Enzyme replacement therapies in lysosomal storage diseases

Nariman Fathy Omar, Asmaa Magdy Mohammed Niazy, Al Shaymaa Ahmed Ali

Paediatrics Department, Faculty of Medicine, Zagazig University

Corresponding author: AsmaaMagdy Mohammed Niazy

Email: asmaamagdy867@gmail.com, Mobile: 01098855905

Abstract

Lysosomal storage diseases (LSDs) comprise about 50 unique monogenic autosomal or X-linked diseases with an estimated combined incidence of 1 in 7,000 to 8,000 live births. They occur secondary to genetic mutations that result in deficiency or reduced activity of native intracellular enzymes that catabolize biological macromolecules. These enzyme defects result in accumulation of specific macromolecular compounds within lysosomes in various tissues and organs, causing progressive damage that can become life-threatening in some diseases. LSD management traditionally involved supportive care measures tailored to disease stage, the organs and systems involved, and the degree of impairment. However, enzyme-replacement therapy (ERT) is now commercially available for six LSDs, typically used lifelong with traditional management practices for each.

KeyWords:LSD, ERT, MPS.

DOINUMBER:10.48047/NQ.2022.20.19.NQ99452 **NEUROQUANTOLOGY2022;20(19):4905-4910**

Introduction.

Replacing the defective enzymes with are combinant 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, 3).**

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. 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) implicationsand they may even die in the early years of life owing to cardio respiratory failures (Pompedisease)(**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 dueto the complicated nature of the LSDs, none of these methods addressesall aspects of the disease. Considering the effectiveness and limitations ofeach method when applied alone, combination of ERT and any other therapy is proposed in various studies to over come these limitations(**6**).

Upto 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.,MPSI,II,and IV) aslysosomal storage disorders (Table1)(**5**). Bio Marin Pharmaceutical Company is a global leader in developing and commercializing innovative biopharmaceuticals for the genetically derived are diseases. Aldurazyme®,Vimzim®, and Naglazyme®, as recombinant human enzymes, have been produced by this company forthe treatment of MPS I,IV,VI, respectively.

Table 1: Approved enzyme replacement therapies available forthe lysosomalstorage disorders

LSDs	Deficientenzyme	Inheritance	FDAapprovedERTandBrandname
MPSI(Hurlersyn.)MPS II (Hunter syn.)MPSIV A(MorquioAsyn.)MPSV I(Marateaux-Lamysyn.)	α-L-iduronidaseIduronatesulfataseN-acetylgalactosamine6-sulfataseN-acetylgalactosamine4-sulfatase	AutosomalX-linkedAutosomalAutosomal	Laronidase (Aldurazyme™)/ 2003-FDA,EMA Idursulfase(Elaprase™)/2006-FDA;2007-EMA Elosulfase Alfa (Vimzim™)/ 2014-FDAGalsulfase(Naglazyme™)/2005-FDA;2006-EMA
Fabrydisease	α-galactosidase	X-linked	Agalsidaseα(Fabrazyme™)/2001-EMAAgalsidaseβ(Replagal™)/2003-FDA, EMA
Pompediseas	α-glucosidase	Autosomal	Aglucosidase(Myozyme™)/2006-FDA,EMA Aglucosidase(Lumizyme™)/2010-FDA
Gaucherdisease	β -glucocerebrosidase	Autosomal	Aglucerase (Ceredase™)/ 1991-FDA Imiglucerase(Cerezyme™)/1994-FDA; 1997-EMA Velaglucerase(VPRIV™)/2010-FDA,EMA Taliglucerase(Elelyso™)/2012-FDA
Lysosomalacidlipase deficiency	Lysosomal acid lipase	Autosomal	Sebelipase α (Kanuma™)/2015-FDA,EMA

MPS:mucopolysaccharidosis;**FDA**:U.S.FoodandDrugAdministration;**EMA**:EuropeanMedical Agency(**5**).

The intravenous (IV) administrations of approved enzymes in theLSDs 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 (**7**).

Besides, the major impediment to the development of enzymes asdrugs 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 thelack of such suitable animal models studies, the clinical trials have been performed directly in human patients(**8**).

Immune response and the IgG antibodies (Abs) generation againstthe 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 Abscan reduce the efficacy of ERTs via direct interfering with the enzyme activity (Fig. 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 lysosomalintegral membrane protein 2 (Limp2) receptors for Gaucher disease) that lead toblocking the cellular uptake and

lysosomal targeting of the enzyme (**9**).

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 immune modulation may induce tolerance and result in an optimized therapy (**10**).

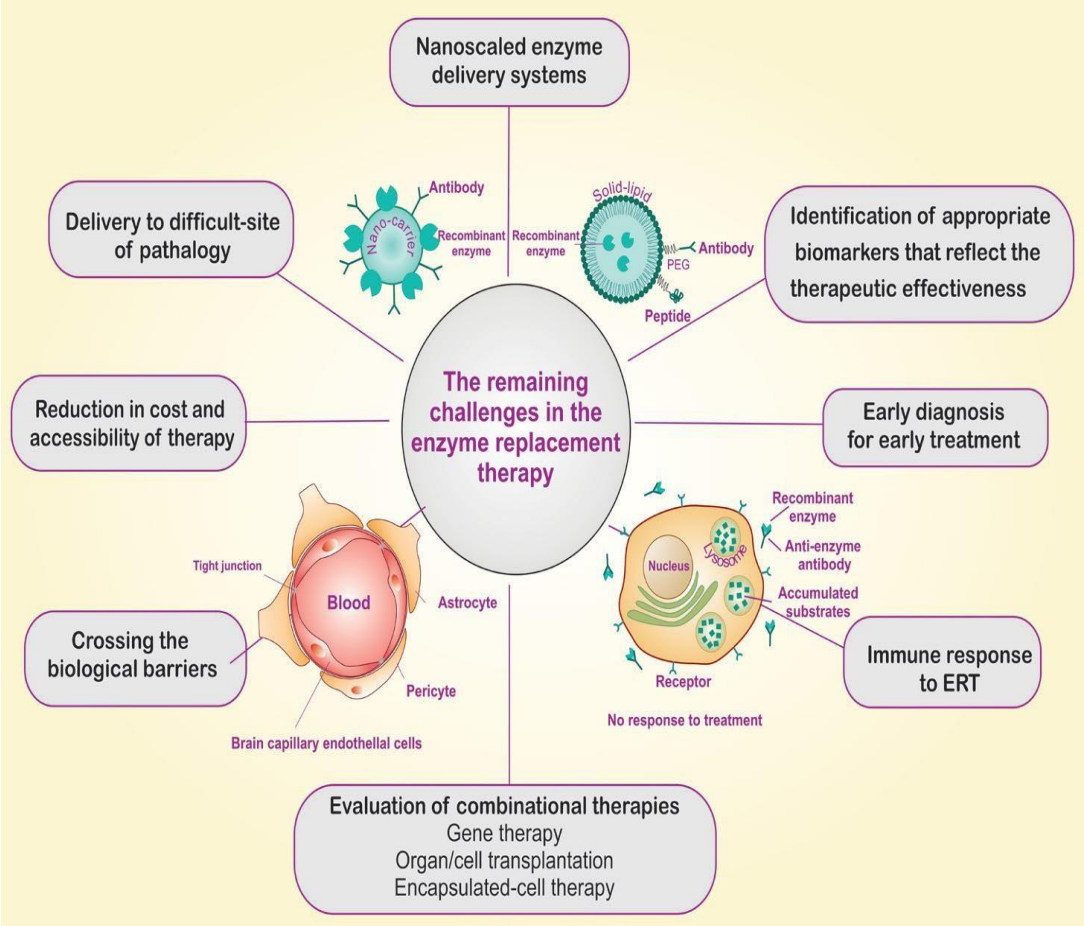

Fig.1: Schematic representation for the remain ing challenges in the enzyme replacement therapy.

Despite the therapeutic features of systemically-administered ERTs against LSDs, the bio distribution of the enzymes into the difficult sites ofpathology (especially into CNS, bone, cartilage, cornea, and heart) stillremains 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 wide spread 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, opticnerve)(**11**).

A clear evidence demonstrates that approximately 75% of LSDspatients with the neurological dysfunctions might not be treated with theavailable ERTs(**12**).

The blood-brain barrier (BBB), as one of the main obstacles in theconfrontation with the enzyme biodistribution, presents an impenetrable barrier between the bloodstream and the CNS, by which controls theinward and outward traverse of mostly hydrophilic enzymes utilized for the treatment of the LSDs selectively(**13**).

Further, as a result, ERT often fails to provide

the desired clinical outcomes, in large part due to its non-specific bio distribution, low bioavailability, and high degradation rate. Therefore, enhancing the therapeutic response by the development of safe and efficient targetedenzyme delivery systems (EDSs) may provide a promising alternative to the currently used treatments in LSDs(**14**).

Different methods have been developed to overcome the limited access of enzymes in to the difficult pathological sites. Based on the receptor-mediated lysosomal enzyme delivery system, it has been shownthat increasing the presence of M6P residues on the recombinant enzymeor enhancing the expression rate of the M6PRs on the target cells can improve the cellular uptake of the enzyme through active targeting mechanism (**15**).

In recent years, unprecedented attention has been paid to the development of enzyme-loaded nano systems (ENSs) using advanced nano biomaterials to enhance the efficacy of ERT while minimizing the side effects(**14**).

Different nano carriers can be utilized for engineering of nano scaled EDSs, including biodegradable nanomicelles, nanoliposomes, and polymer- and lipid-based nanoparticles(**13**).

Enzymeencapsulation canveilth eenzyme and its physicochemical characteristics, which caneradicate some of the key limitations of ERT,Includingundesiredimmunologicreactionsandbiodegradation.Itcanalsoprotecttherecombinantenzymesfromunwanted biological impacts, non-selective biodistribution, and improvethepharmacologicalresponsebyincreasing thedrugabsorption,controlled-releaseofenzymesupply,pharmacokinetics(PK),and pharmacodynamics(PD) properties(**16**).

Besides,targetedNSssuchaspolymeric/lipidicnanoparticles,decorated with homing agents (e.g., aptamers or antibodies), can also beused in crossing the biological barriers such as BBB and blood-ocular-barrier(BOB).Thus,theyarebeingconsideredasinnovativeandeffective approaches for the treatment of brain disorders (**12**).

In addition, encapsulated-cell therapy (ECT) along with anothertreatmentstrategy,hasbeenconsideredasaninterestingcombinedtherapymethodfor thetreatmentofLSDs(**17**).

One of the most pivotal advantages of ECT is to cover engineeredcellsbybiocompatibledevicesthatcanbe surgicallyimplantedintodifferent sites in the host body, especially in difficult-to-access sites suchasthebrainandeyetodeliverconstantamountsoftheenzymeforprolonged periods of time. In the case of the eye, because of the efficientblockades provided by both epithelial and endothelial cells, the targeteddelivery of drugs using advanced technologies and devices might providegreatclinicaloutcomes(**13**).

For example, thermos-responsive sol-gel injectable hydrogels offergreat prospective applications in drug delivery, cell therapy and tissueengineering(**18**).

It should be noted that some of these systems have mostly beenused in the preclinical stages and the clinical researches are essential forthe approval of their long-term safety and therapeutic outcomes. **(3).**

Based on these findings, it is envisioned that the currently usedERT modalities are not completely effective for all types of LSDs. WeenvisionthattheultimatetherapyofLSDsinthefuturewouldbebasedon the gene and/or cell therapy. For example, in the case of Krabbedisease,AAVrh10genetherapyhasbeenshowntoamelioratesthecentral and peripheral nervous system‘s pathologies in murine and caninemodelsof thisdisease(**19**).

At this point, perhaps the main challenge in the treatment of LSDsistodelivertherapeutic agentstothe diseasedcells/tissuepotentiallyusingnanoscaledEDSs.Variousmultimodalnanomedicineshavepreviously been developed against different types of diseases (**20**).

Further,weknowthatthesizeandmorphologyof NSscaninfluence the pharmacokinetics and final fate of cargo drug molecules(**21**).

Depending on the desired biological targets and impacts of theERTs, the use of passive and active targeting mechanisms should berationalized 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 traffic king mechanisms (e.g., clathrin-coated pits and membranous caveolae) in theLSDs should also be fully addressed. Lysosomal compartments, as acidicvesicular machineries of the cells, encompass over 60 different types ofhydrolases 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(**22**).

Interdigitating of lysosomal compartments with other cellular organelles seems to be largely dependent on the function of lysosomal ionchannels and transporters, dysregulation of which might attribute to thepathogenesis of LSDs. We still need to know the roles of cell membrane vesicular entities such as lipidrafts and cytoplasmicmacro molecules such as coat proteins in the vesicular trafficking of the cells. Likewise, totreat the LSDs, a number of issues in relevance to the genetics and/orepigenetics of the lysosomal compartments need to be understood. Taken all together, perhaps, it is the time to change our research perspective from are stricted out look towards a holistic approach. To this end, we need to understand the hallmarks of the LSDs and their biochemical andclinical aspects to be able to improve patients'well-being with moreeffective treatments. In this line, development of nanoscaled personalized medicines against LSDs appears to be an inevitable endeavor **(3).**

References:

1. **Desnick RJ, Schuchman EH**. Enzyme replacement therapy for lysosomal diseases: lessons from 20 years of experience and remaining challenges. Annu Rev Genomics Hum Genet. 2012;13:307–35. doi: 10.1146/annurev-genom-090711- 163739.
2. **Wenger DA, Luzi P, Rafi MA**. Lysosomal storage diseases:heterogeneous group of disorders. Bioimpacts. 2013;3:145–7.doi:10.5681/bi.2013.029.
3. **Safary, A., AkbarzadehKhiavi, M., Mousavi, R., Barar, J., & Rafi, M. A. (2018).** Enzyme replacement therapies: what is the best option?.BioImpacts : BI, 8(3), 153–157.
4. **MuroS**.Strategiesfordeliveryoftherapeuticsint othecentral nervous system for treatment of lysosomal storagedisorders.DrugDelivTranslRes.2012;2:1 69–86.doi:10.1007/s13346-012-0072-4.
5. **SolomonM,MuroS.**Lysosomalenzymereplace menttherapies:Historicaldevelopment,clinical outcomes,andfuture perspectives. Adv Drug Deliv Rev. 2017;118:109–34.doi:10.1016/j.addr.2017.05.004.
6. **Kirkegaard T**. Emerging therapies and therapeutic conceptsfor lysosomal storage diseases. Expert Opin Orphan Drugs.2013;1:385–404.doi:10.1517/21678707.2013.780970.
7. **Herder M.** What Is the Purpose of the Orphan Drug Act?PLoSMed. 2017;14:e1002191. doi:10.1371/journal.pmed.1002191.
8. **Boudes PF**. Clinical studies in lysosomal storage diseases:Past,present,andfuture.RareDis.2013 ;1:e26690.doi:10.4161/rdis.26690.
9. **LeSQ,KanSH,ClarkeD,SanghezV,EgelandM,Vo ndrak KN. et al.**A Humoral Immune Response Altersthe Distribution of Enzyme Replacement Therapy in MurineMucopolysaccharidosis Type I. MolTher Methods Clin Dev.2018;8:42–51.doi:10.1016/j.omtm.2017.09.008.
10. **KishnaniPS,DicksonPI,MuldowneyL,LeeJJ,Ros enberg A, Abichandani R. et al**. Immune response toenzyme replacement therapies in lysosomal storage

*e*ISSN1303-5150

diseasesandtheroleofimmunetoleranceinduction.MolGenetMetab.2016;117:66–83.doi:10.1016/j.ymgme.2015.11.001.

11. **Willoughby C, Ponzin D, Ferrari S, Lobo A, Landau K,OmidiY**.Anatomyandphysiologyofthehumaneye:effects of mucopolysaccharidoses disease on structure andfunction – a review. ClinExpOphthalmol. 2010;38:2–11.doi:10.1111/j.1442-9071.2010.02363.x.
12. **SalvalaioM,RigonL,BellettiD,D'AvanzoF,PederzoliF,RuoziB.etal**.TargetedPolymericNanoparticlesforBrainDeliveryofHighMolecularWeightMoleculesinLysosomalStorageDisorders.PLoSOne.2016;11:e0156452.doi:10.1371/journal.pone.0156452.
13. **Barar J, Rafi MA, Pourseif MM, Omidi Y**. Blood-brainbarrier transport machineries and targeted therapy of braindiseases. Bioimpacts. 2016;6:225–48. doi:10.15171/bi.2016.30.
14. **Schuh RS, Baldo G, Teixeira HF**. Nanotechnology appliedto treatment of mucopolysaccharidoses. Expert Opin DrugDeliv. 2016;13:1709–18. doi:10.1080/17425247.2016.1202235.
15. **Koeberl DD, Luo X, Sun B, McVie-Wylie A, Dai J, Li S.et al**. Enhanced efficacy of enzyme replacement therapy inPompediseasethroughmannose-6-phosphatereceptorexpressioninskeletalmuscle.MolGenetMetab.2011;103:107–12. doi:10.1016/j.ymgme.2011.02.006.
16. **TamVH,SosaC,LiuR,YaoN,PriestleyRD**.Nanomedicine as a non-invasive strategy for drug deliveryacross the blood brain barrier. Int J Pharm. 2016;515:331–42.doi:10.1016/j.ijpharm.2016.10.031.
17. **Baldo G, Quoos Mayer F, Burin M, Carrillo-Farga J,MatteU,GiuglianiR**.Recombinantencapsulatedcellsoverexpressingalpha-L-iduronidasecorrectenzymedeficiencyinhumanmucopolysaccharidosistypeIcells.CellsTissuesOrgans.2012;195:323–9.doi:10.1159/000327532.
18. **Fathi M, Barar J, Aghanejad A, Omidi Y**. Hydrogels foroculardrugdeliveryandtissueengineering.Bioimpacts.2015;5:159–64.doi:10.15171/bi.2015.31.
19. **Rafi MA, Rao HZ, Luzi P, Luddi A, Curtis MT, WengerDA**.IntravenousinjectionofAAVrh10-GALCaftertheneonatalperiodintwitchermicere sultsinsignificantexpression in the central and peripheral nervous systems andimprovementofclinicalfeatures.MolGenetMetab.2015;114:459–66. doi:10.1016/j.ymgme.2014.12.300.
20. **Ranjbar-NavaziZ,EskandaniM,Johari-AharM,NematiA,AkbariH,DavaranS.etal**.Doxorubicin-conjugatedD-glucosamine-andfolate-bi-functionalisedInP/ZnSquantumdotsforcancercellsimagingandtherapy.J Drug Target. 2018;26:267–77. doi:10.1080/1061186X.2017.1365876.
21. **Barar J**. Bioimpacts of nanoparticle size: why it matters?Bioimpacts. 2015;5:113–5.doi:10.15171/bi.2015.23.
22. **Xu H, Ren D**. Lysosomal physiology. Annu Rev Physiol.2015;77:57–80.doi:10.1146/annurev-physiol-021014-071649.

*e*ISSN1303-5150