Osteoporosis & Pain

Andrea Giusti

Bone Clinic,

Department of Gerontology and Musculoskeletal Sciences,

Galliera Hospital,

Genoa
Osteoporosis
Osteoporosis: Definition

Low Bone Mass

Microarchitectural Deterioration

Enhanced Bone Fragility

Fractures

NIH Consensus Conference JAMA 2001
The Consequences of Osteoporosis

Osteoporotic trabecular bone

[Image of osteoporotic trabecular bone]

[Image of X-ray of hip]
Osteoporosis: Inbalance Resorption/Formation

Quiescent bone surface covered by lining cells

Osteoclasts on the bone surface resorbing old bone

Osteoid becoming mineralized

Osteoblasts appearing at the resorption site

Osteoblasts filling the resorption cavity with osteoid

Osteoporosis: Inbalance
Resorption/Formation

Dufresne TE et al. J Bone Min Res 2002
# Osteoporosis in Men & Women

<table>
<thead>
<tr>
<th>Condition</th>
<th>Bone Formation</th>
<th>Bone Resorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenopausal OP</td>
<td>↑</td>
<td>↑↑↑↑</td>
</tr>
<tr>
<td>Idiopathic OP (Young Men)</td>
<td>↓↓</td>
<td>= / ↑</td>
</tr>
<tr>
<td>Involutive OP</td>
<td>↑ / =</td>
<td>↑↑</td>
</tr>
<tr>
<td>Glucocorticoid OP</td>
<td>↓↓↓↓</td>
<td>↑ / =</td>
</tr>
</tbody>
</table>
Thalassemia-associated Osteoporosis: Prevalence
Prevalence Osteoporosis in β-Thalassemia

Mokhtar GM et al. Hemoglobin 2011
Prevalence of Fractures in β-Thalassemia

- Fung EB 2008 (n=152)
- Vogiatzis MG 2009 (n=236)
- Sutipornpalangkul W 2010 (n=136)
- Mokhtar GM 2011 (n=70)
- Vogiatzis MG 2006 (n=379)

Giusti A Bisfosfonati 2012
Prevalence of Fractures according to Age and Fracture Site

Fung EB et al. Bone 2008
Thalassemia-associated Osteoporosis: Pathogenesis
Pathogenesis of Thalassemia-associated Osteoporosis

- Multiple genetic and acquired factors

- Imbalance in bone remodelling:
  - inhibit osteoblast activity
  - increase osteoclast function

- Bone loss and microarchitectural deterioration
Factors contributing to reduced BMD in β-Thalassemia

<table>
<thead>
<tr>
<th>Genetic variants that predispose to reduced BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>COLIA 1 - Collagen type Ia1 gene (Sp1 polymorphism)</td>
</tr>
<tr>
<td>VDR - Vitamin D receptor (FokI and BsmI polymorphisms)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acquired factors contributing to reduced BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow expansion due to ineffective erythropoiesis</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Hypogonadism (as delayed puberty and/or secondary hypogonadism)</td>
</tr>
<tr>
<td>Defective GH-IGF axis</td>
</tr>
<tr>
<td>Iron overload</td>
</tr>
<tr>
<td>Desferrioxamine</td>
</tr>
<tr>
<td>Vitamin D and calcium deficiency</td>
</tr>
<tr>
<td>Reduced physical activity</td>
</tr>
</tbody>
</table>
Prevalence Vitamin D deficiency in β-Thalassemia

- Napoli 2006 (27 yrs)
- Wood 2008 (15 yrs)
- Vogiatzi 2009 (23 yrs)
- Dimitriadou 2010 (23 yrs)
- Fung 2011 (25 yrs)
- Giusti A 2011 (40 yrs)

Healthy Subjects
Pain
Causes of Pain in β-Thalassemia

- Osteoporotic fracture
  - back pain (up to 25% of patients)
  - vertebral fractures

- Arthropathy (up to 30% of patients)
  - Iron overload
  - Iron chelators (Deferoxamine)

- Vitamin D deficiency

- Paraspinal extramedullary hematopoiesis
- Intervertebral disc degeneration
- Spinal asymmetry and overt scoliosis
- Intervertebral disc degeneration
Prevalence of Pain in Thalassemia

Proportion of patients reporting pain in the last seven days by age group

Haines D et al. Br J Haematology 2013
Prevalence of Pain in Thalassemia

Proportion of patients reporting pain in the last seven days by site

Haines D et al. Br J Haematology 2013
Impact of Pain on QoL

Proportion of patients reporting interference in the last seven days by severity

Haines D et al. Br J Haematology 2013
Clinical Approach: Bone Clinic
β-Thalassemia-associated Osteoporosis: Clinical Approach

- Assessment Bone Mineral Density by Dxa
- Laboratory measurements
  - PTH, 25-OH-D
  - Standard laboratory tests
  - Markers of bone turnover
  - Sex steroids
- Assessment of the ten years risk of fracture (major osteoporotic and hip fractures) using clinical risk factors
FRAX: Assessment of 10-yr Risk of Fracture

Kanis JA et al. Osteoporos Int 2008
Prevention & Treatment
β-Thalassemia-associated Osteoporosis: Prevention & Treatment

- General principles
  - physical activity, healthy life
  - smoking discontinuation
  - adequate calcium intake and sun exposure
  - adequate management diseases and its complications

- Hormone replacement therapy
  - Treatment of clinical and subclinical hypogonadism
  - Men and Women

- Pharmacological Therapy
  - Bisphosphonates
  - Teriparatide (?)
  - New Treatments (denosumab)
BPs in the Management of Thalassemia-associated Osteoporosis & Pain

- Literature search (PubMed and references lists) N = 50 articles
- Articles excluded based on screening of titles/abstracts N = 21
- Potentially relevant articles assessed for eligibility N = 29
- Articles excluded after evaluation of the study:
  - Not RCTs (Including 2 case-report) N = 13
  - Duplicate Publication N = 4
  - Review N = 4
  - Not Relevant to the Topic N = 3
- RCTs included in the systematic review N = 5

Giusti A In Press 2014
<table>
<thead>
<tr>
<th>Study Type</th>
<th>N° of Patients (Men)</th>
<th>Active Medication I</th>
<th>Active Medication II</th>
<th>Control</th>
<th>Supplements</th>
<th>Main Inclusion Characteristics/Criteria</th>
<th>Study Duration (years)</th>
<th>Mean Age (years)</th>
<th>Hypogonadic (%)</th>
<th>Regularly Transfused (%)</th>
<th>Chelation Therapy (%)</th>
<th>Type Chelation Therapy</th>
<th>Prevalent Fractures (%)</th>
<th>Bone Pain (%)</th>
<th>Mean Hemoglobin (g/dL)</th>
<th>Main Outcome Measures</th>
<th>Lost to Follow-up (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized, placebo-controlled</td>
<td>25 (8)</td>
<td>ALN 10 mg per os daily</td>
<td>Tablet-placebo</td>
<td>None</td>
<td>Calcium 500 mg daily Cholecalciflor 400 IU daily</td>
<td>Z-score &lt; -2.5 (any site)</td>
<td>2</td>
<td>27</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>Desferoxamine</td>
<td>NA</td>
<td>NA</td>
<td>9.2-9.4</td>
<td>Bone Mineral Density Bone Turnover Markers Safety</td>
<td>0.0%</td>
</tr>
<tr>
<td>Randomized, placebo-controlled</td>
<td>30 (30)</td>
<td>CLO 300 mg iv every 3 weeks</td>
<td>None</td>
<td>None</td>
<td>Calcium (based on diet) Cholecalciflor 400 IU daily</td>
<td>T-score &lt; -2.5 (any site)</td>
<td>2</td>
<td>27</td>
<td>10.0%</td>
<td>100%</td>
<td>100%</td>
<td>Desferoxamine</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Bone Mineral Density Bone Turnover Markers Safety</td>
<td>NA</td>
</tr>
<tr>
<td>Double-blind, randomized, placebo-controlled</td>
<td>66 (22)</td>
<td>ZOL 4 mg iv every 6 months</td>
<td>Placebo every 3 months</td>
<td>None</td>
<td>Calcium 500 mg daily Ergocalciferol 1,000 IU daily (based on 25OHD)</td>
<td>T-score &lt; -1 (any site)</td>
<td>1 +2 extension</td>
<td>43-45</td>
<td>51.5%</td>
<td>47.0%</td>
<td>68.2%</td>
<td>Desferoxamine/Deferiprone</td>
<td>NA</td>
<td>NA</td>
<td>8.3-9.0</td>
<td>Bone Mineral Density Bone Turnover Markers Fracture Incidence Safety</td>
<td>3.0%</td>
</tr>
<tr>
<td>Double-blind, randomized, placebo-controlled</td>
<td>23 (15)</td>
<td>ZOL 4 mg iv every 3 months</td>
<td>None</td>
<td>None</td>
<td>Calcium 500 mg daily Cholecalciflor 400 IU daily</td>
<td>T-score &lt; -2 (any site)</td>
<td>2</td>
<td>28</td>
<td>30.4%</td>
<td>100%</td>
<td>100%</td>
<td>No Therapy</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Bone Mineral Density Bone Turnover Markers Fracture Incidence Pain, Quality of Life Safety</td>
<td>4.3%</td>
</tr>
<tr>
<td>Randomized, placebo-controlled</td>
<td>118 (51)</td>
<td>NRD 100 mg iv every 3 months</td>
<td>None</td>
<td>No therapy</td>
<td>Calcium 500 mg daily Cholecalciflor 400 IU daily</td>
<td>T-score &lt; -2 (any site)</td>
<td>1</td>
<td>33</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>No Therapy</td>
<td>NA</td>
<td>NA</td>
<td>9.7-9.8</td>
<td>NA</td>
<td>0.8%</td>
</tr>
</tbody>
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Giusti A In Press 2014
# BPs in the Management of Thalassemia-associated Osteoporosis & Pain

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<tbody>
<tr>
<td></td>
<td>2-year</td>
<td>1-year</td>
<td>2-year</td>
<td>1-year</td>
</tr>
<tr>
<td>Mean % Change LS-BMD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLO</td>
<td>0.1%</td>
<td>ZOL 8-m</td>
<td>5.8%</td>
<td>-</td>
</tr>
<tr>
<td>ALN</td>
<td>2.9%</td>
<td>ZOL 3-m</td>
<td>15.2%</td>
<td>ZOL 3-m</td>
</tr>
<tr>
<td>Placebo</td>
<td>-4.9%</td>
<td>Placebo</td>
<td>1.4%</td>
<td>Placebo</td>
</tr>
<tr>
<td>Mean % Change FN-BMD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLO</td>
<td>1.4%</td>
<td>ZOL 8-m</td>
<td>4.8%</td>
<td>-</td>
</tr>
<tr>
<td>ALN</td>
<td>5.6%</td>
<td>ZOL 3-m</td>
<td>11.3%</td>
<td>ZOL 3-m</td>
</tr>
<tr>
<td>Placebo</td>
<td>-7.4%</td>
<td>Placebo</td>
<td>2.7%</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

![Graph showing mean % change after 1 year for LS-BMD and FN-BMD](image)

**Mean % Change after 1 year**

- **LS-BMD**
  - ZLD 3-m: 16%
  - ZLD 6-m: 4%
  - Placebo: 0%

- **FN-BMD**
  - ZLD 3-m: 16%
  - ZLD 6-m: 4%
  - Placebo: -2.3%
Neridronate in the Management of Thalassemia-associated Osteoporosis

Forni GL et al. Br J Haematology 2012

![Graph showing the mean percentage change of BMD after 1 year with Ca+D and Neridronate](image)
Neridronate in the Management of Thalassemia-associated Pain

Mean SF-36 Pain Index: higher score more favorable

A concomitant significant reduction (50% group A, 30% group B) in the use of analgesic drugs was noted starting from the third month.

Forni GL et al. Br J Haematology 2012
Conclusions

Osteoporosis & pain and frequent disorders in patients presenting with thalassemia

Their pathogenesis is multifactorial and complex

Osteoporosis & pain reduce the quality of life in subjects presenting with thalassemia

Effective treatments are available
Thank You