Preclinical Studies in the mdx Mouse Model of Duchenne Muscular Dystrophy with the Histone Deacetylase Inhibitor Givinostat

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Previous work has established the existence of dystrophin–nitric oxide (NO) signaling to histone deacetylases (HDACs) that is deregulated in dystrophic muscles. As such, pharmacological interventions that target HDACs (that is, HDAC inhibitors) are of potential therapeutic interest for the treatment of muscular dystrophies. In this study, we explored the effectiveness of long-term treatment with different doses of the HDAC inhibitor givinostat in mdx mice—the mouse model of Duchenne muscular dystrophy (DMD). This study identified an efficacy for recovering functional and histological parameters within a window between 5 and 10 mg/kg/d of givinostat, with evident reduction of the beneficial effects with 1 mg/kg/d dosage. The long-term (3.5 months) exposure of 1.5-month-old mdx mice to optimal concentrations of givinostat promoted the formation of muscles with increased cross-sectional area and reduced fibrotic scars and fatty infiltration, leading to an overall improvement of endurance performance in treadmill tests and increased membrane stability. Interestingly, a reduced inflammatory infiltrate was observed in muscles of mdx mice exposed to 5 and 10 mg/kg/d of givinostat. A parallel pharmacokinetic/pharmacodynamic analysis confirmed the relationship between the effective doses of givinostat and the drug distribution in muscles and blood of treated mice. These findings provide the preclinical basis for an immediate translation of givinostat into clinical studies with DMD patients.