NEW HORIZONS IN OSTEOPOROSIS THERAPY

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DISCLOSURES
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Investigator-initiated grant
Merck

No non-FDA approved recommendations
RISK ASSESSMENT

• All postmenopausal women and older men should be evaluated clinically for osteoporosis risk in order to determine the need for BMD testing

• In general, the more risk factors that are present, the greater the risk of fracture
RISK FACTORS FOR FRACTURE

- **Lifestyle** (low calcium intake, alcohol, smoking, vitamin D insufficiency)
- **Genetic disorders** (OGI, CF)
- **Hypogonadal states** (anorexia nervosa, ovarian failure)
- **Endocrine disorders** (Cushings, diabetes mellitus)
- **GI disorders** (Celiac disease, PBC)
- **Hematologic disorders** (myeloma, mast cell disease)
- **Rheumatic and auto-immune diseases** (RA, ankylosing spondylitis)
- **Miscellaneous diseases** (Depression, MS)
- **Medications** (glucocorticoids (> 5 mg/d of prednisone for > 3 months, GnRH agonists))
RISK FACTORS FOR FALLS

- Environmental risk factors
  - Low level lighting, obstacles, loose throw rugs, lack of assist devices in bathrooms, slippery outdoor conditions

- Medical risk factors
  - Age, arrhythmias, female gender, poor vision, previous fall, medications

- Neuromuscular risk factors
  - Poor balance, weak muscles, kyphosis, reduced proprioception
RISK FACTORS INCLUDED IN THE WHO 10-YR RISK MODEL
Increase risk independently of BMD

- Current age
- Gender
- A prior osteoporotic fracture (including morphometric VF)
- Femoral neck BMD
- Low BMI
- Ever long-term use of oral glucocorticoids
- RA
- Secondary osteoporosis
- Parental history of hip fracture
- Current smoking
- Alcohol intake (3 or more drinks/day)
FRAX CALCULATOR
http://www.shef.ac.uk/FRAX
USE OF FRAX IN THE US

• FRAX developed to calculate the 10-yr probability of a hip fracture and the 10-yr probability of any major osteoporotic fracture (defined as clinical vertebral, hip, forearm, or humerus fracture) taking into account femoral neck BMD and clinical risk factors

• WHO algorithm was calibrated to US fracture and mortality rates

• Economic modeling was performed to identify the 10-yr hip fracture risks above which it is cost-effective, from the societal perspective, to treat with pharmacologic agents
WHO SHOULD BE CONSIDERED FOR TREATMENT?
Postmenopausal women and men age 50 and older

- A hip or vertebral (clinical or morphometric) fracture
- T-score ≤ -2.5 at the femoral neck, total hip or spine after appropriate evaluation to exclude secondary causes
- Low bone mass (T-score between -1.0 and -2.5 at the femoral neck, total hip, or spine) and a 10-yr probability of hip fracture ≥ 3% or a 10-yr probability of a major osteoporosis-related fracture ≥ 20% based on the US-adapted WHO algorithm
The intervention threshold at each age is set at a risk equivalent to that associated with a prior fracture and, therefore rises with age. The proportion of women in the UK potentially eligible for treatment rises from 20 to 40% with age.\(^7\)
CURRENTLY APPROVED (US FDA) THERAPIES FOR OSTEOPOROSIS

**Anti-resorptive**

- Estrogen: Oral, transdermal
- SERM: Raloxifene
- Bisphosphonates: Alendronate, risedronate, ibandronate, zoledronic acid
- RANKL inhibitor: Denosumab

**Anabolic**

- PTH: Teriparatide
RALOXIFENE

• Approved at a dosage of 60 mg/day for the prevention and treatment of postmenopausal osteoporosis
• Reduces the risk of vertebral fractures by ~30% in patients with a prior vertebral fracture and by about 55% in patients without a prior vertebral fracture over 3 years
• Reduces the risk of invasive breast cancer
• Does not reduce the risk of CHD
• Increases risk of DVT, hot flashes
ESTROGEN + BAZEDOXIFENE

- 0.45 mg oral conjugated estrogen/20 mg bazedoxifene
- Approved for the treatment of hot flashes and prevention of osteoporosis
- Minimal/none uterine effects
- Not recommended for long term use
FRACTURE RISK REDUCTION WITH BISPHOSPHONATES

Khosla et al. JCEM 97:2272, 2012
POTENTIAL SIDE-EFFECTS OF BISPHOSPHONATES

• Oral: Difficulty swallowing, inflammation of the esophagus, gastric ulcer

• ONJ

• Sub-trochanteric fractures

• Atrial fibrillation with IV zolendronic acid
OSTEONECROSIS OF THE JAW

- 1-10% incidence with high dose iv bisphosphonate therapy
- With doses used for osteoporosis
  - Population-based data: 1 in 250,000 pt-yrs (0.0004%)
  - Surveys of oral and maxillofacial surgeons: 0.001-0.10%

Khosla et al. JBMR 22:1479, 2007
ATYPICAL FEMUR FRACTURES

- Absolute risk of 3.2-50 cases/100,000 pt-yrs

- Long term use may be associated with a higher risk (~100/100,000 pt-yrs)

Shane et al. JBMR 29:1, 2014
THE “DRUG HOLIDAY”

• Patients whose fracture risk has clearly been reduced by bisphosphonate therapy (BMD improved, no fractures on Rx) may be candidates.
• Not an attractive option for those who are still at high risk for fracture after 5 yrs of therapy (BMD still very low and/or intervening fracture).
• Empirical approach: Bisphosphonate stopped for 1-3 yrs until the return of bone resorption markers (CTX) into the mid-range of young adults.
• In high risk patient, some clinicians using teriparatide during the 2 year bisphosphonate holiday.
OSTEOBLAST REGULATION OF OSTEOCLAST FORMATION/FUNCTION

OSTEOBLASTS

Differentiation and activation

M-CSF

RANKL

OPG

PGE₂

GM-CSF

IL-6

IL-7

Stimulatory Factors

Inhibitory Factors

OC PRECURSORS

ACTIVE OC

OC APOPTOSIS

TGFβ

TGFβ

OSTEOPROGENITOR/OSTEOBLASTS
EFFECTS OF DENOSUMAB ON VERTEBRAL FRACTURES

Cummings et al. NEJM 361:756, 2009
EFFECTS OF DENOSUMAB ON HIP FRACTURES

Cummings et al. NEJM 361:756, 2009
TERIPARATIDE

- Approved at a dose of 20 μg/d for a maximum of 2 years for the treatment of postmenopausal osteoporosis/male osteoporosis/GIOP

- Decreases the risk of vertebral fractures by 65% and non-vertebral fractures by 53% after an average of 18 months of therapy
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THERAPEUTIC OPTIONS ON THE HORIZON

- Modulating Wnt signaling (sclerostin inhibition)
- Cathepsin K inhibition
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WNT SIGNALING IN BONE

WNT SIGNALING IN BONE (Cont’d)

EFFECTS OF SCLEROSTIN Ab ON BONE MASS AND STRUCTURE

Li et al. J Bone Miner Res 24:578, 2009
CHANGES IN BMD AND BONE VOLUME FRACTION

***P<0.001 vs OVX + vehicle

Li et al. J Bone Miner Res 24:578, 2009
EFFECTS ON BONE FORMATION

**MAR (μm/day) Comparison**

- **OVX**
  - SHAM
  - Vehicle
  - Scl-AbII

**BFR/BS (μm³/μm²/day) Comparison**

- **OVX**
  - SHAM
  - Vehicle
  - Scl-AbII

*P<0.05, ***P<0.001 vs OVX + vehicle

†††P<0.001 vs SHAM + vehicle
# DUAL EFFECTS ON OSTEOBLASTS AND OSTEOCLASTS

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Sham + vehicle</th>
<th>OVX + vehicle</th>
<th>OVX + Scl-AbII</th>
</tr>
</thead>
<tbody>
<tr>
<td>BV/TV (%)</td>
<td>15.3 ± 2.5</td>
<td>7.8 ± 1.6</td>
<td>15.9 ± 3.0</td>
</tr>
<tr>
<td>Tb.N (#/mm)</td>
<td>2.6 ± 0.3*</td>
<td>1.5 ± 0.2</td>
<td>1.4 ± 0.2†</td>
</tr>
<tr>
<td>Tb.Tb (μM)</td>
<td>56.3 ± 4.5</td>
<td>53.1 ± 5.1</td>
<td>108.4 ± 13.7‡§</td>
</tr>
<tr>
<td>Ob.S/BS (%)</td>
<td>2.0 ± 0.4</td>
<td>3.1 ± 1.0</td>
<td>10.0 ± 2.3*§</td>
</tr>
<tr>
<td>Oc.S/BS (%)</td>
<td>1.9 ± 0.3‡§</td>
<td>3.9 ± 0.8</td>
<td>0.9 ± 0.3*§</td>
</tr>
<tr>
<td>O.Th (μM)</td>
<td>2.6 ± 0.3</td>
<td>2.3 ± 0.1</td>
<td>3.2 ± 0.2†</td>
</tr>
<tr>
<td>OS/BS (%)</td>
<td>9.0 ± 1.7</td>
<td>18.8 ± 2.7</td>
<td>61.6 ± 7.3‡§</td>
</tr>
<tr>
<td>MS/BS (%)</td>
<td>5.7 ± 1.3</td>
<td>11.4 ± 2.4</td>
<td>65.2 ± 8.4‡§</td>
</tr>
<tr>
<td>MAR (μM/d)</td>
<td>0.58 ± 0.05</td>
<td>0.79 ± 0.09</td>
<td>1.36 ± 0.13‡§</td>
</tr>
<tr>
<td>BFR/BS (μm³/μm²/d)</td>
<td>0.04 ± 0.01</td>
<td>0.09 ± 0.02</td>
<td>0.96 ± 0.17‡§</td>
</tr>
<tr>
<td>MLT (d)</td>
<td>11.7 ± 3.7</td>
<td>7.7 ± 1.7</td>
<td>3.0 ± 0.8</td>
</tr>
</tbody>
</table>

Li et al. J Bone Miner Res 24:578, 2009
EFFECTS OF A SINGLE DOSE OF AMG 785 ON BONE TURNOVER IN WOMEN

AMG 785 (ROMOSOZUMAB): PHASE 2 TRIAL RESULTS - BMD

McClung et al., NEJM 370:412, 2014
AMG 785 (ROMOSOZUMAB): PHASE 2 TRIAL RESULTS – BONE TURNOVER
THERAPEUTIC OPTIONS ON THE HORIZON

- Modulating Wnt signaling (sclerostin inhibition)
- Cathepsin K inhibition
BONE REMODELING AND THE BONE REMODELING COMPARTMENT (BRC)

Khosla, Westendorf, and Oursler JCI 118:421, 2008
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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)
CATHEPSIN K INHIBITORS

- Balicatib (AAE581)
  - Development stopped because of morphea-like skin reactions in 9/709 (1.3%) of the subjects
  - Likely due to lack of specificity for cathepsin K and inhibition of cathepsins B and L, which are expressed in the skin
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- Odanacatib (ODN, MK-0822) has greater specificity for cathepsin K and is in Phase III trials
PHASE II STUDY OF ODN: BMD
Bone et al. JBMR 25:937, 2010

![Graphs showing weight loss data for different bone density measurements over 24 months for Placebo and ODN 50 mg groups.](image)

- **LS BMD**
- **FN BMD**
- **Total hip BMD**
- **One-third radius BMD**

**Data Summary**
- N = 399 for Placebo, N = 320 for ODN 50 mg

**Key Points**
- ODN 50 mg shows significant improvements in all measured bone density parameters compared to Placebo.
- Weighted LS mean % change from baseline increases over time for both groups, with ODN 50 mg showing a steeper increase.

**Further Analysis**
- Detailed analysis and statistical significance provided in the original publication.
PHASE II STUDY OF ODN: RESORPTION MARKERS
Bone et al. JBMR 25:937, 2010

- Placebo
- ODN 50 mg

uNTx, nmol/mmol

sCTx, ng/mL

Geometric weighted LS mean change from baseline

N = 399  N = 320

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PHASE II STUDY OF ODN: FORMATION MARKERS
Bone et al. JBMR 25:937, 2010

sBSAP, ng/mL

Geometric weighted LS mean change from baseline

N = 399
N = 320

sP1NP, ng/mL

Geometric weighted LS mean change from baseline

N = 399
N = 320
• Increase in BMD at multiple sites
• Decrease in bone resorption
• Transient decrease in bone formation; at baseline by 24 months
• No significant skin reactions
ODANACATIB: 5 YEAR EXTENSION DATA

Mean % change from baseline (SE)

Lumbar Spine

- PBO/PBO
- 50 mg/PBO/PBO
- 50mg/50mg/50mg

Total Hip

- PBO/PBO
- 50 mg/PBO/PBO
- 50mg/50mg/50mg

SUMMARY OF ODN STUDIES IN OVX’D MONKEYS

- Preservation of bone mass at multiple sites
- Increase in relatively normal appearing osteoclasts on bone surfaces
- Decrease in bone resorption markers
- Decrease in trabecular bone formation rates
- Increase in periosteal bone formation rates

SCHEMATIC OF THE BONE REMODELING COMPARTMENT
PROPOSED MECHANISMS FOR OSTEOCLAST-OSTEOBLAST COUPLING

Release of growth factors from bone matrix → Net effect on bone formation

Direct effects

Osteoclast  →  Osteoblast

EFFECTS OF BISPHEROSPHONATATES, DENOSUMAB ON OSTEOCLAST-OSTEOBLAST COUPLING

Bisphosphonates, denosumab

EFFECTS OF BISPHOSPHONATES, DENOSUMAB VERSUS ODN ON OSTEOCLAST-OSTEOBLAST COUPLING

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Bisphosphonates, denosumab

ODN

Release of growth factors from bone matrix → Direct effects → Osteoclast

Net effect on bone formation → Osteoblast

Release of growth factors from bone matrix → Direct effects → Osteoclast

Net effect on bone formation → Osteoblast

or no change
OSTEOCLAST CONDITIONED MEDIA STIMULATES MINERALIZATION

Pederson et al. PNAS 105:20764, 2008
MARROW-DERIVED OSTEOCLAST COUPLING FACTOR EXPRESSION

Pederson et al. PNAS 105:20764, 2008
Osteoclast-specific Cathepsin K deletion leads to:

- Increased bone mass
- Increased bone formation and osteoblast numbers
- Preservation/increase in osteoclast numbers

Lotinum et al. JCI 123:666, 2013
UPREGULATION OF SPHK1 FOLLOWING OSTEOCLAST-SPECIFIC DELETION OF CATHEPSIN K
S1P is an important “clastokine” upregulated following Cat K deficiency.

Lotinum et al. JCI 123:666, 2013
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- RANKL inhibitor: Denosumab

**Anabolic**
- PTH: Teriparatide

**Mixed**
- Sclerostin antibody: Romosozumab
- Cathepsin K inhibitor: Odanacatib
RESEARCH SUPPORT

National Institute on Aging

National Institute of Arthritis and Musculoskeletal and Skin Diseases

MAYO CTSA

MAYO FOUNDATION