EDITORIAL

New Treatments for Neuromuscular Disease: Optimism and Obstacles

Neuromuscular disorders (NMDs) comprise a diverse group of inherited and acquired disorders characterized by progressive muscle weakness and wasting in which the primary defect resides in the motor neuron, the peripheral nerve, the neuromuscular junction, or skeletal muscle. People of any age can be affected by NMD, and clinical symptoms show a broad spectrum of severity. Thus, children affected by any of the different forms of congenital muscular dystrophy (CMD) or the infantile form of spinal muscular atrophy (SMA type 1) will typically present at birth or shortly thereafter with profound general hypotonia, whereas first symptoms in patients with oculopharyngeal muscular dystrophy (OPMD) or amyotrophic lateral sclerosis (ALS) usually appear in their fifth or sixth decade of life. Although each individual disease entity is rare, the cumulative prevalence for all NMDs is estimated at 1:2000 to 1:3000 of the general population. Besides the progressive limb muscle weakness and wasting, many NMDs may present because of or be accompanied by scoliosis, cardiomyopathy, or ventilatory failure. Furthermore, NMDs often result in severe handicap of the afflicted patients. Pneumonia, cardiac arrhythmias, and cardiac and respiratory failure are the most frequent causes of death in NMD patients.

Over the past 20 years, research on NMDs has undergone a revolution, changing from a largely phenomenological science into a deeply analytical and technical field. Questions concerning the primary genes and basic immune mechanisms involved in NMDs have been definitely answered for a large number of conditions. A major contributor to this revolution in knowledge on NMDs has been the interaction of scientists focusing on the molecular and cellular basis of NMDs and clinicians working on the delineation of specific phenotypes, the characterization of multiplex families, and new diagnostic approaches. This progress has translated into better and earlier diagnosis, better counselling, and improvement of symptomatic treatments for the majority of NMD patients, with major gains in quality of life and life expectancy. Unfortunately, cure or a near-normal life on treatment are the exception, but they can be achieved in many of the acquired, autoimmune disorders (inflammatory myopathies and neuropathies, myasthenia gravis) and in a few of the inherited NMDs (channelopathies, congenital myasthenic syndromes[1]).

Most patients affected by inherited and degenerative NMDs do not yet have curative treatment options. Generally, progress in therapeutic development has been delayed by the lack of promising drugs or targets, the lack of sufficiently powered clinical trials, and the lack of interest and investment in the many but relatively rare diseases by industries and policymakers. Moreover, the hopes for future gene or stem-cell therapies may have diverted the interest of clinical scientists and patients from conventional drug development that could be more readily achievable.[2] Successful enzyme replacement therapy for infantile Pompe's disease, previously a lethal condition before the age of two years, has demonstrated that treatments can be obtained even for the rarest of NMDs. Novel therapeutic agents are being developed in laboratories across the field, and several are now entering initial clinical trials.

These are reasons for optimism that successful treatments can be developed that do not depend upon correcting the molecular defects that cause inherited neuromuscular diseases. In most diseases, the pathogenic mutation is necessary but not sufficient to cause disease. Thus, in Duchenne muscular dystrophy, all muscles are dystrophin-deficient from before birth. However, weakness is not evident in the first years of life, and even late in the disease some muscles are relatively spared. Moreover, corticosteroids produce a rapid increase in strength and muscle mass and slow muscle breakdown without altering muscle dystrophin.[3] Most inherited muscle diseases have an analogous predilection for some specific muscles and relative sparing of others. Gaining an understanding of the epigenetic or environmental causation of the predilection may hold the key to new treatment strategies.

A further reason for optimism is the recent focus on rare disease research in both the United States and Europe. The expansion of government funding for research on rare diseases has encouraged the training of new investigators in the requisite skills for developing novel treatment strategies (R.C. Griggs, et al, Clinical research for rare disease: opportunities, challenges, and solutions, submitted 2008). The Orphan Drug Act and facilitatory policy shifts at the Food and Drug Administration have made it easier to bring new treatments to market for rare diseases (J. Mitsumoto, et al, Pivotal studies of orphan

drugs approved for neurological diseases, submitted 2008).

Clinical trials in rare disorders entail specific difficulties, and it has become evident that the field of NMDs was not sufficiently prepared to conduct large, multicenter studies, which are ultimately required to obtain market authorization. Among the bottlenecks that have been identified are the lack of standardized animal models for preclinical testing; the lack of standardized diagnosis and care for patients; the lack of standardized biobanks and patient registries; the lack of standardized trial infrastructures; and a lack of patient-important outcome measures to document effectiveness. Recent advancement toward new therapeutic approaches for NMDs has made it essential to overcome fragmentation in the neuromuscular field on a global level. Clinical trials with promising new treatment strategies can only be conducted successfully if researchers and healthcare providers in Europe and the United States reach a consensus on standards of diagnosis and care, and if patients can be rapidly recruited across national boundaries. Therefore, collaborative projects and networks in the United States and in Europe have been launched: TREAT-NMD (www.treat-nmd.eu) and the Muscle Study Group (MSG; http://www.urmc.rochester.edu/msg/). TREAT-NMD is a Network of Excellence, funded for five years (2007–2011) within the Sixth Framework Programme of the European Commission. TREAT-NMD links 21 partner organizations from 11 European countries in a network supporting translational research for neuromuscular diseases. The MSG aims to advance knowledge about the cause(s), pathogenesis, epidemiology, and clinical manifestations of muscle disease and related neuromuscular disorders and to develop and implement strategies to examine promising therapeutic interventions.

It is exciting to compare the state of the art with regards to the experimental therapeutics of neuromuscular disease by looking at the treatment and lack of treatment 30 years ago[4] *versus* today. This issue of *Neurotherapeutics* includes state-of-the-art reviews on a wide range of acquired and inherited NMDs, highlighting current treatments, new developments, and clinical trials. We expect that some of these treatments will be available in the next decade, improving quality of life and life expectancy for many patients with NMD.

Hanns Lochmüller, M.D.
Professor of Experimental Myology
Institute of Human Genetics
University of Newcastle
Newcastle upon Tyne, UK
Robert C. Griggs, M.D.
Professor of Neurology
Chair, Muscle Study Group Executive Committee
University of Rochester School of Medicine
and Dentistry
Rochester, New York

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