Biomaterials in The Treatment of Amyotrophic Lateral Sclerosis

Fardin Nabizadeh[1,2]*

1. School of Medicine, Iran University of Medical Sciences, Tehran, Iran
2. Neuroscience Research Group (NRG), Universal Scientific Education and Research Network (USERN), Tehran, Iran

Abstract

Amyotrophic Lateral Sclerosis (ALS) is a progressively debilitating disease characterized by selective neurodegeneration of upper motor neurons in the brain and lower motor neurons in the brainstem and spinal cord. Degeneration of upper and lower motor neurons leads to spasticity and atrophy respectively, which begins with focal weakness and then spread to other muscles including the diaphragm, and finally died as a result of respiratory paralysis. To date, there are only two drugs approved by US Food and Drug Administration (FDA) for ALS treatment: Riluzole and Edaravone. The approval of only two drugs is evident of minimal progress in ALS treatment over the past decades. However, more drugs are currently under investigation, and we hope more drugs will be available for ALS treatment, but many challenges in developing new therapeutic agents may remain such as blood-brain barrier (BBB), targeting, clearance, biostability, and degradation. Advances in biomaterial proposed utilizing nanoparticles to package and delivery pharmaceuticals to CNS to protect against absorption, clearance, and facilitate the transportation across BBB. Designing and engineering nano-bio materials loaded with agents such as riluzole or other efficient substances provide prospective advances in therapeutic approaches and drug delivery systems for neurodegenerative disease, particularly ALS. Here we reviewed biomaterials used in ALS therapeutic approach over the last years.

Keywords: Amyotrophic Lateral Sclerosis, Riluzole, biomaterials, nanoparticles

Correspondence to Fardin Nabizadeh, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

Email: Fardinnabizade1378@gmail.com

Check for updates

Introduction

Amyotrophic Lateral Sclerosis (ALS) is a progressively debilitating disease characterized by selective neurodegeneration of upper motor neurons in the brain and lower motor neurons in the brainstem and spinal cord. Degeneration of upper and lower motor neurons leads to spasticity and atrophy respectively, which begins with focal weakness and then spread to other muscles including the diaphragm, and finally died as a result of respiratory paralysis (1). The main pathological hallmark of ALS is the death of motor neurons, and more widespread in ALS with Frontotemporal dementia. Corticospinal degeneration cause thinning and scarring of the lateral spinal cord, while in the brainstem and spinal cord motor neuron loss, thinning of ventral roots and denervation atrophy occur (2). The clinical signs appear in ages between 40 to 70 years and occur in 2.16 of 100,000 people per year (3). Approximately 90% of cases are sporadic and occur without a family history, and the remaining 10% are familial with Mendelian inheritance patterns (4). Recent advances that have been made in ALS understanding, indicated the complexity of the disease and multifactorial motivation. Both sporadic and familial ALS are the same clinically and pathologically, so it is believed that they share common pathogenetic features, and there is a convergence in events that leads to ALS (4). Mutation in *SOD1*, which encodes cytosolic superoxide dismutase account for nearly 20% of familial cases, and 2-7% of sporadic ALS (5).

The most common gene mutation that accounts for 40% of familial cases and 5-7% of sporadic cases is an expansion in an intronic hexanucleotide repeat of *C9orf72* that can cause ALS and Frontotemporal dementia (6). Moreover, a mutation in two genes that encode RNA binding proteins, *FUS* and *TARDBP*, each accounts for 5% of familial ALS (7).

Multiple underlying pathophysiological mechanisms have been proposed to induce familial and sporadic ALS including mitochondrial dysfunction, axonal transport, aberrant protein aggregation, impaired protein degradation, prion-like spreading, excitotoxicity, decreased neurotrophic support from non-neuronal cells, oxidative stress, hypermetabolism, inflammation, RNA metabolism defects, and altered RNA metabolism. Although over 30 genes have been linked to familial ALS, the physiopathological process is clustered into three main categories, RNA metabolism, proteins homeostasis, and trafficking and cytoskeleton dynamics (8). Any deficits in these pathways can lead to nonneuronal cell activation including astrocytes, microglia, and oligodendroglia that decrease motor neuron viability (2, 9). *SOD1* mutation forms intracellular aggregates peptides that can lead to proteosomic dysfunction, and disrupt axonal transportation (10). The exact mechanism of why *C9orf72* expansion leads to neurodegeneration is not clearly understood. However, it is thought to be a *C9orf72* protein dysfunction, RNA toxicity, and disruption of RNA binding proteins (11). Furthermore, the mutation in *FUS* and *TARDBP*, enhances stress granules formation that contains RNA complexes then protein aggregation, and more, this process can be disseminated within and between cells, accounting for the spread of disease in the neurons (12). Mutation in several other genes also leads to deviated trafficking of aggregated proteins including proteins optineurin (OPTN), valosin-containing protein (VCP), and TANK-binding kinase 1 (TBK1), and p62/sequestosome (13, 14).

Biomaterials

To date, there are only two drugs approved by US Food and Drug Administration (FDA) for ALS treatment: riluzole and edaravone. The approval of only two drugs is evident of minimal progress in ALS treatment over the past decades. As glutamate accumulation is known as a key feature of ALS, riluzole can decrease glutamate excitotoxicity in the way of inhibiting the excess release of glutamate (15). Also as described oxidative stress is one of the main factors that leads to neural death in ALS pathology, edaravone was recently approved as an efficient free radical scavenger (16). However, more drugs are currently under investigation, and we hope more drugs will be available for ALS treatment, but many challenges in developing new therapeutic agents may remain such as blood-brain barrier (BBB), targeting, clearance, biostability, and degradation (17, 18). For example, riluzole exhibits a low accumulation in the CNS and is partly limited by BBB (19).

Advances in biomaterial proposed utilizing nanoparticles to package and delivery pharmaceuticals to CNS to protect against absorption, and clearance, and facilitate the transportation across BBB (20). Designing and engineering nano-bio materials loaded with agents such as riluzole or other efficient substances provide prospective advances in therapeutic approaches and drug delivery systems for the neurodegenerative disease particularly ALS (21). Here we reviewed biomaterials used in ALS therapeutic approach over the last years.

There are various biomaterials applied as a carrier for riluzole to deliver the drug to CNS and targeted cells. Solid lipid nanoparticles loaded with riluzole demonstrated successful results in delivering and targeting the brain through endocytose in rats because of the lipophilic features of such nanoparticles (22). Moreover, a low level of drug was found in off-targeted organs including the liver, spleen, heart, kidneys, and lung, and consequently lower side effects.

Riluzole-loaded carbon nanotubes prepared by Chigumbu et al. were used as a treatment for ALS (23). Carbon nanotubes can rapidly translocate to cellular components and provide a drug delivery system. This in vitro study compared toxicity as a result of carbon nanotubes utilization. However, the comparison did not show any cytotoxicity due to carbon nanotubes and opened the way for further investigation for using this biomaterial as carriers for drugs.

In a different study, chitosan nanoparticles were used to carry riluzole, while chitosan was cross-linked with tripolyphosphate (24). Due to the physicochemical properties of chitosan and the size of nanoparticles, results showed an efficient drug release within 24h hours and precise targeting of the CNS. Another study by Nabi et al. also was performed on the application of riluzole-loaded chitosan nanoparticles through the ionic gelation method, which demonstrated a 24h controlled drug release and greater accumulation in the brain similar to prior described study (25).

Additionally, another study develop a liposome filled with riluzole and verapamil for reducing efflux pumps and thereafter better transportation of drugs to the CNS (26). Liposomes were loaded by the lipid film hydration method. These studies demonstrated that riluzole and verapamil co-loaded liposomes have the potential for use in ALS treatment.

Parikh et al. develop a nanoemulsions system to carry riluzole to the brain through the post-nasal administration in comparison to oral uptake (27). Nanoemulsions properties such as nasal cytotoxicity resistance make it stable for three months. Also, brain uptake of post intranasal riluzole-loaded nanoemulsion was considerably higher than oral administration of such nanoparticles.

Direct injection via intrathecal is considered one of the most promising solutions for ALS treatment and also this approach can provide a large dose of therapeutic agents to CSF (28). Another study measures the drug delivery properties of PEG-coated AuNanoparticles in mice and found that these

nanoparticles induce high brain accumulation, biostability, and precise targeting (29).

Newly cell-based therapy showed therapeutic potential for ALS treatment via stem cells (30). However, utilizing biomaterials in cell-based delivery can improve the efficiency of such a procedure due to the low survival rate of cells and off-targeted engraftment. Vieria and colleagues developed injectable manganese-based biocompatible hydrogel blends, that can provide an image-guided cell delivery (31). The methacrylate gellan gum and hyaluronic acid hydrogel blends can physically support the cells during the injection and enhance the survival time of the cells in the intrathecal space.

Minocycline was proven to have a low neuroprotective effect in ALS animal models due to pharmacokinetic challenges including biostability, absorption, and targeting based on recent studies, while it is shown that it can be effective in some diseases, suggested it could be useful if delivered appropriately (32). Wiley et al. encapsulate minocycline in Lipopolysaccharide Modified Liposomes for targeting TLR4 on microglia in SOD1 mice. Microglia over-activation is recognized as one of the key factors leading to ALS. They aimed to introduce encapsulate minocycline in Lipopolysaccharide Modified Liposomes as an approach to reducing neuroinflammation and development of disease in mice model (32).

A different study performed adapalene encapsulate nanoparticles in SOD1 mice to investigate the therapeutic application of adapalene after resolving the obstacles such as inadequate water solubility and rapid clearance of adapalene that resulted from prior works. They utilized intravenous administration nanoparticles composed of poly(lactic acid)-poly(ethylene glycol) loaded with adapalene in SOD1 mice. Results revealed a robust improvement in retinoid signaling, life span, neuroprotection, and motor performance (33). Retinoic acid dysregulation is also reported in ALS and is believed to be a crucial mechanism in disease pathophysiology. Adapalene is a RA receptor β agonist that can potentially activate retinoids in SOD1 mice, but recent studies demonstrate poor efficiency in ALS treatment due to earlier described challenges (34).

In conclusion, it seems that the use of biomaterials to deliver the currently approved drugs can improve therapeutic outcomes. However, future human studies are necessary to validate the use of biomaterials in the treatment of ALS.

Deceleration

Funding
We do not have any financial support for this study.

Conflict of interest

The author declares no conflict of interest regarding the publication of this paper.

Ethical approval

Since the data in this paper were obtained from the ADNI database (adni.loni.usc.edu), it does not include any research involving human or animal subjects.

Availability of data and material

The datasets analyzed during the current study are available upon request with no restriction.

Consent for publication

This manuscript has been approved for publication by all authors.

References:

1.   Lyon MS, Wosiski-Kuhn M, Gillespie R, Caress J, Milligan C. Inflammation, Immunity, and amyotrophic lateral sclerosis: I. Etiology and pathology. Muscle & Nerve. 2019;59(1):10-22.
2.   Brown RH, Al-Chalabi A. Amyotrophic Lateral Sclerosis. The New England journal of medicine. 2017;377(2):162-72.
3.   Logroscino G, Traynor BJ, Hardiman O, Chiò A, Mitchell D, Swingler RJ, et al. Incidence of amyotrophic lateral sclerosis in Europe. Journal of neurology, neurosurgery, and psychiatry. 2010;81(4):385-90.
4.   Loeffler JP, Picchiarelli G, Dupuis L, Gonzalez De Aguilar JL. The Role of Skeletal Muscle in Amyotrophic Lateral Sclerosis. Brain pathology (Zurich, Switzerland). 2016;26(2):227-36.
5.   Rosen DR, Siddique T, Patterson D, Figlewicz DA, Sapp P, Hentati A, et al. Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. Nature. 1993;362(6415):59-62.
6.   DeJesus-Hernandez M, Mackenzie IR, Boeve BF, Boxer AL, Baker M, Rutherford NJ, et al. Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. Neuron. 2011;72(2):245-56.
7.   Renton AE, Chiò A, Traynor BJ. State of play in amyotrophic lateral sclerosis genetics. Nature neuroscience. 2014;17(1):17-23.
8.   van Es MA, Hardiman O, Chio A, Al-Chalabi A, Pasterkamp RJ, Veldink JH, et al. Amyotrophic lateral sclerosis. Lancet (London, England). 2017;390(10107):2084-98.
9.   Nabizadeh F, Balabandian M, Sharafi AM, Ghaderi A, Rostami MR, Naser Moghadasi A. Statins and risk of amyotrophic lateral sclerosis: a systematic review and meta-analysis. Acta Neurologica Belgica. 2021.
10.   Bruijn LI, Houseweart MK, Kato S, Anderson KL, Anderson SD, Ohama E, et al. Aggregation and motor neuron toxicity of an ALS-linked SOD1 mutant independent from wild-type SOD1. Science (New York, NY). 1998;281(5384):1851-4.
11.   Gendron TF, Belzil VV, Zhang YJ, Petrucelli L. Mechanisms of toxicity in C9FTLD/ALS. Acta neuropathologica. 2014;127(3):359-76.
12.   Bosco DA, Lemay N, Ko HK, Zhou H, Burke C, Kwiatkowski TJ, Jr., et al. Mutant FUS proteins that cause amyotrophic lateral sclerosis incorporate into stress granules. Human molecular genetics. 2010;19(21):4160-75.
13.   Johnson JO, Mandrioli J, Benatar M, Abramzon Y, Van Deerlin VM, Trojanowski JQ, et al. Exome sequencing reveals VCP mutations as a cause of familial ALS. Neuron. 2010;68(5):857-64.
14.   Salameh JS, Brown RH, Jr., Berry JD. Amyotrophic Lateral Sclerosis: Review. Seminars in neurology. 2015;35(4):469-76.
15.   Dharmadasa T, Kiernan MC. Riluzole, disease stage and survival in ALS. The Lancet Neurology. 2018;17(5):385-6.
16.   Rothstein JD. Edaravone: A new drug approved for ALS. Cell. 2017;171(4):725.
17.   Rosenfeld J, Strong MJ. Challenges in the Understanding and Treatment of Amyotrophic Lateral Sclerosis/Motor Neuron Disease. Neurotherapeutics. 2015;12(2):317-25.

18.	Petrov D, Mansfield C, Moussy A, Hermine O. ALS Clinical Trials Review: 20 Years of Failure. Are We Any Closer to Registering a New Treatment? Front Aging Neurosci. 2017;9:68-.

19.	Abrahao A, Meng Y, Llinas M, Huang Y, Hamani C, Mainprize T, et al. First-in-human trial of blood-brain barrier opening in amyotrophic lateral sclerosis using MR-guided focused ultrasound. Nature communications. 2019;10(1):4373.

20.	Tsou YH, Zhang XQ, Zhu H, Syed S, Xu X. Drug Delivery to the Brain across the Blood-Brain Barrier Using Nanomaterials. Small (Weinheim an der Bergstrasse, Germany). 2017;13(43).

21.	Mazibuko Z, Choonara YE, Kumar P, Du Toit LC, Modi G, Naidoo D, et al. A review of the potential role of nano-enabled drug delivery technologies in amyotrophic lateral sclerosis: lessons learned from other neurodegenerative disorders. Journal of pharmaceutical sciences. 2015;104(4):1213-29.

22.	Bondì ML, Craparo EF, Giammona G, Drago F. Brain-targeted solid lipid nanoparticles containing riluzole: preparation, characterization and biodistribution. Nanomedicine (London, England). 2010;5(1):25-32.

23.	Chigumbu N LS, Pillay V, Ndlovu S. In vitro evaluation of the physicochemical effects of drug loaded carbon nanotubes on toxicity. J Nanomed Nanotechnol 2012;3.

24.	Shanmukhapuvvada Y VS. Design and development of Riluzole loaded chitosan nanoparticles by emulsification crosslinking. Int J Pharm Pharm Sci 2012;4(4):244–8.

25.	Nabi B, Rehman S, Fazil M, Khan S, Baboota S, Ali J. Riluzole-loaded nanoparticles to alleviate the symptoms of neurological disorders by attenuating oxidative stress. Drug development and industrial pharmacy. 2020;46(3):471-83.

26.	Yang T, Ferrill L, Gallant L, McGillicuddy S, Fernandes T, Schields N, et al. Verapamil and riluzole cocktail liposomes overcome pharmacoresistance by inhibiting P-glycoprotein in brain endothelial and astrocyte cells: A potent approach to treat amyotrophic lateral sclerosis. European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences. 2018;120:30-9.

27.	Parikh RH, Patel RJ. Nanoemulsions for Intranasal Delivery of Riluzole to Improve Brain Bioavailability: Formulation Development and Pharmacokinetic Studies. Current drug delivery. 2016;13(7):1130-43.

28.	Wang GY, Rayner SL, Chung R, Shi BY, Liang XJ. Advances in nanotechnology-based strategies for the treatments of amyotrophic lateral sclerosis. Materials today Bio. 2020;6:100055.

29.	Spinelli A, Girelli M, Arosio D, Polito L, Podini P, Martino G, et al. Intracisternal delivery of PEG-coated gold nanoparticles results in high brain penetrance and long-lasting stability. Journal of Nanobiotechnology. 2019;17(1):49.

30.	Baloh RH, Glass JD, Svendsen CN. Stem cell transplantation for amyotrophic lateral sclerosis. Curr Opin Neurol. 2018;31(5):655-61.

31.	Vieira S, Strymecka P, Stanaszek L, Silva-Correia J, Drela K, Fiedorowicz M, et al. Methacrylated gellan gum and hyaluronic acid hydrogel blends for image-guided neurointerventions. Journal of materials chemistry B. 2020;8(27):5928-37.

32.	Wiley N, Madhankumar, A. , Mitchell, R. , Neely, E. , Rizk, E. , Douds, G. , Simmons, Z. and Connor, J. Lipopolysaccharide Modified Liposomes for Amyotropic Lateral Sclerosis Therapy: Efficacy in SOD1 Mouse Model. Advances in Nanoparticles. 2012;1:44-53.

33.	Medina DX, Chung EP, Teague CD, Bowser R, Sirianni RW. Intravenously Administered, Retinoid Activating Nanoparticles Increase Lifespan and Reduce Neurodegeneration in the SOD1(G93A) Mouse Model of ALS. Front Bioeng Biotechnol. 2020;8:224-.

34.	Ali S, Rawat N, Husain A, editors. A Review on a Third Generation Retinoidal Agent: Adapalene2016.