Limitations of Sniff Nasal Pressure as an Outcome Measurement in Amyotrophic Lateral Sclerosis Patients in a Clinical Trial

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Key Words

Sniff nasal inspiratory pressure • Forced vital capacity • Clinical trial

Abstract

Background: The forced vital capacity (FVC) is an established measure in amyotrophic lateral sclerosis (ALS) clinical trials. Recently the sniff nasal inspiratory pressure (SNIP) test has been increasingly used as a respiratory measure. **Objectives:** It was the aim of this study to assess the feasibility of SNIP as an outcome measure in a phase III clinical trial with a lead-in design. **Methods:** Twenty patients were enrolled in a randomized clinical trial. FVC, SNIP in sitting (SNIPsitt) and supine (SNIPsup) positions, and the ALS functional rating scale score (ALSFRS-R) were measured every 4 weeks. **Results:** Complete data were available for 19 patients over 5 months. Baseline values were normal for FVC ($101 \pm 14\%$) but abnormal for SNIPsitt and SNIPsup ($84 \pm 34\%$ and $82 \pm 33\%$). While FVC and ALSFRS-R declined in parallel, SNIPsitt measures declined significantly less compared to ALSFRS-R ($p < 0.05$) and FVC ($p < 0.001$) up to 4 months after enrollment. Over 50% of patients still had values equal to or above baseline SNIPsitt measures after 3 months despite abnormal baseline values. **Conclusions:** The delayed decline in SNIP measurements suggests a learning effect over time. The op-

timal number of SNIPs in ALS clinical trials has yet to be determined. SNIP measures should be used with caution in trials with a lead-in design.

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Introduction

Although only a minority of patients with amyotrophic lateral sclerosis (ALS) initially presents with respiratory symptoms [1, 2], most patients develop these symptoms during disease progression and eventually die due to respiratory failure. Since the rate of respiratory function decline is an independent prognostic marker for survival in ALS [3–5], respiratory function tests have been used as secondary outcome measures in many clinical trials [6–8]. The most commonly applied parameter is forced vital capacity (FVC), which is a recommended outcome measure for ALS clinical trials [9, 10]. In addition, the decline in FVC in ALS patients seems to be linear in relation to the ALS functional rating scale (ALSFRS), a more global ALS assessment score [11]. However, FVC evaluation requires hermetic sealing around

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Table 1. Parameters by visit

Measurements	v1 (n = 19)	v2 (n = 19)	v3 (n = 17–19)	v4 (n = 19)	v5 (n = 19)	v6 (n = 19)	v7 (n = 19)
Days	0	12 ± 2	40 ± 4	67 ± 4	95 ± 3	122 ± 6	154 ± 7
Weeks	0	2	6	10	14	18	22
ALSFRS-R	100 ± 10	99 ± 10	98 ± 10	96 ± 12	95 ± 13	93 ± 14	92 ± 16
FVC	100 ± 14	102 ± 16	97 ± 28 (n = 18)	94 ± 19	93 ± 20	94 ± 22	92 ± 24
SNIPsitt	100 ± 31	104 ± 32	101 ± 35	102 ± 35 ^{#, **}	104 ± 38 ^{#, ***}	102 ± 40 [*]	94 ± 36
SNIPsup	100 ± 30	105 ± 33	102 ± 32 (n = 17)	103 ± 37 [*]	99 ± 34	97 ± 37	89 ± 39

Percent change from baseline (mean ± standard deviation) for all parameters. At no time point did the drop for baseline differ between ALSFRS-R and FVC. Comparisons were significantly different for SNIPsitt and SNIPsup versus ALSFRS-R ([#] $p < 0.05$) and versus FVC (^{*} $p < 0.05$, ^{**} $p < 0.01$, ^{***} $p < 0.001$).

the mouthpiece, possibly compromising the results in patients with bulbar involvement. As an alternative, the sniff nasal inspiratory pressure (SNIP), which is independent of facial muscle strength [12], has been introduced as a respiratory test in ALS patients. SNIP correlates well with invasive and nonvolitional tests of diaphragmatic strength [5] but also with the function of the sternocleidomastoid muscle [13]. Several longitudinal studies have demonstrated its usefulness to monitor respiratory function [4, 14] and to predict survival [4]. SNIP has also been used as an outcome measure in a current interventional trial applying inspiratory muscle training [15]. Despite all of these advantages, SNIP and its relation to the ALSFRS or FVC has not been used as an outcome measure in any of the large-scale phase III randomized controlled trials testing disease-modifying medications.

As there is an unmet need for suitable outcome measures which can be applied throughout the course of the disease, we sought to compare the FVC as an established outcome measure with the SNIP test in a phase III trial with a lead-in design [16].

Material and Methods

Subjects

All patients participating in this sub-study were enrolled into a multicenter, phase III, randomized, placebo-controlled trial [16]. In this trial the effects of the investigational drug TCH346 were studied. The primary outcome measure was the rate of change in ALSFRS-R; a secondary outcome measure was FVC. In this sub-study, exclusively conducted at our center, we also measured SNIP in a sitting position (SNIPsitt) and in a supine position (SNIPsup). The trial design included a 16-week lead-in phase (until visit 6; v6) to determine each patient's rate of disease progression. The trial revealed no significant differences between pla-

cebo and active treatment groups in the mean rate of decline in ALSFRS-R or in any of the secondary outcome measures including FVC and manual muscle testing [16].

The authors obtained institutional review board approval for both the primary study and the sub-study. Informed consent was obtained from all patients. Twenty ALS patients were enrolled into the study. Eligible patients were between 18 and 80 years of age with a definitive, probable, or probable laboratory-supported ALS diagnosis based on the revised El Escorial criteria [17]. Selection criteria included disease duration of no more than 3 years at the time of enrolment and an FVC of more than 70% of the predicted value.

ALSFRS-R Testing

The ALSFRS-R is a validated questionnaire which evaluates the patient's degree of functional impairment [18]. The questionnaire covers 12 different items of daily functions rated on a five-point scale from 0 (cannot do) to 4 (normal ability). The individual item scores are summarized. The lowest score is 0 (worst) and the highest is 48 (best).

Respiratory Testing

SNIPsitt, SNIPsup, and FVC were measured at baseline (v1) and after 2 weeks (v2). During the following 5 months (v2 to v7) respiratory function tests were performed at monthly intervals (table 1). EasyOne™ Diagnostic 2.15 and MicroRPM® were used for FVC and SNIP measurements. The first measurement at v1 was performed to assess whether eligible patients tolerated FVC and SNIP respiratory testing and to obtain baseline values. FVC values were normalized and expressed as a 'percent of the predicted value'. SNIP values were age- and sex-corrected [19, 20] and presented as a 'percent of the lowest predicted value'. All pulmonary function tests were performed at the beginning of the study visit by an experienced respiratory technician familiar with the applied methods. Three consecutive measurements of FVC were recorded at each time point and the best value was documented. SNIP measurements were performed as originally described [19]. A sealing plug was used to occlude one nostril during sniff performance. The plug consisted of a waxed flexible tissue fastened around the tip of a catheter connected to the pressure transducer (MicroRPM). Patients were asked to breathe normally with a

Fig. 1. Smoothened time series of measures. ALSFRS-R, FVC, SNIPsitt, and SNIPsup are expressed as the percentage change compared to v1 (baseline). Dots represent individual measures. Time points of measurements at certain visits may differ for several days (see table 1).

closed mouth and to perform at least five maximal sniffs, each separated by 30 s. No visual or verbal feedback was provided. Measurements were performed in upright (SNIPsitt) and supine (SNIPsup) positions. All maneuvers were recorded and the highest pressure was selected. If the maximal value was not obtained within five sniffs, additional maneuvers were recorded until the pressure dropped. The following criteria were used to select a suitable sniff: (i) a pressure curve showing a regular upstroke and a sharp peak and (ii) a total sniff duration of less than 0.5 s.

Statistics

To compare the four parameters ALSFRS-R, FVC, SNIPsitt, and SNIPsup across the time course (v2 to v7), the percent change from baseline (v1) was calculated for each parameter. A linear mixed effect model with the dependent variable percent change

from baseline, fixed factors time, method, and the interaction between time and method was performed. Subject was treated as a random effect. Differences in means between the four methods for each time point, 95% confidence intervals, and corresponding p values were also calculated. $p < 0.05$ was considered statistically significant. All analyses were performed using R version 2.12.0.

Results

One enrolled patient had to be excluded from this analysis because the diagnosis had to be changed. Nineteen patients (13 males and 6 females), with a mean age of

Fig. 2. Percentage of patients with values equal to or above v2 respiratory measurements. Individual measurements of FVC, SNIPsitt, and SNIPsup at v3 to v7 were determined and compared with the corresponding previous measurement at v2. In cases of equal or higher values compared to the v2 value, the patients were defined as 'nondecliners'.

58 years (range 32–75), were included in the analysis. Two patients had familial ALS; one carried a mutation in the *SOD1* gene (L144F). The mean disease duration at the time of enrollment was 19 ± 9 months (range 7–34). Two patients had bulbar onset and 17 had limb onset disease. In the latter group, only one patient had bulbar signs at the time of enrollment into the study. At the baseline evaluation (v1) the mean ALSFRS-R was 42 ± 4 and the mean FVC was still within the normal range ($101 \pm 14\%$). A high ALSFRS-R score indicates a low degree of impairment. In contrast, the baseline age- and sex-corrected mean SNIPsitt and SNIPsup values [14] were $84 \pm 34\%$ and $82 \pm 33\%$ of the predicted value. Complete data were available until v7. After v7 at week 34, two patients had died. Data of a further 5 patients were missing at 42 weeks because of the inability to perform respiratory function tests invalidating statistical analysis at later time points. Within the 5-month observation period (until v7) a continuous decline in FVC paralleled the decline in ALSFRS-R (fig. 1). At no time point did the comparison between FVC and ALSFRS-R reach a significant difference (table 1). In contrast, SNIPsitt declined significantly less compared to ALSFRS-R (v4 and v5, $p < 0.05$) and FVC (v4, $p < 0.01$, v5, $p < 0.001$ and v6, $p < 0.05$). The differ-

ence for SNIPsup compared to FVC only reached significance at v4 ($p < 0.05$) (table 1).

In addition, the proportion of patients whose SNIPsitt values were equal to or higher than the v2 value (so called 'nondecliners') was calculated. In contrast to FVC, the proportion of 'nondeclining' patients remained above 50% until v5 (fig. 2). Patients with continuous values lower than v2 SNIPsitt measures between v2 and v5 were older ($n = 5$, 66 ± 6 vs. $n = 14$, 55 ± 12 , $p < 0.05$) but did not differ from nondecliners regarding baseline ALSFRS-R score, respiratory measurements, or disease duration.

Discussion

Consistent with previous studies [4, 11, 14], we found that the decline in FVC and ALSFRS-R was linear within a 5-month observation period (v2 to v7). In our cohort the decline in FVC and ALSFRS-R was already obvious during the initial follow-up visits. Our results are also in agreement with previous studies reporting that SNIP measurements were more sensitive than FVC measurements to show impaired respiratory function [4, 12, 14, 21]. While the mean of values (percent change predicted) at study entry were normal for FVC measurements (101%) they were reduced for SNIP measurements (84 and 82%, respectively), indicating impaired function of inspiratory muscles. This is most likely due to the fact that SNIP measurement correlates well with diaphragmatic function [5] and other muscles important for inspiratory function such as the sternocleidomastoid muscle [13, 14]. The most important finding in this exploratory trial is that SNIP measurements at monthly intervals in the sitting position declined significantly less compared to ALSFRS-R and FVC up to 4 months after baseline evaluation. In addition, over 50% of patients had values equal to or above baseline SNIPsitt measures within a 3-month period after study enrollment. It is unlikely that this improved performance is investigator related since all measurements were performed by the same experienced respiratory technician. It is also unlikely that the order of tests had an impact on measures since respiratory function tests were always performed at the beginning of the study visit. Given the fact that at study entry the mean values of FVC measurements were within the normal range but SNIP measures were already $\sim 20\%$ below normal, indicating impaired diaphragmatic function, the only possible explanation is a learning effect for the SNIP maneuver in a proportion of patients. In contrast, other longitudinal studies have detected a significant decline in SNIP

measures over time [4, 14]. Several reasons may account for this discrepancy. First, the interval of measurements in our study was 4 weeks compared to mean intervals of 5.2 months [4] and 3 months [14]. It is obvious that, with progressive diaphragmatic dysfunction, longer intervals are associated with a greater chance of detecting changes over time. In fact, after v5 (3 months) a decline in SNIP measurements became apparent in our cohort. It is also reasonable to assume that any putative learning effect will be more pronounced if a maneuver is performed 4 times a week compared to, for example, 3 times a month. Second, in our study the proportion of bulbar onset patients (10%) was underrepresented compared to other studies (1/3), which may have affected mean SNIP values. Our results might be relevant to studies (i.e. those with a lead-in design) where the slope of decline of a run in period is compared with the decline during intervention. If SNIP measurements had been used in our study as an outcome measure, the decline would have coincided with the beginning of the intervention (4 months after randomization), leading to false interpretation of the data.

Previous studies have suggested a learning effect in neuromuscular patients when repeated sniff maneuvers are performed within one session [22]. For example in one study, the overall SNIP values in non-ALS neuromus-

cular patients increased by 11% with up to 20 repeated measurements compared to measures with only up to 10 sniffs [22]. The same applies to healthy subjects [22]. A persistent learning effect over months after performing 10 sniffs per session could not be seen in healthy individuals [23, 24]. It is unknown whether this is also the case in ALS patients. In our study only 5–10 sniffs per visit were performed, raising the question of whether SNIP measurements should be performed 10–20 times in ALS patients. However, in clinical settings (e.g. during regular study visits) repeated measurements over 10 times are, in our experience, not practical due to increased fatigability of the muscles [25]. This is relevant especially as the disease progresses. In line with the latter assumption, only a marginal improvement in SNIP values was obtained after increasing the number of sniffs from 10 to 20 [12]. This finding related to only 3 ALS patients who had mild to moderate impaired respiratory function [12].

In conclusion, longitudinal SNIP measurements in ALS patients might not be as reliable as previously suggested, and the optimal number of repeated measures in clinical trials with ALS patients still needs to be determined. Until then, SNIP measures in ALS patients should be used with caution in trials with a lead-in design.

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