STATE-OF-THE-ART ADVANCES IN DUCHENNE MUSCULAR DYSTROPHY

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ABSTRACT

Duchenne muscular dystrophy (DMD) is a severe and fatal muscle condition affecting young children. Without interventions, affected boys lose the ability to walk independently by the age of 10 and develop progressive cardiac and respiratory failure. The last 20 years have seen a change in the natural history of DMD following improvements in clinical care and proactive interventions to manage complications of the disease. An international collaboration of DMD experts has created care imperatives for best practice in DMD; these are now available in 30 different languages and are disseminated worldwide. An update of these care recommendations is currently under review.

More recently, the field has seen encouraging scientific progress in regard to new therapeutic approaches of which a large number are currently being evaluated in clinical trials. With time, improvements in clinical care and access to new treatments and innovations are changing the natural course of DMD, from a relentless progressive illness with death in teenage years to a more chronic illness with a good quality of life and increased life expectancy. This is a particularly encouraging time for DMD, and experiences built in the muscular dystrophy field are likely to be of benefit to the development of new approaches and therapies in other rare diseases.

Keywords: Duchenne muscular dystrophy (DMD), dystrophin, genetic diagnosis, standards of care, clinical trials.

INTRODUCTION

Duchenne muscular dystrophy (DMD) is the most severe and common muscular dystrophy in children affecting approximately 1 in 3,500–10,000 male births.[1] It is an X-linked recessive condition affecting mostly boys. Clinically, it presents with progressive muscle weakness and wasting affecting all body muscles, including the heart and the respiratory muscles. Historically, boys with DMD lost the ability to walk independently by the age of 10 years and progressively developed heart and respiratory insufficiency, eventually leading to death in their late teens or early 20s. In recent years, there have been significant developments in both clinical care and scientific research in DMD. Following the implementation of care recommendations, including corticosteroids, respiratory and cardiac management, orthopaedic intervention, and rehabilitation, the natural history of DMD has changed from a rapidly progressive and life-limiting condition to a more chronic illness with an increase in life expectancy.[2-3] Recent studies have reported a good quality of life,[4] with the research field of DMD thriving, and the hope of finding a disease-modifying drug which will further slow the deterioration in muscle function. In this article, we summarise recent developments in the diagnosis and management of DMD and provide an update on clinical research in the field.

DUCHENNE MUSCULAR DYSTROPHY

Pathogenesis

DMD is caused by mutations in the dystrophin gene, the largest gene in the human genome, consisting of 79 exons. The mutation rate of the dystrophin

gene is relatively high and about one-third of cases are caused by new (*de novo*) mutations.[5] In the remaining two-thirds of patients, the mutation is passed on from the mother (X-linked), who usually does not show any clinical manifestation of the condition (asymptomatic carrier). The size of the gene, together with the high mutation rate, explains the variability of mutations in DMD including large deletions (68%), duplications (11%), and small mutations (20%).[5] Small mutations include small deletions, insertions, and point mutations, resulting in stop codons or disrupted splicing.

The hotspot for mutations in the dystrophin gene lies between exon 45 and 55 (deletions) and exons 2 and 10 (duplications), but mutations have been reported along the entire gene. There are no strict correlations between the location of the mutation and the severity of the clinical presentation, although several exceptions to this general rule have now been described.[5-8] Mutations causing an interruption of the 'reading frame' (out-of-frame) lead to DMD because protein synthesis is disrupted, resulting in the total absence of the encoded protein, dystrophin. Mutations in the same gene which do not alter the reading frame (in-frame mutations) lead to the production of a shorter but still partially functioning protein and result in a milder phenotype (Becker muscular dystrophy).

The protein dystrophin is expressed in skeletal muscles, the heart, and the brain. In muscles, dystrophin acts as a shock absorber during muscle contraction; in its absence, muscle fibres undergo membrane fragility, inflammation, chronic damage, and finally replacement by fibrotic tissue and fat. These pathological changes manifest clinically with progressive loss of muscle strength and mass. Although the role of dystrophin in the brain remains largely unknown, intellectual impairment is reported in about 30% of DMD subjects.[9]

CLINICAL FEATURES

The hallmark of DMD is progressive muscle wasting and weakness. Although the pathological changes start *in utero*, the condition does not usually manifest clinically until the age of 2–4 years. It can present with a delay in motor milestones or with symptoms of muscle weakness. Typical early clinical features of DMD include difficulty getting up from the floor (Gower's manoeuvre), difficulties with running, jumping, hopping, an abnormal or tip-toe gait, and frequent falls. On examination, calf hypertrophy, hypotonia, and neck flexor weakness can be detected from an early age.[10] Speech and language delay and behavioural problems, including autistic spectrum disorders, have also been described and can present before muscle weakness has become apparent. With the progression of the disease, muscle weakness affects all skeletal muscles, leading to loss of independent walking, reduced motor function in the upper limbs, and scoliosis due to axial weakness. Joint contractures result from a combination of reduced mobility and changes in muscle structure, following replacement of muscle fibres with connective tissue. The heart and the respiratory muscles undergo similar pathological changes, leading to progressive dilated cardiomyopathy, arrhythmia, and restrictive lung disease.[10]

Early heart involvement has been reported in DMD, although generally the incidence of cardiomyopathy increases with age.[11] The clinical challenge remains recognising heart failure in DMD, which often is asymptomatic, even at late stages. Respiratory insufficiency in DMD is more predictable, usually presenting after the loss of independent ambulation. The diaphragmatic involvement significantly contributes to the drop in forced vital capacity, observed as an early sign of respiratory impairment, increasing susceptibility to chest infections, and sleep-disordered breathing.[12,13]

DIAGNOSIS

If there is a clinical suspicion of DMD, a blood test to measure creatine kinase (CK) levels should be promptly arranged as the first screening test. CK is a muscle enzyme which is released in the blood stream as a response to muscle damage. CK levels are always significantly elevated in DMD, and values in the thousands should trigger the diagnosis, although other neuromuscular diseases might also be considered. CK testing has been used for neonatal screening, as increased levels are present from birth. CK newborn screening was in place in some countries e.g. Wales and the USA, however at present it has been discontinued due to concerns regarding its sensitivity and specificity when performed around the time of birth.[14-16] At the time of writing, CK neonatal screening is not routinely adopted in any country.

A child with clinical evidences of muscle weakness and elevated CK levels should be referred to a neuromuscular centre for genetic testing for dystrophin gene mutations. Multiplex ligation-dependent probe amplification[17] is the most

reliable and cost-effective test to detect deletions and duplication, analysing all exons of the dystrophin gene. If multiplex ligation-dependent probe amplification does not identify any mutation, gene sequencing will allow the identification of small deletions/insertions and point mutations, although it is more expensive, time-consuming, and available only in specialised laboratories.

Muscle biopsy, which historically represented the diagnostic test for DMD showing the total absence of dystrophin expression in muscle fibres associated with utrophin upregulation, is today often avoided and replaced by genetic testing in centres where this is available. A muscle biopsy can still be useful in some rare cases when genetic testing does not reveal a mutation but the patient shows a clear DMD phenotype or when there is a discrepancy between the reading frame rule and the clinical presentation.

Delays in Diagnosis of Duchenne Muscular Dystrophy

Despite the tremendous advances in the management of DMD for children over the last decade, published data show that there is still a delay in the diagnosis of the condition across different countries.[18-23] This is due to both presentational delay (time from onset of symptoms to presentation to a health professional) and diagnostic delay (time from first medical assessment to genetic diagnosis). The mean age at diagnosis ranges from 4.3–4.11 years and has not significantly improved over the past 20 years.[18-23] Recommendations to lower the age of diagnosis include raising awareness of DMD in the community, primary care to ensure DMD is recognised as a differential diagnosis in children presenting with signs of muscle weakness and/or speech delay, and promoting early CK level testing as a cost-effective, readily available screening tool for DMD. To reach these targets, a mnemonic (MUSCLE: Motor milestone delay, Unusual gait, Speech delay, CK ASAP, Leads to Early diagnosis of DMD) has been developed for use in primary care to improve the diagnostic process in DMD.[18]

Establishing an accurate genetic diagnosis of DMD at a young age is important as it allows genetic counselling and family carrier testing, prenatal diagnosis, early access to treatment, consideration for mutation specific therapeutic options (e.g. ataluren), or participation in clinical trials with new investigational drugs.

MEDICAL MANAGEMENT

Corticosteroids

Corticosteroids are currently the only medication available to all patients with DMD to slow down the progression of the condition and are part of the care recommendations. Although the benefits of corticosteroids are well-documented, they only postpone disease milestones without altering the natural course of the disease. Moreover, corticosteroids are associated with several side effects which limit their prescription worldwide.

Corticosteroids have been shown to prolong ambulation and stabilise respiratory function.[24-27] In addition, corticosteroids have cardio-protective properties and prevent or reduce the need for spinal (scoliosis) surgery.[25,28,29] The most frequently prescribed corticosteroids in DMD are prednisone (or prednisolone) (0.75 mg/kg/day) and deflazacort (0.9 mg/kg/day), with several regimes currently used.[30] Corticosteroids are generally introduced when the child's motor skills plateau, around the age of 4–5 years. Emerging evidence suggests that early treatment might be associated with better long-term outcomes, including prolonged ambulation, however further research is needed to evaluate the impact of early and prolonged corticosteroid treatment in a growing child.[31]

Although corticosteroids have been prescribed for >20 years in DMD, a worldwide debate is ongoing as to which corticosteroid should be prescribed, which regime, from what age, and for how long. The main concerns are related to the management of steroid-related adverse effects which have led to inconsistency in prescribing practices across different centres and different countries. The more common steroid-related side effects and their management strategies according to the care recommendations are summarised in Table 1.[3] Daily regimes appeared to be more effective but with more frequent side effects compared with intermittent regimes.[32] Limited data comparing the effects of different corticosteroids are available: there are some indications that deflazacort is associated with less weight gain and possibly a better effect on muscle strength and function, but longer term longitudinal data are awaited.[33-35]

A double-blind randomised control study FOR DMD is ongoing to compare the three most commonly prescribed corticosteroid regimes in DMD regarding efficacy and side effect profile (NCT01603407).[35]

Table 1: Summary of adverse effects of corticosteroid therapy and their management.

Steroid-related adverse effects	Management
Cosmetic (cushingoid features, weight gain, hirsutism, skin changes)	Offer dietary advice and review acceptability of the changes
Adverse behavioural changes (mood changes, emotional lability, hyperactivity)	Often worsen in first weeks of starting corticosteroids. If prolonged, refer for behavioural management, consider assessment for DMD-related behavioural disorders (30% of children with DMD), and refer appropriately
Immune suppression	Ensure immunity to varicella, avoid live vaccines, proactive approach in managing infections (early antibiotics)
Adrenal suppression	Additional steroid cover in illness/surgery. Be alert about missed doses (if not tolerating steroids, consider intramuscular/intravenous steroids)
Hypertension	Blood pressure monitoring at each clinic visit. Use age-appropriate blood pressure centile charts. If BP >99th centile, advise weight loss, salt reduction in diet, or medical treatment
Glucose intolerance	Urine dipstick at each clinic visit. If positive for glucose, check fasting blood glucose
Gastric reflux and peptic ulcer disease	Enquire about symptoms at each clinic visit, and advise to avoid NSAIDs. Manage symptoms and signs with ranitidine or proton pump inhibitor
Cataracts	Yearly ophthalmology review. Cataracts more common with deflazacort. If present, refer for ophthalmology for assessment and treatment if necessary
Bone demineralisation (increased risk of fractures)	Ensure high calcium intake with diet and adequate vitamin D levels. Annual bone density scan (DEXA). Review fracture history carefully. Consider bisphosphonate treatment for vertebral fractures
Growth retardation and delayed puberty	Monitor height at each clinic visit; if static (<2 cm per year), refer to endocrinology. Assess puberty and if delayed consider endocrine assessment and testosterone treatment if appropriate

DMD: Duchenne muscular dystrophy; BP: blood pressure; NSAIDs: non-steroidal anti-inflammatory drugs; DEXA: dual energy X-ray absorptiometry.

The study aims to clarify the long-standing equipoise of the use of corticosteroids in DMD, and provide families and clinicians a (long-awaited) evidence-based recommendation on the use of corticosteroids and standardised management of steroid-related side effects. Whilst awaiting the outcome of this study, the choice of treatment is currently made based upon personal experience of the clinician in charge, availability of the formulation (e.g. deflazacort is not available in the USA), and patient and family's choice. An informed discussion on benefits and side effects with the family is mandatory to ensure compliance with the treatment and the management of side effects. Whichever steroid and regime is prescribed, the potential risk of adrenal failure should be considered when the child is unwell, in case of surgery and prior to anaesthetics. Each patient should be provided with an up-to-date alert card which details steroid treatment (including regime) and offers advice with regards to steroid replacement in emergencies.

Clinical Care Recommendations for Duchenne Muscular Dystrophy

As established by the care recommendations published in 2010, DMD is a complex multi-system disorder and requires a multidisciplinary approach. This involves different specialities such as neuromuscular specialists, paediatrics, cardiology, respiratory, orthopaedics, endocrinology, physiotherapy, occupational therapy, speech and language therapy, and psychology.[2,3] The role of each speciality team varies according to the disease stage the patient is in and the progression of the symptoms, however all teams should be involved from the point of diagnosis. The role of the tertiary neuromuscular team is co-ordinating the patient care and ensuring that the right specialists are involved at the correct time to provide a proactive model of clinical care in which interventions (such as cardiac medications, access to non-invasive ventilation, etc.) can be swiftly organised when needed. Surveillance in DMD is

centred around early detection of disease complications but also ensuring that patient-specific needs are identified and managed in order to optimise their physical, social, educational, and psychological status. The best practice of care in DMD has been translated into 30 different languages and a summary outlining the imperatives in DMD care has recently been published[36] to facilitate optimal care to families living with DMD worldwide (Table 2). An update of the care recommendations is currently in progress reflecting the more recent changes and improvements in patient management.

Regardless of the extensive effort in disseminating the DMD care recommendations worldwide, a recent survey has shown an unexpected discrepancy between the published recommendations and care provision as reported by patients and families across different countries.[37] The survey highlighted concerns in all countries regarding access to routine follow-up by neuromuscular, cardiac, and respiratory specialists, physiotherapy, and access to medical devices. In addition, the survey showed a worrying lack of access to psychosocial therapy in DMD: this is of particular relevance in view of the continuous improvement in life expectancy for this patient population, leading to a new adult group of patients who live with a chronic and disabling condition and for whom psychological and social support will become essential to ensure good quality of life.

Table 2: Imperatives in Duchenne muscular dystrophy care.

Imperatives in DMD	
Diagnosis	• When to suspect DMD • Importance of early CK testing • Genetic diagnosis
Support groups	• Encourage parents to seek support from online resources and trustworthy patient organisations
Corticosteroids	• Start early • Discuss benefits and side effects of steroids • Review response and side effects of steroids regularly
Heart	• Regular cardiac review, including echocardiogram • Start cardiac medication early if any evidence of left ventricular dysfunction • Screen for arrhythmia (sign of heart failure)
Respiratory	• Yearly lung function tests, flu, and pneumococcal vaccinations • Low threshold for treating respiratory infections • At later stages, discuss cough assists and review need for assisted ventilation
Mechanical diagnosis and therapy (physiotherapy, occupational therapy, rehabilitation)	• Regular review by physiotherapy • Discuss stretching exercises, contracture devices, wheelchairs, and home adaptations (adapted beds, hoists, etc.) based on disease stage
Bone density	• If taking steroids, review vitamin D status yearly, and provide supplements if needed • Regular bone density scans, and review spine for scoliosis and vertebral fractures
Mental health	• Consider presence of learning disabilities • Review emotional and mental status at each visit
6-monthly clinic reviews	• Monitor: weight (under or overweight), other side effects of corticosteroids (hypertension, cataract, behavioural problems, abdominal pain and gastro-oesophageal reflux, glycosuria, delayed puberty), diet, swallowing difficulties
Final stage	• Provide each patient with a DMD alert card, detailing steroid treatment and plan for emergencies • Be aware of risk of anaesthetics in DMD

DMD: Duchenne muscular dystrophy, CK: creatine kinase.

Table 3: List of Duchenne muscular dystrophy studies open (actively recruiting or active) as per April 2016.

Approach	Target	Selected population	Current studies
Exon skipping	Exon 51 skippable mutations	Ambulant, 4–6 years old	A Phase II, open-label, safety, tolerability, and efficacy study with eteplirsen in ambulant DMD subjects (USA)
		Ambulant, 7–16 years old	A Phase III, confirmatory efficacy study with eteplirsen in ambulant DMD subjects (USA)
		Non-ambulant, 7–21 years old	A Phase II, open-label, safety and tolerability study with eteplirsen in non-ambulant DMD subjects (USA)
		Ambulant and non-ambulant, 7–13 years old	A Phase IIb, open-label extension study to assess the ongoing efficacy, safety, and tolerability of treatment with eteplirsen in DMD subjects who have previously received eteplirsen (USA, Canada)
		Ambulant, >5 years old	A Phase III, open-label extension study to assess safety and efficacy of drisapersen in DMD subjects who previously participated in a drisapersen study (USA)
	Exon 53 skippable mutations	Ambulant, 6–15 years old	A randomised, double-blind, placebo-controlled, safety and tolerability study followed by an open-label efficacy and safety evaluation with *SRP-4053* (morpholino AON) in ambulant DMD subjects (EU)
		Ambulant, 5–18 years old	A Phase I/II, open-label study to assess safety and efficacy of *PRO053* in ambulant DMD subjects (EU)
	Exon 45 skippable mutations	Ambulant, >5 years old	A Phase IIb, open-label study to assess safety and efficacy of *PRO045* in ambulant DMD subjects (EU)
		Ambulant, 5–10 years old	A Phase I/II study to evaluate the safety, tolerability, efficacy, and pharmacokinetic profile of DS-5141b in patients with DMD and to determine the dosage for subsequent studies (Japan)
	Exon 44 skippable mutations	Ambulant and non-ambulant, 9–20 years old	Open-label extension study to assess the ongoing efficacy, safety, and tolerability of treatment with PRO044 in DMD subjects who have previously received PRO044 (EU)
Stopcodon read-through	Nonsense point mutations	Ambulant, >5 years old	A Phase III extension study to evaluate safety and efficacy of ataluren in ambulant DMD subjects who took part in the Phase III ACT DMD study (worldwide)
		Ambulant and non-ambulant, >5 years old	A Phase III, open-label extension saftey and efficacy study for subjects previously treated with ataluren (worldwide)
Gene-therapy	All	Non-ambulant, >7 years old	A Phase I pilot study to evaluate safety and biological activity of the rAAVrh74.MCK.micro-Dystrophin vector administered by an intramuscular route in subjects with DMD
	All	>7 years old	A Phase I/II clinical intramuscular gene transfer of rAAV1.CMV.huFollistatin344 trial to DMD subjects
	All	Non-ambulant, >9 years old	A Phase I safety and tolerability study with intramuscular injection of rAAVrh74.MCK.GALGT2 in non-ambulant DMD patients (USA)
Stem cells	Subjects with confirmed DMD associated cardiomyopathy	Ambulant and non-ambulant, >12 years old	A randomised, open-label study of the safety and efficacy of multi-vessel intracoronary delivery of allogeneic cardiosphere-derived cells in patients with cardiomyopathy secondary to DMD
	Available haplotype-compatible donor	>16 years old	A Phase I/II study to evaluate safety and local effects on muscle strength of normal myoblast transplantation in DMD (Canada)
Anti-myostatin	All	Ambulant, 6–10 years old	A Phase II, randomised, double-blind, placebo-controlled study with *PF-06252616* in ambulant DMD subjects (worldwide)
	All	Ambulant, 5–10 years old	A multi-site, randomised, placebo-controlled, double-blind, multiple ascending subcutaneous dose study to evaluate the safety tolerability and pharmacokinetics of *BMS-986089* in ambulatory boys with DMD (US, Canada)
	All	Ambulant, >4 years old	A randomised, double-blind, placebo-controlled, multiple ascending-dose study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of *ACE-031 (ActRIIB-IgG1)* in subjects With DMD (Canada) - Terminated based on preliminary safety data

Table 3 continued.

Approach	Target	Selected population	Current studies
Utrophin upregulation	All	Ambulant, 5-10 years old	A Phase II proof of concept study with SMT-*C1100* in ambulant DMD subjects (UK)
NK-B inhibition	Steroid naïve	Ambulant, 4–7 years old	A Phase IIa, open-label, multiple ascending dose study to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of vamorolone in boys with DMD (USA)
	Steroid naïve	Ambulant, 4–7 years old	A Phase I/II, open-label study to assess safety of *CAT-1004* in ambulant DMD subjects (USA)
Anti-inflammatory/ anti-fibrosis	Steroid naïve	Ambulant, 4–7 years old	A double-blind, randomised study to investigate efficacy and side effect profile of the three most commonly prescribed corticosteroid regimes in ambulant DMD subjects (FOR DMD) (worldwide)
	All	Ambulant, 6–14 years old	A Phase Ib, open-label study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple ascending oral doses of rimeporide in patients with DMD (EU)
	All	6–10 years old	A Phase II HT-100 study to evaluate long-term safety and pharmacodynamics of *HT-100* in patients with DMD who have previously received *HT-100* (USA)
	All	Ambulant, 7–11 years old	A Phase I/II study to assess the safety and tolerability, pharmacokinetics, and effects on histology and different clinical parameters of givinostat in ambulant children with DMD (Part II) (Italy)
	All	Non-ambulant, >12 years old	A Phase II, open-label, single arm trial of *FG-3019* to estimate FG-3019's efficacy in non-ambulatory subjects with DMD.
Anti-oxidants	All	Ambulant, 5–10 years old	A Phase II/III, double-blind, placebo control study to assess safety and efficacy of Sunphenon Epigallocatechin-Gallate (*EGCg*) in ambulant DMD (Germany)
Neuronal nitric oxide synthase activators	All	Ambulant, 7–10 years old	A double blind randomised placebo controlled efficacy and safety study of L-citrulline and metformin in ambulant subjects with DMD (Switzerland)
	All	Ambulant, 7–14 years old	A randomised, double-blind, placebo-controlled, safety and efficacy Phase III trial of tadalafil for DMD (US and EU) - terminated for lack of efficacy
Cardio-protection	Absence of cardiomyopathy	Ambulant and non-ambulant, 2–45 years old	A Phase IV randomised prospective study to compared the effect of carvedilol and Ramipril on heart function in DMD subjects (Italy)
	All	Non-ambulant, >10 years old	A Phase III non-inferiority study of spironolactone vs. eplerenone in preserving cardiac and pulmonary function in patients with preserved left ventricular ejection fraction (USA)
	Absence of cardiomyopathy	Ambulant and non-ambulant, 10–15 years old	A Phase III randomised, double-blind, placebo-controlled, study to evaluate the effect of nebivolol, for the prevention of ventricular systolic dysfunction in DMD subjects, recruiting (France)
Other	Confirmed delayed puberty	Ambulant and non-ambulant, 12–17 years old	An observational study of clinical outcomes for testosterone treatment of pubertal delay in DMD (UK)

Studies non-specific for DMD (e.g. also recruiting patients with other neuromuscular conditions) are not included. Completed studies are not listed with the exception of two studies which were terminated only recently. Due to the continuous progress of the research in the field, this list is likely to change quickly and should therefore only be used as an indicator or number of studies in DMD and current approaches. Full details of clinical trials in DMD can be found on www.clinicaltrials.gov

DMD: Duchenne muscular dystrophy; AON: antisense oligonucleotide; NK-B: neurokinin-B.

PROGNOSIS

Life expectancy for patients with DMD has increased dramatically over the last 20 years, with a mean age of survival currently between 23.0–27.8 years.[38-41] The prolonged survival is the result of improved disease management leading to a delay in the development of complications.

This includes clinical care, corticosteroid treatment, proactive cardiac monitoring and treatment, access to respiratory interventions, rehabilitation, and orthopaedic procedures. The main cause of death in DMD remains progressive cardiorespiratory failure, although the percentage of primary cardiac deaths in DMD is rising because management of respiratory complications has improved.[42-44] Cardiac abnormalities in DMD progress with age and are characterised by initial left ventricular enlargement, followed by dilated cardiomyopathy with left ventricular dysfunction, arrhythmia, and heart failure.[43] Whether prophylactic cardiac treatment is able to prevent or postpone the onset of cardiac involvement still needs to be demonstrated. Early onset cardiomyopathy has been associated with poor response to treatment, and worse prognosis.[45]

Early access to overnight ventilatory support has been the most successful intervention so far in prolonging survival in DMD.[38] However, in practice this intervention is not always well-tolerated and therefore may be refused or delayed, increasing the risk of severe respiratory complications and death. Respiratory physiotherapy and proactive management of chest infection with up-to-date vaccinations, low threshold for antibiotic treatment, and devices to assist cough (e.g. Ambu bag, cough assist machine) can also impact outcomes.

Even with this positive trend and the continuous increase in survival rates in DMD, unexpected young deaths have been anecdotally reported. Teenage years seem to be a particularly fragile phase in this population and increased surveillance might be required in patients showing an unexpected deterioration around this time. Although the causes of these young deaths often remain largely unclear, several risk factors have been suggested. These include insidious worsening of respiratory function, presence of malnutrition, subtle cardiac arrhythmia, stress-induced adrenal failure in patients undergoing long-term corticosteroids treatment, fat embolism following trauma, psychological distress, and poor attendance to follow-up appointments. Awareness of these risk factors is important in order to minimise the risk of an untimely (sudden) death in DMD.[46]

THE FUTURE OF DUCHENNE MUSCULAR DYSTROPHY

The last 10 years have seen an enormous effort in developing new therapeutic approaches for DMD. Improvements in clinical care have already significantly changed the natural course of the disease, and recent investments in new potential treatments for the condition mean a promising future lies ahead. Several clinical trials in DMD are currently running, offering different approaches. These range from mutation-specific strategies aiming to correct the underlying genetic cause of the disease (exon skipping, reading through), to gene and stem cell therapy and non-mutation-dependent strategies directed to address downstream pathological pathways (anti-myostatin, utrophin, vamorolone, etc.).[47] One of these approaches, tested in clinical trials, has led to the successful approval of a drug for DMD by the European Medicines Agency (EMA) called ataluren (Translarna™, conditional approval). Moreover, parallel studies investigating new treatments for the cardiac and respiratory complications (e.g. idebenone, eplerenone, nebivolol, etc.) have been developed in recent years. This illustrates that the clinical multidisciplinary approach also extends into the field of research. A list of the currently open studies is summarised in Table 3, however the list will continue to evolve over time.

The rapid development of research in DMD has raised concerns on feasibility of multiple clinical trials in rare diseases where the patient population is limited, especially for targeted approaches (e.g. mutation-specific interventions). This is further complicated by the current requirements of a very narrow patient population (with regard to eligibility criteria; e.g. age, stage of the disease, mutation, etc.) being recruited in clinical trials, in order to reach study primary outcomes timely and efficiently. Currently a number of clinical trials exclude participants who have previously received any investigational drug, further obstructing recruitment and drug development in rare diseases. Although the results of some of the recent studies have been disappointing, lessons have been learnt from the clinical trial experience with the disease over the past years. This has raised awareness of the gaps which need to be addressed in order to ensure more cost-effective studies in the future and the ability to provide clearer outcomes on safety and efficacy of new investigational drugs. This includes: the importance of patient registries to allow identification of patients for large international studies; a better understanding of outcome measures for DMD; the impact of age, corticosteroid treatment, provision of standardised care on motor performance, and outcome measures. Other factors to take into consideration include

the importance of disease-specific biomarkers breaching clinical outcomes; the possible impact of mutation type and location on clinical severity; the ethical requirement to involve older patients in clinical research, and the current lack of longitudinal natural history outcome data on this non-ambulatory population; the need for harmonisation of the regulatory processes, and requirements to facilitate the conduct of international studies in rare diseases. Finally, the need to develop a new health economic model applicable to rare diseases, and to ensure objective evaluation of the clinical effectiveness of investigational drugs without discouraging future drug development.[48]

CONCLUSION

Historically, DMD was considered an incurable condition and as such was approached with very limited proactive management. The development and dissemination of care recommendations for DMD has significantly changed this approach, leading to improved survival and quality of life, and allowing the prospect of an adult life for most patients diagnosed today. The field has seen large investments in terms of new therapeutic approaches which have now been taken into clinical trials and have resulted in one of the tested drugs receiving conditional approval by the EMA. Finally, there is hope that the future for boys and young men with DMD will significantly improve in the upcoming years. This leads to a new set of challenges, including social and psychological impacts of longer-term survival which need to be addressed in parallel with the continued improvement in care and treatment. The experience built over the last 20 years in DMD (implementation of diagnosis, dissemination of care recommendations, acquiring essential natural history data, and delivery of clinical research with investigational drugs) is likely to be of extreme value for the future of DMD patients. It also provides a learning experience for the development of new therapeutic approaches in other rare diseases.

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