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Overview of Gaucher Disease, Consequences and Treatment Options

[1]Feras Khalid Mimarji, [2]Redwan Muneer Fargal, [3]Ali Hassan Busanah, [4]Mojahid Ibrahim Ghazi, [5]Hussain Abdulillah Iraqi, [6]Ahmed Faisal Basalam, [7]Abdulrahman Mohammed Hamzah

Abstract: **The aim of this review was to discuss the Gaucher disease from different aspects, and highlight the treatment options for the symptoms and consequences following this disease. Comprehensive computerized review was conducted using several databases such; Medline, PubMed, Embase, to find relevant studies published up to March,2017, discussing the treatment options of Gaucher disease, we limited our search for English language articles, and references lists of those articles were reviewed for more relevant studies that could have support our review. Oral medicine that inhibits glucosylceremide synthase (substrate reduction treatment) as well as may partially raise glucocerebrosidase enzyme task (chaperone mediated treatment). Research studies showed that miglustat did boost the biochemical end results of patients with mild to moderate type 1 Gaucher during clinical trials varying from 6 to 36 months, however there wants proof to show if treatment will maintain both professional and also biochemical results over a long-term duration, or on its performance in dealing with the bones and preventing severe elements such as pulmonary hypertension.**

Keywords: **Gaucher disease, symptoms, treatment, biochemical results, pulmonary hypertension.**

1. INTRODUCTION

Gaucher disease (GD) is a chronic, multisystem disease resulting from lacking task of the lysosomal hydrolase glucocerebrosidase [(1)]. This enzyme is needed for the malfunction of glucocerebroside (glucosylceramide), which accumulates if there is insufficient enzyme activity. The condition is clinically divided into 3 subtypes: Type 1, or non-neuronopathic disease; Type 2, or acute neuronopathic disease; as well as Type 3, or subacute or chronic neuronopathic disease. All arise from mutations in the very same gene, glucosidase, beta, acid (GBA), located on chromosome 1q21, and are inherited in an autosomal recessive fashion. Kind 1 is without a doubt one of the most typical of the three kinds, and is defined in better detail below. Types 2 and also 3 generate substantial and progressive neurological impairment, and also are life-shortening. Type 1 GD is the most usual lysosomal storage space disease, and also the most common genetic disorder amongst individuals of Ashkenazi Jewish descent. In this populace, estimates of incidence variety from 1 in 450 to 1 in 1000 [(1,2)]. The incidence in Sephardi Jews and also non-Jews is less particular, with quotes varying from 1 in 20,000 to 1 in 57,000 [(3,4,5)].

Because of the build-up of GlcCer, Mistry et al. determined one more metabolic pathway in a computer mouse design (**Figure 1**) [(6)]. GlcCer is likewise the substratum of a different path in which a ceramidase transforms it into glucosylsphingosine (or Lyso-glucosylceramide), which then diffuses into fluids due to its decreased hydrophobicity. This pathway is preferred in cases of GCase deficiency. In the cytoplasm, glucosylsphingosine is metabolized by a second GCase that is active at a neutral pH (GBA2 genetics), creating sphingosine and then sphingosine-1-phosphate (S1P) [(7,8)]. Sphingosine could be particularly harmful to bone; in this design, removal of GBA2 might turn around the Gaucher disease phenotype, particularly the bone abnormalities. In addition, the buildup of glucosylsphingosine could create neuronal disorder as well as death, leading mainly to GD-related neurological signs and symptoms [(9)]. Glucosylsphingosine is usually absent from the human brain, but it is noticeable in the minds of patients with GD-related neurological lesions, even if Gaucher cells are not observed in their nervous system. Glucosylsphingosine can represent a more particular and sensitive biomarker than chitotriosidase or CCL18 [(7,10)].

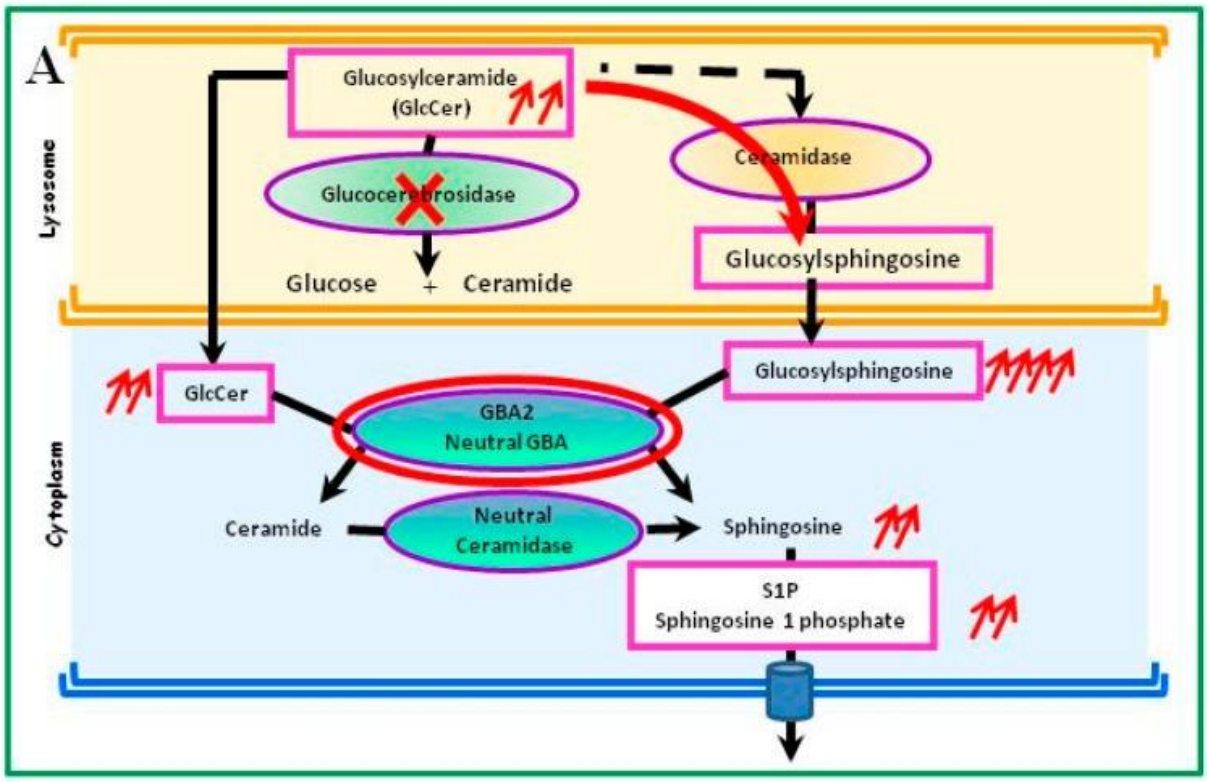

Figure 1: Alternative metabolic pathway of the glucosylceramide (GlcCer) accumulation due to the glucocerebrosidase (GCase) deficiency

The aim of this review was to discuss the Gaucher disease from different aspects, and highlight the treatment options for the symptoms and consequences following this disease.

2. METHODOLOGY

Comprehensive computerized review was conducted using several databases such; Medline, PubMed, Embase, to find relevant studies published up to March,2017, discussing the treatment options of Gaucher disease, we limited our search for English language articles, and references lists of those articles were reviewed for more relevant studies that could have support our review.

3. RESULTS

- **Pathophysiology Gaucher disease:**

Mutations in the GBA1 genetics result in a marked reduction in GCase task. The effects of this deficiency are usually credited to the accumulation of the GCase substratum, GlcCer, in macrophages, inducing their transformation right into Gaucher cells. Under light microscopy, Gaucher cells are commonly enlarged, with eccentric cores and also compressed chromatin as well as cytoplasm with a heterogeneous "messed up cells paper" appearance (**Figure 2**). This function is connected to the visibility of GlcCer accumulations in characteristic twisted, fibrillar arrangements that can be visualized utilizing electron microscopy [(11)]. Gaucher cells generally penetrate bone marrow, the spleen, and also liver, but they also penetrate other body organs and are considered the major protagonists consider the disease's signs. The monocyte/macrophage lineage is preferentially modified due to their role in removing erythroid and leukocytes, which have big quantities of glycosphingolipids, a source of GlcCer. GlcCer build-up in Gaucher cells is thought about the first step to bone involvement, resulting in the vascular compression which is the source of necrotic difficulties [(12)]. The pathophysiological devices of neurological involvement remain badly described; GlcCer turnover in neurons is reduced and its buildup is just substantial when residual GCase activity is significantly reduced, i.e., only with some kinds of GBA1 mutations [(13)]. Constant with this, recent work with a Drosophila model of neuronopathic GD showed autophagy problems in the GCase-deficient fly minds [(14)].

Recent observations show that Gaucher cells do not only result from the change of macrophage cells, however correspond to a distinctive M2 subpopulation from an alternative distinction pathway [15]. There are numerous useful states of macrophage polarization, and they can be totally polarized as well as obtain a specific phenotype like M1 (particular macrophage activation) or M2 (different macrophage activation). These particular phenotypes depend upon the tissue and also certain microenvironment where the macrophages are. The M2 subpopulation has actually been called cells with anti-inflammatory, immunomodulatory and cells repair service residential or commercial properties, as well as includes macrophages that get rid of irregular hematopoietic cells or phagocytose erythroblast cores. The in vivo situation appears a lot more complicated given that the plasma cytokine account and also the characteristic monocytes circulating in the blood program simultaneous activation of inflammatory M1 macrophages, most likely linked in the "pseudo-inflammatory" state that was explained several years ago and also in the heterogeneous symptoms of the disease [16,17]. Thus various cytokines, chemokines as well as other particles-- consisting of IL-1β, IL-6, IL-8, TNFα (Tumor Necrosis Factor), M-CSF (Macrophage-Colony Stimulating Factor), MIP-1β, IL-18, IL-10, TGFβ, CCL-18, chitotriosidase, CD14s, and also CD163s- are present in raised amounts in Gaucher patients' plasma and also could be linked in hematological and also bone complications [18,19]. Just a few of these particles are revealed by Gaucher cells themselves. This is the case for chitotriosidase as well as CCL18, which thus constitute rather details disease biomarkers [14]. Weakening of bones might be linked to IL-10, which inhibits osteoblast task, but additionally to M-CSF, il-1β as well as il-6, MIP-1α as well as MIP-1β, which boost bone traction by enhancing osteoclast task [18].

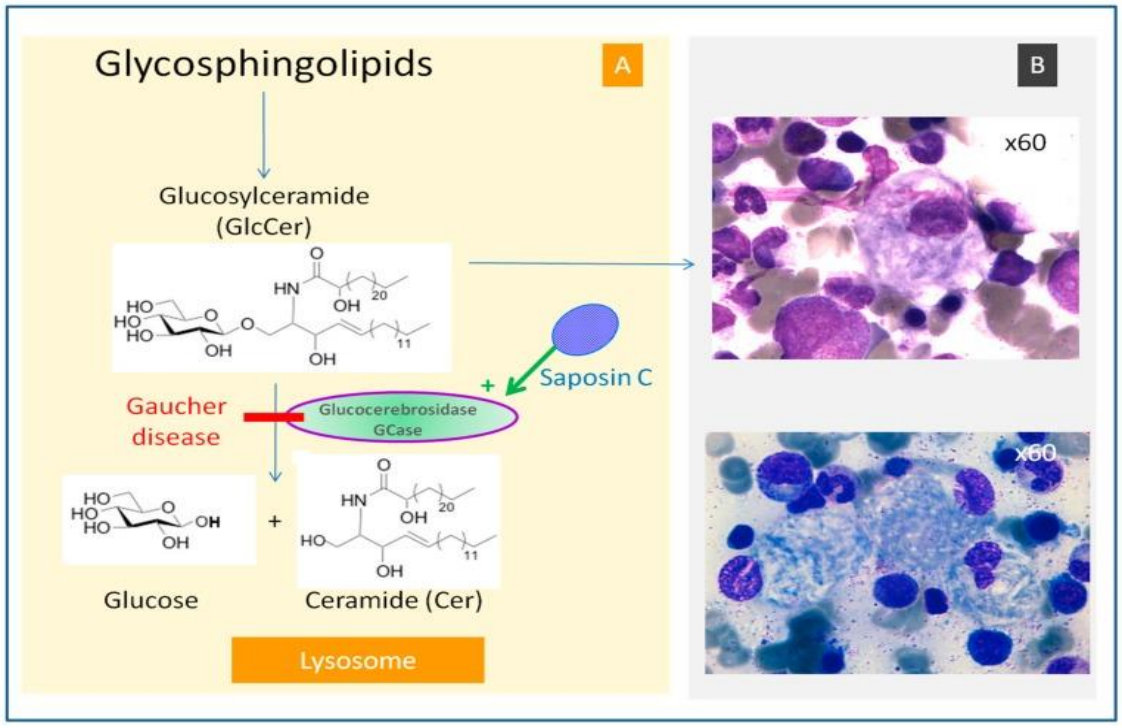

Figure 2: Hydrolysis of glucosylceramide (GlcCer) by glucocerebrosidase (GCase) in the lysosome

- **Type-1 Gaucher Disease and its treatment approach:**

Type-1 GD (GD1), typically identified by the absence of neurological impairment, is one of the most typical kind of the disease (occurrence: 90%-- 95% in Europe as well as North America). Its professional discussion varies, varying from asymptomatic throughout life to early-onset kinds presenting in childhood years. The initial signs and symptoms differ substantially as well as patients can be detected at any type of age [20]. Depending on the research, the average age of medical diagnosis is from 10 to 20 years old [20,21]. The general mean beginning of patients in the Gaucher Registry (run by the International Collaborative Gaucher Group) is at 20.4 years old, the majority (56%) of patients experienced beginning before 20. This Registry mainly includes symptomatic and also treated patients, as well as thus the mean age is possibly manipulated. 2 thirds (68%) of this group were diagnosed prior to 10 years old and also almost fifty percent (48%) before the age of 6 [22,23]. GD1 could often limit lifestyle as well as is frequently connected with considerable morbidity, but is hardly ever harmful. Tiredness is common (50% of patients) and also usually has an effect on school life or socio-professional tasks. In children, growth retardation and postponed the age of puberty are common (growth <5th percentile in 34% of children) [22].

Splenomegaly is observed in more than 90% of patients and is occasionally massive, with a spleen weighing as much as several kilograms as well as triggering stomach pain or distension. It may be the only scientific sign, leading to unneeded examinations if GD is not considered. Splenic infarction may make complex issues; spleen rupture only takes place very rarely [24,25].

Up to 40% of GD1 patients have a focal sore in the liver and/or spleen. A gaucheroma is one of the most likely diagnosis, yet a hepatocellular carcinoma or a lymphoma of the spleen are various other feasible diagnoses. Gaucheromas have differed imaging qualities and also it is consequently challenging to distinguish a gaucheroma from another lesion [26]. Bleeding sensations could be observed at diagnosis. These are rarely extreme and generally connected to thrombocytopenia (60% - 90% of cases) or to coagulation or primary hemostasis problems [27] or, more seldom, to platelet problems [28]. Mucocutaneous blood loss (epistaxis, gingival blood loss, menorrhagia, and so on) prevails; postoperative hemorrhage or blood loss throughout birth and spontaneous hematomas (e.g., psoas hematomas) have additionally been reported. Anemia, observed in 20% - 50% of cases, is typically modest. Leukopenia is rare. Bone participation causes acute pain shown up as very excruciating bone situations, mainly in the pelvis as well as reduced arm or legs (even more rarely in the top arm or legs), and/or chronic pain that must be evaluated utilizing a visual analog scale or digital scale [29]. The extent of the pain varies, however it could have an effect on useful prognosis. The pathophysiology of bone symptoms is improperly recognized as well as warrants using usual terms. The unpleasant bone dilemmas are possibly related to ischemic vaso-occlusive phenomena. It appears that they might be relatively easy to fix and do not show up as lesions in medical imaging. They usually cause abnormalities referred to as bone infarcts on lengthy bones (diaphyses or metaphyses) as well as flat bones, as well as lesions referred to as avascular death (AVN) on the epiphyses. Along with the vascular theory describing the ischemic events (bone infarcts as well as AVN), a mechanical concept has likewise been put forward to clarify the spontaneous or trabecular microfractures that are observed (mechanical or spontaneous AVN), especially on the femoral head, the tibial plateau and the femoral condyle. The pathophysiological mechanism could involve various other potential factors, such as alterations in the bone marrow or immune cells, inflammation, macrophage-derived factors, cytokines, and also hormones [30,31]. When magnetic resonance imaging (MRI) is not readily available, common radiographs may be utilized to observe bone remodeling disorders with enlargement of the metaphyseal/diaphyseal region of the thigh's reduced part, referred to as the Erlenmeyer flask bone deformity, appearing throughout childhood years [32]. The sequelae of AVN and bone infarction, thinning of the cortical bone, focal lysis, cracks and osteo arthritis could additionally be observed. Radiographs could additionally be used to keep an eye on patients after joint substitute surgical treatment. MRI is the referral exam as well as is utilized to externalize bone marrow seepage (80% of instances) at a really onset, as well as bone infarcts, AVN and also bone lysis. Bone marrow infiltration and also Erlenmeyer flask bone defects do not appear to correlate with the other bone complications [33].

Pulmonary participation could be related to infiltration of the lungs by Gaucher cells, developing an interstitial disease that could lead to lung fibrosis, restrictive lung disease second to spine deformation, or pulmonary arterial high blood pressure [34,35]. The last is extra common in splenectomized patients, especially females, or may be triggered by hepatopulmonary syndrome making complex hepatic cirrhosis. Lung participation is uncommon in all GD phenotypes and also appears more frequent in patients homozygous for the 1448G (L444P) anomaly [36].

Rarely, kidney participation, manifested as proteinuria and also hematuria, reflects infiltration of glomeruli by Gaucher cells [37]. Skin participation appears as yellow-brown hyperpigmentation, usually on the former parts of the cheeks and shins [38]. Contrary to the conventional definition of GD1, particular neurological symptoms connected with this phenotype have actually been explained in the last few years. Patients with GD1 have actually an enhanced risk of developing Parkinson's disease (4 - 20 times better), typically at an earlier age compared to in regular PD The prevalence of minimally symptomatic peripheral neuropathies and also small fiber neuropathies is 14% as well as consequently higher than in the basic population [39,40].

- **Type-2 Gaucher Disease:**

Type-2 GD (<5% of cases in most countries, but up to 20% in some cohorts [41] is characterized by early and severe neurological impairment starting in infants aged 3–6 months old and by systemic involvement with hepatosplenomegaly. The triad consisting of rigidity of the neck and trunk (opisthotonus), bulbar signs (particularly severe swallowing disorders), and oculomotor paralysis (or bilateral fixed strabismus) is very suggestive of the disease. These signs may be associated with trismus and hypertonia with pyramidal and possibly extrapyramidal rigidity [42].

Apnea related to increasingly frequent and lengthy laryngeal spasms occurs after a few months. Psychomotor development is then altered, although some children may still continue to acquire skills. Seizures occurring later manifest as myoclonic epilepsy that is resistant to antiepileptic drugs. Splenomegaly is almost always present, associated with thrombocytopenia in 60% of cases. Growth retardation (30% of patients) may be the first sign, sometimes associated with cachexia. Lung lesions are sometimes also observed, resulting from repeated aspirations and pulmonary infiltration by Gaucher cells. There is no bone involvement in GD2. Death occurs before the third year of life, following massive aspiration or prolonged apnea [41]. The mean survival age of GD2 is 11.7 months (range 2–25 months), and pulmonary symptoms (GD-pneumopathy) and aspiration caused by Gaucher disease or the aggravation of respiratory conditions such as central apnea are the cause of 50% of fatal cases [43, 44].

- **Type-3 Gaucher Disease:**

Also called juvenile or subacute neurological GD, the type-3 form (usually 5% of cases, but up to 33% in some cohorts [41] exhibits the visceral manifestations described in GD1, usually combined with oculomotor neurological involvement, which appears before 20 years of age in most cases. Like GD1, GD3 phenotypes are very heterogeneous, particularly with regard to neurological involvement. Some patients present moderate systemic involvement with horizontal ophthalmoplegia as the only neurological symptom, whereas others present more severe forms with varying neurological signs including progressive myoclonus epilepsy (16% of patients), cerebellar ataxia or spasticity (20%–50% of patients), and dementia in some cases [45,46]. Neurological signs may occur several years after the visceral manifestations, even in patients initially identified and treated as having GD1. Disease onset is more common in young children, with neurological symptoms appearing before 2 years of age in half the cases [45]. Behavioral changes and unexpected death are described in some patients [47].

Spinal surgery may be required for the sometimes severe and progressive kyphosis that may develop, through an unknown mechanism, despite specific GD treatment. Cardiac involvement (with valve calcification) [48], corneal involvement and hydrocephaly are reported mainly in patients with GD3 of the c.1342G < 5 % of instances in most nations, yet up to 20 % in some accomplices [41] is identified by early as well as extreme neurological disability starting in infants aged 3 - 6 months old as well as by systemic participation with hepatosplenomegaly.

- **Treatment of Gaucher disease:**

Prior to the development of specific therapies for GD, treatment was symptomatic. Analgesics, and specifically, patient-controlled-analgesia with morphine, provide relief from bone crises until they spontaneously abate. Partial or total splenectomy were the only effective long-term options for treatment of severe anemia and/or thrombocytopenia. However, there is substantial evidence that bone disease progresses more rapidly following splenectomy (49,50), and therapy for bone disease was limited to casting of fractures, bracing, joint replacement, and the use of assistive devices to preserve mobility. Vitamin and mineral supplementation beyond the minimum recommended doses have had no effect on bone mineralization. Bisphosphonates have been shown to increase bone mineral density, and may be an important adjunctive therapy in some patients, particularly in postmenopausal women (51,52,53). Allogeneic hematopoetic stem cell transplantation (bone marrow transplantation) essentially ‘cures’ type 1 GD, since the Kupffer cells in the liver, and macrophages in other organs, are replaced by donor cells (53,54). Bone marrow transplantation has the obvious disadvantage of procedure-related mortality, morbidity and graft-versus-host disease, and is now rarely performed. Several approaches to gene therapy have been explored. In mice, retrovirus-mediated transduction of bone marrow cells (55), and virus-mediated gene transfer (56,56) have successfully transduced the recipient cells, with resultant production of human glucocerebrosidase, and reduced levels of stored glucocerebroside in mouse models of GD. Human studies have been limited to viral transduction of bone-marrow-derived stem cells, and autologous transplantation (57,58). Unfortunately, persistent expression of the transduced genes, at a level sufficient to clear stored glucocerebroside, has not yet been achieved in humans. Short of a truly curative therapy (e.g., gene therapy), specific therapeutic strategies have been directed toward replacement of the deficient enzyme with normal glucocerebrosidase of exogenous origin (see below), enhancement of residual enzyme activity, and reduction of substrate synthesis. Enhancement of residual enzyme activity through the administration of pharmacological chaperones is an emerging approach to treatment, and one that holds great promise. Several agents are currently in clinical trials. This approach assumes that the reduced enzymatic activity in Gaucher tissues results in part from premature degradation of the mutant protein, rather than reduced activity of the enzyme protein itself. Pharmacological chaperones (generally small-molecule competitive inhibitors of glucocerebrosidase) apparently stabilize the mutant peptides, and prevent their degradation through the misfolded protein response. Substrate synthesis inhibition is an alternative approach to reducing the accumulation of toxic substrates, and a single agent (miglustat; Zavesca, Actelion Pharmaceuticals,) has been approved by the FDA and European Medicines Agency (EMEA). Other agents are still in clinical trials. Miglustat is taken orally, and has been shown to improve

the visceral and hematologic aspects of GD. However, its usefulness is limited by frequent adverse events and safety concerns; current labeling specifies its use 'for the treatment of adult patients with mild-to-moderate type 1 Gaucher disease for whom enzyme replacement therapy is not a therapeutic option (58,59).

Enzyme replacement therapy:

In the 1950s Straus [60] and also others showed that macromolecules, consisting of healthy proteins, could be taken up by undamaged cells as well as local in a 'droplet' containing subcellular portion, which also had acid hydrolases. De Duve ultimately showed that this portion contained the lysosomes, and also illuminated their features [61]. Following Hers' presentation that type 2 glycogen storage disease (Pompe disease) was triggered by a deficiency of the lysosomal enzyme α -glucosidase [62,63], De Duve suggested that it as well as other problems arising from deficiency of lysosomal enzymes may be treated by 'replacement' of the absent enzyme [64,65]. This concept was examined that exact same year, when a three-month old girl with Pompe disease got day-to-day injections of α -glucosidase cleansed from Aspergillus niger [65]. A liver biopsy acquired after 18 days showed two times typical enzyme task, and also noticeably minimized lysosomal glycogen. While this provided proof of principle, the administration of a non-human healthy protein predictably provoked an immune reaction, and also the deadly course of the disease was not altered. Progress towards establishing effective enzyme substitute therapy (ERT) was obstructed by difficulty getting adequate amounts of cleansed human enzyme, and also variable uptake of instilled enzyme by ideal cells. It was not anticipated that ERT would certainly be reliable in problems entailing the main nervous system (CNS) due to the fact that of the blood-- brain barrier [65].

4. CONCLUSION

Oral medicine that inhibits glucosylceremide synthase (substrate reduction treatment) as well as may partially raise glucocerebrosidase enzyme task (chaperone mediated treatment). Research studies showed that miglustat did boost the biochemical end results of patients with mild to moderate type 1 Gaucher during clinical trials varying from 6 to 36 months, however there wants proof to show if treatment will maintain both professional and also biochemical results over a long-term duration, or on its performance in dealing with the bones and preventing severe elements such as pulmonary hypertension. Bone manifestations are thought about amongst the most devastating and uncomfortable components of type I Gaucher. ERT can enhance the bone signs and symptoms yet it takes much longer to attain acceptable outcomes However, lately published information programs that miglustat may well boost bone density and also avoid bone situation.

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