

# Early treatment with Ataluren of a 2-year-old boy with nonsense mutation Duchenne dystrophy

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Duchenne muscular dystrophy (DMD) is an X-linked myopathy caused by mutations, in most cases deletions and duplications, in the dystrophin gene. Point mutations account for 13% and stop codon mutations are even rarer. Ataluren was approved for the treatment of DMD caused by nonsense mutations in 2014, and several clinical trials documented its efficacy and safety. However, few real-life experience data is available, especially in pediatric age. We report the case of a 2-year-ambulant child affected by DMD caused by the stop-codon mutation c.10801C > T, p.Gln3601X in exon 76, who was early treated with Ataluren at a dosage of 40 mg/kg/die, and presented a rapid improvement in both muscle strength and cognitive and social skills.

**Key words:** ataluren, nmDuchenne dystrophy, stop codon point mutations, early treatment

## Introduction

Duchenne muscular dystrophy (DMD) is an X-linked recessive muscular disease caused by mutations in the dystrophin gene, which is the most common muscle disorder in childhood. In most cases, the disease causing mutations are deletions and duplications, but in about 10-15% of cases, DMD is caused by nonsense mutations (nmDMD) in the gene that encodes for dystrophin, resulting in a premature stop codon in the mRNA that affects the production of a full-length functional protein<sup>1</sup>. Clinically, the disease is characterised by progressive muscle weakness and atrophy due to the absence of a functional dystrophin, which results in premature death due to heart and respiratory failure<sup>1</sup>. Until few years ago, the treatment of DMD was mainly limited to corticosteroid therapy, which only mitigates the rate of muscle degeneration<sup>2</sup>. In July 2014, the European Medicines Agency (EMA) approved Ataluren (Translarna<sup>®</sup> by PTC Therapeutics) for the specific treatment of nmDMD in walking patients aged 5 years and older. Ataluren enables ribosomal readthrough of mRNA containing premature stop codons allowing cellular machinery to bypass nonsense mutation in the genetic material, continue the translation process, and restore the production of a full-length functional protein<sup>3</sup>. In July 2018, the European Commission (EC) authorized the prescription of ataluren in younger nmDMD patients aged two to five years<sup>4</sup>. The decision was supported by the results obtained in the clinical study 030, in which ataluren demonstrated a positive risk-benefit ratio in Duchenne patients of this age group.

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In Italy, PTC has notified the Italian Medicines Agency AIFA of the activation of the expanded access therapeutic use program, following the Ministerial Decree 07/09/2017, for the use of ataluren in nmDMD ambulatory patients, aged between 2 and 5 years.

To date, numerous articles in the literature demonstrate both the efficacy and safety of Ataluren<sup>5,6</sup>; however, few real-life experience studies are available, especially in children. Herein, we report the results in the outcomes of a walking child affected by nmDMD who started the treatment with ataluren, at the age of 2.

## Case report

A 3-month-old baby came to our observation for the finding of increased values of Creatinekinase (CK, 5941 UI/L), CK-MB (243 ng/ml) and myoglobin (1857 ng/ml). The neurological examination was normal for age. Cardiological and pneumological investigations showed no alterations. NGS (Next Generation Sequencing) identified the stop-codon point mutation c.10801C > T; p.Gln3601X in exon 76, consistent with a diagnosis of nmDMD. In the follow-up, the mother reported delay in the acquisition of motor (autonomous ambulation acquired at 21 months) and language milestones. At the age of 21 months, the neurological examination revealed evidence of Gower's manoeuvre, but no calf pseudohypertrophy. The North Star Ambulatory Assessment (NSAA), administered to measure functional motor abilities, showed a total score of 10/34. The Bayley Scales of Infant and Toddler Development-Third Edition<sup>7</sup>, used for the neurocognitive evaluation, showed that the child had lower composite scores across all domains (see Table I). Laboratory tests confirmed elevated serum CK levels (15813 UI/L). Cardiological investigation showed only a bland patent foramen ovale. No therapy was prescribed. When the child turned 2 years old, an early treatment with ataluren was initiated, at a dosage of 750 mg/day (40 mg/kg/day) according to EMA SmPC guideline<sup>8</sup>. Eight months later, the neurological examination still showed waddling gait, slight proximal muscle weakness, reduced deep tendon reflexes, partial Gower maneuver and slight delay in global neurodevelopment. However, the patient's muscle strength, upper limb movements and motor skills in walking, jumping and running were significantly improved. NSAA showed a total score of 19/34. No change in heart function was observed, nor deterioration of respi-

ratory function. Serum CK levels were persistently high (20753 UI/L). After 16 months from the beginning of the ataluren therapy, the child appears participant and able to walk and rise up on his own with negative Gower's sign. Gower's sign is a classic maneuver observed in children with DMD, that indicates weakness of the proximal lower limb muscles. Its negativization indicates a clear improvement in proximal lower limb muscle strength, not expected in the natural history of children with DMD. He still shows waddling gait but not reduced strength in the 4 limbs during repetitive or prolonged movements. Muscle trophism is good. He has discrete dynamic equilibrium, good bimanual manipulation of objects and only a slight weakness in the execution of fine movements. NSAA shows a further improvement in the total score: 21/34. Respiratory function assessed by dynamic night pulse-oximetry does not show alterations. Cardiological visit and echocardiogram are normal. Cognitive, motor and language skills are also improved (Tab. I).

## Discussion

We report the clinical follow-up of a child with nmDMD starting treatment with ataluren at 2 years. After 16 months of treatment, the patient showed an improvement in both motor and cognitive skills compared to the baseline evaluation. The disease progression in young boys affected by Duchenne muscular between age 3 and 6 years ( $\pm 3$  months), using the NSAA scale was documented by Coratti et al.<sup>9</sup> in 153 DMD boys (573 assessments) younger than 6 years (mean: 4.68, SD: 0.84) with a genetically proven DMD diagnosis. They showed that NSAA scores progressively increased with age, the largest increase being between age 3 and 4 years. A further increase until age of 6 was steadily observed. They also observed that, irrespective of age and pharmacological treatment, DMD boys having a mutation between exon 44 and 62 presented reduced NSAA score by 0.64 points compared to those having a mutation before exon 44. Furthermore, having a mutation after exon 63 reduced NSAA score by 4.67 points compared to those having a mutation before exon 44 and of 4.03 points compared to mutations between exon 44 and 62. Our patient, of about 3.5 years, achieved an NSAA score of 21/34, much higher than the average observed at the same age in the Coratti cohort, both naive (13.64) and treated with steroids (16.33). The improvement is even more remarkable if we keep in mind

**Table I.** Bayley Scales of Infant and Toddler Development – Third Edition composite scores.

|                 | Cognitive           | Language            | Motor              |
|-----------------|---------------------|---------------------|--------------------|
| Pre-therapy     | 80 (percentile 9°)  | 65 (percentile 1°)  | 73 (percentile 4°) |
| 16 months after | 85 (percentile 16°) | 83 (percentile 13°) | 79 (percentile 8°) |

the mutation site (exon 76) for which, again according to the data of Coratti et al, a lower score of 4.67 points is expected. Our findings are in line with previous studies demonstrating efficacy of Ataluren in pediatric patients with nmDMD10. However, at our knowledge, this is the first time that the efficacy of the drug is documented in DMD boys less than 3 years. This observation has important clinical repercussions because the precocity of the treatment can radically modify the natural history of the disease<sup>10</sup>.

Interestingly, serum CK levels were consistently high during the follow-up, with a peak after 8 months of treatment (20753 IU/L). This suggests that serum CK levels do not correlate with symptom's severity. Furthermore, the increase in CK levels could be explained with the increase in muscle mass and the improvement in motor performance. In conclusion, our data confirm the importance of an early diagnosis with gene analysis and sequencing, as an early initiation of the Ataluren treatment can help to prevent muscle degeneration and achieve better motor-cognitive outcomes in children with nmDMD. Further studies in larger cohorts are needed, to better delineate the potential of Ataluren in very young nmDMD patients.

#### *Ethical consideration*

All procedures were in accordance with the standards of the bioethical committee and the Declaration of Helsinki.

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#### *Conflict of interest*

The Authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

#### *Author contributions*

All Authors participated in data collection, review and modification of the project. IB and CM have provided

substantial contributions to the analysis and interpretation of the data, to the critical review and to the drafting of the manuscript. All Authors approved the submission of the final manuscript and agreed to be responsible for all aspects of the work

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