

Workshop report

236th ENMC International Workshop
Bone protective therapy in Duchenne muscular dystrophy:
Determining the feasibility and standards of clinical trials
Hoofddorp, The Netherlands, 1–3 June 2018

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On behalf of the 236th ENMC workshop participants[#]

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1. Introduction

On 1–3 June 2018, the 236th European Neuromuscular Centre workshop was held in Hoofddorp, The Netherlands, to discuss the issue of bone protective therapies in Duchenne muscular dystrophy (DMD), in particular, the feasibility of developing clinical trials. Twenty-six delegates, that included 19 experts in the neuromuscular and bone clinical and research fields, three representatives from patient organizations, two adults with DMD and two representatives from industry, attended this workshop.

2. Workshop key deliverables

The following were key deliverables of this workshop:

- (1) To review published evidence of strategies to improve bone health and growth in DMD, highlighting gaps in current knowledge and evidence.
- (2) To determine the optimal clinical trial design of bone protective therapy, especially as primary prevention of fractures in DMD.
- (3) To determine the optimal bone and muscle outcome measures in DMD bone protective trials.

- (4) To discuss potential operational barriers to successful conduct of clinical trials, along with strategies to mitigate such hurdles.
- (5) To establish an international consortium of experts on bone and growth issues in neuromuscular conditions with the primary aims of developing a study protocol for a bone protective trial in DMD, and facilitating other research in aspects of endocrine and bone health care in this condition.

3. Clinical manifestations of osteoporosis in DMD and review of the 2018 updated standards of care

Prof. Leanne Ward gave an overview of the extent of osteoporosis in DMD and the rationale for the 2018 updated DMD care guidances [1,2]. Both the underlying muscle weakness and glucocorticoid (GC) therapy contribute to bone fragility. As many as 25% of boys with DMD by late adolescence will have low-trauma extremity fractures even without GC therapy, but in those treated with GC this is reported to be as high as 40% [3]. Up to 50% of boys with GC-treated DMD will have symptomatic vertebral fractures (VF) [3]. However, VF are frequently asymptomatic, particularly in their earlier phases of development, and will go undetected in the absence of periodic spine radiographs [4]. Therefore, the overall prevalence of VF (asymptomatic and symptomatic combined) in DMD remains unknown.

With the establishment of GC exposure as standard of care in individuals with DMD, attention has now turned to

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the relative effects of different GC regimens on various organ systems, including bone. Crabtree et al. [5] recently showed that boys on daily GC retain ambulation for longer compared to intermittent GC, but at the expense of more frequent VF, increases in body mass index Z-scores and reductions in height Z-scores.

Overall, VF are more severe at first identification if boys with DMD have not undergone routine monitoring for asymptomatic VF, and instead present with back pain that then prompts spine imaging. This observation has fuelled recent recommendations put forward by the Centres for Disease Control and its international consortium of experts to carry out lateral thoracolumbar spine radiographs starting around the time of diagnosis, or no later than GC initiation, followed by spine radiographs every 1 to 2 years for those on GC, and every 2 to 3 years for GC-naïve patients or patients who have stopped GC treatment [1].

Untreated, VF are linked to chronic back pain and spine deformity [4], while leg fractures can cause premature, permanent loss of ambulation and challenges in daily care for those in wheelchairs [6]. Deaths due to fat embolism syndrome after long bone injuries in DMD have been reported [7]. Since VF typically do not undergo reshaping in the DMD setting (due to the severity, chronicity and progressive nature of the insult to the skeleton), the importance of early identification and treatment, in order to prevent the “vertebral fracture cascade”, is the underlying rationale for the 2018 updated DMD care guidances [1,2].

4. The muscle-bone cross talk

Dr. David Weber gave an overview of the muscle-bone unit in health and disease. The normal physiology of the muscle-bone unit is altered in DMD as a result of muscle weakness, immobility, inflammation and GC exposure. The mechanostat theory of bone adaptation highlights the importance of muscle forces in driving bone strength, by inducing mechanical challenges that are sensed by osteocytes, as bone tissue is strained during loading. Increases in muscle strength during childhood and with activity promote bone formation, while muscle loss with aging and inactivity leads to a loss of bone mass and strength [8].

Updated models of the muscle-bone unit incorporate bidirectional endocrine/paracrine cross-talk between muscle-bone. Muscle-secreted factors stimulate bone formation (insulin-like growth factor-1) or bone loss (myostatin) [9]. Bone-secreted factors that may impact muscle function include osteocalcin and interleukin (IL)-6 [10,11]. Emerging therapies that improve muscle function may benefit bone, and the possibility of beneficial effects of bone targeted therapies on muscle in DMD requires future exploration.

5. Lessons from animal studies on bone strength and growth in DMD

Dr. Susan Novotny gave an overview of the skeletal phenotype in animal models of DMD. Mouse models

are widely used for pathomechanistic, prognostic and therapeutic implications of DMD. Despite the variety of models, the skeletal phenotype of dystrophic mice has most comprehensively been characterized in the *mdx* mouse [12]. The shortcomings of this model include relatively mild muscle weakness, and the lack of disease progression as seen in boys with DMD. In particular, *mdx* mice experience muscle regeneration and restoration of muscle function, resulting in a near normal lifespan [13].

Deficits in femur structural and material properties along with cortical and trabecular morphometry have been reported in *mdx* mice as early as 3 weeks of age compared to wild-type mice [14]. This presence of a skeletal phenotype, prior to muscle degeneration and weakness, suggests that compromised bone quality is not exclusively the result of a disturbed muscle-bone relationship. Exposure of healthy calvarial bones to 10% serum from older *mdx* mice, with significantly elevated IL-6, led to increases in osteoclastic activity in those healthy bones which were reversed with IL-6 antibody [15]. This suggests that circulating cytokines like IL-6 may play a role in DMD-related bone loss. Despite some limitation of the *mdx* mice, recommendations for standardization of experimental studies in the *mdx* mice are available and should be adhered to [16]. Skeletal and growth phenotypes of other DMD animal models are now needed.

6. Status of glucocorticoids and other treatments in DMD

Dr. Michela Guglieri provided an update on current status of GC treatment and clinical trials in DMD, and discussed the implications for future bone health trials in DMD. Currently, GC (prednisone/prednisolone and deflazacort) are the only drugs available worldwide for all subjects with DMD. From around 2002, GC treatment was incorporated into the clinic and is now the international standard of care [17]. In DMD, GC treatment delays loss of clinically meaningful milestones.

Concerns about side effects have led to large discrepancies in clinical practice regarding time of GC initiation, GC type, dosing and time of discontinuation. Variation in treatment factors like different GC regimens may have an impact on benefits and side effect profiles, including fracture risk and growth [5,18]. The results of a large, ongoing double-blind randomized controlled study investigating the three more commonly prescribed GC regimens, called “Finding the Optimum Regimen for Duchenne Muscular Dystrophy” (FOR DMD, ClinicalTrials.gov Identifier NCT01603407), are expected in 2020 and are anticipated to improve our understanding of the relative merits and side effects from different GC prescriptions [19].

Worldwide, there are currently more than 50 clinical trials recruiting patients with DMD. More investigational drugs, including gene therapy, will be tested in this population in the upcoming years. Other investigative agents including vamorolone inhibit the nuclear factor kappa beta (NF- κ B) pathway, similar to the way in which traditional GC exert their benefit. Vamorolone is a “dissociative steroid”, meaning it has significantly reduced transactivation activity and is therefore

anticipated to have fewer side effects than conventional GC therapy. Edasalonexent is another compound that attenuates the NF- κ B pathway. These two compounds have been tested in phase 1 and phase 2a studies [20,21]. The extent of their impact on muscle strength and function and their side effect profiles are currently under investigation in international pivotal trials.

Dr. Guglieri concluded by pointing out that the design of bone health trials will need to consider the heterogeneity of conventional GC therapy as a potential confounding factor. Solutions include recruiting subjects on a particular GC regimen or stratification for GC regimen at randomization.

7. Outcomes for adults with DMD treated with glucocorticoids

Dr. Ros Quinlivan discussed adult outcomes of GC-treated boys with DMD and implications for bone monitoring in this population, a proportion of which will also have had spinal surgery. The natural history of DMD has improved dramatically in recent decades due to the introduction of non-invasive ventilation, scoliosis surgery, proactive cardiac treatment and GC therapy [22].

Dr. Quinlivan presented data from her 108 adults with DMD (aged 17–40 years) of whom 70 were GC-treated and 36 were GC-naïve (naïve defined as GC-treated for less than one year). Thirty-four patients were GC treated for more than 10 years. The remainder had received GC for two to five years. Eight out of 108 patients were ambulant at the time of transition to adult services and all of these individuals were on GC except for one who had stopped three years earlier. Eighty percent of GC-naïve and 48% of GC-treated patients required non-invasive ventilation. Bone monitoring in this population tended to occur locally, with some individuals being discharged from local adult bone service despite ongoing risk factors for bone fragility. Furthermore, bone protective treatment, if it was prescribed, was inconsistent, with some receiving oral and others intravenous bisphosphonates.

Dr. Quinlivan concluded that while the benefits of GC therapy generally outweigh the side effects, there is a need for evaluation of the side effect profile like fracture in adults with DMD. There is also a need to implement bone health monitoring and treatment in the adult population according to the recently updated care guidances, given that those recommendations apply across the age span [1].

8. Challenges of bone protective trials in DMD

Dr. Jarod Wong introduced discussions on the feasibility and design of bone protective trials in DMD. A recent study showed that fractures are of concern to families and subjects with DMD [23]. However, the use of placebo, insufficient information on risks of novel therapies, and inadequate information about study requirements were identified as major barriers for the participation in clinical trials. Confidence that the research will improve understanding of bone health and

osteoporosis, and guarantee that treatment will be provided after a successful trial were deemed as facilitators [24].

Justus Kuijer, a 27 year old man with DMD, shared his experience of painful VF including the impact on his quality of life and the lack of recognition amongst clinicians, leading to delayed diagnosis. Justus thinks that research into bone protection in DMD is important. Frank van Ieperen, a 36 year old man with DMD, emphasised that assessment of quality of life in bone protective trials is very important, in particular, evaluating aspects of socialization. Ms. Pat Furlong and Ms. Elizabeth Vroom representing Parent Project Muscular Dystrophy and Duchenne Parent Project, respectively, shared their views. Both expressed their concerns about recruitment to DMD osteoporosis trials with a placebo arm. Recruitment and participation into bone protective trials require flexibility to allow inclusion into other trials, which can be done by adopting “master protocols” [25]. If a placebo-controlled trial of bone protective therapy is designed, the shortest possible period of placebo treatment should be considered.

9. Bone densitometry and vertebral fracture assessment outcome measures

Dr. Crabtree gave an overview of bone densitometry and VF assessment. Assessment of bone mineral density (BMD) in boys with DMD involved in clinical trials aimed at reducing fracture risk should take into account tolerability, accessibility and cost. The technique needs to be precise and sensitive to change, with good availability and reproducibility across multiple sites.

Dual energy absorptiometry (DXA) is widely available and affords patients a low radiation dose. The main disadvantage of DXA is that it is a two-dimensional technique which measures the ratio of bone mineral content to projected bone area, i.e. areal BMD, which is highly dependent on bone and body size. Among individuals with short stature, a frequent finding in DMD, it is essential to adjust the data using one of the recognised size adjustment techniques, such as volumetric BMD, also known as bone mineral apparent density (BMAD) for lumbar spine BMD, or height for age Z-scores for total body BMD [26].

In boys with DMD, the relationship between DXA BMD (unadjusted and size adjusted BMD) and fracture risk is less clear. Studies have demonstrated “normal” volumetric BMD at lumbar spine even in the presence of VF [5]. Given that VF and fragility fractures are not always associated with low DXA BMD, a Z-score diagnostic threshold is not appropriate [27]. It is now clear that spinal imaging for early identification of VF is the most important diagnostic test for osteoporosis in DMD and GC-treated conditions of the young [4,28]. Recent studies evaluating DXA-acquired images of the lateral thoracolumbar spine for VF assessment compared to radiographs show promising validity [29,30]. The use of DXA to screen for VF as part of routine bone health monitoring in children is now under review by the International Society for Clinical Densitometry.

Techniques such as quantitative computed tomography (QCT) allow separate assessment of size-independent cortical and trabecular bone densities, in addition to bone geometry and strength. Dedicated peripheral QCT scanners enable the assessment of fracture-prone long bones, as well as muscle geometry, with minimal radiation exposure. High resolution QCT scanners now give almost in-vivo bone biopsy-type structural outputs such as trabecular volume, and trabecular separation. However, small measurement regions, long scanning times and a high susceptibility to movement artefacts are disadvantages [31]. Most recently, bone assessment by magnetic resonance imaging (MRI) has been established. The advantage of MRI is that it uses non-ionising radiation to assess bone architecture and muscle structure [32].

In summary, it was emphasized that beyond surrogates for bone strength such as BMD, bone outcome measures in clinical trials should include bone fragility assessments as key outcomes, including VF and low-trauma long bone fractures.

10. Bone biochemistry outcome measures

Dr. Francesca Broggi gave an overview of bone turnover markers in the context of DMD. Biochemical markers of bone turnover can be measured in biological fluids (serum, plasma and urine); they are mainly represented by products of collagen type I synthesis (N-Propeptide of collagen type I [PINP]) or degradation (beta-crosslaps of C-telopeptide of collagen type I [CTX]), as well as enzymes (Bone Specific Alkaline Phosphatase), non-enzymatic peptides (Osteocalcin), or small biomolecules needed for cellular cross-talk and mutual regulation (Receptor activator of nuclear factor kappa- β ligand [RANKL], Osteoprotegerin).

In DMD, declines in bone mass were associated with increases in bone resorption markers, especially in the early phases [33]. Other studies suggested that both bone formation and resorption were low in DMD, an observation that is corroborated by dynamic histomorphometry in boys following years of GC treatment [34]. Serum CTX, a marker of bone resorption, and PINP, a marker of bone formation, may be considered in clinical trials but require comparison with robust normative data [35] and adjustment for delayed growth and puberty for appropriate interpretation.

11. Muscle outcome measures in DMD bone protective clinical trials: functional assessment, imaging and biomarkers

Prof. Volker Straub discussed the issue of muscle outcome measures. A good outcome measure needs to be reliable, valid and sensitive. In order for it to be reliable, it has to show an excellent inter-rater and intra-rater reliability and a low measurement error. The validity is related to the degree to which an assessment measures what it intends to measure, and an outcome measure is sensitive when it holds the ability to detect clinically meaningful changes. In addition, a good outcome measure should be cost efficient,

easy to administer and standardised. The choice of outcome measure for interventional studies in DMD will depend on the mechanism of action of the tested compound, the duration of the study and the cohort included. At a recent workshop dedicated to outcome measures in DMD trials, specific clinical, imaging, blood biomarker and muscle biopsy outcome measures were suggested for various age groups and for different interventional mechanisms [36]. A combination of multiple timed function tests, like the six minute walking distance, with imaging outcomes, like the muscle fat fraction measured by MRI, can enhance the predictive value and the possibility of identifying patients with differing disease progressions.

A recent ENMC workshop was dedicated to the discussion of outcome measures using particular biomarkers in DMD [37]. Regulatory authorities specifically define biomarkers as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention. It was emphasized that biomarkers can be (1) diagnostic, showing that something is wrong, (2) prognostic, predicting whether the disease course is mild, moderate or severe and (3) therapeutic, predicting to what degree a therapy shows efficacy.

The choice of muscle outcome measure in a bone protective trial depends on several factors including expected impact of the investigative agent on muscle function; age or phase of the condition; and availability of the test if the trial includes multiple sites. In a bone protective trial recruiting both ambulant and non-ambulant subjects, the performance of upper limb assessment may be suitable [38].

12. Quality of life outcome measures in DMD bone protective clinical trials

Prof. Ulrike Schara discussed quality of life assessments. Factors which may impact negatively on quality of life in DMD following fragility fractures include pain and reduction in mobility and daily activities, which may lead to restricted social experiences.

In a thorough overview of DMD quality of life research [39], thirteen different instruments for assessing quality of life were used in 19 publications. The review showed that whilst the physical domains of quality of life correlated with physical functioning and disease progression, changes in psychosocial domains did not parallel changes in disease status. The PedsQL Inventory and DISABKIDS are often used as multidimensional instruments, although these tools may not evaluate psychosocial aspects. The International Classification of Functioning, Disability and Health (ICF, WHO 2001) is a classification of health and health-related domains that may be suitable for use in osteoporosis clinical trials.

To date, an ideal quality of life instrument in DMD for osteoporosis trials does not exist but should incorporate assessments of pain, loss of function including mobility, the impact of fracture-related surgery, dependency and socialization.

13. Bone protective agents

Prof. Zulf Mughal, Prof. Jonathan Adachi, Prof. Margaret Zacharin and Prof. Leanne Ward discussed bone protective agents in relation to DMD clinical trials. Osteoporosis therapy falls into two general categories: anti-resorptive (bisphosphonates and RANKL antibody) and anabolic therapy (growth hormone, androgens, parathyroid hormone and anti-sclerostin antibody).

13.1. Anti-resorptive therapy

13.1.1. Bisphosphonate

Systemically administered bisphosphonates (pamidronate, neridronate and zoledronate) are increasingly used to treat children and adolescents with primary and secondary medical disorders associated with fragility fractures. Results of observational studies in children with moderate or severe forms of osteogenesis imperfecta (OI) showed that treatment with intravenous bisphosphonates is associated with improvements in mobility, areal BMD, increase in cortical thickness and trabecular bone volume on trans-iliac bone biopsy, reshaping of compressed vertebral bodies and reduction in long-bone fracture rates [40].

The main pharmacological action of bisphosphonates is inhibition of osteoblast-mediated bone resorption. Oral bisphosphonate therapy during childhood is not recommended as data from controlled trials in paediatric OI show improvements in the height of vertebral bodies in those treated with intravenous [41] but not oral [42] bisphosphonates. These observations are likely influenced by the low bioavailability of oral agents [43]. This lack of improvement in vertebral height with oral agents is particularly relevant to DMD where the frequency of VF is high, and supports the use of intravenous bisphosphonates as first-line therapy despite their less convenient mode of administration [1].

To date, there are no randomised trials of bisphosphonates in DMD. Treatment of seven boys with DMD who among them had total of 27 painful VF using intravenous pamidronate or zoledronate for two years led to improvement in volumetric BMD at lumbar spine, back pain and stabilisation or partial reshaping of previously fractured vertebral bodies [44]. Prophylactic treatment with oral risedronate in 52 individuals with DMD who were GC treated resulted in stabilisation of volumetric BMD at lumbar spine and fewer VF compared to 15 untreated historical controls, although duration of follow-up and therefore GC therapy was longer in the historical controls [45].

13.1.2. RANKL antibody

Denosumab is a recently developed anti-resorptive agent that is administered subcutaneously. RANKL is an essential mediator of osteoclast formation, function and survival [46]. Denosumab is a human monoclonal antibody that targets RANKL to prevent the activation of RANK, thereby inhibiting bone resorption and increasing bone strength at both trabecular and cortical sites without directly interacting

with bone surfaces [47]. A large study on women with post-menopausal osteoporosis showed that administration of denosumab every 6 months for three years reduced fracture rates without an increased risk of side effects compared to placebo during the trial period [48,49]. Denosumab is also approved in multiple countries for adult GC-induced osteoporosis.

Given its convenient route of administration, acceptable safety profile and demonstrated efficacy in adults, denosumab now merits further exploration in children. Preliminary evidence suggests a positive role of RANKL inhibition on muscle, including in the *mdx* mouse [50]. Osteoprotegerin, the decoy receptor that binds to RANKL, exerts an inhibitory effect on the pre-osteoclastic differentiation process and is also a key regulator of muscle integrity. Treatment of *mdx* mice with recombinant osteoprotegerin preserved muscle strength especially in fast twitch fibres [51].

As a monoclonal antibody to RANKL, the effect of denosumab is much shorter than bisphosphonates. It is now recognised that cessation of denosumab results in rebound of bone turnover markers, increases in fracture rates and declines in BMD in post-menopausal osteoporosis [52] and in children with OI [53]. This is postulated to result from vigorous re-activation of osteoclasts as the effect of denosumab wears off [54]. Therefore, any study which uses denosumab as bone protective therapy in DMD must take steps to mitigate the rebound phenomenon by continuing denosumab long-term, or by succeeding denosumab therapy with (longer-acting) bisphosphonate treatment.

13.2. Anabolic therapy

Individuals with DMD would theoretically benefit from osteoanabolic therapy, since bone turnover on trabecular surfaces was reduced in boys with DMD even prior to bisphosphonate therapy (50% of the healthy average) and then fell further (to 10% of the healthy average) after two years of pamidronate or zoledronate therapy when given to treat VF [34].

13.2.1. Growth hormone

Boys with DMD treated with GC have short stature in addition to bone fragility. GC-associated growth failure occurs via several mechanisms, but largely due to its direct effects on the growth plate via an increase in chondrocyte apoptosis [55]. To date, the only published study using recombinant growth hormone treatment (rhGH) in DMD was a retrospective study of 39 GC-treated ambulatory boys which showed that height velocity increased from 1.3 cm/year to 5.2 cm/year [56]. At the end of treatment, the boys were still shorter than average with height Z-scores of approximately -3.0 SD. There were no significant differences in muscle function [56]. No bone outcome data was reported. Adverse events including benign intracranial hypertension and impaired glucose tolerance were reported [56]. Since numerous studies have shown that the main effect of GH on bone strength is mediated by increases in muscle strength,

and since muscle damage and fibrosis begin early in DMD, it is unlikely that rhGH would be a major benefit to bone strength in this context.

13.2.2. Androgens

Puberty is almost universally severely delayed, if not absent, in those treated with daily GC. Assessment of puberty is now recommended from the age of nine years in the 2018 updated care guidances [17]. Discussion around testosterone initiation for pubertal induction should be considered in boys without signs of puberty by 14 years, and can even be considered as early as 12 years [17].

The only retrospective study of testosterone therapy, in 14 adolescents with DMD treated with GC, showed that height velocity increased from 0.5 cm/year to 3.2 cm/year. At the end of treatment, the boys were still shorter than average with height Z-scores of approximately -5.0 SD. No bone age or DXA BMD data were reported, but testosterone was well-accepted and appeared to increase maturity and peer social acceptance [57]. Addressing puberty with testosterone therapy and restoring the normal hormonal milieu in the adolescent with DMD is paramount [17]. However, the role of testosterone to improve bone mass and reduce fracture risk in DMD is currently unknown. A few adult studies in elderly men (without DMD) have shown positive effects of testosterone on bone density when administered as replacement therapy [58]. On its own testosterone may be a relatively weak modifier of bone strength in the face of high dose GC and underlying muscle wasting, although studies in DMD are needed.

Given that the updated care recommendations support the consideration of testosterone therapy for management of puberty in DMD [17], future bone protective clinical trials involving adolescents will need a plan for puberty management or stratification for testosterone therapy.

13.2.3. Parathyroid hormone (PTH)

Teriparatide, recombinant human PTH, is approved by the Food and Drug Administration for initial treatment of women with post-menopausal osteoporosis who are at high risk of fracture, those who failed prior osteoporosis therapy, and GC-associated osteoporosis in adults [59]. Teriparatide significantly reduced the risk of VF and non-VF in women with post-menopausal osteoporosis [60]. Teriparatide, however, should not be used in those with open epiphyses because of concern over the development of osteosarcoma in a strain of growing rats (where high doses were used) [61]. Teriparatide appears to have a dramatic effect on spine BMD, without evidence for effect at the hip and forearm [60]. The effect of teriparatide on bone appears to be blunted in adults when administered following bisphosphonate therapy [62], a factor to consider when switching therapy in adults with DMD who received bisphosphonates during childhood.

13.2.4. Sclerostin antibody

Sclerostin is produced by osteocytes and inhibits bone formation by interacting with the low-density lipoprotein receptor-related protein 5/6 receptors on osteoblast surfaces. These receptors contribute to the activation of Wnt signalling, which regulates bone formation. Sclerostin can be inhibited by anti-sclerostin antibody, resulting in rapidly increased bone formation and reduction in bone resorption (anabolic and anti-resorptive effects), followed by increases in BMD at the spine and hip [62]. The largest human study of anti-sclerostin antibody (romosozumab) treatment to date was carried out in over 4000 women with post-menopausal osteoporosis [63]. Patients were randomized to monthly sub-cutaneous romosozumab or weekly oral alendronate for one year. There was a 48% lower risk of new VF, a 38% reduction in hip fractures and a 19% reduction in non-VF in the romosozumab arm. Trials of anti-sclerostin antibody in paediatric OI are expected in the near future.

Like RANKL antibody (denosumab), anti-sclerostin antibody therapy is also short acting. In adults, PINP returns to baseline levels by about 6 months despite ongoing therapy with anti-sclerostin antibody, and subsequent injections seem to have smaller effects on bone formation [64]. Like denosumab, it may be necessary to ‘lock in’ the gains of antibody-based osteoporosis treatment upon discontinuation, with subsequent long-acting anti-resorptive agents such as bisphosphonates.

14. Funding opportunities for supporting research into musculo-skeletal health in DMD

Prof. Volker Straub and Prof. Faisal Ahmed gave talks on funding opportunities for bone protective drug trials and promoted the development of a consortium to facilitate research in endocrine and musculoskeletal health in neuromuscular conditions.

Seeking research funding requires clear interlinked short, medium and long-term strategies. The long-term strategy needs to be ambitious, and although a narrow focus on musculoskeletal health will allow the consortium to address its research questions, it is clear that there are other knowledge gaps in endocrine-metabolic consequences of DMD and GC therapy (for example obesity, metabolic syndrome and glucose homeostasis) that may be interlinked with growth and skeletal development. The proposed consortium should also develop a clear plan for improving awareness as well as advocacy.

The Consortium needs to have clarity of vision regarding research and therapeutic trials. It needs to explore how it can use existing resources and show clear evidence of collaborative activity, including with industry. Funding is available at several levels for development of a network or platform for scientific collaboration to explore data curation and exchange through national and international registries. The network should also work together to perform preliminary studies or small-scale research trials to secure funding to develop large-scale clinical efficacy trials that pave the way for regulatory approval. It is important that

the consortium is not seen as ‘reinventing the wheel’. The consortium should work in collaboration with patient advocacy groups, translational research networks like the TREAT-NMD Alliance, and industry to refine existing guidance and plans based on contemporary evidence. The European Medicines Agency has issued some guidance on the design of clinical trials in the field of secondary osteoporosis (https://www.ema.europa.eu/documents/report/report-paediatric-osteoporosis-expert-meeting_en.pdf)

15. Workshop recommendations

The workshop participants agreed that there is a need for well-designed randomised controlled trials of bone protective therapy in DMD, ideally focussing on primary prevention (prevention of first fractures). The relative merits of different therapeutic agents require careful consideration in deciding on the choice of drug, and ideally trials will be powered on reduction of fractures, including VF. The workshop participants also felt that clinical trials of newer investigative agents in comparison with bisphosphonates following identification of fractures are also needed, especially treatments that are better tolerated. A number of barriers to osteoporosis clinical trials in DMD exist. Collaborations between specialties and with patient organization and industry are paramount. Finally, dissemination and implementation of the new DMD care guidances (2018) in relation to bone and endocrine management in children and adults with DMD [1,17] were also highly recommended.

16. Workshop participants

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