Decline in Slow Vital Capacity Predicts Respiratory Insufficiency, Use of Assisted Ventilation, Tracheostomy, or Death

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BACKGROUND

Death and disability in ALS are strongly related to respiratory failure, most often assessed in clinical settings by measuring vital capacity

Vital capacity, assessed either using Forced Vital Capacity (FVC) or Slow Vital Capacity (SVC) is thus an important outcome measure for clinical trials

Tirasemtiv, a selective fast skeletal muscle troponin activator, was evaluated in a phase 2b clinical trial in patients with ALS (BENEFIT-ALS) which showed a statistically significant reduction of the decline in percent predicted SVC over 12 weeks in patients treated with *tirasemtiv* compared to patients receiving placebo

OBJECTIVES

To investigate the natural history of SVC decline, to determine what demographic variables impact decline of SVC and how changes in SVC predict function and other clinically meaningful events in patients with ALS

METHODS

We queried the data set from the placebo group in the dexpramipexole phase 3 clinical trial, EMPOWER, one of the largest clinical trials conducted in ALS with 943 patients enrolled (Cudkowicz *et al.*, 2013)

In EMPOWER, patients were assessed for at least one year, with regular measurements of SVC, Sniff Nasal Inspiratory Pressure (SNIP), ALS Functional Rating Scale-Revised (ALSFRS-R), and quantitative strength measurements using hand held dynamometry (HHD). Time to respiratory failure, defined as tracheostomy with permanent assisted ventilation or use of non-invasive ventilation for ≥ 22 hours per day for ≥10 consecutive days and survival, was also collected.

STATISTICAL METHODS

All 469 patients randomized to placebo in the EMPOWER clinical trial were included with a maximum duration of follow-up of 1.5 years

Slope of decline in SVC was estimated using a repeated measures mixed model and adjusting for baseline SVC

Pearson Product Moment correlation coefficient (*r*) was used to evaluate the strength of association between the decline in SVC and other continuous clinical outcomes variables

Cox proportional hazards regression was used to model the time to clinical event variables from the Month 6 visit to the end of the follow-up period using the slope of SVC change from baseline to the Month 6 visit as an explanatory variable, adjusting for baseline *riluzole* use and ALSFRS-R score

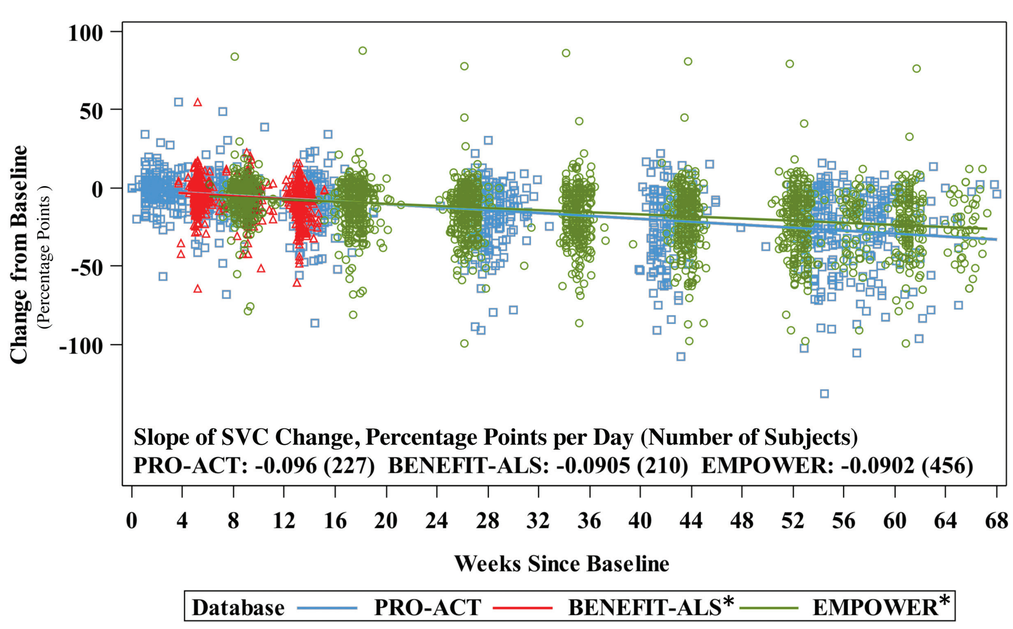
The respiratory clinical outcomes included the earlier of time to death or:

1) time to decline in any of the three questions of the respiration subdomain of ALSFRS-R
2) time to the first onset of respiratory insufficiency
3) time to tracheostomy

All cause mortality was evaluated as well

RESULTS

Figure 1: Rate of Decline in SVC is Similar in Three Large Data Sets



* From the placebo arms of BENEFIT-ALS and EMPOWER

Fall in SVC by Subgroup

Age

Table 1: Analysis of Slope of Change in % Predicted SVC from Baseline by Age Group

Age Group	Number of Observations	Slope (percentage points/day)	95% CI of Slope	P-value
<50	641	-0.075	-0.091, -0.059	0.005*
50-65	1164	-0.086	-0.096, -0.076	0.007**
>65	532	-0.120	-0.142, -0.097	---

* <50 compared to >65
** 50-65 compared to >65

Sex

Table 2: Analysis of Slope of Change in % Predicted SVC from Baseline by Sex

Group	Number of Observations	Slope (percentage points/day)	95% CI of Slope	P-value
Male	1541	-0.086	-0.0973, -0.075	0.5605*
Female	796	-0.098	-0.111, -0.086	---

* Male compared to Female

Riluzole Use

Table 3: Analysis of Slope of Change in % Predicted SVC from Baseline by *Riluzole* Use

Riluzole Use	Number of Observations	Slope (percentage points/day)	95% CI of Slope	P-value
No	517	-0.102	-0.122, -0.081	0.2547*
Yes	1820	-0.088	-0.097, -0.079	---

* No *Riluzole* compared with *Riluzole*

RESULTS (CONTD.)

Fall in SVC by Subgroup (contd.)

Baseline SVC

Table 4: Analysis of Slope of Change in % Predicted SVC from Baseline by Baseline SVC

Group	Number of Observations	Slope (percentage points/day)	95% CI of Slope	P-value
<65%	93	-0.073	-0.137, -0.008	0.1796*
65-75%	295	-0.094	-0.118, -0.069	0.0940**
>75%	1949	-0.090	-0.099, -0.081	---

* <65% compared to >75%
** 65-75% compared to >75%

Site of ALS Onset

Table 5: Analysis of Slope of Change in % Predicted SVC from Baseline by Site of Onset at Randomization

ALS Onset Site	Number of Observations	Slope (percentage points/day)	95% CI of Slope	P-value
Bulbar	477	-0.104	-0.125, -0.083	0.059*
Other	1860	-0.086	-0.094, -0.077	----

* Bulbar compared to Other

Baseline ALSFRS-R

Table 6: Analysis of Slope of Change in % Predicted SVC from Baseline by Baseline ALSFRS-R

Group	Number of Observations	Slope (percentage points/day)	95% CI of Slope	P-value
≤39	1095	-0.102	-0.113, -0.091	0.0001*
>39	1242	-0.076	-0.088, -0.064	---

* ≤39 compared to ≥39

SVC Correlates Weakly with SNIP and Individual Respiratory Items of ALSFRS-R

Table 7: Correlation between Changes from Baseline in % Predicted SVC and SNIP or Individual Respiratory Subdomain Questions of the ALSFRS-R (*p < 0.0001 for all instances)

Pearson Correlation Coefficients*	Change from Baseline in SNIP	Change from Baseline in ALSFRS-R Dyspnea	Change from Baseline in ALSFRS-R Orthopnea	Change from Baseline in ALSFRS-R Respiratory Insufficiency
Change from Baseline in % Predicted SVC	0.33	0.23	0.26	0.28

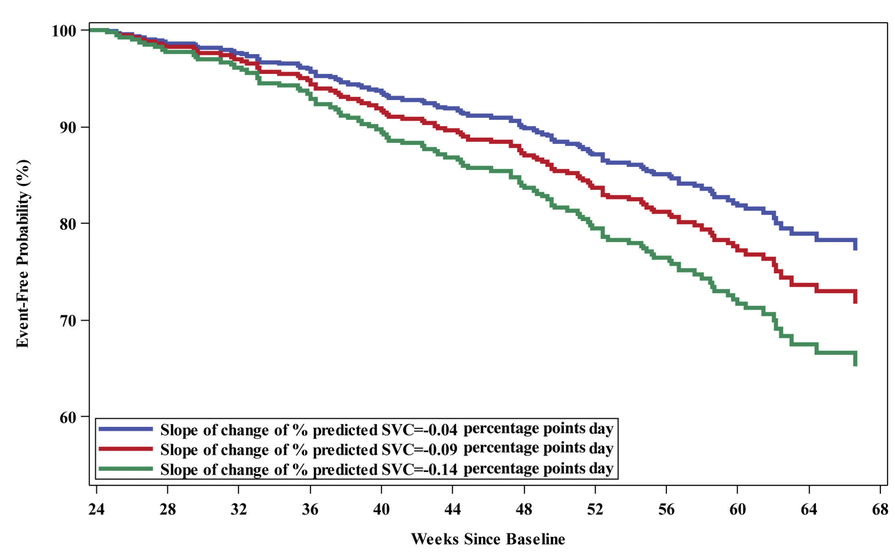
Relationship of SVC to the Risk of Other Clinically Meaningful Events and Measures in ALS

Table 8: Modeling a Reduction in the Decline of Percent Predicted SVC by 0.05%/day*

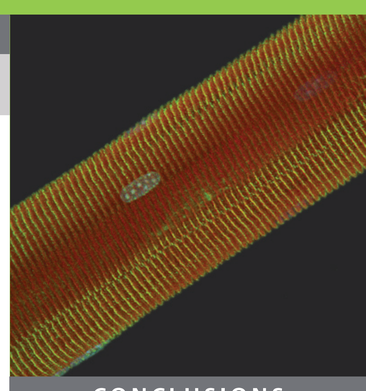
A decrease in percent predicted SVC decline by 0.05%/day predicts**:	Risk Reduction
Decline in respiratory domain of the ALSFRS-R or death	19%
First onset of respiratory insufficiency or death	22%
First occurrence of tracheostomy or death	23%
Death at any time after month 6	23%

* Based on a Cox proportional hazards regression to model time to clinical events
** P<0.0001 in all cases

Figure 2: Probability of Respiratory Failure-Free Survival Predicted by Slope of SVC Change*



Note: Based on a Cox proportional hazards regression to model time to clinical events
* P<0.0001



CONCLUSIONS

1. The rate of decline of SVC in ALS is consistent among the three data sets evaluated
2. From the EM-POWER data set, age and baseline ALSFRS-R had a significant interaction with rate of decline of SVC
3. The change in SVC explained a minority of the variability in the respiratory items of the ALSFRS-R and SNIP
4. The change in SVC strongly predicts meaningful clinical events, including respiratory failure or death in ALS

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