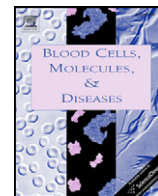




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Letter to the Editor

Recommendations for treating patients with Gaucher disease with emerging enzyme products

To the Editor,

With the current shortage of imiglucerase (Cerezyme®) a meeting of European Gaucher disease experts was convened in London UK on October 16, 2009, to discuss the needs of European Gaucher disease patients.

The EMEA produced guidelines at the end of June to identify those patients most in need of treatment with imiglucerase; these were subsequently revised in mid-August [1]. The guidelines were met with concerns from the Gaucher community and were followed by a publication from the European Working Group for Gaucher Disease (EWGGD) and European Gaucher Alliance (EGA), that provided guidance regarding the equity of distribution, identification of patients at risk and their monitoring, and potential access to alternative emerging treatments (velaglucerase alfa [Shire Human Genetic Therapies, MA, USA] and taliglucerase alfa [Protalix Biotherapeutics, Carmiel, Israel]) [2]. After this publication, EMEA guidelines were amended in October [3].

These enzyme preparations have completed phase 3 clinical trials and have been assigned fast-track status by the US Food and Drug Administration (FDA); in July 2009, both manufacturers were approached by the FDA with a request to increase manufacture of their recombinant human glucocerebrosidase proteins and, in the face of a global shortage of imiglucerase, to come forward with protocols by which Gaucher patients can gain expanded access to their products. In the EU and other regions, Shire continues to engage with national and regional authorities to provide velaglucerase alfa to those Gaucher patients most in need as part of a preapproval early access program.

The objective was to guide prioritization of patients with type 1 Gaucher disease for access to emerging therapies that are as yet unlicensed. We intend that this guidance will assist physicians whose experience of Gaucher disease is limited. The meeting was supported by Shire HGT, but the clinical recommendations were developed independently.

Clinical criteria for early access were proposed in advance, and the recommendations were made after discussion. All the participants reviewed the recommendations; opinions were also sought from other EWGGD members.

Two broad groups of patients with Gaucher disease are considered suitable for the emerging treatments during the period of imiglucerase shortage: (1) patients receiving imiglucerase at reduced or suboptimal doses and (2) patients who were previously receiving imiglucerase therapy, who are not considered to be at high risk for the development of complications as previously defined [2], but whose disease is sufficiently active to pose a risk of symptomatic illness if therapy is not instituted before the shortage is resolved.

The following are the patients in the first category (receiving imiglucerase at reduced doses):

- Symptomatic children who show progression of disease while on a reduced dose of imiglucerase (<18 years old; velaglucerase alfa only)
- Symptomatic adults at high risk as defined previously (1) and who show progression of disease while on a reduced dose of imiglucerase
- Pregnant women who show progression of disease while on a reduced dose of imiglucerase (taliglucerase alfa only)
- Patients who experience significant recent and recurrent bone events such as bone crises, osteonecrosis or fractures
- All other categories of patients that are identified as being at high risk and who cannot be adequately treated with the dose of imiglucerase that is available to them

The following are the patients in the second category (patients who were previously receiving imiglucerase therapy, who are not considered to be at high risk for the development of complications, but whose disease is sufficiently active to pose a risk of symptomatic illness if therapy is not instituted before the shortage is resolved):

- Presence of antibodies against imiglucerase
- Severe bone involvement:
 - Fractures and/or osteonecrosis at any time
 - Recent and recurrent bone crises
 - Persisting bone pain that is convincingly related to Gaucher disease
 - Osteoporosis and/or active or newly identified lesions evident on magnetic resonance imaging. It is difficult to define activity solely on MRI in the absence of a radiologist with experience of Gaucher disease and without corroborative clinical evidence.
- Splenectomised patients (increased risk for skeletal complications, liver disease and pulmonary hypertension)
 - If asplenic and have thrombocytopenia or other cytopenias
- Haematological parameters
 - Platelets
 - If counts have decreased to <50,000, or by >20% during drug interruption.

Upon restoration of imiglucerase, patients whose disease is well controlled by either of the emerging enzyme preparations should be given the option of continuing the new therapy.

Attendees

Clinicians present at the meeting: Nadia Belmatoug, MD, Reference Centre for Lysosomal Diseases, Hôpital Beaujon, Clichy, France; Timothy M. Cox, MD, Department of Medicine, Addenbrooke's Hospital, University of Cambridge, UK; Pilar Giraldo, MD, PhD, Hospital Universitario Miguel Servet, Zaragoza. CIBERER, Spain; Atul Mehta, MA, MD, FRCP, FRCPATH, Lysosomal Storage

Disorders Unit, Royal Free Hospital, University College London, UK; Eugen Mengel, MD, Villa metabolica, University Medical Centre, Mainz, Germany; Panagiotis A. Tsiftaris, MD, Laiko Hospital, Athens, Greece; Ari Zimran, MD, Shaare Zedek Medical Centre, Jerusalem, Israel.

Post-meeting advice received from: Bruno Bembi, MD, Centro di Coordinamento Regionale per le Malattie Rare, Ospedale Universitario, S. Maria della Misericordia, Udine, Italy; Derralynn Hughes, MA oxford DPhil, MRCP, DIPRC, Path, Lysosomal Storage Disorders Unit, Royal Free Hospital, University College London, UK; Olaf Bodamer, MD, PhD, FACMG, Institute of Inherited Disorders of Metabolism Salzburg, Austria; Allan M. Lund, MD, Department of Clinical Genetics, Copenhagen University Hospital, Copenhagen, Denmark; Anna Tytki-Szymanska, MD, Clinics of Metabolic Diseases, Endocrinology and Diabetology, The Children's Memorial Health Institute, Warsaw, Poland.

References

- [1] European Medicines Agency (EMA). Questions and answers on the shortages of Cerezyme and Fabrazyme. 14-8-2009.
- [2] C.E.M Hollak, et al., Force Majeure: therapeutic measures in response to restricted supply of imiglucerase (Cerezyme) for patients with Gaucher disease, *Blood Cells Mol. Dis.* (2009) Oct 3. [Electronic publication ahead of print].
- [3] European Medicines Agency (EMA) Updated temporary treatment recommendations for Cerezyme. Doc. Ref. EMA/665112/2009 22-10-2009.

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