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Eteplirsen Use in a Boy with Duchenne Muscular Dystrophy and Sickle Cell Anemia

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Abstract
Eteplirsen is an antisense oligonucleotide used in the treatment of Duchenne muscular dystrophy (DMD). The safety of eteplirsen use in individuals with rare comorbid conditions is not known. We present the case of a 4-year-old boy with a DMD exon deletion amenable to treatment with eteplirsen and comorbid sickle cell anemia. He has received eteplirsen treatment for 3 years with no clear adverse effects, including no increase in sickle cell crises.

Introduction

Duchenne muscular dystrophy (DMD) is the most common childhood muscular dystrophy, and it is characterized by progressive weakness secondary to diminished dystrophin production [1]. DMD should be considered in boys with falls, weakness, and significantly elevated creatine kinase levels [2]. Genetic testing is performed in suspected cases, with deletions, duplications, or point mutations in the *DMD* gene, confirming the diagnosis. Over the past 5 years, several therapies have been approved for DMD which include anti-inflammatories and targeted molecular therapies. Anti-inflammatory treatments, typically corticosteroids, have been used for decades to help decrease damage from inflammation that follows muscle breakdown [3]. Studies have demonstrated that corticosteroid treatment of DMD improves muscle strength in the short- to long-term period [4]. It is believed that these

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therapies delay the replacement of functional muscle mass with fibrous connective tissue, which is characteristic of DMD. Among targeted molecular therapies are antisense oligonucleotides (ASOs), such as eteplirsen, golodirsen, viltolarsen, and casimersen, which are used to modify the reading frame and restore function of the *DMD* gene [5, 6]. Eteplirsen is a 30-nucleotide phosphorodiamidate morpholino oligomer type of ASO, which hybridizes to exon 51 of DMD and results in skipping during splicing [7]. This process amends the inaccurate transitional reading frame and produces shortened functional dystrophin proteins. Eteplirsen is thus indicated for patients with deletions ending at exon 50 and starting at exon 52, which covers approximately 13% of all individuals with DMD. Due to the water soluble, neutral characteristics of phosphorodiamidate morpholino oligomers, eteplirsen distributes well to muscle tissue.

At times, boys with DMD may have other significant medical conditions that should be considered when using ASO therapies. For example, in this case report, we present the use of eteplirsen in a 4-year-old boy with DMD and sickle cell anemia (SCA). SCA is a common hemoglobinopathy that results from a mutation to the beta subunit of hemoglobin [8]. Since ASOs are a new type of therapy, it is important to report their use in those with comorbidities, such as SCA.

Case Presentation

A 2-month-old boy was diagnosed with SCA based on an abnormal newborn hemoglobin screen and known sickle cell trait in both of his parents. Hemoglobin electrophoreses pattern revealed HbA 0%, HbF 84.9%, HbA_2 0.4%, and HbS 15.7%, which is consistent with SCA. He began hydroxyurea therapy 300 mg/day at 9 months of age. His medical history also included premature birth, bronchiolitis, constipation, a chordee release, hepatosplenomegaly, and sickle cell crises.

At the age of 16 months, he presented with an elevated creatine kinase (>14,000 units/L), gross motor delay (started to sit and crawl at 12 months, cruising at 14 months, and was unable to walk independently at 16 months), and delayed language development. DMD was suspected and genetic sequencing confirmed a deletion in the *DMD* gene encompassing exons 45–50. Given he had an amenable mutation, he initiated treatment with eteplirsen 30 mg/kg weekly via an implanted port and home infusions in June 2018. He continues to receive this treatment weekly and has done so uninterrupted. Elevations of AST and ALT occur in boys with DMD without SCA, but in this case, it should be noted that since the administration of eteplirsen, the elevation of AST, ALT, and platelets has been steady and consistent with levels expected in patients with chronic SCA [9]. Additionally, his creatine kinase levels have remained at elevated levels, consistent with DMD. No clear adverse effects have been noted. From birth to the age of 22 months (when eteplirsen was started), he experienced 2 sickle cell crises, and since he has been on eteplirsen, he has experienced one sickle cell crisis.

Discussion

We are not aware of any other reports of individuals with DMD and SCA and are not aware of any reports of ASO use in individuals with SCA. This is of importance because medications can precipitate sickle cell crises, and ASOs have not been extensively studied in individuals with SCA. Furthermore, preclinical trials of some ASOs in animal models have demonstrated dose-dependent thrombocytopenia and nephrotoxicity [10]. These findings

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are of potential concern in an individual with SCA due to the possible exacerbation of anemic events and nephrotoxicity. The thrombocytopenia and nephrotoxicity observed in clinical studies appear to be compound-specific rather than an oligonucleotide class effect [11]. Although the FDA recommends renal monitoring in certain ASOs, such as golodirsen, it is not indicated for eteplirsen.

The evolving field of novel molecular therapies targeting muscular dystrophies is particularly appealing because it directly targets the loss of function mutations. Traditional treatments, such as corticosteroids, pose the risk of significant adverse effects. Long-term administration is associated with weight gain, endocrine disturbances, osteoporosis, and behavioral difficulties [12]. For such reasons, ASOs present as an attractive alternative to glucocorticoids, given their safety profile and targeted approach.

As this is a single case report, it has limitations. Systematic testing for adverse events was not conducted. However, this child has been followed closely (every 4 months in clinic), and only one sickle cell crisis has occurred during 3 years of eteplirsen therapy. No other adverse events have been detected.

To date, eteplirsen, golodirsen, viltolarsen, and casimersen have been approved in the USA for the treatment of DMD, and these medications can be used in approximately 29% of boys with DMD [6, 13]. At the moment, eteplirsen has no listed interactions with other drugs, so future evaluation of eteplirsen and other ASOs in individuals with SCA should be conducted, and adverse events need to be consistently reported.

Statement of Ethics

Ethical approval is not required for this study in accordance with local guidelines. Written informed consent was obtained from the parent of the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors of this manuscript certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

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Author Contributions

The authors confirm contribution to the paper as follows. Study conception and design: Michael Stephen Cartwright, MD, MS[2]; draft manuscript preparation: Gregory M. Aiello, BS[1]. Further inquiries can be directed to the corresponding author.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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