Osteoporosis: Where are we now? Where are we going?

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University of Wisconsin
School of Medicine & Public Health

Wisconsin Rheumatology Association Meeting
March 2018
Proposed Moratorium on Denosumab
Multiple clinical vertebral fractures following denosumab discontinuation

A. D. Anastasilakis¹ · P. Makras²

Severe spontaneous vertebral fractures after denosumab discontinuation: three case reports

B. Aubry-Rozier¹ · E. Gonzalez-Rodriguez¹ · D. Stoll¹ · O. Lamy¹

2016: Case reports of multiple fractures after stopping denosumab
Severe Rebound-Associated Vertebral Fractures After Denosumab Discontinuation: 9 Clinical Cases Report

Olivier Lamy, Elena Gonzalez-Rodriguez, Delphine Stoll, Didier Hans, and Bérengère Aubry-Rozier

Bone Unit, Lausanne University Hospital, 1011 Lausanne, Switzerland

9 women
50 spontaneous vertebral fractures
Most women had low risk of fracture
Fractures occurred 9-16 months after stopping DMAB
6 of the 9 women had FRAX scores <20%
6 women had no prior compression fracture
3 women had received only 2 doses of denosumab
Fractures occurred 9 to 16 months after stopping denosumab
Hip BMD returns to baseline after stopping denosumab

- 38 women 81±3 years old
- DMAB for ≥7 years in FREEDOM
- No osteoporosis Rx after DMAB
- BMD ~17 months later
- BMD dropped at all sites

Relative losses:
- 35% of gains in spine BMD
- 100% of gains in total hip BMD

CTX was high at 996±307 pg/mL (normal = 550±226 pg/mL)

Zanchetta, Osteoporosis Int 2018, Volume 29, Issue 1, pp 41–47
Fig. 1

Timing of bisphosphonate consolidation after denosumab cessation.
Vertebral fracture before or during denosumab increased odds of new fractures by almost four-fold
Declines in BMD after stopping denosumab vs teriparatide
Denosumab and Teriparatide Study (DATA)

BMD 1-2 years after study
No treatment led to drops in BMD
Drops are greater after stopping denosumab, vs teriparatide

Leder, Bone 2017;98:54-58
Zoledronate after Denosumab

One year after DMAB therapy ended, treatment with:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Spine BMD Retention</th>
<th>Hip BMD Retention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nothing</td>
<td>22%</td>
<td>8%</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>73%</td>
<td>87%</td>
</tr>
<tr>
<td>Risedronate</td>
<td>41%</td>
<td>64%</td>
</tr>
</tbody>
</table>

Horne, Calcif Tissue Int 2018; in press
Zoledronate infusions occurred 191-353 days after the last denosumab dose.

No clear relationship between timing of zoledronate dose and retention of BMD.
Summary of Denosumab Discontinuation

- After stopping denosumab, patients have a dramatic increase in bone resorption.
- Simultaneously, the hip and spine bone mineral density plummets toward baseline.
- In this setting, patients can experience multiple painful compression fractures.
- Fractures are more likely in patients with prior vertebral fractures, but also occur in patients with low FRAX scores and no prior fractures.
- Bisphosphonates offer an “exit strategy” from therapy.
Potential candidates for DMAB

- GFR <35 mL/min
- Not a candidate for anabolics due to prior use, patient refusal, risk of osteosarcoma, hyperparathyroidism, etc…
- Patient has taken 10 years of bisphosphonates and remains at high risk of fracture
- Adherence to oral or daily SQ therapy is low, and not candidate for zoledronate
- Failure to respond to other medications
Building a Better Anabolic Agent
Building a Better Anabolic Agent
Abaloparatide
Anabolic, with limited bone resorption

hPTH 1-34
(Forteo)

hPTHrP 1-34

Abaloparatide

100 % PTHrP
22
34
38 % PTHrP

Empirically inserted amino acids to maximize anabolic effect
Homology of amino acids between PTH and PTHrP
Abaloparatide

- Abaloparatide is a 34-amino acid peptide
  - Synthetic analogue of PTH related Peptide
- In preclinical and clinical studies abaloparatide:
  - Increased BMD
  - Improved bone microarchitecture
  - Increased bone strength
- Unique mechanism of action at the PTH1 receptor
  - Stimulates bone formation
  - Limited bone resorption, so potentially less hypercalcemia
  - Superior to teripartide

Doyle et al. ASBMR 2014; Bahar et al. ENDO 2015.
ACTIVE (Abaloparatide Comparator Trial In Vertebral Endpoints)

- Multicenter, multinational, double-blind 18 month trial
- Abaloparatide vs. placebo vs. teriparatide
- Postmenopausal women aged 49 to 86 years old
- T-score between -2.5 and -4.9 and
  - At least 2 grade 2 vertebral fractures or
  - One moderate vertebral fracture or
  - A non-vertebral major osteoporotic fracture within 5 years

Miller et al. JAMA 2016.
“ACTIVE” STUDY

Excluded if

- Over four compression fractures
- Less than 2 vertebrae could be assessed on DXA
- Unable to measure hip BMD
- Metabolic bone disease (high PTH or high alk phos)
- Malabsorption
- Bisphosphonate >3 months within past 5 years
- Denosumab within past year
- Osteosarcoma
ACTIVE Trial Design

Randomization

- Placebo (n=821)
- Abaloparatide 80 µg SC daily (n=824)
- Teriparatide 20 µg SC daily (n=818)

Calcium + vitamin D

N=2463

Miller et al. JAMA 2016.
**ACTIVE: Bone Mineral Density**

ITT Population, n=2463

Abaloparatide caused greater gains in femoral neck & spine BMD than teriparatide (†)

*p<.001 compared with placebo; †P<.01 compared with teriparatide. Missing BMD was imputed using last observation carried forward. Miller et al. JAMA 2016.
Percent with New Vertebral Fracture

96% reduction with abaloparatide vs. placebo
Percent with Major Osteoporotic Fracture

Abaloparatide vs. Placebo = 70% reduction
Abaloparatide vs. Teriparatide = 55% reduction

- Placebo n=711
- Abaloparatide-SC n=690
- Teriparatide n=717
Time to First Non-vertebral Fractures

Abalo superior to placebo

Logrank $P$-value = .049
Abaloparatide vs. placebo

Miller et al. JAMA 2016. ITT Population N=2463
and now for...Side Effects

- Abaloparatide caused less hypercalcemia than teriparatide
  - 3% vs. 6%, p=0.006
  - Defined as calcium corrected for albumin ≥10.7 mg/dL
- Abaloparatide group had significantly higher withdrawal rate due to side effects than placebo or teriparatide groups
  - 10% vs. 6% vs. 7%
- Common side effects:
  - Nausea  2%
  - Dizziness 1%
  - Headache 1%
  - Palpitations 1%
ACTIVE-Extend

Eligible if:
- Completed 18 months of therapy with abaloparatide or placebo
- Were >80% adherent to treatment
- Had no contraindication to alendronate

Excluded if:
- Treatment related serious adverse event
- Non compliant
- Withdrew from ACTIVE
ACTIVE and ACTIVExtend Trial Design

92% of completers entered extension n=1139

Placebo (821→637)

Abaloparatide (824→606)

Teriparatide 20 µg daily SC

Randomization

Month 6 12 18

6-month planned interim analysis

Alendronate 70 mg QW (n=581)

Alendronate 70 mg QW (n=558)

Full duration of extension, 24 months

*1-month gap in treatment allowed for rollover from ACTIVE to ACTIVExtend. †Investigators and patients remained blinded to original treatment assignment for the first 6 months of the extension study.

ACTIVExtend: Spine BMD

ITT Population N=1139
ACTIVATE: Total Hip BMD

ITT Population N=1139

ACTIVExtend: Femoral Neck BMD

ITT Population N=1139

ACTIVExtend: New Vertebral Fractures

Modified ITT Population
N=1112*
ACTIVExtend: Nonvertebral Fractures

ITT Population N=1139

New Kid on the Block?
Romosozumab

- Monoclonal antibody
- Binds to & inhibits sclerostin
- Sclerostin inhibition has dual effect on bone
  - Stimulates bone formation by promoting osteoblast number & activity
  - Reduces bone resorption by inhibiting RANK ligand expression
  - Increases BMD markedly
Arch Study Design

- Phase 3, multi-center randomized double blind trial

- Inclusion:
  - Postmenopausal woman
  - Hip T-score ≤-2.5 and
  - Fractures (≥1 moderate/severe, ≥2 mild compression or a hip fracture within 24 months)

- Exclusion:
  - Contraindication or unable to take bisphosphonate
ARCH Study Design

- Primary endpoint: clinical fractures and vertebral fractures at 24 months

- Secondary endpoints:
  - Changes in spine and hip BMD
  - Non-vertebral fractures
Arch Study Design

4093 Patients were enrolled

Double-Blind Period
- 2047 Received alendronate, 70 mg orally every wk

Open-Label Period
- Received alendronate, 70 mg orally every wk
- Daily calcium (500–1000 mg) and vitamin D (600–800 IU)

2046 Received romosozumab, 210 mg subcutaneously every mo

Primary Analysis
- Received alendronate, 70 mg orally every wk

Month
0 6 12 18 24 36

Radiography of the thoracic and lumbar spine
Dual-energy x-ray absorptiometry
Serum studies of bone-turnover markers

Bone Mineral Density & Bone Turnover

A Change in Bone Mineral Density at the Lumbar Spine
- Romosozumab (N=1750)
- Alendronate (N=1757)

B Change in Bone Mineral Density at the Total Hip
- Romosozumab (N=1826)
- Alendronate (N=1829)

C Change in P1NP Level
- Romosozumab (N=137)
- Alendronate (N=128)

D Change in β-CTX Level
- Romosozumab (N=137)
- Alendronate (N=127)
Incident Fractures

A. Incidence of New Vertebral Fracture

12 Months

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Alendronate (128/2047)</th>
<th>Romosozumab (82/2046)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk ratio</td>
<td>0.63</td>
<td>P=0.003</td>
</tr>
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</table>

24 Months

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Alendronate (243/2047)</th>
<th>Romosozumab (127/2046)</th>
</tr>
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<tbody>
<tr>
<td>Risk ratio</td>
<td>0.52</td>
<td>P&lt;0.001</td>
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B. First Clinical Fracture in Time-to-Event Analysis

C. First Nonvertebral Fracture in Time-to-Event Analysis

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Month</th>
</tr>
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<tbody>
<tr>
<td>Alendronate</td>
<td>0</td>
</tr>
<tr>
<td>Romosozumab</td>
<td>12</td>
</tr>
<tr>
<td>Alendronate→</td>
<td>24</td>
</tr>
<tr>
<td>Alendronate</td>
<td>36</td>
</tr>
<tr>
<td>Alendronate</td>
<td>48</td>
</tr>
<tr>
<td>Romosozumab→</td>
<td>6</td>
</tr>
<tr>
<td>Alendronate</td>
<td>12</td>
</tr>
<tr>
<td>Romosozumab</td>
<td>24</td>
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<td>36</td>
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<td>Romosozumab</td>
<td>48</td>
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<tr>
<td>Alendronate</td>
<td>48</td>
</tr>
<tr>
<td>Romosozumab→</td>
<td>6</td>
</tr>
<tr>
<td>Romosozumab</td>
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</table>

P<0.001

P=0.04
ARCH STUDY RESULTS

- At 24 months in 4,093 subjects, romosozumab compared to alendronate:
  - Reduced vertebral fracture by 50%
  - Reduced clinical fracture by 27%
  - Reduced non-vertebral fracture by 19%
  - Reduced hip fracture rate significantly
Concern about cardiovascular safety has delayed FDA approval
Serious cardiac AEs 2.5% romosozumab vs. 1.9% alendronate
Summary

- Denosumab is an effective treatment for osteoporosis but…
- Cessation of denosumab suddenly increases bone resorption, increases fracture risk and decreases BMD back toward baseline
- Bisphosphonate consolidation does not fully protect patients from BMD loss after stopping denosumab
- Abaloparatide is a new anabolic agent that increases BMD and reduces major osteoporotic fractures beyond the effects seen with teriparatide
- Romosozumab still under FDA review…. stay tuned
### 2018 Cost of One Year Rx

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost for one year, GoodRx.com</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>$108</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>$1,000 plus infusion charges</td>
</tr>
<tr>
<td>Denosumab</td>
<td>$2,900 plus injection charges</td>
</tr>
<tr>
<td>Abaloparatide</td>
<td>$19,400</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>$39,228 (for now)</td>
</tr>
</tbody>
</table>

**FDA NEWS**

**FDA denies Amneal request to block approvals of generic Forteo**

January 10, 2018

The FDA has rejected Amneal Pharmaceuticals’ citizen petition to refrain from approving any abbreviated new drug applications for generic versions of teriparatide as treatment for osteoporosis.
Top Therapeutic Classes Contributing to Pharmacy Spending for Specialty Drugs in 2006

- Rheumatoid arthritis: 25.2%
- Multiple sclerosis: 18.0%
- Cancer: 15.5%
- Growth hormone: 6.5%
- Anemia: 5.1%
- Anticoagulation: 4.6%
- Hepatitis C: 4.6%
- Other: 20.5%

*The drugs in this class may also be used to treat plaque psoriasis, Crohn's disease, ankylosing spondylitis, and other conditions. The class includes Enbrel®, Humira®, and Remicade®.

Can we afford a better osteoporosis drug?

- The average American citizen spends $858 annually on pharmaceutical drugs.
- In 19 other industrialized nations, this cost is $400 per person.
- Biologic drugs cost more than $1 billion/year.
- Four of the top ten biologics sold in US are used to treat RA.
The physician’s dilemma

- We want to treat our patients to get the best outcome possible
- Insurance plans must contain costs
- Government and society must contain costs
- Patients must also be able to afford their medications

Alendronate is first line therapy for osteoporosis
Expect more restrictions to using biologics
Questions?
## ADULTS ≥40 YEARS OLD WITHOUT CHILDBEARING
POTENTIAL

Fragility fracture *or*
Man ≥50 years old or postmenopausal women with T-score ≤-2.5 *or*
FRAX ≥10%

<table>
<thead>
<tr>
<th>No=Low Risk</th>
<th>Yes= Medium - High Risk</th>
</tr>
</thead>
</table>
| Calcium 1000-1200 mg/day  
vitamin D 600-800 IU/day  
Balanced diet, healthy weight, regular exercise, limit alcohol, avoid tobacco | Calcium, Vitamin D, healthy lifestyle, *plus* |
| Monitor | First-line: oral bisphosphonate  
2nd: IV bisphosphonate  
3rd: Teriparatide  
4th: Denosumab  
5th: Raloxifene (postmenopausal) |
**ADULTS <40 YEARS OLD**

Fragility fracture or
Z-score < -3 at spine or hip or
>10% loss of spine or hip BMD over one year and
continuing prednisone for ≥6 months at ≥7.5 mg/day

<table>
<thead>
<tr>
<th>No = Low Risk</th>
<th>Yes = Medium - High Risk (Fertile Women any age)</th>
<th>Yes = Medium - High Risk Non-fertile Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium 1200 mg/day vitamin D 600-800 IU/day Balanced diet, normal weight, exercise, limit alcohol, avoid tobacco</td>
<td>Calcium, Vitamin D, healthy lifestyle, <strong>plus</strong></td>
<td>Calcium, Vitamin D, healthy lifestyle, <strong>plus</strong></td>
</tr>
<tr>
<td>Monitor clinically every 12 months, repeat BMD if a risk factor listed above is noted</td>
<td>First-line: oral bisphosphonate 2nd: Teriparatide 3rd: IV bisphosphonates 4th: Denosumab (teratogen)</td>
<td>First line: oral bisphosphonate 2nd: IV bisphosphonates 3rd: Teriparatide 4th: Denosumab</td>
</tr>
<tr>
<td>√ BMD if risk factors</td>
<td>Repeat BMD in 2-3 years</td>
<td>Repeat BMD in 2-3 years</td>
</tr>
</tbody>
</table>
FRAME Study

7,180 patients were enrolled.

- **Double-Blind Period**
  - 3,591 received placebo subcutaneously every month
  - 3,589 received romosozumab, 210 mg subcutaneously every month
  - Daily calcium and vitamin D

- **Open-Label Period**
  - Received denosumab, 60 mg subcutaneously every 6 mo

- Extension study

**Month**

- Radiography of the thoracic and lumbar spine
  - Month 0, 6, 12, 18, 24

- Dual-energy x-ray absorptiometry
  - Month 0, 6, 12, 18, 24

- Serum studies of bone-turnover markers
  - Month 0, 6, 12, 18, 24
A  Incidence of New Vertebral Fracture

Risk ratio, 0.27
P<0.001

12 Mo

1.8% (59/3322)

0.5% (16/3321)

24 Mo

Risk ratio, 0.25
P<0.001

2.5% (84/3327)

0.6% (21/3325)

B  First Clinical Fracture in Time-to-Event Analysis

C  First Nonvertebral Fracture in Time-to-Event Analysis

No. at Risk
Placebo 3591 3316 3134 3037 2955
Romosozumab 3589 3317 3148 3050 2968

Month

No. at Risk
Placebo 3591 3318 3145 3052 2967
Romosozumab 3589 3318 3149 3051 2970
A Change in Bone Mineral Density at Lumbar Spine

B Change in Bone Mineral Density at Total Hip

C Change in Bone Mineral Density at Femoral Neck

D Change in P1NP Level

E Change in β-CTX Level
BMD at 24 Months

A  Change in Bone Mineral Density at Lumbar Spine

No. of Patients
Romosozumab 65
Placebo 61

B  Change in Bone Mineral Density at Total Hip

No. of Patients
Romosozumab 66
Placebo 62

Cosman et al. NEJM Oct 2016
Clinical Fractures

Nonvertebral and symptomatic vertebral fracture. Nonvertebral fractures comprised the majority (more than 85%) of clinical fractures. Kaplan Meier curve based on data through month 24. \( n = \) number of subjects at risk for event at time point of interest. \( P \)-value based on RRR.