CLINICAL INVESTIGATION

Velaglucerase alfa in the treatment of Gaucher disease type 1

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Gaucher disease is an autosomal recessively inherited lysosomal storage disease that results from the defective activity of the enzyme acid β-glucosidase (glucocerebrosidase). Velaglucerase alfa was recently developed and approved as an alternative form to imiglucerase enzyme therapy. Despite differences in primary structure and glycosylation patterns, recent preclinical and clinical trials of the preparation have shown similar efficacy and safety profiles to those of imiglucerase. The development of alternative therapies, such as velaglucerase alfa for Gaucher disease, is providing clinicians with a larger armamentarium of therapies, allowing for a more personalized approach to patient care.

Keywords: clinical trial • enzyme therapy • Gaucher disease • lysosomal storage disease

Gaucher disease is an autosomal recessively inherited lysosomal storage disease resulting from defective activity of the enzyme acid β-glucosidase (EC3.2.1.45, glucocerebrosidase [GCase]) due to mutations in the *GBA1* gene. The lysosomal storage disease occurs in the European and North American populations with a frequency of approximately 1/57,000 and approximately 1/855 in the Ashkenazi Jewish population [1].

In visceral tissues, defective GCase activity results in the accumulation of glucosyl ceramide in cells of monocyte/macrophage origin. These lipid-laden cells, termed Gaucher cells, accumulate in the liver, spleen, cortical bone and bone marrow, lymph nodes and lungs resulting in the disease signs of hepatic and splenic enlargement, anemia and thrombocytopenia, destructive bone disease, lymphadenopathy and, occasionally, pulmonary dysfunction.

Three phenotypes of Gaucher disease have been described based upon the absence or presence and severity of neurological involvement. Gaucher disease type 1, the non-neuronopathic variant, accounts for approximately 85–90% of Gaucher disease in the Western world and has highly variable manifestations that are primarily restricted to the visceral organs and have onset from childhood to adulthood [1]. Gaucher disease types 2 and 3 are neuronopathic variants, and are distinguished by their ages of onset and rates and degrees of progressive primary CNS disease. Worldwide, types 2 and 3 probably account for a larger population of affected patients than the type 1 variant.

The general lack of primary CNS disease in Gaucher disease type 1 made it a model for enzyme replacement therapy (ERT) in the treatment of genetic disorders; the inability of intravenously administered large proteins to cross the blood–brain barrier in therapeutically significant amounts limits such approaches to accessible visceral manifestations. ERT for Gaucher disease type 1 first became commercially available in 1991 with the US FDA approval of human placenta-derived glucocerebrosidase (Ceredase®, alglucerase; Genzyme Corporation, MA, USA). Owing to the inherent limitations of human placenta and potentials for biocontaminants,

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recombinant human GCase, imiglucerase (Cerezyme®, Genzyme Corporation), was developed and subsequently FDA approved in 1994. Imiglucerase is produced in bioreactors containing Chinese hamster ovary (CHO) cells that express human GCase from a stably transfected and amplified human cDNA. Over the past 15 years, ERT with imiglucerase has become the standard of care for treatment of significantly symptomatic Gaucher disease type 1 and safety and efficacy data as well as dose-response characteristics are available on more than 5000 such patients [2,3]. Recent production and manufacturing issues with imiglucerase, resulting in shortages of the preparation and consequential challenges for the individuals with Gaucher disease and their managing physicians, have highlighted the need for alternative sources or production facilities for the therapeutic products for such orphan diseases.

Velaglucerase alfa (VPRIV®, Shire Human Genetic Therapies, Inc, MA, USA) was developed as an alternative ERT product for Gaucher disease. This biologic uses Gene-Activation® in which the expression of the endogenous *GBA1* in a human fibrosarcoma cell line expresses GCase. It was recently approved in the USA and Europe for the treatment of Gaucher disease type 1.

Here, the available biochemical/pharmacokinetic, and safety and efficacy data of velaglucerase alfa and imiglucerase are compared. Also, similar comparisons have been made to the human placental-derived GCase, alglucerase.

Biochemical/pharmacokinetic properties

Velaglucerase alfa is an endogenous GCase produced in a human fibrosarcoma cell line using Gene-Activation technology. This approach is a targeted recombination of the *GBA1* locus with a promoter that greatly enhances endogenous GCase production within the cell line. Velaglucerase alfa is an approximately 63 kDa monomeric glycoprotein containing 497 amino acids that are identical to that of the natural placental human protein. In comparison, imiglucerase and taliglucerase (a human GCase produced in carrot cells) differ from velaglucerase alfa and the natural placental protein by an arginine to histidine substitution at amino acid residue 495 [4]. Taliglucerase also contains additional N- and COOH- terminal non-natural amino acids [5].

To achieve mannose termination of N-linked oligosaccharide on GCase, velaglucerase alfa is produced by culturing the fibrosarcoma cells in the presence of kifunensine, an α-mannosidase I inhibitor. This treatment alters the composition of the glycans attached to the four N-glycan sequons of this glycoprotein. This treatment results in secretion of a GCase whose N-glycosylation residues contain high mannosyl-type glycans, with six to nine (predominant) mannose residues each. Some heterogeneity in the length of the α-mannosyl-terminated glycan chains is present among the sites; small amounts of mannose-6-phosphate complex glycan structures also have been detected [4].

In comparison, the oligosaccharide chains on imiglucerase are derived primarily from complex-type glycans with core fucosylation that terminate with an *N*-acetylglucosamine tri-mannosyl core. To achieve α-mannosyl termination of the Chinese hamster ovary-produced human GCase, sequential deglycosylation with specific exoglycosidases are conducted to expose the core mannose residues. Imiglucerase also displays some glycan microheterogeneity at the glycosylation sites, with lower levels of core structures terminating in *N*-acetylglucosamine, as a result of incomplete digestion by *N*-acetylglucosaminidase [4].

The crystal structures of velaglucerase alfa and imiglucerase are identical to one another, and nearly identical to taliglucerase. The structures consist of three noncontiguous domains with the active site being located in domain III, a typical $(\beta/\alpha)_8$ barrel [4]. From these data, the $Arg^{495}His$ substitution in imiglucerase has no impact on the overall structure of the enzyme. In addition, detailed characterizations of GCase with either Arg^{495} or His^{495} [6] as well as direct comparisons of velaglucerase alfa and imiglucerase [4,7] show essentially identical enzymatic functional properties.

In addition, the glycosylation composition differences seem unimportant to the *in vitro* kinetic parameters (K_{cat}, K_m, and K_i) of these enzymes for a variety of substrates and active site-directed inhibitors, as they differ by approximately 10–15% for each preparation [4,7]. Similar profiles for these two enzymes were obtained with the activity enhancers phosphatidylserine and saposin C, a natural nonessential protein activator of GCase. Furthermore, the *in vitro* pH inactivation (denaturation) rates and sensitivity to cathespin D digestion were very similar for these two enzyme preparations [7].

The pharmacokinetics of these preparations in humans are also very similar, with elimination following first-order kinetics. The peak plasma concentration (C_{max}) of both preparations coincides with the end of the infusions. At doses of 1–1.5 mg/kg (45–60 U/kg), mean serum half lives ($t_{1/2}$) were approximately 10 min, mean serum clearances were 13 ml/min/kg, and apparent volumes of distribution (V_{ss}) were approximately 18% of body weight for velaglucerase alfa, which are similar to those observed for imiglucerase (3.6–10.4 min, 14.5 ml/min/kg and 12%, respectively). C_{max} and area under curve were linearly proportional to dose, whereas $T_{1/2}$ and V_{ss} were independent of dose [8,9].

Both preparations are internalized into macrophages via oligomannan compatible receptors (e.g., the macrophage mannose receptor). Interestingly, Brumshtein

and colleagues concluded that velaglucerase alfa adhered to U937-derived macrophages approximately 2.5-fold more effectively than imiglucerase. The researchers hypothesized that this corresponded to an increase in internalization of velaglucerase alfa, which was related to the presence of long chain high mannose-type glycans compared with the core mannose structure found on imiglucerase [4].

Effects of velaglucerase alfa in the Gaucher mouse model

Xu *et al.* compared the pharmacokinetic/pharmacodynamic profiles and glucosyl ceramide degradative efficacy of velaglucerase alfa and imiglucerase in the D904V/null Gaucher mouse model [7]. After bolus tail vein injection, $T_{1/2}$ of either enzyme in mouse serum were similar to one another and comparable to those previously reported in humans (~8–11 min) after intravenous infusions [8,9]. By 20 min postinjection, serum activities of injected velaglucerase alfa and imiglucerase were less than 10% of the baseline values. Concurrent assessments of GCase protein demonstrated similar partial denaturation of either protein due to their instability at serum pH.

The uptake and disappearance of velaglucerase alfa and imiglucerase were evaluated in liver, spleen and lung tissue in 5- and 20-week-old D409v/null mice over a period of 42 h. Overall, the majority (60–70%) of injected velaglucerase alfa or imiglucerase was recovered from the liver, whereas approximately 2–3% and less than 0.2% of the enzymes were recovered in the spleens and lungs, respectively. The majority of either enzyme was localized to the hepatic interstitial cells, including Kupffer cells, in periportal regions. The remaining enzyme was either localized to other organs, such as splenic macrophages, or was degraded.

Similar half-lives of disappearance of enzyme activity and GCase protein were found in all tissues examined. Only minor differences in these parameters were observed between the two enzyme preparations in mice at 5 or 20 weeks, suggesting that the degree of disease involvement, particularly in the liver, had small effects on distribution and degradation of the exogenous enzymes. Interestingly, disappearance of both administered enzymes occurred more rapidly in the 5-week-old mice (less involved) compared with the 20-week-old mice. Furthermore, velaglucerase alfa appeared to be cleared somewhat more rapidly from the livers of 5-week-old mice than imiglucerase; however, there were no differences in this parameter with the 20-week mice. For both preparations, the enzyme activity and protein levels returned to baseline levels approximately 20–42 h after the infusions. Importantly, assessments of the time courses for catalytic capacity (K_{cat}) of these GCases demonstrated that the enzymes retained nearly full function, that is, they were not denatured but proteolitically degraded.

Comparisons of ability of either preparation to degrade glucosyl ceramide *in vivo* were also performed with weekly injections of 5, 15 or 60 units/kg of either velaglucerase alfa or imiglucerase for 4 or 8 weeks, and then sacrificed for studies 1 week after the last injection. Glucosyl ceramide levels in the livers of mice treated with velaglucerase alfa and imiglucerase (5 or 15 U/kg/week) decreased by approximately 50–70% at 4 and 8 weeks. A dose–response trend was observed, as greater reductions in glucosyl ceramide levels were observed in mice treated with 60 U/kg/week (~80–85% decrease for either enzyme after eight weeks of therapy). Within liver tissue, the number of storage cells significantly decreased in all treatment groups; no significant differences between the two preparations were shown. The degree of change correlated with dosage and length of therapy. At doses of 60 U/kg/week of velaglucerase alfa, near complete elimination of Gaucher cells in liver occurred by 4 weeks. Despite this, there was still evidence of excess glucosyl ceramide within liver tissue, suggesting storage of glucosyl ceramide occurs within cells other than typical Gaucher cells.

For all dosing groups, the glucosyl ceramide levels in spleen were reduced by approximately 10–15% at 4 weeks and approximately 20–30% at 8 weeks; no significant difference was detected between the two preparations. Wild-type glucosyl ceramide levels were not achieved at any time or at any dose. The numbers of Gaucher cells decreased but were not absent at 8 weeks.

Glucosyl ceramide levels in lungs were unchanged at doses of 5 and 15 U/kg/week with either preparation. Although a suggested trend with 10% decrease of glucosyl ceramide levels was observed in the lung at 60 U/kg/week for either preparation at 8 weeks, this was not statistically significant. No decreases in the number of Gaucher cells in velaglucerase alfa- or imiglucerase-treated mice, compared with saline controls, were observed at either 4 or 8 weeks. This provides further evidence for previous reports that certain tissues/organs (e.g., lungs) appear to be sequestered from ERT in patients with Gaucher disease [10].

As expected, both human GCases were significantly more immunogenic in mice than has been observed in humans, as antibodies (IgG and/or IgE) against human glucocerebrosidase were detected in many mice. A significant number of mice developed anaphylactic-like reactions after several doses of either preparation. Interestingly, although there was no difference in IgG and IgE positivity rate, significantly more mice treated with imiglucerase died compared with those receiving velaglucerase alfa. The significance of this finding for

human patients is unclear. Similar direct head-to-head studies of these two drugs in humans with Gaucher disease have not been reported.

Clinical trials

A 9 month Phase I/II open-label, single center trial, followed by a long-term extension study was conducted to evaluate the safety and efficacy of velaglucerase alfa [11]. The study was performed in 12 untreated adults with Gaucher disease type 1. The first three patients received three escalating doses (15, 30 and 60 U/kg) of velaglucerase alfa to evaluate the safety of the preparation; there were no issues. The subsequent nine were treated with velaglucerase alfa at a dose of 60 U/kg/2 weeks for 9 months.

A total of 11 patients completed the 9-month Phase I/II study (one person dropped out for personal reasons), and 10 elected to enroll in the long-term extension trial. After approximately 6–9 months of the extension study, all patients achieved at least two of four therapeutic goals for improvement in anemia, thrombocytopenia, hepatomegaly and/or splenomegaly (as defined by Pastores *et al.* (Table 1) [12]) and underwent a step-wise dose reduction from 60 to 45 U/kg/2 weeks for 3 months, followed by a reduction to a dose of 30 U/kg/2 weeks. In one patient the dose was increased to 60 U/kg/2 weeks 24 months after dose reduction due to worsening bone pain; however, the bone pain did not subsequently improve. This person subsequently withdrew from the extension study owing to pregnancy.

Within 3 months of the Phase I/II study, statistically significant improvements were observed from baseline in hemoglobin concentration and platelet counts. Statistically significant improvements were also noted in the mean percentage change from baseline to 9 months for hemoglobin concentration (+19.2%), platelet counts (+67.6%), liver volume (-18.2%) and spleen volume (-49.5%). Improvements in clinical parameters continued to be observed after that time, and normalization of hemoglobin was observed in all patients by 24 months. Furthermore, mean percentage change from beginning of the study to 48 months was statistically significant for hemoglobin concentration (+21.7%), platelet counts (+157.8%), liver volume (-42.8%) and spleen volume (-79.3%). Of the patients for whom a complete data set was available (8/9), all therapeutic goals were met and/or maintained within 48 months of initiation in therapy [13].

In the Phase III (TKT032), randomized, double-blind, international study, the efficacy and safety of velaglucerase alfa (45 U/kg/2 weeks vs 60 units/kg/2 weeks), was evaluated in 25 patients (pediatric and adult) who were naive to ERT or who had not received any treatment for a minimum of 30 months prior to enrolling in the study [14]. After 12 months, the mean hemoglobin concentration increased by 2.4 g/dl (~23–24%, $p \leq 0.0001$) in both treatment groups and mean platelet counts increased from baseline in the 60 U/kg and 45 U/kg groups by 51 × 10^9/l ($p = 0.0016$) and 41 × 10^9/l ($p = 0.0111$), respectively. Mean spleen volumes, normalized to body weight, decreased from baseline by 50% ($p = 0.0032$) and 40% ($p = 0.0085$) for the 60 and 45 U/kg cohorts, respectively. Additionally, mean liver volume,

Table 1. Therapeutic goals for Gaucher disease.

Parameter	Goal	
	Short term (1–2 years)	Long term (2–5 years)
Anemia		
■ Children ≤12 years	≥11.0 g/dl	Maintain improved hemoglobin achieved after first 1–2 years
■ Females >12 years	≥11.0 g/dl	
■ Males >12 years	≥12.0 g/dl	
Platelets		
■ Splenectomized patients	Normalization by 1 year of treatment	Maintain normalized platelets achieved after first year
■ Moderate baseline thrombocytopenia (60–120 × 10^9/l)	Increased platelets by 1.5–2.0-fold by year 1	Platelets approaching low–normal by year 2
■ Severe baseline thrombocytopenia (<60 × 10^9/l)	Increased platelet count by 1.5-fold by year 1	Continue to improve platelet count slightly (doubling by year 2)
Liver volume	20–30% reduction in liver volume or reduce/maintain liver volume 1.0–1.5 × normal	40-40% reduction in liver volume or reduce/maintain liver volume 1.0-1.5 × normal
Spleen volume	30–50% reduction in spleen volume	50–60% reduction in spleen volume or reduce/maintain spleen volume ≤2–8 × normal
Skeletal pathology	Lessen or eliminate bone pain/crises	Improved bone mineral density

Adapted from [12,13].

normalized to body weight decreased from baseline by 17% (p = 0.0282) and 6% (p = 0.3149). However, despite the appearance of statistical significance (p = 0.0282), based on a multiple testing strategy, the decrease in liver volume was not statistically significant. As has been previously seen with imiglucerase, a greater response was observed at higher doses of velaglucerase alfa. These responses compare favorably to patients receiving imiglucerase 45–60 U/kg for 12 weeks [15].

A 12 month, international, multicenter, Phase III clinical trial (TKT034) investigated the stability of clinical parameters in adult and pediatric patients with Gaucher disease type 1, who had been previously treated with imiglucerase for at least 30 consecutive months [16,17]. Patients were assigned to receive velaglucerase alfa at the same dose as their prior imiglucerase regimen. Of 41 patients enrolled in the study, 40 patients were included in the intent-to-treat analysis and 38 patients (93%) completed the study. One patient discontinued before receiving the study drug. Two patients receiving doses of 15 U/kg/2 weeks discontinued the study; one due to a hypersensitivity reaction during the first infusion with velaglucerase alfa, and a second at week 31 caused by perceived lack of improvement. In patients completing the study, hemoglobin concentration, platelet counts, and liver and spleen volume were maintained within the predefined efficacy criteria. Furthermore, levels of the biomarkers chitotriosidase and CCL-18 were also sustained over the 12-month treatment period.

A randomized, double blind, multicenter, head-to-head study comparing the effects of velaglucerase alfa and imiglucerase (60 units/kg/2 weeks for 9 months) in treatment-naive Gaucher disease type 1 patients with anemia and either thrombocytopenia or organomegaly has been completed (HGT-GCB-039). A total of 35 patients were randomized, and 34 patients received study drug (17 velaglucerase alfa; 17 imiglucerase). The baseline characteristics of both groups were similar. After 9 months, the estimated mean treatment difference in hemoglobin concentration from baseline between the velaglucerase alfa and imiglucerase treatment groups was not statistically significant. Additionally, no statistically significant differences in the secondary end points (platelet counts, or spleen volumes and liver volumes) were identified [18].

Compared to velaglucerase alfa, the long-term efficacy of imiglucerase has been well documented for Gaucher disease type 1 in adults and children. However, few randomized prospective clinical trials with imiglucerase have been performed. The majority of data regarding the safety and efficacy is from retrospective studies, much of which comes from the ICGG Gaucher Observational Registry.

Weinreb and colleagues evaluated the effectiveness of ERT in 1028 patients with Gaucher disease type 1 who were treated with alglucerase/imiglucerase for 2–5 years [3]. **Among these patients, hemoglobin concentrations** increased to normal or near normal during the first 6–12 months, with a continued response through 5 years of treatment. However, mild anemia persisted in some patients after 24 months of therapy, particularly those with baseline hemoglobin levels of <10 g/dl. **In thrombocytopenic patients with splenomegaly**, the most rapid response to therapy occurred during the first 24 months of therapy, with slower, sustained responses for 3–5 years. The likelihood of achieving normal platelet count directly correlated with the baseline platelet count. Conversely, in patients who had undergone splenectomy, platelet counts normalized within 6–12 months, with a continued response noted at 3–5 years.

Liver volume decreased by approximately 20–30% within 24 months of therapy with enzyme, with reductions of approximately 30–40% by 5 years. However, the likelihood of achieving normalization of liver volume during therapy was inversely related to baseline liver volume. Splenic volume decreased by approximately 30–50% after 1–2 years of therapy with enzyme, but demonstrated little further decrease after 3–5 years of treatment. Although the overall decrease in spleen volume was directly related to baseline spleen volume, the likelihood of achieving spleen volumes at most five-times normal was inversely related to initial spleen volume (51% of patients with moderate splenomegaly (>5–15-times normal) versus 4% of patients with severe splenomegaly (>15-times normal) after 24 months of therapy).

Improvement in skeletal disease (as measured by occurrence of bone pain and bone crises) also improved. Indeed, in patients with previous reports of bone pain and/or crises at baseline, 52 and 94%, respectively, fewer reports of bone pain or bone crises were received after 2 years of therapy. Occurrence of bone pain and/or crises after 2 years of therapy in patients without a previous history of these features was unusual (i.e., ≤5% of patients).

Data from the ICGG Gaucher registry were used to evaluate achievement of therapeutic goals (Table 1) in patients with Gaucher disease type 1 treated with imiglucerase [19]. Of the 195 patients for whom 4 years of data were available, 41.5% met all six therapeutic goals after 4 years of therapy, compared with only 2.1% at the first infusion. Comparably, the proportion of people meeting up to five therapeutic goals increased from 12.8–76.9%; at least four goals from 37.4 to 92.8%; at least 3 goals from 70.8 to 99.0%, and at least two goals from 95.4–99.5%. The percentage of

patients meeting specific therapeutic goals increased for all parameters between the first infusion and 4 years of therapy: hemoglobin 68.2–91.8%; platelet count 24.6–79.5%; spleen volume 25.6–78.5%; liver volume 45.6–90.8%, bone pain 62.6–70.3% and bone crises 91.8–99.0%.

The effectiveness of imiglucerase in children was documented based upon retrospective analysis of data from 884 patients in the ICGG Gaucher registry [2]. After 8 years of ERT, the median height Z-score increased from -1.4 to -0.3. The latter was not significantly different from the median height in the unaffected population. Hemoglobin levels, platelet counts, and liver and spleen volumes significantly improved over the first 1–2 years of treatment, with continued improvements throughout the 8 years of therapy. Indeed, after 8 years of therapy, many therapeutic parameters were normal or nearly normal. These findings were essentially the same as in the Weinreb *et al.* study [3]. For bone disease, only 2.5% of patients who had never had a bone crisis at baseline reported experiencing a crisis during the follow-up period. This compares to an approximate 10% rate for bone crisis in untreated patients. Conversely, in patients who had previously reported a bone crisis at baseline, only approximately 16% of patients reported a bone crisis after initiation of treatment and no further bone crises were reported after 2 years of enzyme therapy.

Imiglucerase therapy shows clear dose response for signs of Gaucher disease. Weinreb *et al.* found that only 24% of patients treated with doses of less than 30 U/kg/4 weeks, versus 40–54% of patients treated at doses of over 30 U/kg/4 weeks attained all six therapeutic goals after 4 years of treatment [19]. The great heterogeneity in Gaucher disease type 1 has confounded such analyses. To minimize such effects, propensity score matching of the patient phenotypes was used to evaluate imiglucerase dose–response relationships for the hematological and visceral manifestations of Gaucher disease type 1. Incremental treatment effects were observed between the 15, 30 and 60 U/kg/2 week, specifically incrementally greater therapeutic responses were observed with larger doses [15]. Despite the identification of differential responses to therapy, after longer (~8 years) treatment, these differences disappeared in the 30 and 60 U/kg/2 weeks groups. While similar studies have not been performed with velaglucerase alfa, one might expect that similar dose–response relationships.

Despite the lack of long-term safety data, which is available from vast experience with imiglucerase, velaglucerase alfa appears to be safe. Indeed, in the Phase I/II and subsequent extension studies, there were no drug-related serious adverse events. Of the 12 Phase I/II patients, all experienced one or more treatment-emergent adverse events, all of which were mild-to-moderate, and the majority were not attributed to the study drug. The most common possible or probable drug-related adverse events during these studies included dizziness, migraines, headaches, nausea, back pain, bone pain, increased body temperature and abdominal pain [11].

In the follow-up Phase III TKT032 and TKT034 studies, mild–moderate treatment emergent adverse events similar to those observed in the Phase I/II study were reported [14,16]. The majority of drug-related adverse events were considered infusion related. In the TKT032 study, two patients experienced severe adverse events and one serious adverse event occurred; however, these events were deemed unrelated to the study drug by the investigators. In the Phase III TKT034 study, one patient (in the 15 U/kg/2 weeks group) experienced a hypersensitivity reaction during the first infusion (specific symptoms not reported) that led to discontinuation [17]. In the HGT-GCB-039 study, one patient receiving velaglucerase alfa experienced a treatment-emergent severe adverse event (allergic skin rash), which was considered to be probably related to the study drug. However, no patients discontinued therapy due to an adverse event [18].

Utilizing sensitive antibody detection techniques, Ruiz and colleagues reported seroconversion in 1% of patients treated with velaglucerase alfa compared with 23% of patients treated with imiglucerase [20]. These percentages are similar to those reported by Mehta and colleagues [18]. This rate is somewhat higher than the well documented conversion rate of 13–15% with imiglucerase [21]. In the absence of a standardized assay, these data are difficult to interpret. This data suggests differential antibody responses between velaglucerase alfa and imiglucerase. Interestingly, in the TKT034 study, three patients tested positive for IgG antibodies to imiglucerase at screening; however, these antibodies did not react with velaglucerase alfa and no patients developed IgG antibodies to velaglucerase alfa [16,17,20]. This is a rather surprising finding given that the enzymes are essentially identical, except for their glycosylation patterns. Therefore, it is unclear why antibodies for imiglucerase would not also recognize velaglucerase alfa. Again, differences in glycosylation patterns must be considered as a potential explanation for the variability in antibody recognition.

Similar adverse events have been reported in patients treated with imiglucerase and are usually temporally associated with infusion administration. Most of these infusion-associated reactions are effectively managed by decreasing the rate of infusion, or pretreatment with antipyretics and/or antihistamines. Over time, most patients become tolerant of the medication at a

regular infusion rate, and no longer require premedication. Few patients have had to discontinue using imiglucerase owing to these infusion-related reactions. Seroconversion frequently develops within 6 months of initiating therapy and rarely after 12 months of therapy. However, seroconversion does not appear to affect the efficacy of the treatment. IgE seroconversion appears to be quite rare, compared with ERT for other conditions, for instance Fabry disease.

Comparisons of the safety and efficacy of imiglucerase and alglucerase were previously conducted. Alglucerase and velaglucerase alfa are derived from human placenta and a human fibrosarcoma cell line, respectively, and have identical amino acid sequences (although the glycosylation patterns are different). Therefore, it is worthwhile to consider the differential safety and efficacy profiles of imiglucerase and alglucerase for extrapolation to potential differences between velaglucerase alfa and imiglucerase. No differences in the rate or extent of improvement in hematological parameters, biomarkers or hepatic and splenic volumes were observed in treatment-naive patients with either alglucerase or imiglucerase. Interestingly, the incidence of IgG antibody conversion was greater in the alglucerase group (40%) than in the imiglucerase group (20%) in this study of 30 patients. The researchers attributed this to the presence of trace impurities, denaturation or abnormal conformations of the administered natural protein [22].

Future perspective

The degree of interest in developing alternative sources of therapy for an orphan disease has been remarkable. The need for such alternative sources of therapy has been highlighted by the challenges faced by caregivers and patients as a result of shortages of imiglucerase, which, until recently, was the only ERT approved for the treatment of Gaucher disease. The development of alternative sources of therapy for Gaucher disease provides clinicians with a larger armamentarium of therapies from which they may select the most appropriate preparation to provide optimal care for their patients. This is significant as it advances the clinicians ability to provide personalized medicine to their patients, a novel concept for the treatment of genetic diseases. This is particularly important because some patients may respond better to one preparation than to another for reasons that are unclear at this time. For example, we have a patient who would develop chills and difficulty breathing, often within a few minutes of starting an infusion of imiglucerase, despite negative skin testing to imiglucerase and its components (although she did possess IgG antibodies to the preparation), and required significant doses of steroids and antihistamines to control these symptoms. However, once transitioned to velaglucerase alfa, she no longer these symptoms, and she was weaned from her extensive premedication regimen.

Despite the obvious benefits of having alternative forms of therapy for the disease, it remains to be seen how the market will accommodate multiple forms of therapy for an orphan disease, given that to date, approximately 5000 patients with Gaucher disease are being treated. With the availability of multiple therapies for Gaucher disease, deciding upon which of these therapies to prescribe for a patient, in

Executive summary

- Velaglucerase alfa has been approved as a safe and effective form of enzyme replacement therapy for the treatment of symptomatic individuals with Gaucher disease type 1.
- Owing to differing manufacturing techniques, differences in the primary structure and glycosylation patterns of velaglucerase alfa and imiglucerase exist; however, both preparations have similar crystal structures, as well as biochemical and pharmacokinetic properties.
- Studies of the biochemical/pharmacokinetic properties and safety/efficacy of velaglucerase alfa in a Gaucher disease mouse model demonstrated similar properties to that of imiglucerase.
- Review of published clinical trials for velaglucerase alfa demonstrate that it is safe and efficacious in the treatment of Gaucher disease. Furthermore, velaglucerase alfa seems to be as efficacious as imiglucerase for Gaucher disease type 1, specifically with regards to hematologic and visceral manifestations.
- Recent data suggest differential antibody responses between velaglucerase alfa and imiglucerase. However, in the absence of a standardized assay these data are difficult to interpret. Nonetheless, this finding is intriguing and may be related to differences in glycosylation patterns between the two preparations.
- The need for alternative sources of therapy for Gaucher disease has been highlighted by recent challenges faced by caregivers and patients as a result of shortages of enzyme replacement therapy. However, it remains to be seen how the market will accommodate multiple forms of therapy for an orphan disease, such as Gaucher disease.
- The long term safety and efficacy of velaglucerase alfa will need to be addressed further. It is almost certain that a registry for patients receiving velaglucerase alfa, similar to the ICGG Gaucher Registry for imiglucerase, will be utilized to address these unanswered questions.

the absence of compelling medical differences, will undoubtedly pose a significant challenge for prescribers. However, whether justified or not, it is almost certain that differences in manufacturing technique, biochemical properties, efficacy and safety (i.e., antigenicity) will be cited as reasons for or against prescribing each preparation.

Many hope that the resulting competition will result in a lowering of the overall cost of the preparations. This has been seen to some degree, as the cost for velaglucerase alfa (actual wholesale price, US$1620; 400 unit vial) is approximately 15% less than imiglucerase (actual wholesale price, US$1903.20; 400 unit vial). However, the overall costs of these preparations have not decreased as dramatically as some had hoped.

Financial & competing interests disclosure

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