Mechanisms of Anabolic Therapies for Osteoporosis

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Conflicts of Interest
Associate Editor- UpToDate
NEJM
Outline

- Anabolics
  - How do they work?
    • Work of the osteoblast?
    • Formation > Resorption
    • Increase osteoblast progenitors

- PTH, PTHrp, Romosozumab
  - Drugs:
    • PTH
    • Abaloparatide-PTHrp
    • Romosozumab
    • Others????

### PTH1R Agonists That Activate the Anabolic Program

![Diagram showing PTH and PTHrp actions on osteoclastic and osteoblastic pathways.](image)
Effect of PTH (1-34) on lumbar spine BMD

Effect of Teriparatide on Incidence of Vertebral and Non-Vertebral Fractures in Postmenopausal Women with Osteoporosis

Patients (%) with fracture

New vertebral fracture

Non-vertebral fractures

P< 0.01

P< 0.01

Patients (% with fracture)

Placebo 20 μg PTH

Placebo 20 μg PTH

0 2 4 6 8 10 12 14 16 18 20

0 2 4 6 8 10 12 14 16 18 20

65%

53%

How do Anabolic Agents Increase the Work of the Osteoblast?

Baseline

Follow-up

Patient 1124

B3D-MC-GHAC

UCSF - Jiang

Female, age 65

Duration of therapy: 637 days (approx 21 mos)

BMD Change:

⇒ Lumbar Spine: +7.4% (group mean = 9.7 ± 7.4%)

⇒ Total Hip: +5.2% (group mean = 2.6 ± 4.9%)

Major Clinical Trials With Teriparatide

• Reduction in vertebral (65%) and non-vertebral (53%) fractures (Neer et al. N Eng J Med. 2001)
• As effective in women with mild or severe previous fragility fractures (Gallagher et al. 2004)
• As effective in women with 1, 2 or more previous fragility fractures (Gallagher et al. 2004)
• Reduced back pain (McClung et al. 2005; Miller et al. 2006)

PTH Light!!

Does once weekly PTH work?
Biochemical Markers of Bone Turnover with PTH once weekly

- Mean Change CTX (%)
- Mean Change P1NP (%)

Graphs showing changes in bone markers over time with PTH treatment compared to placebo.
PTH once weekly Fracture Trial-56ug: 1-34

Nakumara, 2012

FIG. 1. Trial profile

FIG. 2. Incidence of new fractures during the 72-wk study period was confirmed by radiology. A. Kaplan-Meier method, statistical significance assessed by a log-rank test. RR, Relative risk. B: Incidence values of new vertebral fractures assessed every 24 wk by Fisher’s exact test. 95% CI is presented for the results of fracture incidence. C: Incidence of clinical fragility fracture in the teriparatide group were significantly reduced compared with placebo.
Abaloparatide (BA058): Introduction

Abaloparatide is a novel analog of hPTHrP (1-34)

<table>
<thead>
<tr>
<th></th>
<th>Abaloparatide</th>
<th>Placebo</th>
<th>Teriparatide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>68.9 (6.5)</td>
<td>68.7 (6.5)</td>
<td>68.8 (6.6)</td>
</tr>
<tr>
<td>Time since menopause, mean (SD), y</td>
<td>20.6 (8.3)</td>
<td>19.9 (8.1)</td>
<td>20.8 (8.2)</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>61.1 (10.0)</td>
<td>61.2 (10.2)</td>
<td>61.2 (10.3)</td>
</tr>
<tr>
<td>Body mass index, mean (SD)*</td>
<td>25.0 (3.5)</td>
<td>25.1 (3.6)</td>
<td>25.2 (3.6)</td>
</tr>
<tr>
<td>Race, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>663 (80.5)</td>
<td>655 (79.8)</td>
<td>645 (78.9)</td>
</tr>
<tr>
<td>Asian</td>
<td>128 (15.5)</td>
<td>131 (16.0)</td>
<td>137 (16.7)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>26 (3.2)</td>
<td>23 (2.8)</td>
<td>24 (2.9)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (0.8)</td>
<td>12 (1.5)</td>
<td>12 (1.5)</td>
</tr>
<tr>
<td>T score, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoral neck</td>
<td>-2.3 (0.6)</td>
<td>-2.2 (0.7)</td>
<td>-2.1 (0.7)</td>
</tr>
<tr>
<td>Total hip</td>
<td>-1.9 (0.7)</td>
<td>-1.9 (0.8)</td>
<td>-1.9 (0.8)</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>-2.9 (0.9)</td>
<td>-2.9 (0.8)</td>
<td>-2.9 (0.9)</td>
</tr>
<tr>
<td>Bone mass density, mean (SD), g/cm²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoral neck</td>
<td>0.730 (0.094)</td>
<td>0.732 (0.099)</td>
<td>0.732 (0.096)</td>
</tr>
<tr>
<td>Total hip</td>
<td>0.766 (0.090)</td>
<td>0.767 (0.098)</td>
<td>0.773 (0.094)</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>0.829 (0.109)</td>
<td>0.823 (0.100)</td>
<td>0.831 (0.108)</td>
</tr>
<tr>
<td>≥1 Prior vertebral fracture(s), No. (%)</td>
<td>177 (21.5)</td>
<td>188 (22.9)</td>
<td>220 (26.9)</td>
</tr>
<tr>
<td>No history of prior fracture, No. (%)</td>
<td>305 (37.0)</td>
<td>307 (37.4)</td>
<td>308 (37.7)</td>
</tr>
</tbody>
</table>
Figure 2. Change From Baseline in Bone Mineral Density

Fracture Efficacy for Abaloparatide
How Does PTH or PTHrp Work?

Wein et al, *Nature Communications*, 2
OB Choices for Fuel Utilization

Glucose → Pyruvate → Lactate

"Warburg effect"
"glycolysis"
ATP+NADH

Acety-CoA → TCA

"glutaminolysis"
ATP+NADH

AMPK

Normal metabolism

Tumor metabolism

Long et al, 2014
Aerobic glycolysis in bone: lactate production and gradients in calvaria - PTH induces glycolysis

W. F. Neuman, M. W. Neuman, R. Brommage
American Journal of Physiology - Cell Physiology
Jan 1978

What happens if we reduce or prevent PTH1R activation?

![Diagram showing the effects of PTH on bone metabolism](attachment:bone_metabolism_diagram.png)
PTH1R deletion in pre-OBs

Fan et al, Cell Metabolism, 2017
Hypoparathyroidism- High BMAT and Decreases with PTH

MSC Fate in the Marrow Niche

PTH in the Marrow Niche

osteoblast

PGDGR
C/EBPs
Zif423
Zifp467
Prx1

Pre-OB
ColIa1, Ocn, BSP

Runx2, Prx1, Sp7

mesenchymal stromal cell (mMSC)

Pre-adipocyte
Pref-1

PPARG, Fabp4, Pim1, FASN

adipocyte

Ocy

??

??
• PTH and PTHrp stimulate bone formation and resorption- Super-remodelers
• Fracture efficacy established for both
• PTH stimulates progenitor differentiation and glycolysis via actions on IGF-I, SOST, and Sik2
• PTH inhibits adipocyte differentiation

Antibodies to Sclerostin: The Next New Anabolic?
Sclerosteosis

A member of Dan/Cerb family

- Expressed in Bone…limited synthesis in non skeletal tissue
  - Osteocytes
  - Increased by BMP and during osteoblast differentiation
- PTH down regulates
- High affinity for BMP 6, 7 not 2 or 4
- A BMP and Wnt antagonist (binds LRP5)
Increased bone mass throughout skeleton.
Good quality, fracture resistant bone.

Photo: Janssens and Van Hul.

Sclerostin

Osteocyte
LRP5 signaling pathway: Inactivation by Dkk proteins

LRP5 signaling pathway for osteogeneiss: Canonical Pathway; SOST Blocks WNT-Lrp5 signaling
Inhibition of Sclerostin by Monoclonal Antibody Increases Bone Formation, Bone Mass, and Bone Strength in Aged Male Rats

Xiangdong Li,1 Kelly S Warmington,1 Qing-Tian Niu,1 Franklin J Asuncion,1 Mauricio Barrero,1 Mario Grisanti,1 Denise Dwyer,1 Brian Stouch,1 Theingi M Thway,2 Marina Stolina,1 Michael S Rinsky,1 Paul J Kostenuik,1 William S Simonet,1 Chris Paszty,1 and Hua Zhu Ke1

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Monoclonal to Sclerostin vs Alendronate and PTH

Fig. 2.
Romozosumab Reduces Fractures
Summary: New Anabolic Treatments

- PTH builds bone by suppressing SOST, stimulating glycolysis and shifting progenitors towards OBs
- Abaloparatide enters the market as a PTH like agent at lower cost and possibly greater benefit?
- Monoclonal antibodies to sclerostin increase bone mass by enhancing the work of bone formation
- Romosozumab works but safety has not been fully established due to potential cardiovascular risk