Imiglucerase low-dose therapy for paediatric Gaucher disease — a long-term cohort study

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Background. Gaucher disease is the most common lysosomal storage disorder caused by the insufficiency of the lysosomal enzyme, glucocerebrosidase. This deficiency results in absent or inefficient conversion of glucocerebroside (a membrane lipid) to ceramide and glucose. Accumulation of glucocerebroside occurs primarily in macrophage lysosomes (i.e. monocytes and macrophages) during phagocytic degradation of red blood cells. Clinical symptoms arise due to the displacement of normal cells by lipid-engorged Gaucher cells. Enzyme replacement therapy (ERT) targets the macrophage system and has been shown to be successful in the treatment of type 1 Gaucher disease in adults and children. ERT (60 U/kg) every 2 weeks decreases and often reverses organomegaly and haematological complications and improves quality of life for patients with type 1 Gaucher disease. The present study describes the course of 9 paediatric patients followed up for 2 - 10 years receiving low-dose imiglucerase therapy (± 10 U/kg every 2 weeks) for moderate to severe type 1 Gaucher disease.

Objectives. To evaluate the efficacy of low-dose imiglucerase therapy in paediatric Gaucher disease.

Subjects and methods. Data were recorded at a single centre for 9 paediatric patients. Assessment of response included serial measurements of haemoglobin (Hb) concentrations, platelet count, angiotensin-converting enzyme (ACE) and total acid phosphatase (TAP) levels. Growth was assessed by serial determinations of body weight and height, plotted against standard growth charts. Organ size (liver and spleen) was measured clinically and also radiologically, where possible.

Results. In this low-dose imiglucerase treatment group: (*i*) there was a significant increase in Hb over time — normal Hb levels were achieved in 7 of the 9 patients after a mean of 3.7 years; (*ii*) platelet counts increased over time, reaching normal levels in 7 patients; (*iii*) there was a significant decrease in both ACE and TAP over time; (*iv*) heights and weights of the subjects increased significantly over time with treatment, normalising to the expected growth percentiles; and (*v*) organ size (liver and spleen) reduced with therapy in all patients measured.

Conclusion. ERT with low-dose imiglucerase (± 10 U/kg/fortnight) ameliorates Gaucher disease-associated anaemia and thrombocytopenia. Low-dose ERT is effective and may be considered in resource-poor clinical situations when other alternatives are not available.

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Gaucher disease is a multisystem, heterogeneous, autosomal recessive inherited disease associated with striking variation in its clinical manifestations, severity and course. It is a pan-ethnic disease with an estimated 30 000 cases worldwide.[1]

In type 1 (non-neuronopathic) Gaucher disease, deficiency of the enzyme glucocerebrosidase results in the accumulation of glucocerebroside, mainly in the cells of the macrophage system. There are no discernible neuronopathic manifestations such as gaze palsies, ataxia, seizures or cognitive disturbances. Type 1 Gaucher disease is associated primarily with parenchymal disease of the liver, spleen, bone and bone marrow and in severe cases, the lung. Types 2 and 3 Gaucher disease are associated with varying degrees of neurological manifestations. The correlation between clinical phenotype and genotype is not consistent. Mutations, such as the N370S allele, are known to have a protective effect against neurological involvement.[2]

Typical manifestations in type 1 Gaucher disease include fatigue, splenomegaly, hepatomegaly and osseous manifestations (including osteopenia, osteoporosis, avascular necrosis and lytic lesions of bone).[1] Hypersplenism can lead to anaemia, bleeding and recurrent bacterial infection associated with neutropenia. Growth retardation in children and delayed puberty in adolescents are frequently noted.[1] Studies of the natural history of untreated Gaucher disease indicate that the disease is heterogeneous and shows variable progression in individual patients.[3]

Before the development of enzyme replacement therapies, traditional therapy for Gaucher disease was palliative, consisting primarily of analgesia, blood transfusion and partial or total splenectomy, thereby correcting hypersplenism.[4] Bone

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marrow transplantation corrects the enzymatic abnormality in haematopoietic cells in Gaucher disease. However, this therapy is dependent on the availability of suitable donors and is associated with significant morbidity.[5]

Enzyme replacement therapy (ERT) targets the mannose-receptor of macrophages and has been highly successful in the treatment of type 1 Gaucher disease in both adults and children.[6,7] ERT enables definitive correction of the underlying enzyme deficiency with amelioration, and in some cases, almost complete reversal of the clinico-pathological effects of the disease. ERT reduces hepatosplenomegaly, improves haematological parameters and has a positive effect on health-related quality of life.[8] However, the complex osseous and pulmonary complications of Gaucher disease may remain refractory to ERT and complete arrest of bone involvement is not established in all cases.[9,10] Cessation of enzyme therapy or decreased frequency of treatment may be associated with recurrence of disease activity with the risk of bone crises and rapid deterioration in blood parameters of the disease.[11]

A novel oral treatment that decreases the formation of glucocerebroside, N-butyldeoxynojirimycin (OGT 918), has been shown to be safe and effective in adults with Gaucher disease.[12,13] Inhibition of substrate formation lowers the formation of glycosphingolipids to rates at which the residual enzyme activity in a given patient can catabolise stored and incoming lysosomal substrate.[12]

Current treatment for symptomatic adult and paediatric patients with Gaucher disease in South Africa is ERT with imiglucerase, an analogue of the human enzyme beta-glucocerebrosidase.

There have been divergent views on the optimal dosage of imiglucerase. Initial doses of 60 U/kg body weight by intravenous infusion once every 2 weeks have improved haematological and visceral parameters within 6 months of therapy.[14] Prolonged treatment over 3½ years with the 60 U/kg regimen has a positive effect on bone in both the axial and appendicular skeleton.[9] However, ERT is expensive and several alternative regimens of ERT have been evaluated.[11] Doses as low as 2.5 U/kg body weight three times a week or 15 U/kg body weight once every 2 weeks improve haematological parameters and organomegaly.[7,11] These low-dose, high-frequency regimens are not in widespread use and data are insufficient to assess efficacy in resolving skeletal manifestations.[11]

Recent data from the International Collaborative Gaucher Group show that most patients treated with ERT achieve normal haemoglobin levels within 2 years of initiation of therapy using a dose of 60 U/kg every 2 weeks.[15] Platelet counts increase in patients with or without spleens within the first 6 months and levels are sustained or increased for up to 5 years. Liver and spleen sizes decrease by 20 - 30% within 1 - 2 years of treatment with reductions of 30 - 40% after 5 years.[15]

There is a high prevalence of growth retardation in children and adolescents with type 1 Gaucher disease.[14] Treatment with ERT has been shown to be effective in normalising growth within 4 - 30 months of treatment.[16]

In South Africa, because of limited resources, only low-dose imiglucerase therapy is available. This cohort study is a long-term follow-up of 9 paediatric patients with type 1 Gaucher disease undergoing treatment with low-dose imiglucerase (± 10 U/kg every 2 weeks).

Methods

All paediatric patients from the Johannesburg Hospital Gaucher Clinic were included in the study. All participants had type 1 Gaucher disease. There was no control group. Patients had baseline (pretreatment) data recorded. One patient had had a partial splenectomy. Follow-up varied from 2 to 10 years. Seven of the 9 children were monitored for at least 6 years. Annual data were collected by selecting a data point each year for each patient. The number of observations per subject over the period ranged from 3 to 11, with a median of 9.

Demographic data

The age of subjects at the beginning of the study ranged from 5 to 14 years, with a mean of 8.9 years. Three patients were female and 6 were male (Table I).

Mutation analysis

Genomic DNA samples were screened for five common Gaucher disease mutations (N370S, L444P, 84GG, IVS2 + 1,

Table I. Patient data

Patient	Gender	Ethnic group	Genotype Allele 1 Allele 2
1	F	Caucasian (Afrikaner)	N370S Unidentified
2	M	Coloured	N370S V230A*
3	M	Caucasian (Ashkenazi)	84GG R496C
4	M	Caucasian (Afrikaner)	N370S R496H
5	M	Caucasian (Afrikaner)	N370S P387L*
6	F	Caucasian (Afrikaner)	N370S Unidentified
7	M	African	Delta T36 99G>C*
8	M	African	Delta T36 Rec Nci1
9	F	African	Delta T36 Rec Nci1

*Novel mutations.

R463C), using the single-stranded confirmation polymorphism (SSCP) method.[17]

Patient's DNA carrying an unidentified allele was subjected to further analysis. Long template PCR, selectively amplifying the functional GBA gene, was performed and all 11 axons were subjected to DNA sequencing.[18,19]

Dosage

Treatment dosage and frequency of administration were individualised according to patient response. The dosage given varied from 6 to 13.5 units, with a mean of 10.1 units per kilogram body weight per fortnight.

Ethical approval

Ethical approval was granted by the University of the Witwatersrand Human Research Ethics (Medical) Committee.

Measurements

Angiotensin-converting enzyme (ACE) is a nonspecific indicator of lipid storage. Serum ACE activity is generally elevated in untreated patients with Gaucher disease. Effective enzyme replacement therapy decreases serum ACE levels. However, elevated ACE levels alone are not unique indicators of the clinical severity of Gaucher disease. Tartrate-resistant acid phosphatase (TRAP) is a metallo-enzyme produced by the liver. It is one of multiple isoforms of acid phosphatase. High serum levels of TRAP are seen in untreated cases of Gaucher disease. Serum TRAP activity may serve as a nonspecific indicator of lipid storage. While regular monitoring of TRAP is ideal, consistent measurement of total acid phosphatase (TAP) activity is usually representative of the same trend.

Chitotriosidase (chito) is a recognised marker of lipid storage. This test has only recently been introduced in South Africa. Chito levels are uniquely increased in Gaucher's patients. Gaucher cells secrete large amounts of chito and serum levels of chito correlate directly with the number of Gaucher cells present. However, 5 - 7% of the population in South Africa are chito deficient. The dosage of ERT replacement therapy can be titrated to chito levels — if an increase in serum chito is seen following initiation of ERT, this is a likely sign that the individual requires a higher dose of enzyme.

In this study, haemoglobin (Hb) values, platelet counts and ACE levels were serially measured at baseline and at least annually for all patients. TAP levels were recorded occasionally. Weight and height were serially recorded for all patients. Organ sizes (liver and spleen) were measured clinically and radiologically, where possible.

Definitions

Anaemia was defined based on the Hb level — below the normal value of 13 g/dl. Thrombocytopenia was defined based on the platelet count — below the normal value of 370 000 cells/mm^3. Normal ranges for ACE activity are 8 - 32 U/l, while normal TAP levels ranged from 0 to 4.5 U/l.

Outcome measures

Outcome data are presented as serial changes among patients who had data at baseline and annually for at least 2 years after initiation of ERT.

Statistical analysis

In the absence of a control group, effectiveness was assessed by evaluating changes in the selected parameters over time. Random effects regression models for longitudinal data were fitted to evaluate changes over time. In these models adjustment was made for the dosage received and age at baseline (where these were found to be of some importance). Gender effects were examined. The rate of change of the parameter over time was estimated adjusting for these effects. The use of the random effects longitudinal models enables both variability between subjects and variability within subjects over time to be evaluated.[20]

Results

Haemoglobin (Fig. 1)

On average the Hb increased significantly by 0.31 units per year (95% confidence limits 0.23 - 0.39). Normal Hb levels were achieved and sustained in 7 of the 9 patients after a mean of 3.7 years. Two patients who failed to achieve normal Hb levels had a lower mean Hb at baseline (8.15 v. 12.24 g/dl) (Fig. 1).

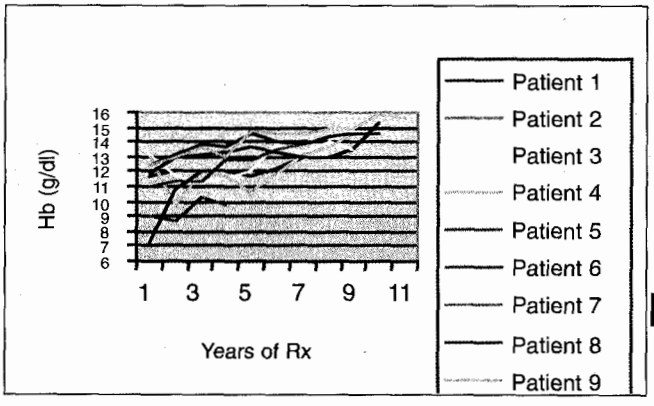

Fig. 1. Haemoglobin levels.

Leucocytes

The change over time was not significant, viz. an increase of 0.046 units per year (95% confidence limits 0.046 - 0.137).

Platelets (Fig. 2)

There was strong evidence of a dose-response effect. On average the platelet count increased by 5.68 for each extra unit of enzyme, and increased by 3.76 units per year, after adjusting for dosage. The observed increase in platelet count was not statistically significant (95% confidence limits 0.27 - 7.79).

In terms of clinical response, only 1 patient did not achieve a normal platelet count and the normal platelet count was not sustained in 2 other patients. The 3 subjects who did not sustain a normal platelet count or who did not achieve a normal platelet count had lower platelet values at baseline. These 3 subjects also had a lower white blood cell count, a higher ACE and a higher TAP at baseline.

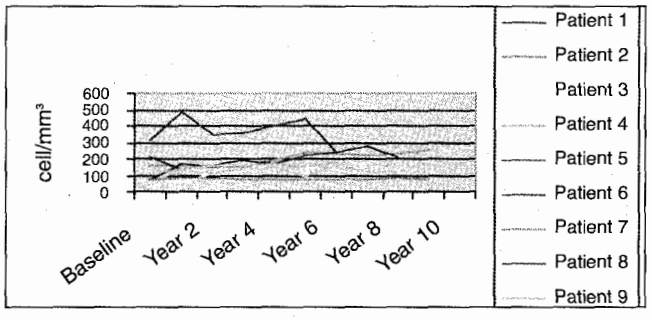

Fig. 2. Platelet counts.

Angiotensin-converting enzyme (Fig. 3)

There was strong evidence of a gender effect, with ACE being on average about 108 units lower in males than females. On average, the ACE decreased by 14.4 units per year (95% confidence limits for the decrease are 8.6 - 20.2). The effects of age at entry and dosage were not significant. All patients showed a consistent reduction in ACE levels. No patients achieved normal ACE limits.

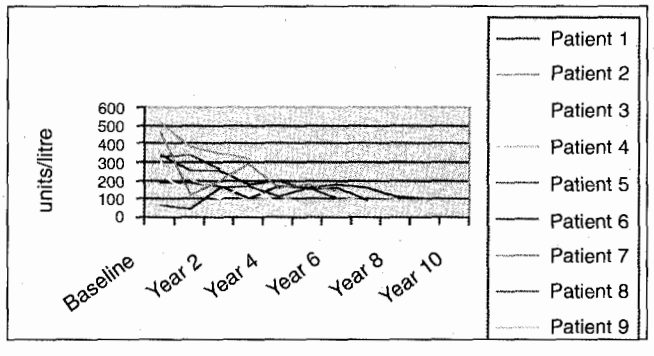

Fig. 3. Angiotensin-converting enzyme levels.

Total acid phosphatase

TAP decreased on average by 3.46 units per year (95% confidence limits 0.67 - 6.24). Although the TAP levels decreased in all patients, only 4 patients achieved normal TAP levels. TAP reductions, however, were not sustained.

Height and weight

Patients in the study grew by on average 5.6 cm per year (95% confidence limits 5.2 - 6.0 cm). Adjusting for the age at entry, weight increased significantly over time by an average of 3.92 kg per year (95% confidence limits 3.60 - 4.24 kg/year).

Reduction of organomegaly

Radiological determinations of hepatic and splenic volume were not conducted uniformly in all patients. However, all patients demonstrated a volume decrease within 6 months of initiating ERT.

Discussion

This report extends the data available on response to ERT in patients with Gaucher disease. The response rates to low-dose imiglucerase are important to note, given the cost of ERT. Analysis of the data from this study has shown that: (*i*) there was a significant increase in Hb over time — normal Hb levels were achieved in 7 patients after 3.85 years (range 1 - 7 years) of low-dose treatment; (*ii*) the increase in leucocytes and platelets over time was not statistically significant; (*iii*) there was a significant decrease in both ACE and TAP over time — however, neither ACE nor TAP levels reached normal limits in this study; (*iv*) heights and weights of the subjects increased significantly over time; and (*v*) organ size (liver and spleen) reduced with therapy in all patients.

Although no bone density evaluations were undertaken, no patient developed a new clinical bone problem.

The interpretation of the data in this study is qualified by several limitations. The frequency of assessment was hampered by logistical difficulties of patients in reaching the clinic. The low-dose regimen and patient monitoring were influenced by limited resources in the health system. The results of this study may not be applicable to a specific patient because type 1 Gaucher disease is characterised by substantial clinical variability and is influenced by genotype. The conclusions that can be drawn from the study should be tentative given the small sample size, the range of ages on entry and the fact that there was no comparator group — in particular no 'normal dose' comparator or a control group.

Conclusion

This study suggests that low-dose ERT with imiglucerase for 2 - 10 years ameliorates anaemia in paediatric patients with

type 1 Gaucher disease. Hb levels normalise after a mean of 3.7 years, as opposed to the 2-year normalisation value achieved with the 60 U/kg dose. In conclusion, therefore, although the response to low-dose ERT with imiglucerase may be delayed, low-dose ERT is effective and should be considered in resource-poor clinical situations when other alternatives are not available.

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