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RESEARCH ARTICLE

Noninvasive ventilation use by patients enrolled in VITALITY-ALS

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Abstract

Objectives: To evaluate the prescribing practices of noninvasive ventilation (NIV) and patient compliance during VITALITY-ALS. *Methods:* VITALITY-ALS enrolled patients with a slow vital capacity (SVC) ≥70% of predicted who were not using NIV at screening. Physicians prescribed NIV without restriction following randomization. Reason(s) for NIV prescription, dates prescribed and initiated, and compliance were recorded. Compliance was recorded as prescribed but never initiated, used ≥2 h/24 h, used ≥4 h/24 h, or used ≥22 h/24 h. In addition to other outcome measures, SVC and the revised ALS functional rating scale (ALSFRS-R) were performed at all visits. Patients were followed up to 56 weeks. *Results:* 565 patients were randomized and dosed with placebo or *tirasemtiv* in VITALITY-ALS; 195 (34.5%) were prescribed NIV: of these, 78.5% used it for ≥2 h/24 h, 71.3% for ≥4 h/24 h, and 11.8% for ≥22 h/24 h. The three most common reasons NIV was prescribed were decline in vital capacity, respiratory symptoms, and sleep-related symptoms. During the trial, 179/565 (31.7%) patients had a decline of SVC below 50%; of these patients, 122/179 (68.2%) were prescribed NIV. Reasons for prescribing NIV were different for patients from North America compared with Europe. *Conclusions:* Despite allowing for NIV initiation at any point following randomization in VITALITY-ALS, only slightly more than two out of three patients whose SVC fell below 50% were prescribed NIV; this was similar in Europe and in North America. Underutilization of NIV could influence survival outcomes in patients with ALS including those involved in clinical trials.

Keywords: *Noninvasive ventilation, amyotrophic lateral sclerosis, respiratory insufficiency, tirasemtiv, slow vital capacity, clinical trial*

Introduction

Amyotrophic lateral sclerosis (ALS) is a disease characterized by progressive motor neuron loss leading to weakness of skeletal muscles, including those involved with respiration. Neuromuscular respiratory failure is the leading contributor to mortality (1,2) with death occurring in most patients within 2–5 years (1,3–5). As respiratory muscle strength declines, dyspnea, orthopnoea, aspiration, reduced cough and poor sleep quality may result (6). Noninvasive ventilation (NIV) is used in the management of patients with ALS with the aim to extend survival and/or time to mechanical ventilation or death in addition to improving quality of life (7,8). Despite prior studies demonstrating NIV in ALS improved survival and slowed the decline in slow vital capacity (SVC) when used at least 4 h per 24 h (7,8), a third of patients with ALS may be noncompliant with its use, and noncompliance may be even higher in those with bulbar involvement and frontotemporal dysfunction (7–10). In a study of French patients with ALS,

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only 33% of them had been using NIV at the time of death despite having a mean forced vital capacity (FVC) of 44% predicted at the visit prior to death (11).

In addition, there are substantial regional differences in the guidelines for instituting the use of NIV in patients with ALS. In the United Kingdom, the National Institute for Health and Care Excellence (NICE) guidelines for instituting NIV include FVC $< 50\%$ of predicted in the absence of symptoms or when FVC is $< 80\%$ of predicted in the presence of symptoms; additionally, NIV may be implemented based upon results of maximum inspiratory pressure (MIP) or sniff nasal inspiratory pressure (SNIP) (12). The European Federation for Neurological Societies guidelines acknowledge that there is an absence of good evidence as to when to initiate NIV but propose using presence of either symptoms or abnormalities on respiratory tests including an FVC $< 80\%$, SNIP < 40 cm, or a morning blood gas with $PaCO_2 > 45$ mm Hg (13). The American Academy of Neurology guidelines endorse following respiratory symptoms and performing serial measurements of respiratory function and recommend using NIV to treat respiratory insufficiency but include no specific criteria regarding when to institute NIV (14,15). In the United States, the timing of NIV use may be influenced by insurance regulations for coverage. Medicare is the insurance most frequently used by disabled patients with ALS. In keeping with the guidelines from the American Academy of Neurology that recommend using NIV to treat respiratory insufficiency, Medicare provides coverage of NIV in ALS when at least one of the following criteria is met: FVC $< 50\%$ of predicted, MIP < 60 cm H_2O, desaturation on sleep oximetry of $<88\%$ for 5 or more minutes, or an arterial blood gas in an awake state that reveals a $PaCO_2$ of at least 45 mm Hg (16).

VITALITY-ALS was a large phase 3, international, randomized, double-blind, placebo-controlled trial of *tirasemtiv*, a selective fast skeletal muscle troponin activator, in patients with ALS that included sites in North America and Europe; results have been reported (17). The double-blind part of the trial was 48 weeks in duration; overall trial participation was up to 56 weeks. As part of the trial, sites recorded when NIV was prescribed, the reason(s) it was prescribed, and the extent of its use. In addition to providing descriptive results of NIV use, a further objective was to determine how uniformly it was used across geographies during the trial given the known variability in recommendations for initiation. This was important because one of our secondary outcome measures was time to the first use of noninvasive ventilation, invasive ventilation or death during all 48 weeks of the trial.

Methods

Participants

Key inclusion criteria for VITALITY-ALS included the diagnosis of possible, probable, or definite ALS according to El Escorial revised criteria (18) made within the past 24 months and an upright SVC $\geq 70\%$ of predicted for age, height, and sex. Patients using any form of NIV at screening were excluded; however, following randomization, NIV use could be prescribed without restriction. Participating patients were from 11 countries in North America (Canada and the United States) and Europe (Belgium, France, Germany, Ireland, Italy, Netherlands, Portugal, Spain and the United Kingdom).

All patients provided written informed consent, and institutional review board approvals were received from sites prior to screening. The study was conducted in accordance with the Declaration of Helsinki. An independent data and safety monitoring board monitored unblinded data throughout the study. The study was registered with ClinicalTrials.gov (NCT02496767).

Assessments

Outcomes measures including revised ALS functional rating scale (ALSFRS-R) and SVC were performed at all clinic visits. Baseline demographics including age, sex, and site of ALS onset were recorded for all patients. Site investigators were free to prescribe NIV according to their usual practices; no recommendations regarding its institution were included in the protocol or the study manual. There were no restrictions regarding obtaining additional pulmonary measures beyond what was required by the protocol and using those results to determine interventions. If pulmonary measures not included in the protocol were performed, results were not recorded in the electronic case report form. For those patients who were prescribed NIV, the date of the prescription was recorded. The extent of NIV use was also documented, with the following options: prescribed but never initiated, used ≥ 2 h per 24 h for at least 5 consecutive days, used ≥ 4 h for per 24 h for at least 5 consecutive days, and used ≥ 22 h per 24 h for at least 10 consecutive days. Hours of NIV use were self-reported. The possible reason(s) for the patient being prescribed NIV included SVC, respiratory symptoms, sleep-related symptoms, SNIP, overnight pulse oximetry, blood gas $PaCO_2$, or other. Sites could choose as many options as needed. Frequency of NIV use and prescription reasons were presented in terms of the number and percentage of patients in North America and Europe. Comparisons between categorical variables were performed using the Cochran–Mantel–Haenszel general association test stratified

by riluzole use or nonuse, pooled *tirasemtiv* and placebo. Comparisons between continuous variables were performed using ANCOVA stratified by riluzole use or nonuse, pooled *tirasemtiv* and placebo.

Results

Eligible patients first entered a 2-week open-label phase to confirm *tirasemtiv* was tolerated; of the 744 patients enrolled, 565 tolerated the drug in the open-label phase, were randomized, and received either double-blind placebo or one of three dose levels of *tirasemtiv*. As previously reported, there was no difference in NIV use after randomization as a function of treatment assignment (17), and therefore this analysis includes all patients prescribed NIV independent of treatment assignment. Of the 565 patients who were dosed with placebo or *tirasemtiv* in VITALITY-ALS, 195 (34.5%) were prescribed NIV (this includes three patients who were prescribed NIV prior to the screening visit and one patient listed as "No" to NIV prescription but with an NIV start date recorded; these four patients were treated as patients prescribed NIV). Of these, 19 (9.7%) never initiated use (reason was not tracked); this was more likely in North America than in Europe (12.1% vs. 2.2%, $p = 0.049$). Otherwise, extent of use was similar across the geographies. The largest percentage (78.5%) of patients who used NIV did so at least 2 h per day, with only a slightly smaller percentage (71.3%) using it at least 4 h per day (Table 1). Among the patients who were prescribed NIV, 50% started 4-h NIV use on day 1; the mean time to 4-h NIV use was 58.3 days (the time to 22-h use in 50% of the patients was not estimable). The mean time to 22-h use was estimated as 245.3 days. In terms of patients who were started on NIV and then stopped based on ALSFRS-R Q12 responses, eight patients started NIV and then discontinued, seven patients used it intermittently, and one had used it all night. In each instance, all patients returned to reporting no NIV use by the subsequent scheduled visit.

Reasons for prescribing NIV differed in North America compared with Europe. The most common reason to prescribe NIV in North America was SVC results, while respiratory symptoms was the most common reason in Europe. Overnight pulse oximetry was a reason NIV was prescribed in 10.3% of patients overall; it was much more likely to be a reason in Europe than in North America (26.1% vs 5.4%, $p = 0.0002$). Frequency of prescribing NIV for sleep-related symptoms, SNIP values, and results of arterial blood gases were similar in North America and Europe (Table 2).

No significant differences in baseline characteristics of age, sex, site of onset, or the ALSFRS-R scores related to sialorrhea, dyspnea, or orthopnoea at the time of the prescription were noted between patients who used NIV at least 4 h per

Table 1. Details of NIV use.

NIV use	Patients prescribed NIV ($n = 195$) n (%)	North America ($n = 149$) n (%)	Europe ($n = 46$) n (%)	p Value (North America vs Europe)
Never initiated	19 (9.7)	18 (12.1)	1 (2.2)	0.049[a]
≥2 h/24 h[b]	153 (78.5)	114 (76.5)	39 (84.8)	0.21
≥4 h/24 h[b]	139 (71.3)	106 (71.1)	33 (71.7	0.85
≥22 h/24 h[c]	23 (11.8)	17 (11.4)	6 (13.0)	0.79

[a]p Value derived from Fisher exact test.
[b]For ≥5 consecutive days.
[c]For ≥10 consecutive days.
NIV: Noninvasive ventilation.

Table 2. Reasons for prescription of NIV.

Reasons NIV prescribed, n (%)	Total ($n = 195$)	North America ($n = 149$)	Europe ($n = 46$)	p Value[a] (North America vs. Europe)
SVC	105 (53.8)	87 (58.4)	18 (39.1)	0.0277
Respiratory symptoms	90 (46.2)	60 (40.3)	30 (65.2)	0.0039
Sleep-related symptoms	46 (23.6)	37 (24.8)	9 (19.6)	0.5536
SNIP	6 (3.1)	5 (3.4)	1 (2.2)	1.00
Overnight pulse oximetry	20 (10.3)	8 (5.4)	12 (26.1)	0.0002
Blood gas $PaCO_2$	8 (4.1)	5 (3.4)	3 (6.5)	0.40
Other	13 (6.7)	8 (5.4)	5 (10.9)	0.19

Note: Totals are greater than the number for whom NIV was prescribed because investigators could choose more than one reason for the prescription.
[a]p Value derived from Fisher exact test.
NIV: Noninvasive ventilation; SNIP: sniff nasal inspiratory pressure; SVC: slow vital capacity.

day and those who used it less or not at all (Table 3). Of note, cognitive impairment was an exclusion criterion for the trial. We compared the extent of NIV for patients prescribed the device for findings alone (results of SVC, sleep studies, arterial blood gas studies, and MIP) to patients in whom it was prescribed for symptoms (dyspnea, orthopnoea, daytime fatigue, dry throat, excessive secretions, sleep complaints) with or without findings. NIV was used ≥4 h per 24 h by 48/74 (64.9%) patients who were prescribed NIV because of findings only and in 89/116 (76.7%) patients who were prescribed it for symptoms only or symptoms in combination with findings ($p = 0.08$).

Overall, 195/565 patients (34.5%) were prescribed NIV during the trial, with similar proportions in North America and in Europe (35.0% and 33.1%, respectively). No geographic difference was observed in the SVC value at the

Table 3. Baseline demographics and symptoms of sialorrhoea, dyspnea, and orthopnoea at time NIV prescribed.

	Never used/used NIV <4 h per 24 h[a]	Used NIV at least 4 h per 24 h	*p* Value
Number of patients	55	139	
Mean age (SD), y[b]	57.2 (11.3)	58.7 (9.7)	0.40
Sex[c], *n* (%)			
Female	17 (30.9)	41 (29.5)	0.54
Male	38 (69.1)	98 (70.5)	
Site of onset[c], *n* (%)			
Bulbar	11 (20.0)	22 (15.8)	0.35
Extremity	44 (80.0)	116 (83.5)	
ALSFRS-R Q2[b,d]			
n	54	135	
Mean (SD)	2.94 (1.28)	3.24 (0.95)	0.36
ALSFRS-R Q10[b,d]			
n	54	135	
Mean (SD)	2.87 (1.08)	2.89 (1.08)	0.95
ALSFRS-R Q11[b,d]			
n	54	135	
Mean (SD)	3.07 (1.08)	3.21 (1.07)	0.58

Note: One patient who was prescribed NIV did not provide an answer to NIV use and was excluded from the analysis.
[a]Patients who never initiated NIV or who used but never increased use to ≥4 h for 5 days or greater.
[b]*p* Value was obtained from an ANCOVA model with treatment (pooled *tirasemtiv* or placebo), riluzole use or nonuse, and indicator of NIV use (never used/<4 h, or used at least 4 h) as fixed effects comparing patients who never used/used <4 h vs. patients who used NIV for at least 4 h. Baseline was included in the model when applicable.
[c]*p* Value was obtained from Cochran–Mantel–Haenszel general association test stratified by riluzole use or nonuse, pooled *tirasemtiv* and placebo comparing patients who never used/used NIV < 4 h vs. patients who used it at least 4 h.
[d]Last ALSFRS-R assessment prior to NIV prescription was included in the analysis.
ALSFRS-R: Revised ALS functional rating scale; ANCOVA: analysis of covariance; NIV: noninvasive ventilation; Q: question; SD: standard deviation.

Table 4. Summary of SVC findings as related to NIV prescription.

	Total ($n = 565$)	North America ($n = 426$)	Europe ($n = 139$)	*p* Value (North America vs. Europe)
Number of patients prescribed NIV, *n* (%)[a]	195 (34.5)	149 (35.0)	46 (33.1)	0.45
SVC value at time NIV prescribed, mean (SD)[b]	($n = 190$) 63.14 (19.70)	($n = 144$) 63.12 (19.28)	($n = 46$) 63.21 (21.15)	0.23
Patients with SVC < 50% and NIV not prescribed/patients with SVC < 50%, *n*/*N* (%)	57/179 (31.8)	38/133 (28.6)	19/46 (41.3)	0.21

[a]Three patients who were prescribed NIV prior to the study start and one patient who answered no to NIV prescriptions but recorded NIV start date were also treated as patients prescribed NIV. *p* Value obtained from Cochran–Mantel–Haenszel general association test stratified by riluzole use or nonuse, pooled *tirasemtiv* and placebo comparing North America vs. Europe.
[b]*p* Value is obtained from an ANCOVA model with baseline, region (North America or Europe), treatment group (pooled *tirasemtiv* or placebo) and riluzole use or nonuse as fixed effects comparing North America vs. Europe. Last SVC assessment prior to NIV prescription was included in the analysis.
ANCOVA: Analysis of covariance; NIV: noninvasive ventilation; SD: standard deviation; SVC: slow vital capacity.

Table 5. NIV use in patients with SVC < 50% by country and region.

Country	Total number of patients prescribed NIV *N*	Patients using NIV with SVC < 50% *n* (%)
Europe		
Belgium	1	1 (100)
France	3	2 (66.7)
Germany	7	2 (28.6)
Ireland	7	4 (57.1)
Italy	17	12 (70.6)
Netherlands	1	0
Portugal	3	1 (33.3)
Spain	5	4 (80.0)
United Kingdom	1	1 (100)
Total Europe	46	27 (58.7)
North America		
Canada	40	25 (62.5)
United States	109	70 (64.2)
Total North America	149	95 (63.8)

NIV: Noninvasive ventilation; SVC: slow vital capacity.

time of prescription. There were 179 patients (with similar proportions in the two regions) who had a recorded SVC below 50% of predicted, and of those 31.8% were not prescribed NIV. The proportions of patients with an SVC <50% of predicted who were not prescribed NIV were similar between geographies (Tables 4 and 5).

Discussion

In a survey of US and European ALS experts, insurance regulations were reported to play a role in NIV initiation more in the United States than in Europe, with vital capacity measurement reported as most likely to drive the decision for US experts, while symptoms of dyspnea or orthopnoea were the most common deciding factor for European experts. In the presence of respiratory symptoms, European ALS experts reported they would initiate NIV at a higher vital capacity than reported by US experts. In evaluating respiratory status in patients with ALS, European respondents were more likely to use overnight pulse oximetry or arterial blood gas analyses than those in the United States (18). Given these survey responses, in addition to recognizing insurance coverage for NIV in many European countries is more favorable to earlier NIV use, we expected the proportion of NIV use in European patients would be higher and patients would be prescribed NIV at higher SVC values compared with North American patients enrolled in VITALITY-ALS. In contrast, the proportion of patients prescribed NIV in Europe compared with North America was nearly identical (33.1% and 35.0% respectively), as was the SVC at the time of prescription (63.2% and 63.1%, respectively). The three most common reasons for initiating NIV were SVC results, respiratory symptoms, and sleep-related symptoms, with SVC being the most common reason in North America and respiratory symptoms being the most common reason in Europe. These results are in line with what was reported in the survey of ALS specialists (18).

One of the earliest reports of NIV use in patients with ALS found that one-third of patients refused to try it, one-third used it less than 4 h per 24 h, and one-third used it 4 or more h per 24 h (described as NIV tolerant) (8). In VITALITY-ALS, these numbers are much improved, with only 9.7% of patients refusing to try it, and 71.3% meeting the criteria for tolerating NIV, a very similar value for tolerance reported in an article published in 2005 (9). This trend to improvement in the percentage of patients tolerating NIV over time may be multifactorial and include better mask interfaces and advancements in the machines. We relied on self-reporting the number of hours NIV was used, which is a limitation of the study given that patients tend to over-estimate such use. We did not find tolerance to be impacted by sialorrhea as determined by the response to Question 2 in the ALSFRS-R. This question is answered as what best describes their symptoms even if they are receiving treatment to diminish saliva production. Therefore, the relative lack of sialorrhea could be either from absence of this symptom even without treatment, or the response to treatment. We compared the combined scores for Q1 (speech) and Q3 (swallowing) for those patients who used NIV $\leq$ 2 h to those who used it $\geq$ 4 h; the least square mean difference was $-.0574$ ($p = 0.0073$) suggesting patients with worse speech and swallowing function used NIV for fewer hours. While a prior study found orthopnoea was the best predictor of NIV compliance (19), we did not find that the reason for NIV prescription was predictive of tolerating NIV. Earlier studies suggested patients with bulbar onset disease were less likely to be NIV tolerant (9,19) or less likely to benefit regarding survival (7). However, an Australian study recently found even bulbar onset patients may tolerate NIV and also had a survival benefit conveyed by NIV use (20); this may be related to more aggressive sialorrhoea management prior to initiating NIV. An Italian study found that very early (instituting NIV with a SVC $\geq$ 80%) compared to later (SVC < 80%) NIV use was associated with improved survival for both extremity and bulbar onset patients (21). Our findings, together with the Australian and Italian studies, suggest that bulbar onset disease does not necessarily preclude prescribing NIV. We acknowledge, however, that facial weakness may make the mask fit problematic and may preclude patients, while awake, from utilizing the sip and puff mode if they are using a

ventilator to provide their noninvasive ventilation. Sialorrhea, if not treated, may result in the mask filling with saliva. Managing NIV in patients with bulbar involvement may take more time and adjustments from the physician and respiratory therapist.

Perhaps most surprising was the finding that nearly one-third of patients with an SVC below 50% of predicted were not prescribed NIV. This is despite multiple published studies that have found a survival benefit in addition to improved quality of life for those patients with ALS who tolerate using it (7–9,20). A study of NIV use from the pooled resource open access ALS clinical trial (PRO-ACT) database reported only 52.5% of patients whose vital capacity was below 50% used NIV (22). Given that our patients and those in the PRO-ACT study were being seen regularly at ALS centers as part of clinical trials, with more frequent visits than occur during routine ALS care, the number of patients not prescribed NIV despite a reduced vital capacity may be even higher in patients seen in different settings. Clinical judgment may not be predicated on a single measure, particularly in a clinical trial setting, when patients are reviewed on a regular basis and receive more intensive follow-up than the general population. We did not ask the PI's why a patient with an SVC below 50% was not started on NIV. The physician may have believed the result was inaccurate (for example, the patient had marked facial weakness that precluded a good seal). The provider may have wanted to avoid adding burden, particularly if the patient had no symptoms of orthopnea or dyspnea and had limited hand use, and so would have needed assistance from a caregiver to take the mask on or off. In addition, following a discussion with their physicians about NIV, patients may have declined it outright, and therefore it may have never been prescribed although it had been recommended. These factors may have contributed to why some patients may not have been prescribed NIV despite their SVC results, although other factors may have played a role as well.

Future studies to improve our understanding of NIV use could include a question to the physician when the patient's VC falls below 50% and NIV is not initiated, to determine why it was not begun. Similarly, if the physician initiates a conversation with the patient about NIV prior to a decline in VC below 50% predicted and the patient refuses, recording why the conversation was held and the reason(s) for the patient's refusal could be important. There are diverse brands and models of devices that can be used to provide noninvasive ventilation, different modes of delivering ventilatory support, and at least some machines have the capability of recording data on hours of use per day. Gathering this additional information from patients living in different countries, along with initial and subsequent ventilatory settings, could be helpful to better understand NIV initiation and acceptance, and if there are differences between compliance as well as symptomatic and survival benefits depending upon these variables.

Overall, patients were willing to initiate NIV when it was recommended regardless of the reason, and the vast majority tolerated it for at least 4 h per 24 h. However, even when SVC was below 50% of predicted, it was not always prescribed in our study, raising the question of how frequently NIV is not prescribed when VC falls below 50% predicted in clinical practice. Insufficient NIV use may result in worse outcomes both for patients participating in clinical trials and those receiving care outside clinical trials. Patients participating in clinical trials may be more aggressive about pursuing therapeutic interventions for their ALS, and so one might expect higher utilization of NIV for trial participants than for patients not involved in clinical trials. Better understanding of how VC correlates with other measures, such as overnight pulse oximetry and SNIP, particularly in those patients whose disease may make VC testing problematic, is needed to fully understand the repercussions of inconsistent NIV use. In the meantime, continued

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physician and patient education regarding when to consider NIV for patients with ALS may be useful in improving rates of NIV use and, over time, may improve survival.

The VITALITY-ALS study group

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