The Influence of Clinical Study Inclusion Criteria on Baseline Characteristics and Disease Progression in Amyotrophic Lateral Sclerosis

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BACKGROUND

- The clinical course of amyotrophic lateral sclerosis (ALS) shows a high degree of variability in disease progression[1]
- This heterogeneity creates challenges for conducting clinical studies in ALS[1]
- As a result, a variety of strategies have been employed to help reduce heterogeneity while selecting for patients who are expected to experience adequate disease progression to allow for measurement of intervention effect[2]
- One of the main strategies employed is the use of specific study inclusion criteria[2]
- However, despite the many combinations of inclusion criteria that have been used in clinical studies, little is known regarding their effects on baseline characteristics or on natural disease progression in the selected cohorts of patients

OBJECTIVE

- To assess disease progression rate predictors and correlations among study entry criteria, baseline characteristics, and the outcome of a slope change in scores on the ALS Functional Rating Scale-Revised (ALSFRS-R)

METHODS

- Literature searches identified randomized, controlled clinical studies in ALS published during the past 15 years
- Studies were selected for analysis based on the availability of ALSFRS-R outcomes data
- The following clinical study data were extracted for each study

Entry Criteria	Baseline Characteristics	Outcomes
• Disease duration • FVC/SVC • El Escorial diagnosis category	• Disease duration • FVC/SVC • Age • Gender • Initial symptom • Riluzole use • ALSFRS-R total score	• ALSFRS-R slope

- The following analyses were conducted
  - Correlation analysis
  - Linear regression modeling analysis
  - Decision tree analysis
- The 10 studies included in the current analyses are listed in **Table 1**

Table 1. Studies included in the analyses

			Entry Criteria			Baseline Characteristics							Outcome
First author	Drug	Pbo N	El Escorial	Disease duration	Respiratory function (%p)	Men	Age, yr (mean±SD)	Disease duration (mo)	FVC/SVC (%p)	Initial symptom (% limb)	Riluzole use (%)	ALSFRS-R score	ALSFRS-R slope (units/mo)
Meininger et al[3]	Ozanezumab	151	Def, Prob, Lab, Poss	≤2.5 yr	SVC ≥65%	64%	55.5±11.0	17.9	95.7%	78%	87%	38.4	−0.84
Ludolph et al[4]	Rasagiline	125	Def, Prob, Lab, Poss	≤3 yr	SVC ≥50%	67%	60.4±10.2	17.9	85.4%	78%	100%	38.3	−1.02
Miller et al[5]	NP001	42	Def, Prob	≤3 yr	FVC ≥70%	69%	53.7±9.52	17.2	*92.4%*	83%	69%	38.2	−0.89
Cudkowicz et al (2013)[6]	Dexpramipexole	468	Def, Prob, Lab, Poss	≤2 yr	SVC ≥65%	64%	57.3±11.3	15.5	89.1%	76%	75%	37.9	−1.12
Statland et al[7]	Rasagiline	20	Def, Prob, Lab	≤2 yr	FVC ≥75%	65%	57.5±8.5	16.4	94.4%	85%	80%	35.9	−1.25
Gordon et al[8]	Minocycline	206	Def, Prob, Lab	≤3 yr	FVC ≥75%	64%	57.7±10.9	18.1	93.8%	80%	66%	37.9	−1.04
Cudkowicz et al (2014)[9]	Ceftriaxone	173	Def, Prob, Lab, Poss	≤3 yr	FVC >60%	58%	55±10	18.0	91%	79%	74%	36.9	−1.22
Elia et al[10]	TUDCA	17	Def, Prob	≤1.5 yr	FVC ≥75%	67%	54.0±12.2	13.2	94.9%	*80%*	100%	38.7	−1.69
Writing Group[11]	Edaravone	68	Def, Prob	≤2 yr	FVC ≥80%	59%	60.1±9.6	12.7	97.4%	79%	92%	41.8	−1.358
Amirzagar et al[12]	GCSF	20	Def, Prob	≤2 yr	FVC >50%	60%	52.5±11.6	15.7	*92.4%*	*80%*	70%	36.6	−1.61

Data in italics are imputed as the column average of non-missing data.
FVC=forced vital capacity; GCSF=granulocyte colony-stimulating factor; SVC=slow vital capacity; TUDCA=tauroursodeoxycholic acid.

RESULTS

Correlation analysis

- Analyses of correlations between entry criteria and baseline characteristics were conducted with combined data from the placebo group and the active treatment group
  - The disease duration and FVC entry criteria cutoffs correlated with baseline disease duration and ALSFRS-R score (**Table 2**)
  - FVC cutoff and El Escorial entry criteria correlated with baseline FVC (**Table 2**)
- Analyses of correlations with the study outcome, ALSFRS-R slope, were conducted only with placebo group data
  - Among baseline characteristics, baseline disease duration correlated with the final ALSFRS-R slope outcome (**Table 3**)

Table 2. Spearman correlation analyses of entry criteria with baseline characteristics

		Baseline Characteristics						
		Disease duration	FVC/SVC	ALSFRS-R	Age	Gender	Initial symptom	Riluzole use
Entry Criteria	Disease duration	**0.833; *P*<.001**	−0.137; *P*=.543	**−0.453; *P*=.020**	0.038; *P*=.855	0.289; *P*=.152	0.224; *P*=.316	−0.345; *P*=.084
	FVC/SVC	−0.357; *P*=.062	**0.731; *P*<.001**	**0.516; *P*=.005**	0.273; *P*=.160	−0.01; *P*=.962	0.389; *P*=.0734	0.181; *P*=.376
	El Escorial	0.246; *P*=.207	**−0.636; *P*<.001**	−0.194; *P*=.324	0.197; *P*=.314	−0.101; *P*=.608	−0.404; *P*=.0623	−0.129; *P*=.531

Table 3. Pearson correlation analyses of baseline characteristics with ALSFRS-R slope outcome

Baseline Characteristic	Pearson Coefficient	*P*-value
Disease duration	**0.72013**	**0.0188**
FVC/SVC	−0.31224	0.452
ALSFRS-R score	−0.00101	0.998
Age	0.29263	0.412
Gender	0.34771	0.325
Initial symptom	−0.1004	0.813
Riluzole use	−0.2239	0.534

Multiple linear regression modeling

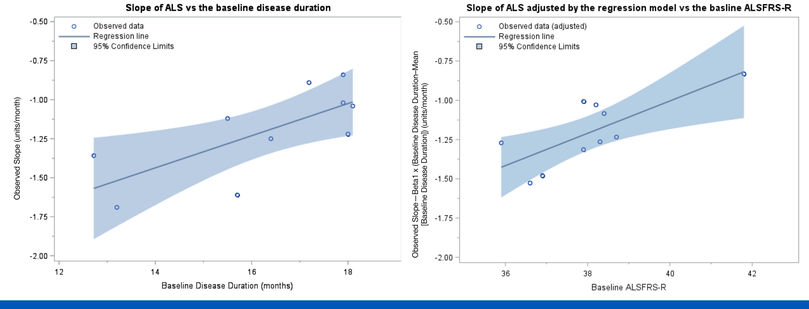
- A total of 8 covariates were considered for the initial model
  - Entry criteria: FVC/SVC cutoff and El Escorial
  - Baseline characteristics: Disease duration, ALSFRS-R score; age, gender, initial symptom, and riluzole use
- Baseline disease duration and baseline ALSFRS-R score were the strongest predictors of ALSFRS-R slope (**Figure 1**)
  - Final model: ALSFRS-R slope = Intercept + beta1×baseline disease duration + beta2×baseline ALSFRS-R (**Table 4**)

Table 4. Linear regression parameters

Parameter	Estimate	*P*-value	95% CI
beta1	0.149	.0026	(0.0719, 0.226)
beta2	0.103	.0390	(0.00691, 0.199)

CI=confidence interval.

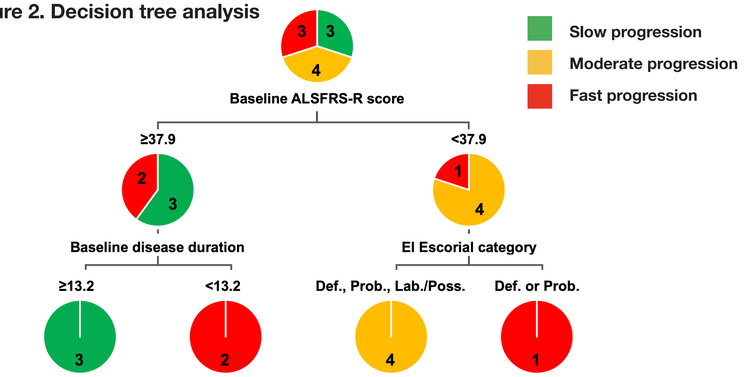
Figure 1. Linear regression graphs



Decision tree analysis

- To facilitate the analysis, ALSFRS-R slope was split into 3 groups (**Figure 2**)
  - Slow progression <1.02 points/month
  - Medium progression ≥1.02 and ≤1.33 points/month
  - Fast progression >1.33 points/month
- Decision tree analysis indicated that separation of the study populations into fast, medium, and slow progressors was predicted by a combination of baseline ALSFRS-R score, baseline disease duration, and El Escorial entry criteria

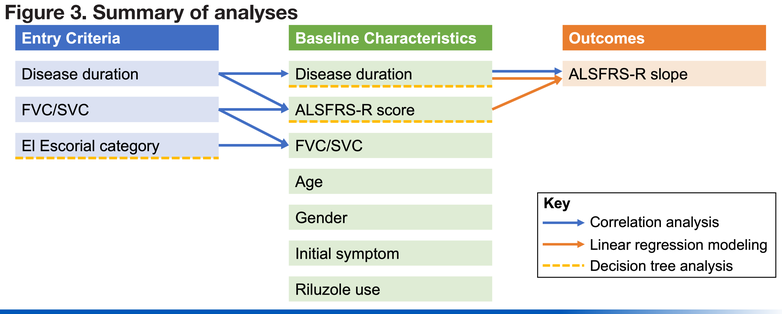
Figure 2. Decision tree analysis



Summary of effects

- **Figure 3** summarizes the correlations and effects observed in the current study
- Among the entry criteria, disease duration and FVC/SVC had the greatest influence on baseline characteristics, including baseline disease duration, ALSFRS-R score, and FVC/SVC
- Among the baseline characteristics, disease duration and ALSFRS-R score had the greatest influence on disease progression during the study (ALSFRS-R slope)

Figure 3. Summary of analyses



CONCLUSIONS

- Analysis of ALS clinical studies indicated that disease duration and FVC inclusion criteria may have important effects on baseline characteristics, such as disease duration and ALSFRS-R score
- These 2 baseline characteristics, in turn, may affect the ALSFRS-R slope outcome
- Thus, selection of entry criteria (especially disease duration and FVC) may have an important impact on disease progression during clinical studies in ALS
- These findings show that slope outcomes from studies based on different entry criteria cannot be compared with one another

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