GNYACSM Abstract

Impact of Nusinersen Treatment on Measures of Exercise Intolerance in Spinal Muscular Atrophy

DAVID UHER, ASHLEY M. GOODWIN, DARRYL C. DE VIVO, JACQUELINE MONTES, CAROL EWING GARBER, FACSM

Department of Rehabilitation and Regenerative Medicine, Columbia University Irving Medical Center, New York, NY

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Advisor / Mentor: Ewing Garber, Carol (ceg2140@tc.columbia.edu)

ABSTRACT

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder, marked by insufficient production of SMN protein, leading to motor neuron dysfunction. Although ubiquitously produced throughout the body, motor neurons and muscle cells are selectively impacted by decreased SMN, which has been linked to impaired oxidative phosphorylation causing altered metabolic function and exercise intolerance. Nusinersen, administered directly to the central nervous (CNS), is an approved therapy that increases SMN protein in an effort to restore motor neuron function. **PURPOSE:** To evaluate the impact of treatment on markers of exercise tolerance in children and adults treated with nusinersen is not known. **METHODS:** Nusinersen treated ambulatory children and adults with SMA completed a maximal cardiopulmonary exercise (CPX) test on a cycle ergometer at two visits 6 months apart. Oxygen uptake (VO_2) at peak exercise, oxygen uptake efficiency slope (OUES), and ventilatory equivalent for oxygen (V_E/VO_2) at peak exercise were determined. Paired sample t-tests were used to evaluate change between visits. **RESULTS:** Nine ambulatory children and adults with SMA (89% male) (mean age=32.4, range=13-57 years) were included. The average length of time participants had received treatment was 1.05 years (range= 0.59 – 1.30 years). VO_2 significantly increased from 13.49 ml•kg^{-1}• min^{-1} to 16.52 ml•kg^{-1}• min^{-1} (P = 0.03), OUES increased from 1324 to 1495 ml•min^{-1} O_2/L• min^{-1},and V_E/VO_2 increased from 44.9 to 49.0 after 6-months. No significant differences were found in OUES or V_E/VO_2 after six months of treatment.(P< 0.05) **CONCLUSION:** These results show potential to mitigate exercise intolerance with nusinersen treatment in individuals with SMA. VO_2 was significantly improved, but an attenuated OUES and exaggerated hyperventilation response, representative measures of efficiency, persists. As aerobic capacity reflects the integrative function of multiple body systems, the improvement observed may be attributed to tissues not directly targeted by Nusinersen. Exercise testing is a valuable method of assessing muscle oxygen kinetics and suggested mitochondrial dysfunction observed in SMA. Combining exercise with drug therapies may further enhance benefits seen by treatment alone and developing specific muscle-targeted therapies may be warranted.

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