Mini Review

J Mucopolysacch Rare Dis 2018;4(1):7-10
https://doi.org/10.19125/jmrd.2018.4.1.7
pISSN 2465-8936 · eISSN 2465-9452

JMRD
Journal of Mucopolysaccharidosis and Rare Diseases

Enzyme Replacement Therapy for Lysosomal Storage Disease in Indonesia

Damayanti Rusli Sjarif and Cut Nurul Hafifah

Department of Pediatrics, Cipto Mangunkusumo Hospital, Faculty of Medicine, University of Indonesia, Jakarta Pusat, Indonesia

Rare diseases are life threatening or chronically debilitating diseases with a low prevalence (less than 2,000 people in a population), which includes lysosomal storage diseases. These diseases are often seen as unimportant especially in developing countries, such as Indonesia, due to small number of patients. National Rare Disease Center in Indonesia was pioneered almost 20 years ago and officially established in 2017 by the Indonesian Minister of Health. Lysosomal storage disease become the most commonly found inborn errors of metabolism (IEM) in Indonesia due to easily accessible diagnostic facilities. Currently there are 7 patients receiving ERT in this mixed-donation scheme, one patient with Gaucher disease and 6 patients with MPS type II. Few challenges for ERT in Indonesia include importation through special access scheme, preparation of ERT infusion in intensive care settting, and cost of treatment. Even with limited resources, healthcare professionals in Indonesia have been giving the best care possible for rare disease patients, especially to provide diagnostic facilities through collaboration and treatment options for treatable rare diseases. Improvements in care for rare disease patients are still needed.

Keywords: Mucopolysaccharidoses, Enzyme replacement therapy, Indonesia, Rare diseases

Introduction

Rare diseases are life threatening or chronically debilitating diseases with a low prevalence and a high level of complexity. Different countries may have different definition for rare diseases[1]. Indonesia defines rare disease as a disease affecting less than 2,000 people in population.

Rare diseases are often seen as unimportant especially in developing countries due to small number of patients, but collectively these diseases are quite common. Over 8,000 different rare diseases have been identified to date, affecting the lives of millions in Asia[2]. It is estimated that around 22 million people in Indonesia is affected by various rare diseases[3]. A few of these treatable rare diseases are inborn errors of metabolism (IEM), including lysosomal storage diseases (LSD). However, only few health centers in Indonesia are able to provide care and treatment for these diseases. The objective of this article is to introduce what has been done in Indonesia regarding the care of rare disease, including LSD and its treatment.

Rare Disease in Indonesia

Indonesia is a middle income country with a population of 252.5 million in 2014[4]. National Rare Disease Center in Indonesia was pioneered almost 20 years ago and officially established in 2017 by the Indonesian Minister of Health[5]. Patients with rare diseases from all over Indonesia come to our center to find diagnosis and treatment in this center. They usually come to the outpatient clinic and undergo clinical and laboratory examination. Enzyme assays for diagnostic confirmation of LSD are performed in Taiwan in collaboration with National Taiwan University Hospital Indonesia (NTUH). Thus, lysosomal storage disease become the most commonly found IEM in Indonesia due to readily accessible diagnostic facilities. There are over 50 patients from all

Received June 2, 2018; **Revised** June 10, 2018; **Accepted** June 11, 2018
Correspondence to: Damayanti Rusli Sjarif
Department of Pediatrics, Cipto Mangunkusumo Hospital, Faculty of Medicine, University of Indonesia, Jl. Diponegoro no. 71, Jakarta Pusat 10430, Indonesia
Tel: +62-21-3915715, Fax: +62-21-3907743, E-mail: ukk.npm.idai@gmail.com

over Indonesia with this form of IEM (Table 1).

Enzyme Replacement Therapy in Indonesia

Lysosomal storage disease is now treatable with several treatment options, such as enzyme replacement therapy (ERT), substrate reduction therapy (SRT), chaperone therapy, and gene therapy. Enzyme replacement therapy was one of the first treatment developed for LSD. The first enzyme replacement therapy was developed for Gaucher disease by Dr. Roscoe Brady in 1973. This ERT was then approved by US Food and Drug Administration (FDA) in 1991. Enzyme replacement therapy (ERT) has now been the mainstay for many lysosomal storage disease since then.

Table 1. Five most common rare disease in the National Rare Disease Center

Type of rare diseases	Number
Mucopolysaccharidosis	33 (Indonesia 43)
Glycogen storage disease	11
X-linked adrenoleukodystrophy	9
Gaucher disease	8
Niemann pick disease	7

There are at least nine lysosomal storage disease (LSD) which can be treated by ERT, including Gaucher disease, mucopolysaccahridosis type (MPS) I (Hurler syndrome), MPS type II (Hunter syndrome), MPS type IVa (Morquio syndrome), MPS type VI (Maroteaux-Lamy syndrome), Pompe disease, and Fabry disease[6]. The latest ERT approved by FDA in 2017 were Brineura for late infantile neuronal ceroid lipofuscinosis type 2 (Batten disease) and Mepsevii for MPS type VII (Sly syndrome)[7,8].

Once the diagnosis of LSD and available treatment is confirmed, patient in Indonesia either fund their own treatment or be enrolled in mixed-donation scheme (for Gaucher disease, MPS type I, II, Fabry disease, and Pompe disease). In this mixed-donation scheme, the treatment is partially covered by the national insurance and the drugs are available from donation through Sanofi-Genzyme humanitarian program.

The ERT was performed in intensive care setting to prevent risk of severe allergic reaction. Every patient stays overnight after the enzyme infusion for the first 3 months. If they do not experience any allergic reaction, they come regularly for 4 hourly ERT infusions. Our multidisciplinary team, who manage patients with rare diseases, includes paediatrician and their subspecialties, radiologists, ENTs, physical therapists, anesthesiologists, psychiatrists, intensive care nurses, and pharmacists.

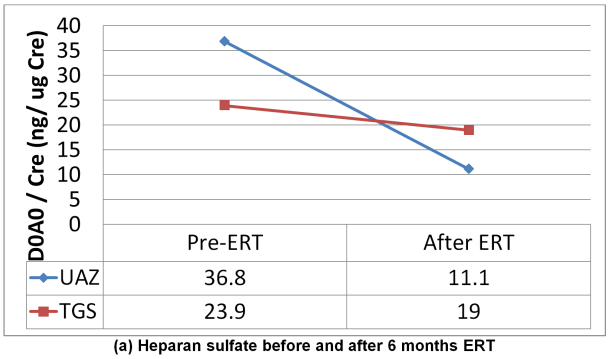
Table 2. Infusion protocol for enzyme replacement therapy in Indonesia

Standard infusion protocol			Infusion protocol after severe allergic reaction		
Time	Infusion rate	Prophylactic allergic medication	Time	Infusion rate	Prophylactic allergic medication
12 hours before ERT		Antihistamine (po) & steroid (po)	12 hours before ERT		Steroid (po) & H_2 antagonist (po)
1 hour before ERT		Antihistamine (po) & steroid (po)	3 hours before ERT		Steroid (po) & antihistamine (iv)
0–30 minutes	3 ml/hour		0–60 minutes	3 ml/hour	H_2 antagonist (po)
30–60 minutes	6 ml/hour		60–120 minutes	6 ml/hour	
60–90 minutes	12 ml/hour		120–180 minutes	12 ml/hour	
90–120 minutes	18 ml/hour		180–240 minutes	18 ml/hour	Steroid (po) & antihistamine (iv)
120–150 minutes	24 ml/hour		240–300 minutes	24 ml/hour	
150–180 minutes	30 ml/hour		300–360 minutes	30 ml/hour	
After 180 minutes	36 ml/hour		After 360 minutes	36 ml/hour	
			3 hours after ERT		Steroid (po) & antihistamine (iv)
			7 hours after ERT		H_2 antagonist (po)
			9 hours after ERT		Steroid (po) & antihistamine (iv)

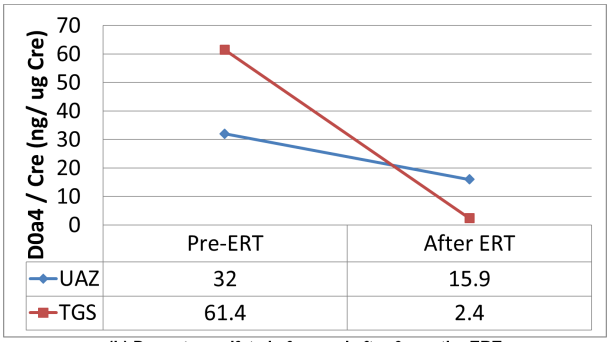
ERT, enzyme replacement therapy; po, per oral; iv, intravenous.

Currently there are 1 MPS IVA patient receiving ERT in private scheme, while 7 patients receiving ERT in this mixed-donation scheme. Patients in the later scheme includes one patient with Gaucher disease and 6 patients with MPS type II. The infusion protocol for ERT is described in Table 2. Patients are given prophylactic antihistamine and steroid 12 hours and 1 hour before treatment. The results of ERT in 2 MPS patients who have been on treatment for more than 6 months are very good, proven by clinical improvement and urinary glycosaminoglycans (GAG) reduction (Fig. 1). However one MPS type II patient experienced severe allergic reaction during idursulfase alfa infusion. This patient then received prophylactic antihistamine and steroid more rigorously every 6 hours during his infusion and a desensitization protocol was developed. Even after the prevention measures has been taken, the patient still experienced severe allergic reaction, it was then decided to stop further ERT for this patient.

Starting ERT in our center was a long and winding journey of preparation. We faced a few obstacles along the way. The first problem was these enzyme replacement therapies have not been registered in Indonesia and require importation through special access scheme. This process takes approximately 3 months for each enzyme importation and must be repeated every time we want to import. Second challenge is anticipating allergic reaction. Intensive care is not readily available in our center due to only 10 PICU beds are available. Therefore in the event of severe allergic reaction due to ERT, we cannot easily transfer the patient to the PICU. To prevent catastrophic event following ERT, first we have to prepare a special room equipped with back-up ventilator and intensive care facilities. Another problem that we had to experience was the cost of treatment was very expensive (around Rp 6 billion per year for treatment of MPS IVa. Above this cost, we also have to worry about duty of imported goods as much as 10% of the total cost. This was one of our main concerns during our discussion with the government officials in the commemoration of The First Indonesia Rare Disease Day in 2016. We managed to receive tax exemption from the Directorate General of Customs and Excise through our collaboration with patient support group.



(a) Heparan sulfate before and after 6 months ERT



(b) Dermatan sulfate before and after 6 months ERT

Fig. 1. Results of ERT in 2 MPS patients receiving idursulfase alfa.

Conclusions

Even with limited resources, healthcare professionals in Indonesia have been giving the best care possible for rare disease patients, especially to provide diagnostic facilities through collaboration and treatment options for treatable rare diseases. Improvement in care for rare disease patients, such as developing its own laboratory facilities and advocating government for reimbursement, are very much needed.

References

1. Franco P. Orphan drugs: the regulatory environment. Drug Discov Today 2013;18:163-72.
2. Shafie AA, Chaiyakunapruk N, Supian A, Lim J, Zafra M, Hassali MAA. State of rare disease management in Southeast Asia. Orphanet J Rare Dis 2016;11:107.
3. Health Grades. Statistics by country for rare diseases. Right diagnosis 2018. [Internet]. Available from: http://www.rightdiagnosis.com/r/rare_diseases/stats-country.htm.
4. Indonesia Central Bureau of Statistics. Perkiraan Penduduk Beberapa Negara, 2000-2014 (article in Indonesian). Indonesia Central Bureau of Statistics; 2018 [Internet]. Available from: https://www.bps.go.id/dynamictable/2015/10/07/960/perkiraan-penduduk-beberapa-negara-2000-2014.html.
5. Indonesia National Rare Disease Centre. Rare Disease Day 2018 Fact Sheet. 2018.
6. Parenti G, Pignata C, Vajro P, Salerno M. New strategies for the treatment of lysosomal storage diseases (Review). Int J Mol Med 2013;31:11-20.
7. Food and Drugs Administration. FDA approves first treatment for a form of Batten disease [Internet]. FDA [cited 2018 May 15]. Available from: https://www.fda.gov/NewsEv-

ents/Newsroom/PressAnnouncements/ucm555613.html.
8. Food and Drugs Administration. FDA approves treatment for rare genetic enzyme disorder [Internet]. FDA [cited 2018 May 15]. Available from: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm585308.html.