Evaluating effects of risdiplam in adults with spinal muscular atrophy: a monocentric study

Received: 10 June 2025
Accepted: 7 Oct 2025

To the Editor:

Spinal muscular atrophy (SMA) is a rare, autosomal recessive neuromuscular disorder caused by reduced survival motor neuron (SMN) protein due to mutations in the SMN1 gene [1]. In humans, this protein is also produced by a "backup" gene, SMN2. Two drugs, nusinersen and risdiplam, are available, which lead to the production of more full-length, functional SMN protein from the SMN2 gene [2].

Research suggests that, in adult SMA, pharmacological therapies improve motor function. However, further evaluation may be necessary to clarify their impact on respiratory function. Indeed, in most studies, forced vital capacity (FVC) was used as the main, or the only, outcome measure to assess drug effects [3, 4]. Adult SMA patients have a rigid and dysmorphic rib cage that may hamper changes in FVC. Besides, their limited ability to open the mouth can make it difficult to hold mouthpieces and result in measurements with poor reliability. Sniff nasal inspiratory pressure (SNIP) has not been used to evaluate respiratory outcomes of pharmacological therapies for SMA, despite its good performance in this disease [5]. Another crucial unknown question is whether changes in lung function, as shown by respiratory tests, are subjectively perceived by the patients.

In this study, we explored: 1) changes in lung function after risdiplam treatment demonstrated by SNIP and FVC, and 2) whether these objective changes are associated with subjective perception of a change.

The study was performed by a multidisciplinary team at the Department of Neurology of the University of Palermo in accordance with the amended Declaration of Helsinki. The project was approved by the Territorial Ethics Committee of the University (approval number: 202513).

22 consecutive patients aged ⩾16, naïve to pharmacological SMA treatment, were recruited. Subjects with recent surgery, infections or pregnancy were excluded. Risdiplam was administered in a single daily oral dose of 5 mg. Patients were not taking other potentially disease-modifying medications. FVC and SNIP were measured immediately before and after 12 months of therapy. They were performed in strict accordance with the guidelines of the American Thoracic Society and the European Respiratory Society [6, 7].

For comparisons, a paired Student's t-test or a Wilcoxon test was used. Treatment effect was quantified using Cohen's *d*. Concordance between FVC and SNIP changes was assessed with Cohen's kappa coefficient. Baseline FVC and SNIP were categorised into quartiles to explore associations with treatment response, clinical phenotype and SMN2 copy number. For this purpose, exploratory bivariate associations were assessed using chi-square or Fisher's exact tests, as appropriate.

For both FVC and SNIP, we aimed to search for the minimal clinically important difference (MCID) between two measures [8]. The patients, blinded to the results of post-treatment assessment, were asked to rate the overall respiratory health change they perceived by answering the following question: "Compared with the first assessment/visit, how much change do you perceive in your overall respiratory and health status after 12 months of treatment?" They had to answer using the Global Rating of Change (GROC) scale [9], a 15-point ordinal scale ranging from −7 ("a great deal worse") to +7 ("a great deal better"). The score +4 has been identified as the threshold value that separates the subjects "improved" from those

Shareable abstract (@ERSpublications)
In adults with SMA, risdiplam therapy may improve respiratory function. In these patients, sniff nasal inspiratory pressure is the most effective test to demonstrate effects of pharmacological therapy. https://bit.ly/3Wk2MCU

Cite this article as: Crescimanno G, Alonge P, Lupica A, *et al*. Evaluating effects of risdiplam in adults with spinal muscular atrophy: a monocentric study. *ERJ Open Res* 2026; 12: 01120-2025 [DOI: 10.1183/23120541.01120-2025].

"stable/not improved" to a moderate to substantial extent [10]. The GROC scale score was employed as the anchor variable to determine MCID. For both FVC and SNIP, determination of MCID was considered appropriate if the Spearman correlation coefficient between change after therapy and GROC score was ⩾0.30 [8]. Using receiver operating characteristic curves, the optimal cut-off for the change in the variable under study associated with a score of +4 on the GROC scale was identified. The value associated with the largest area under the curve was considered to represent MCID. A MCID could not be identified if the area under the curve was <0.7.

One patient was excluded from the analysis after discontinuing the medication at six months due to mild adverse effects. His respiratory function was monitored over time, and it is currently stable. 13 female and eight male subjects completed the study. Mean age was 33.2±14.9 years. 14 patients had SMA type 2 (10 patients with two copies of SMN2 and four patients with three copies) while seven patients had SMA type 3 (five with three copies and two with four copies).

10 patients with SMA type 2 were advised to start noninvasive ventilation, but only five accepted. Changes in respiratory tests did not differ between SMA type 2 patients using or not using this therapy.

After therapy, improvements were observed in both SNIP (52.9±18.5 to 59.3±18.8 cmH_2O, p=0.0038) and FVC (1.30 ±1.0 to 1.39±1.0 L, p=0.020) (figure 1). The Cohen's *d* effect sizes for absolute values of SNIP and FVC were 0.72 and 0.56, respectively.

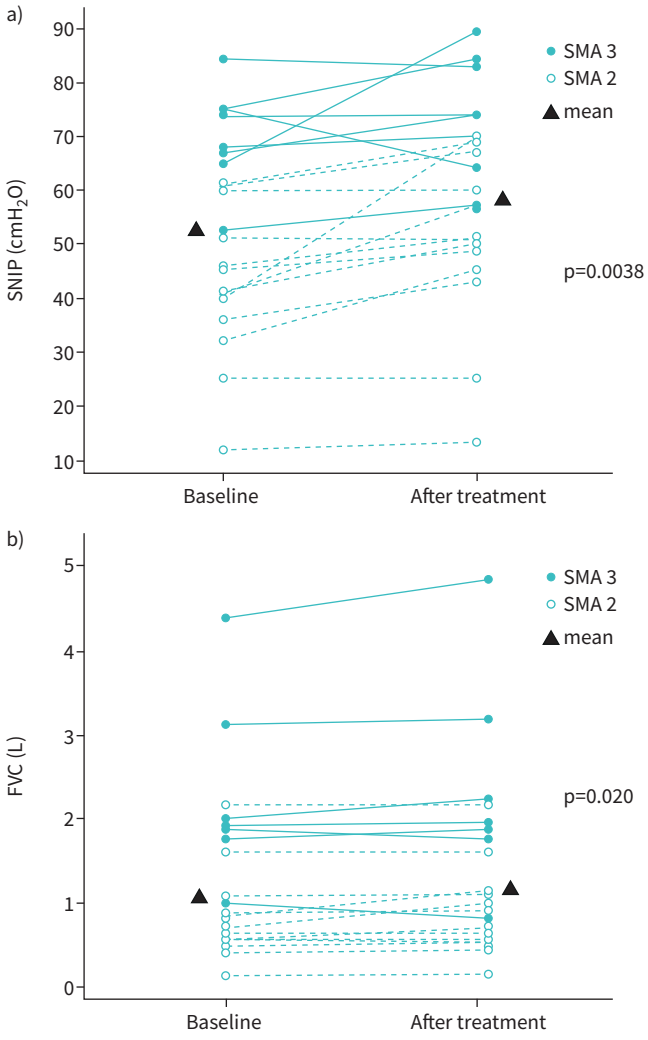

FIGURE 1 a) Plot of individual changes in sniff nasal inspiratory pressure (SNIP) in cmH_2O after 12 months of treatment. b) Plot of individual changes in forced vital capacity (FVC) in litres after 12 months of treatment. SMA: spinal muscular atrophy.

GROC scores were collected in 18 patients. 50% of patients had a GROC score ⩾4 and were considered improved, while the remaining 50% were classified as "stable/not improved". SNIP, but not FVC, increased significantly in the group classified as "improved" (p=0.009), but not in the other group.

GROC scores correlated with changes in SNIP, both as absolute values and as percentages of predicted values (rho=0.44 and 0.45, respectively), but not with changes in FVC. Consequently, the MCID was calculated only for SNIP. The area under the curve for the relationship between SNIP changes and GROC was 0.86 (95% CI 0.69–1.00) for absolute SNIP values, and 0.87 (95% CI 0.73–1.00) for percentage of predicted values, indicating good discrimination between "improved" and "stable/not improved" patients. A change of >6 cmH_2O (sensitivity 75%, specificity 80%) or >6.9% pred (sensitivity 75%, specificity 90%) represented MCID for SNIP.

Nine patients, who showed an increase in SNIP >6 cmH_2O, were considered subjectively improved; 11 patients with a SNIP change <6 cmH_2O were considered in a stable status; the remaining patient, who showed a SNIP reduction >6 cmH_2O, was considered in a worse subjective condition.

FVC increased by ⩾100 mL in seven patients, changed by <100 mL in 12, and decreased by ⩾100 mL in two subjects. SMA phenotype was not related to the direction or magnitude of SNIP (p=0.36) or FVC (p=0.62) change.

Concordance between changes in SNIP and FVC was limited (Cohen's Kappa coefficient=0.052, 95% CI −0.30 to 0.40).

Across all contingency tables performed to evaluate the association of treatment with baseline respiratory function, phenotype, or number of SMN2 copies, effect sizes were generally in the small-to-moderate range (Cramér's V between 0.19 (95% CI 0.07–0.67) and 0.41 (95% CI 0.05–0.72)) with only baseline SNIP showing a stronger effect (Cramér's V=0.49 (95%CI 0.38–0.78)). None of these associations reached statistical significance.

Our results show that, in adult SMA, both SNIP and FVC improve with risdiplam therapy. However, the improvement in SNIP had a greater effect size. Besides, unlike the improvement in FVC, it correlated with changes in patients' sense of well-being. The relative preservation of diaphragm function allows SMA patients to maintain a relatively high SNIP, which was the measurement found to better-correlated to subjectivity. The moderate effect size of FVC may explain why in previous studies with small patient samples, changes in FVC were not significant and were not correlated to subjective feelings of improvement [4]. However, the limited concordance between changes in SNIP and FVC suggests that they may explore partly different functional aspects, so that a comprehensive respiratory evaluation should include both measurements. We did not find differences in response to therapy by baseline respiratory function, phenotype or the number of SMN2 copies, but our sample size may have been insufficient for that demonstration.

In conclusion, in adult patients with SMA started on risdiplam we found improvements in FVC and, consistent with previous studies on children, also in SNIP. SNIP measurements had a greater magnitude of difference with therapy and, unlike FVC changes, correlated with subjective perception of health.

Grazia Crescimanno[1,2], Paolo Alonge[2], Antonino Lupica[2], Vito Tomasello[2], Vincenzo Di Stefano[2], Filippo Brighina[2] and Oreste Marrone[1]

[1]National Research Council, Institute of Biomedical Research and Innovation (IRIB-CNR), Palermo, Italy. [2]Regional Centre for Diagnosis and Treatment of Neuromuscular Disease, Department of Biomedicine, Neuroscience and Advanced Diagnostic (BIND), University of Palermo, Palermo, Italy.

Corresponding author: Grazia Crescimanno (grazia.crescimanno@irib.cnr.it)

Data availability: Data will be made available by the authors for global collaboration upon reasonable request, subject to national restrictions imposed by privacy laws and ethics.

Provenance: Submitted article, peer reviewed.

Author contributions: G. Crescimanno takes responsibility for the integrity and accuracy of the data analysis. Concept and design: G. Crescimanno, P. Alonge, A. Lupica, V. Tomasello, V. di Stefano and F. Brighina. Analysis and interpretation of data: all authors. Drafting of the manuscript: G. Crescimanno and O. Marrone. Critical revision of the manuscript for important intellectual content: O. Marrone. Approval of the final draft: all authors. Statistical analysis: G. Crescimanno.

Ethics statement: the study was approved by the Territorial Ethics Committee of the University of Palermo, Italy (approval number: 202513). All participants provided written informed consent to participate in the study.

Conflict of interest: All authors have confirmed that they have no conflicts of interest to declare.

Support statement: No funding declared.

References

1 Dubowitz V. Ramblings in the history of spinal muscular atrophy. *Neuromuscul Disord* 2009; 19: 69–73.
2 Antonaci L, Pera MC, Mercuri E. New therapies for spinal muscular atrophy: where we stand and what is next. *Eur J Pediatr* 2023; 182: 2935–2942.
3 Aldukain M, Aldukain A, Hobani A, *et al.* The impact of nusinersen treatment on respiratory function in patients with spinal muscular atrophy: a systematic review. *J Clin Med* 2024; 13: 6306.
4 Pascual-Morena C, Martínez-Vizcaíno V, Cavero-Redondo I, *et al.* Efficacy of risdiplam in spinal muscular atrophy: a systematic review and meta-analysis. *Pharmacotherapy* 2024; 44: 97–105.
5 Crescimanno G, Lupica A, Tomasello V, *et al.* Multiple respiratory assessment and thresholds for noninvasive ventilation in adult patients with spinal muscular atrophy. *Sci Rep* 2025; 15: 6478.
6 American Thoracic Society/European Respiratory Society. ATS/ERS statement on respiratory muscle testing. *Am J Respir Crit Care Med* 2002; 166: 518–624.
7 Laveneziana P, Albuquerque A, Aliverti A, *et al.* ERS statement on respiratory muscle testing at rest and during exercise. *Eur Respir J* 2019; 53: 1801214.
8 Klukowska AM, Vandertop WP, Schröder ML, *et al.* Calculation of the minimum clinically important difference (MCID) using different methodologies: case study and practical guide. *Eur Spine J* 2024; 33: 3388–3400.
9 Kamper SJ, Ostelo RW, Knol DL, *et al.* Global Perceived Effect scales provided reliable assessments of health transition in people with musculoskeletal disorders, but ratings are strongly influenced by current status. *J Clin Epidemiol* 2010; 63: 760–766.e1.
10 Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials* 1989; 10: 407–415.