Phosphodiesterase 4 inhibitor and phosphodiesterase 5 inhibitor combination therapy has antifibrotic and anti-inflammatory effects in mdx mice with Duchenne muscular dystrophy

Yasunori Nio, Masayuki Tanaka, Yoshihiko Hirozane, Yo Muraki, Takanori Matsuo, Mitsugi Ookawara, Masatoshi Hazama

Takeda pharmaceutical company

Duchenne muscular dystrophy (DMD) is the most common inherited muscular dystrophy. Patients experience DMD in their 20s from cardiac or respiratory failure related to progressive muscle wasting. Currently, the only treatments for the symptoms of DMD are available.Muscle fibrosis, a DMD feature, leads to reduced muscle function and muscle mass, and hampers pharmaceutical therapeutic efficacy. Although antifibrotic agents may be useful, none is currently approved. Phosphodiesterase 4 (PDE4) inhibitors have exhibited antifibrotic effects in human and animal models. In this study,we showed beneficial effects of the PDE4 inhibitor piclamilast in the DMD mdx mouse. Piclamilast reduced them RNA level of profibrotic genes, including collagen1A1, in the gastrocnemius and diaphragm, in the mdx mouse, and significantly reduced the Sirius red staining area. The PDE5 inhibitors sildenafil and tadalafil ameliorated functional muscle ischemia in boys with DMD, and sildenafil reversed cardiac dysfunction in the mdx mouse. Single-treatment piclamilast or sildenafil showed similar antifibrotic effects on the gastrocnemius; combination therapy showed a potent antifibrotic effect, and piclamilast and combination therapy increased peroxisome proliferator-activated receptor-gamma coactivator-1a mRNA in mouse gastrocnemius. In summary, we confirmed that piclamilast has significant antifibrotic effects in mdx mouse muscle and is a potential treatment for muscle fibrosis in DMD.