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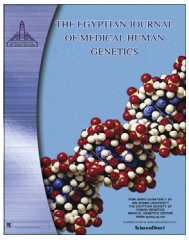

REVIEW

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

reported in imiglucerase more than velaglucerase (10–15% versus 1%) but in most cases the patient is asymptomatic [22].

3.1.2. Taliglucerase (Elelyso)

It is a plant cell expressed enzyme using carrot root cell cultures using recombinant DNA technology. It is approved by FDA on May 1st, 2012 for ERT in adults with symptomatic GD. It does not require additional processing for post-production glycosidic modifications [21]. It is a safe and efficacious initial therapy in adults and pediatric patients with symptomatic GD as well as for those previously treated with Imiglucerase. It can be used also for treatment of hematological manifestations of GD type III [23]. It is administered in a dose of either 30 units/kg or 60 units/kg in type I GD. It reduces the spleen and liver volumes by 29–40% and improves platelet counts and hemoglobin levels. It is also effective in maintaining spleen and liver volumes, platelet counts, hemoglobin levels as well as biomarker levels over a 6–9 month evaluation period in type I GD switched from imiglucerase [21,23].

The most common side effects reported were transient and included infusion reactions, allergic reactions and anaphylaxis. Infusion reactions occur within 24 h of infusion in 44–46% of treated cases [24]. These include headache, chest pain or discomfort, weakness, fatigue, skin redness, increased blood pressure, back pain, joint pain and flushing. Allergic reactions includes angioedema, wheezing and hypotension. Anaphylaxis has been observed in some patients during infusion. In 10% of cases urinary tract infection, common clod like symptoms, arthralgia, headache were also observed. Hypersensitivity reaction occurred and included swelling under the skin, flushing, redness, rash, nausea, vomiting and chest tightness [23,24].

3.1.3. Alglucerase (Ceredase)

This is a placental derived macrophage-targeted GC first introduced in 1991. It leads to reduction in hepatosplenomegaly, improvement of hypersplenism, decreased biomarkers and amelioration of bone pain, it has a reliable safety profile. The original dosage used was 60 units/kg of body weight (BW) every other week (the high-dose regime), which is still the most frequently used in clinical trials and accordingly highly promoted by the manufacturers. [25–28].

3.2. Oral substrate reduction therapy (SRT)

The goal of SRT is to minimize the accumulation of excess material (glucosylceramide) within cells by inhibiting the appropriate synthetic enzyme (glucosylceramide synthase). This will lead to decreased production of dangerous lipids and the ability of the residual enzyme to establish a new steady state [29] and so it (Miglustat) was approved to treat mild to moderate type I GD. Although it can cross the blood–brain barrier, it proved to be non effective in neuropathic forms of GD type III [30].

Reported side effects included significant diarrhea, weight loss, tremors and paresthesia [31]. These sides effects were overcomed by a recent FDA approved drug, Eliglustat, a novel agent with better safety profile and higher efficacy. It does not inhibit intestinal enzymes and so does not cause diarrhea [32]. Also, it has less neurological side effects because it is immediately transported back out of the CNS by a multidrug transporter [33]. This also suggests that eliglustat would have little utility for treating neuronopathic forms of GD [32,34].

A statistically significant reduction in spleen and liver volumes as well as significant increase in hemoglobin levels and platelet counts were documented after 9 months of treatment with Eliglustat. Moreover, no patient discontinued treatment because of side effects in the recently published report of phase three clinical trial [35].

The choice of therapy between different drugs of ERT or SRT should depend on many factors including symptoms, patient's age and need, preference and availability of each type of therapy. Currently, Eliglustat is approved for patients older than 18 years while ERT can be given to both children and adults [36].

3.3. Pharmacological chaperon therapy (PCT)

Pharmacological chaperon therapy (PCT) are competitive reversible active site inhibitors that selectively bind and stabilize the mutant misfolded GC enzyme, thus prevent endoplasmic reticulum (ER), associated degradation in proteosome, restore enzymatic activity and clear stored substrate [37]. It also facilitates trafficking of the enzyme to the lysosomes, and have the potential to attenuate the unfolded protein response and prevent ER stress that can lead to apoptosis and inflammatory response [38]. This approach is especially applicable in GD because only a modest increase in residual GC should be sufficient to ameliorate the phenotype. Another advantage is that PCT can cross the BBB and can be orally available. Combination of ERT and PCT should enhance the effect of ERT, since PCT assists in trafficking of the endogenous mutant GC out of the ER to lysosomes where they may have some residual activity. PCT can also stabilize the recombinant enzyme and increase its half-life in the circulation [39]. The fact that PCs are less expensive, can be given orally and usually cross the BBB, opens up the possibility of treating Type II and Type III GD patients with neurological involvement that are not responsive to ERT.

3.3.1. Isofagamine (IFG)

The pharmacological chaperon iminosugar isofagamine (IFG), have shown these properties in cultured fibroblasts in vivo. This iminosugar can bind, stabilize and promote lysosomal trafficking and increase activity of N370S mutant form of the enzyme GC in cultured fibroblasts in vivo as well as in mice for GCase mutations: V394L, D409H, or D409V [37,40]. IFG can also increase the lysosomal activity of L444p mutant form of GC enzyme in cells and tissues. IFG has also a broad tissue distribution including access to the CNS and multiple tissues thus merit therapeutic option for patients with neuropathic and non-neuropathic GD [41].

3.3.2. Ambroxol

Ambroxol, a mucolytic agent, is also a potential pharmacologic GBA chaperone [42]. It has an advantage of its long history use in humans and its very low level of toxicity.

3.3.3. Bicyclic L-idonojirimycin

Bicyclic L-idonojirimycin derivative has been suggested as a potential therapeutic option acting as PCT for patients with homozygous L444P mutations [43].

Reduced activity of glucocerebrosidase enzyme has been associated with mitochondrial dysfunction. Supplementation of Coenzyme Q10 (CoQ), together with PCT have resulted in restoring enzyme folding and trafficking in fibroblasts. It also improved mitochondrial function and the associated pathophysiological alterations [44].

3.4. Bone marrow (BM) transplantation

For GD and other lysosomal disorders, wild-type donor BM transplantation has been used because monocytes from the peripheral blood can migrate across the BBB and become CNS microglial cells that could affect metabolic cross correction. BM or stem cell transplantation has not been effective for the CNS disease because of the lack of secretable enzyme [45]. Induced pluripotent stem cells are an attractive alternative for generating either hematologic progenitor cells or neural progenitor cells for direct cellular and/or enhanced gene therapy [46].

3.5. Symptom management and care

This includes various pain reduction therapies, blood transfusions, orthopedic surgery for bone and joints and rarely splenectomy. We should not forget routine follow-up for all treated patients, children, and untreated adult patients with unstable parameters; and annual evaluations for adults with stable disease [47].

3.5.1. Partial or total splenectomy

Persistent thrombocytopenia in GD patients treated with ERT for over 4 years relates to refractory splenomegaly. Therefore, life-threatening thrombocytopenia may be one of the few circumstances where splenectomy may still be justified in GD [48].

3.5.2. Transfusion of blood products

Transfusion of blood products for severe anemia and bleeding. Anemia and clotting problems unresponsive to ERT should prompt investigations for an intercurrent disease process. Evaluation by a hematologist is recommended prior to any major surgical or dental procedures or parturition [49].

3.5.3. Bisphosphonate: it can be effective and safe

The use of biphosphonates can be an effective and safe mean to increase bone density and prevent complications [50]. Supportive management for bone pains or bone crises is frequently required, and orthopedic surgery may be necessary in cases of pathologic fractures or osteonecrosis [51].

3.6. Psychological care

Psychological care to reduce mental and emotional impact of disease on patients and their families.

3.7. Professional genetic counseling

Professional genetic counseling to help parents to prevent birth of other affected children by explaining that the disease is an autosomal recessive disease with 25% recurrence risk and 75% chance to have normal children in each pregnancy. Prenatal diagnosis by enzyme assay or molecular studies are both available.

3.8. Gene therapy

Limited trials on GD mouse models showed an evidence for the possibility of developing safe and efficient conditioning protocols for diseases that require only a low level of normal or gene-corrected cells for a permanent and beneficial therapeutic outcome. Although some enzyme has been produced by transduced cells, enzyme production does not appear to be sustained and therefore does not result in a permanent cure. It is anticipated that transduced cells would not have a proliferative advantage over uncorrected cells. Furthermore, it is unlikely that significant metabolic cross-correction would occur as only small amounts of enzyme are secreted into the circulation [52].

In conclusion, several options for the treatment of GD are currently available, the choice of which will depend on many factors including age of patient, availability of drug, cost and side effects. Future therapies will also be offered in the near future with potential efficiency in crossing the BBB and therefore more effective in the neuropathic form.

Conflict of interest

The authors declare no potential conflicts of interests with respect to the authorship and/or publication of this article.

References

[1] Deegan PB, Cox TM. Imiglucerase in the treatment of Gaucher disease: a history and perspective. Drug Des Dev Ther 2012;6:81–106.
[2] Rosenbloom BE, Weinreb NJ. Gaucher disease: a comprehensive review. Crit Rev Oncog 2013;18(3):163–75.
[3] Zimran A. How I treat Gaucher disease. Blood 2011;118(6):1463–71.
[4] Sidransky E. Gaucher disease and parkinsonism. Mol Genet Metab 2005;84:302–4.
[5] Khalifa AS, Tantawy AA, Shawky RM, Monir E, Elsayed SM, Fateen E, et al. Outcome of enzyme replacement therapy in children with Gaucher disease: The Egyptian experience. Egypt J Med Human Genet 2011;12(1):9–14.
[6] Orvisky E, Park JK, LaMarca ME, Ginns EI, Martin BM, Tayebi N, et al. Glucosylsphingosineaccumulation in tissues from patients with Gaucher disease: correlation with phenotype and genotype. Mol Genet Metab 2002;76:262–70.
[7] Bohlega S, Kambouris M, Shahid M, Al Homsi M, Al Sous W. Gaucher disease with oculomotor apraxia and cardiovascular calcification (Gaucher type IIIC). Neurology 2000;54:261–3.
[8] Hruska KS, LaMarca ME, Scott CR, Sidransky E. Gaucher disease: mutation and polymorphism spectrum in the glucocerebrosidase gene (GBA). Hum Mutat 2008;29(5):567–83.
[9] Zhang WM, Tang NL, Meng Y, et al. An analysis of mutations causing Gaucher disease in Chinese population [in Chinese]. ZhonghuaYi Xue Za Zhi 2009;89(48):3397–400.
[10] Pastores GM, Weinreb NJ, Aerts H, et al. Therapeutic goals in the treatment of Gaucher disease. Semin. Hematol. 2004;41:4.
[11] Grabowski GA, Andria G, Baldellou A, et al. Pediatric non-neuronopathic Gaucher disease: presentation, diagnosis and assessment. Consensus statements. Eur J Pediatr 2004;163:58.
[12] Barton NW, Brady RO, Dambrosia JM, et al. Replacement therapy for inherited enzyme deficiency–macrophage-targeted

glucocerebrosidase for Gaucher's disease. N Engl J Med 1991;324:1464–70.
[13] Chen M, Wang J. Gaucher disease: review of the literature. Arch Pathol Lab Med 2008;132(5):851–3.
[14] Grabowski G, Kolodny E, Weinreb N, et al. Gaucher disease: phenotypic and genetic variation. In: Valle D, Beaudet AL, Vogelstein B, Kinzler KW, Antonarakis ES, Ballabio A, editors. The metabolic and molecular bases of inherited disease. New York, NY: McGraw Hill; 2011.
[15] Andersson HC, Charrow J, Kaplan P, et al. Individualization of long-time enzyme replacement therapy for Gaucher disease. Genet Med 2005;7(2):105–10.
[16] Weinreb NJ, Charrow J, Andersson HC, et al. Effectiveness of enzyme replacement therapy in 1028 patients with type 1 Gaucher disease after 2 to 5 years of treatment: a report from the Gaucher Registry. Am J Med 2002;113:112–9.
[17] Mistry PK, Liu J, Yang M, Nottoli T, McGrath J, Jain D, et al. Glucocerebrosidase gene-deficient mouse recapitulates Gaucher disease displaying cellular and molecular dysregulation beyond the macrophage. Proc Natl Acad Sci U S A 2010;107:473–8.
[18] Lebowitz JH. A breach in the blood–brain barrier. Proc Natl Acad Sci U S A 2005;102:14485–6.
[19] Hollak CE, Hughes D, van Schaik IN, Schwierin B, Bembi B. Miglustat (Zavesca) in type 1 Gaucher disease: 5-year results of a post-authorisation safety surveillance programme. Pharmacoepidemiol Drug Saf 2009;18(9):770–7.
[20] Sidransky E, Pastores GM, Mori M. Dosing enzyme replacement therapy for Gaucher disease: older, but are we wiser? Genet Med 2009;11(2):90–1.
[21] Grabowski GA, Golembo M, Shaaltiel Y. Taliglucerase alfa: an enzyme replacement therapy using plant cell expression technology. Mol Genet Metab 2014;112:1–8.
[22] Starzyk K, Richards S, Yee J, Smith SE, Kingma W. The long-term international safety experience of imiglucerase therapy for Gaucher disease. Mol Genet Metab 2007;90:157–63.
[23] Zimran A, Gonzalez-Rodriguez DE, Abrahamov A, Elstein D, Paz A, Brill-Almon E, et al. Safety and efficacy of two dose levels of taliglucerase alfa in pediatric patients with Gaucher disease. Blood Cells Mol Dis 2015;54:9–16.
[24] Pastores GM, Petakov M, Giraldo P, Rosenbaum H, Szer J, Deegan PB, et al. A Phase 3, multicenter, open-label, switchover trial to assess the safety and efficacy of taliglucerase alfa, a plant cell-expressed recombinant human glucocerebrosidase, in adult and pediatric patients with Gaucher disease previously treated with imiglucerase. Blood Cells Mol Dis 2014;53:253–60.
[25] Barton NW, Brady RO, Dambrosia JM, et al. Replacement therapy for inherited enzyme deficiency—macrophage-targeted glucocerebrosidase for Gaucher's disease. N Engl J Med 1991;324, 1464-147.
[26] Weinreb NJ, Charrow J, Andersson HC, et al. Effectiveness of enzyme replacement therapy in 1028 patients with type 1 Gaucher disease after 2 to 5 years of treatment: a report from the Gaucher Registry. Am J Med 2002;113:112–9.
[27] Elstein D, Zimran A. Review of the safety and efficacy of imiglucerase treatment of Gaucher disease. Biologics 2009;3:407–17.
[28] Pastores GM. Recombinant glucocerebrosidase (imiglucerase) as a therapy for Gaucher disease. BioDrugs 2010;24:41–7.
[29] Cox TM, Aerts JM, Andria G, et al. The role of the iminosugar N-butyldeoxynojirimycin (miglustat) in the management of type I (non-neuronopathic) Gaucher disease. J Inherit Metab Dis 2003;26:513–26.
[30] Schiffmann R et al. Randomized, controlled trial of miglustat in Gaucher's disease type 3. Ann Neurol 2008;64:514–22.
[31] Hollak CE, Aerts JM, Goudsmit R. Individualised low-dose alglucerase therapy for type 1 Gaucher's disease. Lancet 1995;345:1474–8.
[32] Mc Eachern KA, Fung J, Komarnitsky S, et al. A specific and potent in-hibitor of glucosylceramide synthase for substrate reduction therapy of Gaucher disease. Mol Genet Metab 2007;91:259–67.
[33] Shayman JA. The design and clinical development of inhibitors of glycosphingolipid synthesis: will invention be the mother of necessity? Trans Am Clin Climatol Assoc 2013;124:46–60.
[34] Platt FM, Neises GR, Karlsson GB, Dwek RA, Butters TD. Nbutyldeoxygalactonojirimycin inhibits glycolipid biosynthesis but does not affect N-linked oligosaccharide processing. J Biol Chem 1994;269:27108–14.
[35] Mistry PK, Lukina E, Turkia HB, Amato D, Baris H, et al. Effect of oral eliglustat on splenomegaly in patients with Gaucher disease type 1: the ENGAGE randomized clinical trial. JAMA 2015;313:695–706.
[36] Balwani M, Burrow TA, Charrow J, Goker-Alpan O, Kaplan P, Kishnani PS, et al. Recommendations for the use of eliglustat in the treatment of adults with Gaucher disease type 1 in the United States. Mol Genet Metab 2015.
[37] Steet R, Chung S, Lee WS, Pine CW, Do H, Kornfeld S. Selective action of the iminosugar isofagomine, a pharmacological chaperone for mutant forms of acid-beta-glucosidase. Biochem Pharmacol 2007;73:1376–83.
[38] Yoshida H. ER stress and diseases. FEBS J 2007;274:630–58.
[39] Rigat B, Mahuran D. Diltiazem, a L-type Ca(2+) channel blocker, also acts as a pharmacological chaperone in Gaucher patient cells. Mol Genet Metab 2009;96:225–32.
[40] Chang HH. Hydrophilic iminosugar active-site-specific chaperones increase residual glucocerebrosidase activity in fibroblasts from Gaucher patients. FEBS J 2006;273:4082–92.
[41] Khanna et al. 2010.
[42] Zimran A, Altarescu G, Elstein D. Pilot study using ambroxol as a pharmacological chaperone in type 1 Gaucher disease. Blood Cells Mol Dis 2013;50:134–7.
[43] Alfonso P et al. Bicyclic derivatives of L-idonojirimycin as pharmacological chaperones for neuronopathic forms of Gaucher disease. ChemBioChem 2013;14:943–9.
[44] de la Mata M, Cotán D, Oropesa-Ávila M, Garrido-Maraver J, Cordero MD, Villanueva Paz M, et al. Pharmacological chaperones and coenzyme Q10 treatment improves mutant β-glucocerebrosidase activity and mitochondrial function in neuronopathic forms of gaucher disease. Sci Rep 2015;5(5):10903.
[45] Enquist IB, Nilsson E, Månsson JE, Ehinger M, Richter J, Karlsson S. Successful low-risk hematopoietic cell therapy in a mouse model of type 1 Gaucher disease. Stem Cells 2009;27 (3):744752.
[46] Grabowski GA. Gaucher disease and other storage disorders. Hematol Am Soc Hematol Educ Program 2012;2012:13–8.
[47] Zimran A, Elstein D. Management of Gaucher disease: enzyme replacement therapy. Pediatr Endocrinol Rev 2014;12(Suppl. 1): 82–7.
[48] Cox TM, Aerts JM, Belmatoug N, Cappellini MD, vom Dahl S, Goldblatt J, et al. Management of non-neuronopathic Gaucher disease with special reference to pregnancy, splenectomy, bisphosphonate therapy, use of biomarkers and bone disease monitoring. J Inherit Metab Dis 2008;31:319–36.
[49] Hughes D, Cappellini MD, Berger M, Van Droogenbroeck J, de Fost M, Janic D, et al. Recommendations for the management of the haematological and onco-haematological aspects of Gaucher disease. Br J Haematol 2007;138:676–86.
[50] Wenstrup RJ, Baily L, Grabowsky GA, et al. Gaucher disease: alendronate disodium improves bone mineral density in adults receiving enzyme therapy. Blood 2004;104:1253–7.
[51] Giuffrida G, Cappellini MD, Carubbi F, et al. Management of bone disease in Gaucher disease type 1: clinical practice. Adv Ther 2014;31(12):1197–212.
[52] Enquist IB, Nilsson E, Månsson JE, Ehinger M, Richter J, Karlsson S. Successful low-risk hematopoietic cell therapy in a mouse model of type 1 Gaucher disease. Stem Cells 2009;27:744–52.