THE GROWING GAP IN OSTEOPOROSIS TREATMENT

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DISCLOSURES
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NONE
OVERALL CONCLUSIONS

• There has been remarkable progress in our understanding of the pathogenesis of osteoporosis and new drugs available to treat the disease

• However, despite this remarkable progress in drug development, there are major challenges to implementing appropriate treatment

APPROVED (US FDA) THERAPIES FOR OSTEOPOROSIS (1988)

<table>
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<th>Anti-resorptive</th>
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POST-MENOPAUSAL OSTEOPOROSIS

F. Albright, Trans Assoc Am Physicians 55:298, 1940

- “There is considerable circumstantial evidence that the stimulus for the osteoblasts to lay down an organic matrix is mechanical stresses and strains. Hence, one of the most clear-cut causes of osteoporosis is lack of such stresses and strains, which leads to ‘atrophy of disuse.’ (Disuse Osteoporosis)

- “Furthermore, just as very elderly people have atrophy of their hair, skin, and tissues in general so do they have atrophy of their bones. This is ‘senile osteoporosis.’ (Senile osteoporosis, Type II osteoporosis)
POST-MENOPAUSAL OSTEOPOROSIS
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• “But we are concerned here with a condition which, until recently, we have been forced to call idiopathic osteoporosis. This condition involves primarily the spine and pelvis, to a much lesser extent the long bones, and least of all the skull.”

• “A survey of 42 such cases sixty-five years or under showed that 40 were women after the menopause; there were only two males; there were no cases in women before the menopause. This form of osteoporosis was found in several women of the pre-menopause age, who had undergone a surgical menopause. In brief, it is our belief that idiopathic osteoporosis is post-menopausal osteoporosis. (Post-menopausal osteoporosis, Type I osteoporosis)
OSTEOPOROSIS: DRUG DEVELOPMENT

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### BISPHOSPHONATES: HISTORY

- Chemically stable analogues of pyrophosphate compounds, which are found widely in nature
- Naturally occurring pyrophosphate (PPi), which circulates in the body as an endogenous "water softener"
- Early uses of bisphosphonates mainly as corrosion inhibitors and as complexing agents in the textile, fertilizer and oil industries
- Subsequently found to inhibit calcification and later found to inhibit bone resorption
- Underlying mechanisms worked out decades after clinical use had been initiated

**Russell RG. Bone 49:2, 2011**
FRACTURE RISK REDUCTION WITH BISPHOSPHONATES

KOHLA et al. JCEM 97:2272, 2012

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## PTH THERAPY FOR OSTEOPOROSIS

- Clinical observation: Chronic parathyroid excess causes marked bone loss due to increased bone resorption, but also increase in bone formation (*Fuller Albright*).
- Animal, and then human, studies showed that in contrast to continuous exposure, intermittent exposure of bone to PTH increases bone formation with smaller increases in bone resorption (*Reeve et al. Lancet*, 1976).
- Abaloparatide is a PTHrP analog drug with perhaps some advantages over teriparatide (*Miller et al. JAMA* 316:722, 2016).
- Despite intensive investigation, the underlying mechanisms for the anabolic effects of intermittent PTH on bone remain unclear.
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OSTEOPROTEGERIN (OPG)

- Transgenic mice overexpressing OPG had marked osteopetrosis due to a profound decrease in osteoclasts
- Mice with targeted ablation of OPG developed severe osteoporosis as well as arterial calcifications (Bucay et al. Genes Dev 12:1260, 1998)

OPGL/RANKL

- Identical to two previously known members of the TNF ligand family (TRANCE, RANKL)
- With M-CSF, RANKL is both necessary and sufficient for osteoclast development
- RANKL KO mice have severe osteopetrosis, defects in T/B cell differentiation, lack lymph nodes, and defects in mammary gland development (Kong et al. Nature 397:315, 1999; Fata et al. Cell 103:41, 1999)
**RANK**

- Once OPGL/RANKL identified as the ligand for OPG, the receptor for RANKL identified easily, as already known to be RANK
- RANK KO mice also had profound osteopetrosis and lacked lymph nodes (Li et al. PNAS 97:1566, 2000)

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**OSTEOBLAST REGULATION OF OSTEOCLAST FORMATION/FUNCTION**

Stimulatory Factors

- IL-6
- IL-7
- PGE$_2$
- GM-CSF

Inhibitory Factors

- RANKL

OC PRECURSORS

- Differentiation and activation

OSTEOBLASTS/OSTEOCYTES

ACTIVE OC

OC APOPTOSIS
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**WNT SIGNALING AND BONE: FROM RARE DISEASES TO A NOVEL THERAPEUTIC**

- Rare families with inactivating mutations in LRP5 which resulted in osteoporosis (Gong et al. Cell 107:513, 2001)
- Conversely, activating mutations in LRP5 led to high bone mass (Little et al. Am J Hum Genet 70:11, 2002; Boyden et al. NEJM 246:1513, 2002)

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CATHEPSIN K INHIBITORS
Background

- Cysteine protease expressed in osteoclasts which degrades the bone matrix
- Mutations in the cathepsin K gene cause pycnodysostosis (Toulouse-Lautrec syndrome): osteosclerosis, abnormalities of the head, face, and spine
- Cathepsin K knock out mice have a similar phenotype (Saftig et al. PNAS 95:13453, 1998)

ODANACATIB: PHASE III TRIAL

- Long-Term Odanacatib Fracture Trial (LOFT)
- 16,713 postmenopausal women, age ≥ 65 yrs
- Unpublished (ASBMR abstract) results:
  - 54% reduction in morphometric vertebral fractures
  - 47% reduction in clinical hip fractures
  - 23% reduction in clinical non-vertebral fractures
  - 72% reduction in clinical vertebral fractures
ODANACATIB: PHASE III TRIAL (Cont’d)

- Adverse events:
  - Morphea (0.1% incidence)
  - No ONJ
  - “Atypical” atypical femur fractures: 10 in ODN group vs 0 in placebo
  - Significant increase in stroke risk (HR 1.32, 95% CI 1.02-1.70, P=0.03)

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SIMILAR PARADIGM SHIFT IN OTHER DISEASES: HYPERCHOLESTEROLEMIA


- Conversely, ~2% of black subjects found to have nonsense PCSK9 mutations, low LDL levels, and low CHD risk (Cohen et al. NEJM 354:1264, 2006)

- Thus, rare disease → underlying biology → new drug
OSTEOPOROSIS TREATMENT: REMARKABLE PROGRESS

• Remarkable progress over the past 25 years:
  - Offering estrogen to women, Ca/vit D to men to now estrogen, raloxifene, 4 bisphosphonates, teriparatide, denosumab, romosozumab, (odanacatib)

• Paradigm for drug development shifted from observational/opportunistic to pathway-based, driven by advances in fundamental bone biology/rare diseases

• A prime example of how investing in discovery science does, in fact, translate into novel therapeutics

OSTEOPOROSIS TREATMENT: REMARKABLE PROGRESS YET PROFOUND CHALLENGES

“Millions of Americans are missing out on a chance to avoid debilitating fractures from weakened bones, researchers say, because they are terrified of exceedingly rare side effects from drugs that can help them.”
US GOOGLE SEARCH ACTIVITY FOR FOSAMAX

PREVALENCE OF BISPHOSPHONATE USE FROM 1996 TO 2012

Jha et al. JBMR 30:2179, 2015
PROBABILITY OF OSTEOPOROSIS MEDICATION USE FOLLOWING HIP FRACTURE WITHIN 12 MONTHS AFTER DISCHARGE

Solomon et al. JBMR 29:1929, 2014

CHANGING HIP FRACTURE RATES: A CAUSE FOR CONCERN?

Lewiecki, et al. ASBMR 2016, 1077
THE PROBLEM FOR THE FIELD OF OSTEOPOROSIS

• Increasingly, patients who clearly need osteoporosis therapy are either not being offered or choosing not to take bisphosphonates (or other osteoporosis drugs) due to the fear of Atypical Femur Fractures (AFFs)
• Incidence estimates for AFFs with prolonged bisphosphonate use vary widely (3.2 to 50-100 in 100,000 person-years) (Shane et al. JBMR 29:1, 2014)
• Nonetheless, best estimates are that with bisphosphonate therapy, 80 to 5,000 fragility fractures would be prevented for every AFF possibly induced by treatment (Black and Rosen, NEJM 374:254, 2016)

THE PROBLEM FOR THE FIELD OF OSTEOPOROSIS (Cont’d)

• Patient/physician attitudes shaped by
  ▪ Media attention to AFFs
  ▪ Concern that they may be vastly under-reported

• Clear that simply quoting statistics to patients without carefully listening and addressing their concerns is not going to work
THE CHALLENGE

• Urgent need to demonstrate to patients that we have heard their concerns and are addressing them in the short-, intermediate- and long-terms

• Key is to diagnose AFFs before they occur and over the longer term, better identify those patients at increased risk even before starting osteoporosis medications

THE CASE FOR NEW DRUG DEVELOPMENT FOR OSTEOPOROSIS

• Still a huge public health problem: The number of women who will experience a fracture in one year exceeds the combined number of women who will experience incident breast cancer, myocardial infarction or stroke across all ethnic groups (Cauley et al. Osteoporosis Int 19:1717, 2008)

• Important gaps in the current therapeutic arsenal:
  - Fear of rare side-effects – need newer agents that lack these complications
  - Efficacy of bisphosphonates beyond 5 yrs unclear – still don’t have the “perfect” long-term anti-resorptive
  - Still a great need for new anabolic drugs – note that the “anabolic window” with teri-/abaloparatide or romosozumab is limited to 3-9 months
THE CASE FOR NEW DRUG DEVELOPMENT FOR OSTEOPOROSIS (Cont’d)

- NIH and pharma need to continue to prioritize osteoporosis as an important public health problem and invest in discovery and translation