106 The effect of enzyme replacement therapy with imiglucerase on bone mineral density in type I Gaucher disease

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Introduction: The objective was to determine the effect of enzyme replacement therapy (ERT; Cerezyme, imiglucerase) on bone mineral density (BMD) in type 1 Gaucher disease (GD).

Materials and methods: The study population included all adults (males 18–70 yr, females 18–50 yr) enrolled in the International Collaborative Gaucher Group (ICGG) Gaucher Registry for whom lumbar spine BMD measurements were available. BMD data with up to 8 years of follow-up were analyzed for 160 patients who received no enzyme replacement therapy (No ERT) and 342 patients treated with ERT alone. BMD was assessed by dual-energy X-ray absorptiometry (DXA) of the lumbar spine. *Z*-scores for patients with GD were compared to a reference population. From the model's estimate, percent of patients by age and sex with osteoporosis (T-score $\leqslant -2.5$) was calculated.

Results: DXA *Z*-scores for patients with GD in the No ERT (untreated) group were significantly below normal (y intercept $= -0.80$ *Z*-score units, $p < 0.001$) and remained approximately one standard deviation below the reference population over time (slope $= -0.010$ *Z*-score units per year, $p = 0.68$). The DXA *Z*-scores for patients with GD who received ERT at a dose of 60 U/kg/2 wk were significantly lower than the reference population at baseline (y-intercept $= -1.17$ *Z*-score units, $p < 0.001$), but improved significantly over time (slope $= +0.132$ *Z*-score units per year, $p < 0.001$). A significant dose–response relationship was noted for the ERT group, with the slopes for the three main dosing groups of 15 U/kg/2 wk, 30 U/kg/2 wk, and 60 U/kg/2 wk of +0.064, +0.086, and +0.132, *Z*-score units per year, respectively. The BMD of patients with GD treated with ERT increased to −0.12 (60 U/kg/2 wk), −0.48 (30 U/kg/2 wk) and −0.66 (15 U/kg/2 wk) standard deviations of the mean of the reference population after 8 years of ERT, approaching the reference population. Estimated risk of osteoporosis of this GD population, if left untreated, ranged from about 10% to 30% in females, and 10% to 25% in males.

Conclusions: ERT with imiglucerase (Cerezyme) may increase BMD in patients with GD. Response to treatment with imiglucerase is slower for BMD than for hematologic and visceral aspects of GD. A normal (age- and sex-adjusted) BMD should be a therapeutic goal for patients with type 1 GD.

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107 Two-year oral miglustat in Gaucher disease type III

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Introduction: Oral miglustat has been shown to be effective in the treatment of Gaucher disease (GD) type 1 by reducing the cellular accumulation of glucosylceramide. GD type 3 is characterised by severe neurological clinical features. Miglustat is a small iminosugar molecule, which has been shown to be able to cross the blood–brain barrier.

Methods: Thirty GD type 3 patients (mean age 10.2 years, range 2–20) were randomized 2:1 in an add-on design to receive either miglustat 200 mg t.i.d. (adjustable for body surface area) or the standard care for 1 year. Subsequently, all patients continued on miglustat for another 12 months. The primary endpoint was the effects of miglustat on velocity and amplitude of vertical saccades Secondary endpoints include neurological and cognitive assessments, lung function, liver and spleen volumes.

Results: All patients have completed at least the 2 years of treatment and no statistically significant differences were seen between the two groups at the 1-year time point. Interim safety analysis at 12 months showed a satisfactory overall safety profile: 3 and 1 SAEs occurred respectively in the treated and the control group and were all non-drug-related. Diarrhea, mostly mild, was common 17 patients in the miglustat group reported diarrhoea; the frequency of diarrhea decreased over the study period. Tremor was observed in 11 treated patients (9 mild, 2 moderate). Mild or moderate weight loss was described in 1 and 4 miglustat patients respectively. Subclinical peripheral neuropathy developed in at least one patient. The results of the full 2-year study, current being analyzed, will be presented and discussed.

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108 Mutant glucocerebrosidase and the synucleinopathies

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Recent studies implicate an association between parkinsonism and mutations in glucocerebrosidase (GBA), the lysosomal enzyme deficient in Gaucher disease. Parkinsonian manifestations have been described in Gaucher disease. Also, GBA mutations are encountered with increased frequency in subjects with parkinsonism, and their obligate carrier relatives, suggesting their role as a risk factor. GBA was sequenced in 75 autopsied brain samples from U Penn including 35 cases with diffuse Lewy body dementia (DLB), 29 with Parkinson disease (PD), and 12 with multiple system atrophy (MSA). Of the 75 subjects, 9 (12%) were heterozygous for GBA mutations (23% in DLB and 4% in PD), expanding the spectrum of synucleinopathies associated with GBA. Immunofluorescence studies and confocal microscopy of brain samples from five subjects with synucleinopathies carrying GBA mutations demonstrated that mutant glucocerebrosidase was present in α-synuclein-positive inclusions in both GBA hetero- and homozygotes with parkinsonism. Mutant glucocerebrosidase was found in ubiquitinated and non-ubiquitinated aggregates, co-localizing with lysosomal markers. In four control samples from parkinsonian subjects without GBA mutations, synuclein-positive aggregates did not show immunoreactivity to glucocerebrosidase. The functional relationship between these proteins was studied by co-transfecting wild-type and mutant glucocerebrosidase with A53T α-synuclein in COS7 cells. Co-expression of A53T α-synuclein and mutant glucocerebrosidase induced the formation of cytosolic LB-like inclusions. These results suggest that GBA mutations may enhance synuclein aggregation by a toxic gain-of-function mechanism or may interfere with the lysosomal clearance of toxic α-synuclein oligomers. Unraveling the relationship between these proteins may advance our understanding of the etiology, genetics, and pathogenesis of the synucleinopathies.

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