Treatment patterns from 647 patients with Gaucher disease: An analysis from the Gaucher Outcome Survey

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ABSTRACT

The Gaucher Outcome Survey (GOS) is an international disease-specific registry established in 2010 for patients with a confirmed diagnosis of Gaucher disease (GD), regardless of GD type or treatment status. For insight into how GD management varies among countries, we analyzed treatment patterns in GOS. As of October 30, 2015, data on GD-specific treatment (enzyme replacement therapy, substrate reduction therapy, or chemical chaperone therapy) received at any time were available for 647 patients. At analysis, velaglucerase alfa (316/573, 55.1%) and imiglucerase (184/573, 32.1%) were the treatments most widely used. Of the 647 treated patients, 446 (68.9%) had been treated for 5 years and 368 (56.9%) had received only one GD-specific drug therapy. There were 377 patients who received velaglucerase alfa. Velaglucerase alfa was most widely used at 20 U/kg every other week (134/492 dose entries, 27.2%), but there were differences in dosing between the three highest-enrolling countries (defined as ≥100 GOS patients enrolled in each), with most patients in Israel receiving <20 U/kg, most patients in the United Kingdom receiving 20 to <40 U/kg, and most in the United States receiving 60 U/kg. This analysis provides a foundation upon which to examine real-life outcomes data from different treatment regimens globally.

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1. Introduction

Patients with Gaucher disease (GD) have a genetic deficiency in the lysosomal enzyme β-glucocerebrosidase. The consequent accumulation of glucosylceramide and other substrates is responsible for disease manifestations, although the exact disease mechanisms remain obscure [1]. The disease is progressive, but age at symptom onset and clinical course are highly variable among patients. Decisions regarding GD management may be complicated by the clinically heterogeneous nature of the disease and patients’ varied responses to treatment. Therapeutic regimens need to be tailored to individual patients [2]. In 2004, a panel of GD experts published a series of therapeutic goals to assist in treatment decision-making [3]. These goals were based on clinical experience with imiglucerase, but new treatment options have become available since their publication. Treatment decisions may be further influenced by country-level directives, insurance or reimbursement issues, patient-specific medical contraindications, patient preference, and physicians’ previous experience.

Six products have been approved for the treatment of GD: four enzyme replacement therapies (ERTs) and two substrate reduction therapies (SRTs). ERT is the standard of care for treating symptomatic type 1 GD patients and is effective for treating disease manifestations including anemia, thrombocytopenia, hepatosplenomegaly, and GD-related bone disease [4,5]. The ERT alglucerase first received marketing authorization in 1991 and was subsequently replaced by the recombinant enzyme imiglucerase, which received authorization in 1994 [6]. Velaglucerase alfa, the human cell line derived ERT, was approved in 2010 [7] and taliglucerase alfa in 2012 (commercial availability of these treatments varies by country; see Supplementary Table 1 for marketing authorization dates of available GD-specific treatments in the United States, the European Union, and Israel) [8].

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In 2009, a viral contamination at the imiglucerase primary production plant resulted in a supply shortage of the drug, which caused significant treatment interruptions or dose reductions for patients worldwide [6]. The imiglucerase shortage stimulated a number of compassionate use and early access programs in many countries that granted patients pre-approval access to velaglucerase alfa and taliglucerase alfa [9,10].

The SRT miglustat, which inhibits the enzyme glucosylceramide synthase to reduce accumulation of glucosylceramide, first received marketing authorization in 2003 [11]. A second SRT, eliglustat, was approved in 2014 (Supplementary Table 1) [12]. Miglustat can ameliorate disease manifestations but is only indicated in patients with type 1 GD for whom ERT is unsuitable (Europe) [13] or not a therapeutic option (United States) [14]. Eliglustat has shown efficacy on disease parameters with an acceptable safety profile, and is approved in the European Union and the United States as a first-line therapy for adults with type 1 GD [15,16].

Pharmacological chaperones, which may assist folding of the mutant β-glucocerebrosidase to enable its correct trafficking to the lysosome, have been investigated as therapeutic options for GD. In particular, ambroxol has been shown to increase the lysosomal activity of some mutant β-glucocerebrosidases, although clinical response in patients who received ambroxol in a pilot study was varied [17,18].

Analysis of real-world treatment patterns can provide a picture of how GD management varies among countries, and can serve as a foundation for analyzing clinical outcomes to assess the effectiveness of different therapeutic approaches globally.

The Gaucher Outcome Survey (GOS) is an international GD-specific registry established in 2010 for patients with a confirmed GD diagnosis, regardless of GD type or treatment status. GOS collects real-world data from GD patients, including information on disease manifestations and treatment history. As of October 2015, 34 treatment centers specializing in the management of GD and other lysosomal storage diseases in 10 countries have participated in GOS, generating data on 1003 patients. GOS is governed by GD experts from participating sites who, among other responsibilities, provide input into the GOS protocol and advice on data collection and analysis. The objectives of the registry include to evaluate the safety and long-term effectiveness of velaglucerase alfa, to characterize patients receiving velaglucerase alfa or other GD-specific treatments, to gain a better understanding of the natural history of GD and to serve as a database for evidence-based management of GD. Here we describe treatment patterns in GOS with a focus on country-level differences.

2. Patients and methods

2.1. Patients

GOS is an ongoing GD registry with participating sites in Israel, the United States, the United Kingdom, Argentina, Brazil, Paraguay, Russia, France, Italy, and Spain at the time of analysis. Patients can be enrolled into GOS regardless of their treatment status or type of treatment received. For enrollment, patients must have a diagnosis of GD confirmed by biochemical analysis of glucocerebrosidase activity and/or by GBA1 genotyping. Patients enrolled in ongoing blinded clinical trials cannot be enrolled in GOS.

Patients in this analysis were enrolled into GOS on a voluntary basis at the discretion of the physician and the patient and were managed under the direction of their physician in accordance with routine clinical practice. Written informed consent was obtained from all patients.

2.2. Data collection

All data were collected via the web-based GOS electronic case report form. For patients who had received any GD-specific treatment at any time (at any point before or after their enrollment into GOS), information on each GD-specific treatment regimen received was collected, including the drug name, treatment dose, frequency of administration, and start and stop dates. GD-specific treatments were defined as all ERTs (alphaglucerase, imiglucerase, velaglucerase alfa, taliglucerase alfa) and SRTs (miglustat, eliglustat), and the pharmacological chaperone ambroxol.

2.3. Analysis

Analysis was conducted on data extracted from the database on October 30, 2015. “Untreated” patients refers to those for whom there was an indication of not having received GD therapy and no records of GD-specific treatment at any time. “Treated” patients refers to those for whom there were one or more records of a GD-specific treatment and a treatment start date specified (Fig. 1.) Patients not
meeting the criteria for classification as “treated” or “untreated” were classified as having missing information and were excluded from the analysis.

Data on GD-specific treatment status and duration of treatment exposure were analyzed overall and by country. Information on numbers of treated patients and treatments received were analyzed overall, by country, and by age group (<18 and ≥18 years of age). Sequences of treatment were analyzed overall for patients who switched from one treatment to another. For patients who received velaglucerase alfa, data on dose and frequency of administration were analyzed overall, by country, and by age group.

3. Results

3.1. Treatment status

Information on GD-specific treatment received at any time (any ERT, SRT, or ambroxol) is available in GOS for 647 patients (Table 1). There are 151 patients reported as having never received ERT, SRT, or ambroxol) is available in GOS for 647 patients from the analysis.

There are 151 patients reported as having never received treatment. Information on treatment status or treatment start date is missing for 205 patients, who were excluded from the analysis (Fig. 1).

At the time of analysis, three countries had enrolled >100 patients into GOS. Israel had enrolled the largest number of patients (n = 460), followed by the United States (n = 344) and the United Kingdom (n = 108). Israel contributed the largest number of treated patients (n = 301) and untreated patients (n = 140) to GOS (Fig. 2). Nearly one-third of Israeli patients in GOS were untreated (140/460, 30.4%).

The majority of patients who had received treatment at any time were ≥18 years of age (569/647, 87.9%; Table 1). Across both age groups, more than two-thirds of patients had been treated for >5 years (446/647, 68.9%; Supplementary Fig. 1).

There were 165 patients who had been spleenectomized, of whom 157 (95.2%) had received GD treatment, whereas only 8 (4.8%) were untreated (Table 1).

In the untreated population, all patients were reported as type 1 GD, except for one patient reported as type 3 GD. For untreated patients with available GBA1 genotype data, the majority were [c.1226A->G] + [c.1226A->G] (N370S/N370S) (95/124, 76.6%), while patients with this genotype accounted for just over one-third of treated patients (162/469, 34.5%; Table 1). For the 64 patients with genotype [c.1226A->G] + [c.1448T->C] (N370S/L444P), 62 (96.9%) were treated, and 2 (3.1%) were untreated. For the 55 patients with genotype [c.1226A->G] + [c.84dupG] (N370S/84GG), 52 (94.5%) were treated, and 3 (5.5%) were untreated.

The proportion of N370S/N370S patients varied between the three highest-enrolling countries. In Israel, 227 of 389 (58.4%) patients with genotype data were N370S/N370S, compared with 46 of 176 (26.1%) patients in the United States and 3 of 51 (5.9%) patients in the United Kingdom (Fig. 3).

3.2. GD-specific treatment patterns

At the time of analysis, 573 patients were receiving GD-specific treatment, with the majority receiving velaglucerase alfa (316/573, 55.1%) or imiglucerase (184/573, 32.1%; Fig. 4). Patients in the United States received the broadest range of treatments (six different treatments). Only one patient <18 years of age was receiving SRT (elagustat): all others were receiving ERT (Supplementary Fig. 2).

An examination of the duration of exposure to individual treatments over 5-year periods showed that most velaglucerase alfa patients had received the drug for ≤5 years (227/377, 60.2%; Supplementary Fig. 3). Imiglucerase had also been received most commonly for ≤5 years (116/425, 27.3%), but there were comparable numbers of patients who had received the drug for between 5 and 10 years (95/425, 22.4%), 10 and 15 years (97/425, 22.8%), and 15 and 20 years (84/425, 19.8%).

Of the 647 patients treated at any time, 368 (56.9%) had received only one type of GD-specific treatment. The remaining patients (279/647, 43.1%) changed treatments once or more, with the most common switch being from imiglucerase to velaglucerase alfa (114/279, 40.9%; Supplementary Fig. 4). There were 199 patients who switched to velaglucerase alfa from other treatments and only 22 patients who switched away to another treatment after having received velaglucerase alfa. For the 13 patients who provided a reason for switching away from velaglucerase alfa, the reasons were parent decision (n = 5), physician decision (n = 2), an insufficient effect on disease parameters (n = 2), pregnancy, reimbursement or insurance issues, weight change, and experiencing an adverse event (n = 1 each).

3.3. Velaglucerase alfa treatment

There were 377 patients who had received at least one dose of velaglucerase alfa at any time. Velaglucerase alfa was administered

| Table 1 Demographics of treated and untreated patients at time of entry into GOS (n = 798). |
|-------------------------------|-------------------|-------------------|
| Treated patients, n (%) (n = 647) | Untreated patients, n (%) (n = 151) |
| <18 years | ≥18 years | <18 years | ≥18 years |
| Sex | Male | 44 (56.4) | 248 (43.6) | 13 (61.9) | 58 (44.6) |
| | Female | 34 (43.6) | 321 (56.4) | 8 (38.1) | 72 (55.4) |
| Ethnicity | Ashkenazi Jewish | 20 (25.6) | 338 (65.0) | 20 (95.2) | 120 (93.8) |
| | Other | 58 (74.4) | 182 (35.0) | 1 (4.8) | 8 (6.2) |
| Missing information | 0 | 49 | 0 | 0 |
| GD type | 1 | 62 (80.5) | 559 (98.8) | 21 (100.0) |
| | 2 | 1 (1.3) | 0 | 0 |
| | 3 | 14 (18.2) | 7 (1.2) | 0 | 1 (0.8) |
| GBA1 mutation alleles | [c.1226A→G] + [c.1226A→G] (N370S/N370S) | 2 (3.3) | 160 (39.2) | 10 (76.9) |
| | [c.1226A→G] + [c.1448T→C] (N370S/L444P) | 9 (14.8) | 53 (13.0) | 0 | 2 (1.8) |
| | [c.1226A→G] + [c.84dupG] (N370S/84GG) | 8 (13.1) | 44 (10.8) | 0 | 3 (2.7) |
| | [c.1226A→G] + other (N370S/other) | 11 (18.0) | 86 (21.1) | 2 (15.4) | 17 (15.3) |
| | [c.1226A→G] + unknown (N370S/unknown) | 0 | 16 (3.9) | 0 | 2 (1.8) |
| | [c.1448T→C] + [c.1448T→C] (L444P/L444P) | 8 (13.1) | 4 (1.0) | 0 | 0 |
| | [c.1448T→C] + other (L444P/other) | 2 (3.3) | 0 | 1 (7.7) | 1 (0.9) |
| | Other/other | 21 (34.4) | 45 (11.0) | 0 | 1 (0.9) |
| Missing information | 17 | 161 | 8 | 19 |
| Splenectomy status | Non-splenectomized | 77 (98.7) | 413 (72.6) | 21 (100) | 122 (93.8) |
| | Splenectomized | 1 (1.3) | 156 (27.4) | 0 | 8 (6.2) |

ERT, enzyme replacement therapy; GD, Gaucher disease; GOS, Gaucher Outcome Survey; SRT, subcutaneous reduction therapy.

a All percentages in table determined from number of patients with available data.

b Patients in GOS who had received GD-specific treatment at any time (any ERT, SRT, and/or ambroxol).

c Patient’s GD type is being confirmed as it is unlikely that a patient with type 2 GD would have been receiving treatment.

d One patient in the registry ≥18 years of age was recorded as having type 2 GD. Because type 2 GD patients rarely survive beyond 2–3 years of age, this patient is included under ‘missing information’ while investigations into the patient’s GD type are ongoing.

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at a variety of doses and frequencies (Fig. 5A). The most common treatment regimen was 60 U/kg every other week (134/492 dose entries, 27.2%), followed by < 20 U/kg every other week (117/492, 23.8%).

Differences were apparent among countries in the dosing of velaglucerase alfa, with most patients in Israel receiving < 20 U/kg, most in the United Kingdom receiving 20 to < 40 U/kg and most in the United States receiving 60 U/kg (Fig. 5B). Of the 117 patients who received < 20 U/kg, 111 were from Israel (94.9%) and 6 were from the United Kingdom; 116 of the 117 patients were ≥ 18 years of age (Fig. 5).

4. Discussion

The clinical management of GD has changed considerably over recent decades. Before the availability of ERT in 1991, management focused on symptom relief (such as splenectomy) for patients with severe disease. The cohort of patients treated in the early 1990s often had a greater burden of disease. With the increased use of ERT over time, symptomatic patients began to receive treatment at younger ages and less severe stages of presentation [19]. Although SRT was introduced in 2002, ERT has remained the gold standard of treatment for GD, and for many years alglucerase and its successor imiglucerase were the only enzyme products available to treat patients worldwide.

The 2009 shortage of imiglucerase had a profound impact on the treatment of GD globally, and highlighted the need for alternative GD-specific treatments. In response to the shortage, the manufacturing timelines for velaglucerase alfa were accelerated and many patients began receiving velaglucerase alfa and taliglucerase alfa before marketing authorization was granted. With three ERTs and two SRTs for GD now available, GOS, as a disease-specific registry, provides a platform for collecting information for the evidence-based management of GD.

In this report, information on GD-specific treatment patterns was gathered from 10 countries, including three countries with 65 or more treated patients (Israel, United States, and United Kingdom). The treatment patterns seen in these three highest-enrolling countries reflect the historical availability (including the imiglucerase shortage) and marketing authorization dates of available GD-specific treatments.

The GOS population at the time of analysis comprised many more treated patients than untreated patients. Notably, the United States and United Kingdom had low numbers of untreated patients compared with treated patients. Conversely, over one-third of GOS patients in Israel were untreated.

There were strong differences in GBA1 genotype representation between treated and untreated patients. More than three-quarters of untreated patients were homozygous for the N370S mutation, a genotype generally (but not always) associated with late symptom onset and mild hematological and visceral disease [20]. The N370S allele has a particularly high frequency among people of Ashkenazi Jewish ethnicity and > 80% of the N370S/N370S patients in GOS are located in Israel, which may explain Israel’s high number of untreated patients compared with other countries in GOS [21]. Nearly all patients heterozygous for N370S and a more severe mutation (N370S/L444P or N370S/84GG) were receiving treatment; these genotypes usually result in early-onset disease that is more severe than that associated with N370S/N370S [22].

Among patients on treatment at the time of analysis, > 95% were receiving ERT, with velaglucerase alfa and imiglucerase accounting for the majority of treatments received. Most patients on taliglucerase alfa were located in Israel, likely reflecting its lack of marketing authorization in Europe and Israel’s participation in its clinical development program. There are relatively few patients in GOS receiving eliglustat, which may be due to it being the newest of the GD-specific treatments and because it does not yet have marketing authorization in Israel, where most GOS patients are located. The United States was the only country to report the use of all available GD-specific treatments, probably because it has a high number of participating sites compared with other countries in GOS and therefore may include a range of local prescribing practices.

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Our analysis of GOS patients treated with velaglucerase alfa showed that most received the drug at 60 U/kg every other week, which is the dose recommended in the prescribing information for treatment-naive patients with type 1 GD. Dosing differed between age groups; ≤20 U/kg was the dose most commonly received by patients ≥18 years of age, whereas ≤20 U/kg was almost never administered to patients <18 years of age, who most commonly received treatment at 60 U/kg.

Clear differences in every-other-week dosing between the three highest-enrolling countries were observed. In Israel, ≤20 U/kg was the most common dose used, compared with 20 to ≤40 U/kg in the United Kingdom and 60 U/kg in the United States. In Israel, administration of low doses of ERT (equivalent to 15 U/kg every other week) was initially chosen to reduce costs, but continues to be used following studies suggesting that low-dose therapy does not compromise clinical benefit [19,23–25]. The policy for prescribing low-dose therapy in Israel is strongly reflected in GOS data on velaglucerase alfa treatment regimens, and may also be related to the high number of N370S/N370S patients (who may have mild disease) in Israel. In the United States, support of an every-other-week dose of 60 U/kg by insurance companies may account for why this treatment regimen is most commonly used.

An observational study with alglucerase and imiglucerase has shown an incremental dose-response relationship for hematological and visceral parameters across a range of typically used

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**Fig. 3.** GBA1 genotypes of patients in the three highest-enrolling countries. Many patients with the N370S/N370S genotype are asymptomatic or have mild GD manifestations. Israel had the highest proportion of N370S/N370S patients (227/398 [58.4%], compared with 46/176 [26.1%] in the United States and 3/51 [5.9%] in the United Kingdom), which may partly explain the high numbers of patients in Israel who were untreated or receiving low-dose treatment (<20 U/kg every other week) compared with the United States and the United Kingdom. GD, Gaucher disease.

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doses [26]. However, the optimal ERT dosing strategy is an unresolved issue in GD [24]. Further examination of outcomes data from GOS and their relationship with dose may help address some of the unresolved questions related to optimal treatment strategies.

A number of limitations of these GOS data are noted. Participation in the registry is voluntary (at the discretion of the patient and the physician), which may result in selection bias, particularly in the reporting of treated patients over untreated patients. Furthermore, because GOS is sponsored by one company, data from velaglucerase alfa-treated patients may be reported ahead of those receiving other GD-specific treatments, leading to a greater percentage of patients in GOS receiving velaglucerase alfa compared with imiglucerase (which is the most widely used ERT worldwide). While physicians are encouraged to enter information for all their GD patients regardless of the treatment they receive, there are other disease- and treatment-specific registries for GD, and some sites may not be able to enroll all patients into all registries for which they are eligible. With nearly half of GOS patients being located in Israel, results could be biased toward treatment approaches used in Israel, where patients may have milder disease and many are untreated. Furthermore, data reported from sites participating in GOS may not be representative of their country’s GD patient population.

5. Conclusions

These real-world data from GOS help to describe the long-term nature of GD treatment. In GOS patients, ERT accounts for over 95% of treatment received and most patients have been treated for >5 years. Although most patients received treatment with a single drug, changes from one ERT to another accounted for the majority of treatment switches. Overall, our data indicate a range of approaches toward GD management globally, which can be influenced by a number of interacting factors including drug availability, treatment cost, local prescribing practices, and disease severity. Further analyses from GOS can help examine the impact of these treatment patterns on real-world outcomes.

Authorship contributions

PD, DF-S, PG, HL, and AZ are investigators involved in GOS. ZP is the GOS medical monitor. All authors contributed to the development of the manuscript, critically reviewed the manuscript during development, and approved the final draft prior to submission.

Conflicts of interest disclosures

PD receives consulting fees from Genzyme, Shire, Amicus, and Alexion; has participated in clinical trials sponsored by Genzyme, Amicus, Protalix, and Shire; and has conducted research supported by Genzyme and Shire. DF-S receives consulting fees from Shire. PG receives consulting fees from Genzyme, Shire, and Pfizer; has participated in clinical trials sponsored by Genzyme, Amicus, Protalix, and Shire; and has conducted research supported by Genzyme, Shire, and Actelion. HL is a member of the advisory board or similar committee of Shire, receives consulting fees from Genzyme/Sanoﬁ and Pfizer; has participated in clinical trials sponsored by Amicus, Biomarin, GlaxoSmithKline, Genzyme/Sanoﬁ, Shire, Pfizer, and Ultragenyx; has participated in clinical studies using products manufactured by Amicus, Biomarin, Genzyme/Sanoﬁ, Pfizer, Shire, and Ultragenyx; and conducts research supported by Genzyme/Sanoﬁ. ZP is an employee of Shire. AZ receives honoraria from Shire, Genzyme/Sanoﬁ, and Pfizer, and his institution receives support from Genzyme, Shire, and Pfizer for participation in their respective registries.

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Appendix A. Supplementary data

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