2022 Santa Fe Bone Symposium

How long to treat, when to change, and how to change.

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DEFINITION OF OSTEOPOROSIS

- A skeletal disorder characterized by
  - compromised bone strength predisposing to
    - an increased risk of fracture.
- Bone strength reflects the integration of
two main features:
  - bone density and
  - bone quality.
Clinical Diagnosis of Osteoporosis

A low trauma fracture makes the diagnosis of osteoporosis INDEPENDENT of the T-score

Fractures “trump” T-scores
NOT ALL PATIENTS WITH FRACTURES HAVE “OSTEOPOROSIS”

**Rotterdam Study**

**Women**
- Non-vertebral fractures:
  - 44% Osteoporosis
  - 13% Normal BMD
  - 43% Low BMD
- Hip fractures:
  - 64% Osteoporosis
  - 31% Low BMD
  - 5% Normal BMD

**Men**
- Non-vertebral fractures:
  - 21% Osteoporosis
  - 61% Normal BMD
  - 18% Low BMD
- Hip fractures:
  - 39% Osteoporosis
  - 5% Normal BMD
  - 3% Low BMD

Suchit SCE et al. *Bone* 2004;34:195-202
Patients who Fracture with Normal BMD Have an abnormality in Bone Quality
Bone Strength

Bone Density

Bone Quality
How do we measure Bone Quality in Clinical Practice?
Dr. Paul Miller’s Patented Bone Quality Meter

$14.95
High Resolution Peripheral QCT: 80 microns
( Cheung A. et al. Curr Osteo Reports 2013)
Trabecular Bone Score
TBS

A partial measurement of bone quality

Hans D  Current Osteoporosis Reports  2017
Normal

Moderate Osteoporosis

Severe Osteoporosis

Courtesy Dr. A. Boyde
Methods Mol Bio 2019
Example of Different Bone Texture (TBS) Despite Same L1-L4 BMD

Two patients with Same L1-L4 BMD

Normal trabecular Bone architecture

Homogeneous: High TBS

TBS L1-L4: 1.457

Degraded trabecular bone architecture

Heterogeneous: Low TBS

TBS L1-L4: 1.132

Adapted from Silva et al. J Bone Miner Res. 2014, 29:518–530
TBS Data Can be Used to Adjust FRAX
Postmenopausal and Idiopathic Osteoporosis in men is a lifelong chronic disease. The pathophysiology does not go away, requiring long term treatment.
The Fundamental Pathophysiology of Osteoporosis

• Bone resorption exceeds bone formation.

• This is true for PMO, Idiopathic male osteoporosis, GIOP, Immobilization, Hyperparathyroidism.
Pharmacological Therapies to treat Osteoporosis
Early Studies With Bisphosphonates

"Diphosphonates Inhibit Hydroxyapatite Dissolution in vitro and Bone Resorption in Tissue Culture and in vivo"
Fleisch H, Russell RGG & Francis MD.
Science 165:1262-4, 1969

Inhibition of Modelling of Metaphysial Bone
The "Schenk Test"
Schenk, Merz, Muhlbäuer, Russell & Fleisch.
Calcified Tissue Research 11, 196-214, 1973
Bisphosphonates

• 1. Are not metabolized
• 2. Are retained within the skeleton and get re-cycled with each remodeling cycle: detach and go to other remodeling sites.
• 3. After a loading period, patients have their own “internal pharmacy.”
• 3. When we die, all of our skeletons will be preserved by bisphosphonates !!!!!!!

Pazianas M et al. Therapeutics and Clinical Risk Management 2010
Bisphosphonate Uptake and Release from Bone Surfaces

Low Affinity BP
- Weak uptake
- High detachment
- Low reattachment
- More diffusion in bone

High Affinity BP
- Avid uptake
- Low detachment
- High reattachment
- Less diffusion in bone

Russell RGG et al. personal communication
Do Bisphosphonates Improve Bone Density and is that increase in BMD associated with reduction of fracture risk?
Do Bisphosphonates Improve Bone Quality?

Pazianas M, Van der Geest S, and Miller PD
Bone Key Reports 2014. (Review)
Horizontal Trabeculae Are Maintained With Risedronate

OVX

Ris. Treated

Borah et al CTI 2003
When Bisphosphonates First Were Registered

• We did not know how long to use them.
• The Pharmacology of bisphosphates were well described.
• Treatment “Forever” seemed reasonable since osteoporosis is a (forever) chronic disease.
BISPHOSPHONATES
How Long to Treat?
For Life?
What Changed?

What we did not expect?
“Atypical” Fractures”

Watts NB and Diab D, J Clin Endocrinol Metab 2010;95:1555-1565
Bisphosphonate-Associated Atypical Femur Fractures Are Associated with Duration of Use

Incidence of atypical femur fractures according to duration of bisphosphonate exposure (unadjusted and age-adjusted, showing incidence and 95% confidence intervals)

Dell R et al JBMR 2012
WHAT
DESTROYED THE TRUST in
Bisphosphonates?
Main stream media
causes fractures of the thigh bone
Bisphosphonate Associated ASFF

1. Fractures not related to age or baseline T-score.
2. Typical hip fracture incident rate BEFORE alendronate: 463/100,000 pt yrs (in clinical trials with VCF rate of 800/100,000 pt yrs) and dropped with BP use to 384/100,000 pt yrs with use beyond 2 years but then has increased again to 544/100,000 pt yrs after discontinuation.
3. 10% atypical fractures seen in non-BP exposed patients.
4. Rare before 3 years of use of bisphosphonates.
5. BP Discontinuation: risk of ASFF drops off abruptly by 70% within 1 year, but may still occur.

Dell R et al JBMR 2012
The 2nd “BLOW” to Osteoporosis Care

The drop in DXA reimbursement for free-standing facilities from $139 to $37
US Hip Fracture Trends 2002-2015 in Women Age ≥ 65 Years with Medicare Part A and B Fee-for-service

- 11,464 additional hip fractures
- $459 million additional expenses
- 2,293 additional deaths

Adapted from Lewiecki EM et al. Osteoporos Int. 2018;29:717-722.
Bisphosphonate “Drug Holiday”

1. Not a topic of discussion when BP 1st launched
2. Became a consideration after July 9, 2002 (WHI JAMA publication) when BP Rx increased
3. Became more widely discussed after FLEX (Black D et al JAMA 2004), and the better science defining BP PK/PD became available.
4. FRAX™ also drove the drug holiday discussion in women (untreated) who had been at low risk before bisphosphonates were started.
5. Not a standard of care in the USA, until.......
FDA NEJM Perspective

• Recommend treatment for 3-5 years and consider discontinuation in “lower risk” patients but consider continuation in “higher risk” patients (prior fracture, older, BMD criteria for osteoporosis).

• Weak and inconclusive recommendations on what to do when discontinuation is begun.

Whitaker M et al NEJM 2012
Monitoring Bisphosphonate Drug Holidays

BMD and Serum CTX

Miller PD NEJM 2022
DMab Metabolism and Discontinuation

DMab is rapidly metabolized and its biological effect is gone by month 6

Miler PD. Therapeutic Advances in Musculoskeletal Diseases 2011
Retreatment: Effect of Denosumab on Serum CTX and BSAP

Median Serum CTX (μg/mL) vs. Months

Median BSAP (ng/mL) vs. Months

- Placebo
- Pooled
- 6 mg Q3M
- 14 mg Q6M
- 100 mg Q6M
- 60 mg Q6M
- Alendronate
- 14 mg Q3M
- Retreatment
- 210 mg Q6M

Miller PD et al BONE 2008
Very Few Reasons to Stop DMab

• 1. Refractoriness to therapy has not been demonstrated.
• 2. Intolerance is uncommon
• 3. Rare AFF (most have been on prior BP), there is no clear signal of any risk associated with the duration of therapy.
• 4. However, most patients discontinue (68% persistence after 24 months).
• 5. Physicians themselves may recommend that treatment be stopped after several years in patients whose BMD has increased sufficiently to move the patient above the threshold of osteoporosis and out of a high-risk category. Possible with BP; not with Dmab.
• 6. Fracture studies after discontinuation suggest increase fracture rates.

McClung MR  Osteoporosis Internat 2016
Denosumab for Life ?
Long Term Denosumab Data

Safety and Efficacy
Continued DMAb Treatment in the FREEDOM Extension for Up to 7 Years

- Maintained reduction in bone turnover
- Was associated with a low incidence of nonvertebral and clinical vertebral fractures
- Remained well tolerated

Placebo Long-term DMAb

Yearly Incidence of Nonvertebral Fractures (%)

- 1.0%
- 1.5%
- 2.0%
- 2.5%
- 3.0%
- 3.5%

FREEDOM EXTENSION

<table>
<thead>
<tr>
<th>Years of DMAb Treatment</th>
<th>Placebo</th>
<th>Long-term DMAb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.1%</td>
<td>2.6%</td>
</tr>
<tr>
<td>2</td>
<td>2.9%</td>
<td>2.1%</td>
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<tr>
<td>3</td>
<td>2.5%</td>
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<td>4</td>
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<td>5</td>
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<tr>
<td>6</td>
<td>1.8%</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>2.0%</td>
<td></td>
</tr>
</tbody>
</table>

n = number of subjects with ≥ 1 fracture. N = number of randomized subjects who remained on study at the beginning of each period.
Percentages for nonvertebral fractures are Kaplan-Meier estimates.

References:
Bone H et al 10 year data Lancet Diab Endo 2017
Ferrari S et al JCEM 2019
Cancel the denosumab holiday

M. R. McClung

Osteoporosis Internat 2016
Vertebral Fractures after Denosumab Discontinuation FREEDOM and Extension

*Prevalent Vertebral Fracture*

A: Any  B: Multiple

Gray bars off treatment

**Patient Disposition**

- Subjects discontinuing
  - > 7 months after last dose
  - N = 122 PBO, 255 Dmab

- Rate of vert fx Dmab dc
  - 12.1/100 (15.6 PBO)

- Multiple vert fx
  - 77.7% : Dmab dc
  - 44.9% : PBO dc

*Cummings SR, et al. JBMR 2018*
What if

You have to stop Denosumab?
What to Do After Stopping DMab

- Reclast doses after stopping DMab: within 3 or within 6 months after stopping DMab.

- Most patients need two infusions 3 or 6 months apart to control the rebound increase in bone resorption.

- "In my clinic we use CTX as a marker and give additional infusions if CTX increases about the upper 75% quartile of the premenopausal reference range for CTX."

Tsourdi E et al JCEM 2021
Kondo H et al JBMR 2020

Professor Bente Langdhal-personal communication
Should we ever stop treatment in the highest risk group?

NO
Who are the Highest Risk Patients?

• Prior fracture is most important risk factor for another fracture\(^1\)
  • Recent Fx suggest very high risk (Osteoporosis Emergency)
    - In over 377,000 women with first fx, absolute risk of another fracture:
      - 10% first year, 18% first 2 years, 31% first 5 years\(^2\)
  • Multiple Fractures also very high risk\(^3\)
  • Proactive Spine Imaging Required to find Vertebral Fractures
    - In NHANES VFA Study 2017, vertebral Fx prevalence:
      - 5% in the 60s, 10% in the 70s, 20% in the 80s\(^4\)

• People with very low BMD: high long-term risk for fracture
  • not necessarily high imminent risk

1. Kanis J Bone 2004
2. Balasubramanian A OI 2018
3. Gehlbach et al OI 20007
4. Cosman F et al OI 2017
IMMINENT FRACTURE RISK

The 2\textsuperscript{nd} Fracture following the First Fracture Constitutes an “Osteoporosis Emergency”

Patients with an imminent (i.e. 2 years) risk of fracture or refracture should be identified in priority in order to receive an immediate treatment and a program of fall prevention.

Roux C and Briot K. Osteoporosis Internat 2017

Baron R et al. Osteoporosis Internat 2020
Treatment of High Risk Patients: Limitations of Most Potent Antiresorptives

- For zoledronic acid\textsuperscript{1} and denosumab\textsuperscript{2}: nonvertebral fracture risk reductions at best 20\%-25\%
- No significant fracture risk reduction seen before 3 years.

Time to First Clinical Fracture Through Month 12

Nonvertebral and symptomatic (clinical) vertebral fracture. Nonvertebral fractures comprised the majority (more than 85%) of clinical fractures.

Subjects Experiencing Event (%)
- Placebo (N = 3,591)
- Romosozumab (N = 3,589)

RRR = 36%
\( p = 0.008 \)

> 85% are non-vertebral

Cosman F al NEJM 2016
Can We Improve Bone Quality Pharmacologically?

YES:
The Anabolic’s: Build New Bone
Improved Trabecular Connectivity After hPTH (1-34) Therapy

Before
CD: 2.9/mm³

After
4.6/mm³

Why Anabolics First in High Risk Patients

• They “build new bone”; and improve bone quality
• Bone quality is why bone strength deteriorates with age (or glucocorticoids, or in diabetics, or in ESRD) that makes an older bone more likely to break than a younger bone at the same BMD or T-score.
• Evidence from randomized, prospective clinical trials indicates that the use of an anabolic first followed by an anti-resorptive provides greater increases in BMD than the opposite sequence.

• “Treatment Sequence Matters”

Compston J and Drake M JBMR 2020

Kendler D et al Lancet 2018
Leder B et al JBMR Plus 2018
Cosman F et al JBMR 2017
Langdhal B et al The Lancet 2019
PTH beyond 2 years

• The “Black Box” warning for Forteo was modified in March 2019.
• The “Black Box” warning for Tymlos was modified in December 2021.

The new label states: “Use of FORTEO/TYMLOS for more than 2 years during a patient’s lifetime should only be considered if a patient remains at or has returned to having a high risk for fracture.”
Profile of Patients for Extended Use of Teriparatide

1. Patients whose PINP is staying high after 2 years.
2. Patients on higher doses of glucocorticoids unable to come off and with prevalent VFC.
3. High risk patients with multiple VCF at baseline and none on teriparatide or abaloparatide.
4. Adynamic renal bone disease.
5. Patients with severe COPD and VCF.

Miller PD, Lewiecki EM, Krohn K, Schwartz E. Cleve Clinic Med J 2021
Why change therapies?
Treatment Failure

• Fracture on therapy ??

• A drop in BMD beyond the LSC on therapy ?

• No change in BTM (bone turnover marker : resorption or formation) beyond their LSC on therapy ?

• Unrecognized secondary disorders (celiac, elevated PTH,)

• Poor compliance

How to Change?

• Decision dependent on Pharmacology of the drug used.

• When changing from teriparatide to DMab, consider using both for 3 months to prevent the drop in BMD at the FN.

• When stopping Dmab, use 2 sequential doses of Reclast, 1-3 month apart to prevent the abrupt rise in bone turnover.

Tsai J et al. Lancet 2013
Tsourdi E et al JCEM 2021
How do we Monitor The Efficacy of our Osteoporosis Therapies?

Change in interval height
Change in BMD beyond the LSC
Change in resorption (CTX) markers on anti-resorptive agents
Change in bone formation (PINP) markers with anabolic agents

Mikula AL et al OI 2017
Effect of 6 Years of Continuous Denosumab Treatment on Serum CTX Levels

Miller PD et al JCEM 2011

CTX < 250 pg/ml

WHY ????

- 55%
Teriparatide:
An Increase in PINP > 10ug/L is highly correlated with an increase in spine BMD and Increase in FEA.

An increase in PINP > 10ug/L highly correlated with increases in BMD and improvements in FEA.
Thank You, Mike

For the kind invitations, your devotion, and for all the historical attendees for 22 years at The Santa Fe Bone Symposium