ONLINE SUPPLEMENT

Pattern of Lung Function Decline in Patients with Amyotrophic Lateral Sclerosis: Implications for Timing of Non-invasive Ventilation

METHODS

Study Design and Data Collection

We reviewed patient-related, disease-related, pulmonary function and survival characteristics for the entire group of patients and for those deemed to required noninvasive positive pressure ventilation (NIPPV). We separated adherence to NIPPV into four groups: 1) Non-users who elected not to use NIPPV at all, 2) non-tolerant patients who continued to use NIPPV but did not meet the criterion of 4 consecutive hours of use during sleep, 3) adherent patient who met the criterion of 4 consecutive hours of use during sleep, and 4) patients for whom adherence could not be determined due to death or loss of follow up.

Pulmonary function tests

In addition to the parameters discussed in the main manuscript, less systematically collected values included arterial blood gases and sniff nasal inspiratory pressure (SNIP). Arterial blood gases were collected when possible, and the SNIP was collected in some patients after March 2006 especially when it was necessary contribute to a treatment decision (such as in a symptomatic patient with maximal inspiratory pressure and forced vital capacity above the NIPPV initiation threshold or those with difficulties performing a FVC maneuver). The SNIP was measured through a nasal olive (from various manufacturers) with a central catheter connected

to a pressure manometer. The olive was used to occlude one nostril and the maneuver conducted from residual volume with the best of several trials selected (generally three). We have always performed the maneuver with the contralateral nostril occluded, with more recent literature supporting this approach compared to the more commonly recommended open contralateral nostril approach.[1]

Statistical Analysis

Categorical factors were described using percentages and compared between groups with a chi-square test. Continuous measures were described with means and standard deviations and compared between groups with an ANOVA for normally distributed data, or medians and inter-quartiles and compared between groups with a Kruskal-Willis test for non-normally distributed data. Survival analysis was compared between groups with a log-rang test. A linear mixed model analysis was used to analyze correlations between variables with repeated measures per subject.

In an earlier model,[2] we assumed that the rate of functional decline would favorably change after NIPPV initiation and set the inflection point to that time point (i.e., b3 = 0).

$$y = b1 + b2/(1 + \exp(t/b4)$$

Segmented nonlinear mixed effects models were used to investigate individual changes of predicted forced vital capacity (FVCP), and to assess the effect of NIPPV on the rates of change. The time variable was partitioned into two intervals, before and after the date of NIPPV initiation, and a separate line segment was fit to each interval (i.e., one for $t < 0$ and one for $t \geq$

0). Maximization likelihood estimation with adaptive Gaussian quadrature was applied to solve the nonlinear models and estimate the model parameters.

RESULTS

Descriptive characteristics for all 507 patients are shown in Table E1 and main results covered in the main manuscript. There were 641 SNIP measurements with a significant correlation between the FVCP and the SNIP in a linear mixed model such that for each unit decrease in SNIP there was a 0.59 decrease in FVCP (FVCP = 34.8 + 0.59*SNIP). There were 677 $PaCO_2$ measurements with a significant negative correlation between $PaCO_2$ and FVCP such that for each unit decrease in FVCP there was a 0.11 increase in the $PaCO_2$ (PaCO2 = 40.1 - 0.11*FCVP). There was also a linear relation between the ALSFRS-R and FVCP such that for each 4 units decrease in FVCP there was a one unit decrease in ALSFRS-R (ALSFRS-R = 17.10 + 0.25 * FVCP).

In 360 patients who died during the course of the study, the median time from the last FVCP measurement to the date of death was 4.7 months (interquartile range [IQR]: 2.0-9.1) with no significant difference in that interval between those with an ALSFRS bulbar score $\leq$ 7 (5.1 IQR: 2.1-9.1) vs. > 7 (4.1 IQR:1.9-9.1) (p = 0.31).

NIPPV was deemed necessary in 419 patients through the course of the study. There were 181 adherent patients, 106 non-tolerant patients, 66 non-users, and 66 with unknown adherence. There was no significant differences in those various parameters between not tolerant patients and non-users. Similarly, for the nonlinear mixed effects models partitioned into two time segments (before and after initiation of NIPPV), there was no difference in the

various parameters between the non-tolerant group and the non-user group (Table E2). Those two groups were combined in all other analyses into a non-adherent group (172 patients) including in the main text. Descriptive characteristics for all subjects for whom NIPPV was deemed necessary are shown in Table E3.

Modelling the course of lung function after diagnosis of ALS showed that an asymptotic model provided a good fit of the data. Specifically, a rapid decline in the FVCP around the time of NIPPV initiation was followed by a slowing the rate of lung function decline to a plateau (Figure E1). Both the pre- and post-NIPPV curves fit the observed data. The post NIPPV curve was associated with a maximal decline in lung function to a plateau FVCP of 34%. In contrast, extrapolation from the pre-NIPPV data predicted a modeled FVCP plateau at the lower asymptote of 12% without NIPPV (Figure E1). Although this pattern suggests a beneficial effect of NIPPV on the final FVCP, the model did not fit the observed pattern in non-adherent patients, who generally had a much higher FVCP at the lower asymptote of 38.5%, indicating that the main assumption of the model (i.e., that the inflection point is due to NIPPV initiation) was incorrect. Subsequent analyses in the main text removed the assumption that NIPPV was the reason for the inflection ($b3 \neq 0$) and did not use a segmented approach.

Application of the revised model to the course of decline of percent predicted forced vital capacity (FVCP) is discussed in the main text. In this revised model, resolution of the parameters for the percent predicted forced expiratory volume in the first second (FEV_1) and percent predicted maximum inspiratory pressures (MIPP) are shown in Table E4 in this supplement and Table 4 in the main manuscript, respectively. The course of all parameters

(FVCP, FEV_1P, and MIPP) is consistent with a biasymptotic course of decline (Figure 4 for FVCP, and Figure E2 for MIPP).

Figure legends:

Figure E1.

Course of decline of lung function with separate logistics models for pre- and post-NIPPV initiation. Extrapolation of the pre-NIPPV initiation is also shown.

Figure E2.

Plot of the course of maximum inspiratory pressure (expressed as percent of predicted) decline in amyotrophic lateral sclerosis after resolution of individual parameters using a nonlinear mixed model regression analysis. Includes overall patients and patients stratified by adherence to NIPPV. The time course is centered at initiation of NIPPV (time 0).

Table E1. Characteristic for all patients

Characteristic *	**Overall Group (507) †**
Patient	
Percent females	44.2
Age at disease onset (years)	62 (53-70)
Height at NIPPV decision (m)	1.70 (1.63-1.78) n = 492
Weight at NIPPV decision (kg)	71.4 (60.4-83.9) n = 492
BMI at NIPPV decision (kg/m^2)	24.7 (21.6-28.7) n = 492
Ever smokers (%)	48.9
Current smokers (%)	10.3
Disease	
Onset to diagnosis (months)	11.0 (7.0-18) n = 501
Bulbar subset of ALSFRS	9 (6-11) n = 424
Cervical subset of ALSFRS	7 (4-9) n = 423
Pulmonary	
FVCP	67 (51-83) n = 497
FEV_1P	67 (49-82) n = 344
FEV_1/FVC	80.6 (72.8-86.7) n = 344
Survival in months	
From onset	34.0 (22.0-59.0)
From diagnosis	21.0 (11.0-39.0)

ALSFRS: ALS Functional Rating Scale; BMI: Body mass index; FEV_1P: Percent-predicted forced expiratory volume in the first second; FVCP: percent-predicted forced vital capacity; NIPPV: non-invasive positive pressure ventilation.

* Characteristic as obtained when first obtained indicated unless otherwise specified.

† Percent or median (interquartile range). n is number of patients in case of an incomplete set of data.

Table E2. Difference in parameter estimates between non-tolerant and non-users for course of percent predicted forced vital capacity in the segmented model (before and after initiation of non-invasive ventilation)

Parameter	Before non-invasive ventilation			After non-invasive ventilation		
	Mean (SE)	**95% CI**	**p-value***	**Mean (SE)**	**95% CI**	**p-value***
Δb1 *	0.2 (5.1)	-9.9, 10.3	0.97	-2.1 (13.7)	-29.2-25.1	0.88
Δb2 *	-4.1 (12.1)	-28.1, 19.9	0.74	11.0 (28.8)	-46.1, 68.2	0.70
Δb4 *	2.4 (2.3)	-2.2, 7.0	0.30	-31.4 (31.4	-93.6, 30.8	0.32

* For the difference between non-tolerant (< 4 consecutive hours of sleep with non-invasive positive pressure ventilation) and non-users (no use at all).

Table E3: Characteristics of patients who meet criteria for non-invasive ventilation

Characteristic*	1: Adherent† (181)	2: Non Adherent † (172)	3: Adherence unknown† (66)	p- value
Patient				
Percent females	42.5	50.0	40.9	0.27
Age at disease onset (years)	60.0 (53-68)	64.0 (53-70.8)	63.5 (55.8-71.0)	0.15
Height (m)	1.70 (1.62-1.80)	1.69 (1.63-1.75)	1.70 (1.60-1.78)	0.46
Weight (kg)	75.9 (63.3-84.1)	67.0 (56.1-78.1)	66.6 (57.3-80.0)	< 0.001 (1 vs. 2)
BMI (kg/m^2)	25.4 (22.7-29.7)	23.5 (20.3-27.5)	23.5 (20.2-29.1)	0.15
Ever smokers (percent)	52.5	46.5	56.1	0.33
Current smokers (percent)	7.7	11.6	13.6	0.30
Disease				
Onset to diagnosis (months)	11.0 (7.0-18.0) n = 178	10.0 (6.0-17.0) n = 171	10.0 (6.0-15.3)	0.44
Onset to NIPPV (months)	21.0 (13.0-33.0) n = 179	22.5 (14.0-35.0) n = 168	20.0 (12.5-27.0) n = 65	0.26
Initial score on bulbar FRS	9 (7-11) n = 158	8 (4-10) n = 139	9 (6 – 11) n = 56	<0.001 (2 vs. 1/3)
Initial score on cervical FRS	8 (6-10) n = 158	7 (3-9) n = 139	6 (3-8) n = 56	0.18
Pulmonary				
FVCP	52.0 (43.0-64.5)	47.0 (38.0-61.0)	43.0 (32.0-53.5)	<0.001 (3 vs. 1/2)
FEV_1P	53.0 (43.0-63.5) n = 173	48.0 (38.0-63.0) n = 167	45.0 (36.5-54.8) n = 64	0.007 (3 vs. 1)
FEV_1/FVC (percent)	80.5 (73.0-88.0) n = 173	80.7 (73.3-88.3) n = 167	83.2 (77.9-91.4) n = 64	0.12
MIPP	35.0 (27.5- 45.0) n = 149	32.5 (22.0-42.0) n = 144	28.0 (18.3-48.0) n = 52	0.07
SNIP	30.0 (22.0 – 40.5) n = 82	30 (20.5-38.0) n = 86	30.0 (20.5 – 41.5) n = 40	0.46
$PaCO_2$ (mmHg)	44.0 (40.1-47.2) n = 84	41.5 (39.0-44.8) n = 110	42.0 (39.1-49.0) n = 40	0.06
PaO_2 (mmHg)	77.0 (71.0-83.5) n = 85	79.0 (72.5-84.3) n = 110	72.9 (66.9-82.0) n = 40	0.09
Survival in months				
From onset	38.0 (25.0-64.0)	32.0 (22.00-53)	25.0 (18.0-33.0)	0.002 ‡
From diagnosis	25.0 (14.0-40.0)	21.9 (10.0-39.0)	13.0 (6.0-19.0)	<0.001 ‡
From NIPPV decision	13.0 (8.0-24.0)	7.0 (4.0-18.0)	3.0 (1.0-5.0)	< 0.001 ‡

FRS: ALS Functional Rating Scale; BMI: Body mass index; FEV_1P: Percent-predicted forced expiratory volume in the first second; FVCP: percent-predicted forced vital capacity; MIPP: percent-predicted maximal inspiratory pressure NIPPV: non-invasive positive pressure ventilation; SNIP: Sniff nasal inspiratory pressure. * Characteristic as obtained at the time NIPPV was deemed indicated unless otherwise specified

† Results reported as percent or as median (interquartile range). n refers to the number of patients in case of an incomplete set of data. ‡for linear trend Groups 1 to 3.

Table E4. Parameter estimates for the course of decline of percent predicted forced expiratory volume in one second.

Parameter	Mean (SE)	95% CI	p-value
b1 (%)	72.4 (1.5)	69.5, 75.4	< .0001
b2 (%)	-30.9 (2.0)	-34.7, -27.0	< .0001
b3 (mo.)	- 5.0 (0.6)	-0.1, -3.8	< .0001
b4 (mo.)	3.0 (0.4)	2.1, 3.8	< .0001

Parameters: b1: percent predicted forced expiratory volume in one second before onset of decline of lung function; b2: magnitude of decline in percent predicted forced expiratory volume in one second to the lower asymptote, represented in the model as a negative number; b3: time (months) relative to initiation of non-invasive ventilation to the mid-point between the two asymptotes, also representing the inflection point of the percent predicted forced espiratory volume in the first second; b4: a time scale factor (months) that reflects the rapidity of decline of percent predicted forced expiratory volume in the first second.

REFERENCES

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