

Enzyme replacement therapy for Lysosomal Storage Disorders

An Overview

Enzyme replacement therapy is a process that provides hope for a considerably improved quality of life for patients who suffer from lysosomal storage disorders (LSD).

Each of the more than 40 individual LSD result from a deficiency in the activity of a specific protein (enzyme) which is normally present in each of the billions of cells that make up our bodies. The role of lysosomes is to degrade waste materials made by these cells into simpler products for re-use. This process of waste removal requires the sequential action of a number of enzymes. If one of these enzymes is present in insufficient amounts, the recycling process cannot proceed and the undegraded material remains stored within the lysosome and, therefore, the cell. As the amount of stored material increases over time, normal cellular functioning becomes increasingly impaired, leading to the emergence of clinical symptoms.

A form of treatment known as enzyme replacement therapy offers some hope for relief from what are devastating clinical conditions. Enzyme replacement therapy refers to the regular (usually weekly) infusion of manufactured enzyme into the circulation of a patient who is lacking that specific enzyme. For LSD, this should enable the stalled recycling process to function normally, thereby reversing the disease-causing process.

Because all LSD share a common biochemical basis, it is expected that

enzyme replacement will prove to be an effective form of treatment for LSD.

Indeed, enzyme replacement therapy has been used in Australia since 1991 to successfully treat most patients affected by a LSD known as Gaucher disease. Its success with Gaucher patients has encouraged the development of enzyme replacement for other LSD. Clinical trials are now in progress to evaluate the effectiveness of enzyme replacement in three other LSD: Fabry disease, Pompe disease and mucopolysaccharidosis (MPS) type I. Trials are also being planned for a further three disorders: MPS types II and VI, and Niemann-Pick disease type B.

However, whilst enzyme replacement therapy is expected to successfully remove already-stored material and prevent further storage in tissues and organs in direct contact with circulating peripheral blood (heart, liver, spleen and joints for example), it is anticipated that storage in lysosomes in the central nervous system (brain) may not be reduced. The major problem that appears to restrict the usefulness of enzyme replacement for brain disease is the presence of a protective membrane surrounding the brain called the 'blood-brain barrier'. Further studies are required to investigate the effectiveness and limits of enzyme replacement therapy for those LSD where the brain is affected, and, where necessary, to develop methods to achieve treatment of patients with brain disease.

Brain pathology is a feature of many LSD. These include Krabbe disease, GM1-gangliosidosis, α -mannosidosis, metachromatic leucodystrophy,

mucopolipidosis, Niemann-Pick disease types A and B, Sandhoff and Tay Sachs diseases, some forms of Gaucher disease, and MPS types I, II and III. In Australia, the proportion of patients with significant central nervous system pathology ranges from approximately one-tenth of patients diagnosed with Gaucher disease, to one-half of patients diagnosed with MPS types I and II, to all patients diagnosed with MPS type III.

At this time, there is considerable promise that enzyme replacement therapy will be available for many common LSD that do not have brain pathology, and this will significantly modify the considerable burden of these diseases to patients and their families. Intensive research on methods to circumvent the blood-brain barrier is continuing.

Progress with the use of enzyme replacement therapy will be provided in future issues of our newsletter. We also intend to provide up-to-date information about the use of alternative therapies for LSD, such as gene replacement therapy and bone marrow transplantation.

It is also our aim to describe the often lengthy and complicated process of developing therapy. This will extend from the identification and isolation of the gene at the laboratory bench to its development by a biotechnology company and its approval by regulatory agencies for use in the clinic.

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