Gene Delivery for Limb-Girdle Muscular Dystrophy Type 2D (LGMD2D).


Abstract

In a previous LGMD2D clinical trial, robust alpha-sarcoglycan (αSG) gene expression was confirmed following intramuscular gene (SGCA) transfer. This paved the way for first in-human isolated limb infusion (ILI) gene transfer trial to the lower limbs. Delivery of scAAVrh74.tMCK.hSGCA via an intravascular route through the femoral artery predicted improved ambulation. This method was initially chosen to avoid safety concerns required for large systemic vascular delivery viral loads. We adopted ILI methods from the extensive chemotherapy experience for treatment of malignancies confined to the extremity. Six LGMD2D subjects were enrolled in a dose-ascending open-label clinical trial. Safety of the procedure was initially assessed in a single limb of a non-ambulant affected adult at the dose of 1x10^12 vg/kg. Subsequently ambulatory children (ages 8-13) were enrolled and dosed bilaterally with either 1x10^12 vg/kg per limb or 3x10^12 vg/kg per limb. The 6-minute-walk-test (6MWT) served as the primary clinical outcome; secondary outcomes included muscle strength (maximum voluntary isometric force testing; MVICT) and SGCA expression at 6 months. Ambulatory participants had pre- and post-treatment muscle biopsies except one. All 4 subjects biopsied had confirmed SGCA gene delivery by immunofluorescence, western blot analysis (14-25% of normal), and vector genome copies (5.4 x 10^3 to 7.7 x 10^4 vg/μg). Muscle strength in the knee extensors (assessed by force generation in kilograms) showed improvement in two subjects that correlated with an increase in fiber diameter post gene delivery. Six-minute walk times decreased or remained the same. Vascular delivery of AAVrh74.tMCK.hSGCA was effective at producing SGCA protein at low doses that correlated with vector copies and local functional improvement restricted to targeted muscles. Future trials will focus on systemic administration to enable targeting of proximal muscles to maximize clinical benefit.