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Therapeutic news in ALS

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by death of motor neurons in the cortex and the spinal cord. This loss of motor neurons causes progressive weakness and amyotrophy. To date, the median duration of survival in patients with ALS, from first symptoms to death, is estimated to be 36 months. Currently the treatment is limited to two options: riluzole which prolongs survival for a few months and edaravone which is available in only a few countries and also has a small impact on disease progression. There is an urgent need for more effective drugs in this disease to significantly improve progression. Over the last 30 years, all trials have failed to find a curative drug for ALS. This is due, partially, to the heterogeneity of the clinical features and the pathophysiology of motor neuron death. We present in this review the various treatment options currently being developed for ALS, with an emphasis on the range of therapeutic approaches being explored, from old drugs tested in a new indication to innovative drugs obtained via biotechnology or gene therapy.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by the progressive loss of both upper (UMN) and lower (LMN) motor neurons in motor cortex, brainstem and spinal cord. This causes weakness and wasting of muscles in all four limbs and the bulbar territory. Death classically occurs once respiratory muscles become involved [1]. ALS is no longer considered as a pure motor neuron disorder since 15-50% of patients develop cognitive disturbances, ranging from cognitive impairment to typical frontotemporal lobar dementia (FTLD) related to injury of the frontal and temporal cortices [2]. Disease incidence is around 2.5/100.000 and the lifetime risk is estimated around 1/300 for men and 1.400 for women [1]. The prognosis of ALS is fatal in all cases with a median duration of survival from first symptoms to death of 36 months [3].

Around 5-10% of ALS cases are considered familial (FALS) with a familial history of motor neuron diseases or FLTD affecting first or second-degree relatives [4]. Since 1993 and the identification of pathogenic mutations in the SOD1 gene, more than 30 genes have been linked to ALS [5,6]: among them, four (C9orf72, SOD1, TARDBP, FUS) explain around 60% of FALS cases [6]. The remaining cases are considered sporadic.

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Although there are no phenotypic differences between sporadic and familial ALS, some features appear rather linked to familial cases: FALS populations may be distinguished from sporadic cases by younger age of onset (50 vs 63 years), predominance of lower limbs onset, and disease duration which exhibits a bimodal survival curve with the majority of cases lasting less than two years or more than five years [7].

To date, there are no reliable diagnostic and prognostic biomarkers for ALS. Diagnosis relies on exclusion of all ALS-mimicking diseases [8]. Diagnostic certainty remains, to date, neuropathological, depending on the presence of inclusion bodies in the cytoplasm in spinal cord and brainstem LMN[9]. These inclusions are labeled by ubiquitin. TDP-43 has been identified as the principal component of these ubiquitinated inclusions which is found in 97% of all ALS cases; SOD1 and FUS are found in 2% and 1% of the inclusions respectively [10].

Only two drugs are currently labeled for ALS: riluzole and edaravone which is available in only a few countries worldwide (USA, Canada, Japan, and Switzerland in Europe) [11,12]. Riluzole principally acts as an anti-glutamatergic drug while edaravone acts as an antioxidant. Since the therapeutic effect of these drugs remains modest with only an extension of survival of a few months, there is an urgent need for new treatments that would have greater impact on the natural history of the disease. Although numerous molecules have been tested in ALS over the last 30 years, none have shown a positive effect in this disease [13]. Among all the hypotheses put forward, important aspects to be stressed include disease heterogeneity concerning age of onset (from 17 to 95 years), site of onset, prominence of UMN or LMN involvement, and disease duration extending from less than one year (in the case of ALS linked to A5 V SOD1 mutation) to decades (in the case of ALS linked to D91A SOD1 mutation) [6]. Disease heterogeneity is also the result of a complex pathophysiology in which glutamate excitotoxicity, neuroinflammation, mitochondrial dysfunction, protein misfolding and aggregation, defect in axonal transport, disturbances of the DNA/RNA machinery, and oxidative stress interact with each other in motoneuron death processes [3]. It is currently obvious that ALS is not determined by a unique cause but, conversely, occurs is the consequence of a combination of complex cellular, molecular and genetic interactions which trigger and sustain motoneuron death [1,3].

Evolving clinical and research approaches to ALS therapeutics have led to numerous clinical trials which allowed emergence of new therapeutic options. Over the last years, numerous trials have been run in ALS testing either old drugs in a new indication or compounds directed at new pathological pathways responsible for motoneuron death (Fig. 1).

Here we present an overview of clinical trials, emphasizing the main therapeutic approaches currently developed in ALS.

2. New indication for old drugs

Certain drugs prescribed for decades in non-neurological indications can also present potential therapeutic effects on neuronal function and survival. These unknown properties might have meaningful effects in neurological disorders.

2.1. *Tudca-ALS*

Tauro-ursodeoxycholic acid (TUDCA), indicated in chronic cholestatic liver and gallstone diseases is well-known to gastroenterologists. TUDCA is orally available and passes through the blood-brain barrier.

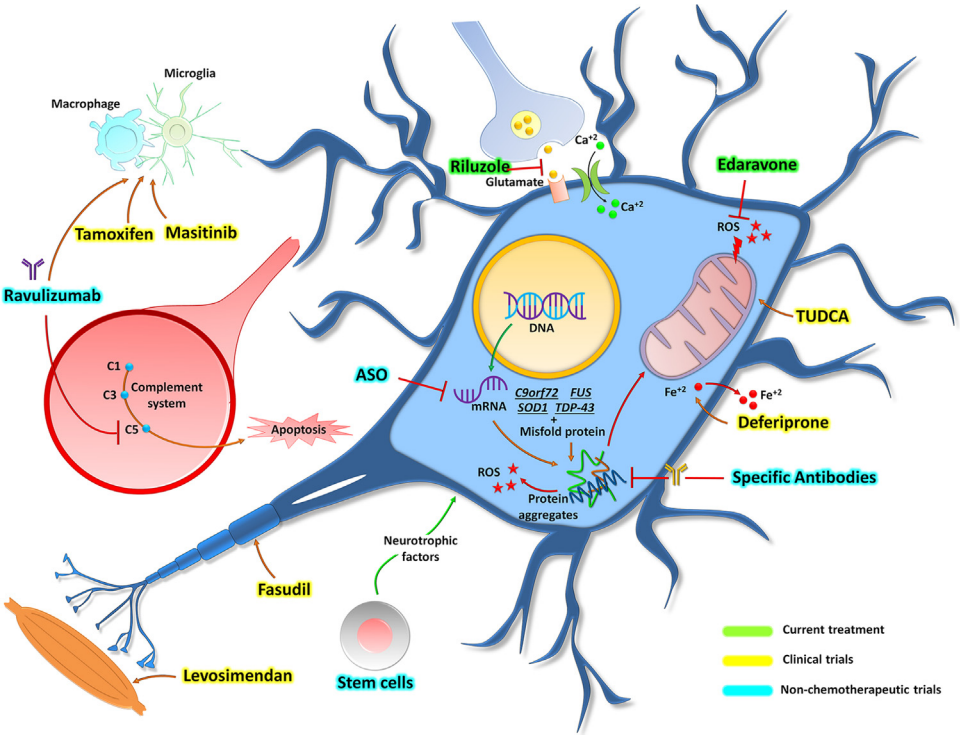

Figure 1 – Mode of action of the candidate drugs presented in this review.

It has been shown that TUDCA is neuroprotective in motor neuron-neuroblastoma hybrid cells expressing mutant SOD1 (mutations A4 V and G93A) against NO toxicity [14]. Moreover, the interest for TUDCA in ALS came forward due to its potent inhibition of apoptosis via interference with the mitochondrial pathway of cell death, resulting in an inhibition of oxygen-radical production, and reducing endoplasmic reticulum stress and caspase activation [15].

Two phase II studies showed promising results in ALS which justified initiating a phase III trial. The first showed that UDCA is well tolerated, measured at a meaningful serum level after oral intake of an appropriate dose, and detected in cerebrospinal fluid [16]. The second study was a proof-of-concept phase II trial which showed that the slope of progression of the ALSFRS-r scale was 7 points/year smaller in the group treated by riluzole + TUDCA vs riluzole [17].

Following these promising results, a European double-blinded placebo-controlled phase III study was designed to carry on these studies (NCT03878654). This trial is in progress and aims to determine whether TUDCA at the dose of 2 g daily will slow disease progression. 440 patients are expected to be enrolled.

2.2. *Tamoxifen*

Tamoxifen has been approved for the treatment of breast cancer for a long time. Its mode of action involves a selective modulation of estrogen receptors. In addition to this anti-neoplastic effect, tamoxifen also shows neuroprotective properties by modulating inflammatory-mediated damage and promoting autophagy [18]. A randomized, double-blind, placebo-controlled phase II study was conducted in 18 ALS patients followed for 12 months. The primary endpoint was disease duration. The results have just been published: in the tamoxifen group (40 mg/d), disease progression was slightly decreased but not significantly [18].

2.3. *Levosimendan*

Levosimendan was first developed in cardiology for the treatment of heart failure. The mechanism of action of this drug relies on a selective binding to troponin C and subsequent sensitization of fast and slow skeletal muscles [19]. Levosimendan improves submaximal contraction of diaphragm fibers (both slow and fast muscle fibers) by around 20% in patients with chronic obstructive pulmonary disease [20]. In addition, levosimendan prescribed intravenously, was shown to improve the neuromechanical efficiency and contractility of human diaphragm function in healthy subjects [21]. Owing to these compelling findings on diaphragm muscle function, a randomized, double-blind, placebo-controlled, crossover, three-period study with six months open-label follow-up was conducted in ALS. The primary endpoint was the slow vital capacity (SVC) percentage measured in the sitting position. This study did not show a positive effect of levosimendan on SCV. Since the drug was well tolerated, and considering the conclusions of the post-hoc analysis in favor of a possible dose-dependent therapeutic effect on supine SCV, a phase III study has been conducted to assess the efficacy of levosimendan at the dose of 1-2 mg daily after 48 weeks of treatment on SCV (NCT03948178) [22]. The open-labeled phase of the study is expected to be completed in the next weeks and the results should be published soon.

2.4. *Masitinib*

Masitinib is an oral tyrosine kinase inhibitor available for the treatment of mastocytosis. This compound has exhibited promising results in animal (rat) models of ALS (SOD1-G93A). The interest in ALS came from its neuroprotective effect on neurons thanks to immunomodulatory properties which target in particular activated microglia and mast cell activity, in both central and peripheral nervous systems [23,24].

Among all the publications focused on this compound in ALS, the results of the double-blind study, placebo-controlled randomized phase II/III study which enrolled 394 patients receiving either riluzole (100 mg/d) plus placebo or masitinib at 4.5 or 3.0 mg/kg/d fostered the proposal of a larger study. The primary endpoint was the slope of decline of the ALSFRS-R scale during the 48 weeks of the study [25]. First, this study showed that masitinib was well tolerated and safe at both dosages. Second, there was a positive effect of masitinib in ALS highlighted by a gain of 3.4 points (9.2 vs. 12.6, $P = 0.016$) on the slope of the ALSFRS-r score after 48 weeks: this corresponds to a 27% slowing in the rate of functional decline. Of note, the positive effect was more meaningful in the fast progressor group (slope of progression $\geq$ 1.1/month) at the dose of 4.5 mg/kg/d. A multicentric, randomized, double-blind, placebo-controlled, parallel groups, phase III study is expected to start soon in Europe and North America simultaneously: almost 500 ALS patients are planned to be enrolled in this study which should last 24 months.

2.5. *Deferiprone*

This trial stems from literature in favor of a role for iron in neurodegenerative diseases and mainly in ALS [26]. Iron is a cofactor of several enzymes involved in motoneuron machinery such as mitochondria aerobic metabolism. Moreover, serum iron, ferritin and transferrin were shown to be increased in ALS patients compared to controls [26]. Of note, postmortem studies which showed iron accumulation in the central motor tract in ALS patients made the hypothesis of the role of iron in ALS strong enough to allow a clinical trial focused on iron metabolism [27]. Finally, the neuroprotective effect and the longer survival in ALS mouse models treated by iron chelators strongly supported initiation of a clinical trial in human ALS [28].

FAIRALS is a randomized, double-blind, placebo-controlled study which aims to assess the efficacy of an iron chelator, deferiprone, in ALS. This study conducted by the French ALS Centre of Lille is currently ongoing. 240 participants are expected to be included, half of whom will receive 600 mg/d of deferiprone taken over 12 months (NCT03293069).

2.6. *Fasudil*

Rho kinase (ROCK) recently became a matter of interest in ALS. This serine/threonine kinase has two isoforms whose isoform ROCK2 is highly expressed in the central nervous system, more importantly with age [29]. ROCK plays a key role in triggering the signal of axonal degeneration once it is activated

by the binding of axonal growth inhibitory molecules to their specific receptors [29]. ROCK inhibitors have already been assessed in neurodegenerative diseases and demonstrated both a neuroprotective and pro-regenerative effect in Parkinson's disease (PD) models [30].

ROCK inhibitors significantly improved survival and motor function in the SOD1(G93A) mouse model of ALS when initiated at a presymptomatic stage [31].

Fasudil is a small ROCK-inhibitor molecule first developed for the treatment of vasospasm following subarachnoid hemorrhage (SAH). In the central nervous system, the effects of Fasudil were assessed in a phase III trial in patients with acute ischemic stroke, which showed a significant improvement of clinical outcome [32].

Although the underlying mechanisms remain to be understood, Fasudil currently emerges as a promising drug prompting proposal of a clinical trial in ALS. A phase IIa, multiple-center, randomized, double-blind, controlled, prospective, dose-finding, exploratory, interventional study is expected to start soon in ALS. Fasudil will be administrated intravenously twice daily for 20 treatment days. There will be three arms: 30 mg/d, 60 mg/d and a placebo group. The primary objective of this study will be the assessment of tolerability and safety.

2.6.1. *Non-chemotherapeutic trials*

2.6.1.1. Would it be possible to improve the survival of ALS patients with suitable nutrition?. Over the last 20 years, there were numerous lines of evidence stressing that malnutrition is a major pejorative factor in ALS. Following the publication of the French team of Limoges which highlighted 20 years ago that malnutrition increased by seven the risk of death in a period of seven months [33], a huge body of literature confirmed that malnutrition and low body mass index are both correlated with shorter survival in ALS [33]. On the other hand, a high-fat high calorie intake diet (HFCD) was shown to improve the evolution of ALS in mouse models [34].

Two European trials have been focused on diet in ALS: the French study named NUTRALS (NCT02152449) is still ongoing and deals with the effect of oral nutritional supplementation in the functional status of ALS patients.

The second trial, LIPCAL-ALS (NCT02306590), was conducted in Germany and the results have been published recently [35]. This trial evaluated the efficacy of HFCD (addition of 45 g of fat intake and 405 Kcal daily) on disease duration. Two hundred and one patients were enrolled and followed for 18 months. There was no evidence of a positive effect of HFCD in this population but post-hoc analysis would suggest a prolonged survival in fast-progressor patients after 18 months: the survival probability was 0.62 in the HFCD group vs 0.38 in the control group: this meant a significant hazard ratio of 0.5 (Cox proportional hazard regression model, $p = 0.02$).

3. Biotechnology

3.1. *Humanized monoclonal antibodies*

Prescription of monoclonal antibodies is obvious in dysimmune disorders, which seems, at first sight, unsuitable in neurodegenerative diseases and, in fine in ALS.

Interest for monoclonal antibodies, like ravulizumab, in ALS came from the huge body of literature on neuroinflammation in ALS. This opened new ways for therapeutic research targeting the microglia and the complement cascade.

There is a growing literature showing that the innate immune complement system drives neuroinflammation in ALS. Besides microglia activation, neuroinflammation is also involved in ALS because of the role of the complement system both in the onset and the progression of motor neuron death in ALS: this has been also matter of important reports which highlighted an impairment of the control processes regulating complement cascade activation in the central nervous system: this led to focus on promising therapeutic targets in ALS via an action on the immune system. One key target of the complement cascade in ALS is C5. This relies on an accumulation of evidence over the last 20 years of a key role for this component in the pathophysiology of ALS: both the deletion of C5aR1 (a specific C5 signaling receptor) and the injection of a C5aR1 antagonist improved survival in a SOD1 mouse model of ALS, strongly supporting a key role for this protein in motoneuron death in ALS [36]. Furthermore, functional and survival benefits of C5 signaling blockade have been demonstrated in animal models of ALS. These findings strongly support the inhibition of C5 of the complement complex to be a promising avenue for the treatment of ALS.

Ravulizumab is a recombinant, humanized monoclonal antibody with high specificity against human C5 component. It acts by blocking the complement activation and is currently approved in paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome.

In ALS, a phase III, randomized, double-blind, placebo-controlled, multiple-center study to evaluate the safety and efficacy of ravulizumab should start recruitment soon in France. An open labeled extension will complete the 50 weeks of the randomized controlled trial. The primary objective of this study is to evaluate the effect of ravulizumab compared with placebo on ALS functional rating scale-revised (ALSFRS-R) score (NCT04248465).

4. Specific antibodies

Protein aggregation is an aberrant process due to misfolding which promotes self-association of a protein. This self-association leads to oligomerization and then to fibrils by polymerization. Due to misfolding, the hydrophobic sites of the protein are accessible to the hydrophobic cellular environment.

Misfolded protein is one of the hallmarks of neuropathological findings in ALS with the presence of TDP-43, C9orf72 dipeptide repeats, phosphorylated neurofilaments, FUS and SOD1 inclusions in motoneurons [37]. These pathological deposits probably exert a toxic effect on neurons. Over the last years, therapeutic strategies have focused on blockade of this abnormal process. Several trials target the misfolding process by specific antibodies to misfolded SOD1 protein (α-miSOD1), fragment of antibodies directed to a specific region of TDP-43, to vaccines against unfolded SOD1 and small molecules which enhance the expression of heat shock proteins and, consequently, promote autophagy, such as colchicine and arimoclomol [38].

5. Antisens- oligonucleotides

Gene therapies have made remarkable progress over the last decade, leading to changes in the course of numerous diseases which were incurable until now. These therapeutic approaches perfectly fit with what clinicians were searching for: a targeted treatment based, in this situation, on the genetic status.

The rationale of this approach relies on the fact that lowering the burden of mutated SOD1 protein in ALS linked to SOD1 mutation may improve the disease prognosis. First trials on antisense oligonucleotides (ASOs) have been launched more than 10 years ago. Since 2010, numerous phase I and phase II trials have been conducted in ALS. ASOs stimulate the degradation of RNA by specific targeting and/or can also correct splicing defects or block miRNA [39].

Following the impressive action of nusinersen in spinal muscular atrophy, major hopes have been put in the development of ASO directed to SOD1 and C9orf72 mutants. A phase III trial is currently underway assessing the efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of tofersen in ALS adults with a SOD1 mutation (NCT02623699). The study is expected to be completed in July 2021. In parallel, a phase I study that will evaluate the long-term safety and tolerability of BIIB078 in ALS patients with abnormal C9orf72 expansion will also start soon (NCT04288856). This study is expected to be achieved in July 2023.

6. Regenerating therapeutics

Transplantation of stem cells gives the opportunity to bring neurotrophic factors into the central nervous system. This might make it possible to re-settle regions affected by the motoneuron degenerative process. To date, there are too many issues that need to be resolved before this approach could appear promising in ALS: among the many uncertainties, the type of cells, the mode of administration, and the number of cells to transplant are still under debate [40].

7. Conclusion: How to proceed for success?

We are currently in an enthusiastic period for ALS clinical trials: there are numerous trials that are ongoing or expected to start soon, evaluating promising drugs tested either in a new indication or specifically developed for ALS. This hopeful period does not have to mask that many issues need to be resolved before we will be able to develop a curative drug for ALS.

As pointed out by numerous clinicians, many elements remain problematic: the design of clinical trials would probably be usefully focused on homogenous (phenotypically? pathophysiologically? genetically?) groups of patients. We also have to define more relevant and suitable primary endpoints in order to evaluate efficacy; we have to use more accurate parameters than survival or delay from symptoms until use of NIV 22 h daily.

We also need to re-consider the preclinical stages of trials in the SOD1 mouse model which does not perfectly fit with humans ALS on neuropathological aspects: this probably explains a large proportion of failures for drugs that show efficacy on animal models. We also need to reconsider trials in animals that started before the onset of the disease; it is clearly impossible to transpose the results to humans who will be treated once the disease has caused weakness and amyotrophy.

In 2018, a conference was held in Airlie House. The revised Airlie House ALS Clinical Trials Consensus Guidelines published after this meeting should serve to improve clinical trial design and accelerate the development of effective treatments for patients with ALS [41].

Disclosure of interest

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The other authors declare that they have no competing interest.

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