

Workshop report

238th ENMC International Workshop: Updating management recommendations of cardiac dystrophinopathy Hoofddorp, The Netherlands, 30 November - 2 December 2018

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1. Introduction

Twenty four neuromuscular experts, cardiologists, patient representatives and a trainee, supported by the *ENMC Young Scientist Programme*, from seven European countries (Belgium, Czech Republic, France, Germany, Italy, Netherlands, United Kingdom) and the United States participated in the workshop, held in Hoofddorp, the Netherlands. The aims of were to: (1) agree diagnostic standards, thresholds for initiating therapy and an optimal therapy regime for cardiac dystrophinopathy; (2) determine whether there are clinically relevant genotype-phenotype correlations for cardiomyopathy in DMD; (3) review current knowledge on the potential of genetic therapies to prevent cardiac dystrophinopathy and (4) agree on guidance for the use of implantable cardioverter defibrillators and left ventricular assist devices in the management of patients with advanced cardiomyopathy.

2. The heart in dystrophinopathy and genotype-phenotype correlations

Presenters from each country summarised their local practice and discussed strengths and weaknesses in cardiac surveillance and management. Several common themes emerged including: (i) recognition that standards for adults

with BDMD are significantly less well developed and coordinated in several countries than those for paediatric patients; (ii) acknowledgment of the physical difficulties for patients and the technical challenges in obtaining quality images of the heart by either echo- or MR-modalities in adult and paediatric patients with BDMD; (iii) patient's phenotype and not genotype should guide clinical decision-making - particularly in the deployment of implantable defibrillators, left ventricular assist devices or patient suitability for cardiac transplantation; (iv) need for greater international awareness to raise standards - particularly appropriate for clinics managing smaller numbers of BDMD patients; (v) in line with latest recommendations, most attendees have begun to deploy angiotensin-converting enzyme inhibitor therapy for prophylaxis of cardiomyopathy from age 10 years [1].

The central role of NMD specialists in coordinating multi-disciplinary care of adults with BDMD was challenged. Having a 'patient-care-coordinator' - facilitating a more individualised, patient-centred, flexible schedule of specialty assessments was considered preferable. An identified patient-care coordinator would navigate the complex scheduling required for an individual with multi-specialty care requirements. Participants also advocated for a multi-disciplinary care clinic model for patients with BDMD (ie: muscle, respiratory, cardiac, bone health, nutritional and psychological support, etc.) rather than a model that requires patients to attend separately arranged specialty clinics. However, such an arrangement might prove physically demanding for some patients.

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3. Disease modifying therapies for the heart in dystrophinopathy

3.1. Differences in the options for cardiac management between DMD and BMD?

Prof E McNally discussed the longer and more variable clinical timeline in BMD and its differences from DMD, noting that cardiac involvement in BMD could be disproportionately severe even in patients with mild skeletal phenotypes [2–6]. She reviewed the limited literature on steroid use in BMD and discussed alternative steroid regimens that may have fewer side effects [7,8]. There was also recognition that as gene therapy modifies the DMD phenotype, these boys would be expected to change to the BMD spectrum, including its associated cardiomyopathy [3]. The transformation will only be realized, however, if gene therapy is highly successful and has a long duration of action. If microdystrophin gene therapy is only partly effective, the phenotype may be more like that of patients currently with intermediate muscular dystrophy.

3.2. Preserving skeletal and cardiac strength in DMD/BMD – is there a conflict?

Dr I deGroot posed the intriguing question as to whether cardiovascular or muscular systems limit exercise performance more in BDMD? Muscle weakness in these patients is explained both by progressive muscle loss and disuse atrophy. Muscle loss increases the effort of daily activities – a disincentive to remaining active [9]. Physical training offers a way of preventing the disuse component. There are several type of training: functional training (eg: walking, cycling or swimming) and training during sports activities (eg: wheelchair hockey). Boys with DMD show a modest metabolic response – as evidenced by a rise in blood lactate levels and heart rate during 6-minute assisted cycling test [10,11 & unpublished work]. Compared to healthy controls, DMD patients have higher resting heart rates, less increase and lower maximum heart rates on walking [9]. In cycling tests, however, heart rate in boys with DMD increased comparably to that of healthy peers, reaching only slightly lower peak rate by its end [10]. Modest exercise training is possible, even in older patients with DMD, and assisted exercise increases beneficial training demands both on muscle and cardiovascular systems [11,12]. On the basis of current evidence, it seems that physical training is beneficial both for skeletal muscle and cardiovascular systems in these patients [12,13]. However, questions remain – particularly about the value, safety and intensity of exercise in patients with more advanced BDMD.

3.3. Newer therapies for dystrophinopathies – what, for whom and equality of access?

In a wide-ranging talk, Dr A Aartsma-Rus reviewed the promise and limitations of stem-cell, gene-editing, utrophin

upregulation and microdystrophin gene-therapy for patients with DMD and what trial evidence was available currently to support each strategy.

Studies by various companies of adeno-associated virus administration of microdystrophin therapy have mainly concentrated on confirming dystrophin expression in the skeletal muscle(s). Therapy seems safe and microdystrophin has been expressed. However, questions remain about the degree and durability of functional benefit, the developed natural immunity to the virus-vehicle and whether immunity to a first therapy will limit the efficacy of repeat administration(s).

Exon skipping strategies (exon 51) have shown a modest increase in dystrophin expression in skeletal muscle. Ongoing research is now focused on modifying the drug(s) to improve delivery and uptake more widely. Exon skipping trials for exons 53 and 45 have not yet reported results.

Ataluren ('Translarna') – a small-molecule for the 13% of patients whose DMD is due to a non-sense mutations, allows dystrophin expression in skeletal muscle but its effect on the heart is unknown. Studies of the vasodilating phosphodiesterase-5 (PDE5) inhibitors tadalafil and sildenafil have not shown benefit in DMD. The multi-mechanistic benefits of steroids are already well established and trials of other anti-inflammatory compounds (vamoralone; anti-NFKbeta) are ongoing. DMD is a condition characterised by massive oxidative stress. Despite the theoretical plausibility for benefit, results from idebenone trials have been mixed. Further trials of idebenone and agents with similar actions – halofuginone, green tea extract, FG3019 (anti-CTGF), pentoxifylline and epicatechin are under consideration. Agents of theoretical benefit in DMD may prove useful also – the histone deacetylase inhibitor (Givinostat) and the selective androgen receptor modulator (SARM).

3.4. DMD therapies likely within 5 years and how to plan for them?

Dr M Guglieri summarised the various known pathways in the DMD pathological cascade and how diverse agents have been developed to target them. Over the period 2007–'19, about 23 non-interventional / natural history studies and 50 other interventional studies have either reported, are underway or are planned for DMD. As summarised by Dr Aartsma-Rus, these include trials of mechanistically very different treatments. The majority of studies to date recruited only paediatric participants but, gratifyingly, more studies have begun to focus and extend recruitment to include non-ambulant adolescents (eg: WAVE; SIDEROS; SOLID; testosterone; tamoxifen) and older patients, who previously have felt excluded from much of BDMD research. Undertaking valid randomised controlled trials of therapies for the heart in patients with BDMD, however, is becoming less easy to control because of the number of patients taking 'over the counter' or internet available drugs (eg: metformin, tamoxifen; idebenone; multi-vitamins) with actions which might confound, counteract or enhance the actions of agents

being tested. Other background patient-variables such as differences in steroid agent, dosage, duration of therapy - potentially also change the trajectory of cardiac function leading to heterogeneity among otherwise similar participants.

4. Cardiac-specific management for patients with DMD

4.1. Cardiac specific drugs – the evidence so far

Prof Duboc began by stating the fact that - since about 40% of patients ultimately die of cardiac causes, proper management of DMD requires treatment of cardiomyopathy. Contrary to initial reservations, the various steroid regimes are now accepted as beneficial for the heart also [14]. Based on the results of the French randomised trial prophylactic, perindopril delays the onset of detectable left ventricular dysfunction and supports diaphragmatic function [15]. Indeed, the only variable that predicted longer term cardiac function and mortality in DMD was early deployment of prophylactic perindopril [16]. Eplerenone benefits cardiac and skeletal muscle function when used in conjunction with ACE-inhibitor therapy [17]. Sacubitril-valsartan ('Entresto') may be able to improve on the benefits of ACE-inhibitor therapy but this has yet to be tested in DMD [18]. Although there is good rationale for adding prophylactic beta-blocker therapy to an ACE-inhibitor, the evidence for this is less clear [19–21].

Dr K Whabi continued - summarising results from the French muscle network data-set on 670 DMD-patients collected between November 1986-March 2017. Using 'emulated trial methodology' they evaluated the effect of long-term ACE-inhibitor or steroid therapy or the combination on mortality (primary outcome), heart failure and severity of respiratory muscle function (secondary outcomes) [22]. In the ACEi analysis, 82 patients died during follow-up - 29 on and 52 not taking long term ACEi drugs, pointing to a mortality benefit from ACE-inhibitor use in DMD. ACEi use also correlated with reduced hospital admissions for heart failure and better preservation of respiratory muscle function. In the steroid analysis, 25 patients died - 3 taking and 22 not taking long-term steroid medications, pointing to a trend in mortality benefit from long-term steroid therapy. Steroids also reduced heart failure admissions and led to better-preserved respiratory function. Mortality on the combination of ACEi and steroid therapy was similar to in those taking ACEi alone. However, steroid therapy was associated with reduced mortality in those not taking ACEi drugs.

4.2. DMD heart protection study

Dr J Bourke presented the results of the *DMD Heart Protection Study* [EudraCT number: 2007-005932-10] [23]. This was a multicentre, randomised, placebo controlled study of prophylactic perindopril and bisoprolol in children with genetically confirmed DMD which completed in March '18. Eighty five patients between the ages of 5 and 13 years with echocardiographically normal heart function at recruitment were treated and followed up with six monthly repeat

assessments for a minimum of 36 months. Therapy was well tolerated with no withdrawals due to adverse effects. Although some patients on placebo were withdrawn because of reducing ventricular function, as per protocol, group mean ejection fraction was not significantly different between those on active and those on matched placebo after 36 months treatment. These preliminary findings are consistent with the 2005 French study at the same time point [15]. The young age of participants, greater use of steroid therapy and the lack of sensitivity of echocardiography as compared to magnetic resonance imaging in detecting evolving cardiomyopathy were all highlighted as contributors to the findings at this early time point. Longer term follow-up of participants is planned.

5. Cardiac specific management for DMD / BMD

5.1. Pacemakers and/or defibrillators in DMD / BMD

Historically, it is thought that patients with DMD/BMD experience significant morbidity and mortality as a result of heart rhythm abnormalities [24]. However, as Prof Cripe explained, there is little natural history data to support this. Since implantable cardioverter-defibrillators were first approved for clinical use in 1985, they have been deployed increasingly in patients with various forms of established cardiomyopathy [25,26]. Not all patients benefit, however, and their deployment is a risk-benefit balance between prevention of sudden death and device-related complications [27,28]. Adults in NYHA functional class II/III, with LVEF < 35% have a class 1 indication for recommending defibrillator therapy [29]. The question remains whether this guidance is appropriate for adult patients with BDMD. There is little evidence to guide ICDs use in paediatric patients generally and virtually none in children with DMD [30,31]. One single-centre study reported a low risk of rhythm abnormalities in paediatric DMD patients whose LVEF was greater than 35% [26]. The lack of natural history data on which to make recommendations both for adults and children with BDMD was readily acknowledged. A higher level of heart rhythm surveillance in patients with lower ejection fractions seems appropriate and will allow the prevalence of arrhythmias and their relationship to overall survival in BDMD to be determined [32,33]. Recommending ICD therapy to patients with BDMD should only be after thoughtful consideration and detailed discussion with the patient - involving carer-givers / family using a shared decision making model - as this choice affects end-of-life. Moreover although data is lacking, it is reasonable to expect that the risks of device implantation will be higher in those with kyphoscoliosis and neuromuscular-related respiratory weakness.

5.2. Left ventricular assist devices and cardiac transplantation

Worldwide there is both a limited supply of suitable donor organs for heart transplantation and an increase in the use of ventricular assist devices to treat end-stage heart failure [34].

Dr G Macgowan explained that to understand how patients with BDMD might be treated with heart transplantation requires an understanding of how the limited number of suitable donor hearts are allocated.

Many countries, including the US and UK, now prioritise the sickest patients - such as inpatients on intravenous inotropes or those receiving temporary mechanical circulatory support [35]. These patients on urgent or super urgent lists typically have had prolonged hospitalisation pre-transplant, lengthy intensive care stays perioperatively and prolonged rehabilitation requirements afterwards. Patients with advanced neuromuscular disease may not be able to undergo such a rigorous physical challenge. Nevertheless, the literature shows that, in those with relatively limited skeletal and respiratory involvement - typically those with BMD and female Duchenne carriers, high quality outcomes can be achieved when suitable organs have been available [36].

Similar issues - prolonged hospitalisation and debilitation, are also barriers to patients with muscular dystrophy receiving ventricular assist devices [LVAD]. The main limitation, however, is cost of devices. However, excellent results have been published for LVAD deployment in patients with relatively mild skeletal and respiratory function phenotypes [37]. The technology of ventricular assist devices is evolving, and devices under development offer potential opportunities in the future for patients with more advanced physical debilitation [38–40].

5.3. Ethical, quality of life and risk-benefit issues in DMD / BMD

Prof N Goemans pointed out that, in parallel with the improved survival for patients, have come developments in technical assisting devices and changes in societal efforts to improve education and increase participation which have also changed quality of life for patients with DMD. These factors have all had an impact on the clinical decision-making process. This is particularly relevant when considering invasive and/or life prolonging interventions, which are based on objective medical indications, subjective issues (quality of life, patient's preferences) and contextual features (eg: society, religion, resources).

Provision of life saving or life prolonging therapies, such as cardiac transplantation or LVADs in an irreversible process is only ethically accepted “if they respect patients well being” [41]. It is generally assumed that reduced physical ability and greater disease severity are the main determinants of quality of life. However, studies have shown that they do not affect life satisfaction and quality of life significantly [42]. Rather, a whole series of other factors (emotional well being, social life, family support, perceived control and recreational opportunities) have greater impact on life satisfaction and furthermore that quality of life is a complex, subjective and multi-dimensional concept. Moreover, quality of life is dynamic. For example, in research studies patients rate their health related quality of life higher than do their parents and much higher than the general public. This is explained

by the fact that others do not make adequate allowance for individuals' ability to adapt to the new or evolving situations that arise in the course of a physical condition or disease (ie: 'response shift') [43]. It is important for clinicians to recognise that both young and adult males with DMD consider their quality of life to be relatively good and how false negative assumptions that ignore that fact can influence medical decision-making inappropriately.

6. Other heart-related topics in DMD / BMD

6.1. Steroid therapy: good or bad for the heart?

Dr M Sediva explained that mineralo- and glucocorticoids act via specific MR and GR receptors. In the heart, the MR, which has a greater affinity to glucocorticoids under hypoxic conditions, has been associated with progression of cardiac disease. The GR receptor seems to be crucial for normal development and maintenance of cardiac function [44–47]. Glucocorticoids, commonly administered in DMD, block the apoptosis of cardiomyocytes and have antifibrotic effects [48,49]. Yet paradoxically, in murine DMD models they were shown to accelerate a dilated cardiomyopathy and increase mortality when their use was associated with increased blood pressure [50,51]. However, several retrospective, observational studies of steroids in DMD patients suggest that glucocorticoids postpone the onset of cardiac dysfunction by an average of two years and improve survival [52–54]. The data for patients with BMD or continuing on steroid therapy in the later stages of DMD are, as yet, unknown.

6.2. Respiratory-cardiac interactions in management of DMD

Prof E McNally explained that intercostal, abdominal and diaphragmatic muscles are all involved in DMD. Effective noninvasive ventilation has been shown not only to improve overall survival in DMD but also to benefit cardiac function and performance [55,56]. Data from animal models of DMD supports a strong interplay between cardiac and pulmonary function and emphasises the importance of the secondary muscles of respiration, especially the abdominal muscles, in influencing cardiac function [5].

6.3. Cardiac assessments in clinical and research settings

Dr A Florian stated that, to be clinically useful, non-invasive imaging of the heart needs to be able to detect changes in the pre-clinical phase of BDMD cardiomyopathy and provide reliable prognostic information. Additionally, the parameters assessed should provide accurate and reproducible surrogate measures for optimal cardiac surveillance and reliable end-points in clinical trials. Trans-thoracic echocardiography (TTE) is the current standard of care in BDMD - being used for diagnosis and patient follow-up. TTE enables the detection of LV (global / regional) systolic and / or diastolic dysfunction. Moreover, reduced global LV

systolic function (ejection fraction, EF or shortening fraction, FS) is associated with reduced survival and ventricular arrhythmias in BDMD [57]. Advanced TTE techniques (eg: deformation and strain imaging by speckle tracking) can detect subtler (regional) functional abnormalities before global impairment become evident [58]. However, TTE has several significant limitations: (1) inability to detect early fibrosis and (2) reduced image quality as the severity advances and with increasing patient age.

Cardiovascular magnetic resonance (CMR) imaging is capable of showing myocardial changes earlier in the process of heart involvement in BDMD by late gadolinium enhancement (LGE; myocardial fibrosis) [59]. Up to 70% of BDMD patients show LGE on CMR, while less than half of patients have a reduced LV-EF at that stage. Moreover, follow-up CMR studies can track the progressive nature of myocardial fibrosis, which correlates with progressive decline in left ventricular function (ie: LVEF%) [60]. Recently, studies have shown that the extent as well as certain patterns of LGE (intramural, septal, trans-mural) fibrosis correlate with the occurrence of ventricular tachyarrhythmias and cardiac death [60,61].

In female carriers of BDMD, CMR can also detect myocardial fibrosis in up to two-thirds of subjects (even up to 65% for DMD carriers) while only a small percentage have impaired left ventricular systolic function on TTE [62].

Advanced tissue characterization by T1-mapping with extracellular volume fraction calculation (ECV) also enables quantitative distinction between myocardial edema, fibrosis and infiltration [63]. CMR techniques now allow even earlier diagnosis of cardiac involvement in BDMD and a more comprehensive assessment of total fibrosis. CMR may be able to provide surrogate outcome measures for clinical trials, acceptable to regulators [63]. How CMR can be applied to clinical decision making - personalised timing for use of cardio-protective therapies and patient follow-up all need to be established.

6.4. Arrhythmia risk / cardiac electrophysiology in DMD

The question of whether a primary cardiac electropathy was part of BDMD - putting patients at risk of sudden death at earlier stages of the condition, was addressed by Dr J Bourke. The prevalence and complexity of ventricular ectopic beats increase both with patient age and severity of left ventricular dysfunction [64,65]. A slowing of trans-atrial conduction, sustained atrial arrhythmias and the development of AV-block have all been documented in DMD. When hypoxaemia / hypercapnia and left ventricular dysfunction interact, the risk of sustained arrhythmias is increased. However, based on the results of ECG-Holter, ECG signal averaging and limited invasive electrophysiology studies in patients with DMD, he concluded that ventricular arrhythmia risk tracks primarily with the severity of left ventricular dysfunction [24,31,65, 66]. As such there is little evidence that patients are at risk of sustained atrial or ventricular arrhythmias until cardiomyopathy is advanced. It is also

evident from the literature that, when clinically justified, implantation of a pacemaker or defibrillator in a patient with BDMD carries a higher than usual risks of procedural complications [27,28]. On the basis of results of studies to date, therefore, antiarrhythmic drug therapy or implantable cardioverter defibrillators could only be expected to have limited impact on survival in patients with DMD.

6.5. Utility of biomarkers in the timing of various interventions

Dr E Pegoraro presented data from a retrospective cohort of 372 DMD patients followed up at *Italian DMD Network* centers with serial echocardiograms over 2.6+3.7 years. Mean patient age was 14.01+7.0 years. The annual change in slope of each parameter and the effect of specific DMD mutations on the rate of change was estimated using generalized estimating equation models. The effects of four known SNP modifiers were also analyzed (i.e.: rs28357094 in the promoter region of the osteopontin-coding SPP1 gene; rs10880 as a marker of the IAAM haplo-type in the latent transforming growth factor-beta binding protein 4 (LTBP4) coding sequence; rs1883832 in the 5' UTR of the CD40 gene) [67,68].

A progressive decline in EF of - 0.7% and SF - 0.4% per year of age was observed, without a linear increase in LV-dimensions. Glucocorticoid treatment showed a non-significant but favorable treatment trend in LVEF, LVSF and tissue-Doppler measures. DMD deletions amenable to exon 53 skipping showed reduced FS% ($p < 0.0007$) and a strong association between the LTBP4 haplo-type and preserved left ventricular function and size (EF+4.5%; SF+4.4%; VTD -10.6 ml/m²; $p < 0.01$) also emerged. 'Distal' mutations - involving Dp140, 'proximal' mutations - involving the first 8 exons, and genotypes at SPP1 or CD40 were not predictive of cardiac function over time. These data support the continued use of steroid treatment after patients have lost ambulation. The findings also suggest the relevance of the LTBP4 haplo-type as a favourable modifier of cardiac involvement in DMD. These findings should help in patient prognostication and counseling and improve selection of patients for inclusion in clinical trials.

6.6. Predicting LV-dysfunction from the prospective French BMD registry

Dr K Wahbi described a French study - ongoing since 2012, of the course of cardiac involvement in 100 patients with genetically confirmed BMD over five years. The object is to develop multimodal approaches - combining imaging and biomarker data to improve prediction of heart involvement and heart failure over time. Baseline assessments included echocardiography (conventional and speckled tracking), cardiac MRI, serum and plasma testing for biomarkers of heart decompensation and DNA banking. The study is planned to complete in 2019.

6.7. Female gene-carriers of Becker and Duchenne dystrophy

Dr K Hor discussed possible explanations for discrepancies in the literature on the prevalence of cardiac involvement in female carriers of BDMD. Depending on the sensitivity of testing used and definitions of cardiomyopathy, female carriers could be 'made out' to be either all 'normal' or 'abnormal'! From his own ongoing study of 129 'carrier' he showed that, although most had normal cardiac measures, left ventricular dimensions were increased in 18% and 5.4% had additional evidence of cardiomyopathy on CMR. He correlated the finding of increased ventricular ectopy during recovery after exercise stress testing with the presence of fibrosis on CMR imaging and an increased incidence of progression to left ventricular dysfunction over time. The results of genetic testing from the same study point to a difference in risk of cardiomyopathy between somatic and non-somatic carriers of BDMD. He urged greater use of CMR and exercise evaluations in assessing the cardiac status of female gene carriers and suggested that detection of scars on CMR could be used as justification for starting cardioactive medications in these patients.

6.8. Burden of testing and therapy - patient advocate perspective

Dr E Vroom stressed that - from the point of view of families, there was no presymptomatic phase of DMD once the diagnosis was made. She challenged researchers in pointing out that suboptimally designed trials amounted to a betrayal of participants! Regulators needed to be 'educated' about therapies for degenerative muscle conditions in general and this included discussions with them about what endpoints they considered provided robust 'clinical evidence'. She also questioned whether data already available from research was being used optimally and a need for greater clarity on the level of evidence needed before clinicians were prepared to make treatment recommendations. She agreed with the general consensus that all future trials should include cardiac measures and endpoints.

6.9. Burden of testing and therapy - patient perspective

Mr van Leperen made a range of insightful comments on the issues raised during the workshop. He was accepting and comfortable with the concept of prophylactic therapy for the heart in BDMD and with the appropriateness of intensifying heart medications further once ventricular dysfunction was confirmed - in the absence of any specific heart related symptoms. He also considered that patients typically found follow-up testing of the heart worthwhile - providing feedback to patients on the response to treatments already deployed. However, he considered cardiac magnetic resonance imaging an arduous test from a patient perspective and that many would find repeating it annually unacceptable. He favoured patients attending a 'mega clinic' - providing access to a range of specialty expertise together and so reducing the

need for multiple separate clinic appointments / attendances. Appropriate data sharing between care teams was important to achieving best outcomes and therefore universally supported by patients.

7. Conclusions and recommendations

The workshop participants agreed that the myocardium in patients with BDMD should be considered 'abnormal from the start'. This paradigm shift means that the optimum time to deploy cardio-active therapies is earlier in the natural history of dystrophinopathy than even current guidelines recommend. The specific drugs to be deployed, in what order and in which combinations are likely to change over time as a result of greater understanding of their mechanisms of action, relative potencies, interactions and tolerability. Ideally regimes should also be changed within an individual to take account of the particular pathological processes active at that stage of their heart's involvement. This may mean more or different combinations of therapy at different stages - ideally guided by biomarker or more sensitive imaging evidence, reflecting active processes that would benefit from specific therapies. This somewhat futuristic management vision is simply a reminder that traditional thresholds for starting heart-specific drug therapies in BDMD - detection of left ventricular dysfunction or confirmation of fibrosis, are crude. Even the best means of heart surveillance and testing - CMR and biomarkers, are not sufficiently validated to guide earlier and more targeted interventions for patients with cardiac dystrophinopathy.

There was agreement also on the need to collect longitudinal data on the effects of different medications/interventions on heart function prospectively over longer periods of time than that possible during clinical trials. Reaching agreement with regulators about clinically meaningful outcome measures is a prerequisite for success in the design and conduct of research studies on heart therapies in patients with DMD for the future.

The workshop concluded by acknowledging the many gaps that remain in our understanding of cardiac involvement in dystrophinopathies but also the promise of treatments currently under evaluation. A number of themes for collaborative research were also identified.

8. Participants

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.nmd.2019.06.598](#).

Appendix 1. Participants responded to the following questionnaire before the workshop

With regard to cardiac management your patients with DMD?

1. What is your main medical specialty of practice?
2. Do you consider cardiac surveillance appropriate for all your patients with DMD?
3. What age range of patients with DMD do you provide care for?
4. a. Are there difficulties in arranging / getting cardiac assessments for your patients? b. If there are difficulties, are they mainly because of funding / affordability issues?
5. At what age do your patients most commonly have their first / baseline cardiac checks?
6. a. What cardiac tests do you routinely include / perform each time as part of surveillance? b. Which biomarkers do you measure routinely in your BDMD patients (none / any / list all)?
7. How frequently do you repeat cardiac testing, if ventricular function was normal previously?
- 7a. If using cardiac MRI as your preferred method of cardiac surveillance - how often would you repeat the MRI-assessment, when the previous result was normal?
8. What is your routine threshold / trigger for starting / recommending heart-specific medications?
9. If starting heart medications prophylactically, which agent(s) do you use routinely (ACE-inhibitor, angiotensin-receptor blocker, sacubitril-valsartan, beta-blocker, eplerenone / spironolactone, other)?
10. If left ventricular systolic function is mild-moderately reduced, which agent(s) do you use routinely (ACE-inhibitor, angiotensin-receptor blocker, sacubitril-valsartan, beta-blocker, eplerenone / spironolactone, other)?
11. a. When heart function is severely reduced do you regularly recommend defibrillator therapy? b. If you discuss ICD therapy with patients selectively, which factors do you take into account?
12. Have any DMD-patients under your care had: pacemaker, implanted defibrillator, left ventricular assist device, cardiac transplant (indicate all that apply)?
13. Do you anti-coagulate your DMD-patients when heart function is severely impaired?

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