Antiresorptive Therapy for Postmenopausal Osteoporosis

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Objectives

- Discuss the indications for the initiation and maintenance of antiresorptive therapy for postmenopausal osteoporosis
- Update current knowledge of anti-fracture efficacy of the most commonly used anti-resorptives
- Define the unique and rare side effects associated with bisphosphonates and denosumab
- Review our current knowledge of the incidence and risk factors for these side effects
Case 1

- 53yo WF requests BMD for health maintenance
- PMHx: GERD, treated HTN
- Menopause at age 49; no symptoms; never on HT
- PE: normal, weight 142#, no kyphosis, no bony pain, height 5’4” unchanged from high school

Case 2, cont

- BMD:
  - L1-4 T-score −1.8
  - Total hip T-score −2
  - Femoral neck T-score −2.1

Now What?
Case 2, cont

- **More History!**
  - Never a smoker
  - Mother without any fractures; pt broke her left arm at age 12 after flying off a bike, no others
  - Works out 4 days a week, never falls
- Screen for secondary causes of bone loss
- Start RDA calcium – citrate as on a PPI
- Start RDA Vitamin D – 600 - 800IU/d
- Repeat BMD in 2 years
Case 2

- 68yoWF presents with mid-thoracic pain after lifting her Kitchen Aide mixer to better clean her kitchen counter
- Height loss of 2.5” since youth
- PE with mild kyphosis, focal pain palpable at T10
- Labs all normal; plain X-ray with compression fracture at T10
- Does she have a diagnosis yet? What do you do?

National Osteoporosis Foundation guidelines for therapeutic management

- A hip or vertebral (clinical or morphometric) fracture
- T-score $\leq -2.5$ at the femoral neck or spine after appropriate evaluation to exclude secondary causes
- Low bone mass (T-score between -1.0 and -2.5 at the FN, TH or LS) AND a 10-year probably of a hip fracture $\geq 3\%$ or of a major osteoporotic fracture of $\geq 20\%$ based upon FRAX
- Clinician’s judgement and/or patient preference may indicate treatment for people with 10-year fracture probabilities above or below these levels

National Osteoporosis Foundation guidelines for therapeutic management

- A hip or vertebral (clinical or morphometric) fracture
- T-score < -2.5 at the femoral neck or spine after appropriate evaluation to exclude secondary causes

Low bone mass (T-score between -1.0 and -2.5 at the FN, TH or LS) AND a 10-year probability of a hip fracture >3% or of a major osteoporotic fracture >20% based upon FRAX

Clinician’s judgement and/or patient preference may indicate treatment for people with 10-year fracture probabilities above or below these levels


Effects of Bisphosphonates on Osteoclast Function

Alendronate (Fosamax)

- Fracture Intervention Trial (FIT)
  - In all pts with T-score <-1.6, sig reduction in vertebral fractures
  - In pts with T-score <-2.5, or 1 or more previous fragility fractures, sig reduction hip and all clinical fractures

Alendronate: FIT and FLEX data

Continuous Increases in Lumbar Spine BMD with Alendronate 10 mg over 10 Years

The mean percent change from baseline to year 10 appears in parentheses following each treatment group.

Zoledronic Acid for treatment of PMO, Reclast

Initial trial evaluating Zoledronic acid in the setting of PMO – One year BMD results


**Reclast Reduced 3-Year Risk of Morphometric Vertebral Fractures (Stratum I)**

*Please see full prescribing information.

**Note:** 1. 2002, relative risk reduction vs placebo (95% confidence interval)
Reclast Reduced Cumulative 3-Year Risk of Hip Fractures (Strata I + II)

Zoledronic acid extension trial

- 1233 postmenopausal women initially receiving Reclast yearly x 3 years randomized to 3 more years of Reclast or three years of placebo
- See plateau in treated groups after three years at the hip
- See continuous rise at LS over three years
- Do NOT see a decline to baseline in the placebo group
Zoledronic acid extension trial: fracture

- Do see greater vertebral fracture reduction in the continuously treated group.

- In the “holiday” group, the modeled vert fracture reduction in the Z3/P3 vs. no treatment at all is significantly reduced.

- After 3 years, do not see a difference in hip fracture in the Z3/P3 vs. Z6 – an issue of n?

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Denosumab – “Prolia”

- Fully human monoclonal antibody to the receptor activator of nuclear factor-kb ligand (RANKL) that blocks its binding to RANK.
- Inhibits development and activity of osteoclasts.
- Decreases bone resorption, increases bone density.
- RANKL expressed on precursors of osteoblasts, marrow stromal cells and activated T cells.
RANKL Pathway Involvement in Bone Remodeling

FREEDOM Trial

- Multicenter randomized, placebo-controlled trial
- 7868 postmenopausal women aged 60-90
- T-score ≤-2.5 at LS or total hip eligible
- Excluded if on bisphos within past 5 yrs
- Everyone received daily calcium and vitamin D
- Study group: denosumab 60mg subcut q6mo for 36 months
- Lat spine Xray performed annually
- BMD measured annually
- BTM only measured on 160 subjects

Cummings S et al, NEJM, August 2009, 756 - 765
FREEDOM Trial: Incidence of new Vertebral Fracture

Cummings S et al, NEJM, August 2009, 756 - 765

FREEDOM Trial: Time to first Non-Vert and Hip fractures

Cummings S et al, NEJM, August 2009, 756 - 765
Denosumab FREEDOM Extension trial

Will continue for a total of ten years
Those initially enrolled in placebo were allowed to ‘cross-over’ to treatment
4550 postmenopausal women are currently enrolled in the Extension Trial


ONJ: Four in the cross-over group; none in the original 3 year trial
Three cases thus far of atypical femoral fracture
One serious skin infection (erysipelas) in the extension trial
Non-FDA approved Therapy

<table>
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<tr>
<th>These drugs are listed for information only. These non-approved agents include:</th>
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<tr>
<td><strong>Calcitriol</strong> This synthetic vitamin D analogue, which promotes calcium absorption, has been approved by the FDA for managing hypocalcemia and metabolic bone disease in renal dialysis patients. It is also approved for use in hypoporarathyroid, both surgical and idiopathic, and possibly hyperparathyroidism. No reliable data demonstrate a reduction of risk for osteoporotic fracture.</td>
</tr>
<tr>
<td><strong>Fluvastatin</strong> An 8-oxo-cholesterol analogue which is the major ingredient in the proprietary “medical food” product Fortimel® and generally reported as safe by the FDA. Calcium may benefit bone health in postmenopausal women but more data are needed to fully understand its effects on bone health and fracture risk.</td>
</tr>
<tr>
<td><strong>Other bisphosphonates (etidronate, pamidronate, alendronate).</strong> Those medications vary chemically from alendronate, ibandronate, risedronate and zoledronate but are in the same drug class. At this time, none is approved for prevention or treatment of osteoporosis. Most of these medications are currently approved for other conditions (e.g. Paget’s disease, hyperparathyroidism of malignancy, ischemic osteitis).</td>
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<tr>
<td><strong>PTH(1-34).</strong> This medication is approved in some countries in Europe for treatment of osteoporosis in women. In one clinical study PTH(1-34) effectively reduced the risk of vertebral fractures at a dose of 100mg/d.</td>
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<td><strong>Sodium fluoride.</strong> A process that is still unclear, sodium fluoride stimulates the formation of new bone. The quality of bone matrix is developed in response, and the evidence that fluoride reduces fracture risk is conflicting and inconclusive.</td>
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<tr>
<td><strong>Strontium ranelate.</strong> This medication is approved for the treatment of osteoporosis in some countries in Europe. Strontium ranelate reduces the risk of both spine and non-vertebral fractures, but the mechanism is unclear. Incorporation of strontium into the crystal structure replacing calcium may be part of its mechanism of effect. These effects have only been documented with the pharmaceutical grade agent produced by Servier. This effect has not been rigorously studied in nutritional supplements containing strontium salts.</td>
</tr>
<tr>
<td><strong>Risedronate.</strong> Risedronate is a specific, osteoclast use agent that may prevent bone loss and reduce fractures despite symptoms but it does not stimulate bone or unique tissue. It is indicated in Europe for the treatment of postmenopausal symptoms of menopause and for prevention of osteoporosis, but it is not approved for use in the U.S.</td>
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Case 3

- 63 yo WF presents for f/u of osteoporosis management
- She had known osteoporosis by DXA and had been on alendronate since 2007
- In 2010 she slipped on some wet grass while gardening, fell onto her outstretched hand and sustained a wrist fracture
- She was started on Forteo which she took from 10/2010 – 10/2012, then she received her first dose of Reclast in November 2012 and second dose 11/2013 – no further fractures since 2010, and she has developed no new risk factors for fracture
- Has been doing well over the past year, except that she has developed some pain over her right upper, lateral thigh
  - Radiates to her right buttock
  - Started after a three day conference for work where she was sitting often
  - Minimally responsive to NSAIDs
Case 3

- You decide to:
  - A) Order an x-ray of her right hip
  - B) Order x-ray of bilateral hips
  - C) Refer her to PT for therapy of muscular strain
  - D) Order MRI of right hip
  - E) Stop the Reclast and start her on Evista

Atypical Femoral Fractures

Scholarly articles for fosamax and fractures
Cost effectiveness of alendronate (Fosamax) for the... "J Rheumatol. Cited by 128... density results of EFFECT (Evaluation of FOSAMAX) -- Sandler. Cited by 87... associated with taking study medication in the fracture... " Skeletal. Cited by 25...

New Cautions About Bisphosphonates - NYT.com

www.wdmd.com/... Jointly-care-fractures-linked-to-osteoporosis... -- "WdMD "

Mar 24, 2010 - Would below-the-knee high fractures linked to Fosamax and other osteoporosis drugs are rare... but even if they injured these injuries, they'll still...

Merck wins battled with Fosamax femur feature trial - F依普Pharma

www.fapo.com/... Fosamax, fracture... " Series " -- Apr 30, 2010 - During the course of the trial, plaintiff's attorney Paul Pennisi said Merck knew Fosamax could trigger the so-called "atypical" femur fractures,...

Fosamax: Is Long Term Use of Bone Strengthening Drug Linked to...
Atypical Femoral Fractures – Similar to Stress Fractures

- Prodome of pain in groin or lateral thigh for a period of weeks
- Hazy periosteal callus
- Evidence of an attempt at repair prior to overt fracture
- Generalized thickening of both cortices
- “beaking”
Atypical femoral fractures and bisphosphonates – causal or not?

- Most patients in most case trials as well as large nationwide analyses have been on bisphosphonates for 3-6 years (in one meta-analysis median of 7 years)
- However, many have also been on glucocorticoids and some display uncontrolled DM
- Dog, rat and human trials show that advancing age, in the absence of BPs, reduces bone turnover and increased microdamage accumulation
- Animal models show lowering of remodeling by BPs does allow accumulation of microdamage and reduction of tissue toughness (energy-absorbing capacity of bone tissue)

SOF and Swedish Nationwide Analysis

- SOF\(^a\)
  - Prospective, population based study of 9704 white women, 65 and older, studied for as long as 24 years
  - Incidence of subtrochanteric fx is low: 3/10,000 person years
  - Vs. overall hip fractures: 103/10,000 person years
- Sweden\(^b\)
  - 12,777 women age 55 or older sustained a femur fracture in the year 2008 – case/control study
  - 59 met criteria for atypical femoral fracture, 78% of these were on bisphosphonates vs. 10% of case controls (who had ordinary subtrochanteric or shaft fractures)
  - Avg bisphosphonate number needed to harm: 2000 per year of use
  - Number needed to treat\(^c\): 90 to prevent one hip fracture; 35 to prevent one nonvertebral fx and 14 to prevent one vertebral fracture

\(^a\)Kelly MP et al. Data from SOF. ASBMR 2010 Annual Meeting, Toronto, Canada
\(^b\)Schilcher Jr et al. NEJM 2011;364:18:1728-1737
\(^c\)Black DM et al. NEJM 2010;362:1761-1771.
ASBMR Task Force 2013
Revised Case Definition of AFFs

- Major Criteria – Must have 4/5:
  - Fracture associated with minimal or no trauma
  - Fracture line originates at the lateral cortex and is substantially transverse, although may become oblique as it extends medially
  - Complete fractures extend through both cortices; incomplete fractures involve only the lateral cortex
  - Noncomminuted or minimally comminuted
  - Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site (‘beaking’ or ‘flaring’)

- Minor Criteria – not required, but can help define these Fx:
  - Generalized increase in cortical thickness
  - Unilateral or bilateral prodromal symptoms
  - Bilateral incomplete or complete femoral diaphysis fractures
  - Delayed fracture healing


AFFs - Considerations

- More likely to happen in patients on BPs > 4 years (median 7 years)
- AFFs are also seen in patients never on BPs
- More likely to occur in younger patients, and in those concomitantly on GCs
- Prophylactic reconstruction nail fixation should be considered with incomplete Fx
- See significant reduction in incidence of AFFs within just one year of discontinuation of BP
Atypical femoral fracture

Recommendations by ABSMR:

• Patients at low risk for osteoporosis-related fracture should not be started on BPs
• Patients who are at high risk for fracture (as outlined by NOF guidelines) should be started on therapy
• Bisphosphonates continue to be first-line therapy for PMO – the risk of atypical femoral fractures is very low
• For patients with relatively normal bone density at the hip, where there is isolated osteoporosis at the LS, SERMs could be considered
• BPs continue to be first line therapy for patients with rapid bone loss due to glucocorticoids, organ transplantation or endocrine therapy for breast or prostate cancer, with regular reevaluation
• There is inconsistent evidence that teriparatide may advance healing of AFFs

**NOF recommendations – to Holiday or not to Holiday?**

- “Although there is no extensive evidence base to guide treatment duration decisions, it is reasonable to discontinue bisphosphonates after 3-5 years in people who appear to be at only modest risk of fracture after the initial treatment period.
- In contrast, for those who appear to be at high risk for fracture, continued treatment with bisphosphonate or an alternate therapy should be considered.”

www.nof.org/hcp/clinicians-guide

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**Case 4**

- 76yo female calls in very concerned about recent incidence of “cracking teeth”
- She has always had excellent dental hygiene, only one cavity in her whole life; however, over the last 9 months she has had three teeth crack. She is contemplating an implant for the worst tooth.
- She has had no radiation to the jaw; no root canals or extractions
- She has significant osteoporosis; her LS T-score is -3.8; she has lost 6” of height and has had three documented vertebral fractures since 2010; she broke her ankle after stepping in a small hole in a field 3 years ago
- She took risedronate faithfully for 5 years with stable BMD and no further fractures, but developed new onset renal insufficiency and so you switched her to denosumab – she received her first dose one year ago, second dose 6 months ago and is now due for her third dose, but she is reconsidering due to her new teeth issues
- What do you do? Is denosumab causing these new poor dental outcomes?
Osteonecrosis of the Jaw
First cases reported by Marx in 2003

• Reports 36 cases of painful bone exposure in the mandible, maxilla, or both, that were unresponsive to surgical or medical treatments
• All patients were receiving IV pamidronate or zoledronic acid therapy
• Most patients presented with painful exposed avascular bone in the mandible (29 [80.5%]), in the maxilla (5 [14%]), or both (2 [5.5%])
• The presentations simulate dental abscesses, “tooth aches,” denture sore spots, and osteomyelitis


ONJ Case Definition
From AAOMS, ASBMR, ESCEO

– Exposed bone in the maxillofacial region
– Unhealed for >8 weeks
– No history of radiation therapy to the craniofacial region

But NOT teeth cracking!

Proposed mechanism for ONJ:

- Suppressed bone turnover
- Infection + inflammation
- Disruption of oral mucosa
- Osteocyte death
- Bone resorption and necrosis
- Bisphosphonate released from bone


AEs Denosumab and Zoledronic acid

<table>
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<tr>
<th></th>
<th>ONJ Years 1-3</th>
<th>ONJ Years 4-6</th>
<th>AFF Years 1-3</th>
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<tbody>
<tr>
<td>Denosumab FREEDOM</td>
<td>2 n=3605</td>
<td>4 n=1827</td>
<td>0 n=3605</td>
<td>2 n=1827</td>
</tr>
<tr>
<td>Zoledronic Acid HORIZON</td>
<td>2 n=3875</td>
<td>1 n=616</td>
<td>? n=3875</td>
<td>0 n=616</td>
</tr>
</tbody>
</table>

*3 cases in PBO

Black DM et al, NEJM 2007 May 3;356(18):1809
Black DM et al, J Bone Miner Res. 2012 Feb;27(2):243-54
Cummings SR et al, NEJM 2009 Aug 20;361(8):758-65
Thanks!

- [www.nof.org/hcp/clinicians-guide](http://www.nof.org/hcp/clinicians-guide)
- Compston J. Pathophysiology of atypical femoral fractures and osteonecrosis of the jaw. Osteoporos Int 2011 Dec;22(12):2951-61

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