Endocrine Fellows from the University of Colorado School of Medicine

- Kelsey DeSalvo
- Kenneth Tompkins
- Adnin Zaman
Osteogenesis Imperfecta: Type III

Ken Tompkins, MD
Endocrinology Fellow
University of Colorado
History Of Present Illness

• 32 yo woman presents to endocrine clinic to discuss therapy for OI
• Diagnosed at birth; no antenatal indications but born with severe deformity of lower limbs, soft skull
• No genetic testing in childhood; diagnosed clinically with Type 3 OI
• Innumerable fractures in childhood
  • Unable to bear weight on legs, immediate fracture when attempts
  • Transported on a pillow by her parents as child, would fracture if she slid off pillow and parents tried to place her back
• No issues with dentition; had braces, tolerated fine
• Last fracture was about 4 years ago, after fall out of power wheelchair
Relevant Medical History

• Past Medical History
  • Restrictive lung disease, on supplemental O2
  • Hypophosphatemia
  • Nephrocalcinosis
  • Chronic Pain Syndrome
  • Asthma, gets pred bursts 1-2x/year
  • Normal menstruation

Soc Hx
• Never tobacco user
• Drinks socially 1-2x/year
• No marijuana or illicit drug use
• Previously worked in customer service, now disabled

Family History
• No family hx of osteogenesis imperfecta or easy fracture
• No family hx of osteoporosis

Meds:
• Albuterol
• Duloxetine
• Fluticasone/Salmeterol
• Gabapentin
• Extended-release Morphine
• Oxycodone
• Sertraline
• Ethinyl-estradiol/norgestimate
Previous Treatment History

• Received alendronate ages 16-18 as part of a clinical trial

• Given dose of zoledronic acid in 2014

• Never followed up after this, noncompliant due to psychosocial issues
Physical Exam

• Vitals: Reported Ht 3’6”, unable to get weight; BP 96/60
• General: **Very short stature**; significant kyphoscoliosis; in power wheelchair
• HEENT: **Fair dentition, no significant caries**, appears to have all her teeth
• Eyes: **Mildly grey sclera**
• Neck: Thyroid not enlarged
• CV: RRR, no m/r/g
• Resp: CTAB, no w/r/c
• MSK: Markedly limited ROM of b/l arms at shoulders, elbows; marked clinodactyly; significant kyphoscoliosis on palpation of spine
Relevant Data

138 3.7 6 90
3.7 30 0.32 9.3

7.6 4.1 PTH 34
11 19 25-OH Vitamin D 24
0.5

 Imaging:

No Recent BMDs

MRI T-Spine January 2018:
- Advanced rotary dextroscoliosis
- Small chronic compression fracture T2, T3; large compression fx T4-T12

CTX 72
Genetic Testing

- Given presence of other metabolic abnormalities (low phos, nephrocalcinosis), recommended genetic testing
- DNA sequencing showed a guanine → adenine point mutation at nucleotide 4237 of COL1A1 Gene
- Substitutes asparagine for aspartic acid in c-terminal domain
- This mutation previously identified in a patient with Type II OI
Questions for Discussion

• Last fracture occurred after she received zoledronic acid. Is this a treatment failure?

• Is there a role for other therapies besides bisphosphonates?
Osteogenesis Imperfecta

- Heritable bone disorder characterized by bone fragility and decreased bone mass
- Mutation affecting Type 1 Collagen formation
- Phenotype can range from easy fracture to severe deformity and organ abnormalities
- Classically characterized by Silence Criteria as phenotypes Types I-IV, with additional types based on new phenotypes, mutations

<table>
<thead>
<tr>
<th>Type</th>
<th>Phenotype</th>
<th>Genetics</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Non deforming, blue sclera, easy fracture</td>
<td>Autosomal dominant</td>
<td>Decreased COL1A1 production, quantitative defect</td>
</tr>
<tr>
<td>II</td>
<td>Severe deformity, pulmonary hypoplasia, fatal in childhood</td>
<td>Autosomal dominant, recessive De Novo</td>
<td>Amino acid substitution causing abnormal folding and aggregation of Type 1 Collagen, qualitative defect</td>
</tr>
<tr>
<td>III</td>
<td>Severe deformities, survive to adulthood</td>
<td>Autosomal dominant, recessive, De Novo</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Moderately severe OI with normal sclera</td>
<td>Autosomal Dominant</td>
<td></td>
</tr>
</tbody>
</table>

V Dijk et al. Osteogenesis Imperfecta: Clinical Diagnosis, Nomenclature and Severity assessment. American Journal of Medical Genetics
Pathogenesis of Osteogenesis Imperfecta

• Defects due to impairment in Type 1 Collagen aggregation, processing, secretion

• Mutations in *COL1A1/2* or enzymes involved in posttranslational processing lead to OI

Type 3 Osteogenesis Imperfecta

• Usually due to glycine substitution in COL1A1 that leads to abnormal collagen folding and bone formation

• Characterized by short stature, osteopenia/fracture noted at birth, very early childhood, progressive skeletal deformity

• Blue sclera, hearing loss, dentogenesis imperfecta may or may not be present

Bisphosphonates in OI

- Bisphosphonates have been mainstay of treatment for OI for years

- Large RCT of 139 patients with OI, including 32 type III patients treated with alendronate:
  - Increases in L spine BMD
  - Decreases in bone turnover markers
  - No change in fracture rate at 2 years

- One controlled trial of 18 children with Type III and IV OI treated with IV pamidronate showed:
  - Increases in L spine BMD
  - Decreased UE fracture

A Le toxch a et al. JBMR, 2005 (20): 977-986
Teriparatide in OI

- Teriparatide stimulates bone remodeling and formation, role in OI?
- RCT of 78 patients with OI, including 14 type III and 12 type IV OI patients:
  - Increased Spine BMD
  - Increased Total hip and Fem Neck BMD
  - Increased spine QCT scores
  - Increased bone formation markers
- But...
  - Subgroup analysis showed patients with type III/IV had changes in BMD similar to placebo
  - P1NP did increase in III/IV but not as significant as type I

E Orwoll et al. JCI 2014; 124 (2): 491-498
Questions For The Panel

• Would you consider the fact that she fractured on zoledronic acid a treatment failure?

• Would you consider teriparatide in her?
QUESTIONS/COMMENTS?

Thank You!
A CASE OF TOOTH RESORPTIVE DISORDER AND OSTEOPOROSIS

Adnin Zaman, MD
University of Colorado
Annual Metabolic Bone Disease Society Meeting
DISCLOSURES

None
HISTORY OF PRESENT ILLNESS

- 65 yo F with tooth resorptive disorder (TRD) and osteoporosis since her 40s with a recent L1 fracture presented for advice on osteoporosis treatment
- Osteoporosis diagnosed in 1990s by dentist who discovered 8 resorptive teeth
- DXA in 1998 revealed low BMD
  - Given alendronate but patient self-discontinued; switched to HRT
  - Poor nutrition and low body weight at time of diagnosis
- Good dental care in youth
  - Had severe overbite with multiple years of braces
- No problems with hearing or vision
- Multiple fractures in the past, due to trauma
HISTORY OF PRESENT ILLNESS

- **Allergies:** Codeine
- **Home Meds:** Estradiol 0.5mg Daily, Ergocalciferol, Progesterone 200mg QHS
- **PMHx:** anxiety, depression, **L1 vertebral fracture, osteoporosis, tail bone fracture, T11 vertebral fracture, thumb fracture, tibia/fibula fracture, toe fracture x2, tooth resorption**
- **PSHx:** multiple oral cavity surgeries, including root canals
- **FHx:** mother – **osteoporosis/hip fracture (age 94),** bladder cancer; father – heart attack
- **SHx:** **tobacco – >75 pack-year smoking history;** alcohol – 2 glasses of wine per week; drugs – none
VITALS: BP 129/76, HR 80, Ht 5’4”, Wt 60.3kg, BMI 22.83

- **General:** A/O x3, well developed and well nourished, no acute distress
- **HEENT:** NCAT, clear oropharynx, *wearing dentures on 10 teeth but missing 14 teeth overall*, normal gums, EOMI, PERRL, **normal sclera**, no icterus, normal neck range of motion, supple, no tracheal deviation, no thyromegaly. No cervical LAD
- **CV:** RRR, no m/r/g
- **Resp/Pulm:** normal effort, CTAB, no w/r/c
- **Abd:** soft, NTND, no rebound or guarding
- **MSK:** normal range of motion, no deformities, **no hyper-flexibility**
- **Neuro:** alerted to person, place, and time. Normal reflexes
24 hour calcium 135
PTH 55
SPEP/UPEP not detected
Anti-TTG Ab <4.0
Vitamin D 24 → 89
TSH 0.92
HgA1c 5.5%
Total cholesterol 184, TG 76, HDL 64, LDL 106
MRI L-Spine without contrast (10/19/17):

1. Subacute superior endplate compression fracture of T11 with mild retropulsion partially visualized. There are no findings to suggest significant central canal stenosis.

2. Mild chronic anterior wedge deformity of L1 unchanged.

3. Lumbar spondylosis resulting in mild foraminal stenosis without significant narrowing of the central canal.
X-Ray Muscle Compare (4/12/18):

- Compression fracture L1 with approximately 30% loss of height
- Compression fracture at T11 with 25% loss of height
- Minimal changes from images obtained November 2017
- Degenerative spondylolisthesis in L4-L5
- Thoracic maximal kyphosis
- Comparison lumbar spine obtained October 2016 shows compression fracture at L1
## COMPARING DEXA SCANS: HIPS

### Region Area [cm²] BMD [g/cm²] T-score Z-score

<table>
<thead>
<tr>
<th>Region</th>
<th>Area [cm²]</th>
<th>BMD [g/cm²]</th>
<th>T-score</th>
<th>Z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck</td>
<td>5.10</td>
<td>0.482</td>
<td>-3.3</td>
<td>-1.8</td>
</tr>
<tr>
<td>Troch</td>
<td>10.66</td>
<td>0.431</td>
<td>-2.7</td>
<td>-1.6</td>
</tr>
<tr>
<td>Inter</td>
<td>19.89</td>
<td>0.760</td>
<td>-2.2</td>
<td>-1.2</td>
</tr>
<tr>
<td>Total</td>
<td>35.66</td>
<td>0.622</td>
<td>-2.6</td>
<td>-1.4</td>
</tr>
</tbody>
</table>

### Region Scan Date Age BMD T-score BMD Δ vs. baseline BMD Δ vs. previous

<table>
<thead>
<tr>
<th>Region</th>
<th>Scan Date</th>
<th>Age</th>
<th>BMD</th>
<th>T-score</th>
<th>BMD Δ vs. baseline</th>
<th>BMD Δ vs. previous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>4/2018</td>
<td>65</td>
<td>0.622</td>
<td>-2.6</td>
<td>-0.028 (-4.3%)</td>
<td>0.009 (1.5%)</td>
</tr>
<tr>
<td></td>
<td>12/2015</td>
<td>62</td>
<td>0.618</td>
<td>-2.7</td>
<td>0.033 (5.6%)</td>
<td>0.033 (5.6%)</td>
</tr>
<tr>
<td></td>
<td>*8/1998</td>
<td>45</td>
<td>0.65</td>
<td>-2.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck</td>
<td>4/2018</td>
<td>65</td>
<td>0.482</td>
<td>-3.3</td>
<td>-0.13 (-21.2%)</td>
<td>-0.015 (-3.0%)</td>
</tr>
<tr>
<td></td>
<td>12/2015</td>
<td>62</td>
<td>0.498</td>
<td>-3.2</td>
<td>0.019 (3.9%)</td>
<td>0.019 (3.9%)</td>
</tr>
<tr>
<td></td>
<td>*8/1998</td>
<td>45</td>
<td>0.612</td>
<td>n.m.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Comparing DEXA Scans: L-Spine

## Region Area [cm²]  BMD [g/cm²]  T-score  Z-score

<table>
<thead>
<tr>
<th>Region</th>
<th>Area [cm²]</th>
<th>BMD [g/cm²]</th>
<th>T-score</th>
<th>Z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>12.08</td>
<td>0.624</td>
<td>-3.3</td>
<td>-1.8</td>
</tr>
<tr>
<td>L2</td>
<td>12.54</td>
<td>0.638</td>
<td>-3.5</td>
<td>-1.8</td>
</tr>
<tr>
<td>L3</td>
<td>15.12</td>
<td>0.595</td>
<td>-4.4</td>
<td>-2.6</td>
</tr>
<tr>
<td>L4</td>
<td>20.72</td>
<td>0.514</td>
<td>-5.0</td>
<td>-3.1</td>
</tr>
<tr>
<td>Total</td>
<td>60.46</td>
<td>0.582</td>
<td>-4.2</td>
<td>-2.5</td>
</tr>
</tbody>
</table>

## Scan Date  Age  BMD  T-score  BMD ∆ vs. baseline**  BMD ∆ vs. previous

<table>
<thead>
<tr>
<th>Scan Date</th>
<th>Age</th>
<th>BMD</th>
<th>T-score</th>
<th>BMD ∆ vs. baseline**</th>
<th>BMD ∆ vs. previous</th>
</tr>
</thead>
<tbody>
<tr>
<td>4/2018</td>
<td>65</td>
<td>0.582</td>
<td>-4.2</td>
<td>-0.043 (-7.0%)</td>
<td>-0.058 (-9.1%)</td>
</tr>
<tr>
<td>12/2015</td>
<td>62</td>
<td>0.645</td>
<td>-3.7</td>
<td>0.020 (3.2%)</td>
<td>0.020 (3.2%)</td>
</tr>
<tr>
<td>**7/2013</td>
<td>60</td>
<td>0.625</td>
<td>-3.8</td>
<td>-0.169 (-21.3%)</td>
<td>-0.108 (-14.7%)</td>
</tr>
<tr>
<td>6/2014</td>
<td>51</td>
<td>0.733</td>
<td>-2.9</td>
<td>-0.061 (-7.8%)</td>
<td>0.061 (-7.8%)</td>
</tr>
<tr>
<td>*8/1998</td>
<td>45</td>
<td>0.794</td>
<td>-2.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Loss of alveolar bone is the most important feature of periodontal disease

Alveolar bone loss may be related to generalized bone loss due to dietary calcium deficiency (in dogs)

Protective layers above the alveolar bone minimize resorption, so extensive trauma may be needed

Multiple older studies, looking at osteoporosis and residual ridge resorption

Resorption likely due to osteoclastic overactivity
Bisphosphonates are chemically absorbed into bone, decrease osteoclast number and activity, and thereby decrease bone resorption.
SAFETY OF ORAL BISPHOSPHONATES: CONTROLLED STUDIES ON ALVEOLAR BONE

• Study 1
  • 335 patients with moderate or severe periodontal disease randomized to placebo or 70mg alendronate once weekly
  • Alveolar bone height were assessed over 2 years
• Results
  • No cases of ONJ with lower incidences of infection and tooth loss in alendronate group

SAFETY OF ORAL BISPHOSPHONATES: CONTROLLED STUDIES ON ALVEOLAR BONE

• Study 2
  • Single-blind controlled study looking at implant success in 50 consecutive patients (210 implants)
  • 25 patients received bisphosphonate and 25 age-matched controls
  • Implant safety and success, rates of ONJ were observed

• Results
  • No cases of ONJ in either group and implant success >99%

REFERENCES


QUESTIONS?

Thank you!
A CASE OF XLH
CASE: 72 YO FEMALE WITH HX OF XLH

Bone History
- Seen as a child at Shriner's St Louis for low serum phos and rickets
- Bilateral tib/fib ostomy age 8 and 15
- Very poor dentition with failed implants and she now has dentures
- Endorses bone pain localized to L fibula, fatigue, and hearing loss. She denies any falls/ fractures

Family History
- Known family h/o XLH (grandmother, mother and brother).
- Has one child, unaffected
TREATMENT HISTORY

- Po phosphorus and Vitamin D as a child. Not treated with GH
- No treatment from age 30 to 67
- At age 67, started on calcitriol 0.25mcg BID, D3 1000 IU daily, and neutraphos 250mg TID
- Tried various doses of Calcitriol and Phosphorus, however pt with persistent elevated alk phos, elevated PTH and bone pain
- Trialed Cinacalcet, however developed hypocalcemia
- Current Regimen: Calcitriol 0.25mcg BID and KPhos 1000mg BID
EXAM

• BMI 21.98, Height: 4’ 10.5,” BP 140/78
• + Bowed legs. No kyphosis
• Strength grossly normal, no trouble standing from seated, cautious gait
DATA:

UCH Labs:

5/2018: Calcium 9.5, Phos 1.5, PTH 104, Alk Phos 109, Vitamin D 25 25,
Vitamin D 1, 25 41

OSH Labs:

9/2015: Calcium 8.7, phos 2.1, Alk phos 174, PTH 156, Urine Calcium 91.5 mg/24 hr

7/2013: Calcium 8.8, phos 2.0, Alk phos 173, PTH 150, Urine Calcium 121.6 mg/24 hr, Vitamin D 25 30

Imaging:

Normal Renal ultrasound
CASE DISCUSSION

- What is XLH?

- Are there any new treatment options?
HYPOPHOSPHATEMIC RICKETS

XLH is a X linked dominant disease
1/20,000 live births
Most common form of hypophosphatemic rickets
XLH: LOSS OF FUNCTION PHEX GENE

- Unclear exact mechanism
- Results:
  - Increased FGF23 (fibroblast growth factor 23)
  - Decreased renal phosphate reabsorption
  - Low serum phosphorus
  - Normal Calcium
  - Normal to elevated PTH
  - Normal serum 25 (OH) D
  - Decreased serum 1,25 (OH)₂D
CLINICAL OUTCOME

- Mild to severe bone disease
- Growth retardation and osteomalacia/rickets
- Limb deformities (bowing, knock knee), waddling gait
- Xray: non mineralized cartilage in epiphyseal regions
- Delayed denition and dental abscesses
- Bone pain as adults, arthritis and osteophytes
- Fractures and pseudofractures
TREATMENT

Conventional Therapy

- Calcitriol: 20-50 ng/kg/day, BID dosing, max 3 mcg
- Phosphorus: 20-75 mg/kg/day, max 2.5 grams
- Toxicities: hypercalcemia, hypercalciuria, nephrocalcinosis, decreased GFR
- Reduced effect on growth

New Alternative

- Burosumab: monoclonal antibody to FGF23
**BUROSUMAB**

- **Pediatrics:** 0.8 mg/kg subq q 2 weeks, titrate
- **Adults:** 1 mg/kg subq q 4 weeks, titrate to max dose 90 mg q 4 weeks
ADULT INDICATIONS TO USE BUROSUMAB?

- 24 week RTC with symptomatic adults with XLH
  - Normalized serum phosphorus
  - Improved stiffness
  - Higher rate of fracture healing (43% vs 8% placebo) (however fractures were asymptomatic)
- But...
  - High cost
  - Unknown effect on fracture prevention
  - Symptoms of hypophosphatemia variable, some patients asymptomatic, treating lab values?
BACK TO CASE

- Patient asks about trying Burosumab
- Considerations for treatment: Pt with continued bone pain. Consider skeletal survey to evaluation for fractures and pseudofractures?
- What do you say?