Best Practice & Research Clinical Endocrinology & Metabolism 29 (2015) 205–218

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

7

The attenuated/late onset lysosomal storage disorders: Therapeutic goals and indications for enzyme replacement treatment in Gaucher and Fabry disease

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MeSH Keywords:
Gaucher disease
Fabry disease
enzyme replacement therapy
therapeutic goals
attenuated phenotypes
late onset

Enzyme replacement therapies have been developed and authorized for commercial use for six different lysosomal storage disorders. For Gaucher disease, Fabry disease and mucopolysaccharidosis type 1, disease-specific treatments have been available for more than a decade. Although long term follow-up data are still sparse, therapeutic goals for patients with Gaucher disease and Fabry disease have been formulated and published for both adults and children. Without adaptation or modification, these goals are often applied in clinical research and in routine patient care across the entire phenotypic spectrum of disease, although in practice, patients commonly manifest high variability in clinical presentation and course of the illness. In this context, establishing goals for the follow-up and treatment of late onset/attenuated phenotypes is particularly challenging. In this chapter, we review current therapeutic goals for Gaucher disease and Fabry disease and discuss approaches for those with attenuated disease manifestations.

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http://dx.doi.org/10.1016/j.beem.2014.08.006
1521-690X/

Introduction

Lysosomal storage diseases (LSD's) are caused by defects in lysosomal hydrolases or activator proteins, resulting in lysosomal accumulation of substrates, with subsequent cellular dysfunction with or without inflammatory responses (see chapter 1). The diversity of these disorders is striking, ranging from severe multisystem disease and early death in infancy to asymptomatic single organ involvement in elderly individuals. More than 50 different LSD's have been described, each with typical features [1]. However, most LSD's encompass a wide range of phenotypes. For example, Gaucher disease may present in early childhood with neurological disease and early death, with severe hepatosplenomegaly without neurological disease, or with asymptomatic splenomegaly in an adult [2]. Alglucerase for Gaucher disease, approved in the early 1990s, was the first lysosomal enzyme replacement therapy (ERT) in non-investigational clinical use [3]. The basic concept is that purified enzyme, after intravenous infusion, is internalized by target cells and transported to the lysosome, where it can "replace" or, more appropriately "supplement" the deficient enzyme. This proof of concept in Gaucher disease stimulated development of ERT for other LSD's (Table 1) [4]. Because LSD phenotypes typically encompass a spectrum of clinical severities, a particular challenge is to identify patients who appear to be mildly affected, to decide when treatment is indicated and to define appropriate therapeutic goals. Because the characteristics of natural disease progression of the disease are usually better known for patients with early onset variants than for those with late onset/attenuated disease, the published general guidelines and local protocols that address which patients to treat and what to expect are not necessarily relevant for patients with milder phenotypes. Here, we describe the clinical disease spectrum for Gaucher disease and Fabry disease, the LSDs with the longest follow-up time, and discuss how proposed therapeutic goals can be applied to patients with attenuated phenotypes.

Gaucher disease

General description

Gaucher disease (GD) is an autosomal recessive glycosphingolipid storage disorder that is characterized by deficient lysosomal glucocerebrosidase activity and intracellular accumulation of glucosylceramide and other glycosphingolipids particularly in tissue macrophages [2]. There are three major phenotypic variants based on the presence or absence of early onset central nervous system manifestations. Type 2 GD, 1% of all GD patients with an estimated prevalence of 1/150,000, manifests at birth or early in infancy. Affected infants have a very short life expectancy of 2–3 years or less. Type 3 GD, with considerably longer survival, accounts for about 5% of all known patients with GD. It is panethnic with patient clusters in Northern Europe, Egypt, and East Asia [2]. Manifestations may include oculomotor apraxia, myoclonic seizures, progressive cognitive and motor impairment and severe systemic involvement including kyphosis and life-threatening pulmonary disease. Because the

Table 1
Pharmacologic products for Gaucher disease and Fabry disease: authorized or in advanced stage of development.

Disorder	Enzyme defect	Enzyme replacement therapy	Company	Year of marketing authorization USA/EU
Gaucher disease	Glucocerebrosidase	Imiglucerase	Genzyme, a Sanofi Company	1994/1995
		Velaglucerase	Shire HGT	2010/2010
		Taliglucerase	Pfizer/Protalix	2012/Refused[a]
		Miglustat	Actelion	2003/2002
		Eliglustat	Genzyme, a Sanofi Company	2014/Under final review
Fabry disease	Alfa-galactosidase A	Agalsidase beta	Genzyme, a Sanofi Company	2001/2001
		Agalsidase alfa	Shire HGT	Refused/2001
		Amigal	Amicus Therapeutics, Inc.	in clinical trial

[a] Marketing authorization of taliglucerase was not recommended by the EMA, despite a positive risk-benefit assessment, due to prior marketing authorization of Shire's velaglucerase alfa for the same condition, which received orphan drug designation, implicating market exclusivity. (Reference: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002250/WC500135112.pdf).