TREAT-NMD
Neuromuscular Network

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This edition of the newsletter features a report on a meeting to discuss additional questions to be added to the EK scale, a function-based questionnaire for non-ambulant patients with DMD or SMA.

There are also reports from the recent ICORD and EC Rare Diseases Research meetings held in Brussels.

Please forward any items that you would like to be included in future editions of the newsletter.

Best wishes,

Katie, Volker, Stephen, Emma, Arron and Rachel – the TREAT-NMD coordination team

Newsletter contents

About this newsletter

This is a fortnightly newsletter sent to all members of TREAT-NMD's "Club of Interest" worldwide. Earlier editions of the newsletter can be found online at www.treat-nmd.eu/news/newsletter/index.htm. If you would like to subscribe directly, please visit our website at www.treat-nmd.eu/ where you will find a subscription form at the bottom of the homepage. You can also use the same form if you no longer wish to receive this newsletter – just select the unsubscribe button.

Working with us

TREAT-NMD aims to be an inclusive rather than an exclusive network, and you do not have to be based in Europe or be a partner to be involved. International collaboration with experts from all over the world is already taking place, and new links are being developed.

If you are involved in any of TREAT-NMD's areas of interest and have something you'd like to say or a suggestion of where we could work together, we encourage you to get in touch by writing to us at info@treat-nmd.eu. The coordination team in Newcastle will be happy to put you in touch with the person most relevant to your particular interest.

Extension to the Egen Klassifikation (EK) Scale

Anna Mayhew, Smart Net Coordinator, Imperial College, London, UK
Michelle Eagle, Consultant Physiotherapist, Newcastle, UK
Birgit Steffensen, Senior Research Physiotherapist, Denmark

RehabiliteringsCenter for Muskelsvind

This month, at a meeting sponsored by TREAT-NMD, Birgit Steffensen, a research physiotherapist from Rehabiliterings Center for Muskelsvind (the national Danish expert centre within rehabilitation of neuromuscular diseases) met in Newcastle with several UK physiotherapists to discuss possible additional questions to the already established Egen Klassifikation (EK) Scale. The original scale is a function-based questionnaire suitable for non-ambulant patients with SMA or DMD. It is an ordinal scale ranging from 0 to 30 points where '0' represents the highest level of independent function and `30' the lowest level. The assessment comprises 10 parts, which are referred to as categories; each category encompasses a major domain of functional ability or impairment, and is scored in four items: zero to three. The EK scale permits a variety of categories and items to be assessed simultaneously by summing individual category scores to attain an overall expression of function called the `EK sum'. The administration of the EK scale consists of an interview of the subject in order to learn how he performs a given task in daily life (categories 1-9) or how he perceives his physical well-being (category 10) and a visual examination of the performance of those tasks which are observable.

The reliability and validity of this scale has already been established, yet it was felt that for SMA the scale could benefit from additional items that may improve its sensitivity. This was the purpose of this primary meeting and ten new questions were created relating to functional activities around feeding, fatigue, ability to get into standing position and walking indoors. This autumn these new items will be tested in various clinical settings in the UK and in Denmark and in the New Year they will be evaluated for sensitivity, feasibility and relevance. At this point we hope they can be made accessible to a wider audience interested in development of this already useful scale.

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or Birgit: bist@muskelsvindfonden.dk

Steffensen BF, Hyde SA, Atterman J, Mattsson E. Reliability of the EK scale, a functional test for non-ambulatory persons with Duchenne dystrophy. Advances in Physiotherapy 4: 37-47, 2002.

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Lyager S, Steffensen B, Juhl B. Indicators of need for mechanical ventilation in Duchenne muscular dystrophy and spinal muscular atrophy. Chest 108: 779-85, 1995.

Steffensen BF, Lyager S, Werge B, Rahbek J, Mattsson E. Physical capacity in non-ambulatory people with Duchenne muscular dystrophy or spinal muscular atrophy. A longitudinal study. Developmental Medicine and Child Neurology 44: 623-32, 2002.

6th International Round Table, Monaco, June 23rd, 2007

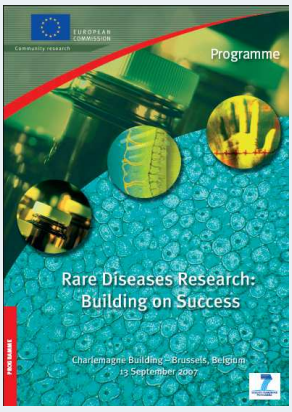
Clinical trials in Duchenne muscular dystrophy: from phase 1 trials to therapeutic benefits

Report by Olivier Danos, PhD, Inserm U781, Hôpital Necker-Enfants Malades, Paris

The 6th Round Table organised by the Association Monégasque contre les Myopathies and Duchenne Parent Project France was attended by 21 scientists and industry representatives and 10 DMD patient organisation representatives. The objective was to discuss the progress from early phase 1 trials in DMD to the development of therapies in clinical use.

To read the full report please click on the link below:

http://www.treat-nmd.eu/assets/documents/Monaco_clinical_trials_report.pdf



Rare Diseases Research: Building on Success

Brussels, Belgium

13th September 2007

by Stephen Lynn

This one-day conference organised by the European Commission was intended to promote rare diseases research as one of the priorities of the EU's political research agenda, as well as increasing the visibility of the needs of rare diseases research in the context of FP7 through dialogue between stakeholders and the European Commission.

The conference was opened with an address by HRH Princess Astrid of Belgium, who has a particular interest in neurological diseases, and she described how a network of neuromuscular disease reference centres has been established across the university system in Belgium.

Some of the challenges facing rare diseases research were recognised, such as the lack of well-characterised animal models of disease, lack of natural history data, and the need for resources to sustain development of new drugs and therapies. The challenges that face clinical development were also discussed, and these include clinical trial design with small patient populations, patient recruitment and complying with the EU Clinical Trial Directive.

The conference addressed some of the lessons learned from research on rare diseases, and how understanding the mechanism behind a rare disease can sometimes offer valuable insights into more common disorders and lead to further innovation. The topic of innovation was illustrated in an excellent talk by Gert-

Jan Van Ommen from Leiden University Medical Centre (LUMC) who presented his work on antisense oligonucleotides as a therapy for Duchenne muscular dystrophy, and who is also affiliated with the TREAT-NMD network. This work is currently undergoing clinical trials in conjunction with the LUMC spin-out company Prosensa.

In his closing address Professor John Burn, Director of the Institute of Human Genetics at Newcastle University, summarised the needs of the research community in tackling rare diseases and talked about the impact that European-funded initiatives like TREAT-NMD are having in addressing the needs of both patients and professionals in the neuromuscular community. The European Union will need to address the long-term funding of such initiatives to ensure that its citizens are best served.

3rd International Conference on Rare Diseases and Orphan Drugs (ICORD 2007)

Brussels, Belgium, 14-15th September 2007

by Stephen Lynn

The overall aim of ICORD 2007 was to develop constructive international collaborations that will result in real advances for patients with rare diseases. The conference was organised into workgroups covering areas such as gaining regulatory approval, product discovery and development, patient recruitment, assessment tools, genetic testing, and identifying patient and family needs. The meeting was attended by representatives from across Europe, the US, New Zealand, and South America.

Industry representatives addressed their particular needs in gaining regulatory approval for orphan drugs, such as the availability of good quality published data on prevalence numbers for rare diseases and global harmonisation of the application process for orphan drugs. It was recognised that a first step would be to harmonise the orphan drug designation before addressing issues such as protocol assistance and market authorisation. To begin addressing these concerns the EMEA and FDA are preparing an agreement to harmonise regulatory issues surrounding orphan drugs. This agreement will be announced in Washington DC in November 2007 and is seen as a major achievement in harmonising EU/US drug development. However, industry would also like to see introduced a parallel assessment protocol for orphan drugs between the two agencies.

One of the major tools in drug development is the availability of biomaterials that are linked to good quality clinical data. The creation of a global database of bio-repositories that is searchable via the internet is currently under development by the Office of Rare Diseases at the NIH. The major aim is to increase access to good quality samples to improve new therapy development. The involvement of the patient organisations on the best use of these valuable patient samples was recognised as a topic for further discussion. This is currently lacking in the EU in regard to rare diseases. However, it is recognised that the role of patients is important in driving clinical and translational research and should be an integral part of any disease network.

US Office of Rare Diseases starts quarterly newsletter

To keep interested parties up-to-date on rare disease activities, information and events, the US NIH Office of Rare Diseases (http://rarediseases.info.nih.gov/) has begun publishing a quarterly newsletter. Focus on Rare Diseases provides highlights of the many and varied ORD research activities and includes a calendar of upcoming ORD-sponsored scientific conferences. The debut issue of the newsletter covers updates in the following areas: rare diseases clinical research network; clinical protocols; the expansion of data safety; monitoring board and protocol review; technologies available for licensing from NIH/FDA and non-profit institutions on rare diseases and conditions; fiscal year 2006 biennial report on rare diseases research activities; and the activities of the Genetic and Rare Diseases Information Centre. The publication welcomes newsworthy contributions.

A new rare disease tool for physicians

ZebraHunter (http://www.zebrahunter.org/) is being developed as an on-line evidence-based search tool using published medical case reports from Medline as its source to help doctors and other professionals retrieve expert documentation of rare clinical case presentations. ZebraHunter will access matches based on signs, symptoms, findings or diagnostic impressions. This public-access resource is currently under development at Columbia University's Department of Biomedical Informatics.

Upcoming conferences, workshops, meetings and summer schools

TREAT-NMD Industrial Liasion Council Meeting

4th October 2007 Basel, Swizerland

Pre-clinical testing for Duchenne dystrophy: End-points in the mdx mouse.

Wellstone Center Workshop, October 27th and 28th, 2007
Children's National Medical Center, Washington DC

12th Annual SMA Research Group Meeting

June 19-21, 2008 at the Boston Park Plaza Hotel.
www.curesma.org

Clinical Trials in CNS

26th-27th November 2007
Copthorne Tara Hotel, London, UK.
http://www.smi-online.co.uk/events/overview.asp?is=4&ref=2736

NORD 2007 Annual Conference

Date: 28-30 September 2007
Venue: Rockville, MD USA
http://nord-rdb.com/

ARCHIVES OF NEUROLOGY

Gene Therapy for Duchenne Muscular Dystrophy

Expectations and Challenges

Louise R. Rodino-Klapac, PhD; Louis G. Chicoine, MD; Brian K. Kaspar, PhD; Jerry R. Mendell, MD

Arch Neurol. 2007;64:1236-1241.

Duchenne muscular dystrophy is a debilitating X-linked disease with limited treatment options. We examined the possibility of moving forward with gene therapy, an approach that demonstrates promise for treating Duchenne muscular dystrophy. Gene therapy is not limited to replacement of defective genes but also includes strategies using surrogate genes with alternative but effective means of improving cellular function or repairing gene mutations. The first viral-mediated gene transfer for any muscle disease was carried out at Columbus Children's Research Institute and Ohio State University for limb girdle muscular dystrophy type 2D, and the first viral-mediated trial of gene transfer for Duchenne muscular dystrophy is under way at the same institutions. These studies, consisting of intramuscular injection of virus into a single muscle, are limited in scope and represent phase 1 clinical trials with safety as the primary end point. These initial clinical studies lay the foundation for future studies, providing important information about dosing, immunogenicity, and viral serotype in humans. This article highlights the challenges and potential pitfalls as the field advances this treatment modality to clinical reality.

http://archneur.ama-assn.org/cgi/content/short/64/9/1236

Comparative Analysis of Antisense Oligonucleotide Sequences for Targeted Skipping of Exon 51 During Dystrophin Pre-mRNA Splicing in Human Muscle

V. ARECHAVALA-GOMEZA, I.R. GRAHAM, L.J. POPPLEWELL, A.M. ADAMS, A. AARTSMA-RUS, M. KINALI, J.E. MORGAN, J.C. VAN DEUTEKOM, S.D. WILTON, G. DICKSON, and F. MUNTONI

Human Gene Therapy 18:798–810 (September 2007)

Duchenne muscular dystrophy (DMD) is caused by mutations in the dystrophin gene that result in the absence of functional protein. In the majority of cases these are out-of-frame deletions that disrupt the reading frame. Several attempts have been made to restore the dystrophin mRNA reading frame by modulation of pre-mRNA splicing with antisense oligonucleotides (AOs), demonstrating success in cultured cells, muscle explants, and animal models. We are preparing for a phase I/IIa clinical trial aimed at assessing the safety and effect of locally administered AOs designed to inhibit inclusion of exon 51 into the mature mRNA by the splicing machinery, a process known as exon skipping. Here, we describe a series of systematic experiments to validate the sequence and chemistry of the exon 51 AO reagent selected to go forward into the clinical trial planned in the United Kingdom. Eight specific AO sequences targeting exon 51 were tested in two different chemical forms and in three different pre clinical models: cultured human muscle cells and explants (wild type and DMD), and local *in vivo* administration in transgenic mice harboring the entire human DMD locus. Data have been validated independently in the different model systems used, and the studies describe a rational collaborative path for the preclinical selection of AOs for evaluation in future clinical trials.

http://www.liebertonline.com/doi/abs/10.1089/hum.2006.061

Partner-specific items

Industrial Liasion Council Meeting

4th October 2007 Basel, Swizerland

Database Curators' Training Course

7-9th November 2007 Inserm, Montpellier, France

Invitations for this hands on traing course were sent out this week.

Minutes from the TREAT-NMD Governing Board Meeting, July 2007

The approved minutes from the Governing Board meeting in July 2007 are now available on the private section of the web site.

Job and Training opportunities

Current job and training opportunities are advertised on the TREAT-NMD website.

www.treat-nmd.eu/jobs.htm

www.treat-nmd.eu/activities/training_educ.htm

Send us your news and views!

We strongly encourage all partners and supporters to send their own news and updates and we will be happy to include them in future editions of the newsletter. Please send your contributions to emma.heslop@treat-nmd.eu