Can Selection of Rapidly Progressing Patients Shorten Clinical Trials in Amyotrophic Lateral Sclerosis?

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Background: The marked variability in progression of amyotrophic lateral sclerosis (ALS) requires large numbers of patients to detect a significant effect in current clinical trial designs.

Objective: To test the utility of a lead-in period to assess rate of progression so that patients with rapidly progressive ALS can be selected for subsequent clinical trials.

Design: Prospective study.

Setting: The ALS Center, University of Lisbon, Lisbon, Portugal.

Patients: Fifty-seven consecutively recruited patients assessed at diagnosis and 3 months later (end of lead-in period).

Interventions: Change in ALS Functional Rating Scale (ALS-FRS) score was analyzed to establish a statistically significant cutoff point to define patients with rapid (group 1) or slow (group 2) progression. Patients from both groups were reexamined 1 and 3 months after the lead-in period.

Main Outcome Measures: Changes in ALS-FRS score, motor unit number estimation, and neurophysiologic index, and resultant grouping of patients according to rate of progression at 1 and 3 months.

Results: Both the 80th percentile and 2 SDs above the mean of the change in ALS-FRS score identified the same patients. Twelve patients showed rapid progression (group 1) and 45 showed slow progression (group 2). One month after the lead-in period there was a significant reduction in ALS-FRS score, motor unit number estimation, and neurophysiologic index in group 1, and after 3 months all these measurements changed significantly in both groups.

Conclusions: This strategy of selecting patients with rapidly progressing ALS for inclusion in exploratory, short phase II clinical trials offers substantial savings in costs and time, and could accelerate the process of testing potentially useful drugs for the treatment of ALS.

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Amyotrophic lateral sclerosis (ALS) is an inevitably progressive disease, but the individual rate of clinical deterioration is quite variable. Prognostic indicators include the clinical presentation (worse for respiratory or bulbar onset), age at symptom onset (better for young patients), delay from first symptom to entering an ALS clinic (a shorter delay meaning more rapid progression), rate of change in scores on the Appel ALS Rating Scale or the ALS Functional Rating Scale (ALS-FRS), forced vital capacity at diagnosis and rate of change in respiratory function, decline in muscle strength measured by maximal voluntary isometric contraction or manual muscle testing, and reduction in motor unit number estimation (MUNE). These considerations suggest that selection of patients with rapid progression might provide a more homogeneous patient population for entry into clinical trials. It is notable that neurophysiologic studies have not been applied as an end point in trials.

There are 2 implications in the identification of a population of patients with ALS with rapid progression. First, observations can be made at shorter intervals, since the rate of change is more rapid. Second, exploratory phase I-II clinical trials could be performed in relatively short periods, as the fast clinical decline and relatively homogeneous population involved implies that a relatively small number of patients would be needed to detect a treatment-related change in progression of the disease. We have previously shown that 2 neurophysiologic measurements, MUNE

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and the neurophysiologic index (NI), are correlated with ALS-FRS and sensitive in evaluating progression in an unselected group of patients with ALS.\(^6\)\(^7\) Each of these measurements showed significant change at 3 months, but not at 1 month.\(^7\) We therefore studied the potential utility of using change in ALS-FRS score in a 3-month lead-in period to select patients with rapid disease progression into phase II clinical trials designed to test drug efficacy. We reasoned that selecting patients with rapidly progressing disease for phase II trials of ALS would allow a much shorter trial duration than current trial designs, thus reducing the financial costs to sponsors and the social cost to patients and caregivers.

Figure. Flowchart of the study design. ALS indicates amyotrophic lateral sclerosis; ALS-FRS, ALS Functional Rating Scale; MUNE, motor unit number estimation; and NI, neurophysiologic index.

METHODS

Fifty-seven consecutively recruited patients (29 men and 28 women; mean age, 61.1 years; range, 32-78 years) with ALS were studied prospectively. The mean disease duration from first symptom to study entry was 16.4 months (range, 2-63 months). Full diagnostic workup was performed.\(^6\) Patients with other conditions, eg, diabetes mellitus, polyneuropathy, and ulnar nerve entrapment, were excluded. At study entry, 42 patients had probable ALS and 15, definite ALS.\(^8\) Forty-four had spinal onset; were excluded. At study entry, 42 patients had prob-

The rapidly progressing group (group 1) contained 12 patients, in whom the ALS-FRS declined more than 8.78% in the 3-month lead-in period. There were 7 women and 5 men in this group (mean age, 59 years; range, 47-69 years) with a mean disease duration of 8.3 months (range, 2-20 months). Eight had spinal-onset and 4 had bulbar-onset ALS. Eight had probable and 4, definite ALS. In these 12 patients, the strength of the abductor digit minimi in at least one hand was greater than 2 on the Medical Research Council scale, and forced vital capacity at the end of the 3-month lead-in period was greater than 60% of predicted. All were taking riluzole. The other 45 slower-progressing patients formed group 2 (Figure).

All patients from group 1 were reexamined clinically 1 and 3 months after the end of the lead-in period (Figure; times 1 and 3, respectively). Of the 45 patients included in group 2, 21 were reexamined at the same times (Figure). The patients in group 2 who were not followed up were living at a distance from the hospital, and their slower rate of progression did not motivate them to attend. We established that there was no difference in age at onset, disease duration, ALS-FRS score at entry, or percentage change in ALS-FRS score during the lead-in period (P>.1) between patients who continued into the second phase of the study as group 2 and those who elected not to continue.

NEUROPHYSIOLOGIC FOLLOW-UP STUDIES

Observations were made 1 and 3 months after the conclusion of the lead-in period by the same evaluator (M.deC.) using the ALS-FRS score, MUNE, and NI. For MUNE measurements we used the incremental technique in this study.\(^9\) The NI is derived from conventional neurophysiologic measurements, including M-wave amplitude, distal motor latency, and F-wave frequency, in the ulnar territory. This index is calculated from the following formula\(^7:\)

\[
\text{NI} = \left(\frac{\text{M-Wave Amplitude}}{\text{Distal Motor Latency}}\right) \times \left(\frac{\text{Percentage of F-Wave Responses per 20 Stimuli}}{\text{Percentage of F-Wave Responses per 20 Stimuli}}\right)
\]

Both right and left ulnar nerve–abductor digit minimi nerve–muscle systems were studied in each subject, using a standardized protocol. At the first investigation, standard ulnar nerve conduction studies were performed below and across the elbow to exclude ulnar nerve entrapment. Ulnar nerves were stimulated bilaterally at the wrist (7 cm proximal to the G1 electrode) using supramaximal stimuli, and motor responses were recorded from both abductor digit minimi muscles with surface electrodes (belly-tendon montage). F-wave frequency was determined from 20 consecutive supramaximal stimuli at 1 Hz; a peak-to-peak deflection from baseline of at least 40 μV was accepted as an F wave. At each visit the M-wave amplitude (peak to peak), F-wave frequency, NI, and MUNE were studied in both hands.\(^6\)\(^7\) The mean value from both hands was calculated for each patient at each session. The temperature of the investigated limb was kept at or above 32°C.

STATISTICAL METHODS

Between-group comparisons were made with the Mann-Whitney test. Data from the longitudinal evaluations in each group were compared by means of the Wilcoxon signed rank test. Differences were considered significant at the P<.01 level.

ETHICS

The Local Research Ethics Committee at the Faculty of Medicine, University of Lisbon, Lisbon, Portugal, approved the study. Each subject gave informed consent to the protocol. All the patients included were followed up at the ALS Center in Lisbon.
Table. Results of Testing and Estimated Sample Sizes to Detect Changes*

<table>
<thead>
<tr>
<th>Time</th>
<th>ALS-FRS</th>
<th>MUNE</th>
<th>NI</th>
<th>ALFS-RS</th>
<th>MUNE</th>
<th>NI</th>
</tr>
</thead>
<tbody>
<tr>
<td>After 3-mo lead-in†</td>
<td>29.58 (2.84)</td>
<td>58.11 (59.32)</td>
<td>2.11 (1.75)</td>
<td>32.19 (5.06)</td>
<td>48.79 (42.89)</td>
<td>2.56 (1.69)</td>
</tr>
<tr>
<td>1 mo after end of lead-in</td>
<td>28.67 (2.81)</td>
<td>58.69 (55.11)</td>
<td>1.93 (1.77)</td>
<td>31.90 (5.23)</td>
<td>44.75 (38.15)</td>
<td>2.40 (1.65)</td>
</tr>
<tr>
<td>% Change</td>
<td>3.10 (2.16)</td>
<td>14.38 (11.40)</td>
<td>13.99 (15.59)</td>
<td>0.98 (1.97)</td>
<td>6.65 (8.00)</td>
<td>7.00 (7.46)</td>
</tr>
<tr>
<td>CV</td>
<td>0.70</td>
<td>0.79</td>
<td>1.11</td>
<td>2.01</td>
<td>1.20</td>
<td>1.07</td>
</tr>
<tr>
<td>3 mo after end of lead-in</td>
<td>26.42 (3.37)</td>
<td>38.67 (49.24)</td>
<td>1.54 (1.76)</td>
<td>30.29 (5.33)</td>
<td>37.03 (28.18)</td>
<td>2.11 (1.61)</td>
</tr>
<tr>
<td>% Change</td>
<td>10.73 (6.93)</td>
<td>37.13 (23.44)</td>
<td>38.62 (27.75)</td>
<td>4.80 (5.11)</td>
<td>18.89 (19.87)</td>
<td>22.22 (25.03)</td>
</tr>
<tr>
<td>CV</td>
<td>0.65</td>
<td>0.63</td>
<td>0.72</td>
<td>1.06</td>
<td>1.05</td>
<td>1.26</td>
</tr>
</tbody>
</table>

Abbreviations: ALS-FRS, Amyotrophic Lateral Sclerosis Functional Rating Scale; CV, coefficient of variation (SD/mean); MUNE, motor unit number estimation; NI, neurophysiologic index.

*aData are given as mean (SD) unless otherwise indicated.
†Comparison of data at the end of the lead-in period between groups 1 and 2 (Mann-Whitney test) showed no statistical difference for ALS-FRS (P = .04), MUNE (P = .8), and NI (P = .4) for P<.01.
‡P<.01 (Wilcoxon signed rank test).
§Sample size calculations assume α = .05 and 90% power.10

RESULTS

The results are summarized in the Table. In group 1, the mean ALS-FRS score was 34.7 (SD, 1.7; range, 32-37) at entry and 29.6 (SD, 2.8; range, 23-33) at the end of the lead-in period. In group 2, the mean ALS-FRS score was 33.3 (SD, 4.7; range, 24-39) at entry and 32.2 (SD, 5.1; range, 23-38) at the end of the lead-in period. There was no difference in the baseline ALS-FRS scores in groups 1 and 2 (P = .9). One month after the lead-in period (Table), there was a significant rate of change (P<.01) in ALS-FRS score, MUNE, and NI in group 1, but in group 2 only the NI showed significant change at time 1. At 3 months (Table), all 3 measurements had changed significantly in group 2 as well as in group 1. Of the 12 patients in group 1, only 1 patient, in whom the ALS-FRS score had progressed from 34 to 31 in the lead-in period, did not continue to show a rapid rate of progression. This patient with bulbar-onset ALS had a score of 34 to 31 in the lead-in period. In contrast, in group 2, change was detected after 1 month only by NI measurement. After 3 months of follow-up, all the measurements had changed significantly in both groups (Table). However, the small changes in the coefficients of variation in the measurements in patients in group 1 (Table) imply that these patients were more homogeneous than those in group 2.

Our data suggest that selection of patients with rapidly progressing disease could facilitate short-duration trials capable of detecting slowing of disease progression. Trials using this method would require smaller numbers of patients and could be concluded in a shorter time than current trial designs. Three months would suffice after the lead-in period. The Table shows the sample size, calculated from these data, required in a clinical trial for 50% or 20% detected change at 90% power.10 These calculations assume the same incidence of rapidly progressing ALS as we have encountered in our prospective study of an unselected population of patients with ALS, and no dropouts. The number of patients needed to be included at entry to the lead-in period remains large because patients with rapidly progressing ALS as we have defined them composed only about 20% of all of our patients with ALS. However, short exploratory trials might even allow some of these to enter a second, later trial, including an appropriate washout period. Another option would be to extend the trial for 6 months to identify a potential delayed positive effect of the tested drug. In this design, the sample size would considerably decrease. For example, in group 1 we found that the ALS-FRS score had fallen to 22.8 (SD, 5.4) at 6 months, a 23% reduction compared with the values observed at the end of the lead-in period. To detect a 20% change over this period in the treated group, the sample size required would be 91 per arm rather than 212 (Table).

Our data show that ALS-FRS is the most sensitive primary end point in clinical trials because, although the

COMMENT

These data show that the ALS-FRS scale can be used to select 2 groups of patients with ALS, based on their rate of disease progression in a 3-month lead-in period, from an unselected population of patients with ALS. It is important that patients with both fast (group 1) and slow (group 2) progression were well matched at diagnosis, the point of entry into the lead-in period, despite their different rates of subsequent progression. In group 1, the rate of disease progression was such that ALS-FRS, MUNE, and NI each detected change after only 1 month (Table).
neurophysiologic measurements showed larger percentage changes, the standard deviation of the mean change in ALS-FRS was smaller (Table). However, the neurophysiologic measurements add important information regarding the mechanism of any potential drug effect, since they provide a direct measure of functional motor unit number and an index that reflects motor unit excitability and lower motor unit reinnervation. A potential pitfall might be that a successful outcome of a trial confined to rapidly progressing ALS might not be generalizable to other ALS syndromes, but, since this trial design offers a way to speed up the process of testing potential new therapies, there are potential benefits for all patients with ALS. Moreover, there is no current evidence of underlying biological diversity between patients with faster and slower progression. Because conventional trial designs carry substantial financial costs to trial sponsors (Table), brief but sensitive exploratory clinical trials in selected populations of patients with rapidly progressing ALS are attractive. In addition, the shorter trials reduce the burden of compliance with trial protocols on patients with ALS and their caregivers. This approach offers a novel strategy to select promising drugs for more detailed study in conventional phase III or even phase IV clinical trials of longer duration designed to address issues such as long-term survival, disability, handicap, quality of life, and health care costs.

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REFERENCES