Old and Possible New Treatments for Osteoporosis: How Do We Choose?

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Osteoporosis Treatment Options - 2013

- Anti-remodeling agents (inhibit bone turnover)
  - Bisphosphonates (oral and IV)
  - Estrogen agonists/antagonist (raloxifene)
  - RANK ligand inhibitor (denosumab)
  - Calcitonin

- Remodeling stimulator (increases formation and resorption)
  - Parathyroid hormone (teriparatide)

- Other (no effect on bone turnover)
  - Strontium ranelate (not available in USA)

Osteoporosis Treatment 2013: Benefits

1. Effective protection from fractures
   - Vertebral fracture by 60-70%
   - Multiple vertebral fractures by 75-96%
   - Hip fracture by 40-50%
   - Non-vertebral fracture by 20-35%

2. Multiple dosing options
3. In general are well tolerated
4. In clinical trials, have been very safe

Choosing Among Treatments for Osteoporosis

- No head-to-head fracture studies in postmenopausal osteoporosis
- Patient populations studied in clinical trials differ among studies
- Very difficult to compare efficacy among drugs

Choosing Among Treatments for Osteoporosis

- Bisphosphonates: always a first line option in absence of contraindications (swallowing difficulties, impaired renal function) or concerns about GI absorption of oral drugs
- Calcitonin: not an appropriate treatment; may be withdrawn from US market
- Raloxifene: appropriate for younger postmenopausal women at risk for spine but not hip fracture, especially if there are concerns about breast cancer risk
- Denosumab: first line option; not contraindicated with impaired renal function. Theoretical concerns about use in immuno-compromised patients
- Teriparatide: for patients at very high risk of spine fracture; effects on hip fracture risks not known. Of special interest in patients on glucocorticoid therapy
Osteoporosis Treatment 2013: Limitations

- Real or perceived intolerance
- Concerns about safety, especially the long-term safety of bisphosphonates
- Inconvenient or awkward dosing regimens
- Poor adherence to therapy
- No agent restores skeletal structure or strength to normal levels
  - i.e., no “cure” for osteoporosis
- Expense

CAT-K and Its Inhibition

- Cathepsin K is major proteolytic enzyme secreted by osteoclasts. It’s action required to resorb bone.
- Genetic deficiency - pycnodysostosis
  - Short stature, high bone mass with skeletal fragility
  - Gelb et al., 1996; Schilling et al 2007

- Inhibition in animals:
  - Decreased bone resorption
  - Increased periosteal bone formation
  - Increased cortical thickness in the radius (30%) and femur

Odanacatib: Bone Mineral Density: 5 Years

- Phase II – 5 year follow-up
  - Modest decrease in bone resorption with little effect on bone formation
  - Progressive increase BMD over 5 years
  - No major safety issues

- Phase III:
  - Event-driven, randomized, placebo-controlled, multi-center, spine and hip fracture endpoint trial
  - >16,000 postmenopausal women with osteoporosis
  - DSMB recently recommended stopping Phase 3 trial because of “robust” efficacy
  - Results and filing anticipated in 2014

http://www.huffingtonpost.com/2012/07/12/odanacatib-osteoporosis-drug-fracture_b_1666631.html
What Will Odanacatib Offer?

- Another option
- Unique mechanism of action
  - anti-resorptive with minimal effect on formation
  - indirect "anabolic" agent
- Better efficacy - possibly
- Different tolerability and safety profile
- Possible combinations with anabolic agents

M McClung. Personal opinion

Anti-remodeling Agents: What They Do Not Do

- Bone Formation
  - Normalize BMD
  - Restore trabecular architecture
  - Increase bone formation

Images Courtesy of Dr. David Dempster

Osteoporosis Treatment: Mechanisms

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Genetic Disorders of LRP5/Wnt Signaling Pathway

- Loss of LRP5 function
  - Osteoporosis pseudoglioma syndrome
  - Activating mutation of LRP5
    - High bone mass
    - Sclerostosis & van Buchem’s Disease
      - Increased bone mass throughout the skeleton
      - Very low fracture risk
    - Due to absence or deficiency of sclerostin (SOST) - a bone formation inhibitor
      - Heterozygotes have increased bone mass and no other abnormalities

LRP5/Wnt Signaling Pathway

BMP  →  PTH  →  LRP5/Wnt  →  β-catenin

LRP5 binding to Wnt receptor activates intracellular β-catenin cascade resulting in increased osteoblast activity and bone formation

Altered transcription of several genes

Enhanced bone formation

Sclerostin and LRP5/Wnt Signaling Pathway

BMP  →  PTH  →  SOST  →  Dkk1

Mechanical Load

β-catenin

Altered transcription of several genes

Enhanced bone formation
Effects of Sclerostin Inhibition

Phase I and II studies in humans:
- Early, marked but transient increase in markers of bone formation
- Modest, persistent reduction in bone resorption
- Substantial increase in BMD
- Phase III studies are underway
- Other anti-sclerostin agents are under development

What Might Anti-sclerostin Therapy Offer?
- Longer duration of "anabolic window"
- Possibility of "cure" with short-term treatment
- Caveat: Tissue specificity is required
  - stimulation of only bone formation
  - no off-target effects

Choosing Among Therapies: Summary
- We have therapies that effectively prevent bone loss and significantly reduce fracture risk in patients with osteoporosis.
- No single treatment is ideal for all patients
- Every drug has its place and its limitations
- In choosing a drug for our patients, we must consider
  - convenience of dosing
  - strength of evidence of fracture protection
  - tolerability
  - serious safety concerns
  - cost

Choosing Among Therapies: Summary
- Recent insights into regulation of bone remodeling are leading to exciting new treatment strategies
- In the future, we will likely use drugs in sequence or combination
- Matching therapy to the needs of the patient is the clinical challenge