30x46 (x1.5) = 45x69

Use of a Prediction Algorithm for Randomized Stratification in an Amyotrophic Lateral Sclerosis Study

VanMeter, S[1]; Becker, P[1]; Zhao, E[1]; Levine, T[2]

[1]Mallinckrodt, ARD Inc., Bedminster, New Jersey; [2]Phoenix Neurological Associates, Phoenix, Arizona

Introduction

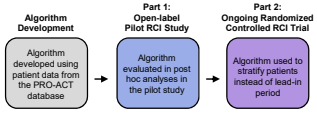
Amyotrophic lateral sclerosis (ALS)

- ALS is a neurodegenerative disorder that affects motor neurons in the central nervous system
- Clinical manifestations of the disease may include limb atrophy, impaired speech and swallowing, and death[1]
- In about half of patients, the disease is lethal within 30 months of symptom onset[1]
- Although ≥30 agents have shown promise in preclinical models of ALS, only one approved product, edaravone, has been shown to slow functional decline in humans[2]
- Repository corticotropin injection (RCI; H.P. Acthar® Gel; Mallinckrodt ARD, Inc., Bedminster, NJ, USA) is a naturally derived product that contains a highly purified porcine analogue of adrenocorticotropic hormone (ACTH)
  - In preclinical models, ACTH activates melanocortin receptors and has anti-inflammatory as well as potential neuroprotective/neuroregenerative properties[3] that may delay or halt ALS progression

An algorithm for predicting ALS progression

- The clinical phenotypes and rates of disease progression of ALS are highly variable[4]
  - This heterogeneity presents challenges for clinical trial design
  - Lead-in periods have been used to predict ALS progression in clinical trials,[5] but lead-in periods have limitations
    - Disease progression slopes derived from lead-in periods are not always predictive, as ALS-related decline in function may not be linear
    - Lead-in periods lengthen the duration of clinical trials and extend the time from enrollment to administration of study drug
- To advance the ability of researchers and clinicians to predict ALS disease progression, an algorithm was developed to predict disease progression in ALS on the basis of information in patients' records[6] (**Figure 1**)
  - This algorithm is one of the 2 award-winning algorithms from the DREAM Phil Bowen ALS Prize4Life Challenge, in which a limited dataset from the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) was provided to developers[6]
    - The algorithm performed well in a larger portion of the dataset versus clinician predictions[6]
- This algorithm predicting ALS progression was used in an exploratory post hoc analysis of an open-label pilot study with RCI (Part 1)
- In the ongoing randomized controlled RCI trial (NCT03068754), the algorithm replaced the lead in phase for stratifying patient randomization (Part 2)

Figure 1. Development[6] and use of an algorithm for predicting ALS progression



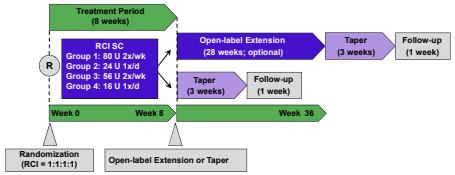
Abbreviations: ALS, amyotrophic lateral sclerosis; PRO-ACT, Pooled Resource Open-Access ALS Clinical Trials; RCI, repository corticotropin injection.

Methods

Part 1: Assessment of a revised prediction algorithm for ALS progression in an open-label RCI pilot study

- Pilot study design
  - Forty-three patients with ALS were randomly assigned to 1 of 4 RCI dosing regimens in an 8-week open-label period followed by an optional 28-week open-label extension and taper (**Figure 2**)

Figure 2. Design of the RCI open-label pilot study



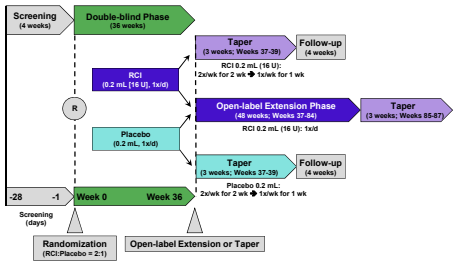
Abbreviations: R, randomization; RCI, repository corticotropin injection; SC, subcutaneous.

- Efficacy and statistical analyses
  - Post hoc assessment of RCI efficacy was conducted in 2 ways: (1) historical control case-match analysis and (2) use of 1 of the 2 ALS disease progression algorithms as previously shown[7]
    - The prediction algorithm for ALS progression[6] was modified to incorporate a random forests learning algorithm with available patient baseline features and characteristics as input
      - Cross-validation of the modified prediction algorithm for ALS progression with a subset of PRO-ACT data was conducted
      - The observed ALS Functional Rating Scale (ALSFRS) total score decline in patients from the pilot study was compared with that predicted by the algorithm

Part 2: Prediction of ALS progression in an ongoing multicenter, double-blind, randomized, placebo-controlled study

- Randomized controlled trial study design
  - Currently, the algorithm is being used in an ongoing multicenter, double-blind, randomized, placebo-controlled study (**Figure 3**, ClinicalTrials.gov identifier: NCT03068754)
  - Approximately 213 patients will be recruited
  - The study begins with a ≤28-day screening period, and eligible subjects are randomly assigned (2:1 ratio) to receive RCI or volume-matched placebo once daily from baseline to 36 weeks
    - Randomization is being stratified on the basis of riluzole use and the predicted 36-week decline in the ALSFRS total score using the revised prediction algorithm described in Part 1
  - Subjects will either taper and discontinue study drug or continue daily RCI during a 48-week open-label extension phase

Figure 3. Multicenter, double-blind, placebo-controlled study design



Abbreviations: R, randomization; RCI, repository corticotropin injection.

- Ongoing randomized controlled trial endpoints and analyses
  - Primary endpoint
    - Change from baseline in the ALSFRS-Revised (ALSFRS-R) total score at Week 36
  - Secondary endpoints include
    - Mean slope of ALSFRS-R total score decline
    - Change of ALSFRS-R total score from baseline over time
    - Mean slope of decline in pulmonary test scores (ie, forced vital capacity [FVC] and forced volume expired in 1 second [FEV_1])
    - Survival
    - Summary of general safety profile (eg, adverse events, serious adverse events, vital signs, laboratory assessments) by study period and over the entire study
  - Prediction algorithm analyses
    - Comparison of the predicted rate of ALSFRS total score decline versus the observed rate of decline to further evaluate the modified prediction algorithm
    - Use of the predicted rate of ALSFRS total score decline as a covariate in the efficacy analysis models
    - Prespecified subgroup analysis based on the predicted rate of ALSFRS total score decline

Results

Part 1: Open-label RCI pilot study

- A modified prediction algorithm for ALS progression was cross-validated using a subset of PRO-ACT data and showed better performance than the original algorithm (root mean square error, 0.517 and 0.559, respectively)[7]
- The actual decline in ALSFRS score during the 9 months of the pilot study was numerically slower than, but not significantly different from, the predicted rate (**Table 1**)

Table 1. Comparison of the observed decline in ALSFRS score during the pilot study versus that predicted by the algorithm

Statistic	Actual Slope From Pilot Study (n=21)	Predicted Slope From Algorithm (n=21)	*P* value*
Mean ± SD	−0.51 ± 0.57	−0.75 ± 0.26	0.087
Median (range)	−0.36 (−2.21, 0.35)	−0.79 (−1.20, −0.29)	

Abbreviation: SD, standard deviation.
* *P* value is generated from a paired t-test.

Part 2: Ongoing randomized controlled RCI study

- As of January 19, 2018, 23 subjects have been randomized (**Table 2**)

Table 2. Enrollment in the ongoing, randomized, multicenter, double-blind, placebo-controlled study as of January 19, 2018

Enrollment Category	No.
Sites activated	26 (all United States)
Patients screened	34
Patients in screening	6
Patients randomized	23
Patients discontinued	3

- The algorithm is being used to predict which patients will have rapid versus slower ALS progression; to date, the algorithm has predicted a ≤1-point ALSFRS score decrease per month for 22 patients and a >1-point ALSFRS score decrease per month for 1 patient

Conclusions

Part 1: Open-label RCI pilot study

- A revised prediction algorithm for ALS progression was cross-validated and shown to be more accurate than the original algorithm
- A post hoc analysis of RCI efficacy using the prediction algorithm yielded results that were directionally similar to those of the analysis that used the case-matched control group from the PRO-ACT database
- The predicted rate of ALSFRS decline in a post hoc analysis using the prediction algorithm was greater than the observed rate of decline in a small sample of patients treated with RCI
  - Although not statistically significant, these results suggest a potential effect of RCI on disease progression

Part 2: Ongoing randomized controlled RCI study

- This study will be the first to incorporate a prediction algorithm for rate of disease progression rather than using a lead-in phase to stratify random assignment of patients with ALS
- The modified trial design minimizes the time for subject enrollment before administration of study drug and shortens the length of the trial
  - These are key benefits because of the rapid morbidity and mortality associated with ALS
- If successful in accurately stratifying subjects with more rapid versus slower disease progression in the randomized controlled trial, this algorithm has the potential for use in future protocols evaluating therapeutic efficacy in ALS by
  - Avoiding lengthy and costly lead-in phases to stratify random assignment of patients
  - Providing better homogeneity between clinical study arms
  - Enriching for patient populations with defined rates of disease progression

References

1. Kiernan MC, Vucic S, Cheah BC, et al. Amyotrophic lateral sclerosis. *Lancet*. 2011;377(9769):942-955.
2. Writing Group; 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*. 2017;16(7):505-512.
3. Starowicz K, Przewlocka B. The role of melanocortins and their receptors in inflammatory processes, nerve regeneration and nociception. *Life Sci*. 2003;73(7):823-847.
4. Taylor AA, Fournier C, Polak M, et al. Predicting disease progression in amyotrophic lateral sclerosis. *Ann Clin Transl Neurol*. 2016;3(11):866-875.
5. Shefner JM. Designing clinical trials in amyotrophic lateral sclerosis. *Phys Med Rehabil Clin N Am*. 2008;19(3):495-508, ix.
6. Küffner R, Zach N, Norel R, et al. Crowdsourced analysis of clinical trial data to predict amyotrophic lateral sclerosis progression. *Nat Biotechnol*. 2015;33(1):51-57.
7. VanMeter S, Becker P, Mackey L, Fang L, Zhao E. Post hoc analyses using the PRO-ACT database to evaluate repository corticotropin injection (H.P. Acthar® Gel) as a potential treatment for ALS. Poster presented at: Northeast Amyotrophic Lateral Sclerosis (NEALS) Consortium; October 3-5, 2017; Clearwater Beach, Florida.

Acknowledgment and Funding

One or more authors report potential conflicts, which are described in the program. Professional writing and editorial support was provided by Carolyn Green, PhD, of MedLogix Communications, LLC, Itasca, Illinois, under the direction of the authors and was funded by Mallinckrodt, ARD Inc. Susan VanMeter, MD, is an employee and stockholder of Mallinckrodt, ARD Inc., and a stockholder of GlaxoSmithKline. Patrice Becker, MD, and Enxu Zhao, MS, are employees and stockholders of Mallinckrodt, ARD Inc. Todd Levine, MD, has nothing to disclose.

Presented at the International Society for CNS Clinical Trials and Methodology 14th Annual Scientific Meeting ● Washington, DC ● 20-22 February 2018