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REVIEW

Transition and management of patients with Duchenne Muscular Dystrophy: a narrative review based on Italian experts' opinion and real-world experience

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Objectives. Duchenne Muscular Dystrophy (DMD) is a severe, progressive, X-linked disorder resulting in muscle wasting, progressive functional loss and cardiomyopathy. Therapeutic strategies feature glucocorticoid corticosteroids plus gene therapy/stop codon read-through, plus standards of care. Prolonged survival, delayed loss of ambulation (LoA), and innovative treatment prescriptions pose new clinical challenges, including identification of new outcome measures/targets and implementation of continuity of care.

Methods. We report on the results of an Italian experts' meeting held in Rome, Italy on 20th April 2022. We aimed to: discuss challenges linked to transitioning from the ambulatory to the non-ambulatory phase, and from pediatric to adult care; collect experience on the importance of ongoing care and treatment in advanced disease stages and on the need to measure clinically relevant outcomes during disease progression after LoA.

Results. Following LoA the main management focus shifts to cardiac, respiratory, orthopaedics, nutrition and upper limbs function. More data on clinical needs, available treatments, standards of care, frequency of follow-up, and transition should be collected in order to facilitate management optimisation. Shared protocols should be developed, especially to improve patients' management in the acute setting.

Conclusions. Transition from paediatric to adult services and from the ambulatory to the non-ambulatory phase require a multidisciplinary approach and the Identification of clinically meaningful outcome measures, which should be described in long-term longitudinal studies.

Key words: Duchenne muscular dystrophy, ataluren, loss of ambulation, transition

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Introduction

Duchenne muscular dystrophy (DMD) is a severe, progressive disorder affecting skeletal and cardiac muscle, presenting in 2-3 years old boys with waddling gait, frequent falls, or difficulties in climbing stairs. Delayed motor milestones, speech delay, muscle weakness,

hypertrophic calves and Gowers sign should raise the suspicion of DMD. Although not all patients with DMD are the same, its evolution over time is predictable, and consists in a stepwise functional loss in the motor, cardiac and respiratory domains. By 10-12 years of age, many patients lose their ability to walk; at around 20 years of age, they become ventilation-dependent, and between 20 and 40 years, death occurs because of respiratory and/or cardiac failure[1].

DMD is a genetic disorder with X-linked inheritance. The *DMD* gene encodes dystrophin, which is essential for maitaining myofibres strength, stability, and function and in protecting muscle from contraction-induced injury. The presence of pathogenic *DMD* genetic variants resulting in the disruption of the reading frame progressively causes muscle degeneration and necrosis[1,2]. Many pathogenic mechanisms are involved, including damage to the sarcolemma, inflammation, ischemia, increased oxidative stress, calcium overload, but also impairment of regenerative mechanisms, resulting in the deposition of fatty and fibrotic tissues in later disease stages[1].

Identifying the specific *DMD* pathogenic variant is mandatory, because it enables diagnostic confirmation, initiation of multidisciplinary care, to perform carrier analysis in the mother and genetic counselling, and to establish whether the patient is eligible for mutation-specific therapies[1,2].

The care of DMD patients require a multidisciplinary team of medical and non-medical professionals[2,3,4], and the administration of drug therapies, which are divided into two groups: the so called "secondary" treatments, targeting the consequences of dystrophin deficiency, and the pathophysiologic approach, with the target of dystrophin restoration[2].

The involved multidisciplinary team needs to address: cardiac, respiratory, orthopedic, endocrinological and nutritional care, rehabilitation targets, gastrointestinal and urological management, neurodevelopmental, cognitive and psychological issues[1,3,4], with a dynamic and inclusive approach.

With their anti-inflammatory action, glucocorticosteroids belong to the first group of drug therapies[1,2]. They need to be started at the beginning of (before significant) motor decline and maintained long-term[1]. The second approach includes small molecules targeting nonsense mutations (ataluren[5,6,7]) and antisense oligonucleotides for out-of-frame deletions (eteplirsen skipping exon 51)[8,9], and golodirsen[10] and viltolarsen[11] (skipping exon 53). Ataluren is a drug designed to promote the readthrough of premature stop codons, secondary to nonsense mutations, in order to obtain full-length dystrophin[12]. It is an orally administered drug which is currently indicated for ambulatory patients with nmDMD, aged ≥ 2 years[13].

Materials and methods

An advisory board of experts in the clinical management of DMD (Rachele Adorisio, Luca Bello, Adele D'Amico, Maria Grazia D'Angelo, Marika Pane, Andrea Vianello and Valeria Sansone) met on 20th April 2022 with the following aims:

1 To collect experts' opinion on real-world evidence from the STRIDE registry and long-term data on the use of ataluren in patients with nmDMD, with special emphasis on patients after LoA (which has already been published)[14];

2 To share preliminary clinical experience on therapeutic continuity in four patients with LoA and nmDMD in Italy (which has already been published)[14];

3 To discuss the challenges faced by patients moving from the ambulatory to the non-ambulatory phase, and transitioning from pediatric to adult care;

4 To gather expert opinion on the importance of continuing management and treatment of patients in advanced disease phases and on the importance of measuring outcomes associated with disease progression in the non-ambulatory phase;

The present paper reports on the results of this experts' opinion meeting regarding transition from pediatric to adult services and from the ambulatory to the non-ambulatory phase, and discusses on the main clinical challenges in the multidisciplinary follow-up of patients with DMD (points 3 and 4 of the meeting agenda).

Results

Transition from the ambulatory to the non-ambulatory phase

Currently, in clinical practice, there is a treatment gap for non-ambulatory patients, as trials and innovative therapies are only offered to younger patients. Thus, the authors think that clinical issues occurring at this stage should be evaluated and managed with higher priority, and that clinically meaningful, patient-centred objectives should be set. 275 patients with a mean age of 24 years (belonging to the early LoA phase in 67% of cases) were asked to fill in a questionnaire[15]. These symptoms were reported to have a major impact on daily life:

- At the functional level: immobility, upper limbs function, hands weakness;
- At the quality of life level: loss of independence and fatigue;
- At the systemic level: respiratory, cardiac and gastro-intestinal involvement.

Importantly, patients' expectations regarding therapies change according to disease stage: while early-stage patients are more focused on treatments improving muscular functioning, late-stage ambulatory patients most desire treatments benefiting systemic functioning[13]. Patients with long disease history report an improvement in their quality of life (i.e. through even small increases in muscle strength) as their main expectation regarding new treatment options, rather than recovery of ambulation. In detail, non-ambulatory patients expect new treatments to improve upper limb functioning and systemic functioning, rather than to regain ambulation[15].

A second topic to be highlighted is the importance to prepare family and caregivers on disease acceptance in a participatory and non-limiting manner. This objective can only be obtained by addressing psychosocial issues, and should be best managed at the community services level. Based on literature data, the panel members think that for most individuals, full participation in planning should be a goal, and this achievement should be prepared since childhood[4]. Moreover, the inclusion of patients' needs and priorities in drug development and evaluation has entered the regulatory apparatus, thus promoting patient-focused drug development[15], therefore patients' perspectives are destined to be increasingly sought for in clinical practice and research. It is the panel's opinion that this kind of process should be implemented by promoting close collaboration between patients,

caregivers and clinicians, in order for clinical trials to generate robust evidence on the most relevant treatment targets.

During the transition phase, psychiatric issues can arise, as patients and families are at increased risk of deflated mood, depression, anxiety, or obsessive symptoms, especially at major transition points[4]. Nevertheless, in the panel members' clinical experience, these issues do not often emerge spontaneously during follow-up consultations. Thus, in our opinion, they should always be considered and actively approached by clinicians. As an example of real-world experience, the NEMO centre in Gemelli Hospital, Rome, as well as the IRCCS E. Medea in Bosisio Parini offer routine psychological follow-up. Psychopathological disorders during childhood or depressive symptoms in adultsreceive active treatment, in accordance with the input coming from the 2018 care considerations.[4]

It is commonly observed that during progression from the "*early non-ambulant*" to the "*late non-ambulant*" phase, patients initially lose their ability to reach their head with their hands, then (in advanced stages), they lose their ability to feed themselves, or to reach the table with their hands. The lastly affected daily activities include using a personal computer or a mobile phone. Based on previous literature, patients clearly link their upper limbs function to the ability to maintain residual independence and to support mental health[15].

The clinical relevance of collecting longitudinal upper limbs function data should also be higlighted, as in non-ambulatory patients maintaining good upper limbs function results in keeping a minimal degree of independence from caregivers. Literature data importantly highlight a positive correlation between upper limb function and quality of life[15]. In some cases, dyspraxia in the upper limbs can precede weakness onset, and this should be evaluated as a treatment outcome for newer drugs.

Furthermore, this phase is accompanied by the inability to sustain an adequate night-time ventilation and by respiratory insufficiency. Thus, in non-ambulatory patients, the panel members think that primary management focus is on cardiac, respiratory, and upper limb function. It is mandatory for involved healthcare specialists (cardiologists, neuromuscular specialists, pulmonologists, nutritionists and physiotherapists) to work as a multidisciplinary team (MDT) in order to better manage comorbidities and improve QoL after LoA. The panel thinks that transferring the correct information on the use of aids to families is also essential.

One final point to address is the issue of therapeutic continuity in patients with nonsense mutation DMD, who were started on ataluren in the ambulatory phase, and whether they should be continued on this medication. Based on current preliminary evidence, and the good tolerability profile the panel of experts (as already reported previously[14]) thinks that this option should be offered and discussed with patients, and that additional data on the longterm use of ataluren after LoA should be prospectively collected.

In patients reaching LoA, clinical outcome differs from that of ambulatory patients. Therefore, two considerations arise. First, during treatment period, it would be advisable to identify responders or non-responders from a respiratory point of view. Secondly, as the main respiratory prognostic factors relate to functional achievements and monitoring in the phase preceding LoA, it would be critical to make respiratory data collected in the registry available in order to evaluate ataluren therapy continuation in patients with nonsense mutation, as the outcome measure would be different from that leading to drug approval. Judgement on efficacy should derive from multiple outcome measures, in order for it to be correctly estimated in real-life practice.

While at present the main research areas on nmDMD include genetic modifiers, associated cognitive and behavioural disorders, quality of life, burden of care, and MRI as a predictive tool for LoA, the advisors propose to also work as an expert team to collect clinical needs, available treatments, standards of care, guidelines, frequency of follow-up, and transition from child to adult clinics, with the aim to facilitate the MDT in the optimal management of patients with nmDMD after LoA.

Transition from paediatric to adult services

It is the panel's opinion, sustained by literature data, that in young adults with DMD, many different clinical but also psychosocial aspects should be evaluated during transition, due to their high impact on daily life, such as work/study activities, independent living, daily routines, transports, or health care[4]. In fact, an observational study found that the majority of people with DMD do not work and do not carry an independent life. In more detail, a paper found that only 20% had an occupation, most frequently in education or administrative support, and 80.7% were still living with their parents[16]. Additionally, while children tend to receive a high input from the community services, teenagers and adults have to rely more on their family members and caregivers[17]. Assistive technology has a big potential to improve quality of life, independence, and clinical management[18]. On the other hand, intellectual functioning can affect compliance to therapy and increase inequality. Increased rates of intellectual disability[19], language delay[20], learning disabilities, and attention-deficit hyperactivity disorder[19,21] have been documented in patients with DMD. Many patients show a typical neuropsychological profile with poor verbal working memory, irrespective of IQ level[22]. Dystrophin expression in the central nervous system is variable, depending on isoforms and specific genetic variations[19]. Further research on the cognitive profiles of patients with DMD, their consequences on quality of life and independence, potential targets of care and ways to remove social barriers are warranted.

Finally, as transition in DMD patients is very complex, and there are no shared protocols in Italy, the panel noted the existence of different, site-specific issues and strengths in the transition process. This lack of uniformity should be addressed in order to guarantee equity.

Challenges in the multidisciplinary management

Medical therapy

Given the advances in therapeutic strategies, transition has changed from a pure management of complications to a transition of therapy. Steroids represent the gold standard in pharmacological therapy, and demonstrate a positive effect on walking, scoliosis, upper limbs function, ventilation and cardiac function[2]. Numerous studies demonstrate the importance of their daily use, as in the longterm they delay LoA compared to historical series[23]. Despite literature evidence, the experts noted that in real life practice, a significant

number of patients withdraw from steroids following LoA. As far as corticosteroids treatment is concerned, low-dose daily deflazacort is preferred over prednisone due to superiority and better tolerability, especially as it causes reduced weight gain. However, the literature supports the experts' observation of a higher incidence of cataracts with deflazacort[24].

Delayed puberty can be a complication of glucosteroids treatment, due to secondary hypogonadism. In the transition process, if, according to published recommendations[2], there is a need to induce puberty, testosterone is administered, with a positive impact on bone and skeletal muscle bulk. Impaired somatic growth is common and can worsen with glucocorticoids treatment. However, the panel highlighted that benefits of growth hormone on linear growth need to be balanced with the potential for relevant side-effects, including glucose intolerance, scoliosis progression or intracranial hypertension[2]. However, in the experts' experience, it has been seldom prescribed.

In order to preserve bone health, early treatment with vitamin D (and intravenous biphosphonates in selected cases) is used, especially with the aim to prevent asymptomatic vertebral fractures[3].

Orthopedic surgery

Expert opinion on orthopaedic surgery has been last delivered in 2018[3]. In the experts' experience, the need to perform vertebral surgery has decreased thanks to the positive impact of corticosteroids on scoliosis progression. Even though scoliosis onset has been delayed to the post-puberal phase, it always develops and shows a progressive course. Regarding vertebral fractures, bone densitometry is being implemented at Padua university hospital. In case ofscolioses with Cobb angle exceeding 40 degrees, if the patient's general clinical conditions allow it, othopedic surgery is being proposed to teenagers soon after LoA.

Quality of life

It is the panel's opinion that, with the advent of new therapeutic options, the social and personal perception of patients with DMD as "terminally ill" patients should be fought against, and awareness should be raised on patients with DMD as persons not necessarily facing reduced life expectancy, and with a strong need to improve their quality of life.

Cardiologic and respiratory issues

Establishing the clinical applications and the prognostication power of cardiac magnetic resonance imaging (MRI) is an additional, relevant field of active clinical research in DMD. Cardiac MRI is considered as the gold standard for assessing ventricular volumes and global systolic function[25]. In addition, it can assess global and regional function, identify fibrosis or fatty infiltration[26] and ventricular dysfunction. It also has the potential to select patients with early cardiac abnormalities in order to evaluate more aggressive therapies. As cardiomyopathy is one of the leading causes of death in DMD patients and the early identification of areas of fibrosis with cardiac resonance imaging might unravel a possible source of arrhythmia, the role of cardiac resonance imaging should be more thoroughly investigated in order to assess its prognostic role[27].

Considering the risk of cardiac detrimental consequences in subjects with DMD maintaining ambulation, and cardiac data emerging from STRIDE[28], it would be clinically relevant to evaluate ECG data from STRIDE patients, but although the registry contains both ECG and heart ultrasound data, these are limited by the observational nature of the study and the lack of a specific protocol for cardiac data acquisition. In the majority of cases, patients with the worse skeletal muscle outcome also have the worse cardiac outcomes. As for heart monitoring, cardiac care gives guidance on preventive strategies for younger children, but clinical guidance or recommendations would be needed for older patients as well.

Patients in their late non-ambulatory stage need to be offered discussion on their preference between non-invasive mechanical ventilation for > 16 hours/day versus tracheostomy. During the phases leading to LoA, respiratory function and respiratory infections are monitored, and, in some cases, patients receive mechanical ventilation.

The main issues related to emergency care for patients with DMD have been reviewed elsewhere, including assessing the presence of restrictions to resuscitation and evaluation of breathing, cardiac, endocrine, and orthopaedic issues as background or as acute medical emergencies[4]. In the experts' experience, in the acute setting, three issues relative to collaboration with the intensive care team need to be stressed:

- Avoiding therapeutic nihilism[29];
- Increasing awareness, in order to enhance timely management or prevention of acute complications (i.e. adrenal insufficiency under stressful conditions)[30];
- Fat embolism syndrome secondary to bone fractures [31].

Advanced disease and end-of-life decisions

In advanced disease stages, care priorities include preventing scoliosis, heart and respiratory damage, and osteoporosis, and managing gastro-intestinal symptoms. Compared to the past, the onset of scoliosis is delayed, thanks to longer maintenance of ambulation and standing posture during growth.

Increasing survival of patients has led to growing prevalence of gastro-intestinal disorders, including acute intestinal pseudo-obstruction and progressive dysphagia. Gastroparesis and constipation are quite common in the immobilized patient. Although this is less common than embolism or pneumonia, it must be correctly identified and managed.

Gastrointestinal and nutritional complications can be favoured by steroids, immobility and decreased resting energy expenditure[2]. Conversely, nutritional issues can negatively affect respiratory, skeletal muscle and cardiac systems[2].

An increasing number of teenage patients experience recurring *ab ingestis* pneumonia, leading to the need to perform a percutaneous endoscopic gastrostomy (PEG) or a radiologically inserted gastrostomy (RIG). Discussion on the indications for these procedures should be anticipated early on and periodically re-evaluated throughout follow-up[2].

The panel of experts thinks that creating a tighter network between referring centers and the community services and local hospitals would have a major impact on the management of acute complications, which are frequent in the late stages. This might be managed by sharing protocols, by implementing medical education and by creating pathways ensuring that the medical team can either address the acute medical needs locally or efficiently refer to the third level centres.

Discussion and conclusions

In this paper, we wished to report narratively on the real-life experience and expert opinion of a group of Italian researchers taking care of patients with DMD. Moving from current evidence and guidance, some issues linked to the challenges faced by patients, caregivers and health professionals regarding transition to adult care and from the ambulatory to the non-ambulatory phase, as well as the need to address emergency care and implementation of multidisciplinary care have been reviewed with the aim to provide topics for future debate and lines of research.

This paper has several limitations, including its design, reporting on experts' opinion, and the inclusion of a limited number of Italian centres managing DMD, although among its strengths we can report the inclusion of some of the main Italian health institutions operating in the field.

Shared protocols should be developed, especially to manage acute phases, as patients now reach older ages and therefore their needs have changed and might be left unmet. Therapeutic continuity with ataluren after LoA in patients with nonsense mutation DMD, the need to change our approach and design specific outcome measures to target clinically meaningful objectives as disease progresses to the non-ambulatory phase and from paediatric to adult servicesshould be evaluated in long-term longitudinal studies.

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Conflict of interest statement

Luca Bello reports honoraria (speaker, consultancy) for PTC Therapeutics, Sarepta Therapeutics, Epirium Bio, Edgewise Therapeutics; research funding from PTC Therapeutics, Santhera Pharmaceuticals. Carlotta Spagnoli, Rachele Adorisio, Adele D'Amico, Maria Grazia D'Angelo, Marika Pane, Valeria Sansone, Andrea Vianello, and Carlo Fusco report no conflicts of interest to disclose.

Authors' contributions

CS: analysis or interpretation of data, drafting of the manuscript, critical revision of the manuscript; MP and PRi: acquisition, analysis or interpretation of data, critical revision of the manuscript; LB, RA, ADA, MGDA, MP, MP, PR, VS, and AV: concept and design, acquisition, analysis or interpretation of data, critical revision of the manuscript for important intellectual content. CF: concept and design, supervision in manuscript writing, critical revision of the manuscript for important intellectual content.

All authors approved the final manuscript.

Ethical consideration

No ethical approval is required for this review study.

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