

The long-term international safety experience of imiglucerase therapy for Gaucher disease

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Abstract

Background: Gaucher disease is a lysosomal storage disorder resulting from a deficiency of the lysosomal enzyme glucocerebrosidase. Since approval by the FDA in 1994 and EMEA in 1997, enzyme replacement therapy with Cerezyme® (imiglucerase for injection) has been the standard of care for the treatment of Gaucher disease.

Objective: To review the long-term international safety experience of imiglucerase from 1994 through 2004.

Materials and methods: All spontaneous adverse event reports captured in the pharmacovigilance database for imiglucerase from 1994 through 2004 were analyzed. All adverse events were classified using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Patients without prior exposure to imiglucerase from 1994 through 2005 were assessed for the development of antibodies to imiglucerase as detected by enzyme-linked immunosorbent and radioimmunoprecipitation assays.

Results: Analysis of the long-term safety experience with imiglucerase therapy demonstrates a stable and low rate of adverse events and seroconversion from 1994 through 2005. The majority of frequently reported adverse events related to imiglucerase were infusion-associated reactions which were predominantly self-limiting in nature and did not require discontinuation of treatment. Between 1994 and 2005, IgG antibodies to imiglucerase were detected in approximately 15% of treatment-naïve patients.

Conclusions: The long-term stability of reported events and seroconversion is a reflection of a well-characterized cell expression system and a mature quality-controlled manufacturing process. Imiglucerase is a safe therapy for the treatment of Gaucher disease with a stable and low rate of reported adverse events and seroconversion.

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Gaucher disease (GD) is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme glucocerebrosidase, which leads to the pathologic accumulation of glucocerebroside within tissue macrophages in multiple organs [1]. The most common of the lysosomal storage disorders, GD is a progressive, heterogeneous, multi-systemic disorder, with a highly variable clinical presentation. GD is often a debilitating disorder and may cause early mortality.

The current standard of care for the treatment of GD is enzyme replacement therapy with imiglucerase. Enzyme replacement therapy for type 1 (non-neuronopathic) GD

first became commercially available in 1991 in the form of human placenta-derived glucocerebrosidase (Ceredase®, alglucerase). In order to manufacture an adequate supply of enzyme and eliminate the potential viral-contamination risks associated with the use of human tissues, Cerezyme® (imiglucerase for injection), a recombinant Chinese hamster ovary (CHO) cell-derived version of glucocerebrosidase, was developed.

Imiglucerase was initially manufactured in limited amounts using a small scale facility. This limited production allowed only a small number of Gaucher patients to be treated with imiglucerase between 1994 and 1997. In 1997, the completion of a large scale manufacturing facility allowed the majority of patients to transition from

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alglucerase to imiglucerase. Imiglucerase was approved for use in the United States in 1994, throughout Europe in 1997, and in many other countries around the world since then. Today over 4500 patients with Gaucher disease world-wide are receiving treatment with imiglucerase and safety monitoring through pharmacovigilance is ongoing.

The World Health Organization (WHO) defines the term *pharmacovigilance* as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems. As detailed in the recently published Guidance for Industry E2E Pharmacovigilance Planning (April 2005), the knowledge upon which a product's safety profile is based is likely to grow significantly in both the immediate and long-term post-approval period as the treated population expands both in number and characteristics of patients treated. Early pharmacovigilance activities to better establish risk-benefit may include routine post-marketing surveillance of adverse events as well as more targeted efforts as needed, such as safety studies to better assess potential risks of known or unknown missing information. In the case of imiglucerase, pre-approval clinical studies did not identify any specific safety concerns. Subsequent pharmacovigilance efforts were directed at a global post-marketing adverse event (AE) surveillance system and a voluntary immunosurveillance program to detect any immediate, previously unrecognized safety concerns and better understand the long-term safety and immunogenicity profile of the product in a larger population.

As with any therapeutic protein, imiglucerase has the potential to elicit an immune response. Since the approval of alglucerase in 1991, Genzyme has maintained a global post-marketing AE reporting system and a voluntary immunosurveillance program. The goal of these programs is to detect, evaluate and communicate potential safety issues in an ongoing fashion and also to better characterize the long-term safety and immunogenicity of imiglucerase over the course of an ever-greater number of person-years of treatment. The current analysis reviewed the safety profile of imiglucerase established over the course of 10 years (1994–2004) based on world-wide post-marketing experience and data collected through immunosurveillance.

Materials and methods

Safety database and analysis

Per International Council on Harmonization (ICH) guidelines and local laws and regulations governing medicinal products, the manufacturer is required to report spontaneously received notifications of AEs as well as reports of potential AEs identified in the literature to the appropriate regulatory authorities. Most of the AE reports are received from health care professionals such as physicians, nurses and pharmacists. Pharmacovigilance and drug safety departments are also alerted to potential AEs through other company points of contact, such as the sales force, case managers, home infusion companies and other means of treatment support. By convention, all spontaneously reported events are considered potentially related to the product but less so in instances where the

healthcare provider reports the relationship of the event to the product as unlikely or unrelated to the product. For the purpose of this analysis, “related events” are defined as those reported to the pharmacovigilance department as possibly, probably, or definitely related to imiglucerase as well as those events where causality is unknown or not assessed by the health care provider.

Spontaneous AE reports captured in the global safety database for imiglucerase from 1994 through 2004 were reviewed by calendar year and presented here. The AEs used in this analysis were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and categorized by body systems (System Organ Class (SOC)). From 1994 to 1997, the total number of new patients was limited and therefore specific reporting rates are not presented and the data are only discussed qualitatively. For calendar years 1997 through 2004, the reporting rates per year for the most common SOC were calculated as the number of unique events grouped by SOC divided by the number of patients treated in that year (estimates based on marketing data).

Seroconversion

Assays

The immunosurveillance program is voluntary and monitors patients for the development of IgG antibodies to imiglucerase using a screening ELISA followed by a confirmatory radioimmunoprecipitation assay. These assays were performed similarly to that described previously [2] except that clinical grade CHO-derived recombinant human glucocerebrosidase was used instead of alglucerase. Briefly, patient serum samples were diluted 1/100 and incubated in glucocerebrosidase-coated plates. Antibody reactivity was detected using goat anti-human IgG Fc specific horse radish peroxidase (HRP) conjugate and o-phenylene diamine as the substrate. The resultant absorbance values were compared to a cut-off established from a normal human serum distribution study (Genzyme Corporation, Internal Validation Study, Unpublished results). All serum samples with values above the established normal range were tested for confirmation of specific antibodies to recombinant glucocerebrosidase in the radioimmunoprecipitation assay. A patient was considered to have developed IgG antibodies to glucocerebrosidase if both the ELISA and the radioimmunoprecipitation assays were positive.

Patients

In order for a patient to be evaluated for seroconversion, patients were required to be naïve to enzyme replacement therapy (not previously treated with alglucerase or imiglucerase) and have a baseline serum sample and at least one serum sample drawn at a minimum of 30 days after the first infusion of imiglucerase. Those previously treated with alglucerase, a placental-derived form of the enzyme, were excluded from the analysis due to the potential for these patients to develop an immune response prior to initiation of the imiglucerase. Seroconversion rates were calculated monthly for the qualified imiglucerase-naïve patients, and a cumulative rate was calculated annually from 1994 through 2005.

Results

Safety

Early post-approval period (1994–1997)

Small scale production limited the use of imiglucerase during the early post-approval period of 1994–1997, which resulted in a small number of treated patients. The number of AEs reported during this time period, therefore, was also limited. Switches back to alglucerase were not responsible for the limited number of patients reporting AEs.

Fifty-nine total AEs were reported in the early post-approval period and 44 of these cases were reported as related (or not assessed). Imiglucerase was continued in all of the 44 cases that were reported as related. The only AEs related to imiglucerase therapy reported more than 4× during the early post-approval period (data not shown) were events temporally associated with infusion administration. Such reactions commonly included nausea, vomiting, headache, pruritus, urticaria, rash, chest pain or tightness, fatigue or asthenia, malaise, flushing and dyspnea. Most of these infusion-associated reactions were managed successfully through slower infusion rates and/or pretreatment with anti-pyretics or antihistamines and did not require further treatment [3,4].

Late post-approval period (1997–2004)

By November of 1997, large scale production and more widespread regulatory approval led to the increased availability of imiglucerase and a concomitant increase in reported AEs as most Gaucher patients treated with alglucerase had switched to imiglucerase. At the end of 1997, a total of 2184 Gaucher patients were receiving enzyme replacement therapy (ERT) world-wide, 753 (34%) with alglucerase and 1431 (66%) with imiglucerase. Data available for the 969 U.S. patients receiving imiglucerase by 1997 indicate that 80% had been transferred from alglucerase treatment, 17% were completely naïve to ERT and 3% continued imiglucerase after clinical study participation.

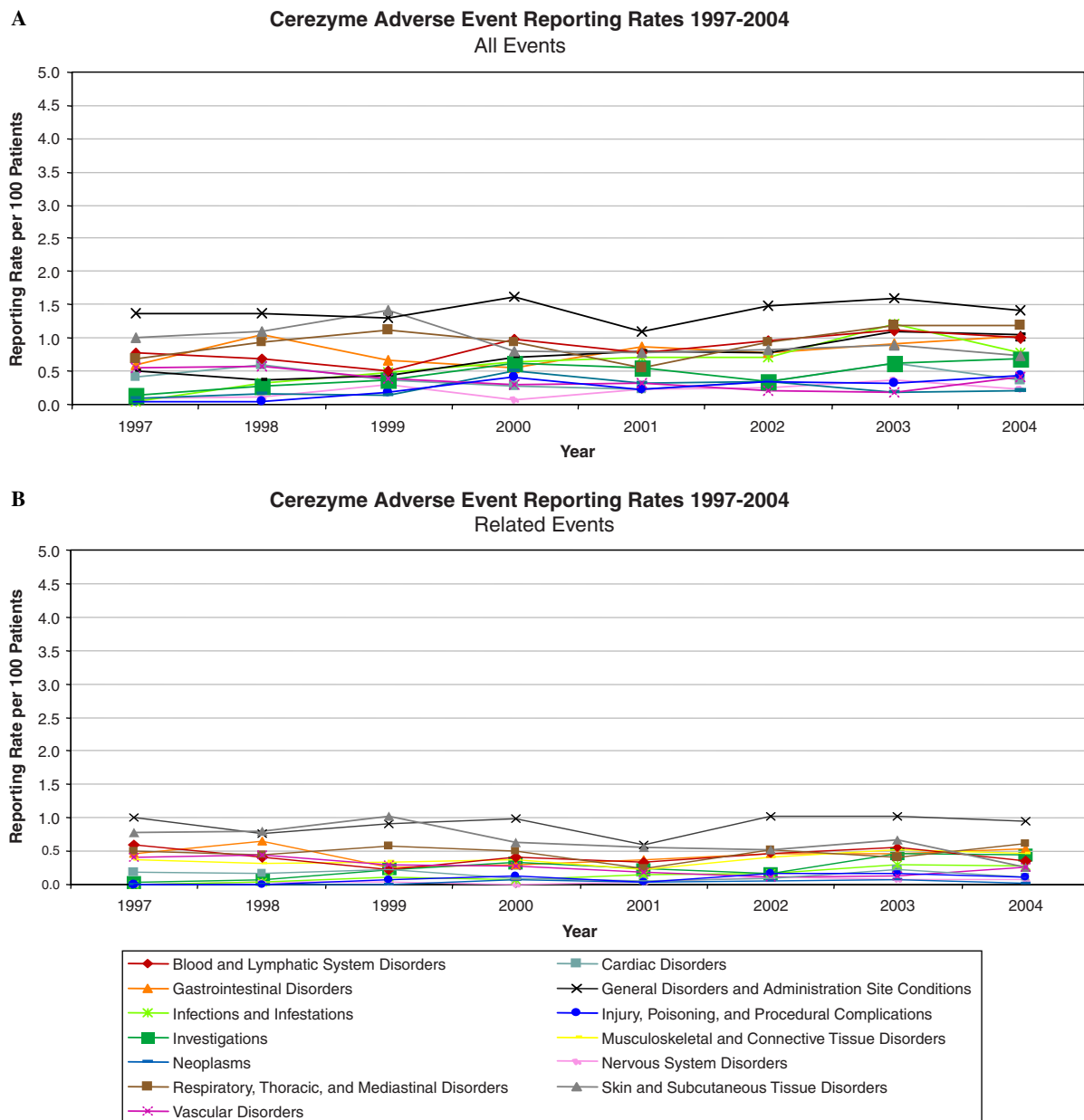


Fig. 1. (A) All adverse events reported for imiglucerase by system organ class from 1997 to 2004. (B) All related adverse events reported for imiglucerase by system organ class from 1997 to 2004.

By the end of 2004, approximately 4200 patients worldwide were receiving imiglucerase. In comparison to the early approval period, the considerable increase in exposure to imiglucerase through the years allowed for more meaningful analysis of reported AEs.

All AEs for patients with any exposure to imiglucerase between 1997 and 2004 were categorized by SOC and placed into categories based on relatedness reported by the patients' health care providers. In this analysis, related events are defined as those events that were reported as definitely, probably, or possibly related to imiglucerase as well as the cases where relatedness was not assessable and/or not reported by the provider. The AEs that fell into the most common SOC ("all events"), regardless of relatedness to imiglucerase, are shown by SOC in Fig. 1A and the "related events" are shown by SOC in Fig. 1B.

There were 209 AEs categorized into 12 SOC's reported over the 8 year late post-approval period from 1997–2004 that were not captured in the graphical displays due to low yearly frequencies (less than or equal to 10 events reported per year per SOC). These SOC's (and total events) include Psychiatric (38), Hepatobiliary (34), Eye (31), Metabolism and nutrition (30), Renal and urinary (28), Immune system (15), Reproductive and breast (12), Pregnancy (8), Endocrine (5), Congenital (4), Ear/labyrinth (3) disorders and Surgical and medical procedures (1). Of these rare events, cholelithiasis, nephrolithiasis, anxiety and depression were most commonly reported.

The most frequently reported related AEs fell under three SOC's: general disorders and administration site reactions; skin and subcutaneous tissue disorders; and respiratory, thoracic and mediastinal disorders. The numbers reported are total AEs in each category (Table 1) and do not take into account the number of patients involved, as one patient may experience more than one event. The most frequently reported events that appear within these SOC's were non-serious infusion-associated reactions. Most AEs showed a consistent distribution across the time intervals (Fig. 1).

Most of the related AEs were temporally related to the infusion of imiglucerase and typical of immune-mediated reactions (Table 1). These types of AEs were predominantly self-limited and effectively managed by either decreasing the rate of infusion or pretreatment with antihistamines [4,5]. With continued treatment and in some cases modifications in infusion rate, the reaction frequency generally decreased. In patients with significant reactions, temporary modifications in dose were made in addition to the lower infusion rate and pretreatment. Over time, most patients tolerated imiglucerase at the regular infusion rate without additional pretreatment. Only four patients with significant infusion reactions subsequently discontinued enzyme replacement therapy. At the time of discontinuation, 3 of the 4 patients were elderly and it is not clear whether or not treatment interruption was directly related to infusion tolerability. Three additional patients experienced infusion reactions that may have resulted in discontinuation of

ERT, but these patients were lost to follow-up and discontinuation of therapy was, therefore, not confirmed. The presence of antibodies was not a factor in the discontinued cases.

Seroconversion

Since antibody testing was voluntary, only a portion (1633) of the total (4237) imiglucerase treatment recipients during the early and late post-approval periods were imiglucerase-naïve and submitted samples. Of the 1633 tested, 1134 had two or more samples (baseline and at least one post-imiglucerase) submitted for seroconversion analysis. The immunosurveillance summary data for these 1134 imiglucerase-naïve patients indicate the cumulative rate of seroconversion for IgG antibody formation remained constant at approximately 15% (mean = 15.6%) from 1994 through 2005 (Fig. 2). The data suggest that patients who develop IgG antibody to imiglucerase produce antibodies within 6 months of initiating treatment and rarely develop antibodies after 12 months of therapy. Seroconversion generally has not been shown to affect the established efficacy parameters to date.

Discussion

At the time of marketing authorization, limited safety information is available for any new drug or biologic. This is especially true of treatments for "ultra-orphan" conditions such as Gaucher disease. In the clinical trials required for the approval of imiglucerase, it was feasible to include

Table 1
The top three system organ class categories (bold text) of related adverse events and the three most frequently reported preferred terms (italicized text) for imiglucerase from the late post-approval period (1997–2004)^a

	Number of adverse events	
	Related events	All events
Total	852	2931
General disorders and administration site reactions	161	455
<i>Pyrexia</i>	25	80
<i>Chills</i>	21	55
<i>Chest discomfort</i>	22	44
Skin and subcutaneous tissue disorders	117	325
<i>Pruritus</i>	28	82
<i>Rash</i>	23	67
<i>Urticaria</i>	24	60
Respiratory, thoracic, and mediastinal disorders	88	298
<i>Dyspnoea</i>	28	75
<i>Cough</i>	12	32
<i>Throat irritation</i>	9	11

^a Each of these events was found to occur in <1% of the total patient population [4]. Each event may have occurred more than once in any individual patient.

only a limited number of Gaucher patients due to the rarity of the condition [6]. Therefore, the information on the safety profile of imiglucerase available at the time of regulatory approval in 1994 was limited. In such a situation, a long-term international post-marketing safety surveillance program plays an essential role in more fully characterizing the safety profile of ultra-orphan drugs. In the case of imiglucerase, the post-marketing safety experience now spans across the more than 4500 patients who received this treatment since 1994. Importantly, this long-term safety experience comes from real-world clinical settings in which imiglucerase is used across a wide range of patients from many countries, in various age groups, of various ethnic backgrounds, and with a wide range of concomitant medications and medical conditions. The current retrospective analysis of the long-term international post-marketing safety experience with imiglucerase therapy demonstrates a stable and low rate of seroconversion and AEs, with the most commonly reported SOC of “general disorders and administration site conditions” reported in approximately 1.5% of patients (Fig. 1A) over the 8 year period.

The type and frequency of all (Fig. 1A) and related (Fig. 1B) reported AEs are remarkably consistent. The

events most commonly and consistently reported as associated with imiglucerase infusions fall under the SOC “general disorders and administration site reactions” (pyrexia, chills, chest discomfort), “skin and subcutaneous tissue disorders” (pruritus, rash, urticaria) and “respiratory, thoracic, and mediastinal disorders” (dyspnea, cough, throat irritation) (Table 1). In a post-marketing database analysis of AE occurrence in children (age 2–12 years), adolescents (age 12–16 years) and adults (>16 years), it was shown that the most common events reported in children included dyspnea, fever, nausea, flushing, vomiting and coughing, whereas in adolescents and adults the most common events reported were headache, pruritus and rash. No correlation between Gaucher disease type (non-neuronopathic versus neuronopathic) and the type and frequency of events experienced related to infusion administration have been identified. Nearly all patients have been able to continue therapy and manage these reported events by slowing the rate of the infusion or pretreatment with antihistamines or anti-inflammatory drugs. Significant AEs in patients treated with imiglucerase which might prevent continuation of treatment, such as anaphylaxis, have been extremely rare.

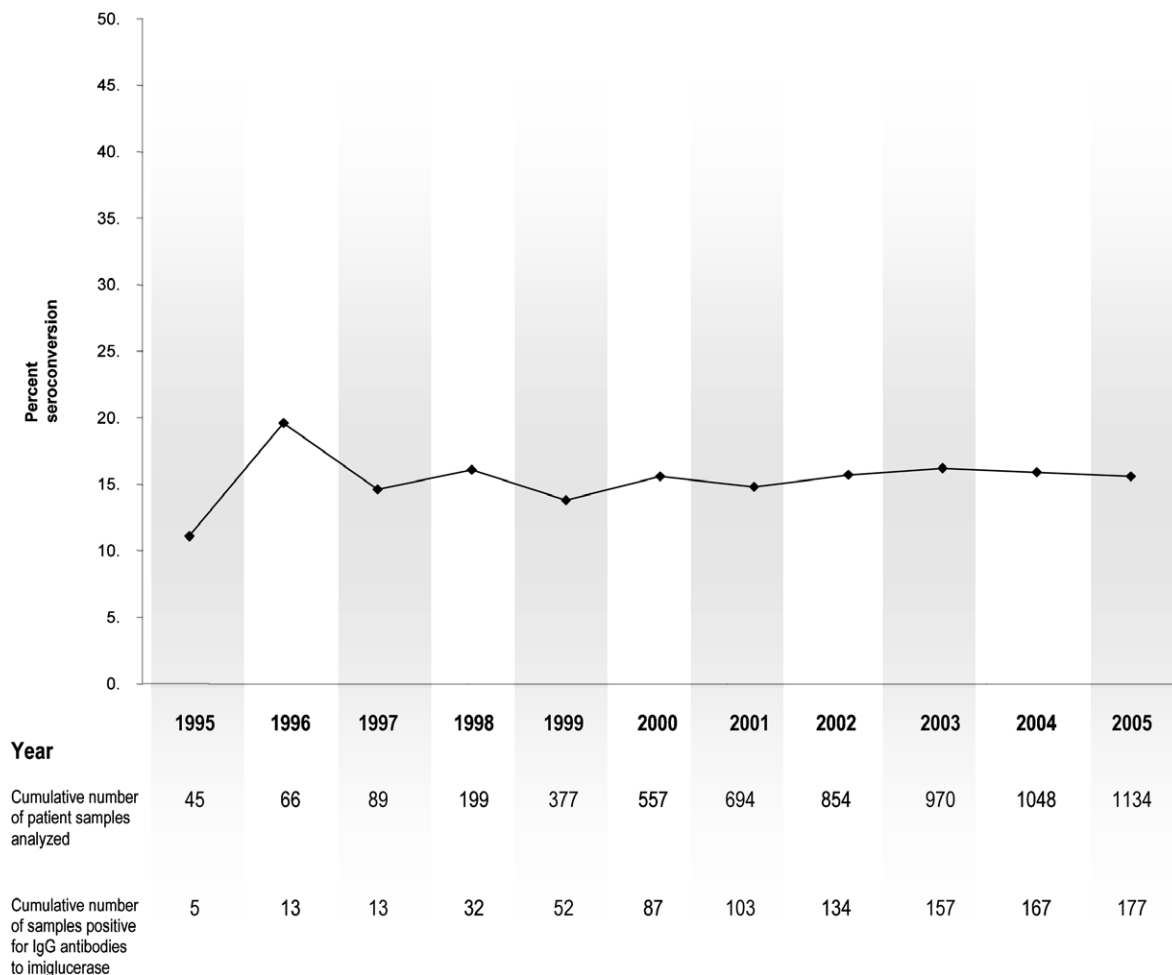


Fig. 2. Immunosurveillance summary data for imiglucerase-naïve patients. Naïve is defined as patients not previously exposed to alglucerase or imiglucerase.

With any therapeutic protein, characterization of the immunologic response to the infusion of an exogenous protein is an important aspect of the safety profile. Factors which may determine the immunogenicity of a therapeutic protein include the size of the molecule, the structural or sequence difference from the native protein, the dose, and the frequency and route of administration [2,7]. Previous experience has shown that repetitive infusions or injection of a normal functioning protein in patients with varying levels of endogenous enzyme would result in an immune response in some patients [2]. In the case of imiglucerase therapy, seroconversion correlates only partially with reports of AEs. Patients with IgG antibody to imiglucerase appear to have an increased risk of hypersensitivity type reactions, as ~46% of patients with IgG report symptoms of hypersensitivity. However, not all patients who have reported symptoms of hypersensitivity have a detectable IgG antibody [8].

The data presented for imiglucerase indicate that the rate of IgG antibody formation has remained remarkably constant at approximately 15% over a 10-year period (Fig. 2). This percentage is low compared to reports in the literature for other biologics [9–12], in particular other enzyme replacement therapies [13]. For example, interferon- α given to chronic hepatitis patients results in antibody development in 50% [12] to 63% [11] of patients. Rates of antibody formation for insulin ranged from 20 to 40% [10]. Other human proteins reported to induce antibody formation are Factor VIII [14], interferon- β [15] and interleukin-2 [16].

The safety profile of a recombinant therapeutic protein is highly dependent on the quality and consistency of a complex manufacturing process [17]. The recombinant DNA technology-based manufacturing process required to produce large-molecule therapeutic proteins is much more complex than the chemical synthesis manufacturing process used for small molecule drugs. Minor differences in the manufacturing process of otherwise similar recombinant proteins can have major safety consequences, as in the case of one brand of recombinant erythropoietin α , Eprex. In the 1990s a 10-fold increased rate in the incidence of pure red cell aplasia (PRCA) in patients receiving Eprex was noted [18]. Patients receiving other brands of recombinant erythropoietins did not experience the same rate of PRCA. Upon subsequent analysis, the differing rates of PRCA were thought to have been due in part to a difference in the manufacturing process for Eprex, as well as possibly a change in the route of administration (from intravenous to subcutaneous).

The stability of the manufacturing process is based in part on the type of cell culture system used to produce the recombinant protein. The long-term stability of the safety experience with imiglucerase reflects the use of the CHO cell, which is well-characterized and has become an industry standard cell culture system for therapeutic proteins such as Factor VIII, recombinant erythropoietin, interferons, and human growth hormone. As of August

2006, 89 therapeutic proteins (not including vaccines) have been approved for use by the FDA in the US [19–23], and 80 therapeutic proteins (not including vaccines) have been approved for use by the EMEA in the EU [19–21,24]. Of the therapeutic proteins approved for use in the US and the EU, about half are produced using mammalian cell culture systems (47 of 89 products (53%) in the US; 39 of 80 products (49%) in the EU), while the remainder are produced in microbial cell expression systems. CHO cells are the most commonly utilized mammalian cell expression system in the US and EU (30 of 47 products (64%) in the US; 28 of 39 products (72%) in the EU). More recently, other mammalian cell culture systems have been used (16 of 47 products (34%) in the US; 8 of 39 products (21%) in the EU). Most of the proteins using other non-CHO cell expression systems are recombinant antibodies produced in murine NSO or Sp2/0 myeloma cells. Other less frequently used mammalian cell culture systems include murine mammary epithelial cells, baby hamster kidney cells, human embryonic kidney cells or human fibroblasts. Therapeutic proteins produced utilizing human cell expression systems have been approved for two products in the US and three products in the EU [19–21,23,24].

Conclusions

The long-term stability of the safety profile of imiglucerase is a reflection of a well-characterized cell expression system and a mature and well-controlled manufacturing process. A review of the long-term safety experience of imiglucerase demonstrates that it is a safe therapy for the treatment of Gaucher disease with a stable and low rate of reported AEs and seroconversion.

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