



The Advance Medicine: An Orphan Drug Idursulfase (Elaprase®) for the Treatment of Hunter Syndrome

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BACKGROUND INFORMATION

A major piece of drug legislation signed by President Reagan on January 4th 1983 was the Orphan Drug Act. The term “orphan drug” reflects the existence of drugs that are used to treat diseases that are “orphaned” (i.e., little research or pharmaceutical company studies have been conducted) because of their rarity, for example: Hunter syndrome.

Hunter syndrome is one of the Mucopolysaccharidoses (MPS) disorders. MPS are lysosomal storage disorders caused by the deficiency of enzymes required for the stepwise breakdown of glycosaminoglycans (GAGs). Clinically they are divided into 9 categories: MPS I-MPS IX. MPS-II (also known as Hunter syndrome) is caused by a deficiency of Iduronate 2-sulfatase (IDS), which is located on chromosome Xq28. Until 2006 there was no treatment for this rare disease.

Since it's approval in 2006 by FDA, idursulfase (Elaprase®), an orphan drug, was first used for treatment of the rare disease (Hunter syndrome) in El Paso in 2007.

CASE PRESENTATION

The patient is a 7 years old male that had growth delay (<3rd percentile), and speech delay since age 2. He was in ECI before 3 years old and now gets service in School. The rest of his history and physical exam showed: Sensory: He failed hearing screen. Nutrition: He eats well on a regular diet. Past medical history: He had multiple ear infection and multiple bronchiolitis. At 2 years of age, he started to have speech delay. At 4 years of age, he presented with coarse facial feature and mild hepatosplenomegaly (HSM). He has decreased ROM at shoulders but no crepitus and no pain. FH: He is the only child and he was conceived after fertility treatment; Mother has four brothers and two sisters who are all healthy. Physical examinations: Coarse facial features (Fig 1); HSM; decreased ROM (shoulder); his hands have short broad fingers; his tonsils are hypertrophied and snores more often; his neck is getting shorter. He had no corneal cloudiness nor brain deformity.

Laboratory and other tests: Ultrasound study of the abdomen shows that the liver is enlarged measuring 10.8 cm. and there were no focal intrahepatic changes. Spinal X ray: Squared off vertebral bodies are evident with inferior beaking at L2. There is also some posterior scalloping of the mid lumbar vertebral bodies. No fracture or malalignment is seen and there is no accentuated kyphosis or vertebral body hypoplasia (Fig.2). Plasma amino acids: WNL; urine organic acids: WNL. Enzyme assay: MPS:

39.8 (<10.5); Beta-glucuronidase from fibroblast: 5.52 (0.34-1.24) The patient was started on idursulfase (0.5 mg/kg once per week) infusion on February 2007 and has been on it since. Idursulfase is a recombinant product of iduronate-2-sulfatase, the enzyme needed to hydrolyze mucopolysaccharides dermatan and heparin sulfate. Serious and sometime fatal anaphylactic reactions have been reported with it's. Other common side effects include: pyrexia, headaches, and antibody development. So far he has had no negative reactions to the treatment (no hypersensitivity, no respiratory distress et al), and his symptoms have been improving (less stiffness, less HSM). Although MPS level still high which was 38 at the latest visit, we hope that it will decrease significantly in the near future.

DISCUSSION

The mucopolysaccharidoses (MPS) are lysosomal storage disorders caused by the deficiency of enzymes required for the stepwise breakdown of glycosaminoglycans (GAGs), previously known as mucopolysaccharides ⁽¹⁻⁵⁾. Fragments of partially degraded GAGs accumulate in the lysosomes, resulting in cellular dysfunction and clinical abnormalities. These are rare conditions, with an estimated total incidence of all types of MPS of approximately one in 20,000 live births.

The MPS disorders are classified as types I through IX. In general, the severity depends upon the quantity of residual enzyme, which is related to the genotype of the affected patient. Mutations that permit small amounts of residual enzyme activity result in less severe clinical phenotypes ⁽⁶⁾. These residual amounts may be less than 1 % of normal and not be detectable by routine assay. Phenotype can vary among affected siblings due to other unknown genetic or environmental factors.

Mucopolysaccharidosis II is also known as Hunter syndrome. This disorder is caused by a deficiency of iduronate 2-sulfatase (IDS), which results in storage of heparan and dermatan sulfate ⁽¹⁾. MPS II is caused by mutations in the gene encoding for IDS, which is located on chromosome Xq28 ⁽⁷⁾. Although the disorder is X-linked, cases in females have been reported ⁽⁸⁻¹⁰⁾.

There are two types of Hunter syndrome: Type A: symptoms occurred in the first two years of life; deaf and mental retardation, may survive into second and third decades. Type B: milder, normal intelligence and may have airway obstruction. Our case has very good cognitive development and somatic function, possible type II that will not have much progression or mental dis-

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ability.

Since our case is the only affected person in his family, he has 1/3 chance to be a new mutation and a 2/3 chances that his mother has a mutant gene on one X chromosome (carrier) and passed to him. DNA testing for mother to be a carrier was done and confirmed that she is the carrier.

Prenatal diagnosis and Carrier detection are important for those who have the family history of MPS disorder and who are concerned about having an affected child. It can be performed for all of the MPS disorders. The most reliable method for prenatal diagnosis is the measurement of enzyme activity in cultured fibroblasts obtained by amniocentesis⁽¹⁾. But to detect carrier, DNA analysis can be used to identify carriers among siblings or other relatives if the mutation is known. If a carrier is concerned about having an affected child, the other parent can be screened for common mutations, which account for approximately 70 percent of the known affected alleles, depending upon the disorder and population. However, absence of one of the known mutations does not definitively exclude a carrier state.

Since 2006 idursulfase was approved as an orphan drug and is available through Shire Company. Multiple studies have shown this enzyme benefits to somatic problems like large organs and joint contractures with still unproven therapy of mental problems. With our case's excellent cognitive function he would be an ideal candidate for enzyme therapy.

As we are still in the trial stages of this orphan drug for treatment of Hunter syndrome, we are hopeful our efforts will prolong the life expectancy and improve the quality of life for this child.

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Coarse facial feature and growth delay



Squared off vertebral bodies are evident with inferior beaking at L2. There is also some posterior scalloping of the mid lumbar vertebral bodies. No fracture or malalignment is seen and there is no accentuated kyphosis or vertebral body hypoplasia.

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