Bisphosphonates and Denosumab in Fibrous Dysplasia

Alison Boyce, MD
Division of Endocrinology and Bone Health Program, Children’s National Health System
Skeletal Clinical Studies Unit, CSDB, NIDCR, NIH
FD Foundation Meeting 2014
What are Bisphosphonates?

- Medications that prevent bone breakdown
- Used to treat disorders with low bone mass or high bone activity
Bone Remodeling Cycle

Osteoclasts chew the bone up

Osteoblasts fill in the holes
How do bisphosphonates work?

• Taken up by bone cells and incorporated into the skeleton’s matrix
• Decrease the activity of the bone resorbing cells
How do bisphosphonates work?

• Taken up by bone cells and incorporated into the skeleton’s matrix
• Decrease the activity of the bone resorbing cells
  – Less bone breakdown -> denser, stronger bone
Types of Bisphosphonates

**Intravenous**
- Pamidronate (Aredia)
  - 3 hr infusion, ~every 3 months
- Zoledronic acid (Reclast)
  - 30 min infusion, ~every 6 months
- Ibandronate (Boniva)
  - Rapid infusion, ~every 3 months

**Oral**
- Alendronate (Fosamax)
  - Weekly pill
- Risedronate (Actonel)
  - Daily or weekly pill
What types of patients use bisphosphonates?

• FDA-approved for treatment of adults with:
  – Osteoporosis
  – Paget’s disease
  – Bone tumors and bone metastases
  – High blood calcium levels

All other uses are “off-label”
What about kids?

• Different factors to consider
  – Kids’ bones are growing
  – Kids have different kinds of bone diseases than adults
  – There are far fewer studies conducted in kids
Bisphosphonates in Kids

- Most major studies conducted in kids with Osteogenesis Imperfecta (Brittle Bone Disease)
- No significant effects on growth or bone shape
- Helpful for pain
- Probably decrease fractures in OI
Side Effects of Bisphosphonates

• **Flu-like symptoms** after first 1-2 doses
  – Temporary, usu manageable with Tylenol/Motrin

• **Low blood calcium**
  – Make sure to eat dairy
  – Take vitamin D supplement; consider calcium supplements

• **GI disease** (reflux, ulcerations): Oral forms only
  – Can be severe!
  – STOP drug if developing symptoms
Osteonecrosis of the Jaw

- Typically adult cancer patients on steroids, given long-term high dose IV infusions, after dental procedures
- No known cases in kids or adolescents
- Few cases in patients with fibrous dysplasia
- Complete planned dental work prior to starting
Bisphosphonates in Fibrous Dysplasia

• Various case reports
  – Most show improvement in pain
  – Conflicting reports about effects on FD lesions

• One clinical trial in alendronate (oral form):
  – No improvement in pain
  – No change in FD lesions
After 2 years of treatment

**Placebo-Treated Patient (no active drug)**

**Alendronate-Treated Patient**

Start of Study

After 2 years of treatment
NIH Experience with Bisphosphonates

- Only use for pain
- IV bisphosphonates (Zoledronate, Pamidronate) relieve pain in most, but not all patients
- Oral bisphosphonates do not relieve pain
- Bisphosphonates are better at relieving body pain than head pain
- It may take more than one infusion to start working
- Pain comes back at different intervals for different patients -> dose as needed
- Try to use lowest dose at lowest frequency to treat pain
Denosumab (Xgeva®, Prolia®)

- Antibody that binds and inhibits RANKL
- **Similarities to bisphosphonates**
  - Also inhibits bone breakdown
  - Also FDA-approved for adults with osteoporosis and bone tumors
- **Key differences to bisphosphonates:**
  - More potent
  - Shorter-acting (6 months vs >10 years)
  - Much less data
RANKL turns on the cells that break down bone

Inactive Osteoclast → RANKL → Bone marrow stromal cell

Activate Osteoclast → BONE BREAKDOWN

Denosumab PREVENTS this process

Adapted from J. Tsai
Why are we talking about denosumab in FD?
RANKL is found in bone from FD patients
RANKL is found in blood from FD patients

RANKL levels are higher in FD patients than in non-FD patients

RANKL levels are higher in patients who have more FD
Denosumab is effective for treatment of Giant Cell Tumors

- Bone lesion involving the same type of cell as FD (bone marrow stromal cell)
- Tissues has very similar appearance to FD
Denosumab and FD

• 3 patients treated at the NIH, 3 additional patients in published reports
  – Improvements in pain
  – Mild-to-severe abnormalities in blood calcium and phosphorus
  – Effect on FD lesions not known
Denosumab and FD: Many Areas of Uncertainty

• Does it work?
• What dose? How frequently?
• Is it safe? What side effects might occur? How should patients be monitored?
• What happens when the drug is stopped?
  – One patient hospitalized with severe hypercalcemia
• What happens to kids?
  – Growth effects? Osteonecrosis?
  – Trial in kids with OI has recently started
Denosumab and FD: Where are we now?

- Pilot study in adults with FD planned to start at NIH in the next year
- At this time we do NOT recommend off-label use, except in very rare circumstances given by practitioners very experienced in FD
Endocrine Disorders in FD/MAS

- Precocious Puberty
- Hyperthyroidism
- GH Excess
- Phosphate wasting
- Cushing Syndrome
Findings in our MAS patients at the NIH

<table>
<thead>
<tr>
<th>Findings</th>
<th>Prevalence (%)</th>
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<tbody>
<tr>
<td>Fibrous dysplasia</td>
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<tr>
<td>Café-au-lait</td>
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<tr>
<td>Precocious puberty</td>
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<tr>
<td>female</td>
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<td>Phosphate wasting</td>
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<td>Growth hormone excess</td>
<td>18</td>
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<tr>
<td>Cushings</td>
<td>7</td>
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</table>
Precocious Puberty

- Most common endocrine disorder in girls (~80%)
  - Transient ovarian cysts -> recurrent, relapsing course
  - In boys, steady testosterone production -> sustained course
- Goals of Treatment:
  - Prevent short stature in adulthood (primary!)
  - Prevent bleeding and sexual development
  - Prevent social and behavioral issues, patient discomfort
Precocious Puberty: Treatment

• NO surgery!
• **Letrozole**: blocks estrogen formation
• **Tamoxifen, Fulvestrant**: block estrogen action
• In boys: testostolactone, flutamide block testosterone action

• **Central puberty** usu occurs after several years. Treat with **Lupron** (injections or implant) to suppress the puberty

Eugster et al, J Peds, 2003
Hyperthyroidism

• Overproduction of thyroid hormone

• First-line initial treatment: Methimazole
  – Twice daily oral medication
  – Monitor liver tests and blood counts

• Permanent treatment
  – Surgery preferred. MUST use experienced endocrine surgeon
Growth Hormone Excess

- Diagnose and treat early. If untreated, increases skull FD expansion and risk of vision loss
- Medications
  - **Octreotide** (Sandostatin): intramuscular injection monthly
  - **Pegvisomant** (Somavert): subcutaneous injection daily
- Surgery
  - technically difficult
  - need to remove the entire pituitary
- Radiation
  - last resort – increased cancer risk
**Phosphate Wasting**

- FD overproduces the hormone FGF23 -> too much phosphate is dumped into the urine
- Increases fractures and bone pain
- Treat with oral phosphate + calcitriol
  - Must give 3-5 times a day
  - Monitor urine calcium
  - Stop medications when immobilized
- Phosphate wasting may improve or resolve with time
What initial testing should be done?

• **Thyroid:** ultrasound, blood tests (TSH, T3)
• **Phosphate:** blood and urine phosphorus levels
• **Growth hormone:** IGF-1, glucose tolerance test, MRI pituitary if needed
• **Cushings:** monitor growth and development in kids under age 3 years
Monitoring Treatment for Endocrine Disorders

• For all endocrine conditions in children: Growth chart, Growth chart, Growth chart!

• In addition:
  – Precocious puberty: Bone age X-ray
  – Hyperthyroidism: Blood tests (TSH, T3)
  – Growth hormone excess: Blood tests (IGF-1)
  – Phosphate wasting: Blood and urine phosphorus, symptoms of pain and fatigue
Frequency of follow-up

- Depends on the issue
- Stable disease – twice a year
- Patients with uncontrolled symptoms or taking medications – every 3-4 months and as needed
## Acknowledgements

### SCSU
- Michael Collins
- Beth Brillante
- Lori Guthrie
- Nisan Bhattacharyya
- Rachel Gafni
- Andrea Burke
- Mary Scott Ramnitz
- Andrea Estrada
- Diana Ovejero Crespo

### CSDB
- Pam Robey
- Larry Fisher
- Marian Young
- Kenn Holmbeck
- Sergei Kuznetsov
- Natasha Cherman

### SCSU Former Trainees
- Sunday Akintoye
- Claudia Dumitrescu
- Todd Theman
- Elizabeth Hart
- Azar Khosravi
- Carolee Cutler
- Penny Andreopoulou
- William Chong
- Diala El-Maouche

### FD Collaborators
- Penny Feuillan
- Paolo Bianco
- Arabella Leet
- John Butman
- Janice Lee
- Clara Chen
- James Reynolds
- Chris Austin
- Wei Zheng
- John Northup
- Shlomo Wientroub
- Harvey Kushner
- Ed FitzGibbon
- Tom Shawker
- Francesco Celi
- Scott Paul
- Jeff Kim
- Jim Inglese
- Catherine Chen