Use of clinical staging in amyotrophic lateral sclerosis for phase 3 clinical trials

Rubika Balendra, Ashley Jones, Naheed Jivraj, I Nick Steen, Carolyn A Young, Pamela J Shaw, Martin R Turner, P Nigel Leigh, Ammar Al-Chalabi

ABSTRACT

Objectives The use of clinical staging in the fatal neurodegenerative disease amyotrophic lateral sclerosis would have value in optimising future therapeutic trials. We aimed to use previous clinical trial data to determine the length of time patients spend in each of four proposed stages, its range and transition patterns to subsequent stages.

Methods Using databases from two multicentre clinical trials, patients were retrospectively staged through the trial course. At each stage we assessed whether patients then progressed to an earlier, consecutive or later stage or death. Duration spent in each stage before progression to a later stage was calculated.

Results There were 725 patients. No patients moved to an earlier stage. More patients at stages 1, 2 and 3 progressed to the consecutive stage rather than skipping a stage. 59.3% of patients at Stage 1 progressed to Stage 2, 54.0% of patients at Stage 2 progressed to Stage 3, 42.3% of patients at Stage 3 progressed to Stage 4 and 47.0% of Stage 4 patients progressed to death. Transition times between stages had a median duration of 3 to 7 months for stages 2 to 4.

Discussion We have shown using trial data that transition times between stages are short. Use of stage duration as an endpoint might allow a shorter trial duration. We have shown face validity in this system as most patients progress through consecutive stages, and none revert to earlier stages. Furthermore, we have shown the system is reliable across populations and therefore has content validity.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive, fatal neurodegenerative disorder affecting upper and lower motor neurons.1 We have previously proposed a clinical staging system for ALS which has been partially validated in a population of 1459 patients with ALS from King’s College Hospital.2 There are four stages, the first three stages defined by functional involvement of regions equivalent to those used for El Escorial classification: bulbar, upper limbs and lower limbs, with functional involvement defined as dysphagia, dysarthria, spasticity, weakness or wasting (table 1). The number of regions involved gives the stage. Stage 4 is reached if swallowing (4A) or respiratory (4B) difficulty is severe enough to require intervention.

Clinical stage defined in this way is simple to apply and has several useful properties. First, each stage tends to be reached on average at a consistent proportion of the way through the disease (with Stage 1, symptom onset, anchored at disease proportion 0, and Stage 3, death, anchored at disease proportion 1), so that Stage 2 is reached on average 0.38, Stage 3, 0.61, Stage 4A, 0.77 and Stage 4B, 0.80 through the disease. Second, stages would be expected to only occur in order, without reversion to earlier stages. It is possible to skip stages but only forwards. Third, clinical stage correlates well with overall functional scores derived from the Revised ALS Functional Rating Scale (ALSFRS-R), the Hospital Anxiety and Depression Scale (HADS) and the EQ-5D scale measuring quality of life and health utility.3 Fourth, since the disease progresses at greatly varying rates between individuals with ALS,5 6 direct meaningful comparisons between patients at equivalent stages can be made regardless of rate of disease progression. Fifth, clinical trials can usefully examine change in functional scores against clinical stage, providing a method for the evaluation of drug effects on function.

A further useful property would be the ability to use clinical stage as a secondary endpoint in clinical trials. An effective drug would be expected to prolong time in earlier stages compared with later stages. This is particularly important since simply prolonging life in a late stage of ALS is not desirable, so a method to demonstrate objectively the point at which a drug is effective is essential.

We therefore used information from two Phase 3 clinical trials of drug therapies in ALS to determine the length of time patients spent in each clinical stage, its range and the transition patterns to subsequent stages.

METHODS

Data sources

Databases of ALS patients who had participated in the Mito Target clinical trial, a double-blind randomised placebo-controlled parallel group trial of oleosome in ALS,6 and the LiCALS clinical trial, a double-blind randomised placebo-controlled parallel group trial of lithium carbonate in ALS,7 8 were analysed. The LiCALS study was ethically approved by the South East Research Ethics Committee, with the reference number 09/H1102/15 (EudraCT number: 2008-006891-31). The Mito Target study was ethically approved by the Comité de Protection
Table 1  Definition of stages

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Functional involvement of one CNS region (symptom onset)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Functional involvement of two CNS regions</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Functional involvement of three CNS regions</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Need for gastrostomy (4A) or non-invasive ventilation (4B)</td>
</tr>
<tr>
<td>Stage 5</td>
<td>Death</td>
</tr>
</tbody>
</table>

CNS, central nervous system.

Determination and analysis of clinical stage

Because clinical stage was not recorded prospectively in these trials, we estimated clinical stage using an algorithm based on the ALSFRS-R. Estimated stage based on the algorithm correlates about 92% with actual clinical stage in other data sets (unpublished data) and clinical stage can be reliably estimated using the ALSFRS-R in historical data and in current data where stage has not been recorded. The ALSFRS-R is a scale consisting of 12 questions each scored from 0 to 4, representing the domains of swallowing and speaking functions, upper limb function, lower limb function, use of gastrostomy and respiratory function with higher scores representing better function.10 Actual dates of gastrostomy insertion and of commencement of non-invasive ventilation were also available and used as a proxy measure for Stage 4. We previously defined Stage 2A as diagnosis and Stage 2B as functional involvement of a second region, but since people entering a trial must have been diagnosed, everyone would be at Stage 2A at least, and this would mean that Stage 1 would be redundant. Furthermore, 2A and 2B occur at similar standardised times through the disease course. We therefore discarded Stage 2A and simply used Stage 2, defined as functional involvement of a second central nervous system region (previously Stage 2B) for the purposes of this study. At each disease stage we assessed whether patients subsequently progressed to an earlier, consecutive or later stage, or did not move from their stage by the end of the trial study period.

Median duration spent in each stage before progression to a later stage was calculated for the entire cohort. The clinical trial databases only capture data from time of trial recruitment, not from disease onset, and since people can only be recruited after diagnosis, which in our previous work corresponded closely in timing with Stage 2,2 we would expect that this retrospective allocation to clinical stage would result in an apparent increase in the duration spent in Stage 1. To assess this possibility, the subset of patients at King’s College Hospital enrolled in the LiCALS trial, for whom data were available preceding the time of recruitment, was separately analysed using the actual timing of Stage 2 based on information from the full medical record. We calculated median duration spent in Stage 1 according to these patients’ medical notes and compared this to duration according to the clinical trial.

Statistical analysis

Baseline characteristics of the two databases were compared using Student t test for averages, and Pearson’s χ² test for discrete variables. Data for duration at each stage in bulbar-onset and limb-onset patients was not parametrically distributed and did not normalise with transformation, therefore was compared using a Mann–Whitney U test. Analyses were performed in SPSS V20.0 (SPSS Inc, Illinois, USA).

RESULTS

There were 725 patients, 511 in the Mito Target trial database and 214 in the LiCALS trial database (table 2).

Comparing the Mito Target population to the LiCALS population, age of onset was younger (p=0.008), diagnostic delay shorter (p=0.007) and follow-up time shorter (p=0.025) in the Mito Target group. The LiCALS study had a higher proportion of patients who died than the Mito Target study (Pearson χ²=17.0, p=3.8×10⁻⁵).

Over the course of follow-up, the total numbers of patients who reached each clinical stage were as follows: all 725 patients reached Stage 1 (by definition), 430 patients reached Stage 2, 463 patients reached Stage 3, 302 patients reached Stage 4 and 260 patients reached Stage 5 (death).

Of the total numbers of patients who reached stages 1, 2 and 3, more progressed to the consecutive stage at further assessment rather than skipping a stage or not moving from their stage by

Table 2  Baseline characteristics of LiCALS and Mito Target databases

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>LICALS database</th>
<th>Mito target database</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country/region of origin</td>
<td>UK</td>
<td>Europe</td>
</tr>
<tr>
<td>Patient numbers</td>
<td>214</td>
<td>511</td>
</tr>
<tr>
<td>Age of onset in years</td>
<td>58.0 (56.6 to 59.5)</td>
<td>55.6 (54.6 to 56.6)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>148 (69.2%)</td>
<td>66 (30.8%)</td>
</tr>
<tr>
<td></td>
<td>331 (64.8%)</td>
<td>180 (35.2%)</td>
</tr>
<tr>
<td>Site of onset</td>
<td>Limb</td>
<td>Bulbar</td>
</tr>
<tr>
<td></td>
<td>168 (78.5%)</td>
<td>46 (21.5%)</td>
</tr>
<tr>
<td></td>
<td>406 (79.5%)</td>
<td>100 (19.5%)</td>
</tr>
<tr>
<td>Duration from symptom onset to diagnosis in months</td>
<td>10.9 (10.0 to 11.7)</td>
<td>9.7 (9.1 to 10.3)</td>
</tr>
<tr>
<td>Follow-up time post disease onset in months</td>
<td>34.1 (32.8 to 35.4)</td>
<td>32.3 (31.4 to 33.2)</td>
</tr>
<tr>
<td>Number of deceased patients in cohort</td>
<td>101 (47.1%)</td>
<td>159 (31.1%)</td>
</tr>
</tbody>
</table>

Values are expressed as Mean (95% CI) or Number (% of total).
the end of the study period (table 3). No patients moved to an earlier disease stage. For example, of all the 430 patients who reached Stage 2 during the course of follow-up, none moved to Stage 1, 54% were found to progress to the consecutive stage (Stage 3) at further assessment, 17% were found to progress to Stage 4 (and skipped Stage 3) at further assessment, 5.3% progressed to death (skipping Stages 3 and 4) and 23.7% did not move from Stage 3 during the rest of the follow-up period.

Duration spent in each stage
Median duration of time spent in any stage was 10.9 months (95% CI 10.4 to 11.4 and IQR: 5.4–17.7). Median durations of time spent in each stage until progression to a later stage were Stage 1: 18.1 months (95% CI 17.4 to 18.5, IQR: 12.8–25.6), Stage 2: 5.5 months (95% CI 4.1 to 5.9, IQR: 2.8–8.8), Stage 3: 6.7 months (95% CI 6.0 to 8.1, IQR: 3.9–10.8), Stage 4A: 5.9 months (95% CI 4.6 to 7.6, IQR: 2.6–9.9) and Stage 4B: 3.2 months (95% CI 2.5 to 4.1, IQR: 1.6–5.8) (figure 1).

We also performed a subset analysis, comparing duration at each stage in limb-onset and bulbar-onset patients. Bulbar-onset patients had a significantly longer duration for transition from Stage 4A to death (8.4 months, 95% CI 5.9 to 11.0, IQR: 5.4–11.6) compared to limb-onset patients (4.5 months, 95% CI 2.4 to 6.2, IQR: 1.4–8.3, p=2.5×10⁻⁶). Durations at other stages were similar across both groups.

There were dates available for Stage 2 from the King’s College Hospital medical notes and from the LiCALS clinical trial for four patients. Median duration in Stage 1 was 15.9 months (IQR 11.4–22.1) according to the medical notes and 22.1 months (IQR 14.7–33.1) according to the clinical trial for these patients, suggesting that the clinical trial data estimate of the timing of Stage 2 is later than the true timing.

DISCUSSION
We have shown in clinical trial data that transition times between clinical stages are short with a median duration of 3 to 7 months for stages 2–4 and could therefore be used as trial endpoints. We have shown face validity in this system by confirming in 725 people that no reversion to earlier disease stages occurred and that most people progressed to the consecutive stage. Furthermore, we show the system is reliable across populations, and therefore has content validity.

Clinical trials in ALS usually use death as an endpoint, based on differences in survival between the treatment and placebo arms.11–14 As a result, they are typically two or more years in length, because an 18-month follow-up is required to have sufficient power to identify an effect on a survival endpoint.15 Use of clinical stage duration or timing as a secondary endpoint might allow a shorter trial duration, with benefits in improving the time between drug development and drug approval, a reduction in drug development costs and a reduction in exposure of patients to potentially harmful drugs.16 Furthermore, the use of survival as an endpoint, while attractive as an objective ‘hard’ measure of success, does not answer the question of whether benefit is gained by simply prolonging the end stage of ALS or improving survival at earlier stages, when quality of life is higher.17 Analysis of the duration spent in each stage, as a secondary endpoint, would allow this distinction to be made.

Confirmation that reversion to earlier stages does not occur in this staging system is important for validation, since the natural history of ALS is one of relentless progression,4–17 so any system for describing disease stage should reflect that. In other suggested staging systems, such as the ALS Milano Torino Staging System18 reversion, while rare, was noted. In further contrast, our staging system is not defined by a functional scale (although it can be estimated from the ALSFRS-R), and so any measurement of function is a true reflection of the relationship between stage and function, rather than being defined by it.

There are limitations to this study. First, clinical stage was not collected prospectively, but was estimated from ALSFRS-R. Because the algorithm used generates results that correlate well with actual stage, this is unlikely to significantly impact results. Second, although ALSFRS-R was collected prospectively, it was collected at 3-monthly intervals during the trial and only once the trial had started. As a result, the resolution for estimating duration in each stage is 3 monthly at best. Despite assessments being conducted at only 3-monthly intervals, the CIs for stage durations

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Proportion of patients moving to each disease stage from the stage in the left column</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients reaching this stage during the course of follow-up</td>
<td>Proportion moving to Stage 1 (%)</td>
</tr>
<tr>
<td>Stage 1 725</td>
<td>N/A</td>
</tr>
<tr>
<td>Stage 2 430</td>
<td>0</td>
</tr>
<tr>
<td>Stage 3 463</td>
<td>0</td>
</tr>
<tr>
<td>Stage 4 302</td>
<td>0</td>
</tr>
</tbody>
</table>

More patients at stages 1, 2 and 3 progressed to the consecutive disease stage than progressing to any other disease stage. N/A, Not applicable. The bold text refers to transition to the next consecutive stage.

![Figure 1](http://jnnp.bmj.com/) Box plot of duration in months spent at each disease stage representing median, IQR and range of values at each stage.

The time between drug development and drug approval, a reduction in drug development costs and a reduction in exposure of patients to potentially harmful drugs. Furthermore, the use of survival as an endpoint, while attractive as an objective ‘hard’ measure of success, does not answer the question of whether benefit is gained by simply prolonging the end stage of ALS or improving survival at earlier stages, when quality of life is higher. Analysis of the duration spent in each stage, as a secondary endpoint, would allow this distinction to be made.

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are narrow and all within a 3-month period, providing validity for these transition times.

A prospective study with a shorter duration between study visits may reveal that transition time between stages is shorter. Timing of stages could probably be determined with 1-week precision and certainly within a month, as most patients can state fairly precisely when an arm or a leg is affected, or when swallowing or speech is affected. Furthermore, duration spent in Stage 1 is difficult to estimate accurately since information to estimate transition to Stage 2 was only collected after enrolment to the trials which occurs after diagnosis. We have previously shown that diagnosis tends to occur at the same time as Stage 2, suggesting that duration in Stage 1 is artefactually long in this study which we have confirmed in a subset of patients from King’s. At the first trial visit, the date of disease onset (Stage 1) is taken from the patient’s clinical history and is usually documented in the patient’s existing clinical notes. There may be an element of recall bias of this exact date, although patients can usually remember reasonably precisely when they first noticed limb involvement and speech or swallowing problems.

A limitation of this clinical trial data set is that only patients fulfilling the revised version of the El Escorial World Federation of Neurology diagnostic criteria with a clinical diagnosis of laboratory supported-probable ALS, probable ALS and definite ALS were included in both trials, which will result in a bias towards individuals in Stage 3 (the minimum stage possible for someone with El Escorial Definite ALS). However, this is a common requirement for clinical trials, and the results are therefore valid for a clinical trial population. In addition, patients with earlier disease stages are well represented in this study. Due to inclusion criteria, a clinical trial database may not be fully representative of a general ALS population, but we have previously demonstrated application of the same staging criteria to a general ALS patient population and the objective of this study was to apply staging to clinical trial data. The strengths of the large clinical trial data set used in this analysis include the involvement of ALS patients from multiple countries and different ALS centres (in the case of this study, 5 countries and 23 separate ALS centres), blinded, frequent and standardised clinical assessments and prospective and standardised methods for data collection. Therefore, this large study using actual clinical trial data suggests that prospective collection of clinical stage, ideally with actual transition dates, would be a useful addition to clinical trial protocols and could usefully provide an effective secondary endpoint. Staging data in a clinical trial would help to ascertain whether therapeutic benefit is gained in the earlier stages of disease when quality of life, function and survival are most favourable, or whether in fact benefit is gained in the later stages of disease when disability levels are high and quality of life is low.

ALSFRS-R is commonly used as a secondary endpoint in clinical trials. While the ALSFRS-R gives a cumulative score measuring functional disability, the staging system describes the pathological spread of disease. Thus, a patient with Stage 2 disease and another with Stage 3 disease could both obtain an identical score on the ALSFRS-R, despite the first patient being on average 40% through their disease course and the second being on average 60% through their disease course. Staging can be used as a complementary measure to the ALSFRS-R to provide additional information about a patient’s disease burden during the course of a clinical trial.

Disease progression in ALS has been shown to be curvilinear, with the most rapid progression occurring in the early and late stages of the disease. Our analysis supports this partly, at least for the later stages of the disease, with the shortest stage being 4B at 3 months (the resolution of the study) and we did not show rapid progression in the first stage of disease, with Stage 1 being the longest stage. Transition from Stage 4A to death is longer in bulbar- compared to limb-onset patients. Malnutrition is a poor prognostic factor in ALS and the main cause of this is dysphagia, with other causes including reduced upper limb dexterity, psychological factors and the hypermetabolic state of ALS. Dysphagia tends to worsen over time, and patients with bulbar-onset disease become more impaired by this symptom than those with limb-onset disease.

Intervention with gastrostomy is recommended when there is progression of dysphagia and weight loss, to improve caloric and fluid intake, leading to weight stabilisation or gain. Patients with bulbar-onset receive this earlier than those with limb-onset.

No randomised controlled trials of gastrostomy versus oral feeding in ALS have been carried out although some studies have reported a survival advantage with gastrostomy insertion. The longer transition time from Stage 4A to death in this study may be explained by bulbar-onset patients having a more prolonged survival after gastrostomy compared to limb-onset patients. A retrospective study also showed a longer median survival time after gastrostomy in patients with bulbar-onset compared to limb-onset disease, which did not reach significance. The decision to accept gastrostomy is one of the most difficult for ALS patients and the procedure is commonly delayed as a result, so that this observation might provide useful evidence to support gastrostomy as soon as possible in those with bulbar-onset disease. Importantly, our results also suggest that there may be a difference in disease course between limb-onset and bulbar-onset patients apparent in the later stages of disease. This sort of analysis is not possible without a staging system, further underlining the importance of a simple, effective method for classifying disease stage.

We have shown that transition times between stages are short in clinical trial data. The key benefit is that by examining time spent in each clinical stage, a drug trial would be able to show whether an effective ALS therapy acted in early, late or all stages. Clinical staging is likely to be a useful addition to clinical trial designs, may be an effective trial endpoint and can reveal features of phenotypic differences not otherwise apparent.

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Competing interests PJS is supported by an NIHR Senior Investigator award. INS: Grant income from MND Association (MND Association); PNL: Consultancy to Biogen Idec and Cytokinetix Inc., Cytokinetix Inc; PNL: Consultancy to Biogen Idec, Cytokinetix Inc; PNL: Consultancy to Biogen Idec and Cytokinetix Inc; PNL: Consultancy to Biogen Idec and Cytokinetix Inc; CAY: Personal payments: Consultancy to Biogen Idec and Cytokinetics Inc; royalties from the book, The Brain (Oneworld Publications) and Complex Disease in ALS; JF: Personal payments: Consultancy to Biogen Idec and Cytokinetix Inc; PNL: Consultancy to Biogen Idec and Cytokinetix Inc; PNL: Consultancy to Biogen Idec and Cytokinetix Inc.

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Ethics approval The LiCALS study was ethically approved by the South East London Psychiatry, Nursing and Midwifery Research and Ethics Subcommittee, reference 09/H1102/15 (Eudract number: 2008-006891-31). The Mito Target study was ethically approved by the Comité de Protection des Personnes Ile de France VI—GH Pitié Salpêtrière with the reference number 122-08 (Eudract 2008-007320-25). This study was classified as a secondary analysis of fully anonymised pre-existing clinical trial data by the King’s College London Psychiatry, Nursing and Midwifery Research and Ethics Subcommittee and therefore did not require ethical approval.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The anonymised data from the LiCALS trial will be available from the MNDA database.

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