Chapter 1
Enzyme Replacement Therapy: Therapeutic Enzymes Used for the Treatment of Hereditary Deficiency Diseases

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ABSTRACT

Enzyme replacement therapy is a therapeutic approach in which the specific enzyme that is absent or inactive in affected individuals is replaced with a functional enzyme molecule derived from biological sources or produced by biotechnology. A large number and variety of enzyme defects have been identified in humans. Over 40 hereditary deficiency diseases were reported. The common feature is that enzyme deficiency leads to the accumulation of undegraded molecules and lysosomal storage, resulting in organ dysfunction. Crude enzyme preparations are often unsuitable for therapeutic uses because of their potential contamination and antigenicity. Advances in gene identification and cloning led to the subsequent production and demonstration of equal efficacy of recombinant human enzyme. The adverse events recorded range from boxed warnings for severe allergic reactions. This chapter summarizes therapeutic enzymes used in clinical practice, with particular reference to those obtained from biological sources and biotechnology processes.

1. INTRODUCTION

Enzymes are biomolecules that catalyze and accelerate chemical reactions. Almost all biological processes require enzymes in order to maintain the homeostasis of cells. They are extremely selective for their substrates, and their activity is highly regulated by substrate concentration, pH, and temperature.

Enzyme replacement therapy (ERT) is a therapeutic approach in which the specific enzyme that is absent or inactive in affected individuals is replaced with a functional enzyme molecule derived from biological sources or produced by DNA technology. The concept of ERT has been around for at least 50 years. For example, de Duve described enzymes as part of therapeutic protocols for genetic deficiencies in the 1960s (Vellard, 2003). A large number and variety of enzyme defects have been identified in

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humans, many leading to diseases produced by altered amounts of metabolites resulting from enzyme deficiency. In the early 1960s, the first metabolic storage disease was identified. Since then over 40 such diseases have been reported. Metabolic storage disorders are life-threatening diseases caused by insufficient activity of enzymes required for the catabolism of biological materials that arise from the normal turnover of body constituents. The severity of symptoms depends on whether the deficiency is partial or complete. The so-called storage diseases provided both the best early examples of a clear association of enzyme deficiency and disease as well as candidates for a successful therapeutic approach to treatment. Lysosomal storage disorders (LSD) are strong candidates for the development of specific innovative therapies. The common feature is that enzyme deficiency leads to accumulation of undegraded macromolecules and lysosomal engorgement, resulting in organ dysfunction.

The importance of ERT in treating LSD was recognized in the early 1990s when an effective enzyme replacement was first developed for Type I Gaucher disease using highly purified placenta-derived β-Glucocerebrosidase. It markedly improved hematological indices and reduced hepatosplenomegaly in patients (Barton, Furbish, Murray, Garfield, & Brady, 1990). Advances in gene identification and cloning led to the subsequent production and demonstration of equal efficacy of recombinant human enzyme produced in Chinese hamster ovary (CHO) cells. The introduction of Cerezyme ® led to the withdrawal of the placental product (Grabowski, Barton, Pastores, Dambrosia, Banerjee, McKee, & Brady, 1995).

The successes of ERT in Gaucher disease established a viable medical and industrial model for the development of ERTs for other LSD. In fact, ERT has been successfully done in other enzyme deficiency disorders like Fabry disease, Pompe disease, mucopolysaccharidosis (MPS), severe combined immunodeficiency (SCID), etc (Table 1). However, even with an early introduction of treatment there are still several limitations of ERT such as delivering therapeutic levels of lysosomal enzymes across the blood-brain barrier and despite efforts, ERT mostly slows down disease progression and attenuates symptom expression.

Research and drug developments fostered under Orphan Drug Product Development Programs have greatly assisted the introduction of efficient and safe enzyme-based therapies for several rare disorders. The Orphan Drug Act was passed in 1983 in the USA to encourage biopharmaceutical companies to develop treatments for these rare disorders affecting only small number of people (<200,000).

Adverse events recorded during ERT range from boxed warnings for severe allergic reactions, including anaphylaxis, to rare effects on the heart, lungs, liver, and blood as well as a variety of mild to moderate commonly seen responses such as gastrointestinal symptoms, headache, and mild skin reactions.

Crude enzyme preparations are often unsuitable for therapeutic uses because of their potential contamination with endotoxins and antigenicity. When the enzyme used is a foreign protein, it can elicit an immune response that alters the clearance rate or induces severe allergic reactions in the host. In the field of modern innovative biotechnology, a relatively small number of recombinant enzymes have been developed as the main active substances of therapeutics.

Advances in the knowledge of therapeutic uses of enzymes have heightened interest in the manufacture and processing of these macromolecules. Moreover, gene identification and cloning led to the subsequent production and demonstration of equal efficacy of recombinant human enzyme produced in CHO cells and various optimization strategies have overcome the current limitations of ERT.

This chapter summarizes therapeutic enzymes used in clinical practice, with particular reference to those obtained from biological sources and biotechnology processes. Some of the pathophysiological features of hereditary deficiency diseases are described. Some of the key advances that have led to successful commercial production of enzymes for ERT will be addressed.