New Therapeutic Directions: Osteoanabolic and Antiresorptive Therapy in Combination Therapy and in Sequence

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Amgen (Consultant, Advisory Board)
Shire Pharmaceuticals (Consultant)
Radius Pharmaceuticals (Advisory Board)
Ultragenyx (Consultant)
Regeneron (DSMB)
Approaches to Combination or Sequential Therapy with Antiresorptives
Why consider double antiresorptive therapy simultaneously?

- Ultimate effects are similar (e.g. reduced bone turnover) among the antiresorptives although the individual mechanisms for their effects are different

- Possible benefits by virtue of different specific mechanisms
Why not consider double antiresorptive therapy simultaneously?

- Little evidence for efficacy of combined antiresorptive therapy
- Possible harm if antiresorptive effect already is maximal
- Greater expense
- Potential for more adverse effects
Why consider sequential therapy with one antiresorptive following another?

- Intolerance to one antiresorptive
- Restarting antiresorptive therapy after a ‘drug holiday’
- Take advantage of a different mechanism of action of two different antiresorptive classes
- Whims and fears of doctors and patients!
Alendronate to Denosumab (STAND Trial)

Effects of Treatment on BMD Over 12 Months

Percent Change From Baseline (Least Squares Mean ± 95% CI)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percent Change</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate 70 mg QW (n = 241)</td>
<td>3.03%</td>
<td>(2.63%, 3.44%)</td>
</tr>
<tr>
<td>Denosumab 60 mg Q6M (n = 246)</td>
<td>1.85%</td>
<td>(1.44%, 2.26%)</td>
</tr>
</tbody>
</table>

Total Hip (primary endpoint)

Lumbar Spine (secondary endpoint)

Study Month

n = number of patients who have a baseline and ≥ 1 postbaseline evaluation.

*P < 0.05; †P < 0.01; CI = confidence interval

Denosumab and Alendronate (DAPS Trial)

Cross-over Treatment after 12 Months

Adapted from: McClung MR, et al. ISCD. 2010

Percent Change From Baseline (Least Squares Mean ± 95% CI)

Denosumab

Alendronate

Treatment naïve patients

Lumbar spine

Total hip

* P <0.05 vs baseline
Denosumab and Alendronate (DAPS Trial)

Cross-over Treatment after 12 Months

Adapted from: McClung MR, et al. ISCD. 2010

Percent Change From Baseline
(Least Squares Mean ± 95% CI)

Denosumab
Alendronate

Lumbar spine

2.8% *

Total hip

1.5% *

* P <0.05 vs 12 months

Adapted from: McClung MR, et al. ISCD. 2010
Denosumab and Alendronate (DAPS Trial)
Cross-over Treatment after 12 Months

Adapted from: McClung MR, et al. ISCD. 2010

Percent Change From Baseline (Least Squares Mean ± 95% CI)

- Lumbar spine
  - Denosumab
  - Alendronate
  - ALN to DMab: Additional gains
  - DMab to ALN: No additional gains

- Total hip
  - Denosumab
  - Alendronate
  - ALN to DMab: Additional gains
  - DMab to ALN: No additional gains

Months

Adapted from: McClung MR, et al. ISCD. 2010
Approaches to Combination or Sequential Therapy with Bisphosphonates/other antiresorptives and PTH

1. Antiresorptive | PTH
2. Antiresorptive | PTH
3. PTH | Antiresorptive
Rationale for considering antiresorptive and osteoanabolic therapy in sequence or in combination

- Take advantage of different cellular and biochemical mechanisms of action
- Limitations of use of osteoanabolic therapy to 2 years and consequences of stopping without follow up therapy
- Concerns about long term use of antiresorptives
Sequential Therapy (BP → PTH)

• Many patients who receive PTH fall into this category
• The more potent the bisphosphonate to reduce bone turnover the greater the delay in subsequent PTH response (Ettinger, 2004; Miller, 2008)
• The delay in response to PTH is not always seen
Sequential Therapy (BP → PTH)

- If there is a delay, it is not clearly related to reduced bone turnover.
- Most patients respond eventually to PTH, irrespective of the prior use of BP.
- It probably doesn’t matter which BP is used and whether one “waits” a few months after BP before starting PTH.

Miller et al. JCEM, 2008
Sequential Therapy (Dénosumab → PTH)

- Small increases in lumbar spine BMD (much less than PTH to Dénosumab or combination to Dénosumab)

- Smaller increases in femoral neck BMD (much less than PTH to Dénosumab or combination to Dénosumab)

- Reduction in distal 1/3 radius BMD

Leder et al., Lancet, 2015
Rationale for combination antiresorptive/osteoanabolic therapy

- Would take advantage of two different mechanisms of action
- Would prevent the increase in PTH-associated bone resorption that may limit the actions of PTH
PTH as an Anabolic Agent for Bone: A Kinetic Model

Index of Bone Turnover

“Anabolic window”

Bone Resorption Markers

Bone Formation Markers

Peak

Months
PTH plus Alendronate: PATH Study

- 238 women with PMO.
- Randomized to alendronate 10 mg/day, hPTH-(1-84) 100 ug/day, or both for 12 months
PTH plus Alendronate: PATH Study

Black et al NEJM 2003
- **Antiresorptive**
  - **PTH**

- **PTH and ALN:** Monotherapy with PTH gives a better BMD response than combination therapy---(ALN “too potent?”)---

- **PTH and Raloxifene**

- **PTH and Zoledronic Acid**

- **PTH and Denosumab**
Combination antiresorptive and anabolic therapy

- PTH and Alendronate
- Teriparatide and Raloxifene (Deal et al, 2005)

- 137 postmenopausal
- Average age, 66
- Teriparatide alone or
  Teriparatide + Raloxifene
- Lumbar spine T-score: -2.80
Teriparatide and Raloxifene: Changes in Bone Turnover Markers

A
Mean CTx (ppm/L)

B
Mean PINP (μg/L)

Change in N-terminal propeptide of type 1 collagen (PINP)

Change in C-telopeptide of type 1 collagen (CTx)

TPTD
TPTD + RLX

Teriparatide and Raloxifene: Changes in Bone Mineral Density

*"p = 0.01 for CTX and 0.04 for hip BMD

Combination antiresorptive and anabolic therapy

• Alendronate and PTH (Black et al, 2003, Finkelstein et al, 2003)
• Raloxifene and Teriparatide (Deal et al, 2005)
• Zoledronic acid and Teriparatide (Cosman et al. 2011)
Objectives

- **Primary**
  - Non-inferiority: Combination therapy with a single Zoledronic acid infusion and daily TPTD vs TPTD alone on lumbar spine BMD at 1 year

- **Secondary**
  - % increase in total hip BMD at all time points
  - % increase in spine BMD at earlier time points
  - Changes in bone turnover markers (β-CTx and P1NP)

_F. Cosman, E.F. Eriksen, C. Recknor, et al._
_J Bone Miner Res, 2011_
Study Overview
(Cosman et al. J Bone Miner Res, 2011)

- Partial double-blind, randomized, multicenter
  - 412 treatment-naive women (45-87 years)
  - T score ≤−2.5 at the femoral neck, total hip, or spine
  - T score ≤−2.0 at any site, plus ≥1 documented osteoporosis related fracture

- 3 active treatment groups, well matched
  - Zoledronic acid 5 mg i.v. at baseline
  - Zoledronic acid 5 mg i.v. at baseline + TPTD 20 μg/day
  - Placebo i.v. at baseline + TPTD 20 μg/day

- One-year follow-up

1 All patients received oral daily calcium (1000-1200 mg) and 400-800 IU vitamin D
Changes in Serum $\beta$-CTx and P1NP
(Cosman et al. J Bone Miner Research, 2011)

**Serum $\beta$-CTx**

*Premenopausal reference range for serum $\beta$-CTx (95% CI): 0.114–0.628 ng/mL\(^1\); †premenopausal reference range for serum PINP (95% CI): 16.3–78.2 ng/mL\(^1\)

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Changes in Lumbar Spine BMD (%)  
(Cosman et al. J Bone Miner Research, 2011)

**Mean % Change in BMD**‡

* *P<0.0001 vs TPTD alone and vs ZOL alone*

† *P<0.0001 vs ZOL alone*
Changes in Total Hip and Femoral Neck BMD (%)  
(Cosman et al. ASBMR, 2009)

[Graph showing changes in BMD for Total Hip and Femoral Neck over weeks.]

<table>
<thead>
<tr>
<th>Mean % Change in BMD‡</th>
<th>Total Hip</th>
<th>Femoral Neck</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ZOL+ TPTD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TPTD alone</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ZOL alone</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

‡least-squares mean (LSM) % changes, controlled for country.

Data on File, Novartis.

*P<0.05 vs TPTD alone
†P<0.05 vs ZOL alone
Combination antiresorptive and anabolic therapy

- **Alendronate and PTH** (Black et al, 2003, Finkelstein et al, 2003)
- **Raloxifene and Teriparatide** (Deal et al, 2005)
- **Zoledronic acid and Teriparatide** (Cosman et al. 2011)
Combination Denosumab and PTH Therapy

- PTH
- Denosumab
- Runx2-expressing osteoblast progenitor
- cAMP/PKA
- CREB
- P
- RANKL
- OPG
- Anabolism
- Catabolism

Factors:
- BMP
- Wnt
- SOST
- Smad4
- β-catenin
- TCF
- CtBP
- TFS
- PTH
- cAMP/PKA
-Denosumab
- Anabolism
- Catabolism
Teriparatide and Denosumab
(Tsai JN et al. Lancet May 15, 2013)

- Design: Randomized, open label
- Study Population: postmenopausal women (> 45 yrs) at high risk for fracture
- Endpoint: Change in BMD
- 3 arms: Teriparatide (20 ug daily) or Denosumab (60 mg q 6 mos) alone or in combination
- Numbers of subjects in each group: 29-33
CLINICAL TRIALS AND MECHANISMS OF THERAPEUTICS: COMBINATION THERAPY WITH DENOSUMAB AND TERIPARATIDE

(Leder et al, JCEM, 2014)

N=100 divided equally among Teriparatide (20 ug daily); Denosumab (60 mg q 6mos); and combination. 83 completed the study.

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Figure 3  Mean (SE) percentage changes in bone-turnover markers (A) Teriparatide. (B) Denosumab alone and teriparatide and denosumab combined. Data for the teriparatide-alone group are shown separately for clarity. *p<0·001 vs denosumab and vs combi...
Aim: Effect of combination Rx on peripheral cortical and trabecular BMD and microstructure

- 94 postmenopausal women: Teriparatide or Denosumab or both for 24 months.
- HRpQCT at 0, 3, 6, 12, 18, and 24 months

Results of combination therapy:
- Tibia: Increased vBMD, cortical vBMD, cortical thickness more than either drug alone
Figure. Mean percent change (SEM) from baseline in bone density and microarchitecture at 24 months.

- ** Total vBMD
- Trab vBMD
- Cort vBMD
- Cort Th

* p value <0.05 compared to baseline for overall 0-24 month change.
** p value <0.05 compared to 12 months for 12-24 month change.

- a p value <0.05 versus teriparatide alone.
- b p value <0.05 versus denosumab alone.

Tsai et al., J Bone Miner Res, 2015
Estimated Strength

Tibia: Failure Load

Tsai et al, 2015
BMD comparisons among studies that employed PTH and an Antiresorptive

Spine BMD

FN BMD

DATA Study
Tsai et al, 2013

Zoledronic Acid Study
Cosman et al. JBMR 2011

PATH Study
Black et al. NEJM 2003
# Single Antiresorptive vs Combination Therapy with DMAB and Teriparatide

## 24-month change in BMD

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Spine</th>
<th>Total Hip</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alendronate</strong></td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>antiresorptive-bisphosphonate</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Zoledronic acid</strong></td>
<td>5-6%</td>
<td>3-4%</td>
</tr>
<tr>
<td>antiresorptive-bisphosphonate</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Denosumab</strong></td>
<td>6-8%</td>
<td>3-4%</td>
</tr>
<tr>
<td>antiresorptive-RANKL-inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Teriparatide</strong></td>
<td>8%</td>
<td>1-2%</td>
</tr>
<tr>
<td>anabolic-PTH analog</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Combination DMAB+TPTD</strong></td>
<td>13%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Limitations to simultaneous combination regimens and their variations

- Bone density and bone markers are only end points
- No long term data
- Limited data on bone quality
- No fracture data
Sequential Therapy

Bisphosphonate
Estrogen
Denosumab
PTH

Treatment followed by no treatment

• A truth for all therapies except the bisphosphonates:
• When treatment is stopped, bone density will rapidly fall with concerns about an increase in fracture risk.
Why do we stop therapy?

- Osteoporosis is virtually the only chronic disease for which therapy is stopped (compare with hypercholesterolemia, hypertension, hyperuricemia, stone disease, etc.)
- Therapies for these chronic disorders also have side effects
- But, we are caught in a vicious cycle of publicity about rare side effects, one of which (AFF) is confounding because it is a fracture!
Osteoporosis Wheel of Fear*

*courtesy of M. Lewiecki, 2018
Sequential Therapy (PTH → BP)

- When PTH is not followed by an bisphosphonate or other antiresorptive, bone density rapidly falls (Kurland, Bilezikian, 2002; Black, 2005)
Change in QCT Trabecular Spine BMD Over 24 Months of Treatment

Sequential Therapy

- Gains with teriparatide are further enhanced (Leder et al, 2015)
Bone Mineral Density

![Lumbar Spine Graph](chart1)

- TPTD→DMAB
- COMBO→DMAB

![Total Hip Graph](chart2)

- TPTD→DMAB
- COMBO→DMAB
Sequential Therapy

- When Denosumab is stopped.....
Brown et al. Discontinuation of Denosumab and Associated Fracture Incidence: Analysis from FREEDOM and Its Extension (ASBMR, 2016)

Serum CTX-1

Lumbar Spine BMD

Includes subjects who enrolled in the off-treatment phase


CTX-1: collagen type 1 C-telopeptide; Q1, Q3: first, third quartile; BMD: bone mineral density; CI: confidence interval
Brown et al. Discontinuation of Denosumab and Associated Fracture Incidence: Analysis from FREEDOM and Its Extension (ASBMR, 2016)

Background: When denosumab is discontinued, BTM rise and BMD falls acutely

Question: Is fracture incidence also increased upon discontinuation of denosumab?

Design: At least 2 doses; followed for > 7 mos; original Rx and crossover arms included (n=1001)

Results:
- New Vert Fx incidence increased in those with and without prior fractures when denosumab was discontinued
#1100: Brown et al. Discontinuation of Denosumab and Associated Fracture Incidence: Analysis from FREEDOM and Its Extension

**All Subjects**

- Placebo: 7.0 (Subj-yrs = 832.5, 363.8)
- Denosumab: 8.0 (Subj-yrs = 4033.3, 786.7)

**Subjects With Prior Vertebral Fracture**

- Placebo: 11.6 (Subj-yrs = 216.4, 83.2)
- Denosumab: 12.1 (Subj-yrs = 987.1, 157.31)

Vertebral Fracture Rate (per 100 Subject-years)

- On-treatment
- Off-treatment

Subj-yrs = Subject-years
Fractures after stopping Denosumab

**SHORT COMMUNICATION**

Rebound-associated vertebral fractures after discontinuation of denosumab—from clinic and biomechanics

A. W. Popp¹ • P. K. Zysset² • K. Lippuner¹

**CASE REPORT**

Severe spontaneous vertebral fractures after denosumab discontinuation: three case reports

B. Aubry-Rozière¹ • E. Gonzalez-Rodriguez¹ • D. Stoll¹ • O. Lamy¹

**LETTER**

Multiple clinical vertebral fractures following denosumab discontinuation

A. D. Anastasilakis¹ • P. Makras²
Comparison of 1001 subjects who discontinued Dmab during FREEDOM or FREEDOM Extension vs. 470 subjects who discontinued PBO

All received at least 2 doses Dmab or PBO and remained in study for at least 7 months after last dose

Spine X-rays were done at scheduled intervals (years 5, 6, 8, and 10 from FREEDOM baseline) and with unscheduled assessments for suspected clinical VFds

Endpoint was new or worsening VFds, especially multiple VFds

Cummings SR et al. J Bone Miner Res. 2017;Epub.
Discontinuation of Dmab vs. PBO

• Off-treatment overall VFs: no difference
  – VFs after stopping Dmab = 7.1 per 100 patient-yrs
  – VFs after stopping PBO = 8.5 per 100 patient-yrs
  – [Similar risk for NVFs in both groups]

• Off-treatment multiple VFs: more after Dmab
  – 61% of Dmab subjects with off-treatment VF had more than 1 vs. 39% of PBO subjects
  – Risk of multiple VFs was 3.4% after Dmab vs. 2.2% after PBO (P = 0.049)
  – Prior VF was greatest predictor of off-treatment multiple VFs
Fracture Risk after Discontinuation

Conclusions:

- Those with prior Vert Fx or who otherwise are at high risk should continue treatment
- Those who discontinue drug should be transitioned to another therapy
Sequential Therapy

- When teriparatide follows denosumab ....
Bone Mineral Density

Lumbar Spine

- TPTD→DMAB
- DMAB→TPTD
- COMBO→DMAB

Total Hip

- TPTD→DMAB
- DMAB→TPTD
- COMBO→DMAB

* indicates statistical significance.
Bone Turnover

Osteocalcin

C-telopeptide

% change vs months

TPTD→DMAB
DMAB→TPTD
COMBO→DMAB
Sequential Therapy

- When zoledronic acid follows denosumab .....
Bone Loss with ZOL After Dmab

Case series of 6 women receiving continuous Dmab for 7 years in FREEDOM and then given a single dose of ZOL 6 months after last dose of Dmab.

Bisphosphonates After Dmab

- Low uptake of ZOL to bone surfaces due to magnitude of suppression of bone turnover with Dmab
- ZOL 6 months after last dose of Dmab does not protect from bone loss
- Consider delay in dosing of ZOL beyond 6 months or oral BP
### Denosumab And Teriparatide Administration Study (DATA-follow-up)

<table>
<thead>
<tr>
<th></th>
<th>Follow-up therapy (n=28)</th>
<th>No follow-up therapy (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time between DATA and follow-up DXA</td>
<td>16 ± 5 months</td>
<td>15 ± 4</td>
</tr>
<tr>
<td>Time between DATA and treatment</td>
<td>4 ± 3 months (0-11 range)</td>
<td></td>
</tr>
<tr>
<td>Post-DATA treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SC denosumab (number)</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>IV zoledronic acid (number)</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Oral ibandronate (number)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Oral alendronate (number)</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Fractures in follow-up period</td>
<td>1 (tibia stress)</td>
<td>1 (patella)</td>
</tr>
</tbody>
</table>

Leder et al, 2017
Denosumab Followed by Denosumab vs Denosumab followed by a bisphosphonate (DATA-follow-up)

BMD changes in patients receiving follow-up therapy

Leder et al. Bone 2017
What to do when Denosumab is stopped?

- **Denosumab**
  - Not a good idea

- **Denosumab**
  - Teriparatide
  - There are concerns but data are limited

- **Denosumab**
  - Zoledronic Acid or other BP
  - Early data need to be followed up but reasonable
Position Statement on Dmab Discontinuation by European Calcified Tissue Society

- Potential increased risk of multiple VFs after Dmab discontinuation (weak level of evidence)

- Assess fracture risk after 5-years Dmab
  - High risk (T-score < -2.0 to -2.5, multiple VFs, high FRAX): continue up to 10 years and switch to BP*
  - Low risk (T-score > -2.0 or -2.5): consider stopping Dmab and switch to BP*

*Optimal BP regimen is not known

Approaches to Combination or Sequential Therapy

- **Antiresorptive**
  - **PTH**
  - Prompt or eventual gains are seen

- **Antiresorptive**
  - **PTH**
  - Denosumab and teriparatide - the most promising combination

- **PTH**
  - **Antiresorptive**
  - This sequence is needed to maintain densitometric gains with PTH

- **Denosumab**
  - **Antiresorptive**
  - This sequence is the most reasonable at this time