Chapter

Introduction to Novel Motor Neuron Disease

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Abstract

Motor neuron disease (MND) is a progressive and fatal neuromuscular disease; the most common and severe form of MND presentation is amyotrophic lateral sclerosis (ALS), commonly known as Lou Gehrig's disease. The majority of ALS patients die within 2–5 years of receiving a diagnosis. Familial ALS is a hereditary form of the disease and accounts for 5–10% of cases, whereas the remaining cases have no clearly defined etiology. ALS affects persons of all ethnicities and races; currently, no curative treatment for ALS is available worldwide. ALS is also the major adult-onset MND and is clinically, pathologically, and genetically associated with fronto-temporal dementia in some cases, which is the second cause of dementia in elderly people. However, MND does not affect sphincter, sexual function, or eye movements. MND is the most common degenerative disorder affecting the upper and lower motor neurons at the same time. Most of the patients presenting MND in our series complained of muscle weakness, muscle wasting, fasciculation, and spasticity plus lower cranial nerve disturbances. According to our bibliographic studies, apart from nusinersen, it seems to be that riluzole and edaravone also improve motor neuron function by acting on SK channels.

Keywords: motor neuron disease, amyotrophic lateral sclerosis, spinal muscular atrophy, riluzole, edaravone

1. Introduction

Motor neuron disease is composed of a group of rare neurodegenerative disorders, such as amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), hereditary spastic paraplegia, primary lateral sclerosis, progressive muscular atrophy, pseudobulbar palsy, O'Sullivan-McLeod syndrome, and Madras motor neuron disease, which are fatal in 50% of affected people within 15–20 months after diagnosis. MND is a progressive neuromuscular disease with a fatal outcome; the commonest clinical presentation of MND presentation is ALS, commonly known as Lou Gehrig's disease. Most of ALS patients pass away within 2–5 years of confirmed a diagnosis. Familial ALS (ALSf) is a hereditary presentation of the disease and accounts for 5–10% of affected people. ALS affects persons of all ethnicities worldwide; no cure for ALS has yet been available at any country. Sometimes, ALS is clinically, pathologically, and genetically associated with fronto-temporal dementia, which is the second cause of dementia in elderly people. In our first book, we reviewed all previous chapters published by INTECH, and in the Introductory Chapter, readers could find summarized information about all publications on ALS

made by INTECH. Trying to illustrate the reached progress, we displayed this information grouped by topics and countries in two graphics. As we saw on that book, the number of publications written about ALS increased remarkably for the past 4 years. To have some idea of this phenomenon, be informed that INTECH published more than 40 chapters on ALS in this period of time, and these books "Amyotrophic Lateral Sclerosis," "Current Advances on Amyotrophic Lateral Sclerosis," and others are fully available on line, for free. Therefore, why we are going to publish another chapter? All novel information about MND were not published. Therefore, some aspects published in 2012 need to be update because new ideas, proposals, findings, experiences, and many other's knowledge have been arising despite of this short period of time. Therefore, for the benefit of the readership community, we included update information not reported before, mainly new contribution of aberrant astrocytes to MND damage and death in the SOD1G93A rat experimental model of ALS; novel genetics studies on ALS; an update of the structural and functional consequences of the spinal muscular atrophy-linked mutations of the survival motor neuron protein; stem cell therapy for MND; and the novel treatment for SMA and ALS in the introductory chapter of this book. Compromises have been inevitable to accommodate our visual and factual updated information in a book of his characteristic on top of many chapters about the same issue published recently.

MND does not affect sphincter, sexual function, or eye movements [1]. Although ALS is not associated with thermoregulatory dysfunction, its progression can affect intensively important cerebral regions that control body temperature and affect multiple functions of this homeostatic activity. Nevertheless, experimental ALS animals can display altered thermoregulation as a consequence of affected energy homeostasis. Indirect evidence suggests, performing studies on the body temperature regulatory system, both as a possible modifier of disease progression in ALS and as a potential biomarker [2].

Although edaravone and riluzole do not cure MND/ALS, it seems to be that both medications can slow its progression. The prevalence of ALS in America was 5.2 per 100,000 populations with a total of 16,583 cases identified from January 1 to December 31, 2015 [3].

MND is the most common degenerative disorder, which affects the upper and lower motor neurons at the same time. There are different clinical modalities of MND being ALS the commonest one, and its incidence is around 1–3 patients every 100,000 people [4, 5].

The higher incidence of ALS is in patients with 60 and 70 years of age, but some younger cases (20–30 years of age) have been reported as well [4]. Between 5 and 10% of the patients have a familiar origin due to Mendelian autosomal dominant transmission.

Most of the patients presenting MND in our series complain of muscle weakness, muscle wasting, fasciculation, and spasticity plus cranial nerve disturbances from the lower brainstem.

The most frequent mutation seen in the familial form of ALS (ALSf) occurs on the gene of superoxide dismutase 1 (SOD1) and on the chromosome 9, among others. The decreased endovascular factor and the hereditary hemochromatosis protein are also genetic mutations. Some variations in the number of copies of Genes 1 and 2 that codify the motor neuron survival factors have been reported [6]. No correlation investigations have been done. However, some genome-wide studies in patients presenting ALS show a series of loci confirming a greater susceptibility to develop the disease such as kinase carbohydrate (FGGY), dipeptidyl-peptidase 6 (DPP6), and Type 2 inositol triphosphate receptor [7–9]. Most of these findings were not able to be replicated in further investigations done. At present, there is not specific cure for this deadly disorder as was mentioned before.

Long time ago, a nitrogenic expansion on the gene C9ORF72 was observed in a number of patients presenting ALS associated with Chromosome 9, which brought more clarity in the ethiopathogenesis of ALS [10, 11], but these findings are also seen in patients presenting fronto-temporal dementia (FTD) and ALS-FTD [10, 11]. Below, we will deliver more comments about this topic.

Future genetic investigations should be focused on non-European populations in order to bring more clarity on new pathogenic loci.

In the forthcoming years, the exome study that is an emerging field will bring novel information about some implicated genes in ALSf.

In 2018, Thompson et al. [12] used a high-throughput proteomic process to distinguish new biomarkers in patient's cerebrospinal fluid (CSF), and they found that three macrophage-derived chitinases had increased concentration in ALS: chitinase-3-like protein 1, chitotriosidase, and chitinase-3-like protein 2. Elevated CHI3L1 was commonly seen in ALS, while CHI3L2 and CHIT1 levels did not. Their results confirmed the important role of macrophage activity in pathogenesis of ALS.

Decreased cough capacity is almost always present in respiratory tract infection and is the most important cause of respiratory failure in ALS patients. Other authors determined whether the lung function measurement could identify the cough function in ALS patients with respiratory tract infection. After screening 48 patients presenting ALS, they found only four presenting a remarkable cough with no assistance. The data that identified unassisted cough effectiveness are peak cough flow. These investigators highlighted that the effectiveness of assisted and unassisted cough function depends on the peak cough flow reached [13].

It is well known that MND does not affect the motor neurons at the oculomotor nucleus in the midbrain. Because it could be remarkably advantageous if neurons of motor system resilience can be modeled in vitro, some authors reached elevated quantities of oculomotor neurons from embryonic stem cells in mouse through transient over expression of PHOX2A in nerve cell progenitors, and they confirmed, using immunocytochemistry techniques, electrophysiology studies, and RNA sequencing, that in vitro-generated neurons are bona fide oculomotor neuron cells based on their neuron properties and similarity to their counterpart in rodent (in vivo) and human beings [14].

Increased cortical excitability, thought to reflect pathological changes in the balance of local excitatory and inhibitory neuronal influences that are commonly seen in patients presenting ALS and non-invasive brain stimulation (NIBS), has been shown to modulate cortical activity, with some protocols showing effects that outlast the stimulation by months. Therefore, NIBS has been proposed as a probable candidate to approach therapeutically these disorders associated with pathological neurophysiology activity, such as ALS, among others [15].

ALS type 8 (ALS8) is a familial presentation of MND, with an important anterior horn cell degeneration, due to mutation of the vesicle-associated membrane protein-associated protein B. Some authors compare the cognitive function of patients with ALS8 and a control group composed by healthy people in order to screen behavioral features in ALS8 patients. These authors found that ALS8 patients showed minimal deficits in executive functions. The total amount of ALS8 patients and the control group have the same scores of facial emotion recognition. They also determined an important clinical expression of psychiatric disorder such as anxiety and depression in 36 and 27% of patients, respectively. However, behavioral disturbances were present in around 30% of participants. They concluded that these patients had mild executive problems and behavioral problems such as apathy, mood disorder, and stereotypic behavior, which suggest that ALS8 is not a motor disorder only, and it is associated with minor cognitive and behavioral changes [16].

Because one of the most effective clinical strategies for SMA is to protect the anterior horn cell, apart from nusinersen (that is a very expensive medication), one anti-epileptic medication levetiracetam has been used as well.

Kepra (levetiracetam) provoked neurite elongation in SMA-iPSCs-MNs. TUNEL-positive anterior horn cell was significantly decreased by kepra in SMA-iPSCs-MNs. On the other hand, the expression level of cleaved-caspase 3 was diminished by levetiracetam in SMA-iPSCs-MNs. Furthermore, kepra improved impaired mitochondrial function in SMA-iPSCs-MNs. On the other hand, kepra did not modify the expression level of SMN protein in SMA-iPSCs-MNs. These results suggest that kepra has a neuroprotective effect for SMA [17].

For patients presenting SMA (most common reason of inherited infant mortality), the gene therapy seems to be the most effective strategy [18].

Another therapeutic modality to treat ALS is the noninvasive brain stimulation (NIBS), which has been shown to modulate cortical activity, with some protocols leading effects that outlast the stimulation by months. NIBS have been suggested as a potential treatment choice in those processes with associated changes in the cortical neurophysiology [15].

A total of 25 genes associated with ALSf and ALS (sporadic form), mutations in fused-in-sarcoma (FUS) and superoxide dismutase 1 (SOD1) have been intensively studied in the past, focusing on modified excitability of motor neurons. Based on their personal experience, Peikkert et al. [19] proposed that the 4-aminopyridine (4-AP), which is a potassium channel blocker, can be utilized as a probable therapy *for ALS patients* due to its demonstrated hypo excitability and high frequency of apoptosis in a FUS/SOD1-ALS-induced multi-potent stem cell from selected motor neuron; they also found that this process is partly reversible by 4-AP.

One of the clinical presentations of MND is SMA, which encompasses a group of autosomal recessively inherited degenerative neuromuscular diseases. SMA is an inherited disorder that causes progressive lesions on the anterior horn cell leading to weakness or paralysis of the affected limbs, and it is caused by elimination or mutation of survival motor neuron (SMN) 1 gene. It is well known that homozygous damage and loss of functional mutations in the survival motor neuron 1 gene (SMN1) at the chromosome 5q13 are the main cause of SMA, which affect 1 in 11,000 newborn infants.

SMA usually has a very poor prognosis after rapidly progressive weakness and early mortality. However, a new medication named Nusinersen has been released for the treatment of all forms of SMA (not on mechanical ventilation) with very good results. In December 2016, this medication was approved in the United States. Nusinersen, an antisense oligonucleotide (ASO), is administered directly into CSF. It alters *SMN2* pre-RNA splicing, so exon 7 is included, increasing expression of functional SMN protein. *Efficacy assessments for patients receiving nusinersen are based on serial assessments of performance on age-appropriate standardized motor scales. Treatment requires complex financial and logistics because of the very high drug cost, intrathecal administration, and medical fragility of the patients. Treatment implementation also engenders ethical considerations related to cost, insurance coverage, limited clinical data on groups of patients not in clinical trials, and questions of duration of treatment* [20].

One in 50 asymptomatic people carries this autosomal recessive neuromuscular code causing SMA in one over 10,000 live births [21].

Based on age at onset, the highest milestone reached, and phenotypic severity: SMA has been separated into four different subgroups such as "Nonsitters" (Type I), "sitters" (Type II), "walkers" (Type III), and "adult onset" (Type IV) [22].

At the present moment, many patients got confirmation of diagnose very late, or the treatment is administered in advance stages. Therefore, poor response is often obtained.

Fortunately, some screening programs are available and accurately and then to identify children in pre-symptomatic stages is possible [23]. However, because some children develop their clinical manifestation far from birth then to decide when to initiate the treatment and whom qualify for therapy is a dilemma.

The majority of SMN2 pre-mRNA transcripts undergo alternative splicing due to a nucleotide substitution leading to exclusion of exon 7. Degradation of the resulting truncated SMN protein is very fast, and the overall lack of full-length SMN protein causes permanent damage on anterior horn cell of the spinal cord [23].

In patients with onset of the disease beyond six months of age, large phase 3 trials confirmed improvement in motor activities, very high event-free and remarkable survival in infantile-onset SMA3, also significant improvement in Expanded version of the Hammersmith Functional Motor Scale scores has been recorded [24, 25].

The copy number of the homologous SMN2 gene is inversely correlated with SMA severity and encoded by SMN1 (except for lack of exon 7), which is identical to the cDNA encoded by SMN2.

Currently, for the therapy of SMA, there are pipelines developed by antisense oligonucleotide (ASO), also available for Huntington disease, ALS, spinocerebellar ataxias, Parkinson disease, and Alzheimer disease, among other options, and the pharmaceutical industry on ASO development has been delivering a promising therapeutic approach. The key care concern to MND patients has been developed, and expert consensus guidelines delivered, and best management for lung diseases, nutritional problems, and palliative care has also been reached. However, in this chapter, we will discuss novel aspects related to treatment and other therapeutic procedures later on.

In pre-symptomatic SMA patient's Types I–III released interim results of a phase 2 trial evaluating the effects of Nusinersen have been done [23].

Some investigators have been working on stage of improvement after the treatment of SMA and confirmed that the first published data supported important good results on the motor function and quality of life from animal models with early restoration of SMN levels for those studied within the first 3 postnatal days. However, for those treated beyond 5 postnatal days, the level of recovery was low, while delivered treatment after 10 postnatal days, it showed no improvement and died [26].

One of the problems found in our preliminary review is the big number of SMA patients diagnosed at late stage. We found Type I patient with 4 months after onset and Type III with 10 months or more after onset [27, 28].

However, newborn screening programs have been a successful process for identifying affected children at an asymptomatic stage, leading to pre-symptomatic initiation of treatment before irreversible anterior horn cell lesion appears. To perform screening methods before birth are certain, and they available and willing to deliver the possibility of distinguish patients at the beginning of pregnancy, giving a chance to perform a prenatal therapeutic management.

Taiwan and Belgium, also have screening programs for SMA, but in America, the leader and an important number of states, further clinical trials have been implemented to evaluate the applicability and economic advantages. Unfortunately, around 5% of mutations in the SMN1 cannot de identified [23].

Chorionic villus sampling or amniocentesis to identify children with higher risk for SMA with an elevated percentage of accuracy can be done, if it is performed during the 10–14 or 15–20 weeks of pregnancy. These procedures can be dangerous for the mother and the baby to be done in *high-risk pregnancies with proven carrier status of the parents recommended* [23]. Nevertheless, isolating circulating fetal trophoblastic cells by noninvasive prenatal diagnosis techniques is also possible [29] or

even getting from maternal blood cell-free fetal DNA [30]. These above-mentioned techniques allow to identify SMA in unborn children with 100% accuracy, promising a better future for SMA patients [23].

At this stage, it is also important to mention that significant ethical issues are involved in this genetic screening methodology and its need to be considered by the medical community before making these procedures fully available [31]. At the present moment, we are not quite sure how to predict disease severity accurately or even its presence because not all patients present clinical manifestation birth or because only few minimal sings are detectable. Treatment algorithm for SMA patients confirmed by newborn screening based on SMN1 deletion analysis in dried blood spots is available since 2005 [28]. Indications of treatment are based on the clinical phenotype of the patients and correlation of SMN2 copy numbers. All patients presenting 2–3 copies should be treated with the immediate effect according to NBS Multidisciplinary Working Group recommendations even if the child is asymptomatic with only one copy, but when four or more copies are present due to milder course of the disease, the treatment must be delayed [28].

In 2017, some authors studied a big number of SMA patients (n = 3500) trying to compare SMN2 copy number with their clinical information and found that patients with 1–4 copies have mild to severe phenotype, respectively, while there was an important overlap among patients with 2–3, confirming any possible phenotype [32], but more than 80% of patients in this group cohort carried two to three SMN2 copies, suggesting the similar problem in medical practice. In these cases, presenting two or three SMN2 copies to predict the severity of the disorder is not certain [23].

It is important to take into account that those SMA patients (families and siblings) presenting the same amount of SMN2 copies have another phenotype [33]; in the context, SMN1 (homozygous) mutations, SMN2 copies in people free of symptoms and signs, and even in SMA Type I have been found [34]. SMN2 transcripts and the SMN2 copy number do not show any correlation in a series of investigations done between 2001 and 2017 [35–38].

Following some recommendations delivered by the Phase 1 trial and studies on its pharmacological process, the investigators found that the half-life of nusinersen in the CFS is 163 days, and the ideal way for administration should be intrathecal (at the dosage of 12 mg) every 4 months. After that period of time, patients should receive five intrathecal injections within the first 6 months of treatment. These authors also confirmed that no correlation exits between concentrations of the CSF, age of the patients, and body weight [39, 40].

Based on results published by Luu et al., the doses of nusinersen according to the age of the patients produce more median exposures in the CSF, which suggest that prescribing fixed dosage programs through all age groups is the best choice [40]. For the other hand, Finkel et al. [41] conducted a Phase 2 dose-escalation investigation confirming that a single dose of 12 mg is better than 6 mg. The best way to assess the outcome for these patients is to measure the advantage of motor milestone, depending on ventilator machine, achievement of motor activities, clinical electrophysiological studies, and overall survival. Twenty patients younger than 1 year of age and less than 10 kg of body weight were screened, and these results confirmed the previous postulate [41]. The results from the small group studied in phase 2 clinical trials and the pharmacological studies done can accurately reflect clinical practice, is an interrogation still no responded.

Taking into account the great variability among SMA patients related to the age at disease onset, residual motor function, body weight, and fixed dose at the same intervals for patients, it seems to be remarkably inaccurate [23]. Reliable biomarkers and screening procedures for proper diagnosis at early stage of the disease are

need more than ever if we are looking for longer survival and positive modifications of the patient outcome. If reliable biomarkers are not available, then determining the SMN protein level and epigenetic modifiers to provide confident information about the intensity of the process is mandatory. When more than three SMN2 copies are detectable, chance for life-saving treatment is not certain. In summary, novel screening techniques, procedures to predict the intensity of the disease, and reliable biomarkers, which support monitoring of the treatment, have been discovered and recently developed, but unfortunately, none of them provide an unequivocal explanation of the pathophysiology of SMA [23].

To develop more accurate diagnostic procedures including confident biomarkers, better therapeutic approaches, and novel predictors to determine the ideal dosing recommendation, more investigations are required. This is the only way to guarantee a reliable long-term treatment and successful outcome [23].

Two years ago, the European Medicines Agency finally approved nusinersen an antisense oligonucleotide (ASO) as the treatment of choice for SMA, and later, this medication has been considered as part of the treatment for patients with Type 2 SMA as well [23]. In patients with SMA presenting spinal bone deformities, severe contractures, scoliosis, spine fusion surgeries, and respiratory distress, the administration intrathecal of nusinersen could be a great challenge.

Recently, with the intention of assess, the accuracy, and feasibility of nusinersen administrated by lumbar puncture (LP) in young patients, Wurster et al. [42] studied in 93 patients in whom the LP is done, highlighting the amount of attempts performed, site of injection, length of the spinal needle, duration of the procedure, medications used for sedative purposes, local anesthesia, level of O_2 saturation in blood, appearance of the CFS, and adverse effects. These results confirm that LP is the best way to administer this medication in adolescent and young adults with later-onset SMA even in candidates with spinal bone deformities and respiratory failure mainly if the patient is managed under a multidisciplinary team.

Nusinersen is not available in Africa as yet but can be found in many European countries for all SMA types.

A few weeks ago, Sansone et al. [43] reported their experience and good results after studied 50 SMA patients treated with intrathecal nusinersen. They concluded that in spite of the severity of the disease and the age of patients, this treatment is feasible, safe, and suitable for SMA patients if they are managed by a good skilled team.

According to the information provided by Gidaro et al., a few weeks ago, in Australia, the commercial availability of the medication from the transition of expanded access programmed its right in corner. While in New Zealand, a broad access to this program is available, and in Canada, negotiators are discussing about the most convenient price at the present moment. However, some problems such as advanced age, patients with respiratory failure depending ventilator machine, and patients presenting spinal fusion still need to be solved [44].

As was mentioned before, the traditional LP for intrathecal administration of nusinersen can be impeded due to deformities of the spinal bone and orthopedic surgical procedures among other impediments commonly seen in SMA patients. However, the accumulated experiences from cervical myelograms serve to recommend this procedure as an ideal approach for cervical intrathecal administration of nusinersen, especially if it can be guided by ultrasound [45]. The same investigators studied 14 patients after the administration of nusinersen by cervical punctured guide by ultrasound with local anesthesia and found that all patients presented no major complications. One of the advantages of this technique is that general anesthesia is no required, and patients can be managed in real-time ultrasound guidance.

The most significant advantage to antisense oligonucleotide (ASO) therapeutics over other small molecule approaches is that acquisition of the target sequence provides immediate knowledge of putative complementary oligonucleotide therapeutics.

In 2019, Scoles et al. [46] described several therapeutic modalities with ASO and how they can be indicated for medical treatment of SMA, apart from the work done to develop novel ASO therapies looking for better results in the management of neurodegenerative disorders [46]. Novel advances of the genetic studies will allow distinguishing different genetic information for many neurological disorders. The mutated protein found and its chance to be placing into the cellular pathway will support a faster development of way for treatment. For the other hands, new opportunities for reliable treatment have been arising from the new capacities of targeting the disorder gene and RNAs. Among other procedures, to target the expression of RNA, some authors highlighted the utilization of ASOs to treat neurological problems. Treatment based on ASOs varies from 18 to 30 base pairs in length. These investigators changed expression of a target mRNA modifying splicing or by recruiting RNase H (cellular enzyme) that recognizes DNA: RNA hybrids causing target degradation [46].

Apart from nursinersen, other ASO therapeutics approved by FDA are eteplirsen to treat Duchene muscular dystrophy 2 and inotersen for managing patients presenting familial amyloid polyneuropathy. For treatment of Huntington disease, ASOs targeting HTT have been used [47]. As we and other authors reported in other publications, the treatment of choices for ALS is SOD1 and C9ORF72 [48, 49] and MAPT (TAU) in cases affected by Alzheimer disease [50]. Because most of the treatment with ASO does not cross the blood-brain barrier (BBB), it is necessary to administer it by injection into the intraventricular system in mouse and by intrathecal administration in humans.

Some investigators have mentioned that nucleic acids are prompt to nuclease degradation, and its protein binding is weak, leading to inefficient tissue uptake and unreliable use as drugs [26, 51].

Most of these changes modify the pharmacokinetic, pharmacodynamic, or endocytic uptake that controls the specific function of the proteins (cell surface) [51, 52].

Oligonucleotide chemistry, methoxyethyl oligonucleotide, constrained nucleic acids, Stereopure PS ASOs, Peptide nucleic acid, 5′-methylcytosine modification, target fate, mixed chemistry, and gapmers are aspects that are not discussed in this chapter and should be considered by interested readers on this matter. In order to get most complete information about it, we recommend checking the article of Scoles et al. [46].

ASOs are being used for some genetic etiology of ALS. Obviously, these biological pathways affecting the recognized mechanism of production of the disorder also modify the results when ASO is used [53].

2. Therapy with riluzole and edaravone

In 1994, the idea about the role of the excitatory amino acid neurotransmitter glutamate in the mechanism of production of ALS was prevalent. At that time, some investigators evaluated the safety and accuracy of the antiglutamate agent riluzole, at the dose of 100 mg daily, in patients presenting ALS. They studied 155 outpatients, and after 12 months of treatment, they found that 74% of the patients were still alive ($P = 0.014$), and the decrease of muscle power was remarkable in patients consuming riluzole compared with the control group

(placebo). Therefore, they concluded that riluzole decreases the speed of progression in ALS patients, and it can prolong the survival period in patients presenting bulbar palsy [54].

Without doubt, nusinersen improves motor neuron function, but riluzole by acting on SK channels also causes similar results [55].

Since 1996, it is well known that one of the etiological pathogenesis of ALS is caused by neural damage due to glutamate excite-toxicity. Riluzole is a synthetic benzothiazole drug with glutamine antagonist activity [56, 57].

The first analyses, and at posteriori meta-analyses done on results obtained from controlled trials by randomization, confirm that riluzole extends survival by 2–3 months and augment the possibilities of an additional 12 months of survival by ~9%. Same authors reported improvements in media survival times over 76 weeks for an important number of ALS patients [58].

In 1995, oral riluzole was approved by FDA as part of the treatment of ALS. Riluzole is a well-known presynaptic glutamate release inhibitor, which can provide neural injury and prevent muscle-power worsening. Currently, this medication has been licensed to be prescribed in many places including the European Union [59].

The dose of 50 mg twice, to be taken 1 hour before meal or 2 hours after it, has been approved by the Institute for Health and Care Excellence since 2001 with good results [60].

One good news is that riluzole is now available in oral suspension (Teglutik®) which presentation (5 mg/ml) and has been shown its beneficial for patients presenting bulbar palsy with functional dysphagia allowing longer therapy [61, 62].

Not randomized controlled trials (RCTs) with riluzole for ALS patients have been performed.

However, other RCTs have been done for patients with cervical myelopathy, chronic psychosis, and autistic spectrum disorder [63–65].

Real-world evidence confirmed that an important prolongation of median survival times in ALS patients treated with riluzole is certain. Based on retrospective/prospective investigations done on large database, these authors concluded that patients under riluzole therapy had better prognosis than those without treatment, mainly at the first stage of the pathological process [58].

Brooks et al. studied two series of ALS patients: one group of 51 patients under riluzole treatment and another group of 241 patients without riluzole (before 1996) and a second series of 112 ALS patients' riluzole-treated and 65 nontreated patients (after 1996). These authors found that Cox analysis concluded that patients on treatment got an extension of survival ($P < 0.0001$) and even remarkable improvements in elderly people and patients in advanced stage. Therapy with riluzole provides a median extension of survival in affected patients between 40 and 72 weeks [66]. Survival benefit would be 36 weeks if patients are managed like prospective RCTs according to other researchers [67]. Based on Cox model technique, Mitchell et al. found that survival times are bigger in riluzole-treated ALS patients than nontreated cases (HR 0.20, $P < 0.001$) [68]. While other authors communicated that Cox multivariate analysis of therapy was related to a prolongation of survival at 48 weeks (HR 0.51, $P = 0.06$) [69].

Retrospective population-based studies on the effect of riluzole on survival of ALS patients done between 1999 and 2008 and made by Lee et al. concluded that Cox multivariate analysis ($n = 1149$) that riluzole provide a longer survival on treated-patients; unadjusted HR 0.32 ($P < 0.001$) and adjusted HR 0.34 ($P < 0.001$) [70].

Georgoulopoulou et al. and Knibb et al. conducted a prospective population-based study on the survival of 193 patients (between 2000 and 2009) and 575 cases

(between 1990 and 2013) consuming riluzole, respectively. According to the Cox multivariate model used during the first series of participants riluzole-treated, they reached a prolonged survival and remarkable delay of pulmonary complications including patients with bulbar palsy and even those with affected four limbs, and the second series of cases riluzole-treated showed a slower progression to pulmonary involvement [71, 72].

Chen et al. also studied a group of ALS patients using the same methodology and concluded that the median survival time in cases riluzole-treated was 268 weeks compared to 256 weeks in nontreated cases (log-rank $P = 0.780$); HR 0.855 ($P = 0.167$) [73].

Based on meta-analysis of RCTs recently done and all data obtained up to date, riluzole prolonged survival in ALS cases by 8–12 weeks and augmented the chance of additional 52 weeks of survival by ~9%.

Other authors reported that riluzole-treated cases can increase their median survival by up to 76 weeks, after reviewing 10 clinical ALS databases with around ~6000 cases [58].

In a series of patients studied by Inoue-Shibui et al., riluzole therapy was interrupted in 20 cases among 92 patients [74]. The most common cause of discontinuation of riluzole was abnormal of liver enzymes (5.4%), followed by interstitial pneumonia, among other causes.

All adverse events happened within 24 weeks of the beginning of riluzole therapy, with 50% of the adverse events occurring within 2 weeks. In almost all patients, adverse events disappeared after stopping the treatment. In the real-world setting, riluzole has been well assimilated for long periods of up to 7 years or more [75].

Recently, two patients presenting recurrent pancreatitis were communicated to the medical literature. In both cases, the diagnosis was done within the first 3 months after initiated the treatment with riluzole [76], being another strong reason to highlight our recommendation about a careful observation of adverse events in the first 6 months of riluzole administration.

A few weeks ago, Jaiswal et al. also confirmed that riluzole delay progression of ALS in animal model based on their experiences and many experimental drug trials done over the past decades, but riluzole did not show similar results in human beings or results are still nonconcluded under Phase I–III trials, which are quite true, and riluzole is the only available medication with some benefits on survival [77]. Nevertheless, an antioxidant drug (edaravone) has been produced by Mitsubishi Tanabe Pharma, and its effectiveness in halting ALS progression during early stages has been found.

In 2015, edaravone (Ridicut) was launched for the management of patients with ischemic stroke at first and later for the treatment of ALS patients [78]. Edaravone is a drug with a free radical scavenger with no remarkable benefits in ALS patients according to Phase III clinical trial, but edaravone is also a strong antioxidant able to prevent oxidative stress leading to motor neuron fatal damage in ALS. These investigators found another study, which confirmed good therapeutic response to edaravone in diagnosed patients by revised diagnostic criteria (El Escorial) of MND/ALS. Other authors investigated the effect of intraperitoneal administration of edaravone in wobbler's mice and demonstrated that elevated dose (10 mg/kg) of edaravone therapy remarkable attenuated paresis and muscle contracture on the extremities and stopped denervation atrophy in the proximal muscles and degeneration in the cervical anterior horn cell neurons compared to control group. After large waiting period of 22 years, the Mitsubishi Tanabe Pharma America acquired an US FDA approval for edaravone (Radicava) in May 2017 for the therapeutic approach of ALS.

To low progression of MND/ALS, edaravone is a good indication according to the previous reports delivered to the medical literature. Recent phase three studies done on ALS patients treated with this medication did not confirm remarkable advantage in the Revised ALS Functional Rating score over the control group [79]. Between November 28, 2011 and September 3, 2014, the Writing Group [80] studied 213 cases and selected 192 candidates. Of these, 137 cases completed the first period for close observation: 69 were selected to be edaravone-treated (randomly), and 68 were assigned to control group to be treated with placebo also randomly, both series were included in the primary efficacy analysis. The results observed from the primary outcome demonstrated that the control group change −7.50 (0.66) in ALSFRS-R score compare with −5.01 (SE 0.64) in the group edaravone-treated. In favor of edaravone, the least-square mean confirmed a difference among two series of 2.49 (SE 0.76, 95% CI 0.99–33: $P = 0.0013$). These researchers concluded that edaravone works in a small subset of ALS patients who met criteria identified in post-hoc analysis of most recent Phase 3 studies, showing a remarkable diminish ALSFRS-R score compared with control group who received placebo. They also highlighted that there is no proof that edaravone might be efficient in a bigger series of ALS cases who do not meet the criteria [80]. The best way to administer edaravone (60 mg) is by slow IV infusion (2 hours duration) every 28 days. Edaravone has demonstrated its capacity to slow down the process of loss of motor function by 33% of ALS cases compared with control group. Being a powerful free radical scavenger, edaravone is able to inhibit nitration of tyrosine in the CSF and to improve the motor neuron cell activity in ALS mouse [81]. Unfortunately, there is no unanimous agreement about the positive effect of riluzole in patients presenting degenerative disorders. At the present moment, most of the neurology community agrees that riluzole is not a remarkable strong effect on the progression of ALS. Because the oxidative stress is considered to be involved in the pathology of ALS, almost all consider that the free radical scavenger edaravone may play a better relevant role for the treatment of cases presenting ALS. Without doubt, the first medication able to provide an efficient inhibition of motor neuron function deterioration in MND/ALS cases is edaravone if it is taken at early stage of this pathological disorder, but the lung function must be well assessed when a deterioration in the respiratory capacity is confirmed [82]. Most reports published in the medical literature show controversial benefits and safety about the edaravone treatment of ALS. Recently, Luo et al. [83] made a meta-analysis research to evaluate the accuracy and safety of edaravone as a therapy of choice for ALS, by searching PubMed, the Cochrane Library, and Embase from the inception of electronic data (April 2018), including randomized, double-blind, placebo-controlled trials reporting ALS cases receiving 60-mg IV edaravone or IV saline solution as placebo for 24 weeks. The study included 367 patients from three randomized controlled trials (183 patients on IV edaravone; 184 receiving IV saline solution). They arrived to the following conclusion: edaravone IV is a good treatment for ALS cases, with no remarkable side effects [83].

3. Other medications for MND

Although there is no available medicine to cure any clinical presentation of MND, during the first semester of this year (2019), a number of medications have been used to treat affected patients. Unfortunately, no remarkable results have been obtained, but some of them still show good action over this disease. In this chapter, we will deliver some comments about the results reached by some authors according to their report to the medical literature. The most common used medications

are EH301, 5Fluoroucil, Tryptophan, RNS60, Rasagiline, Tirasemtiv, Aquaporin, Fasudil, and Lunasil.

de la Rubia et al. [84] evaluated the accuracy and feasibility of Elysium Health's candidate drug EH301 in ALS cases by a single-center, prospective, double-blind, randomized, placebo-controlled pilot study. Thirty-two ALS patients studied underwent for assessment during 4 months. Differences between EH301 and control group were evaluated based on their findings, and EH301 confirmed a remarkable slow progression of ALS compared with nontreated cases and even confirmed clinical benefits in many key outcome measures relative to their baseline.

Searching for drug candidates for ALS, Rando et al. investigated the action of anti-metabolite 5-fluorouracil (5-FU) administered by a single intraperitoneal injection at 150 mg/kg in SOD1G93A model of ALS. Un expectedly, the authors found that 5-FU (anti-cancer drug) increases survival delays of the disorder onset and improves motor function in ALS mice, but they were not able to demonstrate the mechanism of the beneficial 5-FU action in ALS mice. Despite of 5-FU did not improve the modulate motor neuron survival remarkably and did not improve reactive gliosis or change the muscle morphology, their findings recommended that a low dose of 5-FU or its analogs may have good effects on MND/ALS [85].

Other authors postulate that toxic gain of function, spread, and SOD1 misfolding is suggested as part of pathological mechanism of MND/ALS, but the nature of SOD1 toxicity has been hard to describe [86]. Only in SOD1 proteins from humans and other primates, and rarely in other species, a tryptophan residue at position 32 (W32) is predicted to be solvent exposed and to participate in SOD1 misfolding. DuVal et al. considered that W32 is influential in SOD1 acquiring toxicity, as it is known to be important in template-directed misfolding [86].

DuVal et al. highlighted the relevant influence of W32 on cases SOD1 toxicity to upper and lower motor neuron cells morphology and its activities. They assessed pharmaceutical targeting of the W32 residue for rescuing SOD1 toxicity [86]. When RNS60 is administered by IV infusion every 7 days and daily nebulization, it acts as a novel immune-modulator agent able to provide neuroprotective action in MND/ALS preclinical models. Paganoni et al. [87] studied 16 ALS patients during 23 weeks for safety and tolerability. Some investigations were done such as PBR28 positron emission tomography imaging and plasma biomarkers of inflammation. These authors did not find serious reactions, and no participants were removed from the study due to drug-related complications. At the present moment, a large, multicenter, Phase II trial of RNS60 is currently including cases to test the effects of RNS60 on MND/ALS biomarkers and disease deterioration based on the previous findings. They concluded that long-term RNS60 administered by IV infusion (as indicated) is well assimilated by patients and is also accurate [87]. In ALS, the prolong use of immune-modulating therapies has been showing not good results and did not help to understand how the immune system modifies disease outcome [88].

Rasagiline (monoamine oxidase B inhibitor) administered at 2 mg/day has a neuroprotective effect in MNS/ALS cases. In order to verify this postulate, Fernandez et al. performed a trial of 80 ALS patients from 10 hospitals in America. They did not identify any difference between Rasagiline-treated cases and the control group. Therefore, they assumed that Rasagiline did not change disease output compared with control group during 12 months of therapy. Rasagiline was well assimilated, and no serious adverse events were report.

Shefner et al. conducted a multinational clinical trial to study the accuracy of tirasemtiv (125 mg twice daily) using an escalating dosage protocol during 4 weeks [89]. Comparisons between two series of cases with ALS were performed. One group constituted by fast skeletal muscle troponin activator and a second control group by placebo. Of 744 candidates, 565 participants assimilated open-label

tirasemtiv and were treated randomly. As a side effect of tirasemtiv, nausea, weight loss, dizziness, fatigue, and insomnia were more often seen. The frequency of severe side effects was seen equally on both series of cases. Obviously, tirasemtiv did not change the decline of slow vital capacity or remarkable impact secondary outcome assessment and weak tolerability of tirasemtiv may lead to poor effect on MND/ALS.

Aquaporin 4 (AQP4) is present in astrocytes in the nervous system as primary water channel and has been postulated to participate in a myriad of acute, chronic brain disorders and the incidence of MND/ALS. Depolarization of AQP4 causes degeneration of the upper and lower motor neurons via GLT-1, and suppressions increase recovery of motor activity in MND/ALS cases probable due to NGF. No clinical trial targeting AQP4 has been done up to date [90].

Studies made with Fasudil (30 mg for IV application) have shown good results in cell culture and animal research of MND/ALS. This medication is a Rho kinase (ROCK) inhibitor, which has been used in Japan (1995) for the management of Reynaud's syndrome, pulmonary hypertension, and vasospasm secondary to subarachnoid hemorrhage, angina pectoris, and also to treat complications from high blood pressure. Currently, some authors are looking for efficacy, safety and tolerability of a ROCK-ALS of fasudil in MND/ALS cases that started patient recruitment in 2019 [91]. ROCK (serine/threonine kinase) is a novel medication to target for neurodegenerative brain disorders, and it has two isoforms: ROCK1 is mainly for the peripheral nervous system, and ROCK2 is expressed preferentially in nervous central system [92]. Levels of ROCK augment according to age and tissue of MND/ALS cases. Some authors also confirmed increased levels of ROCK2 and downstream targets LIMK1 and coiling [93]. Fasudil also modifies microglia activity [91]. Main side effect of fasudil is intraparenchymal hemorrhage. Nevertheless, in studied population of cases with subarachnoid hemorrhage, the incidence of bleeding did not differ remarkably from the control group. Therefore, hemorrhage is not an expected complication, and it will not put in risk the life in selected patient. Cases with past medical history of intraparenchymal bleeding, congenital or acquire aneurysms or Moyamoya disease should not be included in the therapeutic group.

Lingor et al. confirmed that ROCK-MND/ALS clinical trial provides a well-tolerated, safe, and accurate way of treatment. The biomarker collection associated with this study will deliver additional data as indicators of progression. Finally, we comment about Lunasin a soy peptide that modify histone acetylation in vitro joined to single MND/ALS effect but no remarkable activity on histone acetylation or disorder deterioration in 50 participants treated during 5.5 months by Bedlack et al. [94]. Excellent retention and adherence have been found but not better results than riluzole or edaravone.

As a result of the great interest showed by investigators and participants on different studies done during the first half of this year (2019), today we can see an important number of other therapeutic procedures also looking for the best management of ALS patients. This modality ranges from physical exercises to acupuncture including other choices such as stem cell therapy, treatment for sialorrhea, and spasticity, among others.

In our times, many healthy people do physical exercises on regular basis; some do exercise for slimming purposes, others for prophylactic treatment, rehabilitation, and so forth.

Unfortunately, due to lack of space, these topics will not be included in this chapter.

After reviewing the most recent studies published in the medical literature, we concluded that we still have no curative treatment for MND patients, but a promising future is forthcoming.

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