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REVIEW

Goal-oriented therapy with miglustat in Gaucher disease

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Key words: **Miglustat – Gaucher disease – Substrate reduction therapy – Therapeutic goals**

ABSTRACT

Background: Gaucher disease (GD) is a highly heterogeneous disorder with multisystem involvement. Specific therapeutic goals for each manifestation of type 1 GD (GD1) were established in 2004 by an international panel of experts, to facilitate better management of GD1 patients. The goals were defined based on experience with enzyme replacement therapy (ERT) using imiglucerase. Miglustat, a small iminosugar, is the only commercially available substrate reduction therapy (SRT) for patients with GD1. Several clinical studies have demonstrated the beneficial effects of miglustat on cardinal disease manifestations of GD1.

Objective: To review the currently available data on miglustat, and provide guidance on the attainment of the GD therapeutic goals with miglustat therapy.

Methods: A literature search identified publications on miglustat using MEDLINE, HighWire Press, and Google Scholar databases. Articles were identified using the terms 'miglustat' and 'Gaucher disease type 1'.

Findings: Improvements in hematological manifestations and organomegaly can be expected with miglustat therapy, with disease stabilization achievable over the long term. Recent data suggest that miglustat can maintain stability in patients with mild to moderate GD1 who have been previously treated with ERT. Miglustat may be beneficial with regards to bone manifestations, with reduction in the incidence of patients reporting bone pain and improvements in bone mineral density seen within the first 24 months of therapy.

Conclusions: Several of the therapeutic goals for patients with GD1 can be achieved with miglustat therapy. In select cases, miglustat can be considered an alternative to ERT for the treatment of patients with GD1. Long-term experience with the use of miglustat will help define its overall safety and efficacy; this information will be useful in determining the role of SRT using miglustat in the management of the general adult GD1 patient population.

Introduction

Gaucher disease (GD) is the most common lysosomal storage disorder with autosomal recessive inheritance[1]. It has an estimated global prevalence of 1:200 000[1]. GD is caused by impaired activity of the lysosomal enzyme glucocerebrosidase, which leads to an accumulation of glucosylceramide in various tissues – primarily the liver, spleen, and bone marrow[2]. Consequently, GD is a highly heterogeneous and multifaceted disease. Organomegaly, hematological complications, and bone manifestations are the typical symptoms of type 1 GD (GD1)[3], but pulmonary, cardiac, and renal involvement may also be present[2,4]. While some patients suffer primarily from organ enlargement and cytopenias, others may experience disabling skeletal

manifestations with only slight organomegaly[5]. The rate of disease progression is variable; some patients may experience episodes of rapid decline interspersed with periods of relative stability.

The wide clinical variability in terms of symptoms, disease severity, and progression in GD may be due in part to the large number of glucocerebrosidase gene mutations that have been identified[6]. However, the disease phenotype cannot reliably be fully predicted by the genotype, and so there is a need for more information on the natural history of GD, particularly with regards to the spectrum of neurological manifestations, upon which the clinical classification of GD is based.

GD1, currently classified as a non-neuronopathic variant, represents around 95% of cases. The neuronopathic forms of GD can be either acute (GD2) or chronic (GD3). However, recent studies have described the presence of peripheral and central neurological symptoms in patients diagnosed with GD1[7–10]; this has led to the suggestion that GD may be more correctly described as a continuum of phenotypes, with neurological involvement in a proportion of patients ranging from mild to extreme severity[9].

The heterogeneous nature of GD necessitates an initial comprehensive, multisystemic assessment, followed by regular monitoring of disease status, to ensure that all aspects of the disease are detected and managed appropriately. GD therapy can then be tailored to each individual patient, depending on their specific manifestations and relative disease severity.

Specific therapeutic goals for each manifestation of GD were established in 2004 by an international panel of experts involved in the International Collaborative Gaucher Group, supported by Genzyme Corporation[11], to facilitate better management of GD1 patients. These goals were based on cumulative experience with more than 3000 GD patients worldwide treated with enzyme replacement therapy (ERT) using recombinant mannose-terminated human glucocerebrosidase (imiglucerase). Imiglucerase has been available since 1994, and is approved for the treatment of patients with a confirmed diagnosis of GD1 that results in one or more of the following features: anemia; thrombocytopenia; bone disease; hepatomegaly; or splenomegaly[12]. ERT has been administered to GD1 patients of all disease subtypes, ranging from mild to severe.

Miglustat reversibly inhibits glucosylceramide synthase, the enzyme that catalyses the first committed step in glycosphingolipid synthesis[13]. This pharmacologic approach is usually referred to as substrate reduction therapy (SRT). Miglustat was licensed in the EU at the end of 2002, and subsequently in the USA in 2003, for the treatment of adults with GD1 for whom ERT is unsuitable or not a therapeutic option[14,15]. Numerous clinical studies have demonstrated the beneficial effects of miglustat on the various disease manifestations of GD1 in patients with mild to moderate disease[16–21]. The aim of this report is to review available data on miglustat in order to provide guidance on the attainment of therapeutic goals for GD patients on miglustat.

Methods

An electronic literature search was performed in April 2008 to identify publications on miglustat, using the MEDLINE, HighWire Press, and Google Scholar databases. Articles in which 'miglustat' and 'Gaucher disease type 1' were listed as a major index term were identified and any clinical studies or reports of the use of commercial drug in clinical practice in patients with GD1 were included. Review articles and preclinical studies were excluded from the search. No inclusive date limits were set due to the relatively recent approval of miglustat for treatment of GD1. The literature search was further supplemented by additional relevant references, such as congress abstracts.

Bone manifestations

Bone abnormalities are one of the most debilitating aspects of GD[1,22], and bone manifestations have been identified as being one of the most common GD symptoms[1]. However, until recently there has been relatively little emphasis on the therapeutic management of GD-related bone pathology.

At the clinical level, bone pain is often reported by GD patients as recurrent, and is characterized by acute or chronic episodes of dull, achy bone pain that may or may not correlate with radiological evidence of bone pathology. Gaucher bone 'crisis' is a severe clinical manifestation occurring periodically in approximately 10% of patients[23,24], involving episodes of sustained 'excruciating' bone pain – usually located in the thighs – accompanied by fever, leucocytosis and localized edema in some cases. These episodes often lead to hospitalization[11]. The clinical symptoms of GD bone disease therefore place a heavy burden on patients' quality of life[23,25], with physical limitations (frequently coupled with chronic fatigue) impacting on school, occupation, and social activities.

Bone pathologies in GD can typically be divided into three, often co-existing, categories: local disease featuring potentially reversible abnormalities adjacent to heavily affected bone marrow, such as cortical thinning and long-bone deformities; focal disease involving

irreversible lesions such as osteonecrosis (bone death); and osteosclerosis[22,26]. Additional findings include signs of thrombosis and inflammatory processes, and generalized osteopenia and osteoporosis (reduced bone mass)[22,26].

Local modeling deformities are usually asymptomatic, but serve as useful radiological indicators of GD. The best known of these is the Erlenmeyer flask deformity, which presents in around 80% of patients[27]. Osteopenia, which is found in the majority of GD patients, is detected as a reduction in bone mineral density (BMD); significant bone loss increases the risk of pathological bone fractures[3,22,28]. Bone infarction (ischemic necrosis) can also occur in GD patients, and is associated with severe bone pain. It can lead to focal osteosclerosis, an abnormal hardening of the bone. Chronic focal infarction and ischemic lesions can also lead to osteonecrosis (avascular necrosis), the most severe and clinically significant of the skeletal complications of GD[3,22,29]. Usually involving long bones and the pelvis, focal areas of osteonecrosis can progress to subcortical joint collapse and secondary degenerative arthritis, which may necessitate joint replacement surgery. It is an irreversible process, and so treatment strategies should aim at prevention and early detection[22].

Epidemiological data show that bone manifestations are not limited to GD patients with severe disease[1]. Table 1 illustrates the range of bone abnormalities recorded in the ICGG registry in 2000. Radiological evidence of bone manifestations was found in 94% of patients.

GD affects both the bone marrow and cortical bone tissue compartments. Abnormalities in bone tissue in GD patients can be detected using plain radiography, which is useful for the identification of fractures, modeling disorders and focal lesions, as well as signs of bone marrow infiltration by Gaucher cells (evident as endosteal scalloping). Bone mineral density (BMD) is assessed using dual-energy X-ray absorptiometry (DEXA) or dual-energy quantitative computed tomography (DEQCT)[30–32]. Abnormalities in bone marrow are generally assessed using magnetic resonance imaging (MRI) techniques.

Table 1. *Frequency of bone manifestations in patients from the ICGG registry (reproduced with permission from Charrow* et al[1]*.)*

Manifestation	Frequency, *n* (%)
Bone pain	449/716 (63)
Bone crises	210/644 (33)
Radiological bone disease	706/755 (94)
Erlenmeyer flask disease	323/706 (46)
Osteopenia	300/706 (42)
Marrow infiltration	281/706 (40)
Infarction	174/706 (25)
Avascular necrosis	173/706 (25)
Fracture	108/706 (15)
Lytic lesions	58/706 (8)
Joint replacement	56/706 (8)

Due to physico-chemical properties that enable a wide distribution throughout body tissues, miglustat has the potential to reach effector cells within bone[33]. In addition, recent experimental findings suggest that glycosphingolipids can influence osteoclastogenesis *in vitro*, and inhibitors of glycosphingolipid synthesis have been shown to inhibit osteoclastogenesis[34]. The extent to which changes in osteoclast numbers and/or function occur as a result of miglustat treatment, and the consequences thereof on GD bone manifestations, remain to be established. However, clinical observations indicate beneficial effects of miglustat on bone health in GD patients.

A pooled analysis of the effect of miglustat on bone manifestations and on BMD, using data collected prospectively over 2 years from GD1 patients in three multinational, open-label clinical trials with miglustat, was published in 2007[19]. Data on the effects of the drug on bone manifestations were based on a cohort of 72 adult patients with GD1, of whom 57% had received ERT, and 28% had undergone splenectomy. The overall median treatment duration with miglustat was 568 days. In total, 63% of patients reported bone pain at baseline; only 17% of these individuals reported bone pain after 2 years of therapy (Figure 1). This reduction in incidence of reported bone pain might be expected to decrease the need for painkillers, however, this study did not record the frequency of administration of analgesics.

In the same pooled analysis, early and sustained increases in lumbar spine and femoral neck BMD were seen after starting miglustat monotherapy, with significant increases from baseline evident at 6, 12, and 24 months (Table 2). These improvements were notably higher in splenectomized patients and osteoporotic patients, who are expected to be at higher risk of GD-related bone pathology. No bone crisis, avascular necrosis or bone fracture was reported during 2 years of follow-up. Further information supportive of these observations was obtained in a study of seven patients who were switched from ERT to miglustat. Bone manifestations in these patients remained stable over a 12–18 month follow-up period[35], suggesting that patients switched from ERT can remain stable and

show no evident skeletal deterioration on miglustat therapy alone.

The effects of miglustat on bone marrow infiltration are emerging; a preliminary report by Hollak *et al.*[36] in 2004 noted marked and progressive improvement in bone marrow fat fraction, indicating clearance of Gaucher cells from the bone marrow (Figure 2)[36,37].

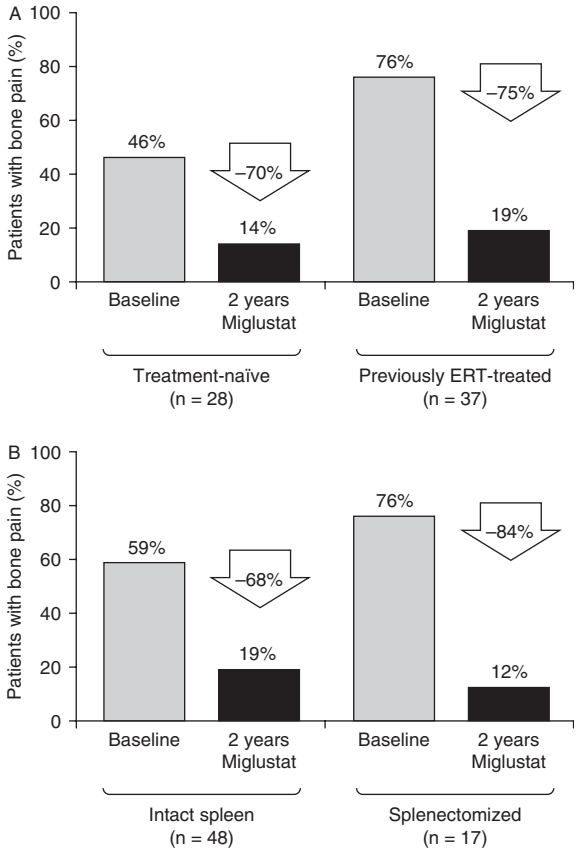

Figure 1. *Proportion of patients without bone pain at baseline and after 2 years of miglustat therapy – response by treatment history (A) and spleen status (B) (reproduced with permission from Pastores* et al.*[19])*

Following on from this initial positive result, Roca *et al.* recently used the Spanish-MRI method[38,39] to monitor bone effects during 12 months of miglustat therapy. Reductions in lumbar, pelvic, and trochanter bone marrow infiltration were observed[39]. Further, a preliminary report on MRI assessments of 7 patients from a 1-year, prospective, open-label study of miglustat in GD1 detected greater clearance of vertebral bone marrow infiltration in treatment-naïve patients compared with patients who had previously received ERT[39].

The specific therapeutic goals for skeletal pathology in GD1 are: to lessen or eliminate bone pain within 1 to 2 years; to prevent bone crises; and to increase trabecular BMD by 3 to 5 years[11]. Data from studies of miglustat in GD1 suggest that reduction in the incidence of reported bone pain and elimination of bone crises within 2 years is a realistic target with miglustat therapy, while improvements in BMD may also be expected within the required time scale (Table 3). However, these data are taken from a small patient cohort ($n = 72$); confirmation of these beneficial effects of miglustat on bone manifestations would require a longer period of observation in a larger number of subjects.

Hematological effects

Anemia is one of the typical manifestations of GD. The main clinical symptom is fatigue, but it may also lead to dyspnea and angina in elderly patients. Chronic fatigue due to anemia is an important contributor to reduced quality of life in GD patients[40]. The standard definitions for anemia are based on age- and gender-specific mean hemoglobin concentrations. For people over 12 years of age, a hemoglobin concentration <12 g/dL

Table 2. *Changes over time in BMD Z-scores at the lumbar spine and hip during miglustat therapy for up to 2 years (reproduced with permission from Pastores* et al*[19])*

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

for men and <11 g/dL for women is considered to indicate anemia[11]. For children, anemia is defined as a hemoglobin concentration <10.5 g/dL for those between the ages of 2 and 12 years, <9.5 g/dL for between 6 months and 2 years, and <10.1 g/dL for children under 6 months of age[11]. Therapeutic goals for hematological parameters in GD must be gender- and age-specific.

Thrombocytopenia is also a common manifestation of GD, and can lead to spontaneous bleeding and bruising. In GD, thrombocytopenia is considered severe enough to require treatment when repeated platelet counts are less than 100,000 μL[11]. The platelet response to GD therapy may depend on the initial magnitude of thrombocytopenia, with patients with moderate severity more likely to achieve a higher platelet count (>120,000 μL) than those with more pronounced thrombocytopenia[41]. Further, patients with intact spleens are more likely to have lower baseline platelet counts than those who have undergone a splenectomy, and may remain thrombocytopenic after treatment despite a significant increase in platelet count[41].

The effects of miglustat on the hematological manifestations of GD have been documented in clinical trials. In the initial 12-month, open-label, Phase I/II trial in 28 patients with GD1[16], an increase of 0.26 g/dL in hemoglobin level was seen after 12 months of therapy ($n=22$), with significant increases from baseline observed during the 24-month extension phase ($n=14$, mean increase 0.74 g/dL, 95% CI 0.33–1.14, $p=0.001$) (Figure 3)[17]. As expected, increase of hemoglobin levels was more prominent in patients with anemia at baseline – in 9 patients with anemia, 5 had an increase of more than 0.5 g/dL at month 12[17]. Platelet counts were also improved, with significant increases evident after the first 12 months of therapy ($n=22$, 8.3×10^9/L, 95% CI −0.5 to 0.57, $p=0.014$)[16], and continued improvements during the extension period, reaching a mean increase of 20×10^9/L by month 36 (95% CI 12–27, $p<0.001$, $n=14$) (Figure 3). Consistent with these findings, results from a second study of miglustat in GD1 patients demonstrated a significant increase in platelet count after 12 months of miglustat therapy ($n=7$, mean change from baseline 13.9×10^9/L, 95% CI 1.8–26.0, $p=0.030$), which continued to improve throughout the 24-month period of observation[18].

Hematological manifestations in patients that have previously been stabilized on ERT therapy can be maintained with miglustat therapy. In a clinical trial in 36 GD1 patients previously stabilized on imiglucerase, there were no significant differences in mean change from baseline hemoglobin levels after 6 months of therapy between three groups of patients (i.e., those receiving imiglucerase or miglustat alone, and those receiving combination therapy)[21]. The efficacy of miglustat in GD1 patients treated in a clinical practice setting was evaluated independently in a prospective cohort study which involved treatment-naïve patients ($n=10$). The responses noted in these patients were compared with historical data from patients with similar disease severity on ERT (ZAGAL study) and who were enrolled in the Spanish registry (FEETEG). This study revealed comparable increases in hematological parameters after 6 months in patients on either ERT or miglustat (Table 4)[20]. In the same study, maintenance or improvement of hematological parameters was demonstrated in all 12 patients who had been switched from ERT to miglustat[20]. After 12 months of miglustat therapy, hemoglobin levels either increased or remained in the normal range and platelet counts remained within the normal range[20]. Similar results were seen in a cohort of 6 patients switched from ERT to miglustat, in whom blood counts remained stable after receiving miglustat for 3 to16 months[42].

In the long term, stabilization of hematological manifestations is an achievable goal with miglustat therapy.

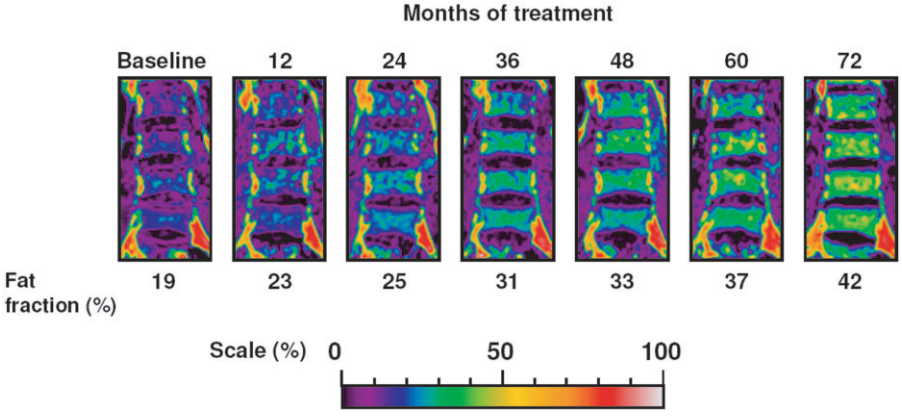

Figure 2. *Marked and progressive improvement in bone marrow fat fraction with miglustat, measured by QCSI over 1 – 6 years (reproduced from Aerts* et al.[37]*, with kind permission from Springer Science and Business Media)*

Table 3. *Potential for attainment of recommended therapeutic goals for adult GD1 patients (based on experience with ERT)[11] with miglustat therapy*

GD1 manifestation	Therapeutic goals	Predicted outcomes with miglustat therapy	Source study and number of patients
Bone	• Lessen or eliminate bone pain within 1 to 2 years	• Reduce incidence of reported bone pain within 2 years	• Pastores *et al.*, 2007[19] ($n = 72$)
	• Prevent bone crises	• No bone crises observed over 2 years	
	• Prevent osteonecrosis and subchondral joint collapse	• No osteonecrosis observed over 2 years	
	• Increase BMD (attain normal or ideal peak skeletal mass) ○ Adult patients: increase trabecular BMD by 3–5 years ○ Pediatric patients: increase cortical and trabecular BMD by Year 2	• Adult patients: increase BMD by 6 months, with continued increases up to 24 months • Pediatric patients: no data available	
Anemia	• Increase hemoglobin levels within 12–24 months to ≥ 11 g/dL for women and ≥ 12 g/dL for men	• Increase hemoglobin levels by 12 months with continuous improvements up to 36 months	Cox et al, 2000[16]; Elstein *et al.*, 2004[17] ($n = 28$) Pastores *et al.*, 2005[18] ($n = 12$) Giraldo *et al.*, 2006[20] ($n = 25$) Elstein *et al.*, 2007[21] ($n = 24$)
	• Eliminate blood transfusion dependency	• No data available	
	• Reduce fatigue, dyspnea, angina	• Reduce fatigue, dyspnea, angina	
	• Maintain improved hemoglobin values achieved after the first 12 to 24 months of therapy	• Maintain improvements achieved after 12–36 months	Heitner *et al.*, 2006[43] ($n = 23$)Mehta *et al.*, 2006[42] ($n = 6$) Giraldo *et al.*, 2006[20] ($n = 25$)
Thrombocytopenia	• All patients: Increase platelet counts during Year 1 sufficiently to prevent surgical, obstetrical and spontaneous bleeding	• Increase platelet counts during Year 1 sufficiently to prevent surgical, obstetrical and spontaneous bleeding	Cox *et al.*, 2000[16] ($n = 28$) Pastores *et al.*, 2005[18] ($n = 12$) Giraldo *et al.*, 2006[20] ($n = 25$) Elstein *et al.*, 2007[21] ($n = 24$)
	• Patients with splenectomy: normalization of platelet count by 1 year of treatment	• No specific data available	
	• Moderate baseline thrombocytopenia: increase 1.5–2.0 fold by Year 1, approaching low/normal levels by Year 2	• Continuous improvements in platelet count up to Year 5	Elstein *et al.*, 2004[17] ($n = 28$) Heitner *et al.*, 2006[43] ($n = 23$)
	• Severe baseline thrombocytopenia: increase 1.5 fold by Year 1 and continue to increase slightly during Years 2–5 (doubling by Year 2), but normalization is not expected	• Continuous improvements in platelet count up to Year 5	Elstein *et al.*, 2004[17] ($n = 28$) Heitner *et al.*, 2006[43] ($n = 23$)

	• Avoid splenectomy (may be necessary during life-threatening hemorrhagic events)	• Avoid splenectomy	Cox *et al.*, 2000[16]; Elstein *et al.*, 2004[17] ($n=28$) Pastores *et al.*, 2005[18] ($n=12$)
	• Maintain stable platelet counts to eliminate risks of bleeding after a maximal response has been achieved	• Maintain stable platelet counts after maximal response achieved	Heitner *et al.*, 2006[43] ($n=23$) Mehta *et al.*, 2006[42] ($n=6$)
Hepatomegaly	• Reduce and maintain liver volume to 1–1.5 times normal	• Reduce liver volume by 12% by Year 1 with continuous improvements up to 36 months of therapy	Cox *et al.*, 2000[16]; Elstein *et al.*, 2004[17] ($n=28$) Pastores *et al.*, 2005[18] ($n=12$) Giraldo *et al.*, 2006[20] ($n=25$) Elstein *et al.*, 2007[21] ($n=24$)
	• Reduce volume by 20–30% within Year 1 and by 30–40% by Year 3–5	• Maintain reductions in liver volume over long-term	Heitner et al, 2006[43] ($n=23$)
Splenomegaly	• Reduce and maintain spleen volume to 2–8 times normal	• Reduce spleen volume by 15% by Year 1 and by 30% by Year 3	Cox *et al.*, 2000[16]; Elstein *et al.*, 2004[17] ($n=28$) Pastores *et al.*, 2005[18] ($n=12$) Giraldo et al, 2006[20] ($n=25$) Elstein et al, 2007[21] ($n=24$)
	• Reduce spleen volume by 30–50% within Year 1 and by 50–60% by Year 2–5	• Maintain reductions in spleen volume over long term	Heitner *et al.*, 2006[43] ($n=23$)
	• Alleviate symptoms due to splenomegaly: abdominal distension, early satiety, new splenic infarction	• Alleviate symptoms due to splenomegaly: abdominal distension, early satiety, new splenic infarction	Cox *et al.*, 2000[16]; Elstein *et al.*, 2004[17] ($n=28$) Pastores *et al.*, 2005[18] ($n=12$)
	• Eliminate hypersplenism	• Eliminate hypersplenism	Cox *et al.*, 2000[16]; Elstein *et al.*, 2004[17] ($n=28$) Pastores *et al.*, 2005[18] ($n=12$)
Pulmonary manifestations	• Reverse hepatopulmonary syndrome	• No data available	
	• Ameliorate pulmonary hypertension (GD therapy plus adjuvant treatments required)	• No data available	
	• Improve functional status and quality of life	• Potential improvements in functional status	Schiffmann *et al.*, 2008[48] ($n=30$)
	• Prevent rapid deterioration of pulmonary disease	• No data available	
	• Prevent pulmonary disease by avoidance of splenectomy	• May prevent pulmonary disease by avoidance of splenectomy	Cox *et al.*, 2000[16]; Elstein *et al.*, 2004[17] ($n=28$) Pastores *et al.*, 2005[18] ($n=12$)

Preliminary results from a multinational safety and efficacy study assessing long-term miglustat therapy in 23 patients have demonstrated stabilization of hemoglobin levels between 36 and 60 months of therapy, with most (70%) patients consistently achieving hemoglobin values of >11.5 g/dL[43]. Platelet counts continued to increase over time, with treatment up to 60 months[43].

Hemoglobin levels in GD1 patients should be increased within 12 to 24 months, to ≥11 g/dL for women and children and ≥ 12g/dL for men[11]. This goal can be effectively met with miglustat therapy, with increases in hemoglobin seen after 12 months, and additional improvements evident in the following 12 months (Table 3). The established therapeutic goals also state that these initial improvements in hemoglobin values should be maintained over the long term; this can be achieved with miglustat treatment, which has been shown to stabilize hemoglobin levels after 36 months' therapy (Table 3).

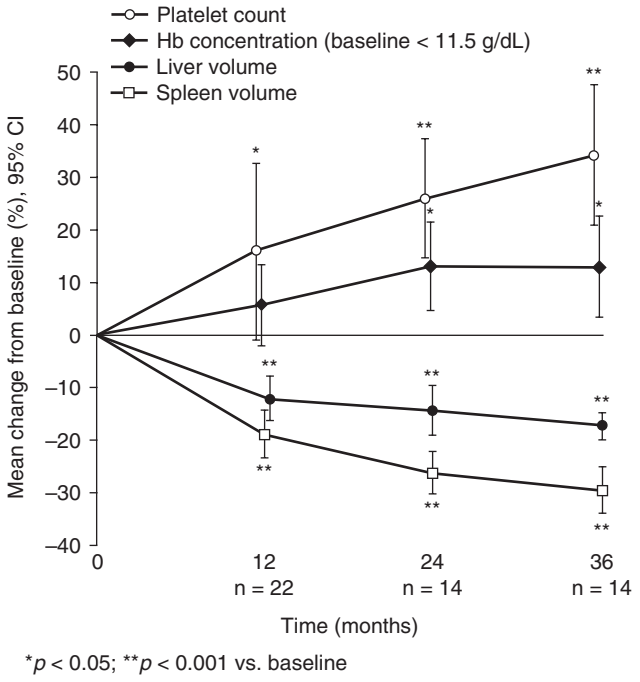

Figure 3. *Effects of miglustat on hemoglobin and platelets and percentage change in mean liver and spleen volume over 36 months[16,17]*

The primary therapeutic goal for thrombocytopenia in GD is to increase platelet counts during the first year of treatment sufficiently to prevent spontaneous as well as surgical or obstetrical bleeding (Table 3)[11]. Miglustat therapy has been shown to provide significant increases in platelet count during the first 12 months of treatment. In patients experiencing an increase in platelet count, no cases of spontaneous bleeding were reported. In patients with an intact spleen, specific treatment goals are to increase platelet counts by 1.5- to 2-fold by Year 1 in patients with moderate baseline thrombocytopenia, approaching a low to normal level by Year 2 (Table 3). Patients with severe baseline thrombocytopenia should experience a 1.5-fold increase during the first year of therapy followed by continued increases over the next 4 years; however normalization may not be expected (Table 3). Data from clinical studies suggest that increases in platelet count with miglustat therapy may occur less rapidly than those seen with ERT, particularly during the initial phase of treatment. However, platelet counts may continue to improve up to 60 months of therapy. The steady, continuous increase in platelet count with miglustat therapy leads to stabilization over the long term. Miglustat therapy therefore meets the second specific therapeutic goal for thrombocytopenia – maintenance of platelet counts once a maximal response has been achieved.

The specific therapeutic goal for thrombocytopenia in splenectomized patients is normalization of platelet count by 1 year of treatment. There are limited data on the effect of miglustat in splenectomized patients; however, preliminary results from the long-term study of up to 5 years' treatment with miglustat ($n = 23$) showed comparable results on hematological

Table 4. *Comparison of previously treatment-naïve GD patients receiving miglustat therapy with historical data from patients receiving ERT (>30 U/kg every two weeks) (reproduced from Giraldo* et al[20]*)*

	Miglustat ($n = 9$)	ERT ($n = 40$)	p-value
Age (years)	46.7 (21–74)	37.4 (17–52)	0.021
Gender M/F	2/7	19/21	–
Severity score index	6.33 (4–9)	6.80 (1–10)	0.683
Previous spleen removal	2	0	–
Mean decrease in spleen size at 6 months (cm)	9.23 (1.5–18)	4.22 (0–80)	0.308
Mean decrease in liver size at 6 months (cm)	0.22 (0–10)	4.29 (1.6–5.7)	0.014
Mean increase in hemoglobin at 6 months (g/dL)	0.77 (0.2–1.8)	0.81 (0–4.0)	0.856
Mean increase in platelets at 6 months ($\times 10^9$/L)	41.5 (10–116)	32.7 (0–95)	0.324
Mean decrease in chitotriosidase activity at 6 months (%)	38.2 (20.6–42.8)	42.8 (0–80.2)	0.136

Numbers in brackets indicate range

parameters in splenectomized patients and those with intact spleens[43].

Organomegaly

Hepatomegaly is defined as a liver mass of greater than 1.25 times the normal (i.e. 2.5% of total body weight in kilograms). It is usually assessed by magnetic resonance imaging (MRI) or computed tomography (CT) as well as by physical examination[1]. GD patients typically exhibit moderate hepatomegaly (liver volume between 1.25 and 2.5 times greater than normal), or severe hepatomegaly (greater than 2.5 times the normal volume)[41]. Patients with moderate hepatomegaly are more likely to achieve normal liver volumes with GD therapy compared with those with severe hepatomegaly[11]; this may be due to the presence of fibrosis in severely affected patients[41]. In these patients, it is important to screen for possible intercurrent illnesses, such as cirrhosis, hepatitis, portal hypertension, and hepatopulmonary syndrome, which may be affecting response to treatment.

Miglustat has been shown to have beneficial effects on liver volume in GD1 patients. In the initial Phase I/II clinical trial and extension in 28 GD1 patients[16,17], mean liver volumes were reduced by 7% (3.4–10.5, $p<0.001$, $n=23$) after 6 months, and by 12% after 12 months of therapy (7.8–6.4, $p<0.001$, $n=22$)[16]. Liver volumes continued to show a statistically significant and progressive reduction from baseline throughout the extension phase, reaching a reduction of 14.5% vs. baseline after 24 months ($p<0.001$, $n=12$) and 18% after 36 months ($p<0.001$, $n=12$) (Figure 3)[17]. Similarly, in the second Phase II study in 12 GD1 patients, significant mean changes in liver volume were observed at 6 months (8.4% decrease, 95% CI -16.1–0.7, $p=0.036$, $n=8$), with a continued reduction up to 18 months of therapy[18]. However, in comparison with ERT, reductions in liver volume appear to occur at a slower rate with miglustat therapy[20] (Table 4).

Splenomegaly is defined as a mass greater than 0.2% of the normal body weight in kilograms, and is usually assessed by CT or MRI[1]. Ultrasonography can also be used to detect Gaucher cell infiltration of the spleen[44]. Splenomegaly in GD1 is associated with spleen volumes typically exceeding five times the normal volume in around 90% of patients. As with hepatomegaly, response to treatment tends to vary in line with the degree of splenomegaly at baseline. Patients with moderate splenomegaly (between 5 and 15 times normal spleen volume) are more likely to achieve normalization of spleen volume than those with initial spleen volumes of more than 15 times normal[11].

In the initial Phase I/II clinical trial and extension phase, a 15% decrease (95% CI 11.8–18.4, $p<0.001$, $n=23$) in spleen volume was observed after 6 months, reaching 19% (95% CI 7.8–16.4, $p<0.001$, $n=22$) at Month 12[16]. Mean spleen volume continued to decrease during the extension phase, reaching a mean decrease of 30% after 36 months ($n=10$) (Figure 3)[17]. Similarly in the Phase II study, consistent reductions in spleen volume were seen throughout the study period, reaching statistical significance at 6 months (19% decrease, 95% CI 30.4–7.6, $p=0.006$, $n=8$) and 18 months (24.3% decrease, 95% CI 33.6–15.1, $p=0.001$, $n=7$)[18].

In two 12-month studies involving patients switched to miglustat therapy after previous disease control on ERT (both $n=12$), spleen volumes remained stable after 12 months[20,21]. Further, comparable decreases in spleen size were demonstrated after 6 months therapy in ten treatment-naïve patients receiving miglustat compared with those on ERT (Table 4)[20].

The primary therapeutic goal for treatment of hepatomegaly in GD1 is to reduce the liver volume to 1–1.5 times normal[11]. A reduction of 20–30% within 1 year, and of 30–40% by Year 3 to 5, is recommended (Table 3)[11]. Reductions in liver volume with miglustat may occur at a slower rate than with ERT; however, data from long-term studies suggest that liver volume continues to decrease with miglustat maintenance therapy[43] (Table 3).

Targets for treatment of splenomegaly are to reduce and maintain spleen volume to ≥2–8 multiples of normal, with reductions from baseline of 30–50% within the first year of therapy and further reductions up to 50–60% by Year 2 to 5 (Table 3). These reductions in spleen volume are aimed at alleviation of the clinical symptoms associated with a new splenic infarction, as well as prevention of the need for splenectomy. Similar to findings in hepatomegaly, reductions in spleen volume seen with miglustat therapy were less rapid than those seen with ERT, reaching 15% by Year 1 and 30% by Year 3 (Table 3). The less rapid effect of miglustat when compared with ERT in reducing spleen volume might be the cause of the slower increase in platelet count seen with miglustat therapy.

Pulmonary involvement

Although the lungs are a site for accumulation of Gaucher cells, pulmonary complications are one of the less common manifestations of GD. Only 1–2% of GD1 patients exhibit pulmonary manifestations, and these are usually in the form of interstitial lung disease, pulmonary hypertension or hepatopulmonary

syndrome[4,45]. Pulmonary complications occur more frequently in type 3 GD[3]. Avoiding splenectomy, if possible, has been associated with prevention of pulmonary disease[11]. Pulmonary hypertension is a serious development, being an important cause of early mortality in GD1[46]. Risk factors for pulmonary hypertension and hepatopulmonary syndrome include splenectomy, female gender, a positive family history, particular deleterious glucocerebrosidase mutations and polymorphisms in the angiotensin-converting enzyme (ACE) I gene[1]. Despite its serious nature, pulmonary hypertension is treatable with targeted therapies such as bosentan, as well as vasodilator therapies[47].

Due to the size and specific physico-chemical properties of miglustat, it is able to penetrate the lung tissue, suggesting that SRT may be an effective means of counteracting pulmonary pathology in GD[33]. As yet there are limited data on the effects of miglustat on pulmonary manifestations. However, in a randomized trial where 30 type 3 GD patients received either ERT alone or ERT in combination with miglustat, patients on combination therapy demonstrated improvements in forced vital capacity after 12 months of therapy (of 20 evaluable patients on combination therapy, 11 patients improved, 4 were stable and 5 deteriorated)[48].

Therapeutic goals for the treatment of pulmonary manifestations in GD1 include reversal of hepatopulmonary syndrome and dependence on oxygen, amelioration of pulmonary hypertension, improved functional status and quality of life, and prevention of rapid deterioration of pulmonary disease and sudden death by avoidance of splenectomy[11]. Limited data on the effect of miglustat on pulmonary disease are available; however, no serious pulmonary adverse events were recorded during clinical trials involving patients on miglustat. Miglustat has been shown to effectively reduce spleen volume, reducing the need for splenectomy, which may contribute towards prevention of pulmonary disease (Table 3).

Disease severity markers

Several plasma proteins have been identified that are elevated in GD patients and are considered useful indicators of disease severity. ACE and tartrate-resistant acid phosphatase (TRAP) have been shown to correlate with disease activity[49,50]. Other potentially useful biomarkers currently being investigated include the chemokine CCL18/PARC[51].

Plasma chitotriosidase is secreted by activated macrophages, and is found to be markedly increased in patients with GD[52,53]. Decreases in chitotriosidase levels with treatment have been shown to correlate with improvements in hematological and visceral symptoms[49]. Progressive reductions in plasma chitotriosidase levels have been demonstrated over 36 months of miglustat therapy (Figure 4)[17], achieving statistical significance at Month 12 (16.4% decrease from baseline, $p<0.001$, $n=22$) and maintaining significance at all subsequent time points. Further, preliminary long-term data have shown a steady and continued decline of chitotriosidase activity in 23 patients during up to 5 years of therapy[43]. In patients switched from ERT to miglustat, plasma chitotriosidase levels remained stable after 12 months in 96% (27/28) of patients[21]. These findings are supported by 'real-world' data from the ZAGAL study (clinical site experience using the commercial drug), demonstrating stable plasma chitotriosidase and CCL18/PARC levels after 12 months of miglustat in 12 patients previously stabilized on ERT[20]. In addition, case studies in patients switched from ERT to miglustat therapy have shown stable or improved chitotriosidase levels after 3–24 months of treatment ($n=7$)[42,54].

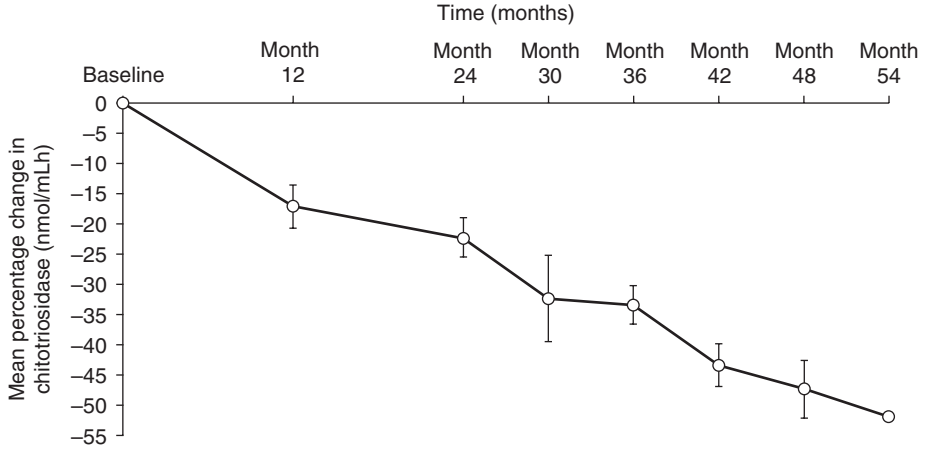

Figure 4. *Change in plasma chitotriosidase levels from baseline after 12, 24, and 36 months of miglustat therapy in patients with GD1 (reproduced from Elstein* et al.*[17], with kind permission from Springer Science and Business Media)*

No therapeutic goals were proposed by the expert panel for biomarker levels in GD1, as absolute levels of biomarkers are not indicative of disease severity in individual patients[11]. Alterations in therapy should not be made based solely on biomarker levels[11]. Rather, biomarker assessments should be used to support other clinical findings. In addition, monitoring of biomarker activity during miglustat therapy may be useful as an indicator of patient compliance, as increases in plasma chitotriosidase are likely to occur during a clinical relapse with poor treatment compliance.

Tolerability

Withdrawal rates due to adverse events during the initial miglustat clinical studies ranged from 7.1% (2/28) over 12 months[16] to 16.6% (2/12) over 24 months[18]. In the ERT and miglustat combination study, 25% (9/36) patients withdrew over the 24-month study due to adverse events[21]. The most commonly reported adverse events with miglustat therapy are gastrointestinal. In clinical trials, diarrhea, weight loss, and flatulence were the most common side effects of treatment, but these tended to improve over time[16–19]. Preliminary results from an ongoing post-marketing surveillance study, in which data have now been obtained from 122 GD1 patients receiving miglustat between March 2003 and April 2008, show withdrawals due to adverse events in 22/122 (18.0%) patients during this five year period.[55] Fourteen (64%) of the 22 cases were due to gastrointestinal disorders. Anti-diarrheal medications such as loperamide have proved effective in managing diarrhea in GD patients receiving miglustat therapy[20]. Further, experience with miglustat in the clinical setting has shown that gastrointestinal disturbances resolve in patients who comply with dietary recommendations[20].

Intestinal disaccharidases are essential for the appropriate digestion of carbohydrates. Food carbohydrates are hydrolyzed to monosaccharides before transport across the microvillus membrane. An incomplete digestion of carbohydrates is the cause of the gastrointestinal disturbances, although other factors could be contributing to a variation in the production of intestinal disaccharidases, such as age[56] or zinc deficiency[57]. These reasons reinforce the importance of recommending a diet low in carbohydrates during the first weeks of exposure to miglustat in order to avoid a depletion of intestinal disaccharidases. Later meals with different contents of carbohydrates can be introduced to explore level of tolerance.

Nervous system related problems were the second most frequent category of adverse events reported during clinical trials with miglustat. Tremor was highlighted as a side effect of miglustat treatment; however, further investigations have shown that tremor is not severe enough to interfere with manual dexterity in most cases, and tends to reduce spontaneously while on continued therapy or with lowering of the miglustat dose[14]. Some cases of peripheral neuropathy were reported in early clinical trials with miglustat in GD1[14,16]. No definite explanation for the occurrence of peripheral neuropathy has been established. However, an epidemiological survey has reported a higher than expected frequency of neurological complaints in GD1 patients[7]. Further, in a 2-year ongoing prospective study specifically designed to investigate the occurrence and progression of neuropathy in GD1 patients not exposed to miglustat, 10.7% (11/103) presented with polyneuropathy and 1.9% (2/103) with mononeuropathy at baseline[10].

Preliminary safety data from the ongoing post-marketing surveillance program are consistent with the findings from the clinical trials, with no new safety concerns observed[55]. To date, 83% of patients in this study have been taking miglustat for at least 24 weeks, 68% of patients have been taking it for at least 52 weeks and 38% of patients have been treated for at least 130 weeks. Adherence to miglustat therapy has been good, with 86 of 122 patients (70.5%) remaining on miglustat therapy at the five-year time point.

The program has not generated any further adverse drug reactions relating to the nervous system. Notably, baseline data from this surveillance program indicated that pre-existing bone disease and neurological manifestations were present in 60 and 23 patients, respectively[55], and a further 23 patients had a history of neurological symptoms, highlighting once again the need for highly comprehensive initial assessments, including physical examination, thorough appraisal of Gaucher-related bone disease and neurological evaluations, in addition to standard measurement of liver and spleen status and hematological indices[31,32]. In any case, there is a need for appropriate monitoring for unexpected events or other potential safety consideration with long-term miglustat treatment.

Implications for clinical management

In 2003, a position statement on the role of miglustat for the treatment of GD1 was published[58]. This represented the consensus view of an independent international advisory council to the European Working Group on Gaucher Disease (EWGGD). Based on the results from three clinical trials[16,17,59], the advisory

council devised a treatment algorithm for the use of miglustat in mild-to-moderate patients with GD1[14]. Miglustat was recommended for the treatment of adult GD1 patients who are unable or unwilling to receive ERT, unable to continue with ERT, or have persistent signs of disabling disease despite ERT treatment[14].

Since the publication of the EWGGD report[58], further data on the efficacy of miglustat in mild to moderate GD1 patients have become available from more recent clinical trials[18,21] and from 'real-world' cohort studies (clinical site experience using the commercial drug) and case reports[20,42,54]. Data from these reports provide guidance on the attainment of therapeutic goals in GD1 patients on miglustat (Table 3). It is hoped that this information will aid physicians in the effective management of GD1 patients receiving miglustat therapy.

In summary, improvements in hematological manifestations and hepatosplenomegaly can be expected with miglustat therapy, with disease stabilization achievable over the long term, although these improvements may occur less rapidly than those seen with ERT. However, the clinical significance of this observation is uncertain, and it is recommended that all patients receiving miglustat therapy be carefully monitored. Miglustat has a potential role in maintaining disease control in patients previously stabilized on ERT, but who are no longer willing or able to receive it. In addition, miglustat may be beneficial for GD-related bone manifestations, with respect to reduction of incidence of reported bone pain and improvements in BMD[11].

GD therapy, whether with ERT or miglustat, should be initiated early, not only to prevent irreversible consequences of GD such as disability from bone-related complications and splenectomy, but also to improve patients' quality of life as quickly as possible. The symptoms of GD, in particular bone-related manifestations, can have a considerable impact upon patients' lifestyle and social function, as well as on their physical wellbeing[25]. Moreover, physicians should bear in mind that therapeutic regimens can also affect aspects of quality of life. For example, dependence on periodic intravenous infusions, as with ERT, can result in significant discomfort and inconvenience[40], and may affect patient compliance with treatment. A preliminary report has suggested that oral therapy with miglustat may offer improved overall convenience and patient satisfaction with treatment compared with ERT[60]. High overall satisfaction and improvements in perception of global health, physical activity, and social functioning have been observed with oral miglustat[20]. In patients showing poor compliance with ERT (e.g. those who have difficulties attending clinic visits or who miss visits due to anxieties regarding the discomfort of intravenous infusions), miglustat may be considered as a therapeutic option.

Physicians should also be aware that for some manifestations of GD, adjunctive therapies may be beneficial. Supplementation of ERT therapy with bisphosphonates may lead to significant improvements in BMD that are not seen with ERT alone[61]. In addition, combination therapy with ERT and miglustat may be beneficial for some patients, particularly those with more severe disease or persistent symptoms[14]. Combination therapy in these patients is not a precluded indication, but is an issue which requires further investigation.

Discussion

Previously established therapeutic goals for GD1 were based on findings from over 3000 patients treated with ERT from the ICGG registry[11]. Comparably fewer data are available relating to miglustat in GD1, and the evidence regarding the efficacy of miglustat has been drawn mainly from clinical trials and published reports of its use in practice[16–18,20,59]. In total, data on the efficacy of miglustat presented in this review are based on over 120 GD1 patients and safety data on over 200 patients[16–18,20,21,42,54,55,59], There are limited data available on naïve patients treated with miglustat, as all three non-comparative, open-label trials (and the extension studies) enrolled a proportion of patients who had previously received ERT[16–18,59]. Furthermore, case reports of the effects of miglustat included patients switched from ERT[42,54]. Only the ZAGAL study provides a specific analysis of the effect of miglustat in treatment-naïve patients[20]. There is therefore a need for further data on naïve patients, which may be obtained via patient registries and surveillance studies.

The studies involving patients switched from ERT to miglustat, and comparisons of miglustat-treated patients with historical data on patients treated with ERT, have demonstrated that miglustat may have a role in disease stabilization among patients previously on ERT (Table 4)[20,21]. Data from clinical trials suggest that miglustat may be slower at reducing organ volume compared with ERT, particularly among patients with marked splenomegaly and hypersplenism, with a lag in improvement in platelet count during the initial phase of therapy. In one study of ERT regimens, low doses resulted in an initially slower improvement in organomegaly and hematological manifestations compared with the experience on high doses of ERT; however,

a similar magnitude of effect was eventually achieved in both groups and there were no statistically significant differences in ultimate outcome between treatment regimens in relation to these parameters[62,63]. Further studies with miglustat may determine whether the same level of reduction in organomegaly and increase in platelet count can be achieved with long-term miglustat therapy as is seen with ERT.

Data from clinical trials also indicate effects on bone manifestations with miglustat, especially with regards to reduction of bone pain and improvements in BMD[19]. Overall, the data suggest that miglustat may be considered a viable alternative to ERT for the treatment of selected patients with GD1. However, it should be noted that clinical studies of miglustat have generally been performed in patients with mild to moderate GD1, whereas ERT has been extensively studied in all patients including those with more severe disease. Close monitoring of miglustat-treated patients is advised so that appropriate changes to the therapeutic regimen can be initiated, if necessary. This allows increased flexibility in managing patients with GD1 as we aim for achievement and maintenance of therapeutic goals.

Goal-oriented therapy is particularly suited to GD, given its multiple manifestations; such an approach allows management that can be tailored to the individual patient's particular circumstances and expectations. Our proposed guidance for the attainment of therapeutic goals in GD1 patients on miglustat are intended to assist physicians involved in the monitoring and treatment of GD1 patients. The guidance is based on current data on the use of miglustat drawn from clinical trials, a cohort study and case reports of patients on commercial drug. Further long-term data from ongoing Gaucher registries such as the ICGG registry[1] and the French Observatoire on Gaucher disease[64], and from post-marketing surveillance studies[55] may provide more information on the role of ERT and SRT in the treatment of GD1 patients.

The literature search underlying this review of treatment of patients with GD1 using miglustat was based on three freely available medical publication databases. This may have limited the robustness of our findings. However, we also included additional references, including recent congress presentations, that could not be identified by the electronic search, and so we believe that this review provides a fully comprehensive assessment of the current evidence on efficacy and tolerability of miglustat. It should be noted that the congress presentations included in this report have not been peer-reviewed, and so these data should be interpreted with caution. Nevertheless, this review should be a valuable resource for physicians involved in the treatment of patients with GD1.

Conclusion

Several of the therapeutic goals for patients with GD1 can be achieved with miglustat therapy. In select cases, miglustat can be considered as an alternative to ERT for the treatment of patients with GD1. However, there is a need for further data, particularly regarding the use of miglustat in treatment-naïve patients. Future long-term experience with the use of miglustat will help define its overall safety and efficacy profile and determine its role in the management of the general adult GD1 patient population.

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