Policy view

Cooperation among stakeholders to overcome challenges in orphan medicine development

The example of Duchenne muscular dystrophy

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Abstract

Duchenne muscular dystrophy (DMD) is a rare, progressive muscle-wasting disease leading to severe disability and premature death. Treatment is currently symptomatic, but multiple experimental therapies are in development. Implemented care standards, validated outcome measures correlating with clinical benefit, and comprehensive information about the natural history of the disease are essential for the regulatory approval of any therapy. However, for DMD and other rare diseases, these are not always in place when potential therapies enter the clinical trial phase. A cooperative effort of DMD stakeholders, including representatives from patient groups, academia, industry and regulatory agencies aimed at addressing this by identifying strategies to overcome challenges, developing the tools required and collecting relevant data. This review illustrates how an open and constructive dialogue among European stakeholders has positively influenced therapy development for DMD, and how this could serve as a paradigm for rare disease therapies' development in general.

1. Introduction

Developing therapies for genetic diseases poses unique challenges as illustrated by the example of Duchenne muscular dystrophy (DMD), a rare, progressive, muscle-wasting disease affecting about 1 in 5000 new-born boys [1;2]. DMD is caused by mutations abolishing production of the muscle fiber stabilizing protein dystrophin. Many experimental therapeutic strategies are being pursued. However, when some of these transitioned into the clinical trial phase, crucial elements for their evaluation were lacking, including comprehensive natural history data, meaningful outcome measures assessing clinical benefit, their correlation with natural history data, and pharmacodynamic biomarkers. During a seminal meeting organized by the European Union (EU) funded (FP6) network of excellence TREAT-NMD (www.treat-nmd.eu) and hosted by the European Medicines Agency (EMA) in 2009 [3] major bottlenecks were identified. This meeting gave rise to a cooperative effort among patients and advocacy groups, academics, health care professionals and industry aimed at collecting the missing data and the development of the tools needed. At the same time, EU regulators commenced developing guidelines to support the development of medicinal products for the treatment of Duchenne and Becker muscular dystrophy [4;5].

This review will use the example of DMD to outline how the collaborative effort of stakeholders in Europe can stimulate and assist orphan medicine development in the EU, with a focus on developing functional outcome measures, biomarkers and regulatory guidelines and on collecting longitudinal natural history data. Finally, the review will discuss future aspects of DMD therapy development.

Panel 1: Aims of this policy view

- To identify challenges in Duchenne muscular dystrophy therapy development

- To outline the collaborative effort of Duchenne muscular dystrophy stakeholders to develop tools and collect data to address the challenges and have this effort serve as a paradigm for other rare diseases
- To identify and prioritize future efforts for Duchenne muscular dystrophy therapy development

2. Duchenne muscular dystrophy and therapeutic strategies

DMD is caused by mutations in the dystrophin encoding *DMD* gene [6]. Lacking functional dystrophin, muscle fibres are more susceptible to damage resulting in chronic damage and replacement by connective and fat tissue, causing progressive muscle wasting and weakness [6-8].

There is currently one compound (Translarna) that has received conditional marketing authorization in the EU for the treatment of ambulant DMD patients of 5 years and older with a nonsense mutation (causative mutation in ~13% of patients)[7;9;10]. Numerous additional therapies are in clinical development, many of which have obtained orphan medicine designation in the EU (Supplementary Table 1). Exon skipping, the most advanced approach, aims to correct the disrupted reading frame in dystrophin transcripts, allowing production of a partially functional dystrophin, as found in the less progressive Becker muscular dystrophy [11]. Exon skipping is induced by short, chemically modified DNA analogues (antisense oligonucleotides (AON)). Because mutations cluster, skipping certain exons applies to relatively large groups of patients [7;10]. A marketing authorization application has been filed with EMA for an AON targeting exon 51 (applicable to ~ 13% of patients) [7;10].

3. DMD Care standards

DMD affects primarily skeletal, respiratory and cardiac muscles. It has a predictable clinical progression with onset in early childhood when boys present with delayed motor milestones and early signs of muscle weakness, followed by the irreversible loss of the ability to walk, self-feed, sit independently and breathe without assisted ventilation (Figure 1). These events are life-changing for affected children and parents, with patients relying on full-time help in the later stages of the disease. Cardiac problems progress inevitably, leading to severe cardiomyopathy and early death.

Standards of care have been generated and disseminated in a collaborative effort of patient organisations and TREAT-NMD which was coordinated and supported by the US Centers for Disease Control and Prevention (CDC) [12-14]. Multidisciplinary care (Table 1) focusing on all different aspects of the disease has resulted in a slower disease progression, extending mean life span to the 3rd – 4th decade, when death generally occurs due to respiratory or heart failure. Nevertheless, recent evidence shows that in several European countries many adult and paediatric DMD patients receive sub-optimal care [15;16] and that care standards for adults need to be developed further [17]. From large, multicentre trials it is becoming increasingly clear that variability in care generates noise in outcome parameters [18-20].

DMD has evolved from a pediatric disease to a severe and chronic adult condition. With increasing age, the management of swallowing and feeding difficulties, smooth muscle involvement with bladder and intestinal dysfunctions, and issues of social integration and quality of life will require further attention. A coordinated, multidisciplinary approach addressing all factors that will determine health and quality of life, should be further guaranteed in the transition to adult care.

4. The regulatory process in the EU

4.1 Benefit-risk assessment

EU legislation requires that marketing authorization for a medicinal product is refused if the benefit-risk balance is not considered favorable, if therapeutic efficacy is insufficiently substantiated or if the qualitative and quantitative composition of the medicinal product is not appropriately controlled. Assessment of quantified and well understood benefits and risks of a potential therapy is therefore key in the process of medicine regulation. To enable regulators to conclude on benefit-risk ratio, reliable measurements to identify and quantify benefits and risks need to be provided. Subjective judgement, input from stakeholders and previous decisions for other products in the field also contribute to benefit-risk assessment. Regulators have adopted a systematic and structured approach to benefit-risk assessment, to make their decisions as explicit and transparent as possible. For products that received marketing authorization, EMA provides relevant information on the benefit-risk assessment in the European Public Assessment Report (EPAR). In addition, patients' participation in benefit-risk evaluation is ensured through a framework allowing them to actively participate in regulatory workshops, scientific advisory groups, scientific advice meetings and committee discussions [21;22].

4.2.Regulatory tools

Regulatory tools are in place to facilitate the development of medicinal products. Disease specific guidelines describe regulators' preferences and standards for the demonstration of quality, safety and efficacy of medicines. For DMD a draft '*Guideline on the clinical investigation of medicinal products for the treatment of Duchenne and Becker Muscular Dystrophy'* was published by EMA in March 2013 [4], discussed amongst stakeholders during a workshop [23] and has now been published [5]. Furthermore, the Food and Drug Administration

(FDA, US) recently published draft guidelines as well (consultation period ended August 8, 2015).

Regulatory agencies also provide scientific advice at any stage of development of a medicinal product to help investigators perform appropriate studies to support a future marketing authorisation. In addition, the EU offers a range of incentives to specifically encourage the development of orphan medicines (Table 2).

For rare diseases such as DMD, increased levels of uncertainty on benefits and risks are more likely to be identified at the time of the assessment. However, specific approval mechanisms exist in the EU to enable early access to medicines fulfilling an unmet medical need in a fatal disease like DMD, subject to the provision of post-marketing data (e.g. conditional approval) [25]. Furthermore, the EU regulation on orphan medicinal products provides market exclusivity for 10 years for a product that has obtained a marketing authorization [24] .

Additionally, EMA is developing a scheme for priority medicines (PRIME), to optimise the development and accelerated assessment of medicinal products of major public health interest, such as rare diseases. The scheme is based on enhanced interaction and early dialogue with medicine developers. The EMA expects to launch PRIME in the first quarter of 2016 [26].

5. Outcome measures

The primary pathophysiological effect of DMD is a decline in muscle strength and motor function and these are therefore important parameters to measure. Any potential outcome measure to be used in DMD should be able to reliably detect and quantify a clinically meaningful effect on patients [23].

5.1 Functional outcome measures in DMD

The regulatory requirements in the EU postulate that an observed treatment effect needs to lead to a clear clinical benefit. Consequently functional improvement or delay of progression and deterioration is considered a relevant outcome for DMD patients.

To assess gross motor function, the 6 minute walk test (6MWT) and the North Star Ambulatory Assessment (NSAA) are used as primary endpoints in most trials in ambulant DMD boys [27;28]. A subset of ambulant DMD patients with behavioural and cognitive problems cannot comply with these assessments, but well defined inclusion and exclusion criteria will help to enrol those patients willing and able to comply with all clinical trial protocol requirements and procedures. When the first trials for DMD were initiated, the availability of detailed longitudinal data for the 6MWT was limited. Due to coordinated efforts of stakeholders, data are now published, describing the evolution over 12, 24 and 36 months in natural history studies performed in Italy and Belgium and by the Cooperative International Neuromuscular Research Group (CINRG) [10;29-32]. Based on this one can depict longitudinal performance: young boys show some improvement in their 6MWT and NSAA scores up to the age of 7, whiles afterwards deterioration usually occurs [27;29;32]. Similar results have been observed using cut off values at baseline for the 6MWT (above/below 350 meters) [27;29;32]. The combination of these two variables allowed the identification of distinct trajectories of progression in different subgroups subdivided by age and baseline values, which can be useful for interpretation of clinical trial results, however the acceptability of historical controls in the pivotal trials in DMD is still a matter of discussion with the regulators [23;33].

The rate of decline and its predictive value on subsequent loss of ambulation has been established for the NSAA from a large database in the UK (UK North Star network) and for the

6MWT using data from CINRG and this was useful in the postulation of their expected minimal clinical important difference (MCID) [27] [27;29;32;34]. Furthermore, knowing the rate of decline and expected variation enables stratification and power calculations. It is recommended that any target effect size is discussed in advance with the regulators, to help define the expectations and agree on what constitutes a clinically relevant change in a given experimental setting.

Evaluation of the quality of life is an important aspect of treatment evaluation as well. In DMD patients a strong correlation was shown between the 6MWT and the global Pediatric Outcome Data Collection Instrument (PODCI) - a health-related quality of life measure of functional ability. Notably, even at high levels of disability, smaller increases in the 6MWT result in a meaningful change in quality of life scores [34].

5. 1.2 New functional outcome measure scales

By definition, the 6MWT and NSAA cannot be used in non-ambulant individuals. Given that the average age at loss of ambulation is ~10.5 years[35] and the median survival of patients is ~30 years[36;37], it follows that the majority of the DMD population is non-ambulant. To address this, a collaborative international group including DMD boys and their families developed the Performance of Upper Limb (PUL) scale to evaluate upper limb function in ambulant and non-ambulant DMD patients [38-40]. The scale has been validated for clinical use against other functional measures such as the 6MWT [41] and longitudinal data are emerging across ambulant and non-ambulant patients, with and without steroids [42]. The scale is awaiting regulatory acceptance.

Studies have been conducted using neurodevelopmental scales in young DMD boys, in some instances even from the neonatal period [43-45], showing that DMD boys have delayed motor milestones most markedly in the gross locomotor and language subscales and that the gap with age-matched peers increases with age for motor skills. This has led to the understanding among stakeholders that should therapeutic interventions be proven effective and safe, it would be important to administer them as early as possible.

5.2 Biomarkers and surrogate endpoints

Biomarkers are important tools to inform and guide medicine development and have regulatory applications, e.g. to confirm mechanism of action (pharmacodynamics biomarker). When a clear relationship with clinical outcomes has been established, they can even be used as a primary outcome measures (surrogate endpoints) instead of a functional outcome measure. Because biomarkers are objectively measured, they are less prone to variation from factors like motivation and compliance with functional tests. However, to fit with regulatory requirements, biomarkers must be validated for a certain context of use (e.g. trial enrichment, surrogate endpoint etc.). A dedicated procedure is in place at EMA for the qualification of biomarkers and novel methodologies to use in the context of research and development of pharmaceuticals [46;47].

5.2.1 Dystrophin

Measuring dystrophin protein production was considered an obvious choice for a pharmacodynamic marker in trials with a compound aiming at dystrophin re-expression and dystrophin detection has been used as a secondary endpoint in early phase dose escalation studies for exon skipping therapies and Translarna [48-52]. In practice, however, it became apparent that dystrophin quantification is not straightforward (reviewed in [53]).

To use dystrophin as a pharmacodynamics biomarker, it will be crucial that dystrophin quantification methods are proven to be reliable and reproducible. Recent efforts of an international working group have demonstrated that by utilizing a carefully devised standard operating procedure, and sharing (in a blinded fashion) the same material, it is possible to stratify patients with different levels of dystrophin production accurately, with good intra- and inter-laboratory reliability and with good correlation between western blot and immunocytochemistry [54] using several dystrophin quantification protocols [55-57]. Further improvements to decrease the coefficients of variations (especially for low dystrophin levels) for these techniques are an important next step in validating dystrophin as a pharmacodynamic biomarker for therapeutic efficacy.

Currently, insufficient data are available to establish a clear correlation between dystrophin levels and muscle function for various stages of disease, thus making their use as a surrogate primary endpoint questionable.

5.2.2 Magnetic resonance imaging

Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS) techniques are promising tools for quantifying disease pathology and progression in a non-invasive and longitudinal fashion. Over the past years, protocols have been developed and validated on numerous different MR-platforms to measure muscle edema and inflammation [58-61]. Now that protocols are validated across platforms and sites, MRI and MRS can be used as quantitative, and in most cases exploratory, outcome measures in a number of ongoing natural history studies and interventional trials. Specialized protocols to quantitatively assess treatment effects have been tested independently globally across neuromuscular centers and the first promising results

have now been published [58-62]. The ImagingDMD consortium in the US, led by Krista Vandenborne and Lee Sweeny and supported by various patient organisations and the NIH, has collected longitudinal data in a large cohort of DMD patients and demonstrated that MR measures of T2 and lipid fraction show excellent sensitivity to detect DMD disease pathology and progression, even in younger boys where functional outcomes improve with time [63]. Furthermore, MRI/MRS is able to detect therapeutic effects of corticosteroids in reducing inflammatory processes in skeletal muscles of boys with DMD [64]. As such, MRI shows promise as a surrogate outcome measure, although more natural history data need to be collected.

6. Extrapolation

Due to the impact of disease stage and age on functional outcome measures in DMD, it is important to have well-defined and homogeneous patient cohorts in clinical trials. This can reduce patients' variability in function, which is crucial for reliably identifying a treatment effect in a specific population. However, it can also affect the indication for which the drug can potentially be approved, because sufficient evidence needs to be available to allow for a separate benefit-risk ratio conclusion in other subgroups of patients (e.g. per disease stage, ambulant vs. non-ambulant).

Currently, most DMD trials are conducted in patients who can comply with the 6MWT, i.e. ambulant patients of 5 years and older (~20-25% of the entire patient population). As mentioned, earlier treatment is anticipated to lead to a larger therapeutic effect. Nevertheless, non-ambulant patients would certainly also benefit from a slower deterioration of their residual muscle function (motor, respiratory, cardiac) and therefore an indication including non-ambulant patients would be a preferable goal.

The extrapolation of data from a trial performed in a certain sub-group to a different patient population (e.g. younger or older patients) will have to be discussed with the regulators on a case-by-case basis. The current position of the EMA is that if supported by the mechanism of action, extrapolation from older to younger (or from younger to older) patients might be discussed in the context of additional real life data needed to be collected post-authorisation. When data is generated in a subset of the patient population, it is likely that, to obtain a broad license, in addition to showing efficacy there will be the need to generate data on pharmacokinetic and pharmacodynamics parameters and safety in patients outside this subset to address the outstanding uncertainties for the other subsets. These aspects are increasingly discussed but for any further consideration a committee for human medicinal products (CHMP) scientific advice should be sought to discuss the most appropriate strategy for development.

7. Future perspectives

Since the first meeting with the European regulators in 2009 [3], the DMD academic and patient communities have become more aware of the regulatory processes. In collaboration with pharmaceutical companies working in the DMD field, they have tried to address the gaps identified at the time. Large amounts of data have been collected and new outcome measures and tools were developed building on the existing resources, such as patient registries, provided by patient organisations and TREAT-NMD [7;65-67]. At the same time the regulators have become more familiar with the specifics of the development of new medicines in DMD and have finalized guidelines on medicine development in DMD and Becker muscular dystrophy [5].

The improved mutual understanding was helpful for a continuous and constructive dialogue that has moved the field forward. A recent stakeholder meeting (London, April 2015) allowed for

further alignment of ongoing work and prioritization of future efforts. These include the following:

1. Efforts to increase international awareness of DMD care standards need to continue, first and foremost because patients deserve access to optimal care. Plans to set up a European Reference Network for neuromuscular disorders will build on the TREAT-NMD care and trial site registry (CTSR) [66] and the CARE-NMD project [16] and facilitate the implementation of DMD care standards throughout Europe. This would complement efforts the Parent Project Muscular Dystrophy (PPMD) is currently coordinating in the US to certify centres that provide care according to international guidelines[68].
2. New centres participating in trials are needed. Many clinical trials are currently conducted in the DMD field, resulting in capacity problems in experienced trial sites. Adhering to the care standards is a first prerequisite to be selected as a trial site by companies.
3. Another PPMD-led initiative is defining core sets of outcome measures to be used in ambulant and non-ambulant patients, which ideally should be used in all DMD trials. This would facilitate the DMD trial process, because personnel will have to be trained only once rather than for each trial. Furthermore, it would allow comparison of results between different trials and facilitate post-marketing surveillance.
4. Regulators offer scientific and regulatory guidance. Platforms are available to discuss specific medicine development, development of biomarkers, functional outcome measures, patient reported outcomes (PROs) etc. Through an increased dialogue, advice will be sought from EMA towards qualification of outcome measures in DMD (e.g. PUL as a functional outcome measure in non-ambulant patients and MRI as a biomarker or surrogate endpoint for DMD). The same platform could be considered for the quantification of dystrophin

expression as a pharmacodynamic biomarker, which has recently been discussed at an FDA and National Institute of Health organized workshop on this topic [69].

5. Developing a therapy for a rare disease like DMD should be a global effort, which implies adequate alignment of regulatory requirements, as well as continued communication among the regulatory bodies in the different regions (EMA, FDA, PMDA, Health Canada etc.) e.g. on guidelines for DMD therapy development and biomarker qualification [70].
6. Publication of data in peer reviewed journals is critical, because this informs the scientific community and regulatory bodies, allowing data to be used in guideline development, scientific advice and medicine assessment. The field already made an effort to publish on natural history and functional outcome measures in ambulant patients and have started publishing on MRI as a potential biomarker for muscle quality. A focus should now also be on producing natural history data and outcome measures for non-ambulant patients (e.g. upper limb function scales, heart and respiratory function).
7. Placebo-controlled trials are currently required to study safety and efficacy of new therapies. However, it is not excluded that in the future natural history data or data from the placebo arm of other trials can be used. Notably, several large natural history studies are being conducted, e.g. one sponsored by BioMarin Pharmaceutical Inc. and one sponsored by the Association Française contre les Myopathies (AFM). It will be critical to align the outcome measures used in ongoing natural history studies and clinical trials and for the groups involved to share the datasets. Currently several initiatives to collect and curate these datasets are ongoing.
8. Most clinical trials are done in selected populations of DMD patients, generally ambulant patients. However, to allow for the extrapolation of efficacy and safety to obtain a broader

indication (e.g. for all DMD patients when the trial was focused on a specific group of ambulant boys), the collection of data to validate the extrapolation exercise would be crucial. As mentioned, data collected in patients outside the inclusion criteria of the trial population will be required. For this the natural history data collection and outcome measure development will be increasingly important as well for the effective assessments in post marketing studies.

8. Conclusion

The collaborative effort of researchers, health care professionals and representatives from industry, regulators and the patient community has been instrumental in moving the DMD field forward in Europe (see panel 2 for take home messages). In parallel comparable efforts are ongoing in the USA (e.g. the Action Plan for Muscular Dystrophies [71]) and the FDA has programs for clinical outcome assessment, biomarker qualification and providing regulatory guidance as well[72-74]. Nevertheless, the work is not yet complete and new focus areas have been identified (section 7). Each of these priority areas will require continued involvement from researchers, healthcare professionals, and representatives from industry, regulators and the patient community. While these tasks may seem challenging, there is a strong basis of prior work, mutual understanding and collaboration that will aid these efforts. While prior work primarily focused on conducting trials to obtain marketing authorization, the field has now started to address challenges around post marketing and treatment access strategies.

Panel2: Take home messages

- A collaborative and constructive dialogue between patient representatives, academics, industry and regulators can facilitate and accelerate therapy development for rare diseases
- For rare diseases, development and implementation of standards of care to decrease variability is crucial for multicentre trials
- Functional and molecular outcome measures should be developed in collaboration with patient representatives and regulators
- High quality data on natural history and outcome measures are crucial for clinical trial design and regulatory approval, and should ideally be developed prior to or in parallel with potential therapies

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Author contribution

AAR prepared the first draft of the review, discussed contributions from all co-authors and approved the final version of the review; AAR, BS, KB & NG generated Figures and Tables for

the review. AAR, ADL, AJ, AP, EM, FM, KB, ME, NG, PB & VS were part of the steering committee of the stakeholder meeting, AAR, AdL, AJ, EM, FM, GC, KB, ME, NG, PB, ST & VS contributed to the briefing document that was generated in preparation for this meeting (http://exonskipping.eu/wp-content/uploads/2015/04/Briefing-Document-COST-and-SCOPE-DMD-EMA-meeting-April-2015-FINAL-VERSION.pdf), AAR, EM, EV, FM, NG, KB, MH, PF, VSB & VS presented at the meeting, all authors participated in discussing the contents of the review and the editing process of the review.

Disclosures

The views presented in this article are those of the authors and should not be understood or quoted as being made on behalf of the European Medicines Agency and/or its scientific committees.

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AAR discloses being employed by LUMC which has patents on exon skipping technology. As co-inventor of some of these patents AAR is entitled to a share of royalties. AAR further discloses being ad hoc consultant for PTC Therapeutics, BioMarin Pharmaceuticals Inc., Global Guidepoint and GLC consultancy and BioClinica, being a member of the Duchenne Network Steering Committee (BioMarin) and of the scientific advisory boards of ProQR and Philae

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MJW is wholly employed by the University of Oxford, and is a coinventor on patents relevant to exon skipping technology. He has consulted for Sarepta Therapeutics and has active research collaboration with Pfizer.

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VAG has been an academic researcher in trials sponsored by Sarepta Therapeutics.

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Search strategy and selection criteria

References for this review were suggested by steering committee members for a stakeholder meeting on exon skipping therapy development for DMD, as being of importance to the topics discussed. Further references were identified through searches in PubMed using search terms "natural history", "exon skipping", "functional outcome measure" OR "functional test", "biomarker", "dystrophin quantification" and "magnetic resonance imaging" OR "MRI"; each in combination (AND) with "DMD" OR "Duchenne muscular dystrophy". Only papers published in English and within the last 6 years were considered (January 2010-March 2016). The final reference list was generated on the basis of relevance to the topics covered in this review.

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Legends to Figures

Figure 1. Schematic depiction of disease milestones

Tables

Table 1: Summary of care aspects for DMD patients

- A coordinated multidisciplinary medical, surgical and rehabilitative approach of symptoms, from diagnosis on, is required to proactively address all medical aspects and co morbid conditions of DMD. Care considerations have been published [12;13], family friendly versions and multiple languages are available on the TREAT-NMD website (http://www.treat-nmd.eu/care/dmd/family-guide/translations/). Imperatives for DMD care were generated by TREAT-NMD in collaboration with DMD patient organisations (http://www.treat-nmd.eu/care/dmd/imperatives-dmd/)(Rodger et al, submitted manuscript).
- Genetic confirmation of diagnosis is needed to enable genetic counseling. Psychological support and patient organization contact information should be offered to parents upon diagnosis.
- Treatment with glucocorticosteroids (GCS) is accepted as standard of care and initiated at a young age, at least before the child is starting to decline (between age 3 to 6 years). Different steroid regimens and compounds are in use with different effect and side effect profiles. Most commonly used are prednisone 0.75 mg/kg/daily or Deflazacort 0.9 mg/kg/daily, but intermittent dosages and on /off schedules are used as well to manage side effects.
- Common practice is continuation of monitored treatment after loss of ambulation, aiming at preventing the development of scoliosis and at delaying loss of upper limb function and cardio-respiratory manifestations. Optimal care includes the prevention, monitoring and

treatment of the side effects of long term chronic GCS use, such as excessive weight gain, hypertension, osteoporosis, impairment of glucose metabolism, delayed puberty and cataract.

- Physiotherapy aiming at contracture prevention and management should be integrated in daily life from a young age
- Orthopedic management includes monitoring spine deformity and timely spine surgery for curves > 30-40°
- Improved pulmonary management has strongly impacted on quality of life and survival. Decline in respiratory function should be monitored with timely provision of airway clearance assistance and non-invasive ventilatory support to palliate symptoms of inefficient cough and hypoventilation
- Cardiac involvement is observed from an early age and may become symptomatic in the second decade. Pharmacological symptomatic treatment for cardiac manifestations includes the standard treatments of dilated cardiomyopathy and arrhythmia (angiotensin converting enzyme (ACE) inhibitors, beta –blockers and diuretics). Encouraging data are emerging on the protective effect of after load reduction by treatment with ACE inhibitors, before left ventricular function is affected.

Table 2. Orphan medicinal product designation and incentives in the EU[24$]

The designation procedure and criteria are laid down in regulation (EC) No 141/2000

- Criteria for designation
    - Product is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting <1 in 2,000 persons in the EU OR a

condition that is life-threatening, seriously debilitating and/or chronic for which it is unlikely that products would be marketed without incentives

    - A product for diagnosis, prevention or treatment of the condition does not exist, or if it does, the new product will be of significant benefit

- Incentives once designation has been obtained
    - Access to free protocol assistance by the EMA
    - Products will be authorised via a centralised procedure (valid in all EU countries, Iceland, Liechtenstein and Norway); fee reductions for marketing authorization applications apply
    - Upon marketing authorization, products have 10 year market exclusivity over similar products, unless these are clinically superior or safer than the marketed product

[$]This is a summary only. For complete information we refer the reader to: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp&mid=WC0b01ac05800240ce

Supplementary Table 1. Overview of substances with orphan drug designation for DMD