Efficacy of Gene Therapy Is Dependent on Disease Progression in Dystrophic Mice with Mutations in the FKRP Gene.

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Abstract

Loss-of-function mutations in the Fukutin-related protein (FKRP) gene cause limb-girdle muscular dystrophy type 2I (LGMD2I) and other forms of congenital muscular dystrophy-dystroglycanopathy that are associated with glycosylation defects in the $\alpha$-dystroglycan ($\alpha$-DG) protein. Systemic administration of a single dose of recombinant adeno-associated virus serotype 9 (AAV9) vector expressing human FKRP to a mouse model of LGMD2I at various stages of disease progression was evaluated. The results demonstrate rescue of functional glycosylation of $\alpha$-DG and muscle function, along with improvements in muscle structure at all disease stages versus age-matched untreated cohorts. Nevertheless, mice treated in the latter stages of disease progression revealed a decrease in beneficial effects of the treatment. The results provide a proof of concept for future clinical trials in patients with FKRP-related muscular dystrophy and demonstrate that AAV-mediated gene therapy can potentially benefit patients at all stages of disease progression, but earlier intervention would be highly preferred.

KEYWORDS: adeno-associated virus; dystroglycanopathy; fukutin-related protein; gene therapy; muscular dystrophy
