

**SUMMARY OF GAUCHER DISEASE
PATIENT PRIORITIZATION FOR TREATMENT
RECOMMENDATIONS FROM THE MEETING OF
GAUCHER TREATMENT EXPERTS
SEPTEMBER 9TH, 2009, CHICAGO, IL**

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ATTENDEES

Clinicians Present at Meeting:

- **Christine Eng, MD**
Professor, Department of Molecular & Human Genetics, Baylor College of Medicine, Houston, TX
- **Gregory Grabowski, MD**
Director, Division of Human Genetics, Cincinnati Children's Hospital Medical Center, Professor of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH
- **Paige Kaplan, MB, BCh** (remote attendee)
Professor of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA
- **Priya S. Kishnani, MD** (remote attendee)
Division Chief, Pediatrics / Medical Genetics, Duke Children's Hospital & Health Center, Durham, NC
- **Gregory Pastores, MD**
Associate Professor, Neurology and Pediatrics, NYU School of Medicine, New York, NY
- **William Rhead, MD, PhD**
Professor of Pediatrics and Pathology, Medical College of Wisconsin, Children's Hospital of Wisconsin, Milwaukee, WI
- **Laurie Smith, MD, PhD**
Assistant Professor, University of Missouri, Kansas City, MO

Pre- and Post-Meeting Advice Received From:

- **Pramod Mistry, MD, PhD, FRCP**
Professor, Pediatrics and Internal Medicine, Yale University School of Medicine, New Haven, CT
- **Barry Rosenbloom, MD**
Tower Hematology Oncology Medical Group, Beverly Hills, CA
- **Neil Weinreb, MD**
University Research Foundation for Lysosomal Storage Diseases, Coral Springs, FL

INTRODUCTION

A meeting of Gaucher disease experts was convened on September 9th, 2009 at the Intercontinental Hotel, Chicago, IL, USA to discuss the current supply shortage for Cerezyme® (imiglucerase) and to better understand the best ways to meet the needs of patients with Gaucher disease through the Cerezyme supply shortage. The objectives of the meeting were to develop treatment prioritization recommendations based on patient disease characteristics and to present the prioritization guidance to physicians and patient groups for their input and discussion. The meeting was organized and funded by Shire HGT, which briefed the experts on the near-term availability of velaglucerase.

Prior to the meeting, a Steering Committee – composed of Dr Gregory Grabowski, Dr Pramod Mistry, Dr Gregory Pastores, and Dr Neal Weinreb – was consulted and the experts provided a list of criteria that could be considered in the development of treatment prioritization recommendations. This list formed a framework for the experts' discussions in Chicago, which has been developed into a guidance document for prioritizing treatment for Gaucher disease patients as Category I, II, III, or IV in terms of risk of disease progression, where Category I is the highest risk. These recommendations were developed after the Chicago meeting, with Dr Gregory Grabowski leading the initiative. All experts attending the Chicago meeting were asked to review the recommendations and a few additional experts who were unable to attend the Chicago meeting have also reviewed and provided comment on the document. Note: The discussions and recommendations are to be considered independent of the treatment modality, e.g., any enzyme or substrate reduction intervention, and thus can be used to help treatment decisions for use of any of these agents.

The overall aims of this endeavor are to:

- **Establish prioritization recommendations for treatment of patients with Gaucher disease based on categorization of disease status**
- **Publish the prioritization recommendations through the National Gaucher Foundation (NGF) Medical Advisory Board**

DISEASE STATUS CATEGORIES

Category I

- Type 2 and 3 patients
- Patients with antibodies or prior adverse reactions, not anaphylactic-type, to treatment, where the physician is concerned that re-starting may be problematic
- Children (<18 years) on treatment
- Young adults (18-<35 years) who had significant disease as children, and who have been on continuous therapy since before they were 18 years
- Patients over 35 years who:
 - Have recent disease-related splenectomy
 - Are long-term splenectomized women
 - High risk of pulmonary hypertension, which is exacerbated by Gaucher disease
- Interstitial lung disease (Gaucher disease and non-Gaucher-related)
- Hepato-pulmonary syndrome
- Pulmonary hypertension
- Portal hypertension
- Not attaining therapeutic goals
- Pregnancy (substrate reduction therapy is contraindicated)
- Menopause
 - Osteoporosis or significant osteopenia (T score < -1.5) in women who are perimenopausal or within 5 years of menopause
- History and signs of rapid disease progression
- Recurrence or development of new *signs* and symptoms since therapeutic change (i.e., dosage reduction, alternative therapies) including marked increases in fatigue and/or bone pain
- Thrombocytopenia
 - Platelet count <30,000 or
 - With dosage change or therapeutic agent change
 - Persistently decreasing platelet count of >20% from previous counts <125,000 before therapeutic change
 - Persistently decreasing platelet count of >40% from previous counts >125,000 before therapeutic change
 - Thrombocytopenia and/or anemia AND splenectomy or not attributable to other etiology than progressive Gaucher disease
- Bone disease
 - Patients with prosthesis or history of pathological fractures
 - Prevention of prostheses instability
 - New symptoms
 - New bone pain or avascular necrosis (AVN) and/or progressive osteopenia
- Significant changes in clinical parameters
 - e.g. progressive hemoglobin decreases not due to non-Gaucher disease etiologies
- Significant to severe concurrent illnesses, e.g., severe Parkinsonism or malignancy requiring intensive chemotherapy that, in the judgment of the attending physician, would be severely and adversely affected by the progression of Gaucher disease signs/symptoms

Category II

- 'Typical' patient characteristics
 - Initiated therapy because of signs and symptoms
 - Age: ≥ 35 years when started on therapy
 - Platelet count: 30,000–70,000
 - Spleen volume: ≥ 8 –15 x normal
 - Liver volume: 1.5 x normal (with abnormal liver function tests [LFTs])
 - Bony lesions or signs not in Category 1
 - No pulmonary disease
 - May have significant osteopenia
 - Slowly progressing disease – assess in 5 year increments
 - May not have met therapeutic goals, but not medically actionable
- Concurrent illness
 - Myelofibrosis
 - Hepatitis B and C
- Hemostasis
 - Prior bleeding history and blood transfusion requirements (How recently or remotely and what was the cause?)
- Monoclonal gammopathies
 - Need to be closely monitored (I know of no solid evidence that the natural history of these are influenced by enzyme replacement therapy [ERT])
- Other co-morbidities that would where progression of Gaucher disease would significantly impact quality of life (not in Category 1)
 - e.g., mild/moderate Parkinson's disease
 - Myeloma, lymphoma or other malignancy requiring cytotoxic treatment including chemotherapy and or radiotherapy – Need for bone marrow reserves
- Chitotriosidase and CCL18 – increasing levels concordant with suggestive signs and/or symptoms of Gaucher disease progression

Category III

- 'Typical' patient characteristics
 - Have met therapeutic goals
 - Age ≥ 45 years when started on therapy
 - Intact spleen
 - No thrombocytopenia
 - Bone lesions, since all Gaucher patients will have some, excluding new avascular necrosis (AVN) or fractures attributable to Gaucher disease
 - No major concurrent illness
 - Exhibited slow disease progression prior to enzyme replacement therapy (ERT)
- Diagnosis following screening at birth
 - Monitor disease progression
- Newly diagnosed
 - Don't assume high risk in absence of a "convincing" history
 - Monitor disease progression for a few months before starting treatment

Category IV

- Not currently on enzyme replacement therapy (ERT), and who have no progressing signs and symptoms of Gaucher disease

A BRIEF GUIDANCE ALGORITHM: QUESTIONS TO GUIDE DECISION FOR GAUCHER THERAPY

1. Is there potentially life-threatening disease? Hepatopulmonary syndrome (HPS), pulmonary hypertension (PHT), cancers, cirrhosis with portal hypertension, severe Parkinson's disease, interstitial lung disease, type 2 Gaucher disease, type 3 Gaucher disease; these all go to Category 1
2. Stratify according to age: all patients aged <18 or who started enzyme replacement therapy (ERT) in childhood go to Category 1 box. Older patients will go to another pathway per items in the document
3. Next is the spleen intact?
 - a. For asplenic patients with history of cytopenia, avascular necrosis (AVN)/joint replacements, fractures, severe osteoporosis; Category 1
 - b. For asplenic patients who have not had any of the above complications; Category 2
4. Special patient populations: pregnancy, immune reactions and advanced osteoporosis with fractures

CONCLUSIONS

During the Cerezyme supply shortage, it will be necessary to conserve supplies of Cerezyme and of new therapies, such as velaglucerase alfa or taliglucerase alfa, in order to ensure that patients at highest risk of disease progression can receive sufficient treatment. Therefore, Gaucher disease patients should be prioritized according to their disease status into one of four categories, with Category I being those patients at the highest risk of disease progression, and Category IV the lowest risk. This group recommends that patients in Categories I, II, and III are in decreasing order of risk of additional disease complications, and medical interventions could be appropriately prioritized using this rank order.