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Disclosures

Genzyme, Shire

• Participation in meetings, travel, hotels

• Speaking, boards, registries, ICGG, GOS <€ 5,000 per year

• Grants and subvention versed to the hospital for clinical trials and research

• The views and opinions expressed in the following slides are those of the presenter. They should not be understood or quoted as being made on behalf of Shire
Bone in Gaucher Disease

- Clinical or radiographic evidence of bone disease has been reported in 70–100% of diagnosed patients

- Skeletal complications are a source of significant disability and morbidity that impacts upon quality of life

- Maintenance of good bone health is a major goal in GD

- Understanding the pathophysiology of bone disease in GD has been increasing in the past few years, but is still unknown

GD, Gaucher disease

Normal bone

- Trabecular, cancellous bone: more important in children
- Cortical bone: more important with age (femoral head)
- Children and adolescents: long bones are filled with red marrow
- Adults: red marrow is located in the metaphysis, long bones are filled with yellow marrow
Function of bone

• Support the body: ability, function, balance
• Muscles attached for movement increase bone metabolism: exercise increases bone metabolism
• Site for blood cell formation: interference with haematopoiesis
• Mineralisation: calcium, phosphate
• Cycle of modelling and remodelling is different with cortical and trabecular bone, time, age, disease
• “Endocrine system”: hormones, Vitamin D, parathyroid hormone...
• Peak bone mass must be achieved between 25–30 years

Available at: http://www.med-health.net/Functions-Of-Bones.html (Accessed 16 June 2017)
Bone in Gaucher disease
Pathophysiology is multifactorial

- A few comprehensive model: animal model, surgical material from femoral head analysis after surgery
- Storage: infiltration and alternative metabolism of accumulating glucosylceramide and bioactive lipids, massive elevation of glucosylsphingosine (GlcSpn) responsible for chronic metabolic inflammation
- Progressive infiltration contributes to changes in the microenvironment of bone
- Dysregulation of bone turnover
- Unbalanced related cytokines production
  - *Increased level of interleukin 6 (strong stimulator of bone resorption)*
  - *Increased level of interleukin 10 (an inhibitor of osteoblastic activity)*
- Dysfunctional angiogenesis
- Vaso-occlusive, ischaemic event
- Fibrosis

Bone marrow infiltration begins in the lumbar vertebrae and then progresses to the pelvis and the appendicular skeleton


Mistry PK, et al. PNADS 2010;107(45):19473–19478
Bone in Gaucher disease

Pathophysiology

Role of inflammatory processes originate from bone marrow mesenchymal stromal cells in GD-related skeletal disease

The degree of bone involvement in GD1 is not always related to the degree of visceral disease, which can hamper the detection and management of bone manifestations

The residual, minimal, activity

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3. Di Rocco M et al, 2012
Many different definitions of bone events

- Reports of bone pain are not rigorous and are often misreported
- Not always attributable to GD
- Definition and description must be rigorous and adopted by registry physicians
- Is it real bone pain?
- Exclude other causes that appear during life-long disease
- Recommendations: precise medical history and physical examination, expertise from rheumatologists, pain specialists, neurologist, radiological confirmation
Clinical Manifestations

Bone pain: must be well characterised. E.g. None, very mild, mild, moderate, severe, or extreme, acute or chronic

Bone crisis: pain with acute onset requiring immobilization of the affected area, narcotics for pain relief and may have been accompanied by one or more of the following: periosteal elevation, elevated white blood cells, fever, or debilitation of >3 days acute severe pain MRI assessment reveals peripheral edema surrounding a hypo-intense lesion in T1 weighted images

Bone infarct: (Pseudo-osteomyelitis) clinical or radiological description?

Osteonecrosis (avascular necrosis [AVN]) follows from the establishment of a bone infarction when the affected bone is located close to a superficial area or joint face. AVN results from destruction of the tissue and secondary collapse of the articular face, different stages

Mistry PK et al, 2012
Bone manifestations

Marrow infiltration

Erlenmeyer flask deformity of the femur describes abnormality of the distal femur and results from impaired modelling within the di-metaphysis and abnormal cortical thinning

Osteopenia: X-Rays and MRI is not a useful tool to assess osteopenia
Osteoporosis: DEXA definition
Fracture: fragility or pathological to fatigue fractures (15%, 26%, 28%)
Cortical thinning
Lytic lesions are focal lesions

Gaucheroma
Plasmocytoma
Myeloma
Bone lymphoma?

DEXA, dual-energy X-Ray-absorptiometry; MRI, magnetic resonance imaging

Bone complication

Saranjam HR et al, 2010
Speaker’s own images (with permissions)
Heterogeneity between twins
Environmental factors

Monozygote twins may have different phenotypes
Clinical manifestations

Impact

- Deformation secondary to fractures
  - Kyphosis if multiple vertebral collapse
  - Kyphosis in type 3 GD
  - Fracture only if pseudarthrosis (consolidation of fracture are usually normal in GD)

- Joint replacement
  - Prosthesis
  - Loosening prosthesis
  - Multiple prostheses in young patients

- Decrease mobility, wheelchair, crutches

- Impaired quality of life

GD, Gaucher disease

Speaker’s personal opinions
MRI

Normal bone: the signal intensity of the normal fatty marrow is high
Normally, the adult bone marrow is composed of 80% fat, 15% water, and 5% protein
Because fat is the major component of marrow, the T1 relaxation time is short and the T2 relaxation time is relatively long resulting in high signal intensity on both T1- and T2-weighted images

Gaucher bone: bone marrow is infiltrated by Gaucher cells which contain glucocerebrosides protein, glycoproteins, and other components. These deposits have a relatively low signal intensity

Gaucher bone: signal intensity of the involved marrow in Gaucher disease is homogeneously or non-homogeneously decreased
Some patients may have a diffuse infiltration and others may have a patchy infiltration, with islands of preserved fatty marrow

MRI, magnetic resonance imaging
STIR, short tau inversion recovery

Oedema, bone infarct
STIR

Speaker’s personal observations
DEXA

**Adults:** L1–L4, total hip or femoral neck

**Children >5 years:** L1–L4, total body less head (TBLH) femur not recommended due to high variability in skeletal maturity

- Results: bone mineral content BMD in $\text{g/cm}^2$
- Measurements are strongly influenced by bone size, skeletal maturity and pubertal stage
- Confounding factors:
  - Avascular necrosis of the proximal femur
  - Vertebral fractures
  - Osteophytes, vascular calcifications, calculi can lead to over-estimation of bone mass

**Pre-menopausal women**

**Men <50 years**

- Z-score ≤−2

**Paediatric population**

- DEXA, dual-energy X-ray absorptiometry

**Menopausal women**

- T-score between −1 and −2.5: osteopenia
- T-score ≤−2.5: osteoporosis

Wenstrup et al, JBMR 2001
Difficulty to understand the mechanism of bone manifestation with and without treatment due to heterogeneity

- Age at onset of symptoms
- Age at diagnosis
- Early diagnosis of GD1 (<1 year after the first clinical symptoms) was reported in fewer patients for whom bone lesions were the first symptoms of the disease compared with those with non-bone manifestations
- Splenectomy
- Time between onset of symptoms and diagnosis
- Time between onset of symptoms and ERT
- Severity of disease at the beginning of treatment
- Genotype
- Availability of assessment MRI, DEXA
- ERT initiation delay: Baseline dose of ERT
- Variation of treatment: ERT, SRT
- Variation of dosage, interval
- Compliance mainly for asymptomatic patients

The time of initiating treatment has an incidence of avascular osteonecrosis:

- <2 years, 1047 pts, risk of AVN n = 41, 4%
- ≥2 years, 1653 pts, risk of AVN n= 172, 10%

AVN, avascular necrosis; ERT, enzyme replacement therapy; DEXA, dual-energy X-ray absorptiometry; GD, Gaucher disease; MRI, magnetic resonance imaging; SRT, substrate reduction therapy

Khan et al, 2011
Difficulty to understand the mechanism of bone manifestation with and without treatment due to heterogeneity

Due to environmental and associated factors:

Diet, calcium

Comorbidities that affect bone metabolism: chronic disease

Medication: calcium, bisphosphonate, corticosteroids, PPI, etc.
Therapeutic goals, short-term management goals for Gaucher disease type 1: ERT/SRT-related mobility

- Reduction or complete resolution of bone pain
- Prevention of bone crisis during the first two years of treatment

Lessen bone pain that is not related to irreversible bone disease within 1–2 years

Decrease bone marrow involvement, as measured by a locally used scoring system (e.g. Bone Marrow Burden score [BMB] or Düsseldorf Gaucher Score [DGS]) in patients without severe irreversible bone disease at baseline

Increase bone mineral density (BMD) by 2 years in adults for patients with a T-score <−2.5 at baseline

Attain normal or ideal peak skeletal mass in children

Normalize growth such that the height of the patient is in line with target height based upon population standards and parental height within 2 years of treatment

ERT, enzyme replacement therapy; SRT, substrate replacement therapy

Therapeutic goals

- **Prevent bone complications:** avascular necrosis, bone crises, bone infarcts and pathological fractures

- **Prevent osteopenia and osteoporosis**

- **Prevent chronic use of analgesic medication for bone pain**

- **Maintain normal mobility or improve mobility** if impaired at diagnosis

- **Compliance with treatment**
  - Treatment interruption for even 3–6 months can result in recurrent organomegaly and skeletal manifestations that may be more difficult to treat after reinitiating ERT

ERT, enzyme replacement therapy

Treatment in Gaucher disease

Results

• Within 1–2 years new bone crises are rare
• Patients with chronic bone pain often experience some relief
• Bone mineral density generally improves in children and younger adults: the therapeutic window of opportunity is at peak bone mineral density in adolescence
• Patients report enhanced quality of life if they don’t have pre-existing irreversible bone disease
• ERT has virtually eliminated the need for splenectomy
• ERT cleared marrow on MRI
• Questions:
  • Increasing cortical thickness, decreasing lytic lesions?
  • Improving advanced lesions in both paediatric and adult patients?

ERT, enzyme replacement therapy; GD, Gaucher disease; MRI, magnetic resonance imaging

### Classification of Risk Groups for BD According to Prognostic Factors in Patients With Type 1 GD

<table>
<thead>
<tr>
<th>Risk group for BD</th>
<th>Prognostic factors</th>
<th>Risk for BD</th>
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<tbody>
<tr>
<td><strong>Low risk</strong></td>
<td>Adherence to ERT ≥80%</td>
<td>Low risk for BD</td>
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<tr>
<td></td>
<td>Early diagnosis (&lt;2 years)</td>
<td>High probability of belonging to Group 1</td>
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<tr>
<td></td>
<td>Early treatment onset (2 years)</td>
<td></td>
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<tr>
<td></td>
<td>High dose of ERT at diagnosis</td>
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<tr>
<td></td>
<td>Absence of splenectomy history</td>
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<tr>
<td><strong>Intermediate risk</strong></td>
<td>Adherence to ERT &lt;80% and ≥60%</td>
<td>Increased probability of reversible BD (BMI)</td>
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<td></td>
<td>Delay diagnosis (&gt;2 years)</td>
<td>High probability of belonging to Group 2</td>
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<tr>
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<td>Delay treatment (&gt;2 years)</td>
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<td></td>
<td>Dose of ERT at the beginning &lt;45 UI/kg/EOW</td>
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<tr>
<td></td>
<td>Absence of splenectomy history</td>
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<tr>
<td><strong>High risk of BD</strong></td>
<td>Adherence to ERT &lt;60% and ≥50%</td>
<td>High probability of reversible BL (BMI infiltration) + chronic sequel irreversible BL (EFD, IO, and NOA)</td>
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<td></td>
<td>Delay diagnosis (&gt;2 years)</td>
<td>High probability of belonging to Group 3</td>
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<td>Delay treatment (&gt;2 years)</td>
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<td>Dose of ERT at the beginning &lt;45 UI/kg/EOW</td>
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<td>Splenectomy</td>
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<tr>
<td><strong>Very high risk of BD</strong></td>
<td>Adherence to ERT ≤50%</td>
<td>Very high probability of reversible BL (BMI + acute and chronic irreversible BL (EFD, IO, and NOA))</td>
</tr>
<tr>
<td></td>
<td>Delay diagnosis (&gt;2 years)</td>
<td>High probability of belonging to Group 4</td>
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<td>Delay treatment (&gt;2 years)</td>
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<td>Dose of ERT at the beginning &lt;45 UI/kg/EOW</td>
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<tr>
<td></td>
<td>Splenectomy</td>
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</tbody>
</table>

AVN, avascular osteonecrosis; BD, bone disease; BI, bone infarcts; BL, bone lesion; BMI, Bone marrow infiltration; EFD, Erlenmeyer flask deformity; ERT, enzyme replacement therapy; GD, Gaucher disease; MRI, magnetic resonance imaging

Bone events during treatment

- Characteristics: less severe than before specific treatment
- Frequency: not mentioned specifically in registry and clinical trial 5–15%
- Cause
  • Delayed efficacy that take time in bone or inefficacy of treatment, long term follow up is needed
  • Low dose treatment
  • Severe disease, splenectomy
  • Residual bone disease activity that persists following treatment: immortal macrophages
  • Additional factors:
    • Hormonal status
    • Genetic, modifying genes
    • Environmental factors: diet, nutrition, alcohol, smoking, medications
    • Pharmacokinetics of treatment, localisation on different subcellular compartments, drug distribution
    • Other bone diseases

ICGG; Charron et Al, Clin Genet 2007
Bone density, effect of treatment Velaglucerase alfa

The effect of velaglucerase alfa on bone parameters was evaluated as exploratory endpoints in 4 pivotal studies and their extension studies: TKT025 and TKT025-EXT which were phase I/II, and TKT032, TKT034, HGT-GCB-039 and HGT-GCB-044 which were phase III. The primary endpoint was either the safety of velaglucerase alfa when administered EOW in patients with type 1 Gaucher disease (TKT025 and TKT025-EXT, TKT034, and HGT-GCB-044), or the change in haemoglobin concentration from baseline (studies TKT032 and HGT-GCB-039). Key secondary endpoints were changes in haemoglobin concentration, platelet count and liver and spleen volumes. Exploratory endpoints in these trials (two trials with 12 or less patients) included baseline and periodic assessments of BMD (Bone Mineral Density) and/or BMB (Bone Marrow Burden). Further confirmatory studies are required to draw any conclusions on clinical bone-related efficacy outcomes.
Bone density effect of treatment

Taliglucerase alfa

Taliglucerase alfa leads to favorable bone marrow responses in patients with type I Gaucher disease

L. van Dussen a, A. Zimran b, E.M. Akkerman c, J.M.F.G. Aerts c, M. Petakov d, D. Elstein b, H. Rosenbaum e, D. Aviezer f, E. Brill-Almon f, R. Chertkoff f, M. Maas g, C.E.M. Hollak a,b

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f Petahia Biotechnology, Carmiel, Israel
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Taliglucerase alfa is not licensed in the EU.

Effect of treatment Eliglustat on BMB and bone density

Skeletal improvement in patients with Gaucher disease type 1: a phase 2 trial of oral eliglustat

Ravi S. Kamath, Elena Lukina, Nora Watman, Marta Dragovsky, Gregory M. Pastores, Elke Avila Arreguin, Hanna Rosenbaum, Ari Zviran, Rasha Aguzzi, Ana Cristina Puga, Andrea M. Norfleet, M. Judith Peterschmitt, Daniel I. Rosenthal

Treatment of bone crisis

Lifestyle recommendations
- Avoid smoking and alcohol
- Diet, nutrition
- Exercise
- Calcium
- Vitamin D
- Anticipate pregnancy

Bisphosphonates: suppression of bone resorption, slowing bone turnover, alendronate,

Teriparatide (human parathyroid hormone (PTH 1–34): 1 GD case: dramatic improvement in both bone mineral density and architecture

Therapeutic Education Programmes to improve compliance

Orthopaedic surgery:
- Long-lasting hip prostheses and newer types of implants prevent early revision in young patient population
- Haemostasis abnormalities must be assessed
- Prosthesis and Infection
- Problem of AVN, prosthesis, pregnancies, deliveries
- Osteosynthesis for fracture
- Instrumentation of a kyphosis
- Cementoplasty in vertebral collapse? No experience
- Corset

AVN, avascular necrosis

Monitoring

Clinical evaluation

Multidisciplinary team: rheumatologist, neurologist, pain department, surgeon, anesthetist, psychologist, physiotherapist, orthopaedic

Patient Reported Outcomes (PROs) reflect how a patient feels and functions to judge the overall effectiveness of any treatment that is prescribed for patients with long-term and other conditions % of improvement

Severity score: not use in routine

Concomitant medication

Concomitant disease
Monitoring

X rays
To follow the course of localised lesion osteoarthritis due to AVN, cortical thinning, lytic lesion

MRI
Every year or 2 years during 5 years, then every 2 years or 3 months BD every year during 5 years then every 3 years

Body MRI

DEXA
Every 2 years

Biomarkers CCL18, Ferritin, Lyso every 6 months

Treatment
60U/kg/2W during 3 to 5 years then 45 U/Kg/2W
30 to 45 U/Kg/2W if there is only bone infiltration
In France, no evidence of efficacy in the French experience of higher dosage

Compliance and understanding of the disease
The frequency of the radiological imaging must be explained
Plan pregnancy, plan surgery
Explain to patient that some bone symptoms are not related to GD

AVN, avascular necrosis; GD, Gaucher disease; MRI, magnetic resonance imaging
Questions & Perspectives

Prevent bone disease, improving quality of life

Efficacy of treatment on lytic lesions, advanced osteoporosis, severely fibrotic marrow disease with sanctuary sites of Gaucher cells?

Why bone manifestations are so heterogeneous
- Environmental?
- Identification of genetic modifiers?
- Mechanisms by which splenectomy exerts a deleterious effect on bone?

Cause of kyphosis in some patients?

Why some bone complications continue to occur despite ERT?