



Enzyme replacement therapies: what is the best option?

Azam Safary^{1,2}, Mostafa Akbarzadeh Khiavi^{3,2}, Rahimeh Mousavi², Jaleh Barar^{2,4}, Mohammad A. Rafi^{5*}

¹ Connective Tissue Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

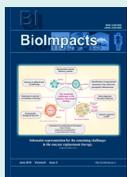
² Research Center for Pharmaceutical Nanotechnology, Biomedicine Institute, Tabriz University of Medical Sciences, Tabriz, Iran

³ Liver and Gastrointestinal Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

⁴ Department of Pharmaceutics, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran

⁵ Department of Neurology, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania 19107, USA

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Summary

Despite many beneficial outcomes of the conventional enzyme replacement therapy (ERT), several limitations such as the high-cost of the treatment and various inadvertent side effects including the occurrence of an immunological response against the infused enzyme and development of resistance to enzymes persist. These issues may limit the desired therapeutic outcomes of a majority of the lysosomal storage diseases (LSDs). Furthermore, the biodistribution of the recombinant enzymes into the target cells within the central nervous system (CNS), bone, cartilage, cornea, and heart still remain unresolved. All these shortcomings necessitate the development of more effective diagnosis and treatment modalities against LSDs. Taken all, maximizing the therapeutic response with minimal undesired side effects might be attainable by the development of targeted enzyme delivery systems (EDSs) as a promising alternative to the LSDs treatments, including different types of mucopolysaccharidoses (MPSs) as well as Fabry, Krabbe, Gaucher and Pompe diseases.

Author's Biosketch

Mohammad Rafi received his PhD in Animal Biology from the University of Montpellier, France, in 1970. He taught Cell and Molecular Biology for over 17 years at the School of Science, Tabriz University, Iran, where he also served as Chair of the Department of Animal Biology. He is currently a Professor of Neurology in the Department of Neurology with a joint appointment in the Department of Neurosciences at Thomas Jefferson University in Philadelphia, USA. Though he has worked on several lysosomal storage diseases, his main research interest is gene therapy of neurodegenerative disorders using animal models of globoid cell leukodystrophy (Krabbe disease). With successful AAVrh10-mediated treatment of murine and canine models, his research is moving towards the treatment trials of human patients.



Replacing the defective enzymes with a recombinant human enzyme in lysosomal storage diseases (LSDs) and restoring the enzymatic activity was first proposed by Christian de Duve in 1964.¹ The LSDs, as a heterogeneous group of disorders, are involved in various genetic defects.² They are a group of 50-60 genetically inherited rare disorders, which are caused by the deficient activity of a specific lysosomal enzyme and the gradual accumulation of its non-degraded substrates, including sphingolipids, carbohydrates, glycogen, glycoproteins, and mucopolysaccharides.³ Lysosomal storage of substrates leads to a number of complications such as metabolic imbalances, widespread cellular dysfunction through cell signaling, communication alteration, and disruption of lipid rafts pathway, as well as downstream of autophagy

processes.⁴ The LSDs patients during their early childhood suffer from multifaceted clinical symptoms that can affect their musculoskeletal system, lung, heart, liver, spleen, and eyes. In addition, most LSDs patients have mild to severe central nervous system (CNS) implications and they may even die in the early years of life owing to cardiorespiratory failures (Pompe disease).¹

Various treatment strategies have been evaluated against the LSDs, including gene therapy, small molecule therapies, enzyme replacement therapy (ERT), lysosome exocytosis, and organ/cell transplantation.⁵ Currently, ERT and hematopoietic stem cell transplantation (HSCT) have been advanced for the clinical trials, but due to the complicated nature of the LSDs, none of these methods addresses all aspects of the disease. Considering the



*Corresponding author: Mohammad A. Rafi, Email: mohammad.rafi@jefferson.edu



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effectiveness and limitations of each method when applied alone, combination of ERT and any other therapy is proposed in various studies to overcome these limitations.⁶ Up to now, several ERTs have been approved for the clinical applications in Gaucher, Fabry, Krabbe, and Pompe diseases, as well as different mucopolysaccharidoses MPSs (e.g., MPS I, II, and IV) as lysosomal storage disorders (Table 1).⁵ BioMarin Pharmaceutical Company is a global leader in developing and commercializing innovative biopharmaceuticals for the genetically derived rare diseases. Aldurazyme®, Vimzim®, and Naglazyme®, as recombinant human enzymes, have been produced by this company for the treatment of MPS I, IV, VI, respectively.

The intravenous (IV) administrations of approved enzymes in the LSDs generally represent significant clinical benefits, including improved walking ability, ameliorated respiration, and improved life-quality.⁷ The LSDs require continuous treatment for optimal clinical outcomes, therefore the cost-effectiveness and accessibility to ERT should be considered as an essential point in the treatment of these diseases. Despite the financial and regulatory advantages for the “orphan drug” in the U. S., pharmaceutical industries have priced the LSDs therapy products among the most expensive treatment modalities in the market. Unfortunately, due to the high-cost of ERT (usually over US\$ 100 000/patient per year), they are not often accessible for countries with fewer fundings.⁸ Besides, the major impediment to the development of enzymes as drugs for the LSDs is the limited clinical trials due to patients paucity in the population. Furthermore, while performing pre-clinical studies in animal models has been strongly recommended, in most cases, due to the lack of such suitable animal models studies, the clinical trials have been performed directly in human patients.⁹

Immune response and the IgG antibodies (Abs) generation against the foreign infused enzymes is another considerable issue of the ERT, which plays a pivotal role in the patients' safety as well as efficacy and success of the

treatment. In fact, the neutralizing Abs can reduce the efficacy of ERTs via direct interfering with the enzyme activity (Figure 1). They can interact with the active site of the enzyme and/or ligands involved in the binding to a receptor on the target cells (mannose-6-phosphate receptors for most LSDs, mannose and lysosomal integral membrane protein 2 (Limp2) receptors for Gaucher disease) that lead to blocking the cellular uptake and lysosomal targeting of the enzyme.¹⁰ In addition, immune reactions intensity appears to be dependent on the presence or absence of residual mutant enzymes. Cross-reactive immunologic materials (CRIM) status may be predicted by genotyping for GAA gene in Pompe diseases, and initial/early immunomodulation may induce tolerance and result in an optimized therapy.⁷

Despite the therapeutic features of systemically-administered ERTs against LSDs, the biodistribution of the enzymes into the difficult sites of pathology (especially into CNS, bone, cartilage, cornea, and heart) still remains as a striking challenge. Further, in the MPS, the accumulation of glycosaminoglycans (GAGs) in the cells and tissues all over the body result in devastating widespread dysfunctions in different tissues and organs. For instance, MPS manifestations in the eye include both the anterior segments (cornea, conjunctiva) and the posterior segments (retina, sclera, optic nerve).¹¹ A clear evidence demonstrates that approximately 75% of LSDs patients with the neurological dysfunctions might not be treated with the available ERTs.¹² The blood-brain barrier (BBB), as one of the main obstacles in the confrontation with the enzyme biodistribution, presents an impenetrable barrier between the bloodstream and the CNS, by which controls the inward and outward traverse of mostly hydrophilic enzymes utilized for the treatment of the LSDs selectively (Figure 1).^{13,14} Further, as a result, ERT often fails to provide the desired clinical outcomes, in large part due to its non-specific biodistribution, low bioavailability, and high degradation rate. Therefore,

Table 1. Approved enzyme replacement therapies available for the lysosomal storage disorders

LSDs	Deficient enzyme	Inheritance	FDA approved ERT and Brand name
MPS I (Hurler syn.)	α-L-iduronidase	Autosomal	Laronidase (Aldurazyme™)/ 2003-FDA, EMA
MPS II (Hunter syn.)	Iduronate sulfatase	X-linked	Idursulfase (Elaprase™)/ 2006-FDA; 2007-EMA
MPS IV A (Morquio A syn.)	N-acetylgalactosamine 6-sulfatase	Autosomal	Elosulfase Alfa (Vimzim™)/ 2014-FDA
MPS VI (Marateaux-Lamy syn.)	N-acetylgalactosamine 4-sulfatase	Autosomal	Galsulfase (Naglazyme™)/ 2005-FDA; 2006-EMA
Fabry disease	α-galactosidase	X-linked	Agalsidase α (Fabrazyme™)/ 2001-EMA Agalsidase β (Replagal™)/ 2003-FDA, EMA
Pompe disease	α-glucosidase	Autosomal	Agglucosidase (Myozyme™)/ 2006-FDA, EMA Agglucosidase (Lumizyme™)/ 2010-FDA
Gaucher disease	β -glucocerebrosidase	Autosomal	Agglucerase (Ceredase™)/ 1991-FDA Imiglucerase (Cerezyme™)/ 1994-FDA; 1997-EMA Velaglucerase (VPRIV™)/ 2010-FDA, EMA Taliglucerase (Elelyso™)/ 2012-FDA
Lysosomal acid lipase deficiency	Lysosomal acid lipase	Autosomal	Sebelipase α (Kanuma™)/ 2015-FDA,EMA

MPS: mucopolysaccharidosis; FDA: U.S. Food and Drug Administration; EMA: European Medical Agency.^{1,5,7}

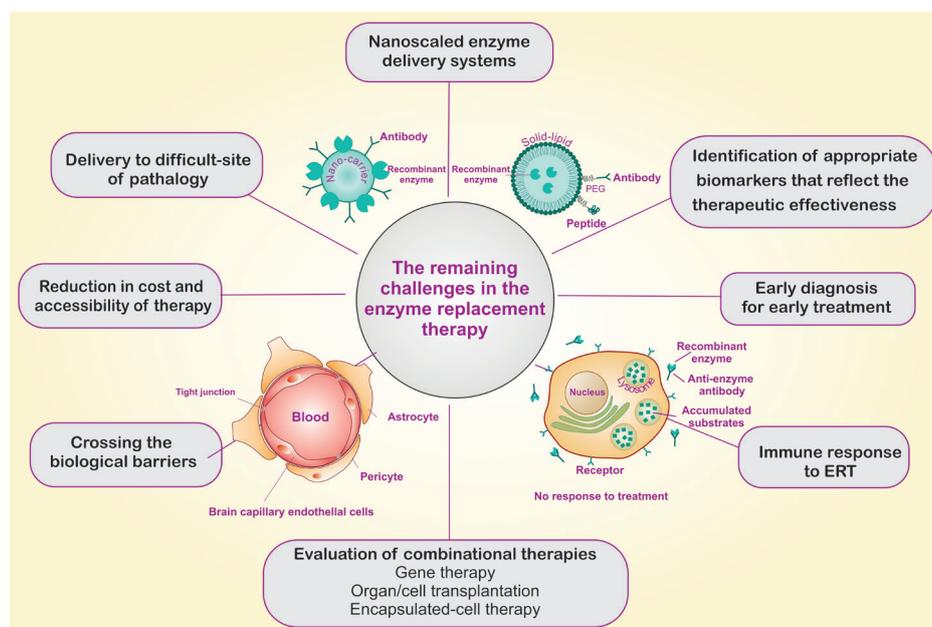


Fig. 1. Schematic representation for the remaining challenges in the enzyme replacement therapy.

enhancing the therapeutic response by the development of safe and efficient targeted enzyme delivery systems (EDSs) may provide a promising alternative to the currently used treatments in LSDs.^{15,16}

Different methods have been developed to overcome the limited access of enzymes into the difficult pathological sites. Based on the receptor-mediated lysosomal enzyme delivery system, it has been shown that increasing the presence of M6P residues on the recombinant enzyme or enhancing the expression rate of the M6PRs on the target cells can improve the cellular uptake of the enzyme through active targeting mechanism.^{17,18}

In recent years, unprecedented attention has been paid to the development of enzyme-loaded nanosystems (ENSs) using advanced nanobiomaterials to enhance the efficacy of ERT while minimizing the side effects.¹⁵ Different nanocarriers can be utilized for engineering of nanoscaled EDSs, including biodegradable nanomicelles, nanoliposomes, and polymer- and lipid-based nanoparticles (Figure 1).¹⁹ Enzyme encapsulation can veil the enzyme and its physicochemical characteristics, which can eradicate some of the key limitations of ERT, including undesired immunologic reactions and biodegradation. It can also protect the recombinant enzymes from unwanted biological impacts, non-selective biodistribution, and improve the pharmacological response by increasing the drug absorption, controlled-release of enzyme supply, pharmacokinetics (PK), and pharmacodynamics (PD) properties.^{20,21}

Besides, targeted NSs such as polymeric/lipidic nanoparticles, decorated with homing agents (e.g., aptamers or antibodies), can also be used in crossing the biological barriers such as BBB and blood-ocular-barrier (BOB). Thus, they are being considered as innovative and effective approaches for the treatment of brain disorders.¹²

In addition, encapsulated-cell therapy (ECT) along with another treatment strategy, has been considered as an interesting combined therapy method for the treatment of LSDs.^{22,23} One of the most pivotal advantages of ECT is to cover engineered cells by biocompatible devices that can be surgically implanted into different sites in the host body, especially in difficult-to-access sites such as the brain and eye to deliver constant amounts of the enzyme for prolonged periods of time.¹³ In the case of the eye, because of the efficient blockades provided by both epithelial and endothelial cells,^{24,25} the targeted delivery of drugs using advanced technologies and devices might provide great clinical outcomes.¹⁹ For example, thermos-responsive sol-gel injectable hydrogels offer great prospective applications in drug delivery, cell therapy and tissue engineering.²⁶ It should be noted that some of these systems have mostly been used in the preclinical stages and the clinical researches are essential for the approval of their long-term safety and therapeutic outcomes.

Based on these findings, it is envisioned that the currently used ERT modalities are not completely effective for all types of LSDs. We envision that the ultimate therapy of LSDs in the future would be based on the gene and/or cell therapy. For example, in the case of Krabbe disease, AAVrh10 gene therapy has been shown to ameliorates the central and peripheral nervous system's pathologies in murine and canine models of this disease.²⁷ At this point, perhaps the main challenge in the treatment of LSDs is to deliver therapeutic agents to the diseased cells/tissue potentially using nanoscaled EDSs. Various multimodal nanomedicines have previously been developed against different types of diseases.²⁸⁻⁴² Further, we know that the size and morphology of NSs can influence the pharmacokinetics and final fate of cargo drug molecules.⁴³ Depending on the desired biological targets and impacts

of the ERTs, the use of passive and active targeting mechanisms should be rationalized and fully addressed in the EDSs. Nevertheless, development of targeted NSs for enzyme delivery to CNS and other hard-to-reach tissue is considered as the main challenge. Vesicular trafficking mechanisms (e.g., clathrin-coated pits and membranous caveolae) in the LSDs should also be fully addressed. Lysosomal compartments, as acidic vesicular machineries of the cells, encompass over 60 different types of hydrolases and 50 membrane proteins and other biological machineries are involved in degradation of biological entities. We still need to understand the holistic roles of the lysosomal membrane transporters involved in the lysosomal trafficking.⁴⁴ Interdigitating of lysosomal compartments with other cellular organelles seems to be largely dependent on the function of lysosomal ion channels and transporters, dysregulation of which might attribute to the pathogenesis of LSDs. We still need to know the roles of cell membrane vesicular entities such as lipid rafts and cytoplasmic macromolecules such as coat proteins in the vesicular trafficking of the cells. Likewise, to treat the LSDs, a number of issues in relevance to the genetics and/or epigenetics of the lysosomal compartments need to be understood. Taken all together, perhaps, it is the time to change our research perspective from a restricted outlook towards a holistic approach. To this end, we need to understand the hallmarks of the LSDs and their biochemical and clinical aspects to be able to improve patients' well-being with more effective treatments. In this line, development of nanoscaled personalized medicines against LSDs appears to be an inevitable endeavor.

Ethical approval

There is none to be declared.

Competing interests

The authors declare no competing interests.

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