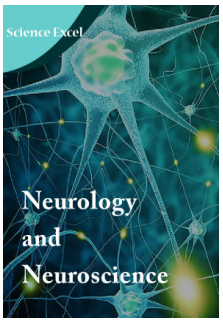
Neurology & Neuroscience

Review Article



Therapeutic interventions of Amyotrophic Lateral Sclerosis (ALS)

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- Received Date: 29 Jun 2022
- Accepted Date: 07 Jul 2022
- Publication Date: 13 Jul 2022

Keywords

ALS, SOD1, Biomarkers, Glutamate, Protein Aggregation, Neurodegeneration

Abstract

Amyotrophic lateral sclerosis (ALS) is a non-demyelinating neurodegenerative disease mostly found in adults between 40 to 60 years old. This disease is usually prevalent in males, however it's irrespective to the different genders. ALS is progressive and within 2-5 years of diagnosis ulimately ends with death. The majority of ALS cases is sporadic (90%) and is recorded without any defined aetiology. The other 10-12% of cases is recognized from mutations in more than 20 genes. The genes reported to cause ALS are Superoxide Dismutase 1 (SOD1), TAR DNA Binding Protein (TDP), Fused in Sarcoma, (FUS), Chromosome 9 Open Reading Frame 72 (c9orf72) and Vesicle-Associated Membrane-Protein-Associated Protein B (VAPB). Furthermore, abnormal lipid metabolism with higher LDL/HDL ratio was reported in ALS patients. The aetiology of ALS is shown in the schematic diagram below (Figure 1)

Due to the multi-nature of ALS causative factors and symptoms, there is no specific therapy for ALS today. However, this paper will touch on potential therapies that are in practice or may come up in the future. The goal is to maintain and improve the function of motor neuron, the well-being and quality of life for ALS patients. Until then, we have to rely on the symptomatic treatment and rehabilitative measures to support the patient's quality of life.

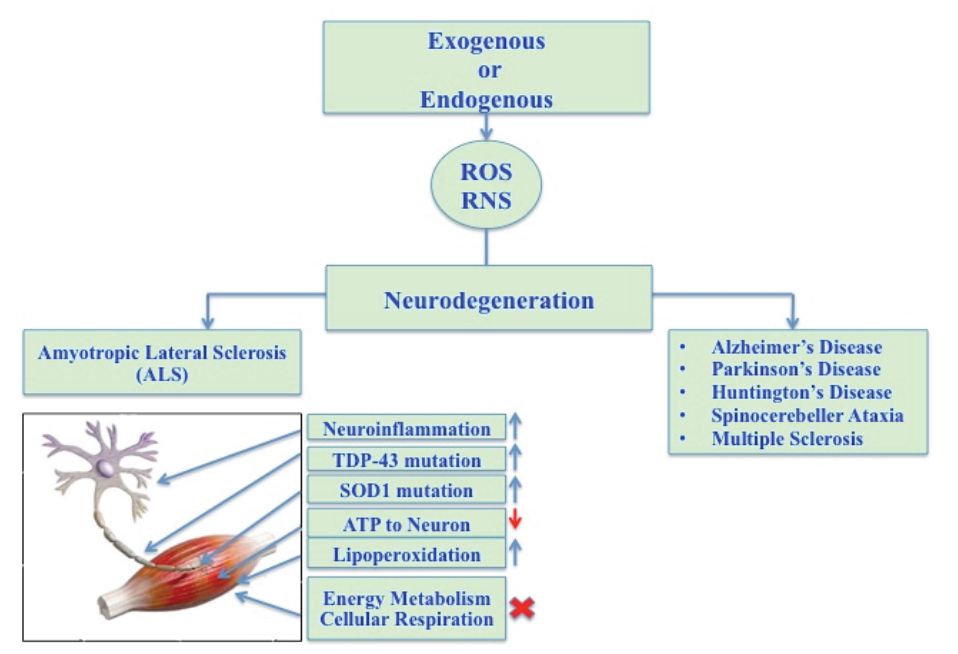

Figure 1. *Aetiology of Amyotrophic lateral sclerosis (ALS)*

Citation: Chakraborty A, Diwan A. Therapeutic interventions of Amyotrophic Lateral Sclerosis (ALS). Neurol Neurosci. 2022; 3(2):1-6

Introduction

Amyotrophic lateral sclerosis (ALS) primarily involves defects in the brain and spinal cord motor neurons. This results in progressive muscular atrophy, paralysis, respiratory dysfunction and disturbances in speech and swallowing. This disease is progressive so typically within 3-5 years after diagnosis, the respiratory failure results in death [1].

Diagnosis

Early diagnosis of ALS is extremely difficult because the disease bears close similarities with other neurological disorders, such as Parkinson's disease (PD) and Alzheimer's disease (AD). Therefore, it's essential to have knowledge on the evaluation of perfect biomarkers for ALS at its early stage, during the progression and treatment stages to understand the proper mechanisms of disease pathology.

An electromyogram (EMG) can differentiate the muscle disorders other than the ALS. Nerve conduction study can determine the nerve damage, if any, unrelated to ALS. An MRI can reveal spinal cord tumors, herniated disks in neck that might be causing the ALS symptoms.

Diagnostic biomarkers (Table-1):

Present management of the complications of ALS patients

Patients with ALS eventually will need devices to help assist their breathing. The muscles progressively weaken, which ultimately leads to respiratory failure and death. Both physical therapy and occupational therapy can help and individual to independently maintain physical function. Other procedures that are commonly adopted include speech therapy, nutritional support and the social and mental health support..

Therapeutic Interventions

A schematic diagram of different therapeutics approaches is shown in Figure 2.

Antidepressants

Riluzole was approved by the US Food and Drug Administration (FDA) in 1995. It was reported to have antidepressant effects in both open-label trials [40, 41] and can be used against ALS [42]. Side effects of this drug include dry mouth and weight gain, which may help with other ALS symptoms of too much saliva in the mouth and weight loss.

Table 1. *Diagnostic biomarkers*

Biochemical Biomarkers	Cellular Biomarkers	Genetic Biomarkers
· Elevated metalloproteinase-9 (MMP-9) [2] · Increased levels of MMP-2 [3,4]	· The loss of motor neurons is the primary neuropathological hallmark of ALS [20]	· Mutations in SOD1 [28]
· Elevated Extracellular matrix metalloproteinase inducer (EMMPRIN) [3]	· Decrease in the expression of human leukocyte antigen by ALS monocytes [21]	· Mutations in tardbp (TDP-43) [29-31]
· Elevated level of Inflammation Markers, like MCP-1, TNFa, IL-6, IL-7, Eotaxin, GM-CSF, OX40, etc. [5-9]	· An increase in the amount of natural killer T lymphocytes [22]	· Binding of mutant C9orf72 to trimethylated histones was detected in ALS mononuclear cells [32]
· Hypermetabolism, and hyperlipidemia [10-12]	· High neutrophil-to-lymphocyte ratio [23]	· Mutations in FUS gene [33-36]
· High concentrations of lead in blood and in the CSF [13-15]	· Decrease in the number of regulatory T cells [21,22]	· Vesicle-associated membrane protein-associated protein B (VAPB) [37]
· Low level of type I procollagen[16-19].	· High levels of neurofilament light chain in the serum of ALS patients [24,25], as also bserved in the CSF [26,27].	

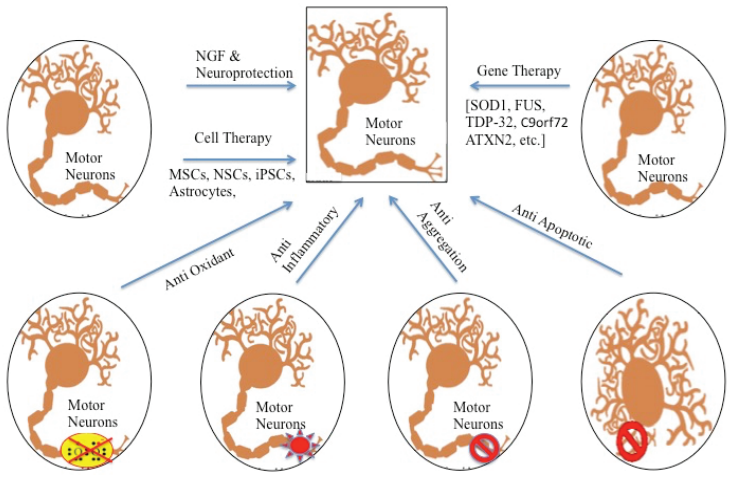

Figure 2. *Outlook of therapies of ALS*

Scope of Gene Therapy

SOD1 Mutation Therapy

Only a few percent of ALS patients have a known gene defect. Gene therapy could be designed for a SOD1 defect, however this therapy may not work for other ALS patients. In fact, if a neuron carries a mutated SOD1 gene, that nerve cell can survive if the neighboring support cells and glia have the normal gene. Gene therapy in ALS can also target the glial cells and neurons to produce positive effects [41].

FUS Mutation Therapy

Ionis is developing another gene therapy called ION363 [42]. This therapy treats patients with FUS mutations. Mutations in this gene are found in about five percent of people with familial ALS and about one percent with sporadic or singleton ALS. Patients that have the FUS mutation tend to develop ALS earlier and have a shorter life span than people with other gene mutations.

Boosting Helpful Trophic Factors

Gene therapy could be the way to provide a steady supply of trophic factors to neurons that are being damaged. In fact, boosting helpful trophic factors directly in the location where the damage exists could be beneficial [43].

A summary of present gene therapy approaches for ALS are tabulated below (Table-2):

Clinical Trials with Gene Therapy

ATLAS is the current phase III clinical trial for tofersen. Basically, this testing is done on people who are pre-symptomatic, which means they do not have any ALS symptoms but are likely to develop them later on [45].

Helixmith is testing a gene therapy called Engensis that could potentially help patients suffering with ALS. This therapy is currently undergoing a phase II clinical trial to determine if it successfully impacts people with ALS [46].

There are many types of stem cells, including induced pluripotent stem cells (iPSCs) that can be used for potential cell therapy of ALS. iPSCs are derived from adult human tissues and shown to differentiate into astrocytes that support the nerve cells. In addition, mesenchymal stem cells (MSCs) and neural stem cells (NSCs) are safe and potentially effective cell types for ALS cell therapy. However, monitoring and verifying these cell types long-term safety and efficacy before using in humans is essential.

MSCs

Mesenchymal stem cells (MSCs) were first described by Friedenstein et al. in 1970 in a study using bone marrow mononuclear cells as adherent clonogenic cells [47]. MSCs are considered fibroblast colony–forming units and are present a high in vitro replication capacity. MSCs can be isolated from a variety of tissues, which include bone marrow, muscle tissue, adipose tissue, skin, cartilage, blood vessels, in menstrual blood and tooth pulp. These cells acquire a fibroblast-like appearance that expresses CD105, CD73 and CD90 markers. Unfortunately, they do not express CD45, CD34 or CD14 markers [48,49].

To date, MSC therapy has no cases of adverse events, such as teratomas reported. Therefore, MSC therapy is considered to be safe and beneficial because there are no ethical limitations associated with embryonic or fetal stem cells. MSCs present the basic properties of stem cells. Such properties include self-renewal, multilineage differentiation potential, clonality, and the capability to regenerate tissue in vivo. MSCs are considered to

Table 2. *Present Gene Therapy Approaches for ALS*

SOD1	Gene Therapy	Gene Therapy	Apic Bio [https://clinicaltrials.gov/ct2/show/study/NCT04856982]
	Antisense oligonucleotide	Tofersen	Biogen [https://www.biogen.com/en_us/pipeline.html]
	Gene therapy		Voyager Therapeutics [https://www.globenewswire.com/en/search/organization/Voyager%2520Therapeutics%CE%B4%2520Inc%C2%A7]
C9orf72	Antisense oligonucleotide	BIIB078	Biogen [https://alsnewstoday.com/news-posts/2022/04/11/biogen-ionis-discontinuing-biib078-development-c9orf72-associated-als/]
	Gene therapy		Pfizer/Sangamo [https://www.pfizer.com/news/press-release/press-release-detail/sangamo_and_pfizer_announce_collaboration_for_development_of_zinc_finger_protein_gene_therapy_for_als]
	Gene therapy	TPN-101	Transposon [https://www.als.net/als-research/clinical-trials/599/]
	Antisense oligonucleotide	WVE-004	Wave [44] WAVE LIFE SCIENCES
ATXN2	Antisense oligonucleotide)	BIIB105	Biogen [https://www.alzforum.org/therapeutics/biib105]
FUS	Antisense oligonucleotide)	ION363	Ionis [https://www.ionispharma.com/medicines/ion363/]

be multipotent cells because they can differentiate into several mesenchymal lineages, like in bone, cartilage, adipose and muscle tissue [48,49].

The therapeutic potential of MSCs is linked to their immunoregulatory paracrine activity, with the secretion soluble factors (secretomes), including other growth factors, like vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF-2), insulin-like growth factor 1 (IGF-1), platelet-derived growth factor (PDGF), and hepatocyte growth factor (HGF) [50]. Anti-inflammatory factors, such as interleukin-10 (IL-10), transforming growth factor beta 1 (TGF-β1), and mechanisms linked to exosome and mRNA release are also included with MSCs [51,52].

Animal studies have yielded promising results for MSC therapy. For example, transgenic mutant SOD1 mice were administered MSCs via intrathecal injection, intravenous injection or a combination of both. The procedure was found to be safe and effectively delayed motor impairment, reduce inflammation and promoted the secretion of cytokines and growth factors. This resulted in the mice having a longer life span because of an increase in cell survival [53,54].

Astrocytes

Recent studies discovered that even with normal aging, astrocytes become less supportive to motor neurons (MNs). This suggests there is a role with aging and the significant MN death when related to astrocytes in a rodent model of familial ALS [55,56]. More importantly, Dass and Svendsen found increased levels of MN survival in co-culture of priming aged wild-type and SOD1-G93A astrocytes with glial-derived neurotrophic factors in the media [57]. Astrocyte precursors or SC-derived astrocytes promote axonal growth, can modulate the host immune response, help deliver neurotrophic factors and provide protective molecules against oxidative or excitotoxic insults. In addition, they support mechanisms involved in myelination and oligodendrocyte myelination along with other positive benefits [58-60]. Astrocyte replacement-based therapies in ALS patients are to alleviate overall astrocyte dysfunction, deliver neurotrophic factors to degenerating spinal tissue and stimulate endogenous CNS repair abilities [60].

NSCs

An ideal source of cell tissue for neural cell replacement must be renewable because that eliminates the need for transplantation of primary fetal tissue. It must also allow viability, sterility, cell composition and cell maturation to be controlled, while being inherently nontumorigenic. Transplanted NSCs exerted their beneficial effects through an immune-modulatory action, which involves both innate and adaptive (local vs systemic) immune responses (e.g., microglial and astroglial scar reduction, T-lymphocyte inhibition, etc.), secretion of trophic factors and cross- correction of missing enzymatic activities.

iPSCs

A recent, yet interesting source of SCs for clinical transplantation is represented by iPSCs. iPSCs can be generated from somatic cell types through ectopic expression of a defined set of transcription factors, acquiring the features of embryonic SCs and thus bearing the potential to give rise to virtually any cell type, including inaccessible tissues such as neurons. This method was described first by Shinya Yamanaka where MNs were derived from an older patient with a familial form of ALS [61,62]. Human iPSCs can be represented as an ideal cell source for cell therapy. If the iPSCs can be derived from the patient, it will prevent an immune rejection. Therefore, iPSC technology may provide benefits for the use of autologous and allologous cell therapy.

On the other hand, iPSC clinical use is still highly debated over because iPSC safety must be demonstrated. iPSCs have a well-known tumorigenic potential [63]. Given the possible genetic causes of sporadic ALS, a genetic alteration could be present in the autologous-derived SCs. The earliest strategies for the induction of iPSCs are by using viral vectors. Unfortunately, the risks of insertional mutagenesis and transgene reactivation can cause limitations during clinical use [64]. In order to bypass these safety concerns, there are numerous alternative methods for inducing pluripotency being developed. Recently, a new small molecule has been identified that provide enhancements for somatic cell reprogramming that can compensate for three of the four canonical factors (Oct4, Sox2, Klf4 and c-Myc) [65].

Stem Cell Therapy in Clinical Trials for ALS

These cells can be injected directly into the muscle or in the spinal canal. Trials in 2016 demonstrated that this treatment was safe and well tolerated. The results showed a slow in the progression of the disease in the six months after the injections started when it was compared to six months prior to the treatment [66].

There is a clinical trial at phase 3 (NCT03280056) that is assessing the safety and efficacy of repeated NurOwn injections. Right now, the trial is currently recruiting patients in the US from California, Massachusetts and Minnesota. ALS patients will basically receive three, intrathecal NurOwn or placebo injections at bi-monthly intervals [67].

Another clinical trial at phase 1/2 (NCT03482050), is investigating the use of astrocytes derived from human embryonic stem cells that is known as AstroRx. 21 patients are currently being recruiting at a single site in Israel. AstroRx will be injected into the spinal cord of patients at the early stage of the ALS disease [68].

Conclusions

- Cell therapy has emerged as a promising treatment strategy for ALS. In fact, there are constant advances being made with the use of biomaterials that enhances the benefits of stem cells.
- However, research and studies still need to be conducted because more information remains to be learned and understood about ALS.
- Further research in the form of basic studies and well-designed clinical trials may shed more light on these promising therapeutic strategies.

Acknowledgements

We acknowledge all our colleagues for their help during the preparation of the manuscript by providing all the relevant information. We are also thankful to Ms. Bethany Pond (Analytical Chemist at AllExcel, Inc.) for editing the manuscript.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Consent for publications

Both the authors have agreed to submit this paper for publication.

Ethical approval

Not applicable

Conflict of interest statement

The authors declare no conflict of interests.

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