Chapter 15
Summary

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Muscular dystrophy (MD) comprises a group of diseases that are clinically manifested as progressive muscle weakness with associated loss of mobility, agility, and body movements due to defects in genes for the production of muscle proteins. Devastating to patients, families, and caregivers, and clinically known for over 150 years, there is as yet no cure for MD.

Despite the challenges to finding a cure, however, the proteins and structures involved in certain disease processes are increasingly being elucidated, raising the number of potential pharmaceutical targets, and resulting in heightened interest in investment, partnership, and collaboration. In addition, several companies pursing potential treatments for MD have advanced to the Phase II and III stages of clinical drug development, and one product may be fully approved in the near future.

There are at least nine major types of MD: Duchenne (DMD), Becker (BMD), congenital, distal, Emery-Dreifuss, facioscapulohumeral (FSHD or FSH), limb-girdle, myotonic dystrophy, and oculopharyngeal. Most of the pharmaceutical and regulatory efforts to date have focused on DMD, because it is the most severe and because of considerable scientific advances regarding its pathology, and BMD, because its disease mechanism is related to DMD.

MD can be inherited in three ways: (1) autosomal inheritance (from a normal gene from one parent and an abnormal gene from another parent), (2) autosomal recessive inheritance (both parents carry and pass on the faulty gene), and (3) X-linked recessive inheritance (when a mother carries the affected gene and passes it on to her son). Sporadic cases may also arise as a result of de novo mutation, in the absence of any family history of affected individuals. The distribution of weakness in MDs includes a limb-girdle pattern, with shoulder and hip girdle muscle

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R.A. Huml (ed.), *Muscular Dystrophy*, DOI 10.1007/978-3-319-17362-7_15

involvement; a humeroperoneal pattern, with predominantly triceps, biceps, and peroneal muscles weakness; or a distal pattern, with distal weakness in the legs and arms. The prevalence of MD ranges from 1.3 to 96.2 per million, with DMD being most prevalent among boys during childhood, and myotonic dystrophy as one of the more common forms of MDs worldwide. Traditionally, the classification of MD is based on a combination of clinical and pathological criteria, including age of onset and distribution of muscle weakness, the extent of disease progression, associated symptoms, systemic features, family history, serum creatine kinase, muscle histology, as well as electromyography and nerve conduction studies (EMG/NCS). Increasingly, diagnosis requires genetic confirmation, as there can be considerable variations and overlaps in the clinical phenotypes.

FSHD is a complex, inheritable muscle disease. Although frequently cited as the third most common type of MD in older reports, many newer sources rank FSHD as the most prevalent type of MD, occurring at a rate of some 7 cases/1,000 persons, as compared with DMD/BMD (5 cases/1,000) and myotonic dystrophy (4.5 cases/1,000). The identification of FSHD as the most common type of MD has important ramifications, for example, when allocating future Federal (U.S.) funding for research, and in terms of the potential market size for future FSHD treatments. FSHD has only recently attracted attention from the pharmaceutical industry, largely due to significant advances in the understanding of the gene/mechanism of disease, including over-expression of a protein called DUX4. Most individuals with FSHD inherit the mutation from a parent with the disease, with 10–33% of all FSHD cases resulting from a de novo (or sporadic) mutation. The major symptom of FSHD is progressive weakening and loss of skeletal muscles. The usual location of these weaknesses at onset is the origin of the name: face (facio), shoulder girdle (scapulo), and upper arms (humeral). There is currently no disease modifying treatment or cure for FSHD. Most treatments proposed to "treat" FSHD have not yet been tested in randomized clinical trials. These may include: hormone supplementation, protein supplements (creatinine monohydrate), or drugs used to decrease inflammation (e.g., prednisone). To better understand and validate their use, many are now being properly investigated in clinical trials.

Duchenne and Becker MD are allelic disorders caused by mutations of the DMD gene located on Xp21, which encodes for the dystrophin protein. DMD is the most common form of MD in childhood, with an estimated incidence of 1 per 3,500 live-born males, and a pooled prevalence of DMD of 4.78 per 100,000 males worldwide. BMD is a generally milder and more variable form of dystrophinopathy, with an incidence of 1 in 18,518 male births, and a pooled prevalence of 1.53 per 100,000 males worldwide. Diagnosis is based on careful review of the clinical features and confirmed by additional investigations including muscle biopsy and/or genetic testing. Suspicion of the diagnosis of DMD is usually triggered in one of three ways, including (1) most commonly, the observation of abnormal muscle function with signs of proximal muscle weakness in a male child; (2) the detection of elevated serum creatine kinase as part of routine screening; or (3) the presence of elevated liver enzymes including aspartate aminotransferase and alanine aminotransferase. Current strategies include promoting proper nutrition, delaying onset of

complications, and optimizing health outcomes through on-going support. Pharmaceutical interventions include corticosteroids for skeletal muscle weakness and afterload reduction for cardiomyopathy. Early recognition and precise genetic diagnosis may allow for new therapeutic options for DMD.

Even though there is currently no cure, respiratory intervention and other supportive strategies have led to improved survival and better health-related quality of life for many affected individuals. For example, patients with DMD lived on average until their late teens in the 1950s; today, they typically live until their late 20s or 30s, which is largely attributable to better supportive care. This may include noninvasive ventilation during the day, and at night, orthopedic care and preventive measures. Current treatment is focused on symptomatic management and rehabilitation, and monitoring for disease complications.

Accurate diagnosis is important as a first step for managing MD. This involves a targeted history and examination, biochemical and genetic testing—sometimes with additional testing such as muscle biopsy—neurophysiological assessment, and muscle imaging. Muscle biopsy used to be the gold standard; however, it is increasingly being replaced by genetic testing. Muscle imaging is becoming more widely accepted as it is noninvasive and various forms of MD often result in unique patterns.

There has been progress in ICH countries toward issuing regulatory guidance for development of drugs for certain types of MD. The EU is most advanced, with draft guidance for DMD and BMD issued in 2013, and a concept paper published in 2011. The U.S. seems to be taking a conservative approach, relying on current programs—such as Fast Track Designation, Breakthrough Therapy Designation, Accelerated Approval, and Priority Review—to help sponsors of MD therapies gain U.S. registration. In an unprecedented move, the FDA solicited the first-ever draft guidance for industry written on behalf of a patient advocacy group with a focus on DMD, although it is possible that the Agency may choose not to formally adopt the proposed guidance. Since there is no other official guidance in the U.S., the PPMD document serves as a precedent for other types of MDs. As of April 2015, there are no disease-modifying products approved for the treatment of MD, but that situation may soon change. In May 2014, reversing an earlier rejection, the EU Committee for Medicinal Products for Human Use (CHMP) recommended early (conditional) approval for PTC Therapeutics' ataluren, a potential treatment for DMD. If the European Commission supports this decision, ataluren would be the first product approved, albeit conditionally, for MD—until the final Phase III data is available.

No MD products have yet been approved in the U.S., and significant hurdles remain to gaining regulatory approval of products to treat all patients with MD. A major challenge in developing therapies is the considerable variation in the severity and rate of disease progression between individuals. Other hurdles include: difficulty in defining and measuring the rate of change in this slowly progressing disease; variation in the goals of treatment at each stage of MD; the lack of protein identification and complete understanding of the mechanism of action in certain types of MD (e.g., FSHD); lack of regulatory agreement on primary and secondary endpoints in the U.S.; and the fact that few patients are available or eligible for study

in clinical trials. Once drug developers identify enough patients to study, but before moving to clinical trials, they need to have a minimum understanding of the natural history for each type of MD and make sure that the preclinical data package justifies the risk/benefit for patients (and caregivers). Until clinical endpoints and other key clinical trial design features are provided in U.S. and EU regulatory guidance, sponsors of drugs will need to collaborate with regulatory agencies on a case-by-case basis and early solicitation is encouraged. Despite the challenges, substantial progress has been made and there are a number of late stage candidates in clinical development primarily for DMD. More work is urgently needed to address the other eight types of MD.

Regarding patient advocacy groups, the first point of call for information and support for newly-diagnosed MD patients and their caregivers in the U.S., is the Muscular Dystrophy Association (MDA, www.mda.org). Other disease-specific groups for several of the nine forms of MD are presented in Chapter 13.

MD registries—collections of secondary data related to patients with one of the nine types of MD—can vary in sophistication from simple spreadsheets accessible only by a small group of physicians, to complex databases accessed online across multiple institutions. Registries can help identify MD patients for scientific research, clinical trials, and later, as products/drugs are approved for the treatment of MD, in the post-marketing surveillance of pharmaceuticals. Registries can also give healthcare providers or patients reminders of the need to undergo certain tests in order to reach quality goals. At present, many registries cover only one geographic area or one or two types of MD. The MDA is attempting to remedy this disparity with two initiatives. First, it is seeking participation from patients with certain myopathies in a patient registry and world map. This database is designed to allow researchers to better understand certain diseases and locate participants for clinical trials and other research studies. Second, to address the lack of a fully operational central registry database for patients with MD, the MDA and Quintiles, a biopharmaceutical services company, formed a partnership in October 2013 to develop and implement the U.S. Neuromuscular Disease Registry.

At no time in the history of MD has the future looked brighter. With over 240 studies listed in the U.S.—and at least 11 candidates in the later phases of drug development (e.g., Phase II or Phase III)—the stage is set for positive change. More groundwork is needed, however, such as the conduct of natural history studies, establishment of more global patient registries, and completion of additional genetic and molecular studies, to better understand MD and to identify promising targets. Indeed, it has historically proven difficult to find preclinical and animal models of disease. Several promising approaches to DMD are in the pipeline, including: “exon skipping” drug candidates, which target the mutation that occurs in the gene for dystrophin in individuals with DMD; gene therapy, aimed at introducing a healthy synthetic copy of the dystrophin gene into the muscles to restore production of dystrophin; “reading through stop signals” by targeting a specific type of mistake in the genetic code called a nonsense mutation, which prevents the production of full-length functional proteins; stem cell therapy, where donor cells are injected with the aim of creating healthy muscle fibers; utrophin upregulation,

aimed at increasing levels of utrophin, a protein that is functionally similar to dystrophin; and reducing muscle damage. As ongoing studies are completed, it is hoped that the mechanism of disease will become better elucidated, more targets will be identified, and more companies will be willing to invest in clinical trials.