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RESPIRATORY AND NUTRITIONAL OUTCOMES DURING SMN-DIRECTED THERAPY IN PATIENTS WITH 5q-SPINAL MUSCULAR ATROPHY

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Introduction. Spinal muscular atrophy (SMA) is a progressive hereditary neuromuscular disorder caused predominantly by biallelic pathogenic variants of the SMN1 gene. Deficiency of functional survival motor neuron protein results in progressive degeneration of α-motor neurons, producing symmetrical muscle weakness, muscular atrophy and progressive loss of motor abilities. Although impairment of motor function represents the most evident clinical manifestation of SMA, respiratory, bulbar and nutritional complications are also major determinants of disease burden and long-term prognosis.

The introduction of SMN-directed disease-modifying therapies has fundamentally changed the natural history of SMA. Modern therapy may stabilize motor function and allow some patients to acquire previously unattainable motor milestones. However, improvements in motor performance are not necessarily accompanied by an equivalent recovery of respiratory and nutritional functions. Respiratory insufficiency in SMA is influenced by respiratory muscle weakness, ineffective cough, recurrent lower respiratory tract infections, scoliosis and chest wall deformity. Similarly, nutritional problems may arise from dysphagia, impaired swallowing safety and progressive

bulbar dysfunction.

Therefore, assessment of treatment effectiveness should include not only standardized motor scales but also respiratory support requirements, incidence of respiratory complications and nutritional status.

Aim. To evaluate respiratory and nutritional outcomes during 12 months of SMN-directed pathogenetic therapy in patients older than 16 years with genetically confirmed 5q-associated spinal muscular atrophy and to assess whether the timing of treatment initiation is associated with differences in these clinical outcomes.

Materials and Methods. A prospective comparative clinical and functional study included 60 patients older than 16 years with genetically confirmed 5q-associated SMA types I–III. Molecular diagnosis was based on identification of biallelic SMN1 abnormalities, while SMN2 copy number was determined using multiplex ligation-dependent probe amplification.

Patients were divided into two groups according to the interval between molecular confirmation of SMA and initiation of pathogenetic treatment. Group I consisted of 30 patients in whom SMN-directed therapy was started within the first three months after diagnosis. Group II included 30 patients in whom therapy was initiated more than three months after diagnostic confirmation.

Clinical evaluation included neurological examination and standardized assessment of motor function using CHOP INTEND, HFMSE and RULM scales. In addition, respiratory status was assessed by the requirement for non-invasive or invasive ventilatory support, need for cough-assistance techniques, occurrence of lower respiratory tract infections and hospitalizations due to respiratory complications. When appropriate, respiratory evaluation also included forced vital capacity and pulse oximetry.

Nutritional assessment included body weight dynamics, mode of feeding, ability to maintain safe oral intake, need for additional enteral nutrition and development or

progression of dysphagia. Patients were evaluated at baseline and during a 12-month follow-up period.

Results. The study population included 27 patients with SMA type I, 25 patients with SMA type II and 8 patients with SMA type III. The groups were generally comparable in terms of SMA phenotype and SMN2 copy number. At baseline, non-invasive ventilation was required by 6 patients (20.0%) in Group I and 11 patients (36.7%) in Group II. Additional enteral nutritional support was used by 3 patients (10.0%) in Group I and 7 patients (23.3%) in Group II.

After 12 months of follow-up, absence of a need for permanent ventilatory support was documented in 28 of 30 patients (93.3%) in the earlier-treatment group and in 24 of 30 patients (80.0%) in the later-treatment group. Although the numerical difference favored earlier treatment, it did not reach statistical significance (p=0.254).

Severe respiratory infections requiring hospitalization were absent during the observation period in 80.0% of Group I patients compared with 60.0% of Group II patients (p=0.158). These findings indicated a favorable tendency toward better respiratory stability among patients treated earlier, although the difference between groups remained statistically non-significant.

Nutritional status was stable or improved in 25 patients (83.3%) in Group I and 19 patients (63.3%) in Group II (p=0.144). New or progressive swallowing impairment was documented in 2 patients (6.7%) in the earlier-treatment group compared with 7 patients (23.3%) among those receiving later treatment (p=0.145).

In contrast to the respiratory and nutritional endpoints, motor outcomes demonstrated more pronounced intergroup differences. Clinically meaningful improvement in motor function occurred in 76.7% of patients treated earlier and 46.7% of those treated later. Acquisition of at least one new motor milestone was documented in 70.0% and 36.7%, respectively.

The frequency of clinically significant adverse events was comparable between the two groups: 23.3% in Group I and 26.7% in Group II, indicating that earlier initiation of therapy was not associated with an increased rate of clinically relevant adverse events.

Discussion. The study demonstrates that the response of different functional systems to SMN-directed therapy is not uniform. Motor outcomes showed the clearest advantage associated with earlier treatment, whereas respiratory and nutritional parameters demonstrated favorable but statistically non-significant trends.

This difference may reflect the complex pathophysiology of respiratory and bulbar dysfunction in SMA. Once severe weakness of respiratory muscles, thoracic deformity, scoliosis, chronic ineffective cough or swallowing impairment have developed, increasing SMN protein availability may not completely reverse established structural and functional abnormalities. Consequently, restoration of motor capacity may occur more rapidly and consistently than improvement in respiratory or nutritional functions.

The findings also emphasize that disease-modifying treatment should not replace comprehensive supportive care. Even in patients demonstrating clear motor improvement, multidisciplinary management remains essential and should include respiratory monitoring, prevention and treatment of respiratory infections, cough assistance, nutritional assessment, swallowing evaluation, rehabilitation and orthopedic surveillance.

The numerically better respiratory and nutritional outcomes in patients treated earlier additionally suggest that timely initiation of therapy may contribute not only to preservation of motor neurons but also to maintaining a higher overall functional reserve. Nevertheless, larger multicenter studies are required to determine the independent impact of treatment timing on non-motor outcomes.



Conclusion. During 12 months of SMN-directed therapy, patients who began treatment earlier demonstrated a tendency toward better respiratory stability and more favorable nutritional outcomes than patients with delayed treatment initiation. The proportions of patients remaining free from permanent ventilation, severe respiratory hospitalization and nutritional deterioration were numerically higher in the earlier-treatment group. However, unlike motor outcomes, most differences in respiratory and nutritional endpoints did not reach statistical significance. These findings support a comprehensive model of SMA management in which early pathogenetic treatment is combined with continuous multidisciplinary respiratory, nutritional, neurological and rehabilitative care.