The ALSFRS @ 20: Evolution of the ALSFRS-R, History, Clinimetric Properties and Future Directions

Jesse M. Cedarbaum[1], Hiroshi Mitsumoto[2], Alan Pestronk[3], Steve Ringel[4], Julaine Florence[3], Mohamed Sanjak[5], Benjamin Rix Brooks[5]

1. Cytokinetics, Inc., South San Francisco, CA. 2. Eleanor and Lou Gehrig MDA/ALS Research Center, Neurological Institute, Columbia University School of Medicine, New York, NY.
3. Washington University School of Medicine, St. Louis, MO. 4. University of Colorado Denver, Aurora, CO. 5. Carolinas Medical Center, Charlotte, NC.

Abstract

- **Background**: The ALS Functional Rating Scale was developed beginning in 1991 for use in clinical trials of new therapeutic agents for ALS. In the 20 years since its inception, the ALSFRS, now in its revised version as the ALSFRS-R, has become the most frequently used ADL assessment instrument in ALS trials, appearing in more than 175 peer-reviewed publications. The ALSFRS and ALSFRS-R have been applied in other patient management and research settings as well. The ALSFRS-R has become an accepted primary endpoint measure for Phase 3 clinical development.
- **Objectives**: To review the history of the development and use of the ALSFRS and ALSFRS-R.
- **Methods**: This presentation will review the concepts underlying the ALSFRS and ALSFRS-R, the clinimetric properties of the scales, and advances in their application over the last 20 years.
- **Results**: The ALSFRS and ALSFRS-R are reliable and reproducible scales with good clinimetric properties. Their administration is easy to standardize, and it is easy for patients and caregivers to use. They have been shown to be effective in retrospective chart reviews of ALS patients. The ALSFRS and ALFRS-R have been validated for administration over the telephone, and may be administered by computer interface as well. The ALSFRS and ALSFRS-R have been translated into and validated in 8 languages, and have been used in clinical studies world-wide. The scales have been adopted in numerous types of research studies, including online registries, and patient-initiated social networking research projects. The rate of progression of ALSFRS-R from onset of disease has been confirmed to predict survival time in ALS patients. Versions of the ALSFRS have been developed for other neuromuscular diseases (IBMFRS) and for advanced stages of ALS. New methods of analysis have recently been proposed which have the potential to increase the validity of the scale in long-term clinical trials.
- **Discussion**: The ALSFRS, as it has evolved into the ALSFRS-R, continues to be a valuable tool in ALS clinical and drug development research, and has become a template for assessing function in ALS and other neuromuscular diseases. Future evolution and application of the ALSFRS-R will be discussed.

Why the ALSFRS?

- When we were contemplating clinical trials with neurotrophic growth factors, the "in-vogue" method of assessing ALS disease status was Quantitative Muscle Testing (QMT; Andres, *et al.* 1987).
- It was also recognized that in ALS, like cancer, survival would be the gold standard for clinical trial outcomes in ALS.
- However, we wanted to have a measure that would be informative about patients' abilities, could be administered to patients unable to attend clinic, and that might ultimately prove to have some prognostic value.
- Clinical rating scales available at the time, the Appel Scale (Appel et al 1987), and the Norris Scale (Norris, *et al.* 1974) combined interview-based functional assessments and observational testing in ways that were not intuitive, were lengthy and required specialized equipment and testing locations.
- Hence, a new scale was needed.

Principles in Design of the Original ALSFRS

- Goals:
  - Develop a simple, 10-item questionnaire-based scale to record ADL performance.
  - Develop a validated rating scale that would complement QMT and be easy to administer.
  - The scale was to be questionnaire-based and not mix testing modalities (i.e., it should not be a composite scale).
- Models included the Unified Parkinson Disease Rating Scale (UPDRS; Fahn and Elton 1987) and the ALS Severity Scale (ALSSS) developed by Hillel et al (1989).
- Features of the Scale:
  - Each item scored uniformly from 0 (unable to do) to 4 (normal function).
  - Queries patients' CURRENT ability to perform selected ADLs; does not reference past performance.
  - Intermediate scale steps described precisely to try to avoid ambiguity in interpretation.

Initial Validation of the ALSFRS

- Initial study (ACTS Study Group, 1996) performed to validate ALSFRS against
  - QMT
  - FVC
  - Maximum Inspriatory Pressure
  - Schwab and England ADL scale (a 10-point scale similar to the Karnofsky performance score used in cancer trials)
  - Global Clinical Impression of Change (GCIC) score
- Assessed both cross-sectional and longitudinal correlations
  - Demonstrated sensitivity, reliability and construct validity of the scale
  - Strong correlation of ALSFRS scores with QMT and other measures
- Factor analysis was performed understand the operation of the scale
  - Found little redundancy in factor analysis and logical grouping of scale items into 4 factors corresponding to 4 functional domains:
    - Fine motor
    - Gross motor
    - Bulbar
    - Respiratory
- The longitudinal performance of the ALSFRS was next evaluated in the clinical trial setting (Cedarbaum and Stambler, 1997)
  - Continued utility and validity demonstrated over a 9-month study, using the placebo group of a large, multicenter trial
  - Correlation with ambulatory status identified
  - Baseline ALSFRS Score and Baseline FVC (but not prior slope) identified as prognostic factors for survival

The Need for Revision

- The original ALSFRS devoted 3 questions to upper extremity, lower extremity and bulbar function, but only one to respiratory function.
- Data from a large multicenter trial of BDNF was used to identify possible additional questionnaire items to be added to the ALSFRS (Cedarbaum, *et al.* 1999).
  - The Sickness Impact Profile data was also available for comparison
  - Data was also available about patients who began using mechanical ventilation during the course of the study.

The ALSFRS-R

- The one ALSFRS question about breathing function was replaced with 3, covering dyspnea, orthopnea, and the need for ventilatory support (Cedarbaum, *et al.* 1999).
- The sensitivity, specificity and construct validity of the original scale were retained.
- Interestingly, the new pulmonary section did not correlate with limb and bulbar function in the factor analysis, indicating that it measured a completely different dimension of the disease and provided information not previously captured by the ALSFRS.

Bulbar	Fine Motor	Gross Motor	Breathing

1. Speech
4. Normal speech processes
3. Detectable speech disturbance
2. Intelligible with repeating
1. Speech combined with nonvocal communication
0. Loss of useful speech

2. Salivation
4. Normal
3. Slight but definite excess of saliva in mouth; may have nighttime drooling
2. Moderately excessive saliva; may have minimal drooling
1. Marked excess of saliva with some drooling
0. Marked drooling; requires constant tissue or handkerchief

3. Swallowing
4. Normal eating habits
3. Early eating problems-occasional choking
2. Dietary consistency changes
1. Needs supplemental tube feeding
0. NPO (exclusively parenteral or enteral feeding)

4. Handwriting
4. Normal
3. Slow or sloppy; all words are legible
2. Not all words are legible
1. Able to grip pen but unable to write
0. Unable to grip pen

5a. Cutting Food / Handling Utensils
4. Normal
3. Somewhat slow and clumsy, but no help needed
2. Can cut most foods, although clumsy and slow; some help needed
1. Food must be cut by someone, but can still feed slowly
0. Needs to be fed

5b. Cutting Food / Handling Utensils (Alt. for patients with Gastrostomy)
4. Normal
3. Clumsy but able to perform all manipulations independently
2. Some help needed with closures and fasteners
1. Provides minimal assistance to caregiver
0. Unable to perform any aspect of task

6. Dressing and hygiene
4. Normal function
3. Independent and complete self-care with effort or decreased efficiency
2. Intermittent assistance or substitute methods
1. Needs attendant for self-care
0. Total dependence

7. Turning in bed
4. Normal
3. Somewhat slow and clumsy, but no help needed
2. Can turn alone or adjust sheets, but with great difficulty
1. Can initiate, but not turn or adjust sheets alone
0. Helpless

8. Walking
4. Normal
3. Early ambulation difficulties
2. Walks with assistance
1. Non-ambulatory functional movement only
0. No purposeful leg movement

9. Climbing stairs
4. Normal
3. Slow
2. Mild unsteadiness or fatigue
1. Needs assistance
0. Cannot do

10. Dyspnea
4. None
3. Occurs when walking
2. Occurs with one or more of the following: eating, bathing, dressing (ADL)
1. Occurs at rest, difficulty breathing when either sitting or lying
0. Significant difficulty, considering using mechanical respiratory support

11. Orthopnea
4. None
3. Some difficulty sleeping at night due to shortness of breath. Does not routinely use more than two pillows
2. Needs extra pillow in order to sleep (more than two)
1. Can only sleep sitting up
0. Unable to sleep

12. Respiratory insufficiency
4. None
3. Intermittent use of BiPAP
2. Continuous use of BiPAP
1. Continuous use of BiPAP during the night and day
0. Invasive mechanical ventilation by intubation or tracheostomy

Reliability and Alternate Modes of Administration for Modern Clinical Trials

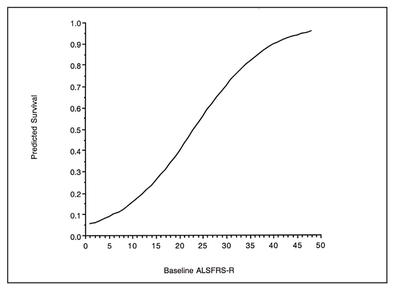
Lou Gehrig
Photo from the Herman Seid collection;
Courtesy of Carl Seid

- Kaufman et al found inter-rater reliability of the ALSFRS-R to be high (ICC 0.93-0.95).
  - Reliability was equally as good when the ALSFRS-R was performed in person or over the telephone.
- Kasarskis, *et al.* found that results from telephone administration of the ALSFRS-R correlated highly with clinic administration ($r > 0.98$).
- The ALSFRS-R has also been validated for self-administration (Montes, *et al.* 2006).
- Accurate scores can also be generated from clinic notes (Lechtzin, *et al.* 2009) or old photographs and movies (Lewis 2007).

ALSFRS-R Predicts Survival; Scores Represent Clinically Meaningful Changes in Disease Status

- Baseline/entry ALSFRS-R scores have been found to be predictive of survival in clinical trial (Cedarbaum, *et al.* 1999); and clinic (Kaufman, *et al.* 2005) populations, as has rate of pre-study decline Kimura, *et al.* 2006).
- ALSFRS-R scores also predict survival for patients on mechanical ventilation (Lo Coco, *et al.* 2007).
- 93% of 65 clinicians surveyed considered that a 20% slowing in the rate of decline of ALSFRS-R to be a clinically meaningful benefit; and all considered a 25% slowing in the rate of progression to represent a clinically meaningful change (Castrillo-Viguera, *et al.* 2010).

Figure 1. Predicted Nine Month Survival as a Function of Baseline ALSFRS-R



(Cedarbaum, *et al.*,1999)

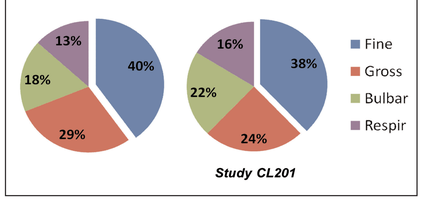
ALSFRS-R Scores and Rates of Change are Robust Over Time and Across Studies

Comparison of Placebo Groups Shows Rate of ALSFRS-R decline is reliably about 1 point/month across studies

Trial	NEALS Creatine	NEALS Celebrex	Novartis TCH346	WALS Minocycline[1]	Columbia multicenter CoQ10	NEALS Lithium	All Placebo
Years	200002	200103	2004	200507	200507	2009	20002009
N Patients*	45	95	108	249	75	44	616
Trial duration	6 mos	12 mos	10 mos	13 mos	9 mos	6 mos	6-13 mos
Symptom durations (years)	0.6 - 4.8	0.4 - 5.1	0.3 - 3.0	0.2 - 3.8	0.5 - 5.5	0.5 - 3.0	0.2 - 5.5
Entry FVC median	82.9	83.5	88.5	91.0	90.0	87.5	89.0
Entry FVC range	47 - 134	57 - 146	39 - 147	72 - 178	61 - 128	56 - 134	39 - 178
Entry FRS-R median	38	40	40	39	36	37	39
Entry FRS-R range	18 - 47	22 - 47	26 - 47	23 - 48	27 - 43	24 - 48	18 - 48
Est. FRS-R Slope/mo	-0.98	-1.06	-0.79	-0.94	-0.82	-1.00	-0.89
Slope 5th, 95th percentile	-2.50 -0.14	-2.49 -0.12	-2.66 +0.03	-2.52 +0.00	-1.75 -0.16	-2.69 +0.25	-2.45 +0.01

*Patients with 2 or more assessments
[1] Includes nonradomized patients
[2] Slopes estimated from linear mixed effects model applied to first 6 months of follow-up; separate estimation for each data subset without reference to other studies.

Figure 3. Percentage contribution to ALSFRS-R Total Score Change for each Sub-Domain from Baseline to 12 Weeks in Placebo-treated Subjects: ***Cedarbaum et al., (1999) vs. Study CL201 (2009)***



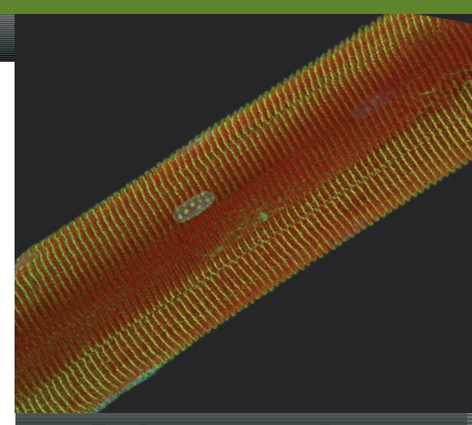
Ingersoll EW (2010), with permission

The ASLFRS-R Has Been Translated Into Multiple Languages, With Cultural Adaptations as Required

Examples:

Chinese: Liu, *et al*. 2009
Dutch: Maessen, *et al*. 2007
French: Benaim, *et al*. 2006
German: (unpublished)
Hebrew: (unpublished)
Italian: (unpublished)
Japanese: Ohashi, *et al*. 2001
Portuguese: Guedes, *et al*. 2010
Spanish: Campos, *et al*. 2010

However, not all of these translations have undergone full linguistic and cultural validation.



The Present and the Future

- Subsequent uses of the ALSFRS have continued to demonstrate its simplicity and utility in both research and practice settings.
- New technologies should enable web-based capture of data from patients who cannot present to the clinic for evaluation.

Challenges for the Future

- Need for standardization
  - Linguistic
  - Cultural
  - Administration and Training Standards
- Further determination of magnitude of change that represents a clinically meaningful benefit
- Potential for modifications/additions
  - Finer grading
  - Supplemental scales: cognition, pain, others
  - Assembly into composite measure with functional test battery
- Eventual acceptance as surrogate outcome measure?

References

1. ALS CNTF Treatment Study Phase I-II Study Group. The Amyotrophic Lateral Sclerosis Functional Rating Scale. Assessment of activities of daily living in patients with amyotrophic lateral sclerosis. *Arch Neurol*. 1996 Feb; 53:141-7.
2. Andres PL, *et al*. Quantitative assessment of meuromuscular deficit in ALS. *Neurology 198*; 36:937-941.
3. Appel V, *et al*. A rating scale for amyotrophic lateral sclerosis: Description and preliminary experience. *Ann Neurol*. 1987; 22:328-333.
4. Benaïm C, *et al*. Functional scales and motor assessment in amyotrophic lateral sclerosis. *Rev Neurol (Paris)*. 2006; 162 Spec No 2:4S131-4S137
5. Brooks BR. Functional Scales: Summary. ALS and other motor neuron disorders 2002 (suppl 1), S13–S18.
6. Campos TS, *et al*. Spanish adaptation of the revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R). *Amyotrophic Lateral Sclerosis. 2010*; 11: 475–477.
7. Castrillo-Viguera, *et al*. Clinical significance in the change of decline in ALSFRS-R. *Amyotrophic Lateral Sclerosis*. 2010; 11: 178-180
8. Cedarbaum JM, *et al*. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. *Journal of the Neurological Sciences*. 1999; 169: 13–21.
9. Fahn S, Elton RI. Unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Goldstein M, Calne DB, editors. *Recent developments in Parkinson's disease, Vol. 2*. Florham Park, NJ: Macmillan Healthcare Information; 1987. p 153–163, 293–304.
10. Guedes, *et al*. Cross-cultural adaptation and validation of ALS Functional Rating Scale-Revised in Portuguese language. *Arq Neuropsiquiatr*. 2010; 68:44-47
11. Hillel AD, *et al*. Amyotrophic lateral sclerosis severity scale. *Neuroepidemiology*. 1989; 8:142-150.
12. Ingersoll, EW,, *et al*. Effects of Treatment with Dexpramipexole on ALSFRS-R Sub-Domain Scores and Cross-Validation of Change in Sub-Domain Scores with Previously Published Data. *Amyotrophic Lateral Sclerosis*, 2010; 11(Suppl. 1): 65-66.
13. Kasarskis EJ, *et al*. Rating the severity of ALS by caregivers over the telephone using the ALSFRS-R. *Amyotrophic Lateral Sclerosis Other Motor Neuron Disord*. 2005; 6:50-54.
14. Kaufman P, *et al*. The ALSFRSr predicts survival time in an ALS clinic population. *Neurology*. 2005; 64:38–43
15. Kaufmann P, *et al*. QALS study group. Excellent inter-rater, intra-rater, and telephone-administered reliability of the ALSFRS-R in a multicenter clinical trial. *Amyotroph Lateral Scler*. 2007; 8:42-46.
16. Kimura F, *et al*. Progression rate of ALSFRS-R at time of diagnosis predicts survival time in ALS. *Neurology* 2006; 66:265–267
17. Lechtzin N, *et al*. L. Accurate ALSFRS-R scores can be generated from retrospective review of clinic notes. *Amyotroph Lateral Scler*. 2009; 10:244-7.
18. Lewis M, Gordon PH. Lou Gehrig, Rawhide, and 1938. *Neurology*. 2007; 68:615-618.
19. Liu XX, *et al*. Revised amyotrophic lateral sclerosis functional rating scale at time of diagnosis predicts survival time in amyotrophic lateral sclerosis. *Zhonghua Yi Xue Za Zhi*. 2009; 89:2472-2475.
20. LoCoco D, *et al*. The Amyotrophic Lateral Sclerosis Functiaonl Rating Scale predicts survival time in Amyototrophic Lateral Sclerosis patients on invasive mechanical ventilation. *Chest*. 2007; 132;64-69.
21. Maessen M, *et al*. Validity of the Dutch version of the Amyotrophic Lateral Sclerosis Assessment Questionnaire, ALSAQ-40, ALSAQ-5. *Amyotrophic Lateral Sclerosis*. 2007; 8: 96–100.
22. Miano B, *et al*. Inter-evaluator reliability of the ALS functional rating scale. *Amyotrophic Lateral Sclerosis Other Motor Neuron Disord*. 2004; 5:235-239.
23. Miller RG, *et al*. Online supplement to Phase II screening trial of lithium carbonate in amyotrophic lateral sclerosis. *Neurology*. 2011; 77: e-pub August 3, 2011.
24. Montes J, *et al*. Development and Evaluation of a Self-Administered Version of the ALSFRS-R. *Neurology*. 2006; 67:1294-6.
25. Norris FH, *et al*. The administration of guanidine in amyotrophic lateral sclerosis. *Neurology*. 1974; 24:721-728.
26. Ohashi Y, *et al*. Study of functional rating scale for amyotrophic lateral sclerosis: revised ALSFRS(ALSFRS-R) Japanese version. *No To Shinkei*. 2001; 53:346-55.
27. Sanjak M, *et al*. Validation of the 6 Minute Walk Test (6MWT) in *Ambulatory Amyotrophic Lateral Sclerosis (ALS) Patients*. Presented at the NEALS Annual Meeting, Clearwater, FL. November 2011.
28. Traynor BJ, *et al*. Functional measures as trial endpoints for ALS. *Neurology*. 2004; 63:1933-1935.