Review Article

Treatment Approaches for Amyotrophic Lateral Sclerosis: Conventional Therapies and Innovative Solutions

Srishti Iyer[1], Lananh Ho[2]

[1]*Lambert High School, 805 Nichols Rd, Suwanee, GA 30024, USA*
[2]*University of Rochester, 204 Robert B. Goergen Hall, Box 270168, Rochester, NY 14627, USA*

ABSTRACT

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease that impairs motor neuron function, causing progressive muscle weakness and paralysis. ALS is extremely rare, affecting only around 30,000 people in the United States. However, it has a very low survival rate; only 10% of patients survive 10 years after disease onset. While the cause is typically unknown, 5-10% of ALS cases are caused by genetic mutations in the *SOD1* and *C9orf72 genes*. Currently, several FDA-approved therapies for ALS exist. These drugs aim to partially correct the *SOD1* mutation, or block cellular and neurological pathways related to motor neuron damage. In clinical studies to date, these drugs either unsuccessfully treat ALS, or are only able to prolong a patient's lifespan up to several months. Scientists are exploring novel therapies that target the root cause of ALS, whether it be damaged neurons, genetic factors, or muscle dysfunction. These therapies include gene therapy, monoclonal antibody therapy, and stem cell therapy. While further research is needed, current data show significant promise, as these treatments directly target the underlying mechanisms of ALS, rather than focusing on select symptoms like conventional approaches, ultimately making new approaches to ALS therapy more sustainable for the future. This paper will discuss and evaluate current FDA-approved therapies for ALS and explore the potential efficacy of novel treatments.

Keywords: ALS; Treatment; Therapy; Neurons; *SOD1* mutation

INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease affecting the motor neurons of the brain and spinal cord (1). The disease causes the weakening of muscles and gradual loss of motor function that eventually leads to fatal ramifications (1). Amyotrophic Lateral Sclerosis is a very rare disease. In fact, according to a 2023 demographic analysis, there are only 9.1 ALS cases for every 100,000 people in the United States (2). However, only 10% of all ALS patients in the United States survive after 10 years (3). ALS can have detrimental effects on a person's health, which are often fatal. Since ALS leads to the degeneration of motor neurons, many individuals are paralyzed and necessary bodily functions and regulatory mechanisms become inefficient. Some common ALS symptoms include struggle to breathe and move, and inhibition of swallowing, all of which can prove to be fatal.

There is currently no curative treatment for ALS, but there are several drugs approved by the FDA, including

Corresponding author: Srishti Iyer, E-mail: srishti.g.iyer@gmail.com.

Received August 8, 2024**; Accepted** August 21, 2024
https://doi.org/10.70251/HYJR2348.227379

Qualsody, Radicava, Rilutek, Tiglutik, and Exservan (4), and they all target the improvement of quality of life for ALS patients. These conventional treatments are primarily targeted towards coping with ALS, rather than addressing the root of the problem. Out of the listed conventional treatments, Qualsody is the only approved drug that targets the genetic cause of ALS: the *SOD1* gene mutation (4). While only around 5-10% of ALS patients have the condition through genetic means, Qualsody is significant as it is the only approved drug that targets the true cause of ALS, rather than provides a temporary solution for the symptoms of ALS (4). The rest of the approved conventional drugs target symptoms of ALS, such as loss of neuronal function, loss of motor function, and improving respiratory health (4). While conventional approaches to ALS treatment enhance respiratory health, reduce neuronal cell death, reduce the frequency of the SOD1 mutation, and provide an increase in muscle function, they do so at a very small margin (5). Due to the stark lack of sustainability and efficiency of the conventional ALS treatments, they are not a solution.

Considerable research efforts have introduced several innovative therapies that could potentially treat ALS. The three main innovative therapy types under research are gene therapy, monoclonal antibody therapy, and stem cell therapies (6). Unlike conventional therapies, all of these treatments aim to directly repair or replace damaged neurons and/or target genetic mutations to completely treat ALS (6). Because they can target the root problems in ALS, these treatments are sustainable and effective, ultimately having the potential to increase survival rates by a significant margin. This paper will evaluate both conventional and innovative approaches to treating ALS and their advantages and disadvantages (Table 1).

CONVENTIONAL THERAPIES

Several drugs are currently approved by the Food and Drug Administration (FDA) for ALS treatment therapy. This section of the paper will provide an in-depth analysis of the mechanism of action of each of these drugs, their effectiveness, and an evaluation of their application for the treatment of ALS.

Qualsody (Tofersen) - An antisense oligonucleotide (ASO) therapy targeting the mutated SOD1 enzyme

Qualsody is unique because it is the first drug that targets a genetic manifestation of ALS: the *SOD1* mutation (7). In fact, mutations in the *SOD1* gene are the second most common cause of hereditary ALS (8). A healthy SOD1 gene is involved in the homeostatic breakdown of toxic products in cells (8). However, when the *SOD1* gene undergoes mutation, it causes defective protein folding and toxic accumulation in motor neurons, inherently leading to the degradation of these motor neurons due to toxic product buildup, and thus ALS (8). Qualsody is a form of an antisense oligonucleotide therapy that targets the RNA produced specifically from the mutated *SOD1* gene (9). Through this mechanism, it decreases neuronal cell death from the *SOD1* mutation. However, it only has a 35% success rate in correcting the *SOD1* mutation, as concluded by the Valor trial, which will be discussed later in the paper (9). A phase 1 clinical trial tested Qualsody's efficacy in 50 people. After examination of the SOD1 level in spinal fluid of participants, the trial showed that Qualsody treatment effectively lowered this level in the treatment group (9). This clinical trial employed a relatively small sample pool and may have had more accurate results if a larger, more diverse population pool would have been examined.

A phase 3 clinical trial, named the Valor trial, was conducted with 108 patients who had ALS specifically caused by the SOD1 mutation (9). This trial tested the effect of 28 weeks of treatment with Qualsody and concluded that there were no statistically significant results (9). However, overall, there was a slight benefit seen with Qualsody, with a follow-up study using 12 months of data showing a slight slowing of the decline of respiratory function (9). Finally, Qualsody is currently being tested in a phase 3 clinical trial called the Atlas Trial (9). This trial is projected to conclude in 2027 (9).

Considering the results of the clinical trials, it can be seen that Qualsody has limited potential as it doesn't cause significant improvement in patients with ALS caused by genetic mutations. When Qualsody was shown to have effects, it was tested in a smaller population of 50 people. However, in the Valor Trial, where it was tested in the target population of patients with ALS caused by the SOD1 mutation, there were no statistically significant results. Qualsody is not a drug that is efficient in targeting ALS symptoms. While the drug is unique in that it targets genetic causes of ALS, it is not effective enough to have a real positive impact on patients. While this drug may be conceptually strong, its limit in the number of targeted patients and efficacy needs to be considered.

Radicava (Edaravone) - An antioxidant therapy targeting muscle degradation

ALS is a disease that has a rapid progression, with an average survival time of only 2-5 years after diagnosis

Table 1. Therapeutic approaches to treat ALS

Treatment	Target	Mechanism	Phase	Outcome	Ref.
Qualsody	*SOD1* mutation	Decreases neuronal cell death from SOD1 mutation	1	35% success	(9)
Radicava	Muscle degradation	Captures reactive oxygen species in order to protect neurons and decrease neurodegeneration	3	Not statistically significant	(12)
Rilutek	Glutamate release	Inhibits glutamate release	n/a	35% decrease in mortality rate Positive response in patients in the later stages of ALS	(17)
Exservan	Glutamate release	Inhibits glutamate release in the form of a dissolvable oral film	n/a	n/a	(18)
Tiglutik	Glutamate release	Inhibits glutamate release	n/a	n/a	(19)
Gene Therapy-Antisense Oligonucleotides	*SOD1* mutation	complement specific mRNAs that are harmful to motor neuronal function, and induce apoptosis	1/2	100mg of ASOs significantly reduces the concentration of the SOD1 mutation, hence slowing down the progression of ALS	(21)
Gene Therapy-RNAi Processing	*SOD1* mutation	destroy the harmful mRNAs through an RNA-induced silencing complex, inhibiting the expression of harmful genes that cause ALS	n/a	39% survival benefit as well as a statistically significant decrease in expression of the SOD1 mutation	(21)
Monoclonal Antibody Therapy-AL0011	C9orf72 protein	trigger the immune system, increasing the concentration of the C9orf72 protein, stopping the progression of ALS	n/a	Ongoing	(22) (6)
Monoclonal Antibody Therapy-Ozanezumab	Neurite Outgrowth Inhibitor (NOGO-A)	stimulates the production of neuronal activators in order to combat the effects of NOGO-A, a protein that inhibits neuronal growth	n/a	not a significant effect of the drug compared to the placebo. In fact, more patients who were treated with Ozannezumab died due to a side effect of respiratory failure of the drug.	(23) (24)
Stem Cell Therapy-	Glial cell line-derived neurotrophic factor (GDNF)	genetically engineered STEM cells produce GDNF and protect neurons and their function, thus treating ALS	1/2	not statistically significant, but there was slowed disease progression in patients who had the stem cell transplant, and these cells were found to be alive three and a half years after stem cell replacement	(25)

(10). This rapid progression is accompanied by the increased progression of symptoms, where motor neuronal functions deteriorate at a high rate (11). Radicava is a drug that aims to slow down the loss of motor function and the progression of ALS, ultimately, aiming to decrease the mortality rate from ALS as well (12). There are certain unstable molecules, called reactive oxygen species, that build up to an excessive amount, contributing to neurodegeneration, a characteristic symptom of ALS (10). Radicava captures these unstable molecules, protecting these neurons and preventing this buildup, thus slowing the symptomatic progression of ALS (12).

A phase 3 double blind placebo clinical trial was conducted in Japan (12). The study concluded that there was not a significant difference in response with the placebo and with the Radicava Drug (12). However, people who had the disease for less than two years did show slight improvement (12). Yet, this clinical trial is not truly insightful because it is not representative of the complete ALS population since it only consisted of Japanese people in the trial. To form accurate conclusions, other variables must be unbiased, such as race, ethnicity, and demographics. This clinical trial failed to do so, hence its results must be taken with a grain of salt. However, another clinical study was conducted by the German Motor Neuron Disease Network, with a much more representative sample of ALS patients. It was again found that there were no significant benefits to patients who received Radicava as compared to patients who did not receive the drug (12). From a statistical perspective, Radicava has a very low efficiency and is not an effective treatment for ALS, nor does it slow down progression to a significant level.

Rilutek, Exservan, and Tiglutik - Glutamate blocker therapies

Glutamate is the major neurotransmitter involved in excitation (13). An excessive release of glutamate causes a phenomenon known as excitotoxicity, where an overactivation of glutamate leads to cell degeneration and death (14). In ALS, there is increased glutamate receptor activation (15). This activation occurs at such a large margin that the glutamate signal pathway becomes a positive feedback loop, with an excess accumulation of glutamate. This in turn leads to cell death and neuronal degeneration (15). With this excess glutamate release contributing significantly to ALS symptoms in patients (40% of all sporadic cases of ALS are caused by glutamate release), there are three current conventional therapies approved to address and inhibit glutamate release (16).

Rilutek is a drug that inhibits glutamate release (5). Rilutek is the only drug statistically shown to improve lifespan in patients with a 35% decrease in mortality rate (17). 959 ALS Patients in Belgium, France, Germany, Spain, Canada, the USA, and the UK participated in a December 1992 to November 1993 study (17). These patients were offered doses of Rilutek at various stages of ALS. It was found that there was a significant positive response in the later stages of ALS (17). While the study was performed well, with a large enough sample size for accurate results, it may not be as relevant today. Even though Rilutek appears to be the most promising conventional therapy, there are unfortunately not enough recent studies to back its efficacy. Additionally, when examining the efficacy of Rilutek from a holistic perspective, it has only a slight impact as it only helps patients in the later stages of ALS, which is not as advantageous as potentially decreasing or stopping disease progression altogether before it worsens.

Exservan and Tiglutik have a similar function to Rilutek in regards to inhibiting glutamate, but approach it in slightly different ways. Exservan is similar to Rilutek; however, it is further centered around patient ease and accessibility by having a different delivery approach. Since difficulty in swallowing is a common characteristic of ALS, Exservan is Rilutek in the form of a dissolvable oral film, making it easy for patients to ingest (18). The oral film is simply placed atop a patient's tongue, and it dissolves on its own (5). This drug has a similar efficiency as Rilutek, but it is especially unique as it is one of the few drugs that takes patient comfort into consideration. Tiglutik has a similar function as Rilutek. It is another conventional drug that acts as a neuroprotective agent, inhibiting the release of glutamate in order to slow disease progression (19). Tiglutik inhibits postsynaptic glutamate receptor signaling and reduces the release of glutamate (19). In other words, Tiglutik inhibits reception in the glutamate signaling pathway, decreasing the probability of excess glutamate accumulation, and hence neuronal damage in ALS. Tiglutik is very similar to Rilutek in its efficiency and effectiveness.

INNOVATIVE THERAPIES

Upcoming treatments for ALS target the root of the problem, focusing on increasing motor efficiency to improve the condition of ALS patients, rather than providing limited compensation for symptoms of the condition.

Gene Therapy

Gene therapy is a method that silences harmful genes by replacing the mutated gene with a healthy counterpart,

ultimately aiming to decrease the expression of the harmful gene (20). Specifically in ALS, single-stranded oligonucleotides called Antisense oligonucleotides (ASOs), are designed to complement specific mRNAs that are harmful to motor neuronal function, and induce apoptosis (21). A series of phase 1 and 2 clinical trials showed that a dosage of 100mg of ASOs significantly reduces the concentration of the SOD1 mutation, a genetic mutation that causes familial ALS, hence slowing down the progression of ALS (21). However, due to the small population size, the clinical trial is projected to extend to phase three, occurring in the next seven years (21). Another approach in gene therapy is RNAi processing (21).

In RNAi processing, RNAs destroy the harmful mRNAs through an RNA-induced silencing complex, inhibiting the expression of harmful genes that cause ALS, such as the mutation of the *SOD1* gene (21). This is a more promising method as RNAi is double-stranded, hence more likely to withhold the pressure of drug delivery and activity, unlike ASOs (21). However, more research must be conducted on this method. In 2022, a mice model with the SOD1 gene mutation was created to test the effect of gene therapy in treating the mutation (21). The study concluded that there was a 39% survival benefit and a statistically significant decrease in expression of the *SOD1* mutation (21). Currently, research is being conducted on people with familial ALS as well (21). Gene therapy is a promising and novel method for combatting ALS as it can directly target the mutations rather than alleviate symptoms in ALS patients, and has produced statistically significant results. Unlike conventional treatments which target symptoms, gene therapy targets the mutated cells themselves, providing long-term relief to patients as well.

Monoclonal Antibody Therapies

Monoclonal antibodies are engineered to serve as a substitute for antibodies to restore optimal cell function (22). Monoclonal antibodies function in several ways, significantly in cellular therapy (22). Monoclonal antibodies can flag cells in order to later locate an attack, play a role in destroying the cell membrane of a dangerous cell, block immune system inhibitors, or deliver treatment to the cell (22).

While this method is primarily applied to cancer cells, there is a new monoclonal antibody that is specifically designed for ALS (23). In a recent mice model, monoclonal antibody treatment can trigger the immune system and slow down the progression of ALS (23). Currently, there is an ongoing clinical trial that evaluates the effect of AL0011 monoclonal antibodies therapy, a recombinant human anti-human sortilin (SORT1) monoclonal IgG1, in the treatment of ALS in human patients. This therapy increases the level of C9orf72 protein (disruption of function results in premature motor neuron death) which is often lower in ALS patients (6). AL001 increases C9orf72 protein concentration, halting ALS progression (6).

An additional new monoclonal antibody therapy for ALS is called Ozanezumab (24). Ozanuzumab is a drug designed specifically for ALS patients; it targets a protein called Neurite Outgrowth Inhibitor (NOGO-A), a protein that inhibits neuronal growth (24). This protein is present at a higher concentration in ALS patients (24). Ozanuzumab stimulates the production of neuronal activators to combat the effects of NOGO-A (24). Since patients with ALS have inhibited neuronal growth and function, Ozanezumab targets this and stops the progression of ALS (24). In a randomized placebo trial testing the efficacy of Ozanezumab, it was concluded that there was not a significant effect of the drug compared to the placebo (25). In fact, more patients who were treated with Ozannezumab died due to a side effect of respiratory failure of the drug (25). Patients with ALS already have deteriorating respiratory health, and Ozanezumab only stimulated this, serving the opposite effect in treating ALS, and furthering adverse effects (25). While Ozanezumab has limited efficacy, the realm of monoclonal antibody therapies for ALS is extremely promising as it is conceptually strong. If more research is conducted, monoclonal antibody therapies may be the solution for ALS treatment.

Stem Cell Therapy

Stem cells are cells that have the potential to differentiate into many different cell types in the body (26). In regards to ALS, these stem cells could potentially develop into functioning neurons and replace the neurons that are damaged due to ALS onset (6). Dr. Clive Stevendson, executive director of the Board of Governors Regenerative Medicine Institute, has done immense stem cell research in the context of ALS (27). He analyzed Glial cell line-derived neurotrophic factor (GDNF), a growth factor that protects motor neurons (27). Dr. Stevenson genetically engineered these stem cells to produce GDNF and protect neurons and hence their function, thus treating ALS (27). While safety and security were a huge concern, a phase 1/2 clinical trial validated that this approach was safe (27). Although this trial was not statistically significant, there was slowed disease progression with patients who had the stem cell transplant. Specifically, the stem cells were found to be alive three and a half years after stem

cell replacement (27). Stem cell therapy has immense potential because it has been shown to have long-lasting effects. While continued research must be conducted, stem cell therapy holds promise for ALS treatment in the future.

CONCLUSION

ALS is a neurodegenerative condition that has irreversible ramifications on afflicted individuals. While the current and conventional approved therapies may improve quality of life slightly, these drugs only target external symptoms of ALS, and that too, at a temporary level. However, the onset of innovative treatments for ALS such as gene therapy, monoclonal antibody therapy, and stem cell therapies spark promise for the future direction of ALS treatment, targeting the condition itself rather than the symptoms, and providing long-term solutions for the issue. While these new drugs require extensive research and testing, current data suggests that they have immense potential to change the trajectory of ALS treatment by a significant margin, making these approaches sustainable for the future.

REFERENCE

1. The ALS Association. (2021, April 26). What is ALS? The ALS Association; The ALS Association. https://www.als.org/understanding-als/what-is-als.
2. What Is the Prevalence of ALS? (2023, October 12). Healthline. https://www.healthline.com/health/als-prevalence#:~:text=It.
3. Stages of ALS | The ALS Association. (n.d.). Www.als.org. Retrieved July 14, 2024, from https://www.als.org/understanding-als/stages#:~:text=And%2C%20while%20the%20average%2.
4. ALS Association. (2021). FDA-Approved Drugs. The ALS Association. https://www.als.org/navigating-als/living-with-als/fda-approved-drugs.
5. FDA-Approved Drugs for Treating ALS | The ALS Association. (n.d.). Www.als.org. Retrieved July 14, 2024, from https://www.als.org/navigating-als/living-with-als/fda-approved-drugs#:~:text=There%20are%20.
6. Tzeplaeff L, Wilfling S, Requardt MV & Herdick M. Current State and Future Directions in the Therapy of ALS. Cells. 2023; 12 (11): 1523. https://doi.org/10.3390/cells12111523.
7. Is ALS Genetic? | The ALS Association. (n.d.). Www.als.org. https://www.als.org/understanding-als/who-gets-als/familial#:~:text=ALS%20is%20similar%20whether%20it.
8. ALS Genes and Mutations. (n.d.). The ALS Association. https://www.als.org/research/als-research-topics/genetics.
9. Tofersen. (n.d.). The ALS Association. https://www.als.org/navigating-als/living-with-als/fda-approved-drugs/tofersen.
10. MS, M. W. (n.d.). The stages of amyotrophic lateral sclerosis (ALS) | ALS News Today. Alsnewstoday.com. Retrieved July 14, 2024, from https://alsnewstoday.com/stages-of-als/#:~:text=ALS%20progression%20timeline&text=While%.
11. Zarei S, Carr K, Reiley L, Diaz K, Guerra O, Altamirano P, Pagani W, Lodin D, Orozco G & Chinea A. A comprehensive review of amyotrophic lateral sclerosis. Surgical Neurology International. 2015; 6 (1): 171. https://doi.org/10.4103/2152-7806.169561
12. Edaravone. (n.d.). The ALS Association. https://www.als.org/navigating-als/living-with-als/fda-approved-drugs/edaravone.
13. Cleveland Clinic. (2022, April 25). Gamma-Aminobutyric acid (GABA). Cleveland Clinic. https://my.clevelandclinic.org/health/articles/22857-gamma-aminobutyric-acid-gaba.
14. Mattson MP. Excitotoxicity - an overview | ScienceDirect Topics. Www.sciencedirect.com. https://www.sciencedirect.com/topics/neuroscience/excitotoxicity. 2019.
15. Foran E & Trotti D. Glutamate Transporters and the Excitotoxic Path to Motor Neuron Degeneration in Amyotrophic Lateral Sclerosis. Antioxidants & Redox Signaling. 2009; 11 (7): 1587–1602. https://doi.org/10.1089/ars.2009.2444.
16. Glutamate - The ALS Association. (n.d.). Web.alsa.org. http://web.alsa.org/site/PageServer?pagename=ALSA_Glutamate.
17. Fang T, Al Khleifat A, Meurgey JH, Jones A, Leigh PN, Bensimon G & Al-Chalabi A. Stage at which riluzole treatment prolongs survival in patients with amyotrophic lateral sclerosis: a retrospective analysis of data from a dose-ranging study. The Lancet Neurology. 2018; 17 (5): 416–422. https://doi.org/10.1016/s1474-4422(18)30054-1.
18. MS, M. W. (2019, November 26). Riluzole for ALS in Dissolving Oral Film Form, Called Exservan, Approved by FDA. Alsnewstoday.com. https://alsnewstoday.com/news/fda-approves-exservan-riluzole-dissolving-oral-film-for-als/.
19. Tiglutik – Thickened Liquid Riluzole – Receives FDA Approval to Treat ALS. (n.d.). The ALS Association. https://www.als.org/blog/tiglutik-thickened-liquid-riluzole-receives-fda-approval-treat-als.
20. Food and Drug Administration. (2018, July 25). What Is Gene Therapy? FDA; FDA. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy.
21. Fang T, Je G, Pacut P, Keyhanian K, Gao J & Ghasemi M. Gene Therapy in Amyotrophic Lateral Sclerosis. Cells. 2022; 11 (13): 2066. https://doi.org/10.3390/cells11132066.

22. Monoclonal antibody drugs for cancer: How they work. (n.d.). Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/cancer/in-depth/monoclonal-antibody/art-20047808#:~:text=Your%20body%20keeps%20your%20immune.
23. Monoclonal antibody shows promise in slowing progression of ALS. (2023, July 31). News-Medical. https://www.news-medical.net/news/20230731/Monoclonal-antibody-shows-promise-in-slowing-progression-of-ALS.aspx.
24. Ozanezumab Overview - Creative Biolabs. (n.d.). Www.creativebiolabs.net. https://www.creativebiolabs.net/ozanezumab-overview.htm
25. Meininger V, Genge A, van den Berg LH, Robberecht W, Ludolph A, Chio A, Kim SH, Leigh PN, Kiernan MC, Shefner JM, Desnuelle C, Morrison KE, Petri S, Boswell D, Temple J, Mohindra R, Davies M, Bullman J, Rees P & Lavrov A. Safety and efficacy of ozanezumab in patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled, phase 2 trial. The Lancet Neurology. 2017; 16 (3): 208–216. https://doi.org/10.1016/s1474-4422(16)30399-4.
26. MedlinePlus. (2016, March 29). Stem Cells. Medlineplus.gov. https://medlineplus.gov/stemcells.html#:~:text=Stem%20cells%20are%20cells%20with.
27. Tomlin C. (2023, November 17). Regenerative Medicine: A New Path for ALS Treatment. Cedars-Sinai. https://www.cedars-sinai.org/discoveries/a-new-path-for-als-treatment.html.