ELSEVIER

Neuromuscular Disorders 18 (2008) 894–903

www.elsevier.com/locate/nmd

Workshop report

Towards harmonisation of outcome measures for DMD and SMA within TREAT-NMD; Report of three expert workshops: TREAT-NMD/ENMC Workshop on outcome measures, 12th–13th May 2007, Naarden, The Netherlands; TREAT-NMD Workshop on outcome measures in experimental trials for DMD, 30th June–1st July 2007, Naarden, The Netherlands; Conjoint Institute of Myology TREAT-NMD Meeting on physical activity monitoring in neuromuscular disorders, 11th July 2007, Paris, France

E. Mercuri [a,*], A. Mayhew [b], F. Muntoni [b], S. Messina [a], V. Straub [c], G.J. Van Ommen [d], T. Voit [e], E. Bertini [f], K. Bushby [c], On behalf of the TREAT-NMD Neuromuscular Network

[a] *Department of Paediatric Neurology, Catholic University, Rome, Italy*
[b] *Dubowitz Neuromuscular Unit, Institute of Child Health, University College London, UK*
[c] *Institute of Human Genetics, University of Newcastle upon Tyne, International Centre for Life, Newcastle upon Tyne, UK*
[d] *Center for Human and Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands*
[e] *Institut de Myologie Université Pierre et Marie Curie Paris VI, Groupe Hospitalier Pitié-Salpêtrière, Paris, France*
[f] *Department of Laboratory Medicine, Unit of Molecular Medicine, Bambino Gesù Hospital, Rome, Italy*

Revised 17 June 2008; accepted 11 July 2008

Keywords: Outcome measures; TREAT-NMD; Harmonisation; SMA; DMD

1. Introduction

TREAT-NMD (Translational Research in Europe for the Assessment and Treatment of Neuromuscular Disease) is a European neuromuscular network aimed at strengthening European excellence in the treatment of rare inherited neuromuscular disorders (NMD) by reducing fragmentation and establishing a common road map for the progression of cutting edge therapies from laboratory to clinic. Defining and disseminating information on relevant outcome measures is the object of one of the work packages of TREAT-NMD (WP 9). The activities of this work package are focused on performing a systemic review of the available outcome measures and on the selection and elaboration of assessment tools to be used as outcome measures in clinical trials. A closely related activity looks at the application of these tools to specific diseases, and with the perspective of trials in Duchenne muscular dystrophy (DMD) and spinal muscular atrophy (SMA) being the most pressing, discussion of outcome measures relevant to these two diseases has been the first emphasis of these activities. Further details of all of these activities can be found at www.treat-nmd.eu.

Since TREAT-NMD was initiated in January 2007 there have been a series of workshops and meetings followed up

* Corresponding author. Address: Department of Child Neurology, Policlinico Gemelli, Largo Gemelli 00168, Roma, Italy. Tel.: +39 06 30155340; fax: +39 06 30154363.
E-mail address: mercuri@rm.unicatt.it (E. Mercuri).

0960-8966/$ - see front matter
doi:10.1016/j.nmd.2008.07.003

with discussions on the TREAT-NMD forum and via videoconferences. This report serves to summarise the recommendations and follow up work from three meetings.

The first TREAT-NMD meeting on outcome measures was held to coincide with a European Neuromuscular Centre (ENMC) workshop on SMA. The scope of the meeting was to assess the application of functional scales in paediatric trials in DMD and SMA. The second meeting, organised with the support of TREAT-NMD and Duchenne Research Collaborative International (DRCI) and with the organisational support of the ENMC, gathered together 42 participants from nine Countries. The scope of the meeting was to assess the current situation with respect to outcomes measures for early trials in DMD. This multidisciplinary meeting was attended by participants from academia, clinicians, industrial representatives, regulatory authorities, charities and patient representatives. The main topics discussed were: the role of preclinical studies in the development of novel therapies for muscular dystrophy, early clinical trial design and the perspective of the regulatory authorities. Finally, a third meeting, jointly organised by the Institute of Myology and TREAT-NMD was convened to discuss activity monitors and to select possible models to record activity and endurance in daily activities and in longer-term multicentric studies.

The outcomes of the meetings are presented relating to the stages of progression of trial planning and selection of outcome measures at each stage through the pathway from lab to clinic, from how the interpretation of studies in animal models impacts on trial planning, to the establishment of outcome parameters in early clinical trials, to the kinds of functional assessments that might be applicable in larger scale studies in SMA and DMD. This represents the first move towards a consensus on outcomes in these various situations.

2. Session 1 – extrapolation from work on preclinical models of disease and how preclinical studies can inform the development of clinical trials in DMD

Animal models were considered in order to assess their pros and cons in preclinical studies. Much experience has already been generated on the use of different preclinical models for DMD, including the *mdx* mouse; the Golden retriever (GRMD) dog and the beagle dog models and on how preclinical studies can inform the development towards clinical trials. In terms of considering the way studies in these models can inform human trials, various questions were addressed; firstly, what are the advantages and disadvantage associated with these models when developing a new therapeutic approach; secondly; what is the best strategy to study these models and what to expect from therapeutic intervention.

While each of these models represents an excellent tool to perform early proof of concept studies (for example restoration of dystrophin expression using antisense oligomers; or drugs to suppress nonsense mutations) all of these models have their own limitations as they do not completely recapitulate the disease course observed in humans. A drug development programme has to take into account these limitations which may be intrinsic to the specific species studied (such as the mild phenotype observed in *mdx* mice); others, such as the very considerable clinical variability observed in the dystrophic dogs, are less well understood and predictable. The variability of the clinical severity of these dog models make them difficult to use for clinical trials, while they represent excellent models for proof of concept studies. The reduced variability of clinical severity in the beagle compared to the GRMD, together with his smaller size makes this potentially a better model to study, however the clinical features of this model are still significantly variable. While issues such as scaling up of dosing can be assessed in these models, assessing functional outcomes of therapeutic interventions and applying the stringent statistic required in human randomised clinical studies can be more problematic.

In addition to the intrinsic limitations of these models, there is also no experience yet related to successful therapies in preclinical models which have led to a successful therapy in patients with muscular dystrophies. Thus there is no experience on how to relate a force improvement in one of these preclinical models into functional benefit for DMD boys. This hopefully will be overcome when we start to have effective therapies.

In respect of the various experimental protocols to assess the extent of the skeletal muscle "rescue" of treated animals, different protocols exist, and there is the need to use agreed and standardised standard operative procedures (SOPs). Two related initiatives are collaborating to take this discussion forward, led by TREAT-NMD (Santhera Pharmaceuticals and University of Basel) and by the Washington Wellstone Centre with NIH support. The outcome of these workshops will be published shortly and interim reports can be found on the TREAT-NMD website. Early involvement of the regulatory agencies is important when working at a programme of drug discovery using preclinical models, especially regarding the level of evidence required from the preclinical models before unnecessary and costly studies are undertaken in multiple models.

3. Session 2 – specific issues related to the planning of early clinical trials in DMD

This is a multifaceted and complex issue and discussion was deliberately focused on a few areas where experience is accumulating. The first related to the difference in the path of development of an experimental therapy for rare neuromuscular disorders which can be considered orphan indications compared to the typical path regarding large scale drug therapies, with the usual progression from phase 1 clinical trials to 2 and 3. Part of the discussion focused on the need for SOPs for some of the assessment of therapeutic success in clinical trials; and on the development of surrogate measures of therapeutic success; finally a significant