

Editorial

Neuromuscular Disease

Discovery of the gene encoding dystrophin as the cause for Duchenne muscular dystrophy (DMD) in 1987 gave hope to many in the muscular dystrophy community that effective treatments would soon be forth coming. Now, almost 30 years later, with three different treatments for DMD under review at the FDA, the hope for effective treatments is greater than ever. The past 30 years have brought significant progress in treating patients with DMD and other neuromuscular disorders. However, this recent progress has not been driven by personalized designer therapies. Rather, the improved natural history of the disease course has been driven by the use of corticosteroids and implementation of a more proactive care model, particularly as it relates to pulmonary care and early use of non-invasive ventilation and early surgery for scoliosis. DMD patients are now living into adulthood which has led to new set of challenges in making appropriate transitions to adult care and fostering independence.

Developments in understanding genetic pathogenesis of neuromuscular disorders such as DMD, myotonic dystrophy type-1 (DM1), and spinal muscular atrophy (SMA) have driven development of targeted therapies which are now on the cusp of approval and clinical use. Broadly speaking these therapies can be considered in three categories, 1) disease modifying therapies, 2) gene modifying therapies, and 3) gene replacement therapies. Therapies for neuromuscular disorders in each category are now in development and over the next several years it is anticipated that these treatments will be available to patients.

Perhaps the most significant disease modifying therapy is corticosteroids for DMD. While implementation is variable, it is clear that steroids prolong ambulation by 2–5 years. The significant side-effects of corticosteroids have resulted in limited use in young children and non-ambulatory individuals, although use beyond loss-of-ambulation is becoming more accepted with an anticipated benefit in upper extremity, pulmonary, and cardiac function. Significant side-effects

have led to the search for steroid-sparing agents that modify disease progression. Active clinical trials include myostatin inhibition, utrophin up-regulation, aldosterone inhibition, phosphodiesterase type 5 (PDE5) inhibition, and others.

Gene modifying therapies in DMD are developing rapidly and target multiple mechanisms. Nonsense read-through is an approach to modify translation of the *DMD* gene by inducing the translation machinery to read past nonsense (stop) mutations. Translarna (Ataluren) was approved by the European Medicines Agency (EMA) in 2014 and is clinically available to patients with non-sense mutation DMD in several countries. A double-blind phase-3 clinical trial has recently been completed and an application is pending at the FDA. Exon skipping therapies use an RNA based approach to target out-of-frame deletion mutations by inducing the splicing machinery to splice out an exon adjacent to the deletion. The result is a transcript with a larger, but now in-frame deletion. Two different compounds targeting exon 51 of the *DMD* gene are now pending review at FDA with decisions expected on both in the first quarter of 2016. Each of these therapies depends on the location and type of the *DMD* mutation. Exon 51 skipping can treat 15% of boys with DMD and nonsense readthrough another 10–15 percent. Exon skipping therapies targeting exons 44, and 45, and 53 are all in development and each account for 5–6 percent of DMD patients. All together, these therapies would account for just under half of DMD patients. Development of targeted therapies for patients with more rare mutations will become increasingly complex and costly. It is hoped that successful demonstration of efficacy on one of these therapies will stimulate additional development for therapies targeting the more rare mutations. It should be noted that both exon skipping and nonsense read-through approaches do not fully correct the mutation in the *DMD* gene, but result in milder Becker MD like mutations.

Several gene replacement approaches have been proposed for DMD. The gene therapies have faced significant hurdles due to the size of the DMD gene, one of the largest in the genome. The most well-developed mechanism to deliver a gene replacement for DMD used an adeno-associated viral (AAV) vector to deliver the therapy. Since AAV vectors can package only 6 kb of DNA, several micro-dystrophin constructs have been developed to capture only the essential elements of the gene. Development of these therapies has been slow due to the difficulty in management of immune reactivity to the vector or the novel protein.

In DM1, several symptomatic therapies have been evaluated. To treat fatigue, there have been several studies of stimulant medications, such as modafinil, that have been shown to improve daytime sleepiness. Myotonia, as manifested by delayed muscle relaxation and gastrointestinal distress, has been shown to be effectively treated by mexiletine. There is an ongoing phase 3 trial that will evaluate the efficacy of this medication in DM1.

DM1 is caused by a toxic RNA that is the result of a CTG_n repeat expansion in the *DMPK* gene. There is an ongoing study designed to modify this effect. Prior studies in a mouse model of DM1 have demonstrated that an antisense oligonucleotide with a gapmer in the CUG repeat can trigger a RNase H reaction to degrade the toxic RNA. This antisense oligonucleotide is currently in Phase I/IIa studies in adults with DM1. This type of approach is well designed and has the potential to significantly modify the course of the disease.

In SMA loss of function of the *SMN1* gene results in severe, progressive weakness to loss of motor neurons. *SMN2*, a pseudogene adjacent to *SMN1* has minimal normal gene product which can significantly modify severity of SMA. Recently developed gene modifying therapies have targeted the *SMN2* gene using antisense

oligonucleotide designed increase production of the normal product from the *SMN2* gene. This approach has progressed to Phase III clinical trials. Among the neuromuscular disorders, SMA has the greatest potential for gene replacement therapies since the *SMN1* gene product is small enough to package intact in existing viral vector systems. An AAV9 vector mediated gene therapy that would replace the *SMN1* gene is currently undergoing phase I/2a clinical trials in patients with type 1 SMA.

Overall, there has been significant advances in therapeutic approaches in neuromuscular disease in the past few years making treatment for these devastating disorders a possibility for the first time. Further development will require careful natural history studies to develop the appropriate clinical endpoints, especially as therapies are developed for more rare disorders. Furthermore, careful attention to clinical care of neuromuscular diseases remains a practical approach to improve the lives of patients with these disorders even as gene modifying and gene replacement therapies are maturing.

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