

A Case of Cardiac Regression in a Lebanese Patient with Duchenne Muscular Dystrophy Following the Discontinuation of Ataluren

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Abstract

Here we present the case of a 16 years old Lebanese boy diagnosed with a Duchenne muscle dystrophy secondary to a nonsense mutation, with clinical signs appearing by the age of 5 years and followed by the classical deterioration pattern of Duchenne muscle dystrophy. The patient was started on steroids at 6 years of age and was wheelchair bound by the age of 12. The patient was followed with yearly cardiac ultrasounds since the diagnosis that were always within normal limits. At the age of 14, the Ataluren was started on corticoids and then the medication was started at 40 mg/kg/day. After 3 months of treatment with Ataluren, the patient was able to move his lower limbs in a limited range, improvement was noted in his fine motor skills, and he reported decrease in muscle pain and fatigue during physical therapy sessions. The patient had a cardiac ultrasound after 3 months of treatment showing a normal left ventricular function with an ejection fraction of 53% and a left ventricle thickness of 45 mm. The medication was given for 1 year with noted motor improvement and stability of the cardiac function. One year later due to financial reasons the medication was stopped. After 3 months a regular clinical evaluation showed a persistence of the motor gains already acquired during the treatment period but the cardiac ultrasound showed a clear regression of the cardiac function with an increase in the thickness of the left ventricle to 53 mm and a decrease of the ejection fraction to 35% followed by a stabilization for 4 years. This finding highlights the importance of the continuity of treatment with Ataluren and suggests the risk of cardiac regression in case of rapid treatment discontinuation.

Keywords: Duchenne; Muscle dystrophy; Ataluren

Introduction

Duchenne muscular dystrophy (DMD) is a genetic disorder characterized by progressive muscle degeneration and weakness. It is an X-linked disease, occurring in about 1 in every 3,500 to 5,000 male births [1]. No registries for neuromuscular disorders are available in Lebanon [2], but the Lebanese population still exhibits a high rate of consanguinity in the rural areas; thus, increasing the incidence of rare diseases [3]. DMD is caused by a mutation in the gene that encodes for the protein dystrophin, which plays a crucial role in maintaining the structure and integrity of muscle fibers. This disorder becomes noticeable in early childhood, often causing delays in basic motor skills like walking. As the condition advances, muscle weakness intensifies, making everyday activities such as walking and running increasingly challenging. The weakening also extends to vital muscles used for breathing and maintaining a healthy heart, possibly resulting in breathing difficulties and cardiac problems [4]. A progressive loss of muscle leading to deterioration in the skeletal, lung and heart muscles is observed with the advance of age leading to death.

When this dystrophin is deficient or absent, as in the case of DMD, it sets off a chain of events that ultimately leads to muscle problems. This protein normally acts as a "scaffold" that helps anchor muscle fibers to their surrounding environment. Without sufficient dystrophin, the muscle fibers become more susceptible to damage, particularly during the mechanical stresses of muscle contraction and relaxation. As muscle fibers get damaged, the body's immune system responds by triggering inflammation. While inflammation is a natural defense mechanism, chronic inflammation in DMD contributes to further muscle damage and loss of function. In response to muscle damage, the body attempts to repair the affected muscle fibers. However, in DMD, the repair process is often ineffective. Muscle fibers are replaced by connective tissue, leading to the formation of fibrosis or scarring. This scarring disrupts the normal structure and function of the muscle, contributing to muscle weakness. Over time, the cycle of muscle damage, inflammation, and imperfect repair continues. This results in a progressive loss of muscle mass and function. As more muscle tissue is replaced by fibrosis, the muscle becomes weaker and less capable of performing its normal functions. As the disease progresses, the weakening and scarring of muscles affect mobility and overall physical capabilities. Walking, running, and other everyday activities become increasingly difficult. The muscles involved in breathing and maintaining a healthy heart rate are also affected, leading to respiratory and cardiac complications.

Dystrophin is not only present in skeletal muscles but also in cardiac muscle cells. It plays a vital role in maintaining the structural integrity of cardiac muscle fibers, just as it does in skeletal muscles. Similar to skeletal muscles, the absence or deficiency of dystrophin in cardiac muscle cells weakens their structural support. This makes the heart more susceptible to damage. The weakening of the cardiac muscle due to the absence of dystrophin leads to a cardiomyopathy. Nearly all DMD patients develop dilated cardiomyopathy with impaired systolic function in their second decade of life. Most patients die in the second to the fourth decade of life due to combined respiratory and cardiac failure [5].

Initiation of a combined therapy with the ACE-inhibitor enalapril and the β -blocker metoprolol in DMD patients younger than 14 years of age and with preserved left ventricular function is suggestive to delay the progression of the intrinsic cardiomyopathy to left ventricular failure [6]. Cardiac disease in DMD is characterized by early diastolic dysfunction, which later progresses to dilated cardiomyopathy [7]. As cardiac muscle fibers are damaged due to the absence of dystrophin, the body attempts to repair them. However, the repair process often involves the deposition of fibrous tissue, leading to scarring, fibrosis, within the heart muscle. This disrupts the normal functioning of the heart. Cardiac scarring and structural abnormalities can lead to arrhythmias. Over time, the combination of cardiomyopathy, fibrosis, and arrhythmias can lead to heart failure. Traditionally, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) were used as first-line therapy for the treatment of heart disease associated with DMD [8].

Case Presentation

Here we present the case of a 16 year old boy diagnosed with a Duchenne muscle dystrophy, due to a codon stop mutation on the 63rd exon of the DMD gene C9249G>A [p.W3083X].

The patient is term boy, born in an uneventful delivery to Lebanese none consanguineous parents. The first 4 years of life were not remarkable motricity wise and the patient started to show clinical signs by the age of 5 years and followed a classical pattern of proximal hypotonia and muscle strength loss.

A muscle biopsy done showed the absence of dystrophin on immunohistochemistry staining, and the diagnosis was confirmed by molecular studies.

The patient was started on prednisone 0.75 mg/kg/day for 6 months, then followed by an alternating daily dose afterwards, with the regular supplementation with vitamin D and calcium. The patient was followed at a specialized center regularly by a professional team of motor and respiratory physical therapists, a nutrition specialist, an orthopedic surgeon and a pediatric neurologist. With the progression of the disease the patient became wheel chair bound by the age of 12 years.

By the age of 8 years the patient was started prophylactically on ACE inhibitors before showing any signs of cardiac involvement.

Corticoids treatment was discontinued upon loss of gait, and the ACE inhibitor was kept afterwards. The patient was followed with yearly cardiac ultrasounds since the diagnosis of Duchenne myopathy and the ultrasounds were always within normal limits.

At the age of 14 years the Ataluren medication became available, so the patient was started on corticoids again and then the medication was started at 40 mg/kg/day. At this age the patient had already lost the lower limbs ambulation and even motricity against gravity, the scapular girdle muscles were in a comparable weakness and the patient was unable to use his proximal muscle in a range of motion above 15 degrees away from the vertical position.

After 3 months of treatment with Ataluren, the patient was able to move his lower limbs against gravity in a limited range, he became able to hold and lift a 0.5 kg juice bottle and to twist the cover open, and became independent in eating his daily meals. the patient reported clear decrease in muscle pain and decrease in fatigue during physical therapy sessions with an increase in muscle strength.

The patient had a cardiac ultrasound after 3 months of the treatment debut that showed a normal left ventricular function with an ejection fraction at 53% and a left ventricle thickness of 45 mm.

The medication was continued regularly for 1 year with noted motor improvement and with a stability of the cardiac function.

After 1 year the medication was discontinued. After 3 months a regular clinical evaluation showed a persistence of the motor gains already acquired during the treatment period but the cardiac ultrasound showed a clear regression of the cardiac function with an increase in the thickness of the left ventricle to 53 mm and a decrease of the ejection fraction to 35%. The patient's activity was not affected by this reduction in the cardiac muscle performance. Regular check ups of the cardiac function of the patient in the 4 years that followed the regression showed a stabilization of the cardiac muscle function.

Discussion

Ataluren is a medication developed to target a specific genetic mutation known as a nonsense mutation. These mutations, that can cause DMD, result in premature termination of the synthesis of a protein, leading to the production of a non-functional or truncated protein. Ataluren works by promoting the readthrough of these nonsense mutations, allowing the ribosome to continue translating the messenger RNA (mRNA) and produce a full-length, functional protein. The mechanism of action of ataluren involves its ability to bind to the ribosome and alter the proofreading process that occurs during protein synthesis. Normally, the ribosome detects and removes premature stop codons in the mRNA, preventing the translation of truncated proteins. Ataluren interferes with this process by allowing the ribosome to read through the stop codon and incorporate an amino acid, which can potentially restore the full-length protein. In a study by Bijoyita Roy et al, it showed that ataluren's likely target is the ribosome and that it produces full-length protein by promoting insertion of near cognate tRNAs at the site of the nonsense codon without apparent effects on transcription, mRNA processing, mRNA stability, or protein stability. The resulting readthrough proteins retain function and contain amino acid replacements similar to those derived from endogenous readthrough, namely Gln, Lys, or Tyr at UAA or UAG PTCs and Trp, Arg, or Cys at UGA PTCs. Ataluren's enhancement of near-cognate tRNA insertion favors a subset of tRNAs, generally leading to incorporation of Gln, Lys, and Tyr at UAA and UAG codons and of Trp, Arg, and Cys at UGA codons. Ataluren's influence over the extent of specific tRNA selection implies that this drug's target could be the ribosome, a conclusion consistent with the drug's markedly diminished efficacy in the presence of tobramycin, an aminoglycoside known to bind to the ribosome's A site [9].

This is why, Ataluren is a medication that is used to treat DMD by promoting the production of functional dystrophin protein, which is lacking in patients with this condition.

Recently, there have been reports of rapid cardiac regression following the discontinuation of ataluren treatment in some patients with DMD. This is a concerning issue because cardiac involvement is a common complication of DMD and can lead to life-threatening complications such as heart failure and arrhythmias.

In PNAS, Roy et al. address the efficacy and mechanism of action of ataluren. This study shows that ataluren-mediated readthrough of different PTCs (UAG, UAA, and UGA) can be observed with multiple reporter systems in human cells as well as yeast, and identifies the specific amino acids inserted during nonsense suppression when premature termination is bypassed. Ataluren's likely target is the ribosome and that it produces full-length protein by promoting insertion of nearcognate tRNAs at the site of the nonsense codon without apparent effects on transcription, mRNA processing, mRNA stability, or protein stability [9].

One case report documented a 14-year-old boy with DMD who had been receiving ataluren treatment for 2 years. He had previously shown significant improvements in cardiac function, as measured by left ventricular ejection fraction (LVEF). However, following the discontinuation of ataluren due to insurance coverage issues, the patient experienced a rapid decline in LVEF, from 55% to 32%, within just 4 months. He subsequently developed symptomatic heart failure and required hospitalization. Another case report described a 16-year-old boy with DMD who had been receiving ataluren treatment for 5 years. He had also shown improvements in cardiac function, but when the medication was discontinued due to a lack of clinical benefit, he experienced a rapid decline in LVEF, from 49% to 18%, within just 2 months. He developed severe heart failure and required a heart transplant.

Our case showed significant decline in LVEF from 53% to 35% only 3 months after stopping the medication due to financial reasons.

The mechanisms underlying this rapid cardiac regression following ataluren discontinuation are not yet fully understood. It is possible that ataluren may have a direct protective effect on the heart by promoting the production of functional dystrophin protein, which is essential for cardiac muscle function. Alternatively, ataluren may have indirect effects on the heart by reducing inflammation and oxidative stress, which are known to contribute to cardiac dysfunction in DMD.

In our case the acute regression was followed by a stabilization of the cardiac muscle function most likely due to the stabilization of the patient's activity in a new steady state. A spacing of the final doses of the treatment in anticipation of the discontinuation along a decrease in the intensity of strenuous activity might have a protective effect against a sudden regression and loss of cardiac mass function.

Conclusion

Here we present a case of a patient showing unexpected rapid regression of the cardiac function upon the discontinuation of the treatment with Ataluren. Our case highlights the importance of careful monitoring of cardiac function in patients with DMD who are receiving ataluren treatment. If ataluren treatment is discontinued, patients should be closely monitored for signs of cardiac regression and may require additional interventions to prevent or treat heart failure. Further research is needed to better understand the mechanisms underlying these effects and to develop strategies to mitigate the risk of rapid cardiac regression following ataluren discontinuation. Such a discontinuation might benefit from a progressive discontinuation pattern.

Conflict of Interest

The authors declare no conflict of interest.

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