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 poses 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 (“Adveksia” 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).

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.6
  - In addition, clinical programs can be designed to use Learning (Phase 2) and Confirmatory (Phase 3) trial designs.7
  - 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.

Conclusion

- Although regulatory guidance for interventional ALS trials encourages responder enrichment8, 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.

References


Acknowledgments and Disclosures

RK, YG, and CL are employees of BrainStorm Cell Therapeutics, which provided support for this study. KR's company is a vendor for the sponsor. NAG, MEC, JDB, KN, RHB, AJW, NS, RGM, and RB are site investigators for an ongoing trial sponsored by BrainStorm Cell Therapeutics.

Presented at the 29th International Symposium on ALS/MND, Glasgow, UK; December 7-9, 2018.