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Plenary Abstract

Gene Therapy: Strategies to Treat Motor Unit Dysfunction

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Pompe disease results from a deficiency or absence of the lysosomal enzyme acid alpha glucosidase (GAA), resulting in lysosomal glycogen accumulation that impacts cardiac, respiratory and neuromuscular function. Respiratory failure is the leading cause of morbidity and mortality in Pompe patients. AAV vectors expressing GAA are currently being evaluated in a phase I/II study in ventilator-dependent pediatric Pompe patients. These studies are based on the finding that accumulation of glycogen in spinal motor neurons contributes to weakness observed in Pompe disease. In a number of preclinical studies we have found that restoration of GAA activity in muscle and neural tissue is able to reverse ventilatory insufficiency by reversing motor neuron dysfunction. The principle defect in motor unit function is related to deficiency in formation of the neuromuscular junction. New evidence also indicates the need for early intervention related to neural dysfunction since motor neurons show evidence of apoptosis in the murine model of Pompe. These deficits are present early in the mouse model and restoration of GAA activity in the muscle and neurons before 6 months of age leads to restoration of *in situ* force production. After 18 months of age, the loss in motor neurons leads to permanent deficits in force production of the tibialis anterior. A clinical trial of AAV1-mediated restoration of GAA activity in the diaphragm and phrenic motor neurons has been conducted. Ten subjects have been enrolled in the study and five have undergone one year of follow up. There were no adverse events related to the study agent. All children had improvement in spontaneous ventilatory endurance from baseline to the one-year study end. We conclude that a complex motor program leads to phrenic motor dysfunction in Pompe disease. The loss of neuromuscular junction formation is a principle cause of weakness and ventilatory failure. Future studies will utilize the ability of AAV9-derived GAA to lead to more efficient targeting of muscle and motor neurons following systemic vector delivery.

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