

New enzyme replacement therapies for lysosomal storage diseases

VITA LERMAN

In the past few years, more and more enzyme replacement products for lysosomal storage diseases have been developed, and these new therapies are drastically improving patients' lives. Enzyme replacement therapies (ERTs) for Fabry disease and Hurler syndrome received FDA approval in 2003, for Maroteaux-Lamy disease in 2005, and for Pompe disease in the spring of 2006.

ERT for Hunter syndrome is the most recent of these new therapies, and children treated by geneticist Barbara Burton, MD, at Children's Memorial Hospital were the first in the country to receive the commercially available treatment, just weeks after the FDA approval in July 2006.

Lysosomal storage diseases are inherited metabolic disorders, in which specific enzymes needed to break down unwanted substances in cells are either missing or deficient. The resulting build-up of materials in the lysosomes of different cells can lead to serious health problems.

In Hunter syndrome, the toxic effects may produce progressive skeletal deformities, decreasing range of motion, enlarging liver and spleen, and profound mental impairment. Patients with the severe form of Hunter syndrome rarely live past their 20s, usually due to complications from upper airway obstruction or heart failure.

The new ERT for Hunter syndrome (idursulfase) reduces the size of the liver and spleen, increases walking distance and improves pulmonary function, according to results from the 1-year randomized, double-blind, placebo-controlled Phase II/III clinical trial. [Muenzer J, et al. *Genetics in Medicine* 2006;8(8):465-47].

Offering new hope for Hunter syndrome patients

The new ERT is bringing exciting benefits to patients with Hunter syndrome at Children's Memorial. "Symptoms improved beyond our expectations," says Burton. "After only 3 months of this therapy, we saw dramatic reductions in liver and spleen size, increased joint mobility, increased energy. We have patients who are able to climb a flight of stairs for the first time – something that was inconceivable for them prior to enzyme replacement therapy. We thought it would take closer to 6 months before we would start seeing any effects on symptoms."

Prior to ERT, no treatment was available for patients with Hunter syndrome, only palliative management of symptoms as they develop.

ERT for Hunter syndrome involves weekly infusions that may need to be continued throughout the patient's life. As with ERTs for other lysosomal storage diseases, this treatment promises to prevent or slow the progression of somatic symptoms. Symptoms that involve the central nervous system, however, are not impacted by ERTs, since enzyme replacement products do not cross the blood-brain barrier.

The Lysosomal Storage Disease Center at Children's Memorial has been treating patients with these disorders since 1991, when the first ERT became available for Gaucher disease. Today, the center is one of the largest in the nation and the only referral site for lysosomal storage diseases in Illinois.

Continuing research

The center also is actively engaged in clinical and outcomes research. “We contribute to international outcome registries for all lysosomal storage diseases for which ERT is available,” says Joel Charrow, MD, who launched the center at Children’s Memorial and heads the hospital’s Division of Genetics, Birth Defects and Metabolism. Charrow is a Board member of the International Collaborative Gaucher Group, which provides scientific direction to the Gaucher Registry. He also serves on the Advisory Board for the Fabry Registry.

Under Charrow’s leadership, Children’s Memorial has been involved in ERT clinical trials for Gaucher disease and Fabry disease. Currently, the hospital is participating in a multi-institutional clinical trial on ERT efficacy for late-onset Pompe disease.



Photo by Andrew Campbell

Joel Charrow, MD, head of Division of Genetics, Birth Defects and Metabolism

Advocacy to expand newborn screening

With more effective treatments becoming available for lysosomal storage diseases, there is a stronger impetus to develop newborn screening programs, so that early intervention could prevent debilitating symptoms.

“In Pompe disease, for example, enzyme replacement needs to be started as early as possible, before the heart and the skeletal system are irreversibly damaged,” explains Burton. Without ERT, infants with Pompe disease suffer from rapidly progressing symptoms, usually dying within the first year of life.

Children’s Memorial is part of a coalition led by the Evanosky Foundation advocating for expansion of the newborn screening program in Illinois to include lysosomal storage diseases. In February, Illinois Senator Dale Righter introduced SB 1566, a bill that would require newborn screening for Krabbe, Pompe, Gaucher, Fabry and Niemann-Pick diseases to begin by July 1, 2008. Currently, these 5 lysosomal storage diseases have validated newborn screening tests.

Additionally, the bill protects monies in the Metabolic Screening and Treatment Fund, which is used to provide newborn screening services, preventing appropriation of these funds into the general fund. The bill also calls for the protection of the Genetic and Metabolic Diseases Advisory Committee, which advises the Illinois Department of Public Health on the disorders that need to be added to its newborn screening test profile.

Physicians can join the advocacy effort by contacting their local Illinois State legislators and the office of Governor Rod Blagojevich, urging them to support SB 1566.

Children’s Memorial contributes to international outcome registries for all lysosomal storage diseases, and has been involved in ERT clinical trials for Gaucher disease and Fabry disease. Currently, the hospital is participating in a multi-institutional clinical trial on ERT efficacy for late-onset Pompe disease.