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Miglustat therapy in type 1 Gaucher disease: Clinical and safety outcomes in a multicenter retrospective cohort study

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ABSTRACT

We evaluated clinical and safety outcomes in adult patients with type 1 Gaucher disease receiving miglustat in clinical practice settings. An observational, retrospective cohort study was conducted in centers across the EU and the USA. Medical chart data were collected from consecutive patients between the 20th November 2002 and 31st December 2008. A total of 115 patients were included; 34 (30%) were enzyme replacement therapy-naïve ('naïve') and 81 (70%) were enzyme pretreated ('pretreated'). Median (range) miglustat exposures in these groups were 15.1 (0.6–52.9) months and 15.2 (0.3–62.1) months, respectively. Low numbers of patients were anemic (10/101) or thrombocytopenic (21/101) at initiation of miglustat therapy. The median (range) hemoglobin concentration at miglustat initiation was 12.8 (10.2–16.4) g/dl in naïve patients and 13.6 (7.3–17.4) g/dl in pretreated patients; median (range) changes in hemoglobin were 0.3 (−2.5–3.6) and −0.3 (−4–4.6) g/dl, respectively. The median (range) platelet counts at miglustat initiation were 101 (37–730) × 10^9/l in naïve patients and 173 (43–382) × 10^9/l in pretreated patients; median (range) changes in platelet count were 8 (−77–145) × 10^9/l and −10 (−144–434) × 10^9/l, respectively. Plasma chitotriosidase was substantially reduced in naïve but not in pretreated patients. Organ volumes were not routinely monitored. Forty-nine (43%) patients discontinued miglustat; most due to gastrointestinal manifestations and some due to tremor. Overall, hemoglobin and platelet counts tended to increase in naïve patients treated with miglustat, and to remain stable or decrease slightly in pretreated patients. The profile of safety and tolerability observed with miglustat in the current study is similar to previous studies.

Introduction

Gaucher disease type 1 (GD1) is an inherited lysosomal disorder caused by impaired activity of β-glucocerebrosidase [1], and is characterized by a range of systemic and skeletal manifestations including hepatosplenomegaly, anemia, thrombocytopenia, osteopenia, bone pain and fractures [2,3].

While enzyme replacement therapy (ERT) forms the mainstay of treatment for GD1, the iminosugar, miglustat (Zavesca®; Actelion Pharmaceuticals Ltd.) represents an alternative treatment strategy — substrate reduction therapy (SRT). Based on clinical trial data [4–6], miglustat was approved in the EU in 2002 and in the USA in 2003 for the treatment of adults with mild-to-moderate GD1 for whom ERT is either unsuitable or not a therapeutic option [7].

In clinical trials in ERT-naïve adults with GD1, miglustat treatment was effective in reducing liver and spleen volume and increasing hemoglobin concentration and platelet count during 12–36 months of treatment [4–6,8,9]. Miglustat has also been shown to improve bone mineral density in both trabecular and cortical bones [10]. Data also indicate that miglustat may serve as maintenance therapy in some patients previously stabilized on ERT [9,11,12].

Abbreviations: CI, confidence interval; CT, computed tomography; ERT, enzyme replacement therapy; GD/GD1, Gaucher disease/Gaucher disease type 1; MRI, magnetic resonance imaging; SD, standard deviation; SRT, substrate reduction therapy.

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The safety and tolerability profile of miglustat has been well established based on data from clinical trials and post-marketing surveillance [4,9,13,14]. Gastrointestinal disturbances (primarily diarrhea and flatulence) represent the main tolerability issue during miglustat therapy and remain the most frequent reason for discontinuation among those who stop treatment [15]. Studies have shown that dietary alterations before initiation and/or during the early weeks of miglustat treatment may reduce gastrointestinal disturbances [15].

A Spanish prospective, open-label investigational study of miglustat in GD1 patients has suggested that the long-term efficacy and safety profiles of miglustat during up to 6 years of use in clinical practice are consistent with findings from clinical trials [11,16]. Nevertheless, data from clinical experience with miglustat remain relatively limited. In particular, there is a lack of data from ERT-naïve patients compared with those who have previously received ERT.

Here we describe clinical outcomes and safety-relevant information from an observational cohort study in ERT-naïve and ERT-pretreated GD1 patients receiving miglustat therapy in clinical practice settings in the EU and USA.

Design and methods

Study design and patients

This was an observational, retrospective, longitudinal cohort study conducted at multiple centers across the EU and USA. At each participating center, consecutive patients aged ≥18 years who had a confirmed diagnosis of GD1 and who were treated with commercial miglustat between 20th November 2002 and 31st December 2008 were included.

Ethical approval or waivers for the study protocol were obtained from the Ethics Committees or Independent Review Boards of all participating centers. Where possible, informed consent for retrospective data collection was obtained from all included patients. As this was a retrospective study, informed consent was not obtained for patients who had died.

Patients were selected regardless of previous ERT; eligible patients could be either 'ERT-naïve' or 'ERT-pretreated' at miglustat initiation. Patients who had previously participated in a miglustat clinical trial or who had a lysosomal storage disease other than GD1 were excluded.

Data collection

Medical chart data on demographics, medical history, treatment and disease characteristics were collected on anonymized case report forms from diagnosis onwards, but no longer than 5 years prior to miglustat initiation. After miglustat initiation, data on GD1 disease characteristics and miglustat therapy were collected regardless of their treatment status until the end of the observation period (last information/visit before the end of the study [31st December, 2008], death or loss to follow-up). Both clinical and laboratory data were collected. Reasons for initiation of miglustat were not investigated in this study.

Data from medical charts were transcribed into the study-specific case record form by the treating physician or a delegate at each center. The treating physicians ensured data consistency and accuracy.

Outcomes

Changes in hemoglobin concentration, platelet count and plasma chitotriosidase activity were calculated in patients with data at miglustat initiation (medical chart information closest to miglustat initiation within a time window of −12 to +3 months from miglustat initiation) and follow-up during the observation period (defined as assessments conducted >3 months after miglustat initiation). Data on changes in liver/spleen volume were analyzed for patients in whom organ volumes were measured at least twice using the same technique (magnetic resonance imaging [MRI] or computed tomography [CT]) at both miglustat initiation and follow-up.

Safety-relevant data included gastrointestinal signs/symptoms and information on any neurological manifestations. Information on doses, duration and reasons for discontinuation of miglustat was also collected.

Statistical analysis

The size of the study population was selected on pragmatic grounds with the expectation that approximately 80 patients would be eligible for inclusion. All data analyses were exploratory in nature [17]. The denominators for analyses were the numbers of patients with corresponding data available; different parameters had different denominators. As the results suggested an asymmetric distribution, aggregated values at miglustat initiation and follow-up are summarized based on medians rather than means. Differences between subgroups were assessed based on 95% confidence intervals of the means, where statistically relevant.

Patient disposition, demographic, clinical, laboratory and safety-relevant data were summarized for an 'all-patients' data set comprising all included patients. A '≥2-year miglustat' data set was also evaluated, which comprised all patients who had ≥730 days of 'continuous' miglustat therapy (i.e. miglustat treatment not interrupted for more than 91 consecutive days).

Outcome analyses were stratified according to previous exposure to ERT. An 'ERT-naïve' group was defined as all patients who had never previously received ERT or had not received ERT for >6 months prior to miglustat initiation. An 'ERT pretreated' group was defined as all patients who received ERT within 6 months of miglustat initiation. At miglustat initiation, ERT-pretreated patients could have switched from ERT to miglustat or received miglustat in combination with ongoing ERT.

Subgroup analyses were also conducted on patients with anemia (hemoglobin < 11 g/dl in females and <12 g/dl in males) and thrombocytopenia (platelet count $< 100 \times 10^9$/l) at miglustat initiation, as defined in previous published reports [8,18]. Further subgroups were defined and evaluated based on platelet counts of $<80 \times 10^9$/l and $\geq 120 \times 10^9$/l, in line with data from a recent analysis indicating a relationship between baseline platelet count and persistent thrombocytopenia during ERT [19].

Results

Patients and treatment

A total of 115 patients were included from 31 centers across 9 EU countries (Austria, Czech Republic, France, Germany, Italy, The Netherlands, Slovak Republic, Spain, United Kingdom) and the USA. Sixty-three (55%) patients were females. GD1 diagnosis was confirmed through both enzymatic and genotyping analyses in the majority (72/115 [63%]) of patients. Demographic, diagnostic and disease characteristics data in the ≥2-year miglustat group (N = 39) were comparable with those in the all-patients data set (Table 1). Among a total of 97 (84%) patients with available genotype data, 81 had at least one N370S glucocerebrosidase mutation.

The most frequent initial GD1 symptoms in the all-patients data set (N [%]) were: splenomegaly (in 87 [76%] of patients), thrombocytopenia (75 [65%]), hepatomegaly (38 [33%]), anemia (24 [21%]) and bone manifestations (avascular necrosis, joint replacement, bone crisis, fractures or osteoporosis; 19 [17%]). One-hundred and eight (94%) patients presented with at least one of these symptoms. Hemoglobin and platelet counts were within normal ranges in the majority of patients at miglustat initiation in the all-patients data set, and plasma chitotriosidase activities reflected mild-to-moderate disease burden (Table 1).