Afinal que diferença clínica tem significado no tratamento farmacológico da Esclerose Lateral Amiotrófica?

Contributo dos ensaios clínicos e análise dos endpoints de eficácia

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Glossary

AALSRS - Appel Amyotrophic Lateral Sclerosis Rating Scale

ALS – amyotrophic lateral sclerosis

ALSAQ-40 – 40-item Amyotrophic Lateral Sclerosis Assessment Questionnaire

ALSAQ-5 – 5-item Amyotrophic Lateral Sclerosis Assessment Questionnaire

ALSFRS - Amyotrophic Lateral Sclerosis Functional Rating Scale

ALSFRS-R - Amyotrophic Lateral Sclerosis Functional Rating Scale revised

ALSQoL - Amyotrophic Lateral Sclerosis Specific Quality of Life

ALSSS - Amyotrophic Lateral Sclerosis Severity Scale

AMPA – alfa-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate

ASO - antisense oligonucleotides

BMI - body mass index

C9orf72 - chromosome open reading frame 72

CAFS - Combined Assessment of Function and Survival

CGI - Clinical Global Impression

CGI – clinical global impression

CNS – central nervous system

CT – clinical trials

EEC – El Escorial criteria

EIM - Electrical Impedance Myography

EMA – European Medicines Agency

EUDRACT – European clinical trials database

FALS - familial amyotrophic lateral sclerosis

FEV – forced expiratory volume

FEV1 - forced expiratory volume in one second

FTLD - frontotemporal lobar dementia

FVC – forced vital capacity

HHD - hand-held dynamometry

IMV - invasive mechanical ventilation

LMN – lower motor neurons

MCID - minimal clinically important difference

MIP - maximal inspiratory pressure

MMT – manual muscle testing

MMV - maximum voluntary ventilation

MND- motor neuron disease

MRC – Medical Research Council

MRI – magnetic resonance imaging

mRNA – messenger-ribonucleic acid

MUNE - Motor Unit Number Estimation

MVIC - Maximum Voluntary Isometric Contraction

MVV - Maximum voluntary ventilation

NGT - nasogastric tube

NIV - non-invasive ventilation

NMDA - N-methyl-D-aspartate

PEF - peak expiratory flow

PEG - percutaneous endoscopy gastrostomy

PImax - maximal inspiratory pressure

PRG - percutaneous radiologic gastrostomy

RCT – randomized clinical trials

rhEPO – recombinant human erythropoietin

RNAi - RNA interference

SALS – sporadic amyotrophic lateral sclerosis

SNIP – sniff nasal-inspiratory pressure

SOD 1 - superoxide dismutase 1

SVC – slow vital capacity

TQNE – Tufts Quantitative Neuromuscular Exam

TUDCA – tauroursodeoxycholic acid

UDCA – ursodeoxycholic acid

UMN - upper motor neurons

US FDA – United States Food and Drug Administration

VAS – visual analogue scale

VC – vital capacity

Resumo

A Esclerose Lateral Amiotrófica (ELA) é uma doença degenerativa do neurónio motor, que apresenta elevada morbilidade e é virtualmente sempre fatal. Por ausência de cura, a abordagem terapêutica foca-se na manutenção da qualidade de vida e no seu prolongamento. Nos últimos 50 anos, todos os ensaios clínicos de fase III, com excepção do Riluzole, não comprovaram eficácia. A maioria destes resultados negativos deveu-se à falta de significado estatístico. O objectivo deste artigo é discutir se as diferenças obtidas nos instrumentos de eficácia usados nos ensaios clínicos mais recentes teriam tido significado clínico para o doente. Realizou-se uma análise descritiva de estudos da história natural, ensaios clínicos de fármacos testados e artigos de revisão sobre os instrumentos de eficácia dos resultados. Pequenos efeitos positivos, que poderiam ter um enorme valor numa doença com tão mau prognóstico como a ELA, podem ter sido negligenciados. Tão importante quanto determinar e alcançar a diferença clínica minimamente significativa para a sobrevivência e medidas funcionais – para as quais a perspectiva do doente também deveria ser tida em conta, dever-se-iam priveligiar os Questionários de Qualidade de Vida enquanto instrumentos de eficácia nos ensaios clínicos dado que, por serem subjectivos, são os que melhor traduzem o que o doente sente ter maior significado para si.

Abstract

Amyotrophic Lateral Sclerosis is a progressive degenerative motor neuron disease, with significant morbidity and virtually always fatal. There is no cure yet, so care is aimed at maintaining quality of life and prolonging life. Over the past half-century, all phase III clinical trials have failed to show efficacy, with the exception of Riluzole. Most of the negative results in clinical trials are due to the lack of statistical significance. The purpose of this article is to discuss whether or not the differences obtained on therapeutic efficacy measures of the most recent failed clinical trials would be meaningful to the patient. A descriptive analysis was performed for natural history studies, clinical trials of tested agents and review articles of outcomes measures. Small positive effects, which could be of great value in a disease with such poor prognosis as ALS, may have been missed. As important as determining – that should also be based on the patients' perspective – and reaching the minimal clinical important difference for survival and functional measures, a greater attention should be paid at Quality of Life Assessment Questionnaires as a key endpoint of efficacy on CT, as these are subjective instruments that may better reflect what patients feel to be meaningful.

Keywords: amyotrophic lateral sclerosis • clinical trials • efficacy endpoints • outcome measures • minimal clinical importance difference • statistical significance

Introduction

More than 50 randomized controlled clinical trials of potential drugs for Amyotrophic Lateral Sclerosis (ALS) have failed to show positive results in the past half-century. [1] Ideally, phase III trials are expected to yield positive results, as they are performed only after evidence of potential efficacy is gathered from preclinical research and phase II studies. [2] However, the transition from phase II to phase III trials remains particularly challenging. The lack of statistically significant results might lead us to ignore a potential effect measured by the efficacy endpoints. The purpose of this article is to compare the variations obtained on therapeutic efficacy measures to their expected variation in the natural history of the disease, without any pharmacological intervention and to discuss whether or not these results would be meaningful to the patient.

Amyotrophic Lateral Sclerosis

ALS is a progressive degenerative motor neuron disease characterized by focal weakness of limb and bulbar muscles that ultimately involve all skeletal muscle and lead to the loss and dysfunction of both upper and lower motor neurons (UMN and LMN, respectively). Although rare, ALS is the most common form of motor neuron disease (MND). Incidence rates for ALS in the United States and most European countries range from 1.5-2.5 ALS cases per 100,000 person per year, according to the ALS consortium of Epidemiologic Studies. Incidence increases with age, peaking between the ages of 50 and 75 years and declining thereafter [3] with an average age of onset of 61,8 years [4].

The majority of the patients have no family history and are termed sporadic ALS (SALS). [5] Its main causes and molecular basis are still unknown even though it seems to have both genetic and environmental influences [6] [7]. Ten to 15% of patients have familial ALS (FALS) based on the presence of a heritable cause. Clinically, FALS and SALS are indistinguishable, although patients with familial disease may be younger at onset and have more protracted disease. Men have higher incidence of sporadic disease whereas FALS, given autosomal dominant inheritance, affects men and women equally. [5]

The most frequent genetic causes of ALS are: mutations in the *chromosome open reading frame 72 (C9orf72)* gene, accounting for approximately 40% of FALS and 5-6% of SALS cases; the *superoxide dismutase 1 (SOD1)* gene, which is present in 20% of FALS cases; the *fused in sarcoma* gene, found in 5%

of the patients with familial disease; and the *TAR DNA-binding protein 43* gene, affecting 3% of the patients with FALS. [8] [4] In rare circumstances, the disease is associated by mutations in other genes. As motor neurons are affected segmentally and to varying degrees in different patients, the symptomatology is diverse and the initial clinical presentation varies considerably. [3]

The disease affects LMNs arising from the brainstem or "bulbar" region, more specifically in the medulla, and from the anterior horn of grey matter of the spinal cord as well as UMNs in the cerebral cortex. Fasciculation, cramps, muscle atrophy and marked weakness are the main LMN signs and may be focal, multifocal or diffuse. Hyperreflexia, spasticity, Babinski sign, snout reflexes, incoordination and weakness are typical of UMN degeneration. [9] [7]

The bulbar signs are caused by the involvement of the somatic nuclei of the VII, IX and XII cranial nerves. Patients present dysarthria, that may progress to anarthria, dysphagia, drooling and an atrophied fasciculating tongue that is very characteristic of bulbar ALS and virtually diagnostic of the condition.[9] [7]

ALS begins in the limbs in about two-thirds of patients, most often in the arms. The first symptoms are usually unilateral and focal. Early findings include foot drop, difficulty walking, loss of hand dexterity or difficulty lifting the arms over the head. Eventually, limb function can be lost. About 30% of patients, typically older woman, have bulbar-onset disease and 5-10% present with more generalized symptoms. [5] [3] [7]

Classically, despite the site of onset, ALS spreads to contiguous, and eventually respiratory, myotomes. [7]

Axial weakness can cause dropped head and kyphosis, features associated with pain and poor balance. [7]

Extraocular and sphincter muscles are characteristically spared in patients with ALS, at least until late in the disease [3] and sensory symptoms are rare. Clinically, ALS is a pure motor neuron syndrome. [9] [3]

A significant number of ALS patients have cognitive impairment. Frontotemporal dysfunction and atrophy, as seen in frontotemporal lobar dementia (FTLD), occurs in up to 50% of patients, which can present with subclinical executive, language or behaviour dysfunction or, in a smaller percentage of cases (15%), meet the formal criteria for the behavioural variant of FTLD, or the non-fluent or the semantic variant of primary progressive aphasia [8] [9]. Personality change, irritability, impaired judgement,

impulsivity and pervasive deficits on frontal executive tests are the commonest manifestations. [3]

Morning headache, weakened cough, orthopnoea and exertional dyspnoea are early respiratory symptoms. [7]

The diagnosis depends on progressive UMN and LMN findings on history and examination. Electromyography confirms widespread LMN disease and excludes other conditions, such as multifocal motor neuropathy with conduction block. Brain and spinal MRI exclude conditions that affect the UMN such as cervical spondylosis. [7] These are the two conditions most commonly mistaken for ALS. [3]

Occasionally, brain MRI shows bilateral signal changes in the corticospinal tracts, a finding that is pathognomic of ALS.

Progressive LMN disease by clinical and electromyographic examination, and clinical UMN signs are, therefore, the core hints for the diagnosis of ALS. The Revised El Escorial Diagnostic Criteria for Amyotrophic Lateral Sclerosis establish the degree of certainty of diagnosis and facilitates timely enrolment in clinical trials and patient-oriented research. [7] [3]

The clinical, pathological and genetic advances indicate heterogeneity in phenotype, pathological substrate and genetic predisposition, suggesting that ALS should be considered a syndrome rather than a single disease entity. [3]

Indeed, a number of distinct clinical phenotypes exist within the ALS disease spectrum, and may be associated with rates of disease progression that differ from those of more typical ALS. Flail-limb variant, along with other LMN-predominant subtypes and pure motor neuron conditions may be characterized by slower disease progression [10] [3]. It is common to admit that lower-limb onset carries a better prognosis than the upper-limb onset [3]. However, there are conflicting data on this subject as some studies showed a poorer prognosis with lower limb onset, presumably due to an increase risk of thromboembolic disease and infections arising from loss of motility [11]. Bulbar and respiratory-onset disease carries the worst prognosis. [3]

Older age (>65), a rapid decline in ALSFRS-R score, psychological distress, coexistence with frontotemporal lobar dementia (FTLD), a lower FVC at diagnosis or FVC <50%, SNIP <40 and definite-EEC diagnosis are all poor prognostic indicators. [11]

A longer delay from symptom onset to diagnosis is a good prognostic factor since a short time delay may indicate a more aggressive disease that led the

patient to seek medical attention more rapidly. [11]

Finally, hyperlipidemia and a higher pre-morbid body mass index (BMI) with the maintenance of BMI and nutritional state along the course of the disease has been associated with improved outcome, with the optimal values of BMI being between 30 and 35 kg/m^2. [12]

There is no cure yet for ALS, so care is aimed at maintaining quality of life and prolonging life as much as possible. [7]

Multidisciplinary care should be provided to all people affected with ALS. Currently treatment focuses mainly on symptomatic treatment, respiratory and nutritional therapies and on the only disease-modifying treatment available, riluzole.

Respiratory complications are the main cause of death in ALS, primary as consequence of diaphragmatic weakness combined with aspiration and infection due to excess secretions and poor airway clearance. Non-invasive ventilation (NIV), usually with a bi-level intermittent positive-pressure ventilator, is the standard intervention for patients with respiratory insufficiency and should be preferred to invasive mechanical ventilation (IMV), which should be used as a last resource. Cough-assist devices and chest wall oscillation can also be offered to increase the effectiveness of assisted ventilation in ALS. Medical treatment of chronic or intermittent dyspnea is recommended. Pneumonia and influenza vaccines are of value as prophylactic measures.

Weight loss at time of diagnosis is an independent prognostic factor of survival in ALS and is a consequence of an increased resting energy expenditure and decreased ingestion of food due to dysphagia. The initial management is based on dietary counseling, modification of food and fluid consistency, high-protein and high-caloric supplements and education of feeding and swallowing techniques. When tube feeding is needed, there are three procedures that obviate major surgery: percutaneous endoscopy gastrostomy (PEG), percutaneous radiologic gastrostomy (PRG) and nasogastric tube (NGT) feeding, usually used in the short-term and when PEG or PRG are not suitable. The timing of PEG/PRG is based on an individual approach taking into account bulbar symptoms, mal-nutrition, respiratory function and the patient's general condition. Early insertion of a feeding tube is recommended. Home parenteral nutrition is possible as an alternative to enteral feeding in patients with advanced ALS and poor respiratory function.

Medications to relieve suffering and dyspnea, including anxiolytics and opioids, can be prescribed.

In addition to the significant morbidity, the disease is virtually always fatal and on average, death from respiratory failure secondary to diaphragmatic paralysis occurs within 3-4 years from the onset of symptomatic weakness. [13] [14]

Survival ranges from months to decades with approximately 10% of patients surviving more than 10 years from the time of diagnosis. [5] [6]

Methods

A search in PubMed for English or Portuguese-language review articles or phase II and III clinical trials, was performed, from the past 5 years and only in humans, using the search terms "*amyotrophic lateral sclerosis*" or "*motor neuron disease*" in combination with "*drug therapy*" and "*outcome measures*". Time restriction was due to the boom of phase II and III CTs concerning this subject in the past five years, and previous studies lacked methodological robustness. Further relevant material were included from reference lists as well as from the European and American Guidelines on the clinical management of Amyotrophic Lateral Sclerosis, EMA Guideline on clinical investigation of medical products for the treatment of ALS and from the websites of clinicaltrials.gov and EUDRACT.

A descriptive analysis was performed for:

- Natural history studies, describing disease progression;
- Trials on approved medication;
- Trials on previously tested agents;
- Review articles of outcomes used for the assessment of efficacy in ALS.

The progression of the outcome measures in the placebo arm of riluzole's clinical trials was also used to assess their variation in the natural history.

All the drugs tested in the past five years were included in this analysis as well as riluzole, as it is the only approved drug to date.

Results

Disease-modifying therapies for ALS

Current experimental ALS drugs are being developed on the basis of presumed pathophysiologic mechanisms. The most accepted hypotheses concerning disease pathophysiology include glutamate-mediated excitotoxic effects, oxidative stress, proteosomal dysfunction, protein

misfolding and accumulation, axonal transport abnormalities, mitochondrial dysfunction, glial activation with a micro-inflammatory process and aberrant neurotrophic/growth factor signalling. [15]

The key used outcomes and the results obtained from the drug trials consulted are presented in the table 1.

Over the last 25 years, despite significant effectiveness of potential therapeutics observed in preclinical trials, all phase III clinical trials have failed to show efficacy, with the exception of Riluzole. [6] [13]

There is a long list of agents with disappointing results in ALS, which could be grouped into the following eleven categories (by its shared mechanism of action): anti-glutamatergic agents, antioxidant therapy, agents targeting autophagy, anti-apoptotic agents, drugs targeting protein misfolding and accumulation, mitochondrial agents, immunomodulatory agents, neurotrophic factors, agents promoting mutant mRNA counteraction, stem-cell therapy and muscle-directed therapy.

More recently, much attention has been focused on stem-cell therapy, antisense oligonucleotides (ASO) and RNA interference (RNAi) as a very promising land of future disease-modifying therapies.

Riluzole

Until the early 1990s, all clinical trials of disease-specific therapy for ALS yielded unfavourable results. Emerging evidence that chronic glutamate excitotoxicity might accumulate to toxic levels and contribute to neuronal death in ALS provided a rational basis for undertaking a clinical trial with riluzole [14], a benzothiazole derivative that possesses anti-glutamatergic properties. [16]

Riluzole has complex effects and the means trough which it influences neurodegeneration in ALS are not fully elucidated. The chief mechanism appears to be via the reduction of glutamate levels at the synaptic cleft [16] by enhancing the uptake of ambient glutamate by astrocytes as well as presynaptic glutamatergic nerve terminals and reducing the endogenous release of glutamate particularly from very active synapses [17]. It may also exert neuroprotective action trough non-competitive post-synaptic inhibition of NMDA and AMPA receptors [16] and inhibition of a persistent Na+ current that support long-lasting firing of action potentials by motor neurons. This depressant effect by riluzole limits neuronal excitability and restricts the

		Agent	Study design	Key outcome	Results
1. ANTI-GLUTAMATERGIC AGENTS		Riluzole	Prospective, multicentre, double-blind, randomized, placebo-controlled, parallel group trial [28] 155 patients 21 months **study 216**	<u>Primary</u> Survival (death from any cause and tracheostomy) Functional status - modified Norris Scales <u>Secondary</u> MRC FVC Clinical Global Impression of Change scale	<u>Riluzole therapy reduced mortality by 38.6% at 12 months and by 19.4% at 21 months</u> – an effect both clinically important and statistically significant 12-month survival: 58% (placebo) vs 74% (riluzole) $p = 0.014$ • Bulbar-onset disease: 35% (placebo) vs 73% (riluzole) $p = 0.014$ • Limb-onset disease: 64% (placebo) vs 74% (riluzole) $p = 0.17$ 21-month survival: 37% (placebo) vs 49% (riluzole) $p=0.046$ • Bulbar-onset disease: 18% (placebo) vs 53% (riluzole) $p=0.0.13$ • Limb-onset disease: 43% (placebo) vs 48% (riluzole) $p = 0.355$ Median survival was 449 days (placebo) vs 532 days (riluzole) For each functional score, the rate of deterioration was slower in the riluzole group • Only the 33.4% reduction in the rate of deterioration of muscle function at 12 months was statistically significant $p = 0.028$

Table 1. Contribute of the clinical trials of riluzole and of the agents with studies posted in the past 5 years in the analyses of the variation of the key outcomes. (part 1/6)

1. ANTI-GLUTAMATERGIC AGENTS		Riluzole	Multicentre, double-blind, placebo-controlled, randomized, parallel group, dose ranging study[29] 959 patients 18 months **study 301**	<u>Primary:</u> Survival without tracheostomy <u>Secondary:</u> MRC Modified Norris Scales VC Clinical Global Impression scale Visual Analogue Scales (for fasciculations, cramps, stiffness, tiredness)	50.4% of the patients alive at study end (placebo) vs: • 55.3% (50mg riluzole) • 56.8% (100mg riluzole) • 57.8% (200mg riluzole) After adjustment for prognostic factors, there was a significant overall drug effect at 12 and 18 months. Survival was greater with each riluzole dose that with placebo. $p = 0.04$, $p = 0.002$, $p = 0.0004$ for the increasing doses At 18 months, the 50 mg, 100mg and 200mg riluzole doses decreased the risk of death or tracheostomy by 24%, 35% and 39%, respectively. Muscle-strength testing, limb or bulbar scores without evidence of a treatment effect. No other treatment effect was detectable with respiratory function tests, visual analogue scales or CGI
			Multicentre, double-blind, randomized, placebo-controlled, parallel group trial (study 302) – advanced stage disease or aged over 75 years [30] 168 patients 18 months **study 302**	<u>Primary:</u> Survival <u>Secondary</u>: MMT scale Modified Norris bulbar and limb scales Clinical Global Impression Scale Visual Analogue Scales (for fasciculations, cramps, stiffness, tiredness) FEV, SVC	<u>Not enough patients to reach adequate power to detect differences in survival.</u> Survival at 18 months: 25.6% (placebo) vs 26.8% (riluzole) $p = 0.77$ No differences in the rate of deterioration of MMT Rate of deterioration of the score of the Norris bulbar scale significantly lower (riluzole). $p = 0.05$ No significant difference among groups for CGI, parameters of VAS or in respiratory function – data not shown.

Table 1. Contribute of the clinical trials of riluzole and of the agents with studies posted in the past 5 years in the analyses of the variation of the key outcomes. (part 2/6)

1. ANTI-GLUTAMATERGIC	EAAT2 astrocytic glutamate transporter modifiers	Ceftriaxone	Multi-phase (phase I-III) randomized, double-blinded, placebo controlled trial [2] 514 patients 6 years **NCT00349622**	<u>Co-primary</u> Survival ALSFRS-R <u>Secondary</u> Changes from baseline in Vital Capacity Changes in upper- and lower-limb muscle strength using Hand Held Dynamometry ALSQoL	<u>During stage I and II</u>: ALSFRS-R functional decline 0.51 +/- 0.24 units per month slower in ceftriaxone group. p = 0.0416 No differences noted for VC. Leg strength declined at a slower rate. <u>Stage III</u>: Failed to show efficacy ALSFRS-R functional decline 0.09+/- 0.08 units per month slower. p = 0.2370 HHD difference in slopes was 0.038+/-0.0192 units per month. p = 0.0550
	Glutamate receptor antagonists	Talampanel	Phase II multicenter, randomized, double-blinded, placebo controlled [31] 59 patients 9 months **NCT00696332**	<u>Primary</u> TQNE arm strength megaslope <u>Secondary</u> TQNE leg strength megaslope VC ALSFRS Timed hand function score survival	<u>Slower decline in ALSFRS-R (less 30%)</u> p = 0.081 • Change from baseline at 9 months of -7.1 in the talampanel group vs -10.1 in the placebo group Slower decline in isometric arm strength (less 15%) p = 0.840 • TQNE arm strength declined 1.9 units/year in the talampanel group vs 2.2 units/year in the placebo group TQNE leg strength declined 1.4 units/year (talampanel group) vs 1.3 units/year (placebo group) p = 0.971 TQNE timed hand function declined 1.0 unit/year (talampanel group) vs 1.5 units/year (placebo group) p = 0.123

Table 1. Contribute of the clinical trials of riluzole and of the agents with studies posted in the past 5 years in the analyses of the variation of the key outcomes. (part 3/6)

2. ANTI-OXIDANT THERAPY		Pioglitazone	Double-blind, randomized, placebo-controlled, multicenter phase II trial [32] 219 patients 2 years **NCT00690118**	<u>Primary</u> Survival <u>Secondary</u> Incidence of tracheotomy and of NIV ALSFRS-R Slow vital capacity EUROQoL EQ-5D	Hazard for death was increased of 21% in the pioglitazone group. $p = 0.48$ Incidence of tracheotomy 6.4% (pioglitazone group) vs 4.6% (placebo group) $p = 0.54$ Incidence of NIV 20.2% (pioglitazone group) vs 26.6% (placebo group) $p = 0.28$ Small difference in ALSFRS-R score (≈ 2 points) at 15 months with pioglitazone $p = 0.66$ and not sustained Slope of EUROQoL EQ-5D and SVC not affected by pioglitazone (not shown)
3. AGENTS TARGETING AUTOPHAGY		Lithium Carbonate	Double-blind, randomized, placebo-controlled, multicenter phase III trial[33] 243 patients *Ongoing* **EudraCT 2008-006891-31**	<u>Primary</u> Rate of survival at 18 months <u>Secondary</u> ALSFRS-R Mental health state measured with hospital anxiety and depression scale EUROQoL EQ-5D	Survival at 18 months 59% (placebo) vs 50% (lithium) $p = 0.20$ • In a post-hoc analysis, after adjusting for study centre and site of onset, the relative odds of survival at 18 months (lithium vs placebo) was 0.71 Annual rate of change in ALSFRS-R score was 9.47 (placebo) vs 9.75 (lithium) adjusted for survival – not statistical significant (*p* value not shown) HADS anxiety/depression scores at 18 months of 3.5/4.71 (placebo) vs 4.55/5.17 (lithium) - *the higher the scores, the poorer the outcome* EUROQoL EQ-5D score at 18 months of 61.95 (placebo) vs 56.36 (lithium)
			Double-blind, randomized, placebo-controlled, multicenter phase II trial[34] 214 patients 13 months **NCT00790582**	<u>Primary</u> Slope of the ALSFRS-R <u>Secondary</u> Rate of decline of mean FVC Quality of Life Weight loss	Estimated mean slope of ALSFRS-R score: 1.20/month (lithium) vs 1.01/month (placebo) $p = 0.04$ Mean slope of decline of the FVC: 2.84/month (lithium) vs 2.91/month (placebo) $p = 0.80$ Rate of decline of QoL: 0.139/month (lithium) vs 0.136/month (placebo) $p = 0.93$ No difference in weight loss

Table 1. Contribute of the clinical trials of riluzole and of the agents with studies posted in the past 5 years in the analyses of the variation of the key outcomes. (part 4/6)

4. ANTI-APOPTOTIC AGENTS		Growth factor erythropoietin (EPO)	Double-blind, randomized, placebo-controlled, multicenter phase III trial[35] 208 patients 18 months **EudraCT 2009-016066-91**	<u>Primary</u> Time from randomization to death, tracheotomy or >23h NIV (14 consecutive days) <u>Secondary</u> ALSFRS-R SVC ALSAQ-40 questionnaire	Rate of overall events: 25% (rhEPO) vs 23% (placebo) $p = 0.88$ • Rate of death 10% (rhEPO) vs 7% (placebo) $p = 0.52$ • Rate of tracheotomy or >23h NIV 15% (rhEPO) vs 16% (placebo) $p = 0.77$ Even after stratification by disease severity and onset, the rate of events did not differ significantly between treatment groups. Survival probability at 12 months 78% (rhEPO) vs 73% (placebo) $p = 0.99$ ALSFRS-R score at 12 months was 28 (rhEPO) vs 26 (placebo) $p = 0.31$ SVC value was approximately 60% (rhEPO) vs 63% (placebo) $p = 0.47$ ALSAQ-40 score at 12 months: +29 points with rhEPO vs +37 points with placebo $p = 0.23$
		Ursodeoxycholic acid (TUDCA/UDCA)	Double-blind, randomized, placebo-controlled phase II trial[36] 34 patients 54 weeks **NCT00877604**	<u>Primary</u> Proportion of responders (improvement of at least 15% in ALSFRS-R slope) <u>Secondary</u> ALSFRS-R Survival time FVC at end study Quality of Life assessed by short form 36 (SF-36) questionnaire MRC scores for right and left muscle groups	Proportion of responders: 87% (TUDCA) vs 43% (placebo) $p = 0.021$ ALSFRS-R at study end: 23.3 (TUDCA) vs 16.3 (placebo) $p = 0.007$ Comparison of the slopes of regression analysis showed slower progression in the TUDCA group (-0.262 vs – 0.388) $p < 0.01$ FVC at end study: 87.7% (placebo) vs 89.1% (TUDCA) $p = 0.778$ SF-3 at end study: physical component 35.0 (placebo) vs 34.8 (TUDCA) $p = 0.951$; mental component 42.3 (placebo) vs 49.0 (TUDCA) $p = 0.173$ MRC scale: right muscle group 47 (placebo) vs 49.2 (TUDCA) $p = 0.695$; left muscle group 43.7 (placebo) vs 47.0 (TUDCA) $p = 0.553$
			Double-blind, randomized, placebo-controlled, cross-over, single center, phase III trial[37] 63 patients 8 months **KFDA and IRB of Seoul National University Hospital (H-0301-099-007)**	<u>Primary</u> Slope of AALSRS <u>Secondary</u> Deterioration rate of ALSFRS-R Deterioration rate of FVC	Slope of AALSRS 2.24 points/month (UDCA) vs 3.88 points/month (placebo) – <u>1.63 points/month slower while in UDCA group</u> – $p = 0.004$ but high attrition rate Time to a 20-points progression in AALSRS total score was estimated to be delayed by 14.9 months in UDCA group (22.5 vs 7.6 months) $p = 0.018$ ALSFRS-R slope of 0.97 (UDCA) vs 1.54 (placebo) $p = 0.22$ FVC slope of 0.76 (UDCA) vs 1.90 (placebo) $p = 0.53$

Table 1. Contribute of the clinical trials of riluzole and of the agents with studies posted in the past 5 years in the analyses of the variation of the key outcomes. (part 5/6)

5. MITOCHONDRIAL AGENTS		Dexpramipexole	Double-blind, randomized, placebo-controlled, multicenter phase III trial[38] 943 patients 12 months **NCT01281189**	<u>Primary</u> CAFS score <u>Secondary</u> Time to death or respiratory impairment <18 months Time to reach <50% predicted upright SVC or death HHD megascore change from baseline at 12 months ALSAQ-5 total score change from baseline ate 12 months	Mean CAFS score at 12 months: 441.76 (dexpramipexole) vs 438.84 (placebo) $p = 0.86$ • change in ALSFRS-R score from baseline: 13.34 (dexpramipexole) vs 13.42 12.35 months (dexpramipexole) vs 12.06 months to death or respiratory impairment for 20th percentile $p = 0.77$ 16 months (dexpramipexole) vs 14.1 months to reach <50% predicted upright SVC or death 50th percentile $p = 0.77$ change of HHD megascore from baseline -0.73 (dexpramipexole) vs -0.70 $p = 0.56$ change of ALSAQ-5 total score from baseline: 21.17 (dexpramipexole) vs 21.35 $p = 0.90$
		Olesoxime	Double-blind, randomized, placebo-controlled, multicenter phase II-III trial [39] 512 patients 18 months **NCT00868166**	<u>Primary</u> 18 months' survival <u>Secondary</u> Rates of deterioration of ALSFRS-R (9-month assessment) SVC Manual muscle testing	Estimated overall survival 67.5% (placebo) vs 69.4% (olesoxime) $p = 0.71$ Small difference in ALSFRS-R global score (≈ 2 points) at 9 months in favor of olesoxime – not sustained after 18 months' treatment nor evident in either stratified bulbar or spinal subpopulations $p = 0.0242$ Analyses of the rate of deterioration in SVC or in MMT did not detect differences between groups.

Table 1. Contribute of the clinical trials of riluzole and of the agents with studies posted in the past 5 years in the analyses of the variation of the key outcomes. (part 6/6)

spread of network overactivity that perpetuates a vicious circle of further excessive release of glutamate and increased neuronal damage [17] [18].

Despite its modest effect on survival and the lack of a positive effect on functional symptoms, riluzole is the only drug approved for the treatment of ALS and is widely prescribed in clinical practice.

It was approved by regulatory agencies in 1995 following two randomized controlled trials, which showed that the drug extends survival in ALS. [16] There was a third trial, in which patients with

advanced disease or aged over 75 years or with vital capacity less than 60% were included, that failed to show any effect on survival.

In the three studies, survival, defined by patients who were alive, not intubated for mechanical ventilation and tracheotomy-free, was the primary efficacy endpoint. Secondary endpoints were functional scales, including the Manual Muscle Scale and the Norris Scales.

When the endpoint taken was mortality only – excluding tracheotomy and intubation – the conclusions did not change, since the rate of tracheotomy and/or intubation were very low and most of these events were followed by death before reaching the cut-off date.

Both the American and European Guidelines recommend that all patients with ALS should be offered treatment with riluzole 50 mg twice daily and that treatment should be initiated as early as possible after diagnosis.

Outcome measures

A review of phase III trials performed in the last 20 years shows a very restricted range of endpoints used. [19]

Major treatment trials undertaken in ALS have focused on survival and other clinical endpoints for efficacy analysis. As ALS remains a clinical diagnosis, clinical measurements strategies are intuitive as research endpoints. In fact, regulatory approval of new therapies by the US FDA and the European Agency for the Evaluation of Medicinal Products requires evidence of improvement of clinical endpoints such as survival, function and strength measures. [10]

The Guidelines on clinical investigation of medicinal products for the treatment of ALS suggest as Therapeutic Efficacy Measures the following ones: survival; functional measures, including ALS Functional Rating Scale and its revised version (ALSFRS-R), the Norris Scale, the Appel ALS Rating Scale (AALSRS) and the ALS Severity Scale (ALSSS); muscle strength measurements using composite manual muscle testing (MMT) scores, hand-held dynamometry (HHD) or more complex quantified methods such as measurement of Maximum Voluntary Isometric Contraction (MVIC); and respiratory function measurements using vital capacity (VC) obtained through forced vital capacity (FVC) or slow vital capacity (SVC), peak expiratory flow (PEF), forced expiratory volume in one second (FEV1), maximal inspiratory pressure (PImax), sniff nasal inspiratory pressure (SNIP) and maximum voluntary ventilation (MVV) test. Assessment of Health Related Quality of

Life is also a valuable measure of therapeutic efficacy, which may be applied as a secondary endpoint, as well as global measures using physician's and patient's Clinical Global Impression (CGI) scale.

As described before, for riluzole, which is so far the only drug approved to treat ALS, survival was the primary outcome measure. Subsequent trials have employed the functional rating scales either the AALSRS, the ALSFRS or the ALSFRS-R. In addition, the muscle strength measures previously mentioned, pulmonary function – primarily using vital capacity, but lately also SNIP and MVV – and quality of life measures have been employed as secondary outcomes. More recently introduced as secondary measures, there is the Motor Unit Number Estimation (MUNE) and Electrical Impedance Myography (EIM), both independent of the subject cooperation. [19]

To this moment, the most used outcomes for primary and key secondary endpoints are presented in the table 2 that summarizes their expected variation in the natural history of the disease and the minimal clinically important difference (MCID).

Measuring survival**.** Improved survival, typically defined as survival without tracheostomy or permanent assisted ventilation, is clearly an important objective for a proposed treatment for ALS [10]. Even though it seems to be an endpoint that reflects underlying disease progression, careful consideration suggests that it may be impacted by many factors independent of progression rate. For instance, the use of the diaphragm pacing system seems to exert a dramatic increase in survival but has no effect on the underlying disease progression [19].

The definition of its MCID is still controversial and a 3-month increase in survival of patients with ALS with no improvement in function has been judged by many as less than a MCID. [20]

Therefore, even though riluzole is approved for the treatment of ALS, its clinical relevance remains debatable and raises ethical issues due to the limited benefit on its primary endpoint, extending survival only 2-months.

Functional assessments. The AALSRS and ALSFRS both in their original and revised forms assess multiple aspects of patient function, including bulbar function, gross and fine motor function, and respiratory status. They all change systematically with progression, and rate of change in these measures correlates well with survival. [19]

Therapeutic Efficacy Measures		Δ Natural history (no intervention)	Clinically Meaningful Effect
Survival		58% alive at 12 months[28] • Bulbar-onset disease 35% alive at 12 months • Limb-onset disease 64% alive at 12 months Median survival 449 days[28] • Bulbar-onset disease 239 days • Limb-onset disease 523 days Improved survival over time in placebo controlled participants enrolled in clinical trials. [40] Median survival 2-4 years from symptom onset [41-43] Median survival 33.6 months from first symptoms [41]	3-month increase in survival (controversial)
Functional Measures	ALSFRS-R	According to different studies: 1 point/month [44] 0.92 points/month [21] 0.7 to 1 point/month [40]	A reduction of 20% or greater in the slope of the score
	Norris Scale	Mean rate of deterioration per year [28]: • Limb functional score: 28.1% • Bulbar functional score 12.3%	Not known
	AALSRS	Slopes range from 0 to 30 points/month change in total score [41]	Not known
	ALSSS	Not known	Not known
	Combined Assessment of Function and Survival (CAFS)	Not known	Not known
Muscle Strength Measurements	MMT scores	Mean rate of deterioration per year: 34.4% [28]	Not known
	HHD	Not known	Not known
	MVIC	Mean rate of decline of MVIC arm megascore (units/month) [40] -0.05 to 0.1 Mean rate of decline of MVIC grip megascore (units/month) [40] -0.06 to 0.1	Not known

Table 2. Therapeutic Efficacy Measures: expected variation with natural history and MCID. (part 1/2)

Respiratory Function Measurements	VC/ FVC/ sVC	3% per month [19] Mean rate of decline of %VC (units/month) [40] -1.1 to -2.8%	Δ 20% in FVC[117]
	PI max	Not known	Not known
	SNIP	Decline 13.52% (+/- 25.84) at 5.2 months [45]	Not known
	MVV	Rate of decline of 4% per month [19]	Not known

Table 2. Therapeutic Efficacy Measures: expected variation with natural history and MCID. (part 2/2)

The changes in slope of decline in ALSFRS/ALSFRS-R do not necessarily imply disease modification. [19]

A clinically meaningful effect is achieved, for ALSFRS-R, with a relatively good consensus among researchers, when there is a change of 20% or greater in the slope of the score [21].

Although ALSFRS-R is the most widely used surrogate marker of disease progression, there are recent metric analyses of the scale that show it fails to satisfy rigorous measurement standards and that should be, at least in part, revised. In these analyses, good internal consistency was shown but it lacked unidimensionality, with ambiguous interpretation of the total score that does not represent a single attribute [22]. The clinical heterogeneity distorts the link between total score and disease severity [10].

Collapsing the scale's 5 level rating into 3 levels improved its metric quality but, at present, ALSFRS-R should be considered as a profile of mean scores from three different domains (bulbar, motor and respiratory function) more than a global total score. [22]

Furthermore, it is demonstrated that clinical factors significantly influences ALSFRS-R decline, including the age of onset, phenotype, body mass index, progression rate at diagnosis, degree of diagnostic certainty according to Revised EEC and FVC% at diagnosis, some of which are also independent prognostic factors for ALS survival. [23]

The higher the heterogeneity of disease progression, the lower the power to detect significant differences in clinical trials [23]. These data emphasize that ALSFRS-R would need an expert revision before it can be appropriately used as a primary or secondary outcome

measure of efficacy in future therapeutic trials as a proxy of disease progression [24].

Despite these limitations, it is a measurement with a clinically meaningful index established, that implies minimal training requirements and has universal applicability. [10]

Combined endpoints have been used in other diseases to decrease the confounding effect of mortality on analysis of functional outcomes [25].

The Combined Assessment of Function and Survival (CAFS) has been proposed as a new endpoint for ALS to provide a more statistically robust measurement of clinical response than survival and functional data alone, and improve the likelihood of identifying a significant effect with treatment [10]. In fact, because a drug might have a disproportionate effect on function or survival, a trial designed with either survival or function as the primary outcome could fail if the wrong primary endpoint was chosen. Moreover, in analyzing trial outcomes, all functional outcome data are missing after a participant dies. For statistical analysis, these data must somehow be inferred but may not be valid and lead to biased results. As a matter of fact, if functional outcome scores are reported as a value of zero after death, the function may be underestimated. On the other side, if functional data is imputed using the last observation of the functional value obtained before death, the function will be overestimated. Thereby, CAFS is a novel endpoint that evaluates function while appropriately accounting for missing data due to deaths in ALS. It ranks each subject according to their outcome, with worst outcome assigned to the subject who dies first in the study and the best outcome assigned to the subject who survives with the least functional decline. In general, combined endpoints are advantageous because they more comprehensively estimate the overall benefit of a particular treatment, allow simultaneous analysis of multiple equally important outcome measures without relying on multiple comparisons or co-primary endpoints that can dramatically increase sample size, cost and time to obtain significant effects on both outcomes, offer additional statistical power and appropriately adjust for missing data owing to deaths and drop-outs. It also provides a balanced analysis of a drug that may have disparate effects on function and survival resulting in an appropriately attenuated mean CAFS rank for the magnitude of treatment group differences. [25]

Muscle strength testing**.** There are three main measurement tools for muscle

strength. Firstly, it may be quantified using the composite manual muscle testing (MMT) scores, which usually involve averaging measures from multiple muscle groups using the Medical Research Council (MRC) muscle strength grading scale. Although there are alternative scales, as the Mayo Clinic Strength Scale, the MRC scale is the most widely used clinical strength scoring system, ranging from normal to the absence of contraction and has already been modified and improved [20].

It is useful for clinical monitoring but more rigorous and objective quantitative techniques are recommended for future clinical trials since MRC scale is non-linear and is particularly insensitive at detecting changes in mild weakness categories [10].

An additional quantitative method is hand-held dynamometry (HHD) which require minimal equipment, is rapid to perform and as comparable accuracy in weak muscles to the third measurement of muscle strength, the maximum voluntary isometric contraction (MVIC). Both HHD and MVIC provide relatively linear measurements at different muscle strengths. However, MVIC presents extensive equipment and training barriers that compromise its widespread application. MMT, HHD and MVIC demonstrate equivalent interrater reliability and reproducibility. [10]

In a longitudinal study, the sensitivity to progressive weakness favoured MMT as opposed to MVIC mainly because as MMT is a simple, fast and inexpensive measure, investigators were able to evaluate and score more muscle than with MVIC which required special equipment and considerable time. [20]

HHD may be an ideal balance between equipment and time costs and accuracy [10]. The simplest valid measure is often the best [20].

As an alternative to the assessment of strength in individual muscles, there is the Tufts Quantitative Neuromuscular Exam (TQNE) that includes measures of bulbar motor function, respiration, timed hand movements and isometric muscle force in the upper and lower extremities. This composite motor assessment has proven to be both a reliable and a responsive index of disease progression. However, the score does not correlate with the patient's perception of deterioration in physical health, which has implications for setting a MCID for clinical trials of ALS [20].

Efforts continue to be done in order to provide a more universal mean of assessing changes in muscle strength, remaining relatively independent of

examiner and patient factors such as baseline muscle strength.

Respiratory muscle strength testing. Respiratory muscle strength has been assessed in most major ALS trials using vital capacity, SNIP and MVV.

Vital capacity has been most thoroughly studied and has shown to decline by about 3% per month throughout much of the disease course. Its rate of decline is strongly correlated with survival, as would be expected given the close relationship between respiratory function and survival in ALS [19]. It can be measured through forced vital capacity (FVC), most commonly used, or slow vital capacity (SVC). A single FVC value obtained at baseline may serve as a clinically meaningful predictor of survival and disease progression [26]. Moreover, the decline in FVC seems to be linear in relation to the ALSFRS.[27] However, the accuracy of FVC measurement is highly dependent on the subject's effort and cooperation and on the coaching of the evaluator [26], requiring hermetic sealing around the mouthpiece [27]. Therefore, its main limitations are the lack of reliability in patients with bulbar or facial weakness as well as being affected by submaximal effort. It may also not be sensitive to detect mild to moderate respiratory muscle weakness and might be affected by chest wall or airway factors. Supine FVC may be more sensitive that routine seated FVC measurement [10].

Despite these limitations, FVC measurement has been established as a recommended test for clinical trials and an important standard of ALS management. It is mainly employed as a secondary outcome measure [19] and remains a routine measurement in clinical care [10].

Because FVC assesses inspiratory muscle strength and does not take into account the important prognostic role of expiratory muscles, additional measures, such as SNIP and maximum expiratory pressure, may be also needed to assess the global respiratory function of ALS patients. [26]

Maximum voluntary ventilation (MVV) is a less commonly used measure and assesses the total amount of air movements over a period of 12 s of deep and rapid breathing. As effort must be sustained, MVV reflects both respiratory muscle strength and endurance. It has not been well studied in ALS but it is suggested a rate of decline of about 4% per month based on a single longitudinal study. [19]

The sniff nasal inspiratory pressure (SNIP) is independent of facial muscle strength and consequently an alternative for respiratory test in ALS [27]. It is

measured during a brief, maximal inspiratory effort. Both SNIP and a related measure, maximal inspiratory pressure (MIP), are reduced and decline over time. They have been infrequently used in ALS trials, [19] even though SNIP is recommended as a noninvasive measure of respiratory muscle weakness, since it can be performed reliably by most ALS patients, including those with orofacial weakness and is more sensitive to change in respiratory muscle strength than FVC, predicting respiratory failure more accurately than VC and MIP. The latter, has the advantages of using portable equipment and being more sensitive to early respiratory weakness than FVC but shares its lack of consistency in patients with bulbar and facial weakness [10].

SNIP balances ease of recording, reliability and accuracy and hence might be the optimal approach [10]. Its increased sensitivity to show impaired respiratory function when compared with FVC measurements, is most likely due to the fact that it correlates well with diaphragmatic strength and other muscles important for inspiratory function such as sternocleidomastoid muscle. However, in an exploratory trial aimed to assess the feasibility of SNIP as an outcome measure in phase III clinical trials, there was evidences that SNIP measurements in ALS patients might not be as reliable as previously suggested, since it appears to exist a learning effect when repeated sniff maneuvers are performed, which affects mean SNIP values obtained over time and resulted in significantly less decline of its measurements when compared with FVC or ALSFRS-R. Until the optimal number of repeated measures in clinical trials is determined, SNIP measures in ALS patients should be used with caution in trials. [27]

Invasive techniques such as esophageal pressures are also accurate but impractical for regular use in the clinic [10].

Discussion

The transition from phase II to phase III trials with positive results has been challenging. The recurrent failures are probably attributable mostly to: a) the disease rarity and heterogeneity, which hamper the evaluation of drug effects; b) the limited knowledge of the exact pathways of neuron loss and the complexity of disease pathophysiology, meaning that a drug that only targets one of the pathogenic mechanisms will exert a small effect that easily can fail to be assessed in screening trials; c) uncertainty about safety and efficacy of

the delivery of the compounds to the CNS; d) lack of established animal models that faithfully recapitulate human pathology; e) flawed trial designs and f) lack of validated, sensitive outcome measures and disease biomarkers.

The choice of the outcome measures does definitely influence the conclusions obtained from clinical trials and this has been a recent topic of debate in ALS. Clinical trials should be conducted in order to detect changes felt to be clinically meaningful. A small effect as measured by a rating scale, even if statistically significant, may not be perceived as important either by the patients or physicians who care for them. Most of the negative results in clinical trials are due to the lack of statistical significance, which is explained by the reasons discussed previously. However, this does not mean that the obtained effect wouldn't have a significantly impact in patient's lives.

The MCID (minimal clinically important difference) was introduced by the Regulatory Authorities to ensure that a positive outcome in a clinical trial was meaningful for the patient and impactful as a measure of disease modification. The difference between treated and placebo groups should be both statistically significant and greater than the defined MCID. However, defining the MCID is not as easy as it may seem, especially in such an heterogeneous disease as ALS. As shown in table 2, for almost all therapeutic efficacy measures, MCID isn't defined yet.

Phase III trials in ALS frequently use survival as the primary outcome but this requires large sample sizes and long study durations. Furthermore, survival measures may be insensitive to potentially significant changes in functional status and patient selection criteria factors may skew the phenotypes of included trial participants and thereby influence survival data.

An alternative endpoint to survival is the use of functional measures. However, these measures often translate poorly into survival endpoints in phase III trials and although functional scales statistically predict survival, the correlation is not absolute.

A treatment that significantly improves survival in ALS would obviously be of great value, although, conversely, a treatment that improves measures as ALSFRS-R, MMT or MUNE without changing survival may be of limited value.

As one can infer from a cautious analysis of table 1, from the agents presented:

- riluzole proved to have an effect both clinically important and statistically significant;
- pioglitazone and lithium carbonate failed to prove to be effective and even showed a potential detrimental effect;
- the other agents tested actually showed small improvements in some of the key outcomes although not statistical significant.

The results of the analysis combining the three trials of riluzole showed that the median survival benefit during 18 month follow-up was approximately 2 months, when taking riluzole, 100mg, daily. However, there was no evidence that riluzole exerted a therapeutic effect on motor function, lung function, fasciculations, muscle strength or motor symptoms, neither a proof of its efficacy in the late stages of ALS.

In spite of its beneficial effects on survival, reservations on the clinical relevance of data observed with treatment of ALS with riluzole always persisted among the scientific community, especially due to the fact that the increase in survival obtained is less than the MCID established and due to the lack of concordance between the benefit on survival and the absence of benefit on functional scales. However, the failure to find any effect on functional endpoints does not affect the reliability of the survival results as the functional scales used have never been validated as a surrogate marker of survival. Nevertheless, there is no doubt that effects on functional endpoints, if established, would help to support the survival results – if the levels of statistical significance attached to the survival effects were marginal, this would have been an important point. However, the levels of statistical significance were sufficiently strong to stand on their own.

Concerning the agents that showed small improvements in some of the key outcomes, there are interesting debatable topics that can be exploited from the analyses of their results. Indeed, a difference of 2 points in ALSFRS-R global score at 9 months, favouring the therapeutic arm, as it was obtained in olesoxime clinical trial, represents a decline of the score 0.22 points/month slower in treated patients, which is greater than 20% reduction in the slope of the score defined as the MCID. Even though this effect wasn't sustained after 18 months' treatment, one should remember that an improved functional status during 9 months would be of great value in a disease with such poor prognosis as ALS. An even greater effect on the decline of ALSFRS-R was

obtained in talampanel's phase II trial. However, some authors state that phase II trials are too small to rule out false-positive error and are deemed positive often based on non-significant trends in the same endpoints ultimately employed in Phase III. ALS trialists often include multiple efficacy outcome measures in phase II trials, reasoning that these are secondary or exploratory outcomes that could support efficacy data, and then throw aside primary outcome measures in favour of promising secondary outcome measures, reporting and interpreting trends lacking statistical power. This increases the likelihood of carrying drugs forward to later phase trials that will ultimately fail.

Similar trends, although slightly smaller than the MCID established, in the slope of the ALSFRS-R were observed in ceftriaxone, rhEPO and UDCA clinical trials, which might suggest that those agents have a positive effect that was neglected and that could have had a significant impact even if just for a subpopulation of patients.

As far as differences in survival are concerned, one cannot exclude that these differences aren't the reflection of different rates of disease progression due to its known heterogeneity. Nevertheless, a 2% benefit of the estimated overall survival at 18 months (as seen in olesoxime CT) or 5% at 12 months' survival (as shown in rhEPO CT) shouldn't be easily placed aside since the rate of survival at 12 months within the natural history of the disease is slightly more than 50%.

Regarding muscle strength measurements, it is more difficult to infer which difference obtained would be clinically meaningful to the patient since they can assess muscle strength of different body segments, their progression with the natural history is not well characterized and they have a considerable degree of variability between clinical trials when used as key endpoints. No study has been performed linking a specific loss of strength to a change in a clinically meaningful activity. In addition, rate of decline in strength measures does not correlate with survival. In fact, respiratory muscle strength decline may occur at a different rate than decline in muscle strength in the extremities or face and this has dramatically different prognostic values. A 2-month delay, for 50% of the population (P50), at reaching <50% of predicted upright SVC or death, such the obtained with dexpramipexole, would mean that those patients would have a longer period free of respiratory complications, which are the main cause of death and of poorer quality of life.

Finally, and even though different questionnaires are used to assess Quality of Life (EUROQoL EQ-5D, SF-36, ALSAQ-5 or ALSAQ-40), these are valuable and reliable efficacy endpoints since they are subjective instruments and truly reflect what patients feel to be meaningful. A difference of 8 points favoring the treatment arm of a CT, as obtained with rhEPO, might be, even if statistically insignificant, an important difference considering the high morbidity of ALS.

The paucity of positive clinical trials results might suggest that outcome measures are failing to assess small treatment effects.

Conclusions

The majority of CT failures, as previously discussed, are due to lack of statistical significance, which almost invariably leads to a wrong interpretation of the results. In fact, contrary to the formal statistical methods for analysing clinical trial data, that are widely accepted by the medical community, the interpretation and reporting of trial results from the perspective of clinical importance has not received similar emphasis. There is a historical tendency to consider clinical trial results that are statistically significant as also clinically important, and conversely, those with statistically non-significant results as being clinically unimportant. The concept of the MCID may be applied to detect clinically important changes of clinical rating scales but the approach to determine it based on the subjective opinions of clinician experts may be neglecting the patients perspective, which should be considered in the determination of a MCID.

As important as determining MCID for survival and functional measures, which are undeniable the variants the researchers want to reach, a greater attention should be paid at Quality of Life Assessment Questionnaires as a key endpoint of efficacy on CT, given the significant morbidity of the disease.

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