Rare sclerosis unmasked: Insights into orphan drugs for amyotrophic lateral sclerosis


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Abstract
Orphan drugs are essential for the treatment of rare diseases, which impacts 3-6% of global population. These conditions are often overlooked by major pharmaceutical companies due to the limited commercial viability, leading to WHO (World Health Organisation) to term them as 'neglected'. This article explores various types of rare sclerosis and focuses on Amyotrophic lateral sclerosis (ALS), its current treatment options and approved orphan drugs. Various types of rare sclerosis include Balo's concentric sclerosis (BCS), Schilder's disease, Tumefactive multiple sclerosis, multiple sclerosis (MS) and Amyotrophic lateral sclerosis (ALS). All these types affect central nervous system (CNS) with varying pathophysiology and symptoms. While no specific orphan drugs exist for these (Balo's concentric sclerosis, Schilder's disease, Tumefactive multiple sclerosis) types, symptoms are managed by corticosteroids, interferons and immunosuppressants. Multiple sclerosis (MS) has disease modifying therapies (DMT) available which includes Beta interferon and Glatiramer acetate. ALS is a progressive neurodegenerative disease that affects motor neurons. Its pathophysiology involves glutamate excitotoxicity, gene mutations, oxidative stress, and neuroinflammation. Current treatments include Riluzole and Edaravone; the combination of Sodium Phenylbutyrate and Taurursodiol was discontinued due to safety concerns. Novel approaches like small molecules, gene therapy, and stem cell treatments are under evaluation. Some drugs were granted Orphan designations for ALS, such as Riluzole (EXSERVAN), Edaravone (RADICSAVA), and Tofersen (QALSODY), while Lenzumestrocel is under clinical evaluation. Despite their small market share, orphan drugs are crucial for addressing rare diseases. Enhancing their identification, diagnosis, prevention, and treatment will result in improved healthcare outcomes for affected individuals.

1. Introduction

In the vast landscape of pharmaceuticals, there exists a remarkable class of medications for their profound impact on patients grappling with some of the rarest and most debilitating diseases known to humanity. These medications, categorized as rare and orphan drugs, serve as beacon of hope for patients and families facing conditions typically neglected during traditional drug development efforts.

Rare disease, as the name suggests, affects only a small fraction of global population around 3-6%. Due to absence of a universal definition, varying criteria have emerged to identify a rare disease across countries (1). In response to their unmet medical and social needs, the concept of orphan drugs emerged. Orphan drugs are designated to diagnose, prevent or treat rare diseases such as acute intermittent porphyria, myasthenia gravis and merkel cell carcinoma (2, 3). The WHO refers to these diseases as “neglected” because they are overlooked by major pharmaceutical companies due to limited commercial viability.

This article delves into the various types of rare sclerosis and highlighting the details on Amyotrophic lateral sclerosis (AML), along with current treatment options and approved orphan drugs.

2. Rare types of sclerosis

There are various types of rare sclerosis that includes Balo concentric sclerosis (BCS), Schilder disease, Tumefactive multiple sclerosis alongside more prevalent ones like Multiple sclerosis (MS) and Amyotrophic Lateral Sclerosis (ALS) (4) as mentioned in the Table 1. All the types of sclerosis affect the CNS with varying pathophysiology and neurological involvement.

Table 1. Types of rare sclerosis (5–8)

Type	Description	Symptoms
Balo’s concentric sclerosis (BCS)	Histological variant with characterized by concentric layers of demyelination (onion ring) in the brain	Headache, weakness, seizures, sensory disturbances and cognitive impairment
Schilder's sclerosis	Diffuse cerebral sclerosis with extensive demyelinating of the cerebral brain with one-two symmetrical bilateral plaque	Spasticity, seizures, visual disturbances and cognitive decline
Tumefactive multiple sclerosis	Rare form of multiple sclerosis which has emergence of large lesions (tumour-like) demyelination in brain	Symptoms may mimic other types of MS but can also cause seizures and changes in mental status
Multiple sclerosis (MS)	Characterized by chronic inflammation and demyelinating of myelin sheath which results in neuron loss in the brain and spinal cord	Vision impairment, numbness, weakness, tremor, constipation, bladder and bowel incontinence and cognitive dysfunction

Currently, there are no orphan drugs available for these types of sclerosis. However, management of their symptoms can be achieved using corticosteroids, interferons and immunosuppressant drugs (8,9).Meanwhile, therapies such Beta interferon (Avonex, Betaseron and Rebif) and Glatiramer acetate (Copaxone) are considered as disease-modifying therapies currently used in the treatment of Multiple sclerosis (MS) (10,11).

3. Amyotrophic lateral sclerosis (ALS), current treatment and approved orphan drugs

It is a rare progressive neurodegenerative disease that affects neurons in the spinal cord and brain (12). Also, known as Lou Gehrig's disease. 'Amyotrophy' refers to muscle fibres atrophy and 'Lateral sclerosis' refers to hardening of motor neurons. It degenerates motor neurons that controls their voluntary muscle control while sensory functions are typically preserved (13). The rate of disease progression varies depending on onset age and site. Typical symptoms include difficulty in speech and swallowing, atrophy and eventual respiratory failure (14).

According to Lu Xu *et al.* in 2019, the worldwide prevalence and incidence were 4.42 and 1.59 per 1, 00, 000 person/year respectively (15). Whereas, worldwide prevalence is between range of 3.4- 12.3 per 10,00,00 persons. Overall, there is slightly higher incidence of male prevalence than female (M: F~ 3:2.4) (16).

The exact pathophysiology that leads to neuro-degeneration of ALS is still unknown. However, various neurodegenerative diseases are mediated through complex interrelated molecular and genetic pathways. Below mentioned pathways as shown in Figure no.1 are implicated in pathophysiology of ALS (17, 18).

3.1 Glutamate excitotoxicity:

The dysfunction of the astrocytic excitatory amino acid transporter 2 (EAAT2) mediates reduction in the uptake glutamate in the synaptic cleft. This leads to the induction glutamate excitotoxicity through activation of Ca 2++ -dependent enzymatic pathways, further, impairing glutamate clearance and ultimately contributing to neurodegeneration.

3.2 Mutations

in c9orf72, TDP-43 and FUS leads to defects in protein degradation pathways leading to dysregulation in RNA metabolism and impaired protein synthesis which causes translation abnormalities and formation intracellular neuronal aggregate.

3.3 SOD-1 Mutation:

Superoxide dismuates-1 (SOD-1) gene mutation results in Neurofilaments, dysfunctional mitochondria and disruption of axonal transportation due to oxidative stress and leads to intracellular aggregates.

3.4 Neuroinflammation:

Microglia activation resulted by secretion of cytokines which leads to inflammation and neurotoxicity.

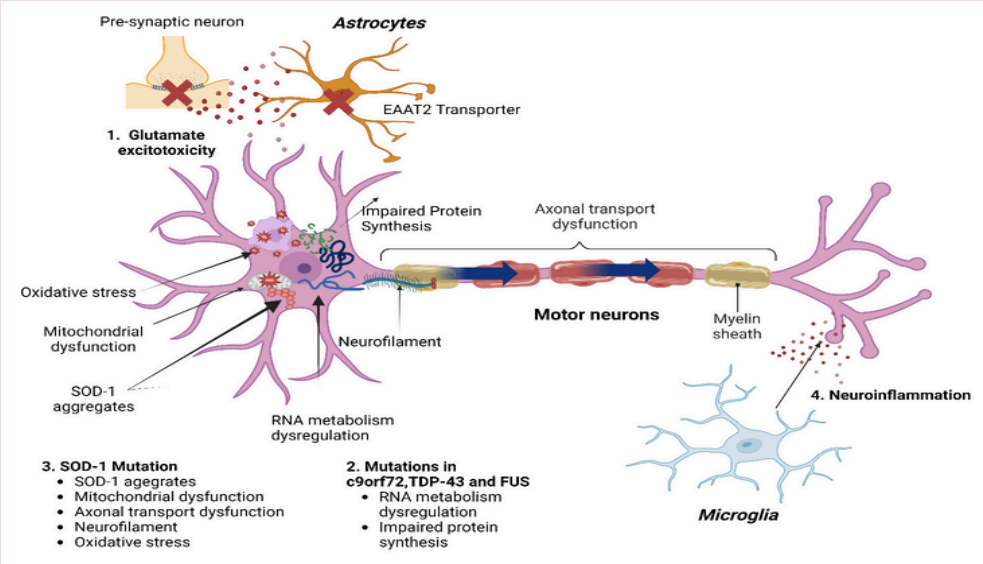

Figure 1. Pathophysiology of Amyotrophic Lateral Sclerosis (ALS) (Created by Biorender)

The current available treatment options help in the management of symptomic relief and slows the progression of the disease. Below mentioned drugs are majorly used in ALS treatment.

- Riluzole was approved initially approved by FDA in 1995 for oral use as the treatment of ALS. Its exact mechanism is unknown, but it acts on glutamate as antagonist. This slows the progression of disease by inhibiting glutamate release (excitotoxicity) in presynaptic neuron (19).
- Edaravone was approved by FDA in 2017. It is available in injectable form as oral suspension powder. It is known inhibits lipid peroxidation that eliminates radicals such as hydroxyl, peroxynitrite, peroxyl hydrogen peroxide that acts as reactive oxygen species (ROS). Hereby, protecting the neurons in the spinal cord and brain by reduction of oxidative stress and lesser neurodegeneration
- Combination of Sodium Phenyl butyrate and Taurursodiol promotes the inhibition of neuronal death by reduction in Endoplasmic reticulum (ER) stress and mitochondrial dysfunction (19). However, post Phase 3 Phoenix III trail Relyvrio was voluntarily discontinue from the market due to safety concerns (10).

Many drugs of different therapeutic categories such as anti-inflammatory, anti-excitotoxicity and anti-aggregation agents are being evaluated for the treatment of ALS. Novel approaches such as small molecules, gene therapy and stem cell are in trials for its assessment as new treatment options (20). Other types of palliative cares such as counselling and rehabilitating therapy that are symptom dependent are needed to improve the quality of life.

The above-mentioned drugs after various clinical trials and years later were approved to treat ALS as designated orphan drugs by different regulatory agencies across the world. The below table 2 represents the approved orphan drugs with product information and mechanism of action (MOA**).**

Table 2. Approved orphan drugs for Amyotrophic Lateral Sclerosis (ALS)

Molecule	Orphan Indication year	Innovator & Brand Name	Dosage & Strength	MOA
Riluzole	2019	Aquestive Therapeutics (EXSERVAN)	Film- 50 mg	Inhibits the glutamate, Inactivates sodium channels (voltage dependent), G-protein activation for transduction process.
Edaravone	2024	Mitsubishi Tanabe Pharma Corp (RADICSAVA)	Oral Suspension 105 mg/5 ml	Inhibits lipid peroxidation
Tofersen	2023	Biogen MA Inc (QALSODY)	Injection 100 mg/15 ml	Targets SOD1 mRNA to lower the SOD1 protein synthesis

The clinical trial ALSUMMIT (NCT04745299) is an on-going Phase III trial conducted at multiple centres and was initiated in 2021. This study design is random, double blind conducted in parallel group with sham procedure-control. It aims to assess the safety and efficacy (long-term) of the Lenzumestrocel- Neuronata-R® Injection to treat ALS patients upto 36 months. The trial involves 115 subjects and is expected to be completed by 2026. Lenzumestrocel has received conditional approval in Korea as orphan cell therapy by its regulatory authority (MFDS) for ALS (21).

4. Conclusion

In conclusion, despite representing a small portion of the pharmaceutical market there is need to emphasis upon understanding and addressing multifaceted nature of rare diseases that includes identification, diagnosis, prevention and development of orphan drugs (22). The encompassing factors includes complex biology, low prevalence rate, expertise in the area, methods and instruments used, developing the tailored drugs for rare diseases (23). By focusing on these areas, we can serve individuals affected by rare diseases and improve their overall healthcare outcome in an effective manner.

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