New and Emerging Therapies for Osteoporosis

Steven T Harris MD FACP
Clinical Professor of Medicine
University of California, San Francisco

2010-2011 Professional Associations

Consultation
* Amgen
* Eli Lilly & Company
* Gilead Sciences
* Merck
* Roche

Sponsored Presentations
* Amgen
* Eli Lilly & Company
* Genentech
* Gilead Sciences
* Novartis
* Roche
* sanofi-aventis
* Warner Chilcott

Key Topics
* Brief review of bone remodeling
* Current guidelines for osteoporosis treatment
* Summary of contemporary osteoporosis treatment options—and the major safety concerns
* New and emerging therapies

Normal Bone Remodeling Sequence
Unbalanced Remodeling

Net bone loss (osteoporosis)

Change In Bone Mass With Age


Postmenopausal Osteoporosis

Increased fracture risk due to low bone density and microarchitectural deterioration: poor bone quality

Pathogenesis of Osteoporosis

Modified from Riggs BL and Melton LJ III. New York: Raven Press, 1986

Net bone loss (osteoporosis)
Assess Risk Factors and Measure BMD if Patient Has Risk Factors

T-score between -1.0 and -2.5

Hip or Vertebral Fractures or T-score ≤ -2.5 (Spine, FN or Total Hip)

Other Fractures after Age 50 (Excluding Fingers, Toes and Face)

10-year Probability of Hip Fracture >3% or Probability of All Major Fractures >20%

Secondary Causes with High Fracture Risk*

*such as glucocorticoid use or total immobilization

2008 NOF Guidelines: Treatment Initiation Post-menopausal Women And Men ≥50

Treatment Summary

- We have the tools to identify patients at risk; in FRAX®, bone mineral density (BMD), age and previous fractures in particular are strong, independent predictors of fracture risk
- Treatments significantly decrease fracture risk:
  - Antiresorptive therapy produces a modest BMD increase, yet decreases fracture risk—especially in the spine—much faster and to a larger extent than predicted by the relatively small change in BMD. This implies an important improvement in bone “quality”
  - Anabolic therapy with teriparatide increases BMD more than antiresorptive treatment, but it is not yet obvious that fracture protection is greater

Objective of Intervention

The most important clinical objective is the prevention of fractures—both vertebral and non-vertebral fractures

Changes in surrogate markers—bone mineral density (BMD) and biochemical markers of bone turnover—are "necessary" but are not "sufficient"

Non-Pharmacological Options

- Taken as a whole, non-pharmacological options seem to be relatively inexpensive, and modestly effective
- Exercise in particular has other health benefits, although the same is likely to be true for diet optimization
- Optimization of the diet, exercise and fall prevention should be viewed as important adjuncts to the treatment of osteoporotic patients
Prevention
Stops bone loss

Treatment
Reduces vertebral fractures

<table>
<thead>
<tr>
<th>Prevention/Prevention</th>
<th>Treatment/Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen</td>
<td>Calcitonin</td>
</tr>
<tr>
<td>Alendronate</td>
<td>PTH (teriparatide)</td>
</tr>
<tr>
<td>Risedronate</td>
<td>Denosumab</td>
</tr>
<tr>
<td>Ibandronate</td>
<td></td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td></td>
</tr>
<tr>
<td>Raloxifene</td>
<td></td>
</tr>
</tbody>
</table>

Normal Coupling of Bone Remodeling

Resorption = Formation

- Most treatment agents (bisphosphonates, SERMs, calcitonin, estrogen) act primarily on the left side of the equation—to decrease bone resorption
- A decrease in resorption is followed by a decrease in formation—and BMD improvement tends to "plateau" after several years
- Only teriparatide acts on the right side of the equation—to stimulate formation

Antiresorptive Treatment: Summary

- Antiresorptive treatment decreases fracture risk more rapidly and to a larger extent than one would predict from the relatively small changes in BMD
  Fracture protection can be observed in the absence of a significant change in BMD
- Fracture protection persists even when the BMD reaches a plateau
  BMD stability does not mean "non-response"
- Fracture reduction is most conspicuous in older patients with prevalent vertebral fractures

Anti-resorptive Agents: Clinical Trial Results

<table>
<thead>
<tr>
<th>Trials of Different Agents Cannot Be Compared Directly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect on fracture risk</td>
</tr>
<tr>
<td>Agent</td>
</tr>
<tr>
<td>--------------</td>
</tr>
<tr>
<td>Estrogen</td>
</tr>
<tr>
<td>Raloxifene</td>
</tr>
<tr>
<td>Calcitonin</td>
</tr>
<tr>
<td>Denosumab</td>
</tr>
<tr>
<td>Alendronate</td>
</tr>
<tr>
<td>Risedronate</td>
</tr>
<tr>
<td>Ibandronate</td>
</tr>
<tr>
<td>Zoledronic acid</td>
</tr>
</tbody>
</table>

+ documented in randomized, controlled trial
- effect not documented
§ effect documented only in a post hoc analysis of a high-risk subgroup (femoral neck T score < -2.5)
Bisphosphonates
Alendronate, Risedronate, Ibandronate and Zoledronic Acid

- The prevention and treatment of osteoporosis—in daily oral, intermittent oral and intermittent parenteral formulations:
  - Alendronate 10 mg daily or 70 mg weekly for treatment, 5 mg daily or 35 mg weekly for prevention
  - Risedronate 5 mg daily or 35 mg weekly; 150 mg monthly; 35 mg weekly after breakfast
  - Ibandronate 150 mg monthly by mouth; 3 mg iv over 15-30 seconds every 3 months
  - Zoledronic acid 5 mg by infusion over a minimum of 15 minutes every year

- Increased bone density in the spine by 5-8% and at the hip by 3-6% after 3 years
- Reduced incidence of vertebral fractures by 40-70%
- Alendronate, risedronate and zoledronic acid reduced non-vertebral fractures (25-40%), including hip fractures (40-60%), in women with osteoporosis
- Ibandronate: overall, no effect observed on non-vertebral or hip fractures. In a post-hoc analysis, non-vertebral fracture reduction was seen in a high-risk subgroup with a baseline femoral neck T-score less than -3.0

Bisphosphonates: Side Effects

- "Class warning" regarding UGI symptoms (no increase in UGI complaints in randomized controlled trials)
- "Class warning" regarding infrequent bone, joint and/or muscle pain
- "Class warning" regarding jaw osteonecrosis
- "Class warning" about atypical fractures following long-term therapy
- Influenza-like symptoms may occur after first monthly oral dose or IV injection

Bisphosphonates: Effects
Alendronate, Risedronate, Ibandronate and Zoledronic Acid

- Increased bone density in the spine by 5-8% and at the hip by 3-6% after 3 years
- Reduced incidence of vertebral fractures by 40-70%
- Alendronate, risedronate and zoledronic acid reduced non-vertebral fractures (25-40%), including hip fractures (40-60%), in women with osteoporosis
- Ibandronate: overall, no effect observed on non-vertebral or hip fractures. In a post-hoc analysis, non-vertebral fracture reduction was seen in a high-risk subgroup with a baseline femoral neck T-score less than -3.0

Atypical Fractures of the Femur
Patients on Bisphosphonate Therapy for Osteoporosis

- Hypothesis that "over-suppression" of bone remodeling could impair the repair of microdamage—and increase the risk of atypical fractures
- Transverse (not spiral) fractures of femoral shaft or in subtrochanteric region
- May begin with stress reaction or stress fracture of lateral femoral cortex (arrow)
- Often bilateral
- Prodromal pain in thigh or groin in 70%
- Can occur in untreated patients, but increased incidence in patients on bisphosphonates > 5 years, often in combination with other drugs, especially steroids or estrogen
**FDA Safety Update**

- Be aware of the possibility of atypical fractures in patients on bisphosphonates
- Evaluate any patient who presents with new groin or thigh pain to rule out a femoral shaft fracture
- Discontinue potent antiresorptive medication in patients with atypical fractures
- Periodically reevaluate the need to continue bisphosphonate therapy, particularly in patients treated for 5 years or more

Link to MedWatch Online Voluntary Reporting Form: https://www.accessdata.fda.gov/scripts/medwatch/

**New and Emerging Therapies**

- Denosumab
- SERMs: lasofoxifene, bazedoxifene
- Strontium
  - strontium ranelate
  - strontium malonate
- Anti-sclerostin antibody
- Cathepsin K inhibitor – odanacatib
- Cyclic analog of PTH (1-31)
- Calcium receptor antagonist – “calcilytic”

---

**RANKL Antibody/RANKL: Activation Of Osteoclasts**

- OPG
- RANK
- RANKL
- CFU-M
- Pre-fusion osteoclast
- Multinucleated osteoclast
- Activated osteoclast

---

**Denosumab vs Alendronate**

<table>
<thead>
<tr>
<th>Month</th>
<th>% Change Spine BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2</td>
<td></td>
</tr>
<tr>
<td>-1</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
</tr>
</tbody>
</table>

- Denosumab 60 mg sq every 6 mos
- Alendronate 70 mg weekly
- Placebo

< 0.001 vs placebo

Adapted in part from McClung MR, et al. 2006;354:821-31
Denosumab Fracture Trial: FREEDOM
Fracture REDuction Evaluation of Denosumab in Osteoporosis every 6 Months

- Phase 3 RCT in postmenopausal women age 60–90 with lumbar spine or total hip T-score < -2.0 and ≥ -4.0
- Randomized to denosumab 60 mg subcutaneously every 6 months vs PBO
- Endpoints
  * Primary: new vertebral fractures at 36 months
  * Secondary: time to first hip and nonvertebral fractures


FREEDOM: Vertebral Fracture Risk Reduction

<table>
<thead>
<tr>
<th>Year</th>
<th>Placebo</th>
<th>Denosumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61% ↓ (P&lt;0.0001)</td>
<td>72% ↓ (P&lt;0.0001)</td>
</tr>
<tr>
<td>2</td>
<td>61% ↓ (P&lt;0.0001)</td>
<td>72% ↓ (P&lt;0.0001)</td>
</tr>
<tr>
<td>3</td>
<td>61% ↓ (P&lt;0.0001)</td>
<td>72% ↓ (P&lt;0.0001)</td>
</tr>
</tbody>
</table>

FREEDOM: Nonvertebral Fractures

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Prolia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>3.2%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Infection</td>
<td>6.5%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Cellulitis *</td>
<td>&lt;0.1%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Concussion *</td>
<td>0.3%</td>
<td>&lt;0.1%</td>
</tr>
</tbody>
</table>

* > 0.1% and p < 0.01

New and Emerging Therapies

- Denosumab
- SERMs: lasofoxifene, bazedoxifene
- Strontium
  - strontium ranelate
  - strontium malonate
- Anti-sclerostin antibody
- Cathepsin K inhibitor – odanacatib
- Cyclic analog of PTH (1-31)
- Calcium receptor antagonist – "calcilytic"

The Concept of a SERM
Selective Estrogen Receptor Modulator
("EAA": Estrogen Agonist/Antagonist)

- Binds to the estrogen receptors
- Produces an estrogen agonist effect in some tissues
- Produces an estrogen antagonist effect in others

The Concept of a SERM
Selective Estrogen Receptor Modulator
("EAA": Estrogen Agonist/Antagonist)

- tamoxifen
- raloxifene
- bazedoxifene
- lasofoxifene

Bazedoxifene: “BZA”: Investigational SERM
Pivotal fracture trial compared placebo, BZA 20 mg daily, BZA 40 mg daily and raloxifene 60 mg daily over 3 years
- Spinal BMD increase at 24 months – roughly 1.5% relative to placebo
- New vertebral fracture risk reduction: 42%, 37% and 42% with BZA 20, BZA 40 and raloxifene, respectively
- Non-vertebral fracture risk reduction of 40% with BZA in a subgroup (FN T-score ≤ -3.0 or ≥ 1 moderate/multiple vertebral fractures), but not in the entire study group
- Increase in hot flashes and venous thromboembolic events, relative to placebo

Lasofoxifene: Investigational SERM
Postmenopausal Evaluation and Risk reduction with Lasofoxifene
The PEARL Trial

Major outcomes at the end of 5 years:
* 42% and 31% reductions in vertebral fracture with lasofoxifene 0.5 mg and 0.25 mg, respectively
* 24% reduction in non-vertebral fracture with lasofoxifene 0.5 mg; no significant effect on hip fracture alone
* 85% reduction in invasive breast cancer with lasofoxifene 0.5 mg
* Reductions in coronary artery disease and stroke
* Increases in venous thromboembolic disease
* Increases in leg cramps, hot flushes, uterine polyps, endometrial hypertrophy, vaginal candidiasis and arthralgias with lasofoxifene
* 38% increase in all cause mortality with lasofoxifene 0.25 mg, no significant increase with lasofoxifene 0.5 mg


New and Emerging Therapies

- Denosumab
- SERMs: lasofoxifene, bazedoxifene
- Strontium
  - strontium ranelate
  - strontium malonate
- Anti-sclerostin antibody
- Cathepsin K inhibitor – odanacatib
- Cyclic analog of PTH (1-31)
- Calcium receptor antagonist – “calcilytic”

Strontium Ranelate

- Orally administered form of strontium
- Increases BMD, due in large part to the strontium itself being incorporated into bone
- Small changes in bone turnover (increase in bone formation and decrease in bone resorption markers)
- Reduction in vertebral and non-vertebral fracture in women with osteoporosis1,2,3
- Approved in other countries—available in Europe as a powder
- Other strontium salts available (none approved in the United States)—no clinical data

3 Cochrane Database Syst Rev 2006;18(4):CD005326

New and Emerging Therapies

- Denosumab
- SERMs: lasofoxifene, bazedoxifene
- Strontium
  - strontium ranelate
  - strontium malonate
- Anti-sclerostin antibody
- Cathepsin K inhibitor – odanacatib
- Cyclic analog of PTH (1-31)
- Calcium receptor antagonist – “calcilytic”
**Regulation Of Bone Mass By Wnt Signaling**

*Wnt, LRP5, Sclerostin Pathway*

Krishnan V, Bryant HU, Macdougald OA. 2006;116(5):1202-9

Sclerostin

- From osteocytes
- Inhibits the anabolic Wnt signaling pathway
- Deficiency results in a sclerosing bone disease (sclerosteosis)
- Antibody to sclerostin restores bone mass and bone architecture in rats and monkeys
- Clinical trials just beginning

**A New Anabolic Approach:**

Inhibit A Regulator Of Bone Formation

- Sclerostin
  - From osteocytes
  - Inhibits the anabolic Wnt signaling pathway
  - Deficiency results in a sclerosing bone disease (sclerosteosis)
  - Antibody to sclerostin restores bone mass and bone architecture in rats and monkeys
  - Clinical trials just beginning

**Anti-Sclerostin Antibody Therapy**

- Rats ovariectomized at age 6 months
- Treatment for 3 months beginning at 18 months of age

**Antibody to Sclerostin – First Human Study**

- 48 healthy postmenopausal women
- Doses: 0.1 to 10mg/kg: single subcutaneous dose
- Followed for 85 days

**Results**

- Dose-related increases in P1NP (similar results for BSAP and OC, two other markers of bone formation)
- sCTX decreased >50% for the 5 and 10mg/kg doses
- Increases in BMD at 3 months with the 5 and 10mg/kg doses
  - Spine: 3-5%
  - Total hip: 1.5-3%
New and Emerging Therapies

- Denosumab
- SERMs: lasofoxifene, bazedoxifene
- Strontium
  - strontium ranelate
  - strontium malonate
- Anti-sclerostin antibody
- Cathepsin K inhibitor – odanacatib
- Cyclic analog of PTH (1-31)
- Calcium receptor antagonist – "calcilytic"

Cathepsin K and Bone Resorption

Cathepsin K is highly expressed in the osteoclast, where it is localized in the lysosomes and released during bone resorption.

Rodan S.E. Duong in T. BoneKey 2008

Cathepsin K Inhibitor – Odanacatib (MK-0822)

- Denosumab
- SERMs: lasofoxifene, bazedoxifene
- Strontium
  - strontium ranelate
  - strontium malonate
- Anti-sclerostin antibody
- Cathepsin K inhibitor – odanacatib
- Cyclic analog of PTH (1-31)
- Calcium receptor antagonist – "calcilytic"
**Ostabolin-C – Cyclic Analog of PTH (1-31)**
- Phase II trial results – 1-year increases in BMD
- N=261; postmenopausal women with BMD T-score ≤ -2
- Doses: 7.5, 15, 30 or 45 mcg/day subcutaneously
- Results
  - Spinal BMD (45 mcg dose) – 11% increase
  - Total Hip BMD (45 mcg dose) – 2.4% increase
  - P1NP: >120% increase; osteocalcin: >100% increase
- Adverse events
  - Mild nausea – transient
  - Hypercalcemia - infrequent
  - Pulmonary inhalation – Phase I

**New and Emerging Therapies**
- Denosumab
- SERMs: lasofoxifene, bazedoxifene
- Strontium
  - strontium ranelate
  - strontium malonate
- Anti-sclerostin antibody
- Cathepsin K inhibitor – odanacatib
- Cyclic analog of PTH (1-31)
- Calcium receptor antagonist – "calcilytic"

**Calcium Receptor (CaR) Antagonist: “Calcilytic”**
- Antagonism of the CaR in the parathyroid gland stimulates endogenous PTH secretion
- Short-term pharmacokinetic studies are modestly encouraging

**Treatment: Summary**
Safe and effective therapies are available

**Antiresorptive agents**
- Prevent bone loss and preserve architecture
- Improve quality of bone
- Reduce the risk of vertebral fractures (all agents)
- Alendronate, risedronate, zoledronic acid and denosumab proven to reduce the risk of nonvertebral and hip fractures

**Anabolic agent: rhPTH [1-34] (teriparatide)**
- Increases bone density and size
- Improves quality of bone
- Reduces the risk of vertebral and nonvertebral fractures; no hip fracture data

Patient factors determine the most appropriate drug to use
The risk of fracture is determined by the complex interactions among bone mineral density (BMD), bone quality and trauma.

Contemporary pharmacologic treatments will typically reduce vertebral fracture risk by 30%-70%, with smaller reductions in non-vertebral fracture risk.

No pharmacologic treatment is likely to reduce fracture risk to zero, in part because of the inability to eliminate trauma.

There are a number of promising pharmacologic agents—with most of the emphasis to be placed on the development of novel anabolic agents.

### Drugs to Treat Osteoporosis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Cost per year[^1]</th>
<th>Effect on Fracture Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raloxifene</td>
<td>$976</td>
<td>✓</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>$1517[^*]</td>
<td>✓</td>
</tr>
<tr>
<td>Brand alendronate</td>
<td>$1103</td>
<td>✓ ✓ ✓</td>
</tr>
<tr>
<td>Generic alendronate</td>
<td>$108</td>
<td>✓ ✓ ✓</td>
</tr>
<tr>
<td>Risedronate</td>
<td>$1110</td>
<td>✓ ✓ ✓</td>
</tr>
<tr>
<td>Ibandronate (oral)</td>
<td>$1024</td>
<td>✓ ✓ ✓</td>
</tr>
<tr>
<td>Ibandronate (IV)</td>
<td>$1938</td>
<td>✓ ✓ ✓</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>$1249</td>
<td>✓ ✓ ✓</td>
</tr>
<tr>
<td>Denosumab</td>
<td>$1650</td>
<td>✓ ✓ ✓</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>$9786</td>
<td>✓ ✓ ✓</td>
</tr>
</tbody>
</table>

[^1]: Average Wholesale Price varies by region and distributor.  

Vert: antifracture efficacy proven in clinical trial  
--: antifracture efficacy not proven in clinical trial