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Workshop report

226th ENMC International Workshop: Towards validated and qualified biomarkers for therapy development for Duchenne muscular dystrophy 20–22 January 2017, Heemskerk, The Netherlands

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1. Introduction

Twenty-three participants from 6 countries (England; Germany; Italy; Sweden, The Netherlands; USA) attended the 226th ENMC workshop on Duchenne biomarkers "Towards validated and qualified biomarkers for therapy development for Duchenne Muscular Dystrophy." The meeting was a follow-up of the 204th ENMC workshop on Duchenne muscular dystrophy biomarkers.

The workshop was organized with the support of Parent Project Muscular Dystrophy (PPMD) and Marathon Pharmaceuticals, which provided travel support for participants from the US via an unrestricted grant to PPMD in addition to ENMC support. It was attended by representatives of academic institutions, industry working in the Duchenne muscular dystrophy field and patient representatives.

1.1. Background to the workshop

1.1.1. Biomarkers

Biomarkers are defined as biological, measurable and quantifiable indicators of underlying biological processes. Different types of biomarkers can be distinguished: diagnostic biomarkers indicate the presence of disease, prognostic biomarkers correlate with predicted disease course, and therapeutic biomarkers are designed to predict or measure response to treatment [1]. Therapeutic biomarkers can indicate whether a therapy is having an effect. This type of biomarker is called a pharmacodynamics biomarker and can be used to e.g. show that a missing protein is restored after a therapy. Safety biomarkers assess likelihood, presence, or extent of toxicity as an adverse effect, e.g. through monitoring blood markers indicative of liver or kidney damage.

Sometimes biomarkers can also be used as primary endpoints in clinical trials instead of functional outcome measures, and these are termed "surrogate endpoints". In Europe [2,3] biomarkers can only be used as surrogate endpoints after going through a rigorous regulatory process to officially qualify them for this purpose. Similar pathways exist in the US, where the Food and Drug Administration (FDA) also supplies a process for qualification of biomarkers for other contexts of use.

1.1.2. Therapy development for Duchenne muscular dystrophy

Duchenne muscular dystrophy (DMD) is a severe genetic disorder that leads to progressive muscle wasting and loss. Treatment is currently primarily symptomatic, and corticosteroids are used to slow down disease progression. Research into potential treatments is ongoing and many potential therapies have moved to the clinical trial phase (e.g. 203 trials were listed for DMD in clinicaltrials.gov Feb 14 2017, of which 57 are currently recruiting). Notably, ataluren (stop codon read through, PTC therapeutics) has received conditional marketing

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authorisation from the European Medicines Agency (EMA) in 2014 and a marketing authorisation application for idebenone (antioxidant, Santhera) is pending in Europe. In the US, FDA granted accelerated approval to eteplirsen for the treatment of patients with eligible mutations (i.e. those where exon 51 skipping can restore the reading frame, to allow the production of a Becker muscular dystrophy like dystrophin protein). Emflaza (deflazacort) received full approval from FDA in 2017.

Therapy development for DMD is challenging [4]. Briefly, for a drug to be approved it is required to show clinical benefit and a positive benefit/risk ratio in a treated group of patients compared to a placebo group. Treatments currently in development for DMD aim to slow down disease progression. However, because DMD is a progressive disease spanning decades, it might be difficult to prove a clinical benefit during short trials. Indeed most clinical trials have durations of less than 48 weeks, which may prove too short in order to observe clear benefit (e.g. the FDA draft guidance for DMD therapy development suggests trials of longer duration (e.g. 96 weeks [5]). Consistent with this, Pfizer and Sarepta are currently conducting 96 week trials for an anti-myostatin drug and exon skipping compounds, respectively. Given the progressive, and age-dependent irreversible loss of muscle associated with DMD, time is of the essence and pharmacodynamic biomarkers that indicate a more rapid response that correlates with longer term functional improvement would accelerate and facilitate therapy development for DMD. These biomarkers need to be quantifiable, reproducibly measureable with small coefficients of variance, and be predictive of a therapeutic effect in a shorter timeframe than existing outcome measures.

Currently no qualified biomarkers exist for Duchenne muscular dystrophy (DMD). To align efforts, an ENMC workshop was organized on this topic and held in January 2014 [5]. This workshop was organized by Profs. Alessandra Ferlini, Peter ‘t Hoen, Kevin Flanigan, Hanns Lochmuller, Francesco Muntoni and Elizabeth McNally and discussed DMD biomarker discovery, validation and interpretation. Given the rapid progress and scale of ongoing research in this area, the organizers and participants recognized the need to continue momentum in this area through another workshop.

The aims of this follow-up workshop were

- To discuss dystrophin quantification and skeletal muscle magnetic resonance imaging (MRI) as biomarkers to be able to prioritize and align the work that still needs to be done towards qualification.
- To compare the biomarkers detected in blood and urine to select the most suitable candidates and discuss future tests to confirm their usefulness
- To set up a way for collecting, storing and sharing blood and urine for biomarker identification and validation

2. Session 1: Setting the stage

2.1. 1-1 Introducing the 226th ENMC WS

Alexandra Breukel, Managing Director of ENMC, welcomed the participants underlining the role of ENMC in promoting research for the neuromuscular community. She encouraged applying for ENMC workshops as translational tools to bridge research and clinical applications.

Annemieke Aartsma-Rus introduced the aims of the workshop, working towards validated and qualified biomarkers for DMD. Indeed, the focus was on translational outputs of biomarker research. Following a period of intense discovery, now we need to prioritize biomarkers and implement their application in the clinic and clinical trial settings. Considering the chronic nature of DMD and the slow response to treatment with novel therapies or in clinical trials, biomarkers remain an ideal option to monitor the clinical course or outcomes in a shorter timeframe.

Alessandra Ferlini summarized the previous biomarker meeting achievements (204th ENMC workshop, held in [6] 2012). The workshop was quite ambitious in terms of deliverables, but this richness was encouraged by the EU BIO-NMD grant which supported many of the participants. The main deliverables and milestones were: i) sharing of data and setting up collaborations on new biomarker projects between Europe and the US; ii) alignment of biomarker discovery modalities in Europe and the US; iii) designing the best model for biomarker validation in larger cohorts to speed up translation in clinical practice; iv) biomarkers prioritization to facilitate the interaction with regulatory authorities.

Although the goals were many, general consensus was achieved especially on the identification of mandatory tools such as shared registries and biorepositories, the availability of clinical trial study samples, the use of dedicated technologies and platforms, often based on -omics approaches, and use of innovative and dedicated bioinformatics. The three conclusive breakout sessions (existing biomarkers; defining actions for combination of biomarker data in different cohorts and; issues related to the regulatory authorities) provided a list of the technically/clinically validated biomarkers in DMD that could be taken further towards a qualification process with the regulators. The consensus was that dystrophin protein measurement and muscle quality assessment by MRI could be qualified as pharmacodynamic biomarkers, while CK measurement was debated and considered not appropriate for DMD monitoring.

Annemieke Aartsma-Rus then presented on interactions with regulators pertaining to DMD biomarker development. Regulatory agencies have a process in place to qualify biomarkers for a specific purpose (‘context of use’) [2,3]. Multiple interactions coordinated by patient organisations, the TREAT-NMD [7] alliance and a cooperation of science and technology (COST) Action (BM1207) [8] have taken place between the DMD field (academics, patient organisations and industry) and the regulators to discuss the specific challenges of DMD therapy development, including biomarkers where the focus thus far mostly has been on dystrophin quantification and magnetic resonance imaging (MRI) [4,9].

The first bilaterally educational effort took place in September 2009. It was hosted by EMA and served to raise awareness about DMD specific challenges with the regulators and regulatory requirements for outcome measures including

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