New analysis shows drug slows down respiratory decline

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Duchenne muscular dystrophy occurs in boys and is characterized by progressive muscle degeneration and weakness leading to a decline in respiratory function. Strategies to arrest this severe progressive deterioration are needed to extend lives and improve quality of life. Results of three clinical trials using eteplirsen, an exon-skipping antisense oligonucleotide, show promising results, according to a study published in the *Journal of Neuromuscular Diseases*.

Muscular dystrophy is a group of genetic disorders that results in increasing weakening and breakdown of skeletal muscles. Near absence of dystrophin, a critical protein, results in inflammation, necrosis, and eventual replacement of functional muscle tissue with fibrosis and fat. Duchenne muscular dystrophy (DMD) is a severe type of muscular dystrophy in boys that has a predictable disease course. Muscle weakness usually begins around the age of four in the thighs and pelvis followed by the arms. Most patients are unable to walk by the age of 12. Natural history data show that respiratory function declines linearly and predictably in the second decade of life. Respiratory decline in glucocorticoid-treated DMD patients is typically 5% annually in patients aged 10 to 18 years. Patients require increasing levels of clinical intervention as the disease progresses.

Investigators led by Navid Z. Khan, Ph.D., Senior Director, Global Medical Affairs, Sarepta Therapeutics, Inc., Cambridge, MA, USA, evaluated respiratory function in eteplirsen-treated patients from three clinical trials and compared them to patients matched by age range,

steroid use, and genotype from the Cooperative International Neuromuscular Research Group Duchenne Natural History Study (CINRG DNHS) global database. These three trials studied eligible ambulatory DMD patients for at least four years (studies 201 and 202), primarily non-ambulatory DMD patients for two years (study 204), and an ongoing open label multicenter study of ambulatory DMD patients aged seven to 16 years (study 301).

The CINRG DNHS, one of the largest prospective natural history studies of DMD conducted to date, comprises more than 400 DMD patients with complete characterization of demographic data, along with assessments of clinical parameters affected by DMD. The three CINRG DNHS cohorts included: glucocorticoid-treated patients amenable to exon 51 skipping (20 patients), all glucocorticoid-treated CINRG patients (172 patients), and all glucocorticoid-treated genotyped CINRG DNHS patients (148 patients). Approximately 13% of cases of DMD are amenable to exon 51 skipping therapies.

Patients in the global patient database experienced respiratory decline at rates in line with the well-established natural history of DMD. In contrast, the respiratory decline in patients treated with eteplirsen was significantly lower, and this was true across all stages of the disease evaluated. Specifically, both ambulatory and non-ambulatory patients demonstrated a slower rate of respiratory decline.

As the disease progresses, patients require increasing levels of clinical intervention including cough assist and ventilation support, and patients are at increased risk of death once this respiratory decline reaches a critical threshold. This work demonstrates that eteplirsen may slow the rate of respiratory decline and therefore may delay time to milestones of decline. This may have notable positive implications on quality of life, and because pulmonary decline is linked to mortality, slowing of decline may result in delayed mortality. The investigators acknowledge that

longer term follow-up is needed.

Eteplirsen is an antisense oligonucleotide approved by the FDA for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

More information: Navid Khan et al, Eteplirsen Treatment Attenuates Respiratory Decline in Ambulatory and Non-Ambulatory Patients with Duchenne Muscular Dystrophy, *Journal of Neuromuscular Diseases* (2019). DOI: 10.3233/JND-180351

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