

● INVITED REVIEW

# Current view and perspectives in amyotrophic lateral sclerosis

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## Abstract

Amyotrophic lateral sclerosis (ALS), identified as a distinct clinical entity by Charcot since the end of the nineteenth century, is a devastating and fatal neurodegenerative disorder that affects motor neurons in the brain, brainstem and spinal cord. Survival of patients with ALS is associated with several factors such as clinical phenotype, age at onset, gender, early presence of respiratory failure, weight loss and treatment with Riluzole (the only disease-modifying drug approved for this disease). Nowadays, there is still no curative treatment for ALS: palliative care and symptomatic treatment are therefore essential components in the management of these patients. Nevertheless, the scientific knowledge in the field of ALS motor neuron degeneration is growing, with the prospect of new treatments. Based on this physiopathological knowledge, several new therapeutic targets are being studied, involving various mechanisms such as excitotoxicity, neuroinflammation, mitochondrial dysfunction, oxidative stress, RNA metabolism and other attractive concepts. Moreover, it is also important to identify reliable biomarkers that will be essential components for future therapeutic development and study design in ALS. In this review, we present the main recent advances and promising therapeutics and biomarkers in the field of ALS.

**Key Words:** amyotrophic lateral sclerosis; Charcot; biomarkers; research; motor neuron; neurodegeneration

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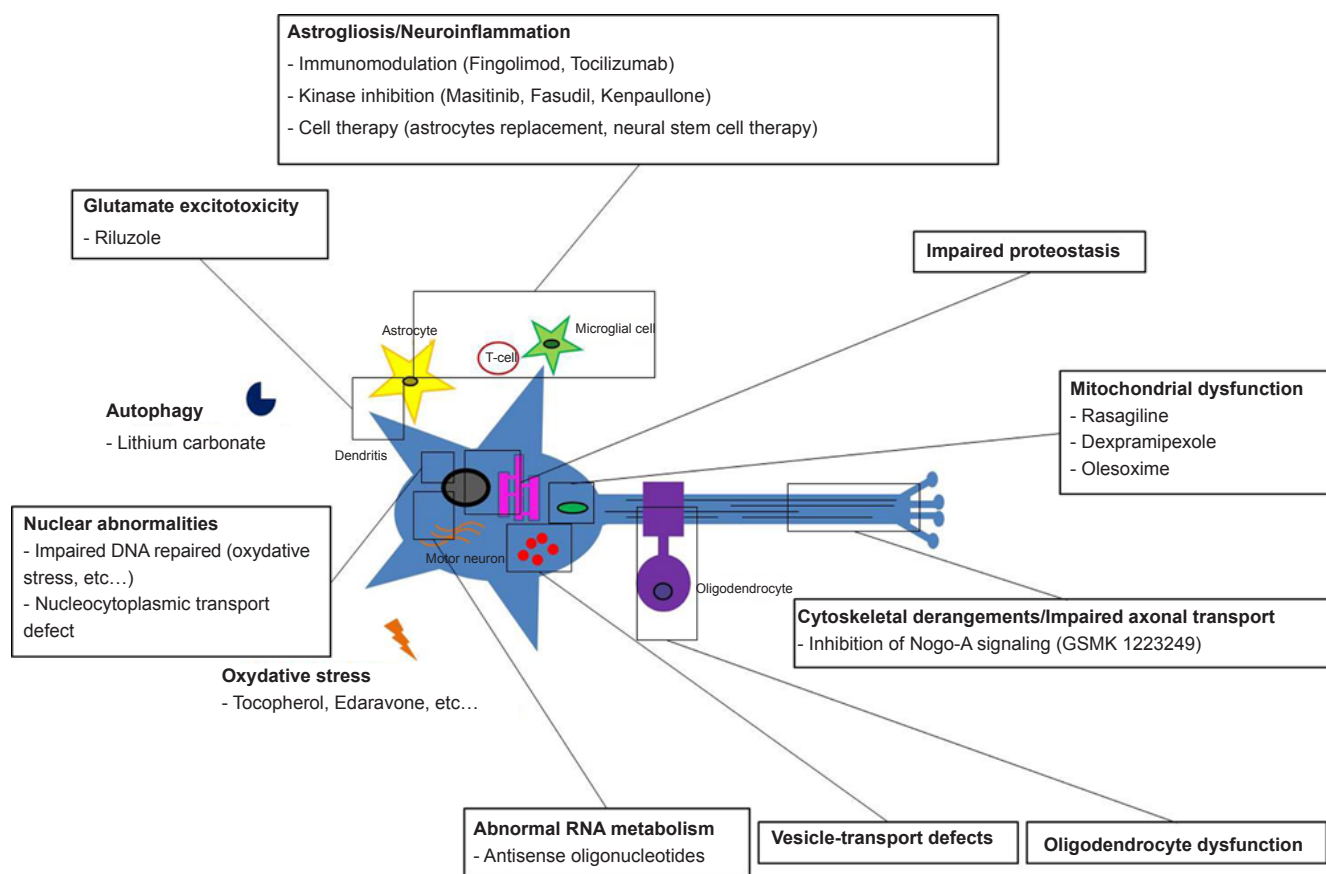
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## Introduction

Amyotrophic lateral sclerosis (ALS), first observed by Charles Bell in 1830 but fully described and named by Jean-Martin Charcot in 1874, is a devastating neurological disorder that results in the selective degeneration of both upper (UMN) and lower (LMN) motor neurons (Mathis et al., 2016). This fatal disease (usually within 3–5 years) is characterized by a progressive and asymmetric weakness and atrophy in limb, thoracic, abdominal and bulbar muscles. However ALS is also regarded as a multisystem degeneration with various other signs: cognitive impairment (sometimes frontotemporal dementia), extrapyramidal features, postural abnormalities, and even small fiber neuropathy and mild oculomotor disturbance. Most of ALS cases are sporadic, but familial forms are reported in 5–10%. The diagnosis of ALS remains phenotypically based, relying on identification of UMN and LMN signs. Clinical criteria for the diagnosis of ALS have been established in 1994 (El Escorial criteria) then revised, and finally changed in 2008 for electro-clinical criteria (Awaji criteria) that have the same specificity but higher sensitivity (Mathis et al., 2016).

## ALS and Biomarkers

In ALS, one of the main focuses of research is the development of surrogate markers (biomarkers) of preclinical and clinical disease in order to make earlier diagnosis and to test the efficacy of drug interventions more efficiently. The first interest for biomarkers in ALS was through a study on amino acids in 1965; since that time, multiple candidate biomarkers have emerged, specifically from the neurochemical analysis of biofluids (cerebrospinal fluid, serum, and urine), advanced neuroimaging (positron emission tomography, magnetic resonance imaging), and neurophysiological techniques, including electromyography (EMG), transcranial magnetic stimulation (TMS), and electrical impedance myography (Turner and Benatar, 2015). EMG is nowadays the only sensitive test routinely used in clinical practice, but the diagnosis delay is still on average 10–12 months; as a consequence, the search for reliable biomarkers is needed. Recently, a study has shown that detection of increased cortical excitability is a diagnosis biomarker in ALS, so that the use of threshold tracking TMS with existing criteria might help to the process of diagnosis (Menon et al.,



**Figure 1** Main key pathogenic processes and potential therapies in amyotrophic lateral sclerosis.

2016); however, it is not possible to detect subclinical disease prior to the onset of symptoms by this way, as shown in *C9orf72* pre-symptomatic patients (Geevasinga et al., 2015). Some molecular biomarkers are also promising. Neurofilament content and organization are important contributors and probable risk factors for ALS: cerebrospinal fluid and blood levels of phosphoneurofilament heavy chain and neurofilament light chain (their increased levels being associated with poor prognosis) or combined phosphoneurofilament heavy chains and vascular endothelial growth factor (VEGF) (Goncalves et al., 2016). The creatine kinase (CK), crucial to energy metabolism (by maintaining intracellular ATP levels), may be mildly to moderately elevated in patients with ALS: patients with elevated CK have better prognosis than others, suggesting that CK may be upregulated to provide energy in the face of metabolic stress in ALS (Rafiq et al., 2016). Oxidative stress is also a pathological feature of many neurological disorders; it stems from increased production of reactive oxygen species (ROS), generated by oxygen metabolism that can in turn leads to lipids, protein, DNA damage, and ultimately cell death (Mathis et al., 2016).

## Excitotoxicity

In ALS, glial-mediated excitotoxicity is mainly caused by

dysregulation of glutamatergic signaling (through intracellular calcium overload) and alterations in neuronal toxicity. This excitotoxic hypothesis has given rise to an extremely active research field aimed at developing neuroprotective drugs blocking the excitotoxic process, such as riluzole (a neuroprotective drug that is thought to block glutamatergic neurotransmission in the central nervous system) (Doble, 1996), the only medication that has proved a modest effect in the survival of ALS patients (two large randomized placebo-controlled clinical trials): oral administration of riluzole (100 mg daily) improves the 1-year survival by 15% and prolongs survival by 3 months (after 18 months treatment), with a clear dose response. Long-term use of riluzole was associated with a better prognosis for ALS patients, whereas short-term use had little effect on survival. Since 1994 and the first use of this antiglutamate agent in ALS, more than 180 clinical trials have been conducted in animal models and/or humans (50 phase II or III clinical trials carried out within the last 20 years) with no positive result (Mathis et al., 2016). The main key pathogenic processes in ALS (and potential therapies) are showed in **Figure 1**.

## Neuroinflammation

Neuroinflammation and immune response is complex in ALS: the early immune response is dominated by protective

cytokines and immune polarization (activation of microglia, T-cells, dendritic, and antigen-presenting cells in corticospinal tracts and in the motor cortex, as well as release of inflammatory markers such as cytokines, C-reactive protein, and ferritin), while the later response is destructive and correlates with rapid disease progression (Komine and Yamanaka, 2015). Neutrophils and monocytes are implicated and may represent important factors in late disease progression. Autoantibodies against calcium channels and certain antiglycolipid antibodies have been reported in sera of some ALS patients, without clear significance (Pagani et al., 2011). However, some authors have recently shown that SGPG (one of the glycolipid target antigens in various peripheral neuropathies) and/or an sulfoglucuronosyl epitope bearing molecule is a target antigen in a significant number of ALS patients, suggesting that anti-SGPG antibody can be used as a serum biomarker and that it may be useful for pre-symptomatic diagnosis and therapeutic monitoring (Li et al., 2016). Based on the hypothesis that proliferation of aberrant glial cells is dependent on kinase receptor activation, masitinib (a selective oral tyrosine-kinase inhibitor) has been used to control neuroinflammation in the *SOD1* rat model of ALS: it may reduce inflammation in the nervous systems (by peripheral monocyte/macrophage system). It has been shown that masitinib (initiated 7 days after paralysis) may prolong post-paralysis survival by 40% compared with controls (Trias et al., 2016). Masitinib appears well-suited for treating ALS patients, but we still wait for results in humans. Another study has shown that fingolimod (an immunomodulator used in multiple sclerosis) extends survival, improves the phenotype, and modulates neuroinflammation in the cortex and spinal cord of ALS mice, suggesting that this drug may be a potential new therapeutic approach to ALS (Potenza et al., 2016).

### Protein Misfolding

Protein misfolding and accumulation has been suspected early (as TAR DNA-binding protein 43 kDa (TDP-43), an RNA-binding protein that regulates RNA metabolism), and is a major component of ubiquitin-positive neuronal inclusions in both ALS and frontotemporal dementia. It belongs to an expanding class of proteins known to be involved in the formation of ribonucleoprotein granules or membraneless organelles: it regulates metabolism of target RNA, pre-mRNA splicing, mRNA stability, and transport. TDP-43 represents a pathological hallmark found in most of cases of ALS, and in half of patients with frontotemporal dementia. TDP-43 mutations and RNA mis-processing may cause disease by altering the phase separation properties of TDP-43; but the link between mutational effects on phase separation and changes in RNA processing (and further downstream effects) has to be clarified. Prion-like propagation of abnormal intracytoplasmic proteins such as TDP-43 has been

proposed to explain the rapid disease progression of ALS. Therefore, regulation of the propagation of these abnormal proteins (by knocking out the relevant gene or by reducing the expression of proteins) will probably be an important goal for disease-modifying therapy of ALS (Polymenidou and Cleveland, 2017).

### RNA Metabolism

Several identified causative genes of ALS are related to RNA metabolism (*ANG*, *FUS*, *TARDBP*), and several ALS-associated proteins (elongator protein 3 (ELP3), senataxin (SETX)) are involved in RNA processing (Chen et al., 2016). Functional studies indicate that microRNA (small endogenous non-coding RNAs having important gene-regulatory roles by pairing to the mRNAs of protein-coding genes to direct their posttranscriptional repression) plays a significant role in a broad range of cellular and developmental processes, such as stem cell maintenance, differentiation, development, and energy metabolism (Brodersen and Voinnet, 2009). The dysregulation in microRNA processing and expression is suspected as a possible mechanism in ALS, so microRNA (stable in the plasma and serum) represents a promising potential biomarker in this disease (as in various neurodegenerative diseases): 11 microRNAs are expressed in the muscle of ALS patients, but only some of them are overexpressed in plasma (miR-424 and miR-206). Skeletal muscle is now considered as an important tissue involved in the pathogenesis of ALS by activating a retrograde signaling cascade that degrades motor neurons; their health and function are regulated by numerous factors including satellite cells, mitochondria, and microRNAs. The regulation of some microRNAs may be a cause of impaired myogenesis or of attempt to rescue this process in ALS; but further studies are needed (Tsitkanou et al., 2016).

Even more challenging but very conceptually attractive is the use of antisense oligonucleotides (synthetic single stranded strings of nucleic acids binding to RNA and thereby altering or reducing the expression of the target RNA): a phase I randomized study in ALS patients (antisense oligonucleotides were delivered intrathecally) has shown that this promising therapeutic is feasible and well tolerated in humans (Evers et al., 2015).

### Mitochondrial Dysfunction

*SOD1* rats have a reduced mitochondrial ability to synthesize ATP and produce increased levels of nitric oxide, superoxide, and peroxynitrite. In ALS, it has been suggested that 'mitochondrial quality control' is ineffective or overwhelmed by the excessive workload imposed by the chronic and extensive mitochondrial damage (Palomo and Manfredi, 2015). Hexokinase 1 (HK1) and voltage dependent anion channel isoform 1 (VDAC1) (a physiological receptor of HK, considered as the master regulator of the mitochondria)

play a key role in the bioenergetics metabolism of the motor neurons and could be considered as a promising therapeutic target in ALS: the reduction of HK1 concentration increases VDAC1 propensity to interact with mutant *SOD1*, producing thus mitochondrial dysfunction and cell death (Magri et al., 2016). Some molecules such as lithium may induce direct mitochondrial protection, mitophagy, as well as mitochondriogenesis; but no efficacy was demonstrated in ALS patients (Mathis et al., 2016).

## Cell Therapy

With the advancement of stem cell (SC) technology, clinical trials have been proposed as a novel therapeutic approach in various degenerative disorders. Preclinical studies in ALS animal models have clearly demonstrated that SC transplantation in critical regions of the spinal cord (involved in crucial functions such as respiratory capacity or the control of limb movements) offer the most significant clinical benefit. Given the massive failures of neuroprotective agents over the past 20 years, cell-based therapies may represent a new therapeutic approach for ALS. But further investigations are needed: a number of consensus points reflecting the design of phase II/III clinical trials of intraspinal SC transplantation have been discussed in a recent document (Atassi et al., 2016).

## Conclusion

In conclusion, if there is still no curative treatment for this fatal neurodegenerative disorder, the results of some recent studies (working on physiopathology, new therapeutics or biomarkers) are promising and the fundamental background knowledge of the disease is undoubtedly growing exponentially. Nowadays, symptomatic treatments (dysphagia, respiratory failure, cognitive and psychiatric symptoms, pain, spasticity, sialorrhea, fatigue, sleep disturbance) and palliative care are crucial in the management of ALS patients. Therapeutic interventions such as non-invasive ventilation (NIV) appears to be an essential point in the treatment of ALS patients with respiratory involvement, extending survival by approximately 7 months in patients without severe bulbar problems (Mathis et al., 2016).

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