Effect of Miglustat on Bone Disease in Adults with Type 1 Gaucher Disease: A Pooled Analysis of Three Multinational, Open-Label Studies

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ABSTRACT

Background: Bone manifestations are a source of disability among patients with Gaucher disease (GD) and a focus of disease management. The effect of enzyme replacement therapy (ERT) on GD bone disease can be limited and may take up to 8 years to become manifest. Miglustat, a glucosylceramide synthase inhibitor, may have a positive influence on GD bone disease.

Objectives: The aim of this analysis was to evaluate the effects of miglustat on bone manifestations and bone mineral density (BMD) in patients with type 1 GD.

Methods: This was a pooled analysis of data collected prospectively over an observation period of 2 years from patients who participated in 3 multinational, open-label clinical trials evaluating the efficacy and tolerability of miglustat 100 mg TID (the currently approved therapeutic dose). Bone manifestations were assessed qualitatively and in relation to treatment and spleen status. The effects of miglustat on BMD were assessed by dual-energy x-ray absorptiometry at the lumbar spine and/or femoral neck. *Bone response* was defined as a positive change in BMD, based on the change in BMD Z-score from baseline to months 6, 12, and 24. Changes in BMD were also analyzed according to spleen status and baseline severity of osteopenia.

Results: The analysis involved 72 patients, including 41 (57%) who had received previous ERT and 20 (28%) who had undergone splenectomy. Patients' mean (SD) age was 41.2 (13.1) years. The most frequent bone-related manifestations at study entry were osteoporosis (43/63 [68%] patients) and bone pain (41/65 [63%] patients). At 2 years, 54/65 (83%) patients reported no bone pain. The reductions in bone pain were comparable among all subgroups, including high-risk patients (ie, splenectomized). No new cases of bone crisis, avascular necrosis, or pathologic fractures were reported. BMD Z-scores were improved from baseline at both the lumbar spine and femoral neck at each time point (months 6, 12, and 24) ($P < 0.001$). As early as 6 months after the initiation of miglustat monotherapy, significant increases from baseline in the BMD Z-score were observed at both the lumbar spine (mean, 0.15; $P = 0.022$) and femoral neck (0.23; $P < 0.001$); the increases remained significant at 12 months (0.19 [$P = 0.012$] and 0.21 [$P = 0.017$], respectively) and 24 months (0.21 [$P = 0.015$] and 0.18 [$P = 0.039$]). Significant increases in BMD Z-scores were observed at the femoral neck in splenectomized patients ($P < 0.001$) and at both sites in osteoporotic patients (lumbar spine: $P < 0.001$; femoral neck: $P = 0.006$).

Conclusion: This pooled analysis of 3 open-label studies of miglustat 100 mg TID suggests that miglustat monotherapy may reduce the incidence of bone pain and improve BMD in patients with type 1 GD, including those with a history of splenectomy and/or osteoporosis. (*Clin Ther*. 2007;29:1645–1654) Copyright © 2007 Excerpta Medica, Inc.

Key words: type 1 Gaucher disease, miglustat, skeletal manifestations, bone mineral density, bone response.

INTRODUCTION

Gaucher disease (GD) is the most common inherited lysosomal storage disorder, with an estimated global

Accepted for publication June 26, 2007.

Express Track online publication August 22, 2007.
doi:10.1016/j.clinthera.2007.08.006
0149-2918/$32.00

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prevalence of 1 in 200,000.[1] It is a multisystem disease associated with hematologic and visceral problems. Bone manifestations, which can negatively affect patients' health-related quality of life, remain a challenge in the management of GD.[1,2] In a study by Giraldo et al,[3] 20% of patients with type 1 GD (GD1) reported having severe restrictions on their physical activity, and >70% reported being limited in their ability to perform strenuous activities before undergoing treatment.

The bone manifestations of GD1 result in a diverse array of symptomatic and radiographic findings.[4,5] The International Collaborative Gaucher Group (ICGG) Registry reported that 63% of patients experience bone pain, and bone crises (ie, acute episodes of severe skeletal pain and fever) develop in 26%.[1,5] Ninety percent of patients have been reported to have radiographically confirmed skeletal findings, with Erlenmeyer flask deformity or bone marrow infiltration present in ~60%, osteopenia in ~50%, and bone infarction or avascular necrosis in ~33%.[6–8] The severity of bone disease has been found to be significantly correlated with other clinical indicators of GD severity, including previous splenectomy ($P \leq 0.006$) and hepatomegaly ($P \leq 0.025$).[8]

Osteoporosis at various skeletal sites, including the lumbar spine and femoral neck, has been reported in patients with GD1.[8] Furthermore, decreased bone mineral density (BMD) has been noted among splenectomized patients with GD1, and the reduction in BMD was found to be correlated with the severity of skeletal radiographic findings.[8]

Early therapies for GD were mainly palliative and were restricted to splenectomy, repair of fractured bones, and treatment of intercurrent infections.[2] Since the early 1990s, the availability of enzyme replacement therapy (ERT) has made effective reduction of organomegaly and improvement in hematologic parameters possible.[9–12] However, the skeletal response to ERT can be limited and may be influenced by the dose of ERT and the severity of bone disease; furthermore, it often requires up to 8 years for a response to become manifest.[13–15]

The miglustat* molecule has physicochemical properties that allow a large volume of distribution (83–105 L in GD patients), indicating that miglustat distributes into extravascular tissues (data on file, Actelion Pharmaceuticals Ltd., Allschwil, Switzerland). This has been confirmed by animal data indicating access to deep organs such as bone.[16] Increased drug delivery to bone may lead to a favorable effect on skeletal manifestations of GD. Miglustat regulates the turnover of glycosphingolipids (GSLs) by reversibly inhibiting glucosylceramide synthase, which catalyzes the first committed step in GSL synthesis.[17]

Miglustat is the only commercially available oral treatment for GD. Its efficacy and safety/tolerability profile in clinical trials enrolling up to 92 patients with GD1 have been described elsewhere.[18–22] In these studies, miglustat monotherapy was associated with significant increases in blood counts and progressive reductions in liver and spleen volume as early as 6 months after the start of treatment ($P < 0.001$). Treatment was well tolerated.

The present analysis was conducted to evaluate the effects of miglustat on bone manifestations in patients with GD1, including assessment of the changes in BMD.

MATERIALS AND METHODS

This was a pooled analysis of data collected prospectively from 3 multinational, open-label studies, all available studies in which patients received miglustat 100 mg TID. All patients with GD1 who received at least 1 dose of miglustat 100 mg TID were included in the analysis.

Assessment of Bone Manifestations and Bone Mineral Density

Skeletal manifestations of GD, including bone pain, bone crisis, new fractures, and incident avascular necrosis (AVN), were assessed over a 2-year observation period. All patients who had a baseline assessment and at least 1 follow-up measurement were included in the BMD analysis, excluding those who were receiving bisphosphonate treatment (5 patients). BMD was assessed by dual-energy x-ray absorptiometry (Lunar, Madison, Wisconsin, or Hologic, Waltham, Massachusetts) at the lumbar spine and/or hip (femoral neck). Standard quality-control procedures were performed on a regular basis according to the manufacturers' recommendations.

BMD assessments in all 3 trials were conducted prospectively based on the standard schedule for the individual investigational sites. The assessments employed BMD Z-scores, which are based on the mean

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BMD for age- and sex-matched healthy subjects. *Bone response* was defined as a positive change in BMD, based on the change in BMD Z-score from baseline to months 6, 12, and 24. BMD changes were also evaluated in splenectomized patients and osteoporotic patients (defined as those with a baseline BMD Z-score less than –1).

Statistical Analysis

Descriptive statistics were used to assess the prevalence of GD bone manifestations at baseline and the incidence of new bone complications for up to 2 years after the initiation of miglustat treatment. Patients' demographic and baseline bone disease characteristics were summarized for treatment-naive patients and those previously treated with ERT. Bone manifestations also were summarized for splenectomized patients and those with an intact spleen. Baseline comparisons between groups were performed using 2-sided tests at the 5% significance level. Analysis of proportions was compared using the Fisher exact test, and means were compared using the 2-sample *t* test. Within-patient changes in BMD from baseline to each time point (6, 12, and 24 months) for the overall population and from baseline to the last observation in splenectomized and osteoporotic patients were tested using the 2-sided paired *t* test. All data analyses were conducted using SAS version 8.2 (SAS Institute Inc., Cary, North Carolina).

RESULTS

The 3 independent multinational, open-label efficacy and safety trials (identified in previous reports as studies 001,[18] 004,[21] and 005[22]) enrolled a total of 76 male and female patients (age ≥18 years) with confirmed GD1. Patients were either treatment naive (ie, unable/unwilling to be treated with ERT) or had been previously treated with ERT. In studies 001[18] and 005,[22] previous ERT had to have been discontinued for at least 3 months before screening; in study 004,[21] patients had to have received continuous ERT for at least 2 years, with the regimen stable for at least 6 months, before being switched to miglustat monotherapy. The recommended dosing regimen in the 3 trials was 100 mg TID, although dose increases were allowed (up to a maximum of 300 mg TID), and dose decreases were implemented in the case of drug-related adverse events. Adverse events were monitored, and the findings have been reported separately.[18,22]

The trials were conducted in accordance with the Declaration of Helsinki (revised Hong Kong, 1989) and the guidelines for good clinical practice. The study protocols were approved by the relevant ethical review board for each participating center. Written informed consent was obtained from all patients before study inclusion. The main features of the 3 trials are summarized in **Table I**.

Three patients in study 004[21] were in the combination arm (miglustat + ERT) of that trial, and 1 patient in study 005[22] discontinued study participation before exposure to miglustat. These 4 patients were excluded from the analytic set. Data for the remaining 72 patients, all of whom received at least 1 dose of miglustat, were pooled and analyzed. Male and female patients were equally distributed in the study population, which had a mean (SD) age of 41.2 (13.1) years. Forty-one (57%) patients had received previous ERT for a median duration of 61 months (range, 18–100 months). Treatment-naive patients were significantly older than patients who had received previous ERT (mean [SD] age, 46.7 [11.7] vs 37.0 [12.8] years, respectively; $P = 0.002$). There were no significant differences in weight and height between treatment-naive and previously treated patients. Twenty (28%) patients had undergone splenectomy before study entry, with a significantly higher frequency in the group that had received previous ERT compared with the treatment-naive group (16/41 [39%] patients vs 4/31 [13%] patients, respectively; $P = 0.018$). **Table II** summarizes the demographic and baseline characteristics of the study population.

Effect on Bone Manifestations

The most frequent GD bone manifestations reported at baseline were osteoporosis (68%) and bone pain (63%) (**Table III**). Osteoporosis was reported in 58% of treatment-naive patients and 76% of those who had received previous ERT. Bone pain was significantly more frequent in the previous ERT group compared with the treatment-naive group (28/37 [76%] vs 13/28 [46%], respectively; $P = 0.01$).

During a 2-year period of miglustat therapy (median duration: 568 days; range, 1–778 days), 54 (83%) of the 65 patients with bone pain at baseline reported no bone pain. Of the 24 patients with no bone pain at baseline, 2 (8%) developed bone pain (one at 3 months and the other at 21 months after initiation of therapy), whereas 22 (92%) patients remained pain free.

Table I. Designs and inclusion/exclusion criteria of the 3 trials included in the pooled analysis.

Characteristic	Trial 001[18]	Trial 004[21]	Trial 005[22]
Duration, y	3	2	2
No. of sites	4	1	1
Study design	Open label	Comparative, open label	Open label
Primary end points	Efficacy and safety of miglustat	Tolerability, safety, and pharmacokinetics of miglustat in combination with ERT compared with ERT and miglustat alone*	Efficacy, safety, and tolerability of miglustat
Study period	1998–2002	1999–2000	1999–2001
No. of patients			
Baseline	28	36*	12
Treatment naive	22	0	9
Evaluable	28	33	11
GD1 confirmed by	Glucocerebrosidase assay	Glucocerebrosidase assay	Genotyping or glucocerebrosidase assay
Age, y	≥18	≥18	≥18
Sex	Male and female	Male and female	Male and female
ERT history	Unable or unwilling to receive ERT, or discontinued ERT for at least 3 mo before screening	Received continuous ERT for at least 2 y, with stable regimen for at least 6 mo before screening	Unwilling or unable to receive ERT, or discontinued ERT for at least 3 mo before screening
Disease severity	Measurable organomegaly; intact spleen (if hemoglobin <11.5 g/dL or platelet count $<100 \times 10^9$/L) or splenectomized with liver weight >2.5% of body weight		Liver weight ≥2.5% body weight
Main exclusion criteria	Pregnancy; history of lactose intolerance or cataracts; active intercurrent medical condition (ie, HIV, hepatitis B/C); clinically significant diarrhea; ERT within 3 mo before screening	Pregnancy; history of lactose intolerance or cataracts; active intercurrent medical condition (ie, HIV, hepatitis B/C); clinically significant diarrhea	Pregnancy; history of lactose intolerance or cataracts; active intercurrent medical condition (ie, HIV, hepatitis B/C); clinically significant diarrhea; ERT within 3 mo before screening

ERT = enzyme replacement therapy; GD1 = type 1 Gaucher disease.

*Patients receiving miglustat in combination with ERT, or miglustat or ERT alone were followed for 6 months. At month 6, those receiving ERT alone had the option of switching to miglustat. Twelve patients were randomized in each arm of the study (ERT alone, miglustat alone, and miglustat plus ERT).

Table II. Demographic and baseline characteristics of patients.

Variable	Treatment Naive (n = 31)	Previous ERT (n = 41)	Total (N = 72)
Age, mean (SD), y	46.7 (11.7)	37.0 (12.8)*	41.2 (13.1)
Sex, no. (%)			
Male	19 (61)	18 (44)	37 (51)
Female	12 (39)	23 (56)	35 (49)
Weight, kg			
Mean (SD)	70.6 (12.4)	66.6 (12.7)	68.3 (12.7)
Range	52.4–97.2	44.5–101.0	44.5–101.0
Mean height, cm			
Mean (SD)	170.0 (9.9)	166.2 (9.9)	167.8 (10.0)
Range	148.0–195.0	140.0–189.0	140.0–195.0
Duration of ERT, median (range)	–	61 (18.0–100)	–
Splenectomy, no. (%)	4 (13)	16 (39)†	20 (28)

ERT = enzyme replacement therapy.
*P = 0.002, t test.
†P = 0.018, Fisher exact test.

Table III. Bone manifestations at baseline (n/N [%] of patients with baseline observations).

Variable	Treatment Naive (n = 31)	Previous ERT (n = 41)	Total (N = 72)
Osteoporosis	15/26 (58)	28/37 (76)	43/63 (68)
Bone pain	13/28 (46)	28/37 (76)*	41/65 (63)
Bone crisis	3/28 (11)	7/37 (19)	10/65 (15)
History of hip surgery	3/22 (14)	8/39 (21)	11/61 (18)
Avascular necrosis	5/31 (16)	4/41 (10)	9/72 (13)
Vitamin B_{12} deficiency†	4/31 (13)	3/41 (7)	7/72 (10)

ERT = enzyme replacement therapy.
*P = 0.01, Fisher exact test.
†A known risk factor for osteoporosis.[23]

When data were analyzed by treatment history (treatment naive vs previous ERT) and by spleen status (intact spleen vs splenectomized), >80% of patients had no bone pain during the 2 years of observation. The results were comparable between treatment-naive patients and those previously treated with ERT and between patients with an intact spleen and those who had undergone splenectomy (**Figure**).

Regarding skeletal events, no bone crisis, AVN, or bone fracture was reported during 2 years of follow-up.

Changes in Bone Mineral Density

BMD Z-scores increased significantly from baseline at both the lumbar spine and the hip (femoral neck) at each time point assessed (months 6, 12, and 24) (P < 0.001) (**Table IV**). As early as 6 months after initiation of miglustat monotherapy, the increase in BMD was statistically significant at both the lumbar spine (mean [SE], 0.15 [0.06]; 95% CI, 0.02 to 0.27; P = 0.022) and the femoral neck (mean [SE], 0.23 [0.06]; 95% CI, 0.12 to 0.34; P < 0.001). The increase in

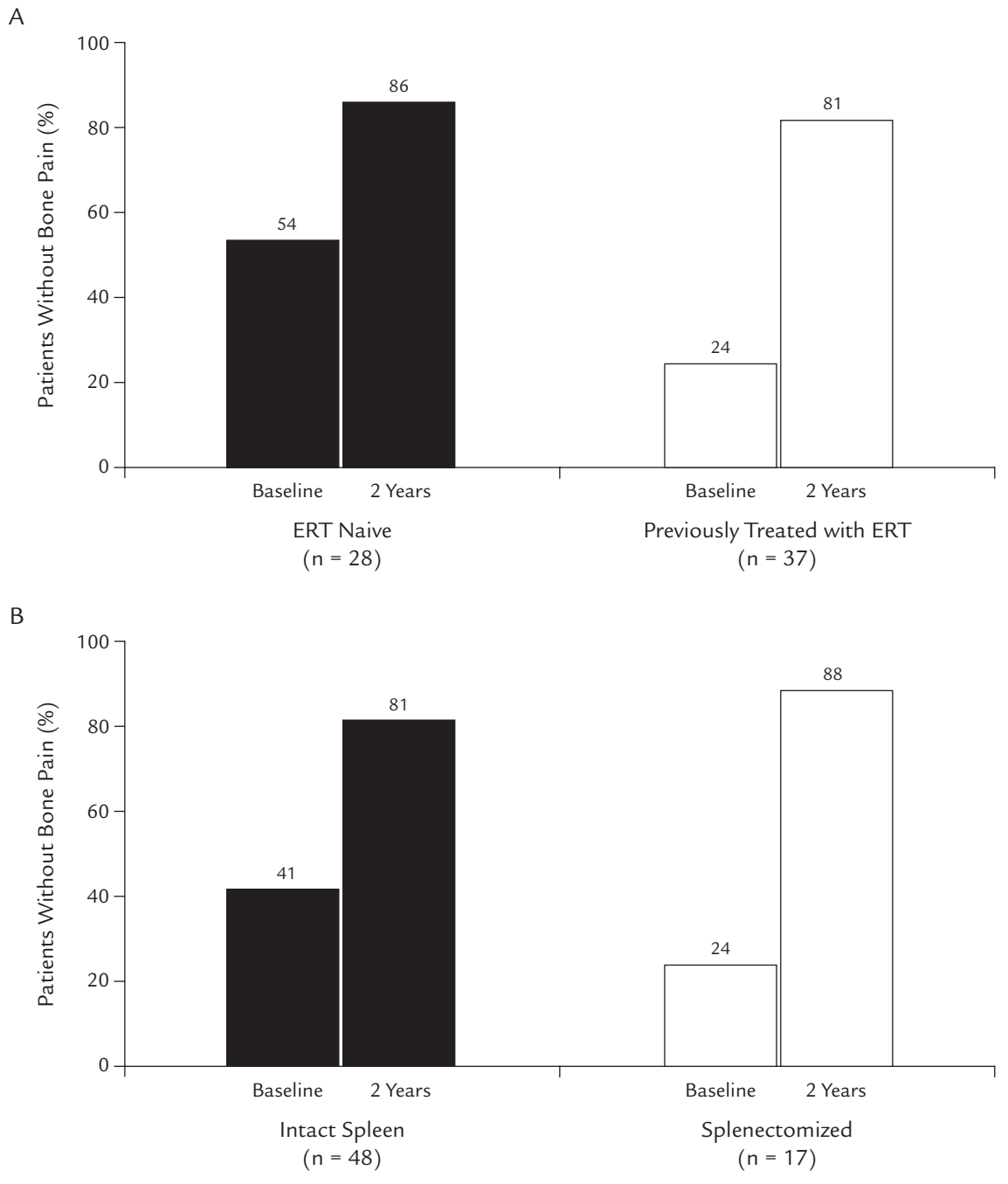

Figure. Proportions of patients without bone pain at baseline and after 2 years of treatment (or at last measurement) with miglustat: Response by (A) treatment history and (B) spleen status. ERT = enzyme replacement therapy.

BMD from baseline was also significant at both sites at 12 (lumbar spine: $P = 0.012$; femoral neck: $P = 0.017$) and 24 months ($P = 0.015$ and $P = 0.039$, respectively).

In splenectomized patients, increases in BMD from baseline to the last value were observed at both the lumbar spine (mean [SE], 0.22 [0.12]; 95% CI, –0.41 to 0.97) and femoral neck (mean [SE], 0.45 [0.08]; 95% CI, 0.06 to 0.79; $P < 0.001$). In osteoporotic patients, there were significant increases in BMD from baseline to the last value at both the lumbar spine

Table IV. Changes over time in bone mineral density Z-scores at the lumbar spine and the femoral neck (hip) in all patients.

Site/Time Point	Baseline, Mean (SD)	Change from Baseline		
		Mean (SE)	95% CI	*P*
Lumbar spine				
Month 6 (n = 29)	–0.83 (1.16)	0.15 (0.06)	0.02–0.27	0.022
Month 12 (n = 26)	–0.98 (1.17)	0.19 (0.07)	0.05–0.34	0.012
Month 24 (n = 17)	–1.46 (1.11)	0.21 (0.08)	0.05–0.38	0.015
Last value (n = 47)	–1.18 (1.16)	0.21 (0.05)	0.11–0.32	<0.001
Femoral neck				
Month 6 (n = 30)	–0.63 (1.43)	0.23 (0.06)	0.12–0.34	<0.001
Month 12 (n = 23)	–0.73 (0.96)	0.21 (0.08)	0.04–0.38	0.017
Month 24 (n = 13)	–0.82 (0.78)	0.18 (0.08)	0.01–0.18	0.039
Last value (n = 43)	–0.76 (1.27)	0.27 (0.06)	0.15–0.38	<0.001

(mean [SE], 0.27 [0.06]; 95% CI, –0.08 to 1.16; $P < 0.001$) and the femoral neck (mean [SD], 0.22 [0.07]; 95% CI, –0.48 to 1.04; $P = 0.006$).

DISCUSSION

This pooled analysis provides evidence of the beneficial effect of miglustat on bone manifestations and osteopenia in patients with GD1, extending earlier observations of improvement in hematologic and visceral parameters in patients with GD1 receiving miglustat.[18,21,22] BMD improved significantly in miglustat-treated patients ($P < 0.001$), and the effect was evident as early as 6 months after the initiation of treatment. Moreover, BMD was increased in patients who had undergone splenectomy or had preexisting osteoporosis, subgroups that are at high risk for bone loss. BMD increased significantly at the femoral neck in splenectomized patients ($P < 0.001$) and at both sites in osteoporotic patients (lumbar spine: $P < 0.001$; femoral neck: $P = 0.006$).

The prevalence of bone pain in this study (63%) was identical to that reported in the general adult GD population by the ICGG Registry.[1] The higher prevalence of bone pain among patients previously treated with ERT is consistent with an earlier report of bone pain in at least 54 of 107 (50%) patients, 105 of whom were receiving ERT.[15] This phenomenon may be partially explained by the higher proportion of splenectomized patients in this group and the likelihood of more advanced bone disease. The results of the present study suggested a beneficial effect of miglustat on bone pain. During 2 years of miglustat treatment, >80% of patients reported no bone pain, regardless of spleen status and treatment history.

The pathophysiology of bone disease in patients with GD remains incompletely defined. Bone tissue and bone marrow play a distinct, though interrelated, functional role. Whereas infiltration of the bone marrow by Gaucher cells (ie, lipid-engorged macrophages) may be the trigger for a focal disease process (leading to infarction and necrosis, osteosclerosis, and osteolysis), the systemic release of cytokines and abnormalities in bone metabolism associated with an imbalance between osteoclast and osteoblast activities could explain the generalized bone disease (bone pain, osteoporosis). Recent in vitro data have indicated an increase in the differentiation and resorptive activity of osteoclasts derived from peripheral blood mononuclear cells from patients with GD.[24] These findings are consistent with the report that GD patients have increased plasma levels of interleukin-6, a cytokine known to induce osteoclastogenesis.[25] In addition, elevated levels of markers of bone turnover have been found in the serum or urine of GD patients in a pattern that mainly reflects increased bone resorption (eg, elevated levels of type I collagen cross-links).[26,27]

ERT is only partially effective in ameliorating extant bone disease in patients with GD.[11–15,19,27–31] It has been reported to decrease the intensity and frequency of bone pain in some patients, but without radiographic signs of skeletal improvement.[8] Conversely, data from the ICGG Registry indicate that between

50% and 60% of patients continue to have bone pain after 2 to 3 years of ERT,[12,32] an estimate confirmed by a recent survey involving 128 patients with GD.[15] In the study by Poll et al[11] in 30 patients with GD1 who had been receiving ERT for a median of 3 years, 37% had no bone marrow response, ERT dose notwithstanding.[11] A recent retrospective cohort study reported that after 2 years of treatment with ERT, including high-dose regimens (60–120 U/kg q4wk), up to two thirds of patients failed to reach predefined therapeutic goals for a bone marrow response.[13] These observations may reflect the limited ability of ERT to alter bone disease, particularly at advanced stages of bone disease. The extent to which the bone response to ERT may be limited because of restricted access to the bone compartment is uncertain. In patients receiving ERT who show clinical improvement in blood counts and a lessening of bone crises, the increase in enzyme activity in the bone marrow may be only 1.7- to 9.6-fold.[33]

The magnitude of change in BMD (particularly in cortical bone) in response to ERT is not clearly established, but an extended period of treatment appears to be necessary for such change to occur. A recent study in patients with GD1 reported that improvement in BMD may require up to 8 years of treatment, even at a high dose,[28] and another study in patients with GD reported no significant increase in BMD before 4.5 years of ERT.[29] Compared with GD1 patients with an intact spleen, splenectomized GD1 patients are at higher risk for osteoporosis; a significant reduction in BMD has been reported in 29 splenectomized patients treated with 2 years of ERT, alone or in combination with calcitriol ($P = 0.001$).[30] Consistently significant reductions in trabecular bone volume (up to 78%) were observed in 5 patients receiving 26 to 32 months of ERT ($P = 0.043$).[31] No published data are available to date on the effect of ERT on BMD at predominantly cortical sites (eg, hip or wrist).

The beneficial effect of miglustat on bone manifestations in GD may be explained by a direct effect on Gaucher cells and the drug's wide tissue distribution, even in deep organs such as bone. The early effect of miglustat on BMD suggests a direct influence on bone turnover, both at the trabecular and cortical levels, as indicated by a concomitant increase in BMD at the lumbar spine and femoral neck. Significant decreases in BMD at both sites ($P < 0.001$), notably more evident in those who had undergone splenectomy, have been reported previously.[8] In the present study, miglustat monotherapy was associated with significant increases in BMD in both splenectomized patients (femoral neck: $P < 0.001$) and those with an intact spleen (lumbar spine and femoral neck: $P < 0.001$, all patients). BMD was also significantly increased in osteoporotic patients (lumbar spine: $P < 0.001$; femoral neck: $P = 0.006$). No published comparative data on the effect of ERT on BMD in this subgroup are currently available. In the recent retrospective analysis of ICGG data,[28] the overall effect of ERT on BMD seems to have been driven mainly by the increase in BMD in patients with baseline BMD Z-scores above the median (BMD Z-score –1.2).

The mechanism of action of miglustat on bone remodeling requires further study. GSLs are involved in osteoclast differentiation.[32] Expression of complex GSLs, such as GM3 and GM1, is increased during osteoclastogenesis.[34] Conversely, a reduction in GSL synthesis by D-threo-1-phenyl-2-decanoylamino-3-morpholino-1-propanol, a glucosylceramide synthase inhibitor, completely inhibits osteoclastogenesis.[34] Because miglustat is also a glucosylceramide synthase inhibitor, its early effect on BMD may be linked to a direct effect on osteoclastogenesis, although this hypothesis needs to be confirmed experimentally.

Limitations of this study include the fact that the data were derived from 3 separately conducted, prospective clinical studies, each with its own design and objectives. Although conclusions based on such data are preferable to those based on data from retrospective studies, the 3 studies did have an open-label design. In addition, none of the studies were designed to compare the bone response to miglustat with the response to other available agents (eg, bisphosphonates). BMD measurements were performed on a schedule that reflected each site's clinical practice; therefore, data were not available for all patients at each time point. Furthermore, a standardized procedure or centralized review of dual-energy x-ray absorptiometry scans was not included in the study protocols.

CONCLUSIONS

Bone disease in patients with GD can be severely debilitating, and managing the disease remains a challenge. This pooled analysis of 3 open-label clinical trials in patients with GD1 found significant increases in BMD Z-scores as early as 6 months after the initiation of miglustat therapy. A majority of patients were

free of bone pain at the end of the 2-year observation period, and none had emergent bone complications. These findings suggest that miglustat had a beneficial effect on bone disease in these patients with GD1. The improvement in BMD Z-scores over time among splenectomized and osteoporotic patients suggests that miglustat may also increase BMD in patients at high risk for bone loss.

ACKNOWLEDGMENTS

This project was supported by a grant from Actelion Pharmaceuticals Ltd., Allschwil, Switzerland. The first draft of the manuscript was prepared by a medical writer based on discussions with the lead author. The manuscript was then revised and rewritten by the first author and was submitted to all authors for review of the findings, their interpretation, and the conclusions drawn.

The authors thank the local investigators, their staff, and the patients who participated in the 3 studies.

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