care-

Most ALS patients eventually experience worse respiratory issues as their muscles

deteriorate. Your doctor may regularly check your breathing and provide you mechanical ventilation equipment to help you breathe at night.

Use a ventilator that has an easy-to-apply and remove mask if you so desire. Non-invasive ventilation is what is meant by this. Some patients finally need surgery to make a hole leading to their windpipe at the front of their neck. A tracheostomy is what is used for this. To assist them breathe, a tube that is put into the hole connects to a respirator. A procedure known as a laryngectomy may occasionally be performed on ALS patients who already have a tracheostomy. By doing this operation, food is kept out of the lungs.

Physical therapy-

Physical therapy can help you stay independent by addressing issues with walking, mobility, bracing, and equipment needs. Low-impact workouts can help you keep your range of motion, muscle strength, and cardiovascular fitness for as long as feasible.

Your sense of wellbeing can also be improved by regular exercise. Stretching properly can relieve pain and improve the way your muscles work.

Using a brace, walker, or wheelchair can help you overcome weakness, according to a physical therapist. The therapist might recommend aids that make moving around simpler for you, including ramps.

Occupational therapy-

An occupational therapist can help you find ways to remain independent despite hand and arm weakness. Adaptive equipment can help you perform activities such as dressing, grooming, eating and bathing.

An occupational therapist also can help you modify your home to allow accessibility if you have trouble walking safely.

Speech therapy-

A speech therapist can teach you adaptive techniques to make your speech more understandable. Speech therapists also can help you find other ways to communicate. These may include using a smart phone app, alphabet board, or pen and paper.

Ask your therapist about the possibility of recording your own voice to be used by a text-to- speech application.

Nutritional support-

In order to make sure you eat foods that are both easier to swallow and meet your nutritional needs, your team typically works with you and your family members. When it gets too difficult to swallow, you could decide to have a feeding tube implanted.

Psychological and social support-

Your team might include a social worker to help with financial issues, insurance, and getting equipment and paying for devices you need. Psychologists, social workers and others may provide emotional support for you and your family.

Conclusion –

Upper and lower motor neurons are both impacted by ALS, a fatal, progressive degenerative motor neuron disease that causes muscle weakness. In the United States, there are just two drugs that have been approved to treat ALS symptoms. In 1995, the drug Rilutek was introduced to the market, and studies have shown that it can add two to three months to one's life expectancy. A different medication known as Radicava, which received approval in 2017, may halt the disease's progression. The drug works to stop the degeneration of motor neurons. The FDA did not deem any of the most frequent adverse effects, including diarrhoea, abdominal pain, nausea, and upper respiratory infections, to pose a major safety risk. It may also be administered in addition to current ALS treatments. People with ALS can enhance their quality of life by keeping in touch with others, prioritising essential connections, assembling a support group, and taking care of themselves.

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