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A Systematic Review of Enrichment Strategies for Current Clinical Trials in ALS

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Background

- Success in ALS clinical trials has remained elusive:
- Since 2007, when Phase 2 and 3 clinical trials were required to be registered, there have been 86 interventional ALS trials listed as completed or terminated.[1]
- These efforts have resulted in the approval of one new treatment.[2]
- ALS is characterized by considerable heterogeneity:[3,4]
- Age of onset, symptoms at onset, genetics, rate of progression, and time till death are among the variable aspects of ALS.
- This heterogeneity presents challenges for ALS clinical trials, affecting study size, duration, and interpretation of results.
- In other fields, such as oncology, patients are routinely stratified according to genetic, clinical, and/or demographic factors with the goal of identifying and treating those most likely to respond to an intervention.
- The application of selection criteria to reduce heterogeneity in ALS clinical trials has the potential to enrich for responders and increase the likelihood of success.[5]

Purpose

- The aim of this study was to determine the extent to which enrichment strategies are being applied to the design of current ALS clinical trials.

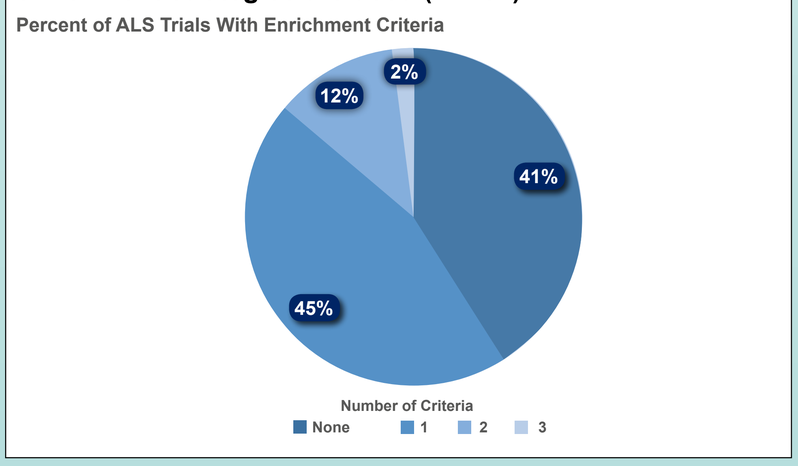
Methods

- We conducted a search of current ALS interventional studies in ClinicalTrials.gov, using the key terms ("Active" OR "Not Yet Recruiting") AND ("amyotrophic lateral sclerosis") AND ("Phase 2" or "Phase 3") AND "Interventional". The search was performed on April 16, 2018.
- Details of each retrieved trial were reviewed to determine whether enrichment criteria were used.
- Enrichment criteria were categorized as follows:
  (1) Rate of Disease Progression as measured by ALS Functional Rating Scale-Revised (ALSFRS-R)
  (2) Use of any biomarkers
  (3) Age: because age of onset is prognostic for outcome, we assessed whether trials enriched for participants based on narrower age-ranges
  (4) Disease characteristics indicative of earlier versus more progressive disease, with earlier disease defined by:
    - Time from symptom onset ≤ 2 years
    - ALSFRS-R ≥ 25
    - Slow vital capacity (SVC) ≥ 65 or forced vital capacity (FVC) ≥ 65
  (5) "Other Characteristics" used to narrow trial entry to a subset of patients with ALS

Results

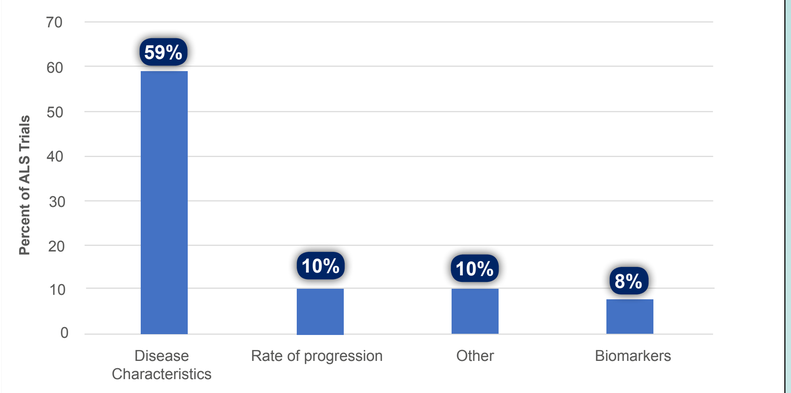
- 52 trials were retrieved, 51 of which include people with ALS.
- In 30 trials (59%), at least 1 category of enrichment is being used.
  - 45%, 12%, and 2% utilize 1, 2, or 3 categories of enrichment, respectively (**Figure 1A**).

Figure 1A. Percentage of current ALS trials in which enrichment strategies are used (N = 51)



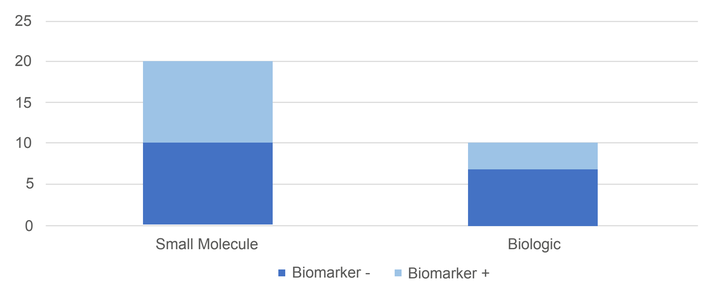
- The most common enrichment category is Disease Characteristics (59%), followed by Rate of Disease Progression (10%), Other (10%), and Biomarkers (8%) (**Figure 1B**).

Figure 1B: Most common categories of enrichment in the studies using them (N = 30)



- Within the Disease Characteristics category, 27% of trials are using at least 2 of the 3 specified sub-criteria.
- With respect to Rate of Disease Progression, 3 of 5 trials require rapid progression (≥ 1 point decline/month in ALSFRS-R)
- Biomarkers used for trial eligibility include the presence of inflammatory markers, level of serum urate, or exclusion due to monogenic causes of ALS.
- Within the Other category, 3 (6%) trials specify Upper Motor Neuron Burden Scale Scores and 2 others (4%) specify motor-evoked potential amplitudes among the inclusion criteria.
- Only two trials had more narrow age restrictions
  - One trial restricted enrollment to adults ≤ 60 and one to ages 40-70.
  - All other trials enrolled adults (≥ 18 or 21) and seniors (≥ 65) with the maximum age ranging from 70 to no limit.
- Among trials using some form of enrichment, 67% were assessing small molecule drugs and 33% biologic therapies (monoclonal antibodies, stem cell-based therapies, or other biologics) (**Figure 2**).

Figure 2: Enriched Trials by Type of Therapy and Use of Biomarkers



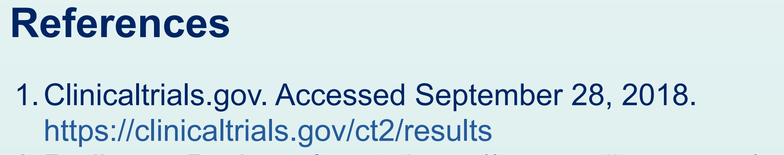
- 50% of small molecule trials included biomarker assessments as part of trial design, but only 30% of trials of biologics included biomarker assessments (**Figure 2**).

Discussion

- Advances in ALS have provided opportunities to improve trial designs via several routes using predictive or prognostic criteria to reduce heterogeneity.
- Trial designs can be improved by selecting clinical subtypes most appropriate for the intended therapeutic, improved delivery through intrathecal or intramedullary routes, and/or based on previous trial experience.
  - The successful trial that led to the approval of edaravone resulted from careful patient selection following previous trial failure.[5]
- In addition, clinical programs can be designed to use Learning (Phase1/2) and Confirmatory (Phase 3) trial designs.[6]
  - Early stage trial data can provide insights into patient characteristics that may predict response.
  - Confirmatory trials can be designed to prospectively assess treatment in a less heterogenous population enriched for likely responders.

- For example, a confirmatory Phase 3 trial of intrathecal mesenchymal stem cell therapy is currently enrolling using disease stage and prognostic criteria to enrich for likely responders, and exploratory biomarker analysis will be included (**Figure 3**).

Figure 3: Confirmatory-Phase 3 ALS Trial Design of MSC-NTF Based on Enrichment



Conclusion

- Although regulatory guidance for interventional ALS trials encourages responder enrichment[7], many current trials are designed with no (41%) or limited (45%) enrichment criteria.
- Greater utilization of enrichment strategies in ALS clinical trials may reduce heterogeneity and optimize treatment outcomes, improved routes of delivery can improve the therapeutic index, and greater use of biomarkers may provide insights into disease mechanisms.

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