Glucocorticoid Steroid and Alendronate Treatment Alleviates Dystrophic Phenotype with Enhanced Functional Glycosylation of α-Dystroglycan in Mouse Model of Limb-Girdle Muscular Dystrophy with FKRPP448L Mutation.

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Abstract
Fukutin-related protein-muscular dystrophy is characterized by defects in glycosylation of α-dystroglycan with variable clinical phenotypes, most commonly as limb-girdle muscular dystrophy 2l. There is no effective therapy available. Glucocorticoid steroids have become the standard treatment for Duchenne and other muscular dystrophies with serious adverse effects, including excessive weight gain, immune suppression, and bone loss. Bisphosphonates have been used to treat Duchenne muscular dystrophy for prevention of osteoporosis. Herein, we evaluated prednisolone and alendronate for their therapeutic potential in the FKRPP448L-mutant mouse representing moderate limb-girdle muscular dystrophy 2l. Mice were treated with prednisolone, alendronate, and both in combination for up to 6 months. Prednisolone improved muscle pathology with significant reduction in muscle degeneration, but had no effect on serum creatine kinase levels and muscle strength. Alendronate treatment did not ameliorate muscle degeneration, but demonstrated a limited enhancement on muscle function test. Combined treatment of prednisolone and alendronate provided best improvement in muscle pathology with normalized fiber size distribution and significantly reduced serum creatine kinase levels, but had limited effect on muscle force generation. The use of alendronate significantly mitigated the bone loss. Prednisolone alone and in combination with alendronate enhance functionally glycosylated α-dystroglycan. These results, for the first time, demonstrate the efficacy and feasibility of this alliance treatment of the two drugs for fukutin-related protein-muscular dystrophy.

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