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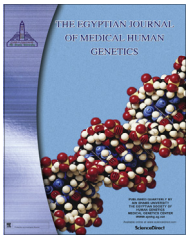

REVIEW

# Treatment options for patients with Gaucher disease

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**Abstract** Gaucher disease is the most common lysosomal storage disorder due to deficiency of ß-glucocerebrosidase. Since the introduction of Ceredase in 1991, enzyme replacement therapy has been the mainstay of treatment with its major disadvantage of long life dependency on biweekly IV therapy. It was more than a decade later when the substrate reduction therapy – an oral treatment – was approved for Gaucher disease. Future therapeutic modalities will include pharmacological chaperon and possibly gene therapy.

The aim of this review is to high light the current and future treatment options for patients with Gaucher disease and to compare their effects and side effects.



**Contents**



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## 1. Introduction

Gaucher disease (GD) is one of the most common lysosomal storage disorders with prevalence of 1 in 75,000 live births worldwide [1]. It is due to inherited (autosomal recessive) deficiency of lysosomal enzyme ß-glucocerebrosidase (GC). This deficiency leads to accumulation of glucocerebroside in lysosomes of the cells of the macrophage–monocyte lineage and subsequently leads to anemia, thrombocytopenia, hepatomegaly, splenomegaly, bone infarcts, aseptic necrosis of bones and osteoporosis [2].

However, some manifestations cannot be explained by glucocerebroside storage alone as immunologic abnormalities, increased prevalence of malignancy, neurologic abnormalities, cardiac valve manifestations and hypertension [3].

GD is classified into three main types: type I (adult type) which is the most common type. The age of onset and rate of progression varies widely ranging from asymptomatic disease to disability in toddlers. It lacks involvement of the brain and the so called non-neuropathic GD although some patients and carriers are risk prone for parkinsonism in adult life [4].

Type II (infantile type or acute neuropathic) which has as infantile onset of severe CNS involvement and death in early childhood. Type III has mild CNS involvement in early childhood or adolescent and has an indolent coarse. However, in Asian and Arab countries including Egypt, type III is the commonest type [3,5]. A perinatal lethal form and a cardiovascular form have been also described. [6,7]

Diagnosis can be confirmed by high chitotriosidase level, low GC enzyme activity and mutation analysis and more than 300 mutations have been identified in this autosomal recessive disease [8,9].

The basic goals of treatment are elimination or improvement of symptoms, prevention of irreversible complications, and improvement in the overall health and quality of life. An additional goal in children is optimization of growth [10,11].

## 2. Aim of review

The aim of this review is to high light the current and future treatment options for patients with Gaucher disease and to compare their effects and side effects.

## 3. Therapeutic options

### *3.1. Enzyme replacement therapy (ERT)*

Macrophage-targeted enzyme replacement therapy (ERT) has long been the standard of care. It is not a cure for GD, i.e.: it does not repair the underlying genetic defect but it can reverse and prevent numerous manifestations of GD type 1 [12–14].

The goal of ERT is to provide sufficient amount of enzyme to allow processing of accumulated material for patients including children with GD who manifest signs and symptoms [10]. ERT is well established as being effective in reducing hematologic, visceral and bone symptoms. Early treatment may prevent development of irreversible pathology. Treatment also improves growth and reduce the impact of disease on physical and psychological development However, it comes with a therapeutic burden due to the need for regular life-long IV therapy as well as high cost [11].

In order to establish the severity of disease and to tailor the initial and maintenance ERT dose, a classification in high- and low-risk type 1 GD patients has been suggested by a panel of experts [15].

Response to ERT was documented by international collaborative Gaucher group (ICGG) registry with decreased liver and spleen volumes and increase in hemoglobin levels and platelet counts within 6 months of therapy [5,16]. However, GD I involvement beyond the monocyte/macrophage system may underlie unmet treatment needs with respect to skeletal, pulmonary, and immune manifestations [17]. Likewise, the CNS manifestations of type II and III GD do not respond well to ERT due to the inability of exogenous enzyme to cross the BBB [18].

The standard dose is 60 units/kg every two weeks and can be individualized according to response and requirements. Higher doses may be needed in the initial stage of GD type III and lower doses may be given as a maintenance dose in GD type I [19].

ERT includes imiglucerase (Cerezyme), velaglucerase alfa (VPRIV), and taliglucerase alfa (Elelyso). Historically, most patients received the recombinant enzyme imiglucerase [20]. All are recombinant GC enzyme preparations based on the human gene sequence but differ in the cell type involved in their production: Imiglucerase is generated from Chinese Hamster ovary cells, velaglucerase alfa is generated from human fibroblast-like cell line and taliglucerase alfa is generated from a carrot cell line. Each formulation is modified to expose the alpha-mannosyl (carbohydrate) residues for enhanced uptake by the macrophage:

#### *3.1.1. Imiglucerase and velaglucerase alfa*

Imiglucerase and velaglucerase alfa are produced in different mammalian cell system and require production glycosylation modifications to expose terminal alpha-mannose residues, which are needed for mannose receptor-mediated uptake by target macrophages: such modifications add to production costs [21]. Side effects are few including pruritis which can be controlled by antihistaminics. Antibody formation has been