Improvement in Bone Mineral Density and Architecture in a Patient with Gaucher Disease Using Teriparatide

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Received: 10 November 2014 / Revised: 04 January 2015 / Accepted: 07 January 2015 / Published online: 03 March 2015
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Abstract Gaucher disease is an autosomal recessive lysosomal storage disorder caused by deficiency of the enzyme acid beta-glucosidase (glucocerebrosidase) due to mutations in the *GBA* gene. The most common form (type I) is associated with severe hematologic, visceral and bone disease. Disease-modifying treatments, such as enzyme replacement therapy and substrate reduction therapy, can improve the hematologic and visceral aspects of the disease but success with improving severe osteopenia, which can increase the risk of fractures, is limited. Our case involves a patient with complex disease affecting bone health including Gaucher disease (type I), Sjögren syndrome, rheumatoid arthritis and corticosteroid use who did not respond to long term use of bisphosphonates. We report an improvement in bone mineral density and bone architecture commensurate with a reduced incidence of

fractures in whom we used teriparatide (human parathyroid hormone (PTH; 1-34) to treat severe osteopenia. We conclude that teriparatide should be considered for further studies as an agent to improve bone mineral density in patients with Gaucher disease.

Introduction

Gaucher disease (OMIM 230800) is an autosomal recessive lysosomal disorder caused by deficiency of the enzyme acid beta-glucosidase (glucocerebrosidase) due to mutations in the *GBA* gene. Accumulation of glucosylceramide in mononuclear phagocytes leads to the characteristic appearance of “Gaucher” cells that can be identified in a number of tissues but most commonly in the bone marrow and liver (Thomas et al. 2014). The most common form of Gaucher disease results in hematologic, visceral, and bone abnormalities with sparing of the central nervous system (type I). Patients can present at any age with anemia, thrombocytopenia, hepatosplenomegaly, and bone disease. The bone disease can have protean manifestations (Wenstrup et al. 2002), but there are three general patterns of bone involvement that lead to adverse outcomes: (1) osteopenia, (2) infiltrative bone disease, and (3) ischemic bone disease. Osteopenia is the most common feature and along with bone pain together is more prevalent in patients that have had a splenectomy (Charrow et al. 2000). Osteopenia in patients with a lumbar spine dual X-ray absorptiometry (DXA) z-score less than or equal to -1.0 can increase the risk of fracture at any skeletal site (Khan et al. 2012). Infiltrative disease, from Gaucher cells, can damage bone architecture, most commonly affects the spine and one of

Communicated by: Maurizio Scarpa, M.D., Ph.D

Competing interests: None declared

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the reasons why disease control should be achieved as soon as possible (Wenstrup et al. 2007; Charrow et al. 2007). Ischemic disease, for which avascular necrosis is the most debilitating disease, is poorly understood but has been related to anemia (Khan et al. 2012).

The only approved disease-modifying treatments for Gaucher disease in Canada are imiglucerase, velaglucerase, taliglucerase (enzyme replacement therapy), and miglustat (substrate reduction therapy). Although these treatments are primarily designed at reducing the burden of accumulated glucosylceramide and generally improve both the hematologic and visceral aspects of Gaucher disease, they are not specifically targeted to treating the bone disease which has been a greater challenge. Fracture prevention strategies have focused on standard osteoporosis therapy recommendations, including attention to calcium and vitamin D status, lifestyle recommendations, and the use of bisphosphonates such as alendronate – the most commonly chosen agent (Cox et al. 2008). Bisphosphonates have been the front-line therapy for postmenopausal osteoporosis for many years, because of strong fracture prevention data in clinical trials, and mechanism of action is thought to be related to suppression of bone resorption and a slowing of bone turnover. The only bone-anabolic agent currently available for clinical use is teriparatide (human parathyroid hormone (PTH 1–34)). Largely because of cost, teriparatide tends to be used in cases where standard osteoporosis therapy appears to be ineffective, such as recurring fractures and loss of bone density (Hanley et al. 2008). This is the first reported case of using teriparatide in a patient with Gaucher disease, and we show a dramatic improvement in both bone mineral density and architecture compared to previous standard treatments. We suggest that teriparatide may be a useful medication to consider for further studies to treat low bone mineral density in patients with Gaucher disease.

Case Report

The patient is a 65-year-old woman with Gaucher disease type I at 30 years of age and a concurrent history of osteopenia and multiple fractures. She also had a diagnosis of chronic obstructive pulmonary disease which was assessed to be the cause of her mild pulmonary hypertension. She had not had a splenectomy. While being monitored and treated for her Gaucher disease and osteopenia, she was also diagnosed 3 years later with rheumatoid arthritis and later Sjögren syndrome. The features of Sjögren syndrome were mild and involved mainly dryness of the mouth and eyes. Her Gaucher disease genotype showed compound heterozygosity with two mutations: (1) N370S=c.1226A>G (p.Asn409Ser) and (2) G377S=c.1246G>A (p.Gly416Ser). Her peripheral T-lym-

phocyte activity of beta-glucosidase was lymphocyte beta-glucosidase activity 1.7 nmol/h/mg protein. She was on standard clinical management of her Gaucher disease. Her average imiglucerase dose during the interval of teriparatide use 54 U/kg, and she was on a prescribed dose of 60 U/kg 3 years prior to the first observation point. From 8 years before the first observation point, she was on 30 U/kg of imiglucerase. Treatments for her rheumatoid arthritis have included Salazopyrin, methotrexate, etanercept, and Arthro-tec. For her osteoporosis, she had 13 years of bisphosphonate therapy with (cyclical etidronate and then alendronate at standard doses). She had very low bone density by DXA and a high rate of fracture with no clinical or densitometry improvement noted during bisphosphonate therapy. She was therefore started on treatment with teriparatide at a standard dose (subcutaneous injections of 20 micrograms daily) from January 2009 to January 2011.

Baseline laboratory parameters and clinical data were monitored, as per her usual clinical care, using intake parameters as per the Gaucher Registry (<https://www.registrynxt.com/Pages/Home.aspx>). The Gaucher Registry is the largest international registry that records voluntary data on patients with Gaucher disease. Serum 25-hydroxy vitamin D levels were normal throughout this period (>80 nmol/L).

Areal bone densitometry (aBMD) of lumbar spine and hip was measured by dual X-ray absorptiometry (DXA) using a Hologic QDR 4500W® (Hologic Inc., Bedford, MA, USA). High-resolution peripheral computed tomography (HR-pQCT) of the peripheral limbs was performed using XtremeCT® (Scanco Medical, Brüttisellen, Switzerland) (Cheung et al. 2013). Baseline measurements were taken 4 months before the start of teriparatide. We used the following measurements from HR-pQCT reported in equivalent mg/cm³ of hydroxyapatite for the entire scanned region: total density in a scanned region (BMD, mg/cm³), cortical density (Ct.BMD, mg/cm³), and trabecular density (Tb.BMD, mg/cm³). Additionally, morphometric parameters included the trabecular thickness, trabecular number (TbTh., mm, TbN, mm⁻¹), and cortical thickness (CtTh, mm). The trabecular number is determined based on a direct analysis of the 3D data, and then trabecular thickness and separation are derived (MacNeil and Boyd 2007; Weinreb et al. 2007).

Results

The hematologic and visceral manifestations of Gaucher disease were considered well controlled in this patient for many years prior to the use of teriparatide. During this time, she maintained a normal and stable peripheral white blood cell and platelet count and hemoglobin level and platelets. Gaucher disease biomarkers ranged from: chitotriosidase

Fig. 1 Areal bone mineral density (aBMD) of the lumbar spine (dotted), left radius (dashed) in g/cm^2 along the right axis, and lumbar spine t -score (solid) along the left axis plotted against the number of

months since the start of enzyme replacement therapy for Gaucher disease along the x-axis. Arrow marks the start of teriparatide

138–557 nmol/h/mL (reference 4–120 nmol/h/mL), angiotensin-converting enzyme (ACE) 30–62 IU/L (reference 25–106), and tartrate-resistant acid phosphatase (TRAP) 4.3–12.6 IU/L (reference 3–10 IU/L). Spleen and liver volumes were normal and stable.

Prior to teriparatide treatment, DXA measurements showed stable lumbar spine aBMD. Pre- and post-teriparatide treatment measured over 25 months showed a 19.7% increase in lumbar mineral density ($0.732\text{--}0.876 \text{ g}/\text{m}^2$), and the t -score increased from -3.2 to -1.8 (measured over 25 months). Right radial aBMD increased by 32% ($0.256\text{--}0.338 \text{ g}/\text{m}^2$) (Fig. 1). A follow-up scan 26 months later showed the lumbar mineral density was sustained at $0.848 \text{ g}/\text{m}^2$, the radial density continued to increase to $0.386 \text{ g}/\text{m}^2$, and the t -score showed a slight decrease to -2.1 standard deviations.

HR-pQCT data showed the left forearm BMD increased by 33% ($127.0\text{--}137.7 \text{ mg HA}/\text{cm}^3$) which closely matches the result from DXA in the same region. The compact (cortical) bone mineral density (Ct.BMD) did not change ($788.7\text{--}793.0 \text{ mg HA}/\text{cm}^3$; $+0.5\%$), while trabecular density increased (Tb.BMD) by 170.4% ($11.5\text{--}31.1 \text{ mg HA}/\text{cm}^3$), cortical thickness (Ct.Th) by 23.9% ($0.46\text{--}0.57 \text{ mm}$), trabecular number (Tb.N) by 28.9% ($0.45\text{--}0.58 /\text{mm}$), and trabecular thickness (Tb.Th.) by 114.3% ($0.021\text{--}0.045 \text{ mm}$) (Fig. 2). These numbers were sustained on an HR-pQCT

scan 3 years later with a radial BMD of $200 \text{ mg HA}/\text{cm}^3$, Ct.BMD $869.6 \text{ mg HA}/\text{cm}^3$, Tb.BMD $35.0 \text{ mg HA}/\text{cm}^3$, Ct.Th 0.72 mm , Tb.N 0.66 mm^{-1} , and Tb.Th. 0.044 mm . The increases in left limb BMD appear to be related to initial increases in trabecular mineral density (Tb.BMD) and remodeling showing increased trabecular number and trabecular thickness. The initial increases in compact bone density were minor, but a larger increase was seen at the 3-year follow-up. Cortical thickness (Ct.Th) improved steadily throughout this period.

Between 21 January 1992 and 19 January 2009, she had 32 bone events (4.6 bone events/year) of which 9 were fractures. Since the teriparatide treatment, she has had five bone events over 5 years (1 bone event/year) of which one was a fracture. A bone event was any one of fracture, avascular necrosis, marrow infiltration, infarction, lytic lesion, or Erlenmeyer flask deformity. Over the past 3 years, she has not reported any fracture despite restarting her corticosteroids to treat her arthritis.

Discussion

Patients with Gaucher disease can have protean manifestations of bone disease that have a significant impact on

Fig. 2 High-resolution peripheral quantitative computed tomography (HR-pQCT) of the left radius before (2009) and after treatment with teriparatide (2011) and at follow-up (2014). Values on the y-axis

correspond to the following units: BMD in mg/cm³, Ct.BMD in mg/cm³, Tb.BMD in mg/cm³, TbTh. in mm, TbN in mm⁻¹, CtTh in mm

morbidity and quality of life (Weinreb et al. 2007). In the general population, fractures can increase morbidity and mortality although mortality from fractures has not been specifically studied in Gaucher disease. Compared to the hematologic parameters and visceral disease that have had traditionally been shown to have a fairly rapid response to enzyme replacement therapy, the responses in the bone have taken a longer time and have been more difficult to study. In this patient, there were a number of underlying factors, including rheumatoid arthritis and oral corticosteroid use that we expect would have impacted bone mineral density. However, very little improvement in bone density was observed after years of using standard doses of enzyme

replacement therapy and bisphosphonates and an adequate intake of vitamin D and calcium.

Low bone mineral density of the lumbar spine has been shown to be a risk factor for fractures in patients with Gaucher disease (Khan et al. 2012). Wenstrup and colleagues showed that treatment with imiglucerase is associated with an increase in BMD *T*-scores in a dose-dependent manner, but the changes could take years to materialize (Wenstrup et al. 2007). In a recently published trial from our centre, Macdonald and colleagues showed teriparatide-improved bone mineral density and architecture using HR-pQCT in postmenopausal women with osteoporosis (Macdonald et al. 2011). We have also shown in

another lysosomal storage disease, Pompe disease, that bone architecture measured using HR-pQCT can provide valuable insight into the remodeling that takes place from different treatments (Khan et al. 2013).

There currently is no standard treatment for osteopenia in Gaucher disease. We feel this case is significant for a number of reasons. This is the first reported case of the use of teriparatide in a patient with Gaucher disease and severe bone disease, showing an improvement in bone mineral density and architecture. The patient's physicians chose to treat her with teriparatide because she was continuing to fracture despite standard osteoporosis management including bisphosphonate therapy. The treatment was well tolerated, and no adverse effects were noted.

The common target of treatment of low bone mass and fractures in Gaucher disease focuses on methods to increase bone mineral density, mass, and strength. DXA is commonly used as an assessment tool but provides an areal density – a two-dimensional surrogate – and does not measure true bone mineral density (a volumetric measurement). HR-pQCT can estimate a true three-dimensional density in both the cortical and trabecular compartments of the region of interest. In this patient, cortical density was normal at baseline, whereas all other architectural measurements were at least two standard deviations below the mean. This indicates that in our patient, cortical mineral density appears to have been defended the greatest prior to teriparatide treatment. This would appear to be a reasonable response since most of the strength in bone is in cortical bone. The most substantial improvements were in the trabecular compartment leading to increased overall density (D100) and trabecular remodeling, and at 3-year follow-up, the cortical thickness was also higher. These observations are entirely consistent with the known action of teriparatide therapy in osteoporosis, with marked increases in trabecular bone mass, especially in the spine, and increased cortical remodeling (Hanley et al. 2008). Increased total bone mineral content during teriparatide therapy is reflected by increased aBMD measurements by DXA as well. We therefore feel our case illustrates that teriparatide therapy strengthens trabecular bone, making more bone rather than simply increasing mineral density of cortical bone, which is likely to be a useful target in the treatment of Gaucher bone disease.

In this patient, there are a number of factors contributing to low bone density. Although the osteopenia and Gaucher disease were diagnosed prior to the diagnosis of rheumatoid arthritis and the use of corticosteroids, at the time of teriparatide use, we cannot delineate the contribution of each of these factors to the osteopenia. However, we note that the improvements after teriparatide use occurred even with the multitude to factors contributing to long-standing osteoporosis that did not respond to years of bisphosphonate therapy.

In conclusion, our case report illustrates improvement in bone mineral density and architecture with no adverse effects from using teriparatide in a patient with Gaucher disease and complex bone disease.

Synopsis

Teriparatide can increased bone mineral density in a patient with Gaucher disease.

Compliance with Ethics Guidelines

Conflict of Interest

Aneal Khan has received speaker honorarium, travel grants, and consultation fees from Genzyme Corporation® (a Sanofi® Company) and is a member of the International Collaborative Gaucher Group (ICGG).

David Hanley and Steven Boyd have declared no conflict of interest.

Colleen McNeil has received travel grants from Genzyme Corporation® (a Sanofi® Company).

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (Wenstrup et al. 2007). Teriparatide is labeled for the use for severe osteoporosis and approved for such use by Health Canada (Drug Identification Number 02254689). Therefore, this case reports an observation on a clinically approved use of the drug, is not a research trial, and does not require application to research ethics for research consent. Dual X-ray absorptiometry is used in standard clinical practice to monitor patients with osteoporosis and does not require research consent. High-resolution peripheral computed tomography is a research application, and we have obtained informed consent for its application in the subject of this case report.

Author Contributions

Aneal Khan helped design the observation plan from which the data was generated, analyzed the data, constructed, and edited the manuscript.

David Hanley helped design the observation plan, analyzed the data, and edited the manuscript.

Colleen McNeil helped analyze the data and review the manuscript.

Steven Boyd helped design the observation plan, analyzed the data, and edited the manuscript.

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