

The Evolving Clinical Trial Landscape in Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis is a neurodegenerative disorder affecting predominantly central and peripheral motor neurons, resulting in progressive weakness and atrophy of voluntary skeletal muscle. The disease was originally described by Charcot and Joffroy (1869) but in spite of the extensive scientific knowledge accumulated to date, there is no effective therapeutic strategies. Clinical presentation, diagnostic criteria, traditional and evolving standards for trial design and the increasing importance of including quality of life and healthcare utilisation data in programmes provide the basis for a review.

Clinical Presentation

The onset of ALS is typically anatomically localised, with subsequent spread into other, usually contiguous body regions. The spinal forms (cervical, thoracic or lumbar) with involvement of the corresponding muscles are most common, comprising approximately 65% of cases. In bulbar forms, which accounts for 30% of cases, the disease starts by involvement of caudal groups of cranial nerves (IX–XII) with dysarthria and dysphagia as leading clinical signs. In 5% of patients, ALS begins aggressively with early respiratory failure.

ALS has heterogeneous phenotype expressed in terms of both clinical presentation (peripheral versus central; with or without cognitive impairment) and the various rate of progression. In more than 80% of patients, it is difficult to predict the rate of progression. The reasons for the heterogeneity of ALS are not yet clearly understood. The survival rates are variable; most patients die within an average time that ranges from two to five years, usually due to respiratory failure, but about 35% of patients will survive five years or more. Longer survival is associated with younger age at disease onset, upper motor neuron involvement and the presence of flail limb phenotype variant, whereas shorter survival is associated with bulbar or respiratory presentation at onset, presence of cognitive impairment and presence of neck flexor weakness. The heterogeneity in onset, presentation, and rates of disease progression have a direct impact on recommended methods of trial design.

The etiology of the disease has also proven to be highly complex, including mitochondrial dysfunction, aggregation of misfolded protein, oxidative stress, excitotoxicity, inflammation and apoptosis, involving both motor neurons and surrounding glial cells. The range of contributory pathophysiological mechanisms accounts for a diverse portfolio of products that have been targeted toward this disorder, and make one unifying hypothesis for disease causality uncertain.

Diagnostic Criteria

The El Escorial criteria help standardise diagnosis for clinical research studies¹. Patients are classified by the number of involved body regions (bulbar, cervical, thoracic and lumbar) as a clinically definite ALS (UMN and LMN signs present in three body regions); clinically probable ALS (UMN and LMN signs present in two

regions); laboratory supported probable ALS (UMN signs in one or more regions and LMN signs defined by electromyography in two regions). However, the El Escorial criteria have been evaluated in terms of impact on clinical trial entry by Traynor *et al*², who found that 44% of 388 patients later clinically diagnosed as having ALS would fail clinical trial entry at initial assessment. It was for these reasons that the Awaji set of diagnostic criteria were devised³. Overall, meta-analysis showed that the diagnostic sensitivity was increased when applying the Awaji criteria (81.1%) compared with the El Escorial Criteria (62.2%)⁴. Awaji criteria introduce a neurophysiological assessment in the diagnostic process, but it should be used in the context of clinical information, not as a separate, standalone set of data. It was suggested that this new set of interpretative guidelines, which essentially followed conventional clinical practice, would increase diagnostic sensitivity without major change in specificity⁵.

Selection of patients with ALS for participation in clinical trials is key to the potential success of the study, and necessitates recruitment of sufficient numbers and the exclusion of patients unsuitable to the patient population. In this indication, high dropout rates may be encountered for a variety of reasons related to disease progression in the context of a long-duration clinical trial. A balance may therefore be required between broader entry criteria to increase the number of eligible patients while maintaining an appropriate study population. The analysis of numerous studies in ALS has showed that enrolling people with better functional status may improve retention⁶. It also found that people with longer disease duration had better retention in ALS trials. The combination of longer disease duration and preserved functional status at enrolment represent a subgroup of people with slowly progressive disease. Enrolling people at early disease stages and with good functional status will not only improve retention in clinical trials, but will also increase the chances of seeing the biological benefits of treatments.

Clinical trials routinely exclude patients with other types of motor neuron disease, and do not characteristically enroll patients with hereditary forms of ALS because of age of onset, signs or symptoms which overlap with other neurodegenerative disorders, behavioural changes and very slow disease progression. A study with Edavarone⁷ has used a lead-in design of 12 weeks prior to randomisation, which was in accordance with a consensus viewpoint of designing and implementing clinical trials in ALS⁸.

Common Trial Design Features

Differences in the rate of disease progression can be accommodated by a design incorporating a lead-in period which provides an opportunity to establish a baseline for each patient, as well as a method of ascertaining the rate and extent of progression in individual patients⁹. Sufficient assessments during the lead-in period, frequently collected over a period of months, will potentially serve as a stratification factor or an eligibility criterion at the time of randomisation. Since differences between treatment groups in rates of disease progression affect trial sensitivity, only subjects with proven disease progression during the lead-in

period will be randomised into a double-blind placebo-controlled study.

The concept of basing patient randomisation upon a pre-baseline assessment of disease history or rate of progression is well-established for this indication and a variety of factors have been suggested prior to randomisation to account for prognostically important clinical variables influencing outcome. Criteria have been based upon location of anatomical onset (e.g., spinal versus bulbar onset), rate of clinical progression prior to randomisation such as through longitudinal application of the ALSFRS, treatment history, and electrophysiological assessments.

The length of published and potentially pivotal studies in ALS has ranged from nine to 76 months, as defined by time from start of study to primary endpoint reported. Assessment times post-baseline among studies vary – contingent upon the nature of the measure – and have included within clinic, remote, and within home assessments. Sample size/treatment arm have varied between ~100-470/group for industry sponsored, interventional studies with product registration as a primary objective.

How a Patient Functions, Feels and Survives

The effect of a new drug in clinical trials in subjects with ALS will be assessed in accordance with regulatory agencies' requests which include clinical endpoints such as survival, function, and strength measures. Improved survival, typically defined as survival without tracheostomy or permanent assisted ventilation, is an important objective for a proposed treatment in ALS, but obtaining meaningful change in these indices requires a longer trial duration, and increased sample size and cost.

Survival measures may also be insensitive to potentially significant changes in functional status. All of the major trials in ALS have included a functional scale as a primary or secondary endpoint. The revised ALS Functional Rating Scale (ALSFRS-R) is most commonly used, and evaluates symptoms related to bulbar, limb, and respiratory function. Rater credentialing, training, and surveillance mechanisms are routinely employed in multicentre trials with ALSFRS-R bulb slope and ALSFRS-R motor slope, together providing a better fit in survival modelling than ALSFRS-R slope as a single variable, and should be considered separately in future analyses of clinical decline, modified by spinal onset versus bulbar onset disease¹⁰.

Metric analysis of the ALSFRS-R has suggested that it may not be an ideal measure of global function¹¹. Composite primary measures, such as the Combined Assessment of Function and Survival (CAFS), have been proposed¹². The CAFS utilises a unique approach, by ranking patients' clinical outcomes by combining survival time and change in the ALSFRS-R.

Such composite endpoints may 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 treatment¹³.

The rate of ALS progression can be measured by respiratory function, which is usually a secondary outcome measure in clinical trials with new drugs, although examples exist in which respiratory assessments become of primary importance when the mechanism of action of the test agent is directed toward maintenance of respiratory function. The assessment is sensitive to the technique of administration, particularly patient positioning (e.g., supine versus sitting) and frequently the first clinical signs

of respiratory insufficiency in ALS are detected when lying down during sleep. Technician-related variables impact patient motivation and effort, and the need for central oversight regarding techniques is required. Supine spirometry should be performed using the same ATS/ERS criteria used for upright spirometry¹⁴, although usually requires extra effort either from patients or lab staff.

Quality of Life Measures

There are several measures used to assess patient quality of life (QoL) in amyotrophic lateral sclerosis (ALS)¹⁵. Generic measures which are not disease-specific but are nevertheless included within many studies are the SF-36, EUROQoL-5D, the McGill Quality of Life Questionnaire, and the Sickness Impact Profile. This latter measure (SIP) demonstrated statistically significant results in contrast to placebo in one pivotal study of IGF-I (myotrophin) in the treatment of sporadic ALS collected through the use of a third-party call centre, providing one of the first examples of using remote data ascertainment to facilitate patient and family compliance with protocol assessments¹⁶.

All QoLs can be self-administered (20 minutes for completion for each measure) but may be administered with the assistance of study site staff or independent staff who are not employed by study sites. Look-back periods vary from the present moment ("How do you feel today?") to four weeks ("Over the last month, which of these statements apply to you?"), and would be reflected in the resulting visit structure.

Two disease-specific questionnaires have been developed for ALS patients, the ALS-Specific Questionnaire-Revised (ALSSQoL-R) and the ALS Assessment Questionnaire (ALSAQ-40). The ALSSQoL was modified from the McGill QoL Questionnaire, the Schedule for the Evaluation of Individual Quality of Life (SEIQoL), the World Health Organization QoL (WHOQoL), and the Functional Assessment of Chronic Illness Therapy – Spiritual Well-Being 12 (FACIT-Sp-12). It addresses negative emotion, interaction with people and the environment, intimacy, religiosity, physical symptoms, and bulbar function. The ALSSQoL has a look-back period of seven days and can be administered on paper or via computer. It takes 15-20 minutes to complete. The ALS Assessment Questionnaire (ALSAQ-40) addresses physical mobility, activities of daily living and independence, eating and drinking, communication, and emotional reactions. There is also a shortened, five-question version of this assessment, the ALSAQ-5. It has a look-back period of two weeks.

The most popular is ALSAQ-40, specifically used to measure the subjective wellbeing of patients with amyotrophic lateral sclerosis¹⁷. It is brief and easy to complete so benefits from an excellent response rate and has undergone rigorous testing for validity, reliability and sensitivity to change and has been shown to be a robust tool for assessing ALS. It was successfully used in the edavarone⁷ study, the first "positive" ALS study in the 21st century, which showed a significant difference in score between active and placebo groups.

Healthcare Utilisation

Changing dynamics of product development across therapeutic areas, and particularly for those illnesses with significant healthcare expenditures, require that budget impact or cost-effectiveness data be prospectively collected during a registration programme. At the time of approval, a product becomes 'available' but not 'accessible', in the absence of information that attests to product value. Methods of acquiring these data



occur either through ‘piggybacking’ outcomes on top of a registration programme, or creating a complementary standalone observational research programme during registration, including representative sites and patients.

The healthcare cost for amyotrophic lateral sclerosis (ALS) within the United States as an example also exhibits variations in coverage and reimbursement, which influence the type and extent of data that are needed. For example, in 2010 the average direct non-medical costs (self and other paid) for ALS were \$17,889 and predicted mean family weighted loss of income was \$62,996¹⁸. Among ALS patients, Medicare (66%), private insurance (17%), Military or VA insurance (9%), and Medicaid (2%) pay for these services¹⁹. Each will differentially weight budget impact versus cost-effectiveness analyses.

For patients that are likely eligible for clinical development programmes, reimbursable payments that might be captured include equipment rental, in-home care, in-hospital expenses, nutritional supplementation, physician visits outside of those associated with protocol, and outpatient facility expenses for various supportive therapies. All become a necessary part of compendia created to inform “product value” at the time of market authorisation.

REFERENCES

- Brooks BR, Miller RG, Swash M, Munsat TL (2000). El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord*, 2000;1:293-299.
- Traynor et al. Clinical features of amyotrophic lateral sclerosis according to the El Escorial and Airlie House diagnostic criteria: a population-based study. *Arch Neurol*. 2000;57(8):1171-1176.
- Carvalho MD, Swash M (2009). Awaji diagnostic algorithm increases sensitivity of El Escorial criteria for ALS diagnosis. *Amyotroph Lateral Scler*, 2009;10:53-57.
- Costa J. et al. Awaji criteria for the Diagnosis of Amyotrophic Lateral Sclerosis. *Arch Neurol*. 2012;69(11):1410-1416.
- Carvalho MD, Dengler R, Eisen A, et al. Electrodiagnostic criteria for diagnosis of ALS. *Clin Neurophysiol*. 2008;119(3):497-503.
- Atassi N. et al. Analysis of start-up, retention, and adherence in ALS clinical trials. *Neurology* 2013;81:1350-55.
- The Writing Group* on behalf of the Edaravone (MCI-186) ALS 19 Study Group† Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol*, Published online 15 May 2017.
- Leigh PN et al. Amyotrophic lateral sclerosis: a consensus viewpoint on designing and implementing a clinical trial. *ALS and other motor neuron disorders* 2004 5, 84–98
- de Carvalho M, Swash M. Can selection of rapidly progressing patients shorten clinical trials in amyotrophic lateral sclerosis? *Arch Neurol*. 2006 Apr;63(4):557-60.
- Rooney J et al. What does the ALSFRS-R really measure? A longitudinal and survival analysis of functional dimension subscores in amyotrophic lateral sclerosis.
- Franchignoni F et al. Evidence of multidimensionality in the ALSFRS-R scale: a critical appraisal on its measurement properties using Rasch analysis. *J Neurol Neurosurg Psychiatry* 2013;84:1340–1345.
- Berry JD, et al. The Combined Assessment of Function and Survival (CAFS): a new endpoint for ALS clinical trials. *Amyotroph Lateral Scler Frontotemporal Degener* 2013;14:162–168.
- Simon NG et al. Quantifying Disease Progression in Amyotrophic Lateral Sclerosis. *Ann Neurol* 2014;76:643–657
- Miller MR et al. Series ATS/ERS TASK FORCE: Standardisation of lung function testing. *Eur Respir J* 2005; 26: 319–338
- Simmons Z. Patient-Perceived Outcomes and Quality of Life in ALS. *Neurotherapeutics* (2015) 12:394–402.
- Lai EC, Felice KJ, Festoff BW, Gawel MJ, Gelinas DF, Kratz R, Murphy MF, Natter HM, Norris FH, Rudnicki SA. Effect of recombinant human insulin-like growth factor-I on progression of ALS. A placebo-controlled study. The North America ALS/IGF-I Study Group. *Neurology*. 1997 Dec; 49(6):1621-30.
- Jenkinson C, et al. Evidence for the validity and reliability of the ALS assessment questionnaire: the ALSAQ-40. *Amyotroph Lateral Scler Other Motor Neuron Disord* 1999; 1: 33–40.
- Obermann M, Lyon M. Financial cost of amyotrophic lateral sclerosis: a case study. *Amyotroph Lateral Scler Frontotemporal Degener*. 2015;16(1-2):54-57.
- The Lewin Group. Cost of Amyotrophic Lateral Sclerosis, Muscular Dystrophy, and Spinal Muscular Atrophy in the United States. 2012.

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