IX Incontro Annuale
La Malattia di Gaucher
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Sicurezza del Registro di malattia di Gaucher: una vera storia clinica di oltre 20 anni

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Definizione

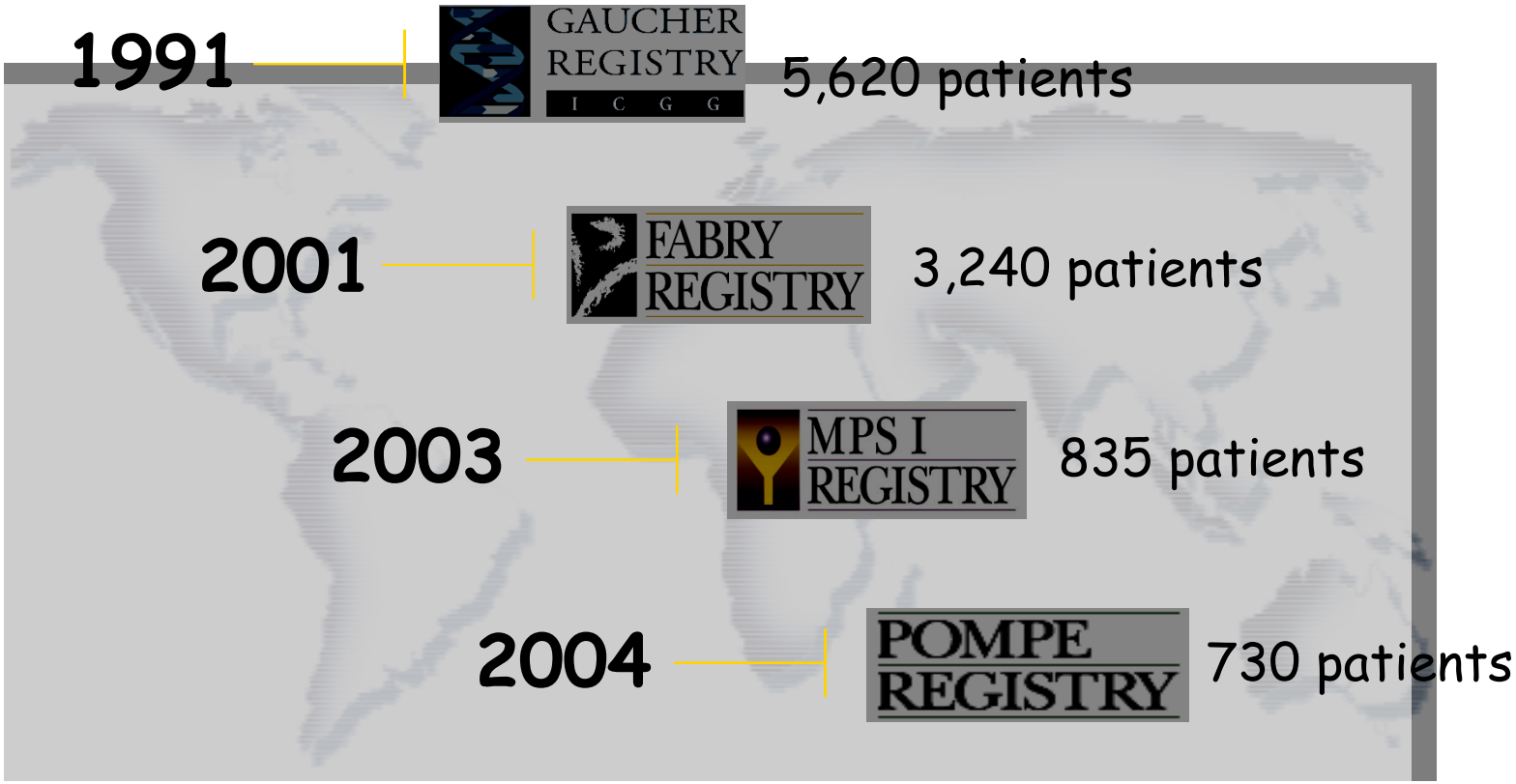
Registro di Malattia

- Database
- Disegnato specificatamente
- Contiene dati osservazionali longitudinali raccolti da medici
- Adesione volontaria tesa ad esplorare e meglio definire l'andamento naturale della malattia e le sue caratteristiche cliniche, nonché a tracciare e caratterizzare la risposta alla terapia.

Obiettivi dei Registri

- Migliorare la conoscenza della variabilità, progressione e storia naturale della malattia
- Aiutare la comunità medica a sviluppare delle raccomandazioni e linee guida per monitorare e gestire i pazienti
- Fornire dati clinici per migliorare la qualità del trattamento dei pazienti

Registri mondiali



Dati raccolti nel Registro

- Dati anagrafici ed anamnestici del paziente (es. data di nascita, età di esordio dei sintomi, età alla diagnosi, genotipo, etc)

- Risultati degli esami strumentali e di laboratorio eseguiti nel corso della normale pratica clinica e nel corso del monitoraggio dei pazienti (esami ematochimici, radiografie)

Dati raccolti nel Registro

- Sicurezza del trattamento?
- Il Registro Gaucher non nasce con questa finalità ma contiene dati che possono essere informativi
- Quale è stata la principale preoccupazione di safety?
- Cosa si è ricavato dal Registro?

Humoral immune response ERT

Table 1. Immune responses in patients receiving enzyme-replacement therapy[a]

Disease	Enzyme-replacement therapy		Product/enzyme name	Percentage of patients with antibody reactivity	Percentage of patients with hypersensitivity reactions	Refs
	Clinical trial	Therapy status				
Gaucher	Phase III	In clinical practice	Cerezyme®	15	13.8	[14]
MPS I	Phase I/II, III	Approved for clinical practice	Aldurazyme®	91	32	[6,7]
MPS II	Phase I/II	Clinical studies in progress	Iduronate-2-sulphatase	11	55	[18]
MPS VI	Phase I	Clinical studies in progress	Aryplase®	100	N/A	[12]
	Phase II			N/A	5	[12]
Fabry	Phase III	Approved for clinical practice	Fabrazyme®	89	52	[10]
			Replagal®	55	10	[11]
Pompe	Phase I/II	Clinical studies in progress	α-glucosidase	66	66	[8,19]

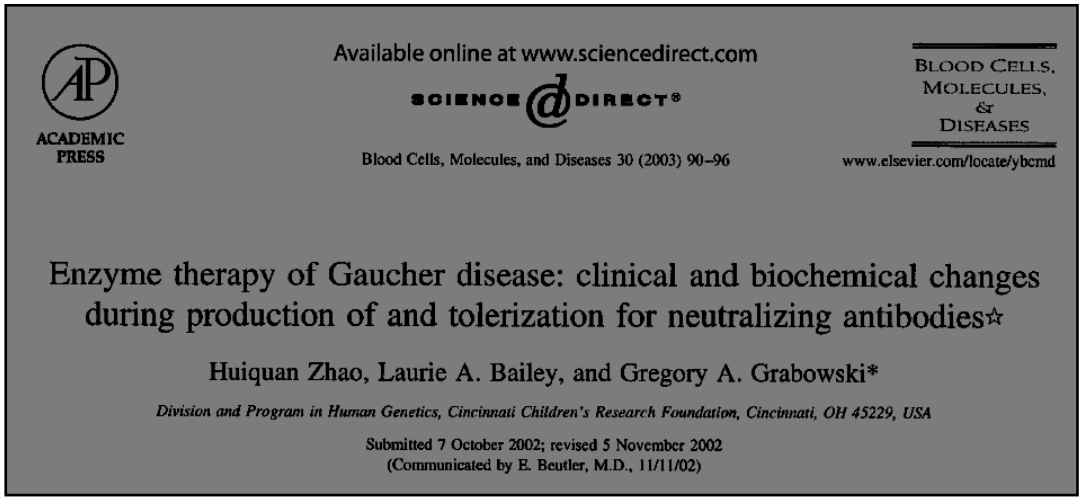
[a]Abbreviations: MPS I, mucopolysaccharidosis I; MPS II, mucopolysaccharidosis II; MPS VI, mucopolysaccharidosis VI; N/A, data not available in reference.

These clinical trials of enzyme-replacement therapy showed that there were different levels of humoral immune response to replacement proteins, dependent on both the inherent antigenicity of the protein being infused and the individual patient. Almost all of the antibody responses in these different patient groups appeared to involve immunoglobulin (Ig) G and not IgE subclass antibody. Although there is currently no standard method

- **15%** of patients with **antibody reactivity**
- **13.8%** of patients with **hypersensitivity** rections

Brooks DA. et al. TRENDS in Molecular Medicine Vol.9 No.10 October 2003

Impact of neutralizing antibodies
Conclusions



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Blood Cells, Molecules, and Diseases 30 (2003) 90–96

BLOOD CELLS, MOLECULES, & DISEASES

www.elsevier.com/locate/ybcmd

Enzyme therapy of Gaucher disease: clinical and biochemical changes during production of and tolerization for neutralizing antibodies☆

Huiquan Zhao, Laurie A. Bailey, and Gregory A. Grabowski*

Division and Program in Human Genetics, Cincinnati Children's Research Foundation, Cincinnati, OH 45229, USA

Submitted 7 October 2002; revised 5 November 2002
(Communicated by E. Beutler, M.D., 11/11/02)

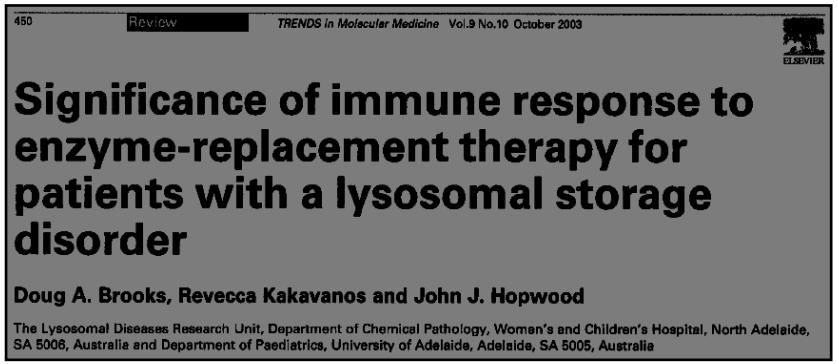
→ The presence of neutralizing antibodies should be suspected in Gaucher disease patients on enzyme therapy who experience diminshed response or deterioration.

→ The **persistence of minimal amounts of in vitro neutralizing antibodies does not interfere with the therapeutic effectiveness**.

→ Plasma chitotriosidase activities were not well correlated with the clinical course in either patient. **Chitotriosidase is not a sensitive marker for the severity of disease or disease progression**.

Zhao H . et al. Blood Cells Molecules and Diseases, 2003, 3081):90-96

For the physician treating patients with a lysosomal storage disorder, the most important question is:



450 Review TRENDS in Molecular Medicine Vol.9 No.10 October 2003

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Significance of immune response to enzyme-replacement therapy for patients with a lysosomal storage disorder

Doug A. Brooks, Revecca Kakavanos and John J. Hopwood

The Lysosomal Diseases Research Unit, Department of Chemical Pathology, Women's and Children's Hospital, North Adelaide, SA 5006, Australia and Department of Paediatrics, University of Adelaide, Adelaide, SA 5005, Australia

IS AN IMMUNE RESPONSE TO REPLACEMENT THERAPY A RISK TO THE PATIENT AND WILL IT RESULT IN ALTERED EFFICACY OF TREATMENT?

Brooks DA. et al. TRENDS in Molecular Medicine Vol.9 No.10 October 2003

Antibodies that neutralize enzyme activity

Neutralizing antibody causing altered clinical improvement/ disease progression has been reported in **<0.5% of Gaucher patients.**

Antibodies that either react with the active site of the infused enzyme or interfere with substrate binding capacity would be expected to be associated with an adverse therapeutic effect. In these cases, **the induction of immune tolerance becomes an important issue, to ensure that patients do not suffer irreversible disease progression.**

Brooks DA. et al. TRENDS in Molecular Medicine Vol.9 No.10 October 2003

Concluding remarks

A humoral immune response can be expected in some patients with a lysosomal storage disorder receiving enzyme-replacement therapy, and hypersensitivity reactions are an important concern. However, most patients with a lysosomal storage disorder who mounted an immune response to a replacement protein have successfully continued therapy with pre-medication using antihistamines or corticosteroids, a reduction in the rate of enzyme infusion and careful monitoring. A low but significant number of anaphylactic reactions have been reported for patients with a lysosomal storage disorder undergoing enzyme-replacement therapy, which reflects an imperative need for vigilant care during and immediately after enzyme infusion. The production of neutralizing antibodies will have an inhibitory therapeutic effect but this appears to be a rare occurrence for most types of lysosomal storage disorders. The effects of antibody on enzyme pharmacokinetics appear to be a relatively minor concern, but might be important for replacement proteins that elicit a high titre, high affinity humoral immune response. Immune response appears to be the only significant complication arising from enzyme infusion into patients with a lysosomal storage disorder but, if properly managed, is not an insurmountable obstacle for most patient groups.

Most patients with immune response to ERT **fully continued with appropriate pre-medication**

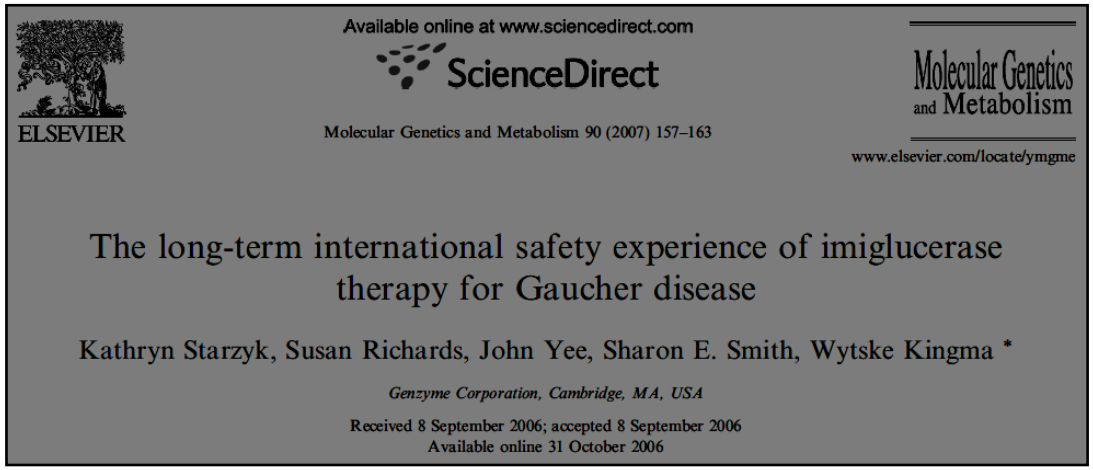
Neutralizing antibodies appears to be a **rare occurrence** for most types of LSDs

The immune response, **if properly managed not an insurmountable obstacle**

Brooks DA. et al. TRENDS in Molecular Medicine Vol.9 No.10 October 2003

LONG-TERM SAFETY EXPERIENCE

Long-term safety experience



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Molecular Genetics and Metabolism 90 (2007) 157–163
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The long-term international safety experience of imiglucerase therapy for Gaucher disease

Kathryn Starzyk, Susan Richards, John Yee, Sharon E. Smith, Wytske Kingma *

Genzyme Corporation, Cambridge, MA, USA

Received 8 September 2006; accepted 8 September 2006
Available online 31 October 2006

Objective	Study description/ Population	Methods
Review the long-term international safety experience of imiglucerase from 1994 to 2004	·Retrospective analysis of adverse events captured in the global safety database ·4,237 patients from 1994 to 2005	·All sponstaneous adverse events captured in the pharmacovigilance database for imiglucerase form 1994 to 2004 were analyzed. ·Patients without prior exposure to imiglucerase or alglucerase from 1994 to 2005 were assessed for development of IgG antibodies. Patients previously treated with alglucerase were excluded from the seroconversion analysis.

Starzyk K. et al. Mol Genet Metab. 2007;90:157-163.

Results

Adverse Events

By the end of 2004, 4,237 patients worldwide were receiving imiglucerase. During the 8-year postapproval period for imiglucerase (Cerezyme) (1997 to 2004), the most frequently reported treatment-related adverse events were nonserious infusion-associated reactions (including pyrexia, chills, and chest discomfort), followed by cutaneous events (pruritus, rash, urticaria) and respiratory tract events (dyspnea, cough, throat irritation). Each of these events occurred in <1% of the total Gaucher patient population. The type and frequency of all treatment-related adverse events were consistent over time (1997 to 2004).

Most of these infusion-related adverse events were self-limited and effectively managed by decreasing the rate of infusion or pretreatment with antihistamines or anti-inflammatory agents and did not lead to discontinuation of treatment.

Seroconversion

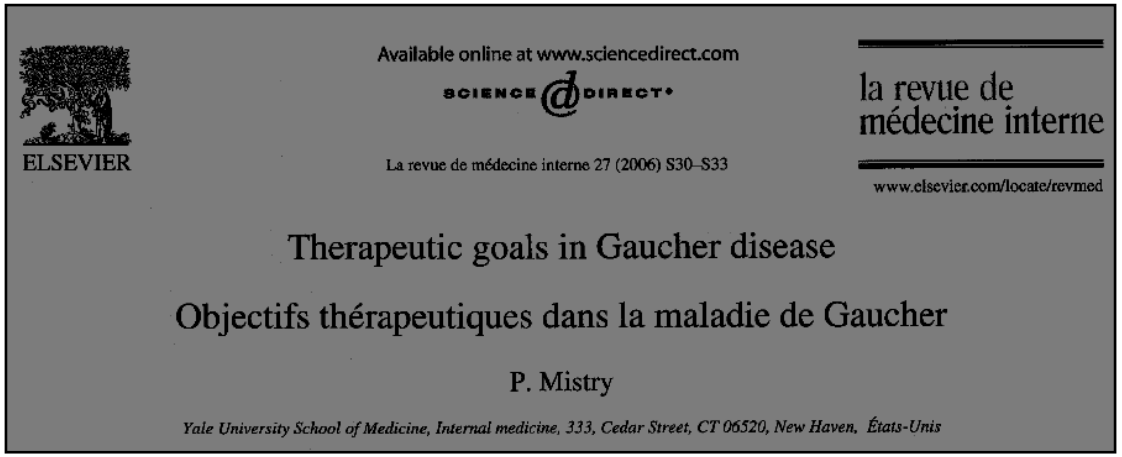
Between 1994 and 2005, IgG antibodies to imiglucerase were detected in ~15% of treatment-naïve patients (n=1,134). Patients who develop antibodies to imiglucerase rarely do so after 12 months of therapy. Seroconversion has not been shown to affect the efficacy parameters of imiglucerase.

Starzyk K. et al. Mol Genet Metab. 2007;90:157-163.

OTHER PUBLICATIONS

GOOD SAFETY PROFILE

Good Safety Profile



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La revue de médecine interne 27 (2006) S30–S33

la revue de médecine interne

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Therapeutic goals in Gaucher disease

Objectifs thérapeutiques dans la maladie de Gaucher

P. Mistry

Yale University School of Medicine, Internal medicine, 333, Cedar Street, CT 06520, New Haven, États-Unis

The recombinant enzyme shows a remarkable safety profile with tolerability at three years greater than 99%. Among patients who started enzyme therapy, more than 99% are still on enzyme therapy at the end of three years and beyond. Furthermore, the incidence of allergic reactions is very low, with less than 1% of patients. There is some weight gain but it is not a side effect. It is an aggregation of hypermetabolic state due to the activated macrophages. Comparatively, only 50% of patients treated by miglustat are able to stay on substrate deprivation treatment after three years because of the number of side effects, mainly of gastrointestinal origin. These data underscore the really good safety profile for Cerezyme®.

Mistry P et al. La revue de medecine interne 27 (2006) S30_S36

Excellent Safety Profile

Biologics: Targets & Therapy

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REVIEW

Review of the safety and efficacy of imiglucerase treatment of Gaucher disease

Deborah Elstein
Ari Zimran

Gaucher Clinic, Shaare Zedek Medical Center, Jerusalem, Israel

Most of the side effects listed for alglucerase and imiglucerase during the clinical trials and afterwards, were infrequently observed, typically mild, and almost always transient in nature. This excellent safety has allowed home therapy in many countries,[78,79] and the administration of ERT during pregnancy despite the original warning in the package insert.[80,81] The development of anti-glucocerebrosidase antibodies has been reported to occur among 15% of patients;[82] primarily non-neutralizing IgG antibodies.

Elstein et al. Biologics: Targets & Therapy. 2009