Duchenne Muscular Dystrophy
Subtopic Management and Treatment

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Group #0

Duchenne Muscular Dystrophy (DMD) is an X-linked recessive disease caused by mutations in the dystrophin gene. Dystrophin is found in muscle fibers where it functions as a support protein providing muscle fibers with strength and stability. Although over 1800 mutations have been identified in muscular dystrophy, DMD is most commonly caused by large deletions resulting in significantly truncated, non-functional proteins (1).

There is no cure for DMD. Prior to 2016, the primary pharmacologic therapies were corticosteroids, which improve mobility, pulmonary function, and may delay cardiomyopathies (2). Although the exact mechanism of action is not clear, the anti-inflammatory benefits of corticosteroid therapy are believed to play a key role (2). Yet, long-term corticosteroid use is associated with weight gain and bone weakening. Currently, glucocorticoid treatments are continued in the absence of significant obesity or intolerable side effects. Afflicted individuals generally succumb to respiratory insufficiency or cardiomyopathy before their 30th birthday (3).

In 2016, the FDA approved eteplirsen, a drug for DMD patients with mutations in exon 51 of the dystrophin gene, about 13% of all DMD patients. Eteplirsen works on the principle of exon skipping. The patients amenable to eteplirsen therapy often have frame shift mutations that produce severely truncated, non-functional proteins. In exon skipping therapy, an oligonucleotide is used to bind a critical region of the dystrophin gene prior to the mutation. The oligonucleotide re-directs splicing so that the mutated region of the gene is excised. The resulting mRNA is missing exon 51, but maintains some functional activity, similar to less severe forms of muscular dystrophy (Beckers muscular dystrophy) (4-6).

Eteplirsen is controversial. DMD is a rare disease, and given that a small percentage of patients have mutations amenable to treatment with eteplirsen, only 30+ patients have been treated with eteplirsen (4-6). These studies demonstrated a clinical benefit, with one study showing a 23% increase in dystrophin-expressing fibers in treated patients compared to placebo-control patients (5). Insurance companies and opponents to eteplirsen argue there is no proof that a 23% increase in dystrophin is sufficient to produce meaningful benefit to patients. Proponents of the therapy claim that given the fatal nature of DMD, any benefit is a step in the right direction.

1. https://www.duchenne.com/genetic-mutations
2. https://www-uptodate-com.archer.luhs.org/contents/duchenne-and-becker-muscular-dystrophy-glucocorticoid-and-disease-modifying-treatment?sectionName=NOVEL%20THERAPIES&search=muscular%20dystrophy%20treatment&topicRef=6181&anchor=H4007909118&source=see_link#H4007909118
3. https://www-uptodate-com.archer.luhs.org/contents/duchenne-and-becker-muscular-dystrophy-management-and-prognosis?search=muscular%20dystrophy%20treatment&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H25
4. Cirak S, Arechavala-Gomeza V, Guglieri M, et. al. Exon skipping and dystrophin restoration in patients with Duchenne muscular dystrophy after systemic phosphorodiamidate morpholino oligomer treatment: an open-label, phase 2, dose-escalation study. Lancet. 2011;378(9791):595.
5. Mendell JR, Rodino-Klapac LR, Sahenk Z, et. al. Eteplirsen for the treatment of Duchenne muscular dystrophy. Ann Neurol. 2013 Nov;74(5):637-47
6. Mendell JR, Goemans N, Lowes LP, et al. Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy. Ann Neurol. 2016 Feb;79(2):257-71.