There are more than 30 different forms of genetic diseases characterized by progressive weakness and degeneration of skeletal muscles that make up the various muscular dystrophies. The most common form of muscular dystrophy is Duchenne muscular dystrophy (DMD), a recessive, X chromosome-linked defect that leads to an absence or near absence of functional dystrophin. Dystrophin is a component of a protein complex that connects the cytoskeletal actin of muscle fiber to the extracellular matrix. By acting as a kind of shock absorber, dystrophin prevents damage to the actin.

When someone has muscular dystrophy and the dystrophin isn’t working right, the constant contraction and relaxation of the muscle proteins leads to damage, inflammation, and eventually, scarring.

Although biochemical and molecular evidence of DMD can be found shortly after birth, DMD does not become clinically evident until between the age of 2 and 3 because normal growth and development obscure the ongoing muscle damage.

DMD is an X-linked disease that mainly affects boys. They are typically diagnosed starting at about age 4 or 5 when they demonstrate waddling gait, toe walking, falls, and delayed speech. These children actually demonstrate improved functional ability until about age 7 when the degeneration and loss of muscle outpaces maturational development and physical growth.

Muscular Dystrophy Drug Could Pave Way for RNA Medications

Sarepta’s eteplirsen functions like an RNA patch so functioning dystrophin gets made. Other drugs like it may be used to treat Ebola and other viral infections.

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After this, DMD patients enter into a relentless and worsening decline in physical function. By their 8th birthday, most DMD patients lose their ability to rise from the floor and climb stairs. They often fall while walking. Between ages 10 and 14, most become dependent on a wheelchair for mobility and by their mid- to late teens they have difficulty breathing. Some people with DMD are living into their 40s and 50s these days but most die in their 20s or 30s from respiratory or heart failure.

Worldwide, the incidence of DMD is between 1 in 3,500 and 1 in 5,000 newborn males with DMD. Links to race, place of birth, and other factors have not been found. According to the best estimates, between 9,000 and 12,000 Americans are living with DMD, or just 0.003% of the population, so it’s a rare condition that is nevertheless relatively well known because Jerry Lewis’s Labor Day telethon raised money for the Muscular Dystrophy Association for decades.

Broken zipper

Currently there are no approved therapies for DMD in this country. Standard medical therapy consists of glucocorticosteroids, which has been demonstrated to slightly delay the loss of ambulation. Nutritional support, a variety of physical and occupational therapies, and psychosocial care, as well as palliative care, are offered to these patients, but they do not generally change the course of the illness.

The most common causes of DMD involve a mutation to one or more of the DMD exons. (An exon is a string of DNA. Different exons have different functions but for the sake of clarity, let’s consider only those exons that code for protein synthesis.) Exons can be identified with advanced genetic testing. A string of exons is transcribed into RNA, which, in turn, is “read” by the ribosomes as a blueprint to assemble proteins by stringing together amino acids.
Several mutations to the dystrophin gene that result in missing exons have been linked to DMD. Deletion of exon 51 is the most common and causes about 13% of all cases of DMD. Deletions of exons 53 and 45 cause about 8% of cases.

When an exon has gone missing, the remaining exons are thrown “out of frame” and protein synthesis stops when the ribosomes get to its location. Think of a zipper that has a missing tooth. When the slider gets to that section, the zipper ceases to close.

Scientists have developed a way to “skip” the missing exon. This involves the creation of an RNA bridge that in turn allows the remaining exons to be realigned, making them “in frame.” By restoring the reading frame, protein synthesis can continue, albeit with a functional but slightly shortened form of dystrophin.

The concept of patching RNA as a way to treat DMD came to light because there is a naturally occurring milder form of muscular dystrophy called Becker muscular dystrophy. It is caused by exon deletion from the dystrophin gene, but the result is a compromised but still functional dystrophin. Becker muscular dystrophy was good evidence that the presence of some dystrophin, albeit shorter, might result in disease amelioration.

**Distinct class**

Sarepta Therapeutics, a Cambridge, Mass., biotech company developed eteplirsen, a drug designed to fool ribosomes into skipping over the missing exon 51 and assemble the dystrophin protein “in-frame.” As in Becker muscular dystrophy, the dystrophin is shorter by a few amino acids but both ends are normal.

Eteplirsen belongs to a distinct class of synthetic antisense RNA compounds known as phosphorodiamidate morpholino oligomers, which are, thankfully, usually referred to by their initials, PMO. PMOs can be assembled in precise sequences that correspond to a section of RNA. Eteplirsen is a sequence of 30 bases that is complementary to the bases in the missing exon 5. However, the compound is structurally distinct from RNA and other RNA analogues as well as other classes of antisense compounds that researchers are studying in hopes that they might be used as medications.

To prove that it was an effective treatment for DMD caused by the missing 51 exon, eteplirsen was studied in two different studies, 201 and 202, although 202 was just the open-label extension of study 201.

Study 201 was a double-blind, placebo-controlled study of eteplirsen in 12 ambulatory boys with DMD. Patients were determined eligible if their DNA demonstrated deletion of exon 51. The 12 patients were randomized into three groups of four. Group 1 received weekly intravenous infusions of 30 mg/kg of eteplirsen, group 2 received 50 mg/kg of the drug, and group 3 received a placebo infusion. After 24 weeks, the four placebo recipients were rolled (two each) into the two different doses of eteplirsen for an open-label study, the aforementioned study 202.

The primary endpoints were a 6-minute walk test (6MWT) and the percentage of dystrophin-positive fibers in a muscle biopsy. The study also measured the North Star Ambulatory Assessment (NSAA), pulmonary function tests, loss of ambulation, and other functional abilities. Clinical data have been collected through Week 168 for patients enrolled in the pair of studies. The results are encouraging at many levels. Functional dystrophin has been found in all of the patients treated with eteplirsen. That alone is exciting proof that agents that target RNA defects and the assemblage of proteins hold promise.

The studies also demonstrated increased levels of dystrophin in the actual muscle fibers relative to levels prior to treatment. This dystrophin production was sustained through week 180 as measured by three different tests that were developed in consultation with the FDA.

The FDA required external comparable control groups to augment the short duration of
the placebo portion of study 201. It is important to note that the manufacturer stated “there was a high degree of homogeneity and comparability between the eteplirsen and the untreated external control patients for baseline characteristics including age, 6MWT, and representation of DMD genetic subtypes.”

Eteplirsen treated patients demonstrated a durable and “large magnitude” improved outcome of 151 meters in the 6MWT over the course of three years when compared with the untreated external control group. The study included a series of sensitivity analyses of the 6MWT that demonstrated statistical significance.

**Uphill battle**

As we went to press, an FDA advisory panel was scheduled to discuss eteplirsen on April 25. The same panel was scheduled to hold that discussion in January, but heavy snowfall forced a postponement. It may be an uphill battle for the drug. Before the postponed meeting, the FDA staff gave eteplirsen a largely negative review. At about the same time, the FDA rejected Kyndrisa, a rival DMD drug developed by BioMarin, a California biotech company.

Yet eteplirsen has been shown to improve the production of a functional form of dystrophin, according to documents on file with the FDA, and improve outcomes relative to a comparative group of patients. If the FDA does ultimately decide to allow the drug on the market, it will be the first drug that treats muscular dystrophy at its source, instead of ameliorating symptoms, although no one is saying that it is a cure.

Approval of eteplirsen might throw open the doors to other uses of PMO technology. First up might be treatments of muscular dystrophy caused by less common exon deletions.

But PMOs might also be a new way to treat some viral diseases. When a virus infects a cell, it inserts its genetic code into the cell’s DNA and RNA and commandeers that cell’s machinery into replicating more virus. By interfering with RNA, PMOs could be used to gum up the works that leads to viral replication. Sarepta is currently working on applying its PMO technology to some of the world’s deadliest viral diseases, including influenza, dengue, Marburg, and Ebola.

Moreover, PMO-based drug development has the potential to address countless diseases not amenable to traditional small molecule or biologic drugs. The human genome contains about 22,000 genes that account for more than 250,000 RNA transcripts and about 150,000 proteins, so there is no shortage of targets for PMO-based therapies. Of course targets are one thing, hitting them in a way that produces an effective treatment is another. 

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