New Drugs for Osteoporosis and Bone Disorders

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Objectives

- Brief review of mechanism
- Osteoporosis drugs
  - New Anabolics
    - Sclerostin antibodies
    - PTH analogs
  - New Antiresorptive
    - Cathepsin K inhibitor
  - Discontinued strategies
- Rare bone diseases
  - Hypophosphatasia

Effective treatments require understanding bone remodeling

Treatment goals: 
1. Bone formation
2. Bone turnover

Disclosures

- Edward Hsiao receives research grant support from Clementia Pharmaceuticals for unrelated clinical trials. He has no conflicts of interest.
- This presentation includes discussion of off-label, investigational use of a commercial product, or drugs that are not FDA approved.
- Care should be guided by expert opinion and literature. As always, we encourage the application of sound clinical judgment on a case-by-case basis.
### Current Treatments for Osteoporosis

<table>
<thead>
<tr>
<th>Increase Bone Formation</th>
<th>Decrease Bone Turnover</th>
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<td>- Parathyroid hormone (PTH, Teriparatide)</td>
<td>- Hormone Therapy (HT)</td>
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<td>- Calcitonin (Miacalcin)</td>
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<td>- Zoledronate (Reclast/Aclasta)</td>
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<td>- (Strontium ranelate)</td>
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<td>- RANKL inhibitors</td>
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<td>- Denosumab (Prolia)</td>
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### Recent Changes in Drugs for Osteoporosis

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<tr>
<th>Anabolics</th>
<th>Antiresorptives</th>
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<tr>
<td>- Anti-sclerostin antibodies</td>
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<td>- PTHrP analog</td>
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**Sclerostin is a Key Mediator of Bone Formation**

[Schematic diagram showing the role of sclerostin in bone formation pathways](image)

Anti-Sclerostin Antibody #1: Romosozumab

- Romosozumab (Amgen/UCB: AMG785, CDP7851)
  - Humanized monoclonal antibody

- Phase 1 study:
  - Single dose of AMG785, 72 men and women;
  - Peak serum concentration achieved after 1 week (72 mg/kg)
  - Half life of 11-18 days
  - Dose ranging was done from 0.1-10 mg/kg
    - 10 mg/kg (maximum dose tested)
    - 120-184% increase in P1NP, BSAP, Osteocalcin
    - 54% decrease in CTX
    - Largest BMD effect at day 85
    - +5.3% lumbar spine BMD
    - +2.8% in total hip BMD

Romosozumab: Phase I

- Additional Phase I study
  - Multiple doses
  - 32 postmenopausal women with low bone mass
    - 6 doses, 1-2 mg/kg every 2 weeks, or
    - 3 doses of 2-34 mg/kg every 4 weeks, or placebo
  - 16 healthy men with low bone mass.
    - 1 mg/kg every 2 weeks, or
    - 3 mg/kg every 4 weeks, or placebo

Romosozumab: Phase II

- 419 postmenopausal women
  - T score between -2.0 and -3.5 in spine, total hip or femoral neck.
  - Monthly sq (70, 140, or 210 mg) or every 3 months (140 or 210 mg), for 12 months
  - Open label comparison to
    - Alendronate 70 mg weekly
    - Teriparatide 20 ug/day
Romosozumab Gives Higher Increase in BMD

- Every 3 months – same as 70 mg/mo dose
  - Approx. 5% increase in BMD at spine
  - Bone formation markers return to normal after 6-12 mo

Romosozumab: Phase III

- Recent announcements indicate that it meets goals, but full publications pending
  - STRUCTURE trial (Sept 2015 press release)
    - 436 postmenopausal women previously treated with bisphosphonates
    - Romosozumab vs teriparatide
    - Met goals for total hip BMD
  - FRAME trial (Feb. 2016 press release)
    - 7180 patients, 210 mg sq/month
    - Reduced incidence of new vertebral fractures at 12 and 24 mo
    - Reduced incidence of clinical fractures at 12 mo
    - Unclear benefit for non-clinical fractures at 12 and 24 mo.

Romosozumab Side Effects (Reported in Phase I-III)

- Injection site reactions
- No clear increase in serious adverse events over alendronate, teriparatide
- 20% develop binding antibodies, with 3% showing in vitro blocking ability, but subjects still showed biologic response
- Awaiting results of Phase III for full profile

Anti-sclerostin Antibody #2: Blosozumab

- Humanized monoclonal antibody
  - Eli Lilly (LY2541546)
- Phase I trials
  - Single and multiple dose regimens tolerated up to 750 mg every 2 weeks for 8 wks
  - 3.4-7.7% increase in lumbar BMD at Day 85

McClim, et al. JBMR 2014
**Blosozumab: Phase II**

- 120 postmenopausal women, T score between -2.0 and -3.5

**Lumbar Spine**

**Total Hip**

Recker, et al. JBMR 2015

**Blosozumab: Phase II Durability of treatment**

- Followup study for 1 year post treatment
  - 88 of 120 women previously studied
  - Suggests antiresorptive will be needed

Recknor, et al. JBMR 2015

**Recent Changes in Drugs for Osteoporosis**

- **Anabolics**
  - Anti-sclerostin antibodies
    - Romosozumab
    - Bisfosozumab
  - PTHrP analog
    - Abaloparatide

- **Antiresorptives**
  - Cathepsin K inhibitor
    - Ondanacatib
  - New considerations for denosumab
  - Restrictions on strontium ranelate (in EU market)
  - Vibration Therapy

**Osteoblast Activation by PTHrP:**

- **Parathyroid Hormone Related Protein**

- PTHrP
- PTH

- Gs GPCR bone anabolic response

Treatment goals: Bone formation Bone turnover
**Abaloparatide: A PTHrP analog**

- Synthetic peptide analog of human PTHrP
- Phase II:
  - 24 weeks of daily sq injections
    - Postmenopausal women
    - 20, 40, or 80 ug vs 20 ug of teriparatide
  - Lumbar spine BMD increased 2.8-6.7%, vs 5.5% in teriparatide and 0.8% in placebo
  - Femoral neck increased 1.4-2.6%, vs 0.5% in teriparatide and 0.4% in placebo

Leiden, et al. JCEM 2015

**Abaloparatide: Phase III**

- ACTIVE fracture prevention trial
  - 2463 postmenopausal women
  - 18 mo daily 80 ug abaloparatide vs placebo vs 20 ug teriparatide.
  - 89% decrease in new fracture rate vs. placebo
  - Teriparatide showed an 80% decrease
    - No significant differences in wrist fractures
    - Increased BMD in spine and hip at 6, 12, and 18 months
  - Major complications: hypercalcemia, and injection site reactions.

- Extension trial in progress

**Recent Changes in Drugs for Osteoporosis**

- **Anabolics**
  - Anti-sclerostin antibodies
    - Romosozumab
    - Bisphosphonate
  - PTHrP analog
    - Abaloparatide

- **Antiresorptives**
  - Cathepsin K inhibitor
    - Odanacatib
  - New considerations for denosumab
  - Restrictions on strontium ranelate (in EU market)
  - Vibration Therapy

**Cathepsin K: Functions in Osteoclast Resorption Pits**

- Resorbs bone
- Cathepsin K
  - secreted by osteoclasts
  - cleaves helical collagen
  - induces bone resorption

- Treatment goals: Bone formation, Bone turnover
Ondanacatib: Anti-Cathepsin K

- Related to two other Cathepsin K inhibitors
  - Relacatib: nonselective inhibitor of K, L, V, and S
    - No clinical information
    - Kumar, et al. Bone 2007 (monkey model)
  - Balicatib: showed BMD increases, but had cutaneous adverse events.
    - Adami, et al. JBMR 2006
- Ondanacatib: selective for Cathepsin K and orally bioavailable.
  - Bone, et al. JBMR 2009

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  - PTHrP analog
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Denosumab

- Human monoclonal antibody that inhibits RANKL (required for osteoclast function and survival)
- Given 60 mg sq every 6 months over 3 years reduces fracture risk (FREEDOM) and Freedom extension

<table>
<thead>
<tr>
<th></th>
<th>Vertebral</th>
<th>Non-vertebral</th>
<th>Hip</th>
<th>N (Ref #)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate (10 mg/yr)</td>
<td>0.56 (0.43-0.69)</td>
<td>0.84 (0.74-0.94)</td>
<td>0.60 (0.40-0.92)</td>
<td>12,068 (2)</td>
</tr>
<tr>
<td>Zoledronate (5 mg/yr)</td>
<td>0.30 (0.24-0.38)</td>
<td>0.75 (0.64-0.87)</td>
<td>0.59 (0.42-0.83)</td>
<td>7,765 (1)</td>
</tr>
<tr>
<td>Denosumab (60 mg sq q6m)</td>
<td>0.95* (0.86-0.97)</td>
<td>0.95 (0.85-1.0)</td>
<td>0.95 (0.85-0.97)</td>
<td>7966 (3)</td>
</tr>
</tbody>
</table>

* Hazard ratios (secondary endpoints of study)

3. Cummings, et al. NEJM 2009 (FREEDOM)
Long-term Denosumab Use

- FREEDOM extension (total of 5 years) just reported, with persistent gains in BMD and fracture risk (1).
- Transition from alendronate to 1 year of denosumab appears safe and may have a slightly improved BMD (no fracture data) (2).
- Likely cost effective, particularly for patients with low compliance to bisphosphonates (3,4).
- Main complications:
  - Skin infection, urinary tract infection, dermatitis/eczema rash.
  - ONJ reported in cancer patients receiving high doses (120 mg every 4 weeks) of denosumab (5,6) and was seen in 2 patients in the FREEDOM extension (1).
  - Likely occurs at same rate as bisphosphonates, during clinical trials.

References:
1. Papaioannou, et al. JBMR 2011
2. Textor, et al. JBMR 2013
5. Smith, et al., Lancet 2012 (Prostate cancer)

Antiresorptives May Have Direct Anti-Tumor Effects

- Denosumab
  - Increased disease free survival in breast cancer (no overall survival data; vs. placebo) (1).
  - Prolongs survival in lung cancer vs. zoledronate (2).
  - Delay metastasis in prostate cancer (3) probably better than zoledronate (4).
- Zoledronic Acid
  - Does not work as an adjuvant for early breast cancer, but does reduce bone metastases (5).

References:
3. Smith et al., Lancet 2012

Meet Thy Neighbor...

Recent Changes in Drugs for Osteoporosis

- Anabolics
  - Anti-sclerostin antibodies
    - Romosozumab
    - Blinostat
  - PTHrP analog
    - Abaloparatide
- Antiresorptives
  - Cathepsin K inhibitor
    - Orlanacatib
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**Strontium Ranelate Restrictions in EU Market**

- Was never FDA approved in the US
  - Previously approved by the EMA in Europe

- Often confused with other forms, such as strontium citrate (available in health food stores)
  - Other forms not studied for bone, so unknown efficacy or toxicity

**Strontium Ranelate Current Recommendations**

- Reportedly increased incidence of cardiovascular events in multiple randomized control trials

- Unclear if this is also seen in real life, as trials may have had higher proportion of subjects with cardiovascular disease

- Recommendation to restrict to severe osteoporosis patients only, and only in patients with low baseline cardiovascular risk (though specifics are still vague)

**Vibration Therapy for Osteoporosis?**

- Originally developed for space flight
  - Vibrations for 25-30 Hz at 0.3 x g can prevent bone loss
  - Vibration studies in sheep forelimbs (20 min/day 5 days/week) can increase bone formation in limbs
  - Seemed potentially useful for osteoporosis

**Vibration Therapy is Falling out of Favor**

- Human trials have been quite variable, with some suggesting gain but others not

- Best trial is of 202 postmenopausal women
  - 30 vib/min, 20 min per day, 0.3 x g (low energy)
  - 90 vib/min, 20 min per day, 0.3 x g

- After 1 year – no difference in BMD

- Main adverse events: dizziness, fainting due to passive standing x 20 min.
Vibration Therapy is not FDA Approved

- Often sold on the internet, and many devices have higher energies (> 1 x g)
- Currently, no FDA oversight for devices
- Being investigated for other situations, such as spinal cord injury
- Vibration exposure is regulated in the workplace as a hazard

Objectives

- Brief review of mechanism
- Osteoporosis drugs
  - New Anabolics
    - Sclerostin antibodies
    - PTHrP analog
  - New Antiresorptive
    - Cathepsin K inhibitor
    - Discontinued strategies
- Rare bone diseases
  - Hypophosphatasia

Hypophosphatasia: treatment by enzyme replacement

- Deficiency of tissue non-specific alkaline phosphatase (ALPL/TNSALP)
  - Partial or complete loss of function
  - Hypomineralization, respiratory compromise
  - Mild forms may show progressive osteomalacia; poor dentition
  - Multiple mutations have been identified
  - Increase pyridoxal 5’ phosphate (PLP), phosphoethanolamine (PEP), and PPI

Major Forms of Hypophosphatasia

- Perinatal – usually autosomal recessive
  - Respiratory distress, renal failure, soft bones
- Adult form – usually partial mutations, heterozygous
  - Skeletal manifestations, early dental loss
  - Low age adjusted alkaline phosphatase
- Traditional treatments:
  - Optimization of calcium and vitamin D
  - Treatment for craniosynostosis
  - Experimental treatments with teriparatide to favor mineralization
Asfotase alfa – a new drug for Hypophosphatasia

- Recombinant TNSAP (ENB-0040) with a peptide tag to target specifically to bone
  - Improved respiratory outcome for infantile form (76% vs 5% from historical controls)
  - Improved skeletal findings; increased PTH levels, requiring calcium supplements

Asfotase Alfa Approval

- FDA approved for perinatal, infantile, and juvenile onset hypophosphatasia
- Also approved in the EU
- Injections 3-6 times/week
- Currently being studied for adult HPP

Conclusions

- Several new medications for osteoporosis and other bone diseases coming to market soon
- New anabolic drugs
  - Anti-Sclerostin Antibodies: Romosozumab and Blosozumab
  - PTHP Analog: abaloparatide
- New anti-resorptive
  - Cathepsin K blocker: Odanacatib
- Novel breakthrough medication for HPP: Asfotase Alfa
- Continued research on indications and complications

“I hear and I forget.
I see and I remember.
I do and I understand.”

- Confucius
Additional Resources

- Vibration therapy: