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Continuitiy of care with ataluren in Duchenne Muscular Dystrophy patients with nonsense mutations after loss of ambulation. Personal experience

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Duchenne Muscular Dystrophy (DMD) includes predictable phases requiring dedicated standard treatments. Therapeutic strategies feature corticosteroids or the more recent gene therapy/stop codon read-through. Ataluren (Translarna®) is an oral drug promoting the readthrough of premature stop codons caused by nonsense mutation (nm) in order to produce full-length dystrophin. It was licensed by EMA in 2014 for ambulatory patients with nmDMD aged ≥ 5 years.
Our aim is to report data on long-term ataluren use in Italian patients with nmDMD, with emphasis on continuity of the treatment after loss of ambulation (LoA).
Four DMD patients aged between 16 and 24 years who lost ambulation between 12 and 14 years continued to take ataluren after LoA. The oldest patient, aged 24 years, is still taking a few steps. Even in those experiencing motor decline, PUL-test performances were stable and respiratory function satisfactory in all; two patients developed severe cardiomyopathy, stable in one.
Therapeutic continuity with ataluren should be offered to all nmDMD patients after LoA given its favourable safety and efficacy profile.
However, further research is recommended to identify additional clinically meaningful outcomes and treatment goals following LoA.

Key words: Duchenne Muscular Dystrophy, nonsense mutations, loss of ambulation, ataluren

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Introduction

Duchenne Muscular Dystrophy (DMD) is a severe X-linked recessive disorder, characterized by progressive muscle weakness. Its prevalence equals 15.9 cases per 100000 live male births in USA, and 19.5 cases per 100000 live male births in UK [1-3].
Progressive muscle degeneration results in muscle weakness, motor delay, loss of ambulation (LoA) generally around 12 years of age, respiratory impairment, and cardiomyopathy. Although clinical course can be variable, death usually occurs in late twenties, mainly due

to cardiorespiratory failure [4,5]. The advances in care provided to DMD patients in last decades have progressively increased the survival up to the 30s and even beyond [6]. Life expectancy, recently reviewed in a meta-analysis, found a median life expectancy of 22 years. However, stratification into three-time periods showed markedly increased life expectancy in more recent patient populations as patients born after 1990 have a median life expectancy of 28.1 years [7].

DMD genetics

The *DMD* gene is the largest known human gene, featuring 79 exons and height promoters [8]. It encodes dystrophin, a cytoskeleton protein linking the sarcomere to the extracellular matrix, providing strength, stability, and functionality to myofibres and protecting the sarcolemma from contraction-induced injury [9,10]. DMD is caused by pathogenic variants such as large deletions or duplications, and small mutations, that result in absent or insufficient functional dystrophin due to disruption of the reading frame [11]. A correct genetic diagnosis is necessary for appropriate care and for eligibility of patients to clinical trials and personalized therapies [12].

Management and therapy

DMD includes several different clinical phases, the timing of which can be predicted and require dedicated standard treatments. The increase in the survival rate has brought out "new" needs, and has shifted care from the objective of increasing longevity to that of improving quality of life[9].

The latest standards of care, published in 2018 [9,13,14], account for the modified natural history of the disease, but need constant update and a multidisciplinary approach.

Current therapeutic strategies in DMD include "secondary" treatments, targeting the deleterious consequences of dystrophin deficiency with anti-inflammatory medications such as corticosteroids[9], and a pathophysiologic approach (gene therapy, exon skipping, or stop codon read-through) aiming to restore dystrophin protein [12,15].

A cornerstone of care is that all the most innovative genetic and molecular therapies must be associated with Standards of Care (SoC), which have been progressively implemented, and play a critical role in preserving patients' functioning.

Approximately 10-15% of patients have a nonsense mutation in the *DMD* (nm*DMD*) gene [12], resulting in a premature stop codon in the dystrophin mRNA, preventing translation into the functional full-length protein. Ataluren (Translarna®) is an oral drug designed to promote the readthrough of premature stop codons, caused by nonsense mutations in order to produce full-length dystrophin [15]. Currently, it is indicated for patients with nmDMD, aged ≥ 2 years who are still ambulatory [16].

A first open-label Phase IIa study (ClinicalTrials.gov identifier: NCT00264888) demonstrated an increase in full-length dystrophin expression in patients with nmDMD treated with ataluren for 28 days [17]. Its effectiveness has then been demonstrated in two randomized, double-blind, placebo-controlled trials: a Phase IIb trial (ClinicalTrials.gov identifier: NCT00592553) on 174 patients [18] and a Phase III trial (ACT DMD; ClinicalTrials.gov identifier: NCT01826487) on 230 patients [19].

In this paper, we report data from four nmDMD patients (two from the Padua University and two from the Gemelli Hospital in Rome) aged between 16 and 24 years who lost ambulation between 12 and 14 years and continued to take ataluren after LoA.

Materials and methods

Relevant clinical information was obtained retrospectively, from the patients' charts. The following clinical data were collected: age at diagnosis, presenting symptoms, clinical evolution, medications history, age when started on ataluren, age at LoA and, if applicable, age when ataluren was discontinued and reintroduced, age at latest follow-up.

The main clinical outcomes evaluated included therapy tolerability, 6-minute walking distance (6-MWD), timed rise from floor, heart function (either by left ventricular ejection fraction, LVEF and by left ventricular shortening fraction, LVSF), respiratory function (forced vital capacity, FVC) [19-21], upper limbs function (Performance of Upper Limb, PUL versions 1.2[22] and 2.0 [23]. The small sample size prevented statistical analysis, so only qualitative data (i.e. mean, median, range) are shown.

Results

Patients from the University of Padua

Patient A is now 18 years old. His mother is a symptomatic carrier with dilated cardiomyopathy.

He had typical onset of symptoms at the age of three, elevated Creatin Kinase (CK) levels, absent dystrophin on muscle biopsy and carries a nonsense mutation. He began treatment with deflazacort at 5 years of age at standard dosage. At age 8, he experienced strength deterioration and adverse events (osteoporosis and weight gain). He was also diagnosed with early-onset left ventricle dilation. At around 10 years, when he started the treatment with ataluren, his 6MWD was 304 m, and his timed rise from floor was 8.5sec. Treatment was well tolerated but he experienced progressive functional decline evolving to LoA two years later. He was enrolled in the STRIDE registry, even though treatment with ataluren was withdrawn when he lost ambulation. At 14 years, he developed severe cardiomyopathy (LVEF: 30%), which required the placement of an Implantable Cardioverter-Defibrillator (ICD). Around the age of 16, after consultation and positive opinion of the local ethics committee, the Veneto region financed the reinstatement of ataluren as an *off-label* treatment. Currently, at the age of 18, his LVEF has stabilized, without cardiological symptoms; the respiratory function is satisfactory (FVC = 41%) and ventilation is not required. Following ataluren restart, the upper limbs function seems to have stabilized.

Patient B is now 16 years old. Family history is negative; he is a sporadic case (mother not carrier). Tiptoe walking was noted at 4 years of age associated with high CK levels. He was diagnosed with DMD and a nonsense mutation in *DMD* gene was identified. He first presented to the Padua center at 7 years old, and at that time he was prescribed deflazacort. Due to dystrophin absence on muscle biopsy, he was enrolled in the STRIDE registry, and started treatment with ataluren at approximately 8 years of age, when his 6-MWD was 424 metres and timed floor climb was 5 seconds. LoA occurred at almost

13 years, so ataluren was discontinued. After the authorization by the local ethics committee, he was put back on ataluren only 10 months after suspension. Though his motor function has declined over the last years, his hand-to-mouth function is still preserved (score 3 at PUL 2.0 entry item A). He did not develop cardiomyopathy (normal echocardiogram at the age of 16, with shortening fraction of 46%) and the respiratory function has so far always been satisfactory (FVC of 81%, at 15 years).

Patients from the Gemelli Hospital, Rome

Patient C is now 17 years old. Family history is negative. High CK levels have occasionally been found during an episode of gastroenteritis at 1 year of age. Following the results of muscle biopsy (dystrophin absence) and the genetic testing for DMD, which identified a nonsense mutation in *DMD* gene, he was diagnosed with DMD. At age 3, he started treatment with deflazacort. He first presented to the Gemelli center when he was 6 years old. He started treatment with ataluren at approximately 8 years, when his 6-MWD was 512 m. LoA occurred at almost 14 years, but he continues to be treated with ataluren in a compassionate use program. Though the motor function has declined over the last years, his hand-to-mouth function is still preserved (score 3 at PUL 2.0 entry item A). He did not develop cardiomyopathy (normal echocardiogram at the age of 16, with LVEF of 64%).

Patient D is now 24 years old. His maternal uncle was diagnosed with DMD and died at 33 years from cardiorespiratory failure; his mother is a DMD carrier. High CK levels were occasionally found around 1 year of age. Given dystrophin absence on muscle biopsy, he was diagnosed with DMD and a nonsense mutation in *DMD* gene was identified. He first presented to Gemelli center at age 8 and began taking ataluren at approximately age 10, when his 6-MWD was 498m and timed rise from floor was 4 seconds. At 11 years, he was prescribed deflazacort. His motor function has declined over the years, but he is still able to walk a few steps without support, and his hand-to-mouth function is still preserved (score 4 at PUL 2.0 entry item A). He developed severe cardiomyopathy, so that he had a left ventricular assist device (LVAD) implanted, at the age of 22. His respiratory function has always been satisfactory (vital capacity of 51%, age 24 years).

Discussion

In this paper, we report our preliminary clinical experience on therapeutic continuity with ataluren, in four patients with nmDMD after LoA. In some Italian regions, nmDMD patients not included in clinical trials nor in the STRIDE registry have been maintained on ataluren after LoA, with the aim to help them to perform better and longer in daily activities (i.e. work, social life), and to reduce their dependence on caregivers.

At present, beyond the patients described above, there are further four nmDMD patients continuing to take ataluren after LoA: one from Veneto, one from Friuli-Venezia-Giulia, one from Emilia-Romagna and one from Marche region. Emilia-Romagna was the first Italian region to define ataluren use in patients losing ambulation as therapeutic continuity rather than off-label use [24].

By comparing the clinical characteristics and outcomes of our patients with those of the STRIDE registry, some features are shared but other are different. In our series, the mean age of patients at the beginning of treatment with ataluren was 9 years (range: 8-10), compared to 9.8 years in the STRIDE registry [25]; furthermore, the follow-up period was longer (mean age at last assessment 18.75 years versus 17.2 years in the interim analysis of the STRIDE 2022 registry) [25]. In our patients, LoA occurred at a median age of 13 years, later than in CINRG (11 years), but earlier than in the interim analysis of the STRIDE 2022 registry (median: 17.0 years) [25]. However, Patient D is still able to take some steps at 24 years old.

Age at loss of ambulation is a critical factor, being predictive of age at onset of loss of upper limb milestones and pulmonary complications. Upper limbs function evaluated by PUL 2.0 documented a score in the baseline item A equal to 3 in two of our patients, and to 4 in one of them at the end of follow-up. Concerning respiratory involvement, two of our patients had, at the last follow-up, a FVC higher than 50% at 16 and 24 years of age respectively, and one a FVC of 41%, at 18 years; in the STRIDE registry a decline of predicted FVC $< 50\%$ occurred at 20.1 years [25].

Two patients in our series developed severe cardiomyopathy, one with stabilization of LVEF after reintroduction of ataluren. A worsening in cardiac function, assessed by echocardiography measured as a reduction in LVEF $< 55\%$, occurred in three patients with an age range of 4.6 -18.4 years, in the 2020 analysis of STRIDE data [2].

Additional literature data, although sparse and preliminary, seem to support the use of ataluren after loss of ambulation. A Swedish retrospective study evaluated the long-term use of ataluren in six patients with DMD, with a mean age at LoA of 13.2 years. Age at LoA showed a positive correlation with the duration of ataluren use: patients who reached LoA before 13.2 years took ataluren for 5 years, while patients who continued to walk after 13.2 years took ataluren for an average 6.5 years until LoA or last follow-up, if still walking. Four of six non-ambulatory patients treated with ataluren had higher upper limb performance scores and five of six patients experienced a slower decline in FVC [26].

In our small series, upper extremity performance stabilized with ataluren or was even preserved (patient C, 17 years old).

In a different clinical scenario [27], off-label use of ataluren was reported in four patients with nmDMD who lost ambulation at a mean age of 10.1 ± 0.5 years and started treatment with ataluren at a mean age of 14.1 ± 1.4 years. Serial echocardiography (LVFS), pulmonary function tests (FVC), and assessment of muscle strength using the Medical Research Council (MRC) scale indicated a mild slowing of disease progression over a period of 18-26 months. However, the low number of patients and intra- and inter-individual fluctuations represent limitations to this study, and can make it challenging to draw conclusions about efficacy. On the other hand, it is important to accumulate real world data, and the present experience confirms a good risk/benefit balance and patient/family satisfaction from continued treatment. Our preliminary results support therapeutic continuity after LoA in line with previous reports.

Conclusions

As treatment goals and clinical needs of patients and caregivers change after LoA, it would be very important to collect more clinical

data on upper limb, heart and respiratory function on larger patients' cohorts to better evaluate long-term efficacy and safety data on ataluren therapy in these patients.

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Conflict of interest

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.

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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 retrospective, observational study.

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