Optimizing Management of High Risk Osteoporosis

Focus on New Mechanisms and Evidence-Based Strategies for Fracture Prevention in High Risk, Postmenopausal Patients

Program Chairman and Moderator
Mone Zaidi, MD, PhD, FRCP
Professor of Medicine and Physiology
Director, Mount Sinai Bone Program
Mount Sinai School of Medicine
New York, NY
Welcome and Program Overview

CME-certified symposium jointly sponsored by the University of Massachusetts Medical School and CMEducation Resources, LLC

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QUESTION AND ANSWER (Q&A) CARDS as program proceeds so we can collect them and discuss during the Q&A session

COURSE SURVEY AND EVALUATION forms to obtain CME credit. Please hand all survey forms to the staff at the desk outside following the program
Program Faculty

MONE ZAIDI, MD, PhD, FRCP, Hon MD  
(Program Chairperson)  
Professor of Medicine and Physiology  
Director, The Mount Sinai Bone Program  
Mount Sinai School of Medicine  
New York, NY

ROBERTO CIVITELLI, MD  
Sydney M. & Stella H. Schoenberg  
Professor of Medicine  
Professor of Cell Biology and Physiology, and Orthopaedic Surgery  
Chief, Division of Bone and Mineral Diseases  
Washington University School of Medicine  
Division of Bone and Mineral Diseases  
The Bone Health Program  
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Mount Sinai School of Medicine  
Doylestown, PA

SUNIL J. WI MALAWANSA, MD, PhD, MBA  
Professor of Medicine  
Director of Regional Osteoporosis Center  
UMDNJ Robert Wood Johnson Medical School  
Professor of Medicine/Endocrinology  
Robert Wood Johnson University Hospital  
New Brunswick, NJ

CME Program Agenda

8:00 AM — 8:25 AM
Chairman’s Introduction and Overview  
New Frontiers and Emerging Paradigms in Fracture Prevention for Postmenopausal Osteoporosis—The Evolving Landscape of Osteoprotection for High Risk Patients

MONE ZAIDI, MD, PhD, FRCP, Hon MD  
(Program Chairperson)  
Professor of Medicine and Physiology | Director, The Mount Sinai Bone Program | Mount Sinai School of Medicine | New York, NY

8:25 AM — 8:50 AM

ROBERTO CIVITELLI, MD  
Sydney M. & Stella H. Schoenberg  
Professor of Medicine | Professor of Cell Biology and Physiology, and Orthopaedic Surgery | Chief, Division of Bone and Mineral Diseases | Washington University School of Medicine | Division of Bone and Mineral Diseases | The Bone Health Program
CME Program Agenda

8:50 AM — 9:15 AM
Strengths and Limitations of Current Landscape for Osteoprotection: Balancing Efficacy Against Issues of Compliance, Tolerability, and Regimen Adherence with Bisphosphonates

SOL EPSTEIN, MD
Professor of Medicine and Geriatrics | Mount Sinai School of Medicine | Doylestown, PA

9:15 AM — 9:40 AM
New Therapeutic Paradigms Focused on Injectable Therapies in Patients at High Risk of Fracture: From Mechanisms of Action to Landmark Trials Focused on Multi-Site Fracture Prevention

SUNIL J. WIMALAWANSA, MD, PhD, MBA
Professor of Medicine | Director of Regional Osteoporosis Center | UMDNJ Robert Wood Johnson Medical School | Professor of Medicine/Endocrinology | Robert Wood Johnson University Hospital | New Brunswick, NJ

9:40 AM — 9:55 AM
Summary and Vision Statement: Emerging Perspectives on Fracture Prevention for High Risk, Postmenopausal Osteoporosis—The Foundation Role of Injectable Agents

MONE ZAI DI, MD, PhD, FRCP, Hon MD
(Program Chairperson)
Professor of Medicine and Physiology | Director, The Mount Sinai Bone Program | Mount Sinai School of Medicine | New York, NY

9:55 AM - 10:35 AM
Interactive ARS Case Study Simulations

10:35 AM — 11:00 AM
Interactive Question and Answer Session

Program Chair and Faculty
New Frontiers and Emerging Paradigms in Fracture Prevention for Postmenopausal Osteoporosis

The Evolving Landscape of Osteoprotection for High Risk Patients

Program Chairman and Moderator
Mone Zaidi, MD, PhD, FRCP
Professor of Medicine and Physiology
Director, Mount Sinai Bone Program
Mount Sinai School of Medicine
New York, NY
"Her chest had dropped, so that she stooped"

*Charles Dickens* in his description of the elderly Miss Havisham

“Dowager’s Hump”

Vittore Carpaccio, ca. 1457

Augusto Rodin, ca. 1885
Jean G.C.F.M. Lobstein
French Pathologist, 1820

Noticed that some patients' bones were riddled with *larger than normal holes*

Coined the term “osteoporosis” or porous bone
How is bone lost?

John Hunter
St. George’s Hospital, London, 1770

First suggested that bone was being constantly remodelled; when new bone was formed, old bone was removed
Fuller Albright
Massachusetts General Hospital, 1940

Menopause causes a loss of bone by enabling more bone to be broken down than is subsequently built up

John Hunter + Fuller Albright

Osteoporosis = Defective “Bone Remodeling”
Bone Remodeling
Osteoclast

Zaidi and Chambers, 1987
Zaidi and Moonga, 1993

Resorption Cavity Due to Osteoclastic Bone Removal

Fractures Due to Osteoporosis

Cases/Year

Breast Cancer  Heart Disease  Osteoporosis Fractures
3% to 5% of hip fracture patients are diagnosed for osteoporosis and treated

3% of wrist fracture patients receive BMD testing

Only 12% of vertebral fractures are diagnosed and 2% are treated
But………

People fracture at normal BMDs
FRAX™

- Femoral neck BMD
- Age
- Sex
- Race
- BMI
- History of fragility fracture
- Parental history of hip fracture
- Current smoking
- Alcohol (>3 units/day)
- Glucocorticoid therapy
- Rheumatoid arthritis
- Secondary osteoporosis

World Health Organization, 2006

Risk Stratification

<table>
<thead>
<tr>
<th>Bone Density</th>
<th>Number of Risk Factors</th>
<th>Hip Fracture/1000 Woman-Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest Third</td>
<td>≥5</td>
<td>27.3</td>
</tr>
<tr>
<td>Middle Third</td>
<td>3-4</td>
<td>14.7</td>
</tr>
<tr>
<td>Highest Third</td>
<td>0-2</td>
<td>9.4</td>
</tr>
</tbody>
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<td>0-2</td>
<td>9.4</td>
</tr>
</tbody>
</table>
### Future Fractures (Fold Increase)

<table>
<thead>
<tr>
<th>Existing Fracture</th>
<th>Wrist</th>
<th>Vertebral</th>
<th>Hip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrist</td>
<td>3.3</td>
<td>1.7</td>
<td>1.9</td>
</tr>
<tr>
<td>Vertebral</td>
<td>1.4</td>
<td>4.4</td>
<td>2.3</td>
</tr>
<tr>
<td>Hip</td>
<td>-</td>
<td>2.5</td>
<td>2.3</td>
</tr>
</tbody>
</table>

### Fracture Risk With Advancing Age

<table>
<thead>
<tr>
<th>Radius Bone Mineral Content (g/cm)</th>
<th>Fracture Risk/1000 Person-Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1.0</td>
<td>8</td>
</tr>
<tr>
<td>0.90–0.99</td>
<td>10</td>
</tr>
<tr>
<td>0.80–0.89</td>
<td>13</td>
</tr>
<tr>
<td>0.70–0.79</td>
<td>17</td>
</tr>
<tr>
<td>0.60–0.69</td>
<td>20</td>
</tr>
<tr>
<td>&lt;0.60</td>
<td>108</td>
</tr>
</tbody>
</table>

- **Age 50-54 years**
- **Age 75-79 years**
### 10-Year Probability of Fracture

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>T-Score 0</th>
<th>T-Score −0.5</th>
<th>T-Score −1.0</th>
<th>T-Score −1.5</th>
<th>T-Score −2.0</th>
<th>T-Score −2.5</th>
<th>T-Score −3.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>3.8</td>
<td>4.7</td>
<td>5.9</td>
<td>7.4</td>
<td>9.2</td>
<td>11.3</td>
<td><strong>14.1</strong></td>
</tr>
<tr>
<td>55</td>
<td>4.3</td>
<td>5.3</td>
<td>6.7</td>
<td>8.5</td>
<td>10.7</td>
<td>13.4</td>
<td><strong>15.8</strong></td>
</tr>
<tr>
<td>60</td>
<td>5.0</td>
<td>6.5</td>
<td>8.2</td>
<td>10.4</td>
<td>13.0</td>
<td>16.2</td>
<td><strong>20.2</strong></td>
</tr>
<tr>
<td>65</td>
<td>5.3</td>
<td>6.0</td>
<td>10.0</td>
<td>12.6</td>
<td>15.6</td>
<td>19.3</td>
<td><strong>23.9</strong></td>
</tr>
<tr>
<td>70</td>
<td>7.1</td>
<td>9.0</td>
<td>11.5</td>
<td><strong>14.6</strong></td>
<td>18.3</td>
<td>22.8</td>
<td>28.4</td>
</tr>
<tr>
<td>75</td>
<td>7.0</td>
<td>9.1</td>
<td>11.8</td>
<td>15.2</td>
<td>19.4</td>
<td>24.5</td>
<td><strong>30.8</strong></td>
</tr>
</tbody>
</table>

### Who Should We Treat Beyond BMD

- 3% for the hip
- 20% (approximately) for major osteoporosis-related fracture
A Goal of Therapy

76 Year-Old With Multiple Risk Factors For Fracture  
Reduce the Fracture Risk

Vertebral Fracture Reduction

- Calcium
- Zoledronic Acid
- Raloxifene
- Alendronate
- Risedronate
- Ibandronate

<table>
<thead>
<tr>
<th>% of Patients with New Vertebral Fracture</th>
<th>HORIZON¹</th>
<th>MORE²</th>
<th>FIT VFA²</th>
<th>VERT NA³</th>
<th>VERT MN³</th>
<th>BONE⁴</th>
<th>MORE²</th>
<th>FIT CFA⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>OP with Prevalent Vertebral Fractures ¹</td>
<td>66%</td>
<td>30%</td>
<td>47%</td>
<td>41%</td>
<td>49%</td>
<td>52%</td>
<td>50%</td>
<td>50%</td>
</tr>
</tbody>
</table>

⁴Harris ST, et al. JAMA. 1999;282:1344-52  

*All reductions are statistically significant.*
Non-Vertebral Fracture Reduction

- Calcium
- Zoledronic Acid
- Raloxifene
- Alendronate
- Risedronate
- Ibandronate

% of Patients with New Non-vertebral Fracture

- HORIZON
- MORE
- FIT VFA
- VERT NA
- VERT MN
- BONE
- MORE
- OP without Vert Fx

Calcium: p = .001 NS NS
Zoledronic Acids: p = .02 NS NS NS NS

N/A = not available; NS = not statistically significant

Non-Inferiority BMD Trials

- **Daily**
  - Alendronate (10)
  - Risedronate (5)
  - Ibandronate (2.5)

- **Weekly**
  - Alendronate (70)
  - Risedronate (35)

- **Monthly**
  - Ibandronate (150)
  - Risedronate (150)

- **Quarterly**
  - Ibandronate (3 iv)

Bridging Trials

- **FRACTURE Trials**
- **OP with Prevalent Vertebral Fractures**
- **OP without Vert Fx**

River Forth, Scotland
Photo: Courtesy Dr. Brendan Boyce
Why Do We Need Rapid Action?

2725 women with PMO and taking calcium studied for 1 year

Number of Baseline Vertebral Fractures

% Incidence of New Vertebral Fracture Within 1 Year

0 1 2 or more

0 5 10 15 20 25

One-Year Fracture Reduction

Control
Risedronate 5 mg

RR = 61%*

Absolute Risk Reduction = 7.4%

Multinational (VERT-MN)
Therefore,……

- Anti-osteoporosis reduce the risk of fracture, **but**

- Patients can, and do fracture while on a bisphosphonate
Bisphosphonate Failure

- BMD Increases
- BMD Stabilizes
- BMD Decreases

Real Decrease in BMD

- “Pseudo” Failures
  - Poor persistence
  - Incorrect intake
  - D-deficiency

- True Failures
  - Secondary cause
Oral Bisphosphonate Absorption = 0.6%
BMD Changes: 30-Min versus 60-Min Post-Dose Fast With Ibandronate

Injectable Therapies for Osteoporosis

- Ibandronate (q 3 mo i.v. injection)
- Zoledronic acid (q 1 yr i.v. infusion)
- Denosumab (q 6 mo s.c. injection)

The First RANKL Inhibitor
*Denosumab: S.C. Once Every 6 Month*

Mouse Genetics: RANK-L is Essential for Osteoclast Formation, Function and Survival
Denosumab Reduced the Incidence of New Vertebral Fractures

Denosumab Reduced the Incidence of Non-Vertebral Fractures
THANK YOU

Optimizing Management of High Risk Osteoporosis
Evolving Strategies, Mechanisms, and Treatment Paradigms
Bone Remodeling and New Mechanism for Inhibition of Bone Resorption

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Washington University School of Medicine
St. Louis, Missouri, USA

Disclosure: Roberto Civitelli, M.D.

Roberto Civitelli M.D. has financial interests to disclose. Potential conflicts of interest have been resolved.

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Consulting / Employment - None
Speakers Bureau / Honoraria - Amgen
MTA – Amgen, Zealand Pharma
The Bone Remodeling Cycle

- Activation
- Resorption
- Quiescence
- Reversal
- Formation

The Cutting Cone

- Osteoclasts
- Bone marrow
- Osteoblasts
- Osteoid
- Calcified tissue
Normal Bone Remodeling

Unbalanced Remodeling: Bone Loss

- Normal Resorption
- Reversal
- Formation
- Quiescence

- Excess Resorption
  - menopause
  - hyperPTH

- Bone Loss
- Quiescence
Mechanical Failure as a Consequence of Unbalanced Remodeling

- Increased Bone Turnover
- Disrupts Trabecular Microarchitecture
- Increases Mechanical Stress Concentration
- Decreases Mineralization Density
- Increases Cortical Porosity
- Accelerates Bone Loss
- Reduces Bone Strength

Effects of High Bone Turnover on Bone Strength
Therapeutic Strategies

Stimulators of Bone Formation
- Fluoride
- Teriparatide
- PTH-(1-84)

Bone marrow precursors

Inhibitors of Bone Resorption
- Estrogen, SERMs
- Bisphosphonates
- Calcitonin
- Denosumab
- Cathepsin K Inhibitors

Osteoblasts

Pyrophosphate
\[ \text{O}^- \quad \text{O}^- \]
\[ \text{O} = \text{P} - \text{O} - \text{P} = \text{O} \]
\[ \text{O}^- \quad \text{O}^- \]

Bisphosphonate
\[ \text{O}^- \quad \text{R}_1 \quad \text{O}^- \]
\[ \text{O} = \text{P} - \text{C} - \text{P} = \text{O} \]
\[ \text{O}^- \quad \text{R}_2 \quad \text{O}^- \]

- Inhibitors of
  - mineral deposition and dissolution
  - bone resorption

Lining cells
Mechanism of Action of Bisphosphonates: Osteoclasts Are Targets

Bisphosphonate attaches to exposed bone mineral surfaces
Osteoclast takes up bisphosphonate → loss of ruffled border, inactivation, detachment
New bone formation by osteoblasts renders bisphosphonate inert, inaccessible

Lining cells
Bisphosphonate
Osteoclast precursors
Osteoclast
Inactivated osteoclast
Osteoblast


Rapid and Prolonged Effect of Single i.v. Infusion of Zoledronic Acid on Bone Turnover

Mean (± SE) Urine NTX (nmol BCE/mmol creatinine)

*P < .05 for ZOL vs ALN at all post-baseline time points.
Saag K, et al. Poster presented at: ECCEO6; March 15-18, 2006; Vienna, Austria.
Effect of Alendronate on Bone Histology

Before treatment

After 6 years on alendronate

Decreased marrow cellularity and lack of osteoid in the trabecular surface


Effect of Alendronate on Bone Histology

Before treatment

After 6 years on alendronate

Absence of double tetracycline labels – low bone turnover

Most Common and Emerging Adverse Events with Bisphosphonates

- Hypocalcemia
- Flu-like symptoms (acute phase reaction), mainly for iv administration
- Arthralgia, myalgia, “bone pain”
- Mineralization defects in persistent vitamin D deficiency
- Atypical subtrochanteric fractures?
- Osteonecrosis of the jaw?

The RANK/RANKL/OPG Pathway: A Key Regulator of Osteoclast Formation

Cytokines
Growth factors
Hormones

Colony-forming unit—macrophage
Osteoclast Precursors

Pre-osteoblast/stromal cell
Differentiation
Fusion
Active osteoclast

Lining cells
The RANK/RANKL/OPG Pathway: A Key Regulator of Bone Remodeling

Pre-osteoblast/stromal cell
Cytokines
Growth factors
Hormones
RANKL
RANK
OPG
OPG blocks RANK/RANKL interaction

Bone formation
Osteoclast apoptosis

The RANK/RANKL/OPG Pathway: Effects of OPG Lack and Excess

Wild-type
OPG Knockout
OPG Transgenic

A
B
C
Normal
Osteoporosis
Osteopetrosis


250 μm
The OPG/RANK/RANKL System

Denosumab (AMG 162)

- Human monoclonal IgG₂ antibody to human RANKL
- High affinity for human RANKL (Kd $3 \times 10^{-12}$ M)
- Blocks binding of RANKL to RANK
- Specific: does not bind to TNFα, TNFβ, TRAIL, or CD40L
- Longer half-life compared with Fc-OPG
The OPG/RANK/RANKL System

Osteoblasts / stromal cells
Osteocytes
Bone Resorptive Hormones
e.g. PTH

M-CSF

RANK

OPG

Hematopoietic Precursors

Osteoclast Precursors

Prefusion Mononuclear Cells

Osteoclasts

Denosumab

Denosumab SC q6mo:
Effect on Serum C-Telopeptide (12 Months)

Denosumab Reduces Risk of Vertebral Fractures in Postmenopausal Women


Denosumab Reduces Risk of Hip Fractures in Postmenopausal Women

Adverse Events in Denosumab Trials

- Infections leading to hospitalization
  - Skin (cellulitis), GI and ear infections, UTIs
  - Patients on immunosuppressant therapy or impaired immune system may be at risk for infections
- Eczema, dermatitis, rashes
- No cases of osteonecrosis of the jaw in trials
  - Two cases adjudicated in extension trials
- No evidence of atypical femoral fractures, delays in fracture healing

Phase 2 Trial of Denosumab in Postmenopausal Women With Low BMD: Treatment Interruption Changes in Lumbar Spine BMD Over Month 48

Miller et al. Bone. 43:222-229, 2008
Pyknodysostosis

- Disproportionate short stature, enlarged cranium, micrognatia, retained deciduous teeth, malocclusion
- Thickened bones, increase bone fragility
- Loss-of-function mutations of \( CTSK \) (Cathepsin K gene)
The Osteoclast

H⁺  H⁺  HCO₃⁻  Cl⁻  Cl⁻  Cl⁻

Cath K

Bone

Odanacatib (Cath K Inhibitor) on Bone Mass in Postmenopausal Women

Odanacatib 50mg weekly

Eisman et al. J Bone Miner Res 2011;26:242-51
Odanacatib (Cath K Inhibitor) on Bone Resorption Markers

Odanacatib 50mg weekly

Eisman et al. J Bone Miner Res 2011;26:242-51

Odanacatib – Adverse Events

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Placebo n=92</th>
<th>50 mg ODN n=97</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>74 (80.4)</td>
<td>76 (78.4)</td>
</tr>
<tr>
<td>Drug-related</td>
<td>10 (10.9)</td>
<td>6 (6.2)</td>
</tr>
<tr>
<td>Leading to discontinuation</td>
<td>4 (4.3)</td>
<td>4 (4.1)</td>
</tr>
<tr>
<td>Serious</td>
<td>8 (8.7)</td>
<td>10 (10.3)</td>
</tr>
<tr>
<td>Skin</td>
<td>15 (16.3)</td>
<td>12 (12.4)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>7 (7.6)</td>
<td>7 (7.2)</td>
</tr>
<tr>
<td>Urinary Tract Infections/ Cystitis</td>
<td>3 (3.3)</td>
<td>12 (12.4)</td>
</tr>
</tbody>
</table>

Eisman et al. J Bone Miner Res 2011;26:242-51
Cath K Inhibitors for Osteoporosis

- Do not affect osteoclast viability, only function
- Anti-resorptive action is fully reversible upon discontinuation
- Odanacatib
  - Can be given orally at weekly doses
  - Overall safe – no cutaneous, GI AEs

Targets for Osteoclast Inhibition

![Diagram showing targets for osteoclast inhibition](image-url)
Osteoporosis in OPG Deficient Mice

Bucay et al., Genes Dev. 12:1260, 1998
Osteopetrosis in RANKL Deficient Mice

Kong et al., Nature 397:315, 1999

Zoledronic Acid Reduced Mean Serum β-CTX

Mean Serum β-CTX (ng/mL)

Annual dose

ZOL 5 mg
Placebo
Premenopausal reference range

Months

ZOL n = 257 237 201 136 191 190 174
PBO n = 260 248 214 156 196 197 170

Black D. NEJM 2007;356(18):1809-1822
Microarchitectural Changes In Osteoporosis

Odanacatib (Cath K Inhibitor) on Bone Formation Markers

Eisman et al. J Bone Miner Res 2010 (Epub ahead of print)
Unbalanced Remodeling: Bone Loss

Normal
- Resorption
- Reversal
- Formation
- Quiescence

Insufficient formation - aging
- Resorption
- Reversal
- Formation
- Quiescence

Bone Loss

A Breakfast, CME Clinical Excellence, Master Forum on Osteoporosis

Optimizing Management of High Risk Osteoporosis
Evolving Strategies, Mechanisms, and Treatment Paradigms
Strengths and Limitations of Established Therapies for Osteoprotection

Balancing Efficacy Against Issues of Compliance, Tolerability and Regimen Adherence with Bisphosphonates

SOL EPSTEIN, MD
Professor of Medicine and Geriatrics
Mount Sinai School of Medicine
Doylestown, PA

Sisyphus

One step forward, two steps backwards
The Osteoporosis Market

- Declining
- 30% decrease in OP prescriptions
- Decrease in therapy days from 2006-2010 from 1400 million therapy days to 800 million.

Reasons:
- Decreased diagnosis (less DXA)
- Concern about side effects
- Availability of generics with declining MD promotion
- Declining economy (less HCP visits)

Objectives

Decision-making for osteoprotection

- Issues with regimen adherence
- What are the consequences of poor adherence?
- Possible solutions
Decision Making by Patients

- Based on medication attributes
- Physician’s recommendation

- Based on medication beliefs
  - Efficacy of the medication in managing the disease
  - Hope of a “CURE”

Issue: How do they obtain the information to come to an informed decision?

Medication Attributes

- Efficacy
- Safety
  - Short term
  - Long term
- Cost
- Delivery system
Bisphosphonate Attributes

► Efficacy
  ● 50% - 70% reduction in vertebral fractures
  ● 40-50% reduction in hip fractures
  ● 20% reduction in nonvertebral fractures
  ● Reduction in Mortality?

► Safety
  ● Short term (GI, APR)
  ● Long term. Longest track record
  ● Rare events (Atyp Fx)

► Cost (impact of Generics??)

► Delivery system

Definitions

Persistence refers to the duration of time during which a medication is taken. Compliance is the proportion of medication taken at a given time according to instructions while persistent. Adherence represents compliance over time and can be estimated within discrete periods using the medication possession ratio.

Compliance, Persistence and Adherence

► For practical purposes these terms are used interchangeably.

► The bottom line is that the patient is not taking the medication as prescribed to improve the outcome of the disease.

The Need for Compliance

► It has been stated that “the #1 problem in treating illness today is the failure of the patient to take prescription medications correctly.”
Importance of Improving Persistence

- Interventions to improve adherence may have greater impact than advances in medical therapies.
- In terms of public health, improving persistence with bisphosphonate therapy by only 20% could have the same impact as a 20.2% increase in efficacy using Markov model simulation.

Cotte FE et al. Med Decis Making 2008

Persistence Curves in Multiple Therapeutic Areas

Note: Therapeutic persistence rates reflect only patients who discontinued therapy altogether (switching not reflected).
Source: Medco prescription data subsample 10/97 - 3/03
Adherence: What is the problem?

Most Patients Discontinue Oral Bisphosphonates Soon After Treatment Initiation

Adapted from Weycker D, et al. Osteoporos Int. 2006;17:1645-1652.
Medication Possession Ratio Overall and by Index Bisphosphonate in the 12 and 24 Months Post-index


<table>
<thead>
<tr>
<th>Medication</th>
<th>Mean MPR ± standard deviation</th>
<th>Median MPR</th>
<th>12 months post-index</th>
<th>24 months post-index</th>
</tr>
</thead>
<tbody>
<tr>
<td>All bisphosphonates</td>
<td>0.58 ± 0.35</td>
<td>0.45 ± 0.33</td>
<td>(n = 33,558)</td>
<td>(n = 22,422)</td>
</tr>
<tr>
<td>Alendronate</td>
<td>0.58 ± 0.35</td>
<td>0.59 ± 0.36</td>
<td>(n = 33,558)</td>
<td>(n = 20,122)</td>
</tr>
<tr>
<td></td>
<td>0.61</td>
<td>0.42</td>
<td>(n = 11,398)</td>
<td>(n = 11,212)</td>
</tr>
<tr>
<td></td>
<td>0.69</td>
<td>0.65</td>
<td>(n = 10,328)</td>
<td>(n = 11,232)</td>
</tr>
<tr>
<td>Risedronate</td>
<td>0.59 ± 0.36</td>
<td>0.59 ± 0.35</td>
<td>(n = 10,107)</td>
<td>(n = 6,998)</td>
</tr>
<tr>
<td></td>
<td>0.62</td>
<td>0.46</td>
<td>(n = 10,107)</td>
<td>(n = 6,998)</td>
</tr>
<tr>
<td></td>
<td>0.67</td>
<td>0.67</td>
<td>(n = 10,107)</td>
<td>(n = 6,998)</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>0.57 ± 0.36</td>
<td>0.47 ± 0.35</td>
<td>(n = 5,063)</td>
<td>(n = 2,492)</td>
</tr>
<tr>
<td></td>
<td>0.58</td>
<td>0.58</td>
<td>(n = 5,063)</td>
<td>(n = 2,492)</td>
</tr>
</tbody>
</table>

Persistence: Significantly Better Persistence with Weekly than Daily Dosing over 12 Months

Log rank, p<0.0001 for weekly vs daily proportion persisting
* Median time to discontinuation p<0.001

Many Patients Take Drugs Incorrectly, Infrequently, or Not at All

In the past 12 months, have you ...

- not filled a prescription?
- delayed filling a prescription?
- taken a prescription medication in smaller doses than prescribed?
- taken a prescription medication less often than prescribed?
- stopped taking a prescription medication sooner than prescribed?
What are the consequences?

Potential Consequences of Poor Adherence to Osteoporosis Therapy

- Poorer clinical outcomes
  - Less effective suppression in the rate of bone turnover\(^1\)
  - Lower gains or greater losses in bone mineral density\(^1,2\)
  - Greater risk of fractures\(^3,4\)

- Resulting in higher medical costs and greater health care utilization\(^5\)

4. Siris E. Et al IN Press
Refill Compliance and Fracture Risk Over 24 Months for Bisphosphonate-Treated Patients

Adjusted Risk of Fracture in New Bisphosphonate Users After the 12-month Post-index Period

<table>
<thead>
<tr>
<th>Adherence MPR</th>
<th>Odds Ratio for Fracture (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.5</td>
<td>Reference category</td>
<td></td>
</tr>
<tr>
<td>0.5-0.8</td>
<td>0.80 (0.65, 0.97)</td>
<td>0.022</td>
</tr>
<tr>
<td>&gt;0.8</td>
<td>0.86 (0.74, 1.00)</td>
<td>0.046</td>
</tr>
</tbody>
</table>


Adjusted Probability of Fracture (months 13 to 24 Post Initiation) by MPR Categories


Refill Compliance and Fracture Risk Over 24 Months for Bisphosphonate-Treated Patients

Cost of Therapies and Probability of Fracture

Refill Compliance (MPR)

Probability of Fracture

0.070 0.075 0.080 0.085 0.090 0.095 0.100 0.105 0.110 0.115 0.120

0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1

“Wasted drug”

Effective Drug


Time to First Fracture After Index Date in Treated and Comparison Patients

Percent without a Fracture

Treated
Comparison

Years of Follow-up

0 1 2 3 4 5 6 7 8

0 20 40 60 80 100
Consequences

- Wasted drug
- Ineffective therapies
- Increased health care costs
- Increased health care utilization

Why are patients non adherent?

The Science and Medicine of Osteoporosis Management
Non-compliance Occurs at 3 Points

► Initial prescription fulfillment

► Taking medication properly (compliance)
  ● Correct dose, timing, and manner of administration

► Persistence
  ● Taking the medication for the prescribed length of time

Primary Non-adherence

► Estimated as high as 35%
► Higher with electronic scripts
  ● Patients forget which pharmacy sent Rx.
  ● Complexity and effort to get the medication if on multiple medications.
  (Arch Internal Med-May 2011)
Reasons for Patient Non-Compliance

- Disbelief in diagnosis
- Questioning treatment
- Low motivation to change behavior
- Complicated dosing schedules
- Lack of observed treatment benefit
- Emotional distress
- Social stigma
- Low health literacy
- Forgetfulness
- Disorganization
- Lack of confidence in following Rx regimen
- Failure to understand need for compliance
- Physical or financial barriers to treatment

Most Patients Actively Choose Whether to Take Medicine as Directed

Reasons why patients don’t fill prescriptions or comply with drug regimens

- Sometimes forget to use or refill: 24%
- Don’t want the side effects: 20%
- The drug costs too much: 17%
- Don’t think I need the drug: 14%
- Can’t get prescription filled, picked up or delivered: 10%
- Don’t know how to use the drug: 10%
- Other: 1%

Percentage of respondents citing each reason.
Patients Who are Most Involved in Their Own Care Represent the Largest Potential Threat and the Greatest Opportunity

In the past 12 months, Have you ...

<table>
<thead>
<tr>
<th>Action</th>
<th>Accepting</th>
<th>Informed</th>
<th>Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not filled a prescription?</td>
<td>5</td>
<td>18</td>
<td>24</td>
</tr>
<tr>
<td>Delayed filling a prescription?</td>
<td>16</td>
<td>23</td>
<td>32</td>
</tr>
<tr>
<td>Taken a prescription medication in smaller doses than prescribed?</td>
<td>11</td>
<td>17</td>
<td>23</td>
</tr>
<tr>
<td>Taken a prescription medication less often than prescribed?</td>
<td>29</td>
<td>28</td>
<td>34</td>
</tr>
<tr>
<td>Stopped taking a prescription medication sooner than prescribed?</td>
<td>25</td>
<td>35</td>
<td>41</td>
</tr>
</tbody>
</table>

Source: BCG analysis: Harris Interactive 10,000 Patient Survey, 2002

Women are Less Likely than Men to Comply with Prescribed Drug Regimens

In the past 12 months, Have you ...

<table>
<thead>
<tr>
<th>Action</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not filled a prescription?</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td>Delayed filling a prescription?</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>Taken a prescription medication in smaller doses than prescribed?</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Taken a prescription medication less often than prescribed?</td>
<td>26</td>
<td>33</td>
</tr>
<tr>
<td>Stopped taking a prescription medication sooner than prescribed?</td>
<td>18</td>
<td>23</td>
</tr>
</tbody>
</table>

Source: BCG analysis: Harris Interactive 10,000 Patient Survey, 2002
Factors Contributing to Noncompliance of Osteoporosis Medication

- The asymptomatic nature of osteoporosis

  Compliance rates for medications for asymptomatic disease are poor

- Long-term nature of the treatment

- Drug-associated adverse effects
Factors Contributing to Noncompliance

- The asymptomatic nature of osteoporosis
- Long-term nature of the treatment
- Drug-associated adverse effects
- Differences in perspective between physicians and patients
- Largely elderly population being treated
- Financial barriers

Differences in Perspective Between Physician and Patient

**The Physician**

Intervention is important to reduce the risk of future fractures. Fractures are viewed as costly to the health care system and a source of disability to the patient. A risk-benefit analysis of safety, efficacy and cost needs to be proven.

**The Patient**

Osteoporosis threatens his/her independence, making the individual dependent on others for their care. It also changes the way he/she looks and feels about his/her physical and emotional self.
Patient Beliefs May Influence Adherence

► Patients may not believe they have osteoporosis
  ● There is no risk for those with no family history of osteoporosis²
  ● How can I have osteoporosis if I exercise and take calcium?

► Patients may not understand the consequences of having osteoporosis
  ● There is no need to treat a silent, asymptomatic disease¹
  ● Osteoporosis is expected as you age

Gold Adherence review in Curr OP reports

Patient Beliefs May Influence Adherence

► Patients may be concerned about the side effects of the therapies
  ● It is preferable to risk fracturing a hip than to take more medications²
  ● Concomitant use of multiple medications will “cancel each other out”²
  ● Treatment benefits do not outweigh side effects³

► Patients may have barriers to taking the medication
  ● I can’t get started in the morning until I have my morning coffee
  ● I can’t wait 30-60 minutes before I have breakfast

Gold Adherence review in Curr OP reports
Physician Perspective

► A Risk/Benefit Analysis
    Efficacy: Fracture reduction (time course of benefit)

    Safety and tolerability: Side effects, long-term safety, drug-drug interactions

    Dosing regimen: Compliance/Aherence issues

    Costs: Diagnosis, therapies, monitoring

Factors Contributing to Noncompliance

► The asymptomatic nature of osteoporosis
► Long-term nature of the treatment
► Drug-associated adverse effects
► Personal beliefs and fears
► Differences in perspective between physicians and patients
► Largely elderly population being treated.
How can we improve adherence?

At Time of Initial Fill

- Use case finding approach to identify high risk patients
  - Based on adherence questionnaires (e.g. GLOW, Morisky)
  - Poor adherence to other medications
  - Based on known risk factors
Improving Adherence by Reinforcing Treatment Efficacy

- Osteoporosis is largely asymptomatic so symptoms do not improve with therapy.
- Effective treatments are available to treat postmenopausal osteoporosis.
- Patient monitoring may be helpful in demonstrating effects of treatment\(^1\)\(^-\)\(^3\):
  - BMD
  - Biochemical markers of bone turnover.
- However, all studies have shown that continued reinforcement by the Physician /N.P. is the simplest and most effective intervention\(^3\).

3. Gold or Silverman review.

Extending Dosing Interval Significantly Improved Persistence with Monthly Ibandronate vs. Weekly Alendronate

- Time-to-failure-to-persist data for the ITT population were used to estimate the probability of persistence at each timepoint.

Marker or Nurse Monitoring Increases Persistence and Compliance

- Monitoring increased cumulative compliance to therapy by 57% at 1 year ($P=0.04$)
- Improvement in compliance and persistence did not differ between marker monitoring and nurse monitoring
- The monitored group tended to persist with therapy 25% longer than those who were not monitored ($P=0.07$)
- Compliance at 1 year correlated with % change in BMD ($r=0.28$; $P=0.01$) and BTM ($r=-0.36$; $P=0.002$)


Do Regular Telephone Reminders Help

- Answer NO.
- Active program whereby patients phoned to remind them to take their O.P. medication vs regular care.
- Results showed no significant difference except in one aged subgroup.

Archiv Intern Med March 2012
Effect of Behavioral Intervention

![Graph showing the effect of behavioral intervention on patients remaining on therapy over time.](Image)

- **Risedronate:**
  - 12 mth: 63%
  - 24 mths: 52%

- **Alendronate:**
  - 12 mth: 56%
  - 24 mths: 46%

Source: PBS Reimbursement Data: Dec 1 2002 through Sep 30 2003

Role of Behavioral Reinforcement

- Long term adherence requires behavioral reinforcement and patient support strategies throughout the continuum of care
  - National Council of Patient Information and Education 2007

- In a meta-analysis of 153 studies, combined education and behavioral techniques were more successful than either alone
  - Roter DL Med Care 1996; 36: 1138-1161
Post Hip Fracture Care

- Establish liaison with orthopedists to consult on every new hip fracture admission to hospital.
- Discuss treatment options with patient
- Establish a computer generated database for automatic discharge follow-up by a physician for treatment.
- Or provide instructions to patient on discharge for follow up.
- Programs have shown success and cost effectiveness in reducing morbidity and recurrent fractures. ie UK Fracture Liaison Service. (Mitchel P et al)

Conclusions

- Adherence is a significant problem
- The primary reason patients do not take their medicine is not forgetfulness
- The vast majority of patients are actively choosing not to take their medicine
- How and why patients make these choices varies
- Adherence interventions to be successful need to be multifaceted beginning at time of fill and throughout the use of the medication
Thank You.

---

**Demographic and Clinical Characteristics of Patients New to Bisphosphonate Therapy at Index**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (N=33,559)</th>
<th>Patients with subsequent fracture (N=935)</th>
<th>Patients without subsequent fracture (N=32,623)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days in health plan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-index</td>
<td>742.8 (264.0)</td>
<td>662.1 (221.5)</td>
<td>745.0 (264.7)</td>
</tr>
<tr>
<td>Post-index</td>
<td>834.0 (284.1)</td>
<td>982.0 (251.1)</td>
<td>829.8 (283.9)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>31,429 (93.7)</td>
<td>856 (94.6)</td>
<td>30,573 (93.7)</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>59.5 (9.2)</td>
<td>64.3 (12.3)</td>
<td>59.3 (9.1)</td>
</tr>
<tr>
<td>Age ≥65 years at index, n (%)</td>
<td>6557 (20.4)</td>
<td>3699 (38.5)</td>
<td>6488 (19.9)</td>
</tr>
<tr>
<td>Pre-index diagnosis, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>17,610 (52.5)</td>
<td>645 (69.0)</td>
<td>16,965 (52.0)</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>10,906 (32.2)</td>
<td>250 (26.7)</td>
<td>10,556 (32.4)</td>
</tr>
<tr>
<td>Pre-index fracture, n (%)</td>
<td>2,426 (7.2)</td>
<td>180 (19.3)</td>
<td>2246 (6.9)</td>
</tr>
</tbody>
</table>

Data are means (SD) unless otherwise noted.

**Distribution of New Bisphosphonate Users by Medication Possession Ratio (MPR)**

12-month, post-index period, stratified by subsequent fracture status

<table>
<thead>
<tr>
<th>MPR</th>
<th>Patients with fracture</th>
<th>Patients without fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vertebral fracture</td>
<td>Hip fracture</td>
</tr>
<tr>
<td>&lt; 0.5</td>
<td>40 (13.1)</td>
<td>32 (10.4)</td>
</tr>
<tr>
<td>0.5 - 0.8</td>
<td>25 (15.6)</td>
<td>9 (10.3)</td>
</tr>
<tr>
<td>&gt; 0.8</td>
<td>50 (11.3)</td>
<td>28 (10.8)</td>
</tr>
<tr>
<td>Total</td>
<td>115 (100)</td>
<td>69 (100)</td>
</tr>
</tbody>
</table>

Number of new bisphosphonate users = 33,558.

Fractures were assessed 12 months post-index. MPR, medication possession ratio.


---

**Optimizing Management of High Risk Osteoporosis**

Evolving Strategies, Mechanisms, and Treatment Paradigms

---

76
New Therapeutic Paradigms Focused on Injectable Therapies in Patients at High Risk of Fracture

From Mechanisms of Action to Landmark Trials Focused on Multi-Site Fracture Prevention

SUNIL J. WI MALAWANSA, MD, PhD, MBA
Professor of Medicine
Director of Regional Osteoporosis Center
UMDNJ Robert Wood Johnson Medical School
Professor of Medicine/Endocrinology
Robert Wood Johnson University Hospital
New Brunswick, NJ

Universal Management Measures

► Risk factor reduction
  - Bone mass
    - Medications- stop or reduce dose if possible
    - Smoking cessation programs
  - Fall Prevention
    - Medications
    - Environment
    - Balance training

► Physical Activity/ Exercise

► Optimal Nutrition
  - Fruits and Vegetables
  - Calcium/Vitamin D
Evolving Concepts in Osteoporosis Therapeutics

► News on an Old Story: Institute of Medicine Report
  - Calcium
    - More is not better
    - Diet better than supplements
  - Vitamin D
    - Target Range: 25OHD 20-30 ng/ml (IOM) or 30-40 ng/ml?
    - Doses to achieve target level highly variable

► Fracture Risk Assessment Beyond BMD
  - Find Prevalent Vertebral Fractures

► Medication for Prevention of Osteoporosis?
  - Rarely: low dose HT, Raloxifene

► Treatment Paradigms
  - Serial Monotherapy
  - Limit Treatment Duration
  - Re-evaluate Treatment Decision Annually

FDA Approved Osteoporosis Treatments

Antiresorptive Agents

► Bisphosphonates
  - Alendronate (Fosamax®)
  - Risedronate (Actonel®)
  - Ibandronate (Boniva®: Oral and IV)
  - Zoledronic Acid (Reclast® IV)

► Estrogen Agonist/Antagonists
  - Raloxifene (Evista®)

► Estrogen/Estrogen-Progestin Combinations

► Calcitonins (Miacalcin, Fortical)

► Denosumab (Rank Ligand Inhibitor; Prolia)

Anabolic Therapies

► Teriparatide (Forteo)
Treating Patients Across the Lifespan

- Maximize benefit/risk: major factors age and severity of disease
  - HT highest benefit/risk profile early after menopause
    - In general <5 years; low dose probably safer
    - ET alone safer, might allow longer duration
  - Raloxifene 50s to late 60s
    - Especially if spine osteoporosis only
    - Can be considered in patients for prevention
    - Hip fracture rare in this age group
  - Bisphosphonates/Denosumab: 60s and beyond
    - Hip and all nonspine fx (not clear with all bps)
  - Teriparatide
    - Can be used at any point, but only 18-24 months
    - Needs to be followed by antiresorptive treatment

Recent Important Treatment Studies and Extension Data

- Zoledronic Acid
  - HORIZON Pivotal Fracture Trial (PFT)
  - Study Extension

- Denosumab
  - Freedom Pivotal Trial
  - Study Extension
HORIZON Study Population

► Inclusion
- 7736 women 65 to 89 years of age
- Femoral neck T-score ≤ -2.5 or ≤ -1.5 with two mild or one moderate prevalent vertebral fracture

► Exclusions
- Current use of bisphosphonates, PTH, or strontium ranelate
- Failure to meet specified washout periods for previous BP use

► Two strata
- Stratum I: No current osteoporosis therapy (80% of total population)
- Stratum II: SERMs, calcitonin, HT/ET, or tibolone at baseline (20% of total population)


Morphometric Vertebral Fracture Results
(Stratum I)

Relative risk reductions (95% confidence intervals) vs placebo
*P < .0001, based on logistic regression with treatment and baseline fracture status in the model using log-likelihood type approach

Cumulative Risk of Hip Fracture
(Strata I + II)

Relative risk reduction (95% confidence interval) vs placebo

Cumulative Incidence (%)

Time to First Hip Fracture (months)

41%*
(17%, 58%)
P = .0024

Placebo (n = 3861)
ZOL 5 mg (n = 3875)

Cumulative Risk of Clinical Non-vertebral
Fracture (Strata I & II)

Relative risk reduction (95% confidence interval) vs placebo

Cumulative Incidence (%)

Time to First Clinical Non-vertebral Fracture (months)

25%
(13%, 36%)
P = .0002

Placebo (n = 3861)
ZOL 5 mg (n = 3875)
Common (≥5% in ZOL) Post-Dose Symptoms Occurring Within 3 Days After Infusion

![Bar chart showing incidence of post-dose symptoms](chart.png)

**Systemic Safety Parameters**

- **Renal safety**
  - Short term: 9-11 day post-dose monitoring in >4000 patients
  - Transient rises in serum creatinine in 1.8% of patients (vs 0.81% placebo) with resolution and all patients redosed
  - Overall, no cumulative impact on renal function

- **Hypocalcemia** (serum calcium < 2.075 mmol/L)
  - 49 cases (2.3%) 9-11 days after 1st ZOL 5 mg infusion, almost none after 2nd (0.1%) or 3rd (0.3%)
  - All asymptomatic and transient

- **Cardiac safety**
  - Atrial fibrillation AEs comparable (2.4% ZOL 5 mg, 1.8% placebo)
  - Atrial fibrillation SAEs more common in ZOL
    - \( n = 50 \) (1.3%) ZOL 5 mg
    - \( n = 20 \) (0.5%) placebo
  - ECG study (\( n = 559 \)) 9-11 days after 3rd infusion:
    - No differences observed between ZOL 5 mg and placebo

Bone Safety Parameters

► Fracture healing
  - Non-union: 1 in ZOL 5 mg, 1 in placebo

► Avascular necrosis (hip or knee)
  - 4 in ZOL 5 mg, 3 in placebo

► Osteonecrosis of the jaw
  - No spontaneous AE reports
  - AE database search of 50 MedDRA terms, with adjudication
  - Case definition: exposed bone in the mouth > 6 weeks
  - 1 in ZOL 5 mg, 1 in placebo
  - Both cases healed with antibiotic therapy and/or debridement

Change in Femoral Neck BMD (%) over 6 Years

- **Z6**: +4.5%
- **Z3P3**: +3.1%

Start of extension trial

P = 0.0007

Change in Total Hip BMD (%) over 6 Years

- **Z6**: +4.3%
- **Z3P3**: +2.8%

Start of extension trial

P < 0.0001
Change in Lumbar Spine BMD (%) over 6 Years (Subset of n=80 at Year 6)

Morphometric Vertebral Fractures by Treatment

Core study (Yr 0-3)  Extension study (Yr 3-6)

PBO  ZOLO  Z3P3  Z6
10.9%  6.2%  52%*  10.9%
(310/2853)  (30/486)  (10%, 74%)  (310/2853)

3.3%  3.0%
(92/2822)  (14/469)
Non-vertebral Fractures by Treatment

- Hip and clinical vertebral fractures: RH not-significant, wide CI’s

HORIZON Extension:
General Safety (Adverse Events)

<table>
<thead>
<tr>
<th>Category</th>
<th>Z6 (N=613)</th>
<th>Z3P3 (N=616)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of patients with an AE</td>
<td>552 (90%)</td>
<td>552 (89%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Serious AE’s</td>
<td>191 (31%)</td>
<td>168 (27%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Deaths</td>
<td>26 (4%)</td>
<td>18 (3%)</td>
<td>0.22</td>
</tr>
<tr>
<td>AEs occurring in &gt;10% patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>119 (19%)</td>
<td>108 (18%)</td>
<td>0.41</td>
</tr>
<tr>
<td>Back pain</td>
<td>117 (19%)</td>
<td>114 (18%)</td>
<td>0.82</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>77 (12%)</td>
<td>94 (15%)</td>
<td>0.18</td>
</tr>
</tbody>
</table>
Cardiovascular Safety (Adverse Events)

<table>
<thead>
<tr>
<th>Category</th>
<th>Z6 (N=613) n (%)</th>
<th>Z3P3 (N=616) n (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial Fibrillation SAES</td>
<td>12 (2.0%)</td>
<td>7 (1.1%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Stroke SAEs</td>
<td>19 (3.1%)</td>
<td>9 (1.5%)</td>
<td>.06</td>
</tr>
<tr>
<td>Stroke deaths</td>
<td>4(0.6%)</td>
<td>0 (0%)</td>
<td>.06</td>
</tr>
<tr>
<td>New Hypertension</td>
<td>48 (7.8%)</td>
<td>94 (15.2%)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Clinical Conclusions: Continuation of ZOL After 3 Years

- Decision to continue long term bisphosphonate treatment must be individualized
  - Women at high fracture risk, particularly for vertebral fracture, might continue ZOL up to 6 years
  - Women at lower risk might take drug holiday for up to 3 years (then re-evaluate)
  - Further details about subgroups who might benefit most are being explored
Study Design

International, randomized, double-blind, placebo-controlled study

Day 1 Visit 36 Months

**Randomization**

Denosumab 60 mg SC Q6M n=3902
Calcium and Vitamin D

Placebo n=3906

**Study Population**
- 7808 postmenopausal women
- T-score <-2.5 at the lumbar spine or total hip and not <-4.0 at either site

**Primary Endpoint**
- New vertebral fracture at 36 months

**Second Endpoints**
- Time to first nonvertebral fracture
- Time to first hip fracture

Selected Baseline Characteristics and Patient Disposition

<table>
<thead>
<tr>
<th>Baseline Characteristic and/or Patient Disposition</th>
<th>Denosumab 60 mg Q6M (n=3902) N(% )</th>
<th>Placebo (n=3906) N( % )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>72.3 (5.2)</td>
<td>72.3 (5.2)</td>
</tr>
<tr>
<td>Mean BMI (SD)</td>
<td>26.0 (4.1)</td>
<td>26.0 (4.2)</td>
</tr>
<tr>
<td>Mean 25 (OH) vitamin D level, ng/mL (SD)</td>
<td>23.1 (11.7)</td>
<td>22.9 (11.3)</td>
</tr>
<tr>
<td>Mean lumbar spine T-score (SD)</td>
<td>-2.82 (0.70)</td>
<td>-2.84 (0.69)</td>
</tr>
<tr>
<td>Mean total hip T-score (SD)</td>
<td>-1.89 (0.81)</td>
<td>-1.91 (0.81)</td>
</tr>
<tr>
<td>Mean femoral neck T-score (SD)</td>
<td>-2.15 (0.72)</td>
<td>-2.17 (0.71)</td>
</tr>
<tr>
<td>Prevalent vertebral fracture, n (%)</td>
<td>929 (23.8)</td>
<td>915 (23.4)</td>
</tr>
<tr>
<td>Completed study, n (%)</td>
<td>3272 (84)</td>
<td>3206 (82)</td>
</tr>
<tr>
<td>Received all doses of study medication, n (%)</td>
<td>3093 (80)</td>
<td>2886 (75)</td>
</tr>
</tbody>
</table>

Adapted from Cummings SR, et al. NEJM 2009;361:756-765
The Effect of Denosumab on Fracture Risks at 36 Months

The Effect of Denosumab on Time on New Vertebral Fractures at Month 12, 24 and 36

Adapted from Cummings SR, et al. NEJM 2009;361:756-765
The Effect of Denosumab on Time to First Nonvertebral Fracture Over 36 Months

Nonvertebral fractures were reduced by 20% (95% CI, 5%-33%)

The Effect of Denosumab on Time to First Hip Fracture Over 36 Months

Hip fractures were reduced by 40% (95% CI, 3%-63%)
**Change in BMD at 36 Months with Denosumab**

- **Lumbar Spine**: ∆=8.8%, p<0.0001
- **Total Hip**: ∆=6.4%, p<0.0001
- **Femoral Neck**: ∆=5.2%, p<0.0001

Data on file, Amgen

---

**Change in BTMs over 36 Months with Denosumab**

- **BTMs Substudy**: N=160
- **Serum CTx-1**: Denosumab 60 mg Q6M
- **Placebo**: Median % Change

Adapted from Cummings SR, et al. NEJM 2009;361:756-765
## Adverse Events

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Denosumab 60 mg Q6M (n=3886) N(%)</th>
<th>Placebo (n=3876) N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All adverse events</td>
<td>3605 (92.8)</td>
<td>3607 (93.1)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>1004 (25.8)</td>
<td>972 (25.1)</td>
</tr>
<tr>
<td>Deaths</td>
<td>70 (1.8)</td>
<td>90 (2.3)</td>
</tr>
<tr>
<td>Adverse events leading to study discontinuation</td>
<td>93 (2.4)</td>
<td>81 (2.1)</td>
</tr>
<tr>
<td>Adverse events leading to discontinuing the study drug</td>
<td>192 (4.9)</td>
<td>202 (5.2)</td>
</tr>
</tbody>
</table>


## Adverse Events

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Denosumab 60 mg Q6M (n=3886) N(%)</th>
<th>Placebo (n=3876) N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>2055 (52.9)</td>
<td>2108 (54.4)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>187 (4.8)</td>
<td>166 (4.3)</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>33 (0.8)</td>
<td>26 (0.7)</td>
</tr>
<tr>
<td>Clinical hypocalcemia</td>
<td>0 (0)</td>
<td>3 (0.1)</td>
</tr>
<tr>
<td>Delayed fracture healing</td>
<td>2 (0.05)</td>
<td>4 (0.1)</td>
</tr>
<tr>
<td>Femoral shaft fracture</td>
<td>0 (0)</td>
<td>3 (0.1)</td>
</tr>
<tr>
<td>Humerus nonunion fracture</td>
<td>0 (0.0)</td>
<td>0 (0.03)</td>
</tr>
<tr>
<td>Osteonecrosis of the jaw</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Adverse events occurring with a ≥ 2% incidence and p ≤ 0.05

| Eczema | 118 (3.0) | 65 (1.7) |
| Fall* | 175 (4.5) | 219 (5.7) |
| Flatulence | 84 (2.2) | 53 (1.4) |

Cummings SR, et al. NEJM 2009;361:756-765  * Excludes falls occurring on the same day as a fracture
### Adverse Events

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Denosumab 60 mg Q6M (n=3886) N(%)</th>
<th>Placebo (n=3876) N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>144 (3.7)</td>
<td>125 (3.2)</td>
</tr>
<tr>
<td>Infection</td>
<td>159 (4.1)</td>
<td>133 (3.4)</td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>186 (4.8)</td>
<td>178 (4.6)</td>
</tr>
<tr>
<td>Stroke</td>
<td>56 (1.4)</td>
<td>54 (1.4)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>47 (1.2)</td>
<td>39 (1.0)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>31 (0.8)</td>
<td>30 (0.8)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>29 (0.7)</td>
<td>29 (0.7)</td>
</tr>
<tr>
<td>Serious adverse events occurring with &gt;0.1% incidence and p &lt; 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulitis (includes erysipelas)</td>
<td>12 (0.3)</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td>Concussion</td>
<td>1 (&lt;0.1)</td>
<td>11 (0.3)</td>
</tr>
</tbody>
</table>


### Extension Study Design

- 7-year, international, multicenter, open-label, single-arm extension study
- Primary endpoint: safety and tolerability up to 10 years of denosumab administration

Adapted from Chapuriat R, et al. Presented at ACR Annual Scientific Meeting, Nov. 7-11, 2010; Atlanta, GA
### Patient Demographics and Baseline Characteristics

Adapted from Chapuriat R, et al. Presented at ACR Annual Scientific Meeting, Nov. 7-11, 2010; Atlanta, GA

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>5-year Denosumab-treated Extension Study Subjects (n=2243)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pivotal Phase III Fracture Trial Baseline</td>
</tr>
<tr>
<td>Age, years</td>
<td>71.9 (5.0)</td>
</tr>
<tr>
<td>Age groups, n (%)</td>
<td></td>
</tr>
<tr>
<td>≥ 65 years</td>
<td>2209 (94)</td>
</tr>
<tr>
<td>≥ 75 years</td>
<td>662 (28)</td>
</tr>
<tr>
<td>Prevalent vertebral fractures, n (%)</td>
<td>559 (23.9)</td>
</tr>
<tr>
<td>BMD T-scores</td>
<td></td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>-2.83 (0.67)</td>
</tr>
<tr>
<td>Total hip</td>
<td>-1.85 (0.79)</td>
</tr>
<tr>
<td>CTx (ng/mL)</td>
<td>0.573 (0.296)</td>
</tr>
<tr>
<td>P1MP (ug/L)</td>
<td>48.85 (18.37)</td>
</tr>
</tbody>
</table>

### Change in Serum CTx and P1NP Through 5 Years with Denosumab

Adapted from Chapuriat R, et al. Presented at ACR Annual Scientific Meeting, Nov. 7-11, 2010; Atlanta, GA
Change in Lumbar Spine and Total Hip BMD Through 5 Years with Denosumab

Yearly Incidence of New Vertebral Fractures Through 5 years

Fracture incidence was not evaluated as an efficacy endpoint in the extension study

Adapted from Chapuriat R, et al. Presented at ACR Annual Scientific Meeting, Nov. 7-11, 2010; Atlanta, GA.
Yearly Incidence of Nonvertebral Fractures Through 5 Years

Fracture incidence was not evaluated as an efficacy endpoint in the extension study

Adapted from Chapuriat R, et al. Presented at ACR Annual Scientific Meeting, Nov. 7-11, 2010; Atlanta, GA

Summary of Adverse Events Through 5 Years
Rate per 100-Patient-Years

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Pivotal Phase 3 Fracture Trial</th>
<th>Extension Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=3883) Rate (Event)</td>
<td>Denosumab (n=3879) Rate (Event)</td>
</tr>
<tr>
<td>All</td>
<td>237</td>
<td>235</td>
</tr>
<tr>
<td>Infections</td>
<td>40.2</td>
<td>39.8</td>
</tr>
<tr>
<td>Eczema</td>
<td>0.7</td>
<td>1.3</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>&lt;0.1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Serious</td>
<td>16.4</td>
<td>17.3</td>
</tr>
<tr>
<td>Infections</td>
<td>1.4</td>
<td>1.8</td>
</tr>
<tr>
<td>Cellulitis or Erysipelas</td>
<td>&lt;0.1 (1)</td>
<td>0.1 (13)</td>
</tr>
<tr>
<td>Malignancies</td>
<td>1.8</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Adapted from Chapuriat R, et al. Presented at ACR Annual Scientific Meeting, Nov. 7-11, 2010; Atlanta, GA
Effects of Denosumab Treatment on Risk of Fracture in Subgroups of Women with PMO

- Prospectively planned subgroup analyses
- Looked at patient characteristics:
  - Age
  - BMD
  - BMI
  - Fracture history
- No significant difference for any of the subgroups for vertebral fracture
- Effect of therapy on nonvertebral fracture risk was greater in subjects with lower femoral neck BMD, lower BMI, and in those without baseline prevalent vertebral fracture.
Summary

► IV zoledronic acid offers fracture protection throughout the skeleton over at least 3 years
  • Effect on BMD and biochemical turnover persistent even after discontinuation
  • Many people can and probably should stop therapy after 3 years

► Subcutaneous denosumab offers fracture protection throughout the skeleton over at least 3 years
  • Effect is rapidly reversible if medication is stopped
  • Decision to continue beyond 3 years must be individualized

► The concept that any osteoporosis medication should be continued indefinitely is no longer viable
Emerging Perspectives on Fracture Prevention for High Risk, Postmenopausal Osteoporosis

Where Do We Stand? Where Are the Trials and Evidence Leading Us?

Program Chairman and Moderator
Mone Zaidi, MD, PhD, FRCP
Professor of Medicine and Physiology
Director, Mount Sinai Bone Program
Mount Sinai School of Medicine
New York, NY

Fundamental Questions Arise

When Do We Treat?

Bone Loss or Lost Bone

How Do We Treat?
When Should We Treat?

Evolving Evidence

- A 65 year-old woman with a T-score of –2.6
  - BMD Diagnosis

- A 80 year-old woman with a T-score of -1.1 and a prevalent vertebral fracture
  - Clinical Diagnosis

- A 72 year-old woman with a total hip T-score of –2.4 and a history of smoking and maternal history of hip fracture
  - High Fracture Risk by FRAX™

FRAX™ Excludes The…

A 53 year-old woman entering the menopause with:

- T-score of –1.9
- Overall fracture risk of 6.5%
- Urinary N-telopeptide of 70 nmol/mmol Cr

..........which is evidence for high-turnover “bone loss”
Continuum of Bone Loss

Osteoclastic Resorption

Bone Resorption Markers

Trabecular Perforation and Loss

Bone Imaging – CT and MRI

"Lost Bone"

BMD

Fracture

Clinical

X-ray

VFA

FRAX™
Steep and Slippery Menopausal Cliff

50% of Total Life-Time Bone Loss

44 year old woman

58 year old woman (LMP ~ 50 y)
Steep and Slippery Menopausal Cliff

Obese

Non-Obese

Across The Menopausal Transition

Trabecular Perforations

Recker (2007)
Why Should We Treat?

*Bone Loss During Early Menopause:*

- Occurs at the most rapid rate
- Is associated with hyper-resorption
- May at least, in part, be FSH-mediated
- Is characterized by trabecular perforation
- Compromises bone strength
Bone Loss or Lost Bone:
Rationale and Recommendations for the Diagnosis and Treatment of Early Postmenopausal Bone Loss.


Goals of Therapy are Different

76 Year-Old With Multiple Risk Factors For Fracture
Reduce the Risk of Fracture

55 Year-Old Early Postmenopausal with Osteopenia
Prevent the BMD Decline
What Should We Treat With?

*Personal Choice*
Estrogen and Designer Estrogens

Reduce Osteoclast Formation
Structure of Bisphosphonates

Bisphosphonate

\[ \text{OH R1 OH} \]
\[ \text{R2 OH} \]
\[ \text{O = P – C – P = O} \]

Polyphosphate

\[ \text{OH OH} \]
\[ \text{O = P – O – P = O} \]

Bisphosphonates

Reduce Osteoclast Function and Survival

Binding to Hydroxyapatite

<table>
<thead>
<tr>
<th>Compound</th>
<th>Binding Constant (K)</th>
<th>(10^6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLO</td>
<td>1</td>
<td>0.24</td>
</tr>
<tr>
<td>ETO</td>
<td>2</td>
<td>0.30</td>
</tr>
<tr>
<td>RIS</td>
<td>3</td>
<td>0.37</td>
</tr>
<tr>
<td>IBA</td>
<td>4</td>
<td>0.44</td>
</tr>
<tr>
<td>ALN</td>
<td>1</td>
<td>0.24</td>
</tr>
<tr>
<td>ZOL</td>
<td>2</td>
<td>0.30</td>
</tr>
</tbody>
</table>
Denosumab

Reduces Osteoclast Formation Function and Survival

Osteoblasts

Osteoporosis Therapy

*The Four Legs*

- Calcium Balance
- Drugs
- Exercise
- Fracture Prevention
Optimizing Management of High Risk Osteoporosis
Evolving Strategies, Mechanisms, and Treatment Paradigms

The Science and Medicine of Osteoporosis Management
Applying Evidence to Patients and Practice
An Interactive Case Study Approach
Case Study #1

RG is a 68-year-old woman who has been on hormone therapy (HT) since menopause

- She initially took HT for hot flashes
- She discontinued HT 1 year ago when she read about the risks of breast cancer, stroke, and heart disease

She is seeing you for routine evaluation and asks you whether she needs additional therapy to treat or prevent osteoporosis

Case Study #1 (continued)

- Medications: No calcium or vitamin D supplements
  - She takes a MVI
  - Occasional PPI
  - She is lactose intolerant
  - She has lost 2 inches in height

- Approximately 10 years ago she broke her forearm when she slipped on the sidewalk

- No family history of osteoporosis
Now has a DXA which shows spine T-score of -2.2 and total hip T-score of -2.0

Does she have osteoporosis?

How high risk is she?

Case Study # 1 (continued)

Now has a DXA which shows spine T-score of -2.2 and total hip T-score of -2.0

*Does she have osteoporosis?*

1) Yes, because she has a wrist fracture
2) No, because her T-scores do not justify the diagnosis of osteoporosis
3) The diagnosis can only be made by using FRAX
Does she have osteoporosis?

1. Yes, because she has a wrist fracture
2. No, because her T-scores does not justify the diagnosis of osteoporosis
3. The diagnosis can only be made by using FRAX

FRAX Score:
FRAX Score show 10-Year Probability of Fracture (with BMD)

Major osteoporotic - 27%
Hip fracture - 4.3%
Case Study # 1 (continued)

Therapeutic Options

► Calcium supplementation 1200 mg and 800-1000 IU vitamin D

► Exercise

► Medication options
  • SERMS?
  • Bisphosphonates yearly, monthly or weekly
  • Denosumab

► Follow-up BMD: One year? two years?

Case Study # 2

Severe Postmenopausal Osteoporosis and Hip Fracture
Case Study # 2 (continued)

A 76-year-old female patient of yours is admitted to hospital with a left hip fracture.

- Has been told she has osteoporosis in the past and she has been taking a weekly oral bisphosphonate for two years
- Her lumbar spine T-score was last year was -2.8
- Hip fracture was repaired successfully last week but she cannot stand easily and reports feeling weak
- Mild dementia after the surgery
- Estimated creatinine clearance was 45 two years ago and is now 42

Case Study # 2 (continued)

- Is she a non-responder? Is she a treatment failure?
- Would you look for a secondary cause of osteoporosis?
- What are the treatment considerations in this patient?
- What would be the reason to consider alternative to bisphosphonates? Denosumab?
What are the treatment considerations in this patient?

- Recent hip fracture
- Recent orthopedic surgery
- Advanced age
- Weakness
- Prior bisphosphonate use
- Renal issues
- Mild dementia

Several treatment options are available:

- How do we select among them? Are there applicable clinical data for this situation?
- If denosumab is selected, how would patient be monitored for side effects?
Several treatment options are available. 
Which would you select?

1) Continue oral bisphosphonate
2) Continue oral bisphosphonate and add raloxifene
3) Stop oral bisphosphonate and start denosumab
4) Stop oral bisphosphonate and start reclast
5) Stop all treatments
Case Study # 2 (continued)

► How do we monitor this patient?
► What should we be documenting?

Case Study # 3

63-year-old woman presents for routine annual assessment
► LMP age 52—no hot flashes or night sweats
► Basically healthy
► History of very high breast density
► 1 prior breast biopsy—benign
Should BMD be done?
What else should be done?
What agent would you treat her with initially?
Patient’s BMD is -2.2

Bisphosphonate therapy initiated
Patient returns in one-year and T-score has fallen -2.2 to -2.4
Is this considered failure of therapy?
1) Yes, as the T-scores has worsened
2) No, because she does not have a fracture
3) We don’t know, as the change may not be significant
74-year-old woman presents for evaluation of possible osteoporosis to her PCP on the recommendation of an astute orthopedist. She met the orthopedist for the first time in the ER after a fall in her bathroom on a slippery floor precipitated a fracture of the humerus. The fracture was comminuted but not displaced and she was treated with sling immobilization, pain medicine and recommendations for PT and osteoporosis evaluation.

She had a relatively unremarkable prior history. She had had no prior fractures. She had mild hypertension controlled on an ACE inhibitor and mild hyperlipidemia on a statin. Recently she began a PPI for control of common heartburn symptoms.
Past Surgical History:

- Breast biopsy 6 years earlier - benign
- Cholecystectomy age 50
- History of thyroid nodule - biopsy negative - treated with suppressive doses of synthroid for several years about 10 years earlier
- Colon polyps removed on colonoscopy on several examinations

Ob/Gyn History: unremarkable

- 3 pregnancies, 2 children
- Menarche 14
- LMP 48, no HT
Family History
► No known osteoporosis but mother was very stooped when she passed away from complications of colon cancer at age 79

Social History
► Diet: on average 1 high calcium dietary source daily (either milk, yogurt, cheese, calcium fortified OJ), also takes three 500 mg calcium supplements, each with some vitamin D

Physical Activity
► No regular exercise program but active in her home, part-time work, helping take care of grandkids

Non-smoker
► Drinks 1-2 glasses of wine on weekend nights

Physical Exam
► Healthy appearing but still in some distress from shoulder pain
► Height 5 feet 3 inches - over 1.5 inches below her peak height (as shown on driver's license)
► Weight 140 lbs
► No exaggerated kyphosis

Lab Eval
► Chemistries normal
► LFTs normal, RFTs normal
► 25OHD level 16
► PTH level 78 pg/ml

BMD
► T Score -2.4 at L1-L4, however, prominent osteophyte overlying L2 where T-Score was -1.5
► T-Score at L1, L3 and L4 -2.8
► FN T-Score -2.9
What Additional Evaluation Should be Considered?

- TTG IgA: Negative
- Serum IgA level low so TTG IgG level done- also negative
- CTX level: High
- BSAP level: High
- SPEP: Normal

Case Study # 4 (continued)

Lateral Spine Imaging

VFA shows possible T12 compression but also some hypertrophic liping- Xray confirms 1 moderate vertebral fracture, 1 mild

Assessment

Patient has severe osteoporosis with several vertebral fractures and a humerus fracture. She is Caucasian, postmenopausal (with menopause a bit earlier than average) and has a possible family history (mother kyphotic). Possible contribution from suppressive dose synthroid and ?PPI.
Management

1. What to do with calcium?
2. What to do with vitamin D?
3. Exercise?
4. Treatment Options?

Case Study #5

► Patient presentation and history
► Patient evaluation
► Assessing the cause of BMD deterioration
► Treatment plan
Case Dilemma

► Patient presentation and history
► Patient evaluation
► Assessing the cause of BMD deterioration
► Treatment plan

125-year-old woman

- Height 142cm, weight 55kg
- Routine follow-up, treatment with daily bisphosphonate for 2 years

Patient Presentation and History (1)

- No agreed thresholds for significant BMD loss; however, these losses are substantial (>3%)
- Patient referred to a specialist for further investigation

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>2 years (current)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spine T-score</td>
<td>−2.12</td>
<td>−2.23, −5.2% change</td>
</tr>
<tr>
<td>Hip T-score</td>
<td>−2.25</td>
<td>−2.38, −5.8% change</td>
</tr>
</tbody>
</table>

*NB. These measurements were obtained using the same DXA machine at the same facility*
### Patient Presentation and History (2)

- Patient has prior fracture of the humerus
- Activity levels are low to moderate
- 1000mg calcium and 600 IU vitamin D per day
- Non-smoker, <3 units of alcohol per day
- No other chronic conditions identified

### Case Dilemma

- Patient presentation and history
- **Patient evaluation**
- Assessing the cause of BMD deterioration
- Treatment plan
Physical Examination and Laboratory Tests

- Physical examination essentially normal
  - No medical conditions that could predispose to bone loss were revealed

- In addition to serum calcium and full blood-count, the following laboratory tests proved normal

<table>
<thead>
<tr>
<th>Condition</th>
<th>Test/ signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthyroidism</td>
<td>TSH</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>Estimated GFR, serum creatinine</td>
</tr>
<tr>
<td>Liver disease</td>
<td>Albumin, alkaline phosphatase and liver transaminases</td>
</tr>
</tbody>
</table>

TSH, Thyroid stimulating hormone
GFR, Glomerular filtration rate

The Science and Medicine of Osteoporosis Management

How would you treat this patient?
Case Dilemma

► Patient presentation and history
► Patient evaluation
► Assessing the cause of BMD deterioration
► Treatment plan

Assessing the Cause of BMD Deterioration

► What investigations are required?
  - DXA measurement details
  - adherence
  - calcium and vitamin D
  - serum 25-hydroxyvitamin D test, if economically feasible
  - medications
  - comorbid conditions
What would you consider as an acceptable threshold for BMD loss?

A. 1%
B. 2%
C. > 3%

Approximately what proportion of patients in your clinical practice experience BMD loss >3%?

A. <5%
B. 5-10%
C. >10%
What would you consider the most common cause for BMD deterioration in your clinical practice?

A. Inaccurate DXA measurement
B. Poor adherence
C. Inadequate calcium and vitamin D levels
D. Concomitant medications that cause secondary bone loss
E. Comorbid conditions
F. Treatment failure

Mis-labelling of Vertebrae

62-year-old woman on alendronate

<table>
<thead>
<tr>
<th>Initial Analysis</th>
<th>Revised Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scan Information</td>
<td>Scan Information</td>
</tr>
<tr>
<td>DXA Result Summary</td>
<td>DXA Result Summary</td>
</tr>
<tr>
<td>[Images of vertebrae]</td>
<td>[Images of vertebrae]</td>
</tr>
</tbody>
</table>
Incorrect Hip Rotation

Assessing the Cause of BMD Deterioration: DXA Measurement Details

► Important to check whether:
  ● Baseline and follow-up DXA measurements obtained using same machine
  ● Accurate repositioning achieved

► These points were confirmed for the present case
Assessing the Cause of BMD Deterioration: Adherence

► The patient’s response on enquiry suggests that she has been taking her medication as prescribed

► Poor adherence to treatment is common in osteopenia and osteoporosis
  ● Risk of non-adherence increases with duration of treatment\(^1\)

► Assessment of bone turnover markers (BTMs), if available, could also help to determine whether this is a case of non adherence/treatment failure


Assessing the Cause of BMD Deterioration: Calcium and Vitamin D

► The patient is taking 1000mg calcium and 800IU vitamin D per day\(^1\)

► 24h urinary calcium and 25-hydroxyvitamin D measurements confirm normal levels:
  ● 24h urinary calcium: 250mg/day
  ● 25-hydroxyvitamin D: 65 nmol/L (normal 80nmol/L)

► In cases where 24h urinary calcium is >400mg/day, the patient should be advised to stop taking calcium supplements for 7–10 days, and the test repeated

Assessing the Causes of BMD Deterioration: Medications

- Medications that can cause secondary bone loss include: ¹
  - aluminum-containing antacids
  - antiseizure medications (only some) such as Dilantin® or phenobarbital
  - aromatase inhibitors such as Arimidex®, Aromasin®, and Femara®
  - cancer chemotherapeutic drugs
  - cyclosporine A and FK506 (tacrolimus)
  - glucocorticoids such as cortisone and prednisone
  - gonadotropin releasing hormone (GnRH) such as Lupron® and Zoladex®
  - heparin
  - lithium
  - medroxyprogesterone acetate for contraception (Depo-Provera®)
  - methotrexate
  - proton pump inhibitors (PPIs) such as Nexium®, Prilosec® and Prevacid®
  - selective serotonin reuptake inhibitors (SSRIs) such as Lexapro®, Prozac®, and Zoloft®
  - Tamoxifen® (premenopausal use)
  - thiazolidinediones (Actos® and Avandia®)
  - thyroid hormones in excess
  - aromatase inhibitors

- The patient is not receiving any of the above medications


Assessing the Causes of BMD Deterioration: Comorbid Conditions

- In addition to preliminary tests (serum calcium, full blood-count, TSH and kidney and liver function) the following tests were normal

<table>
<thead>
<tr>
<th>Condition</th>
<th>Test/ signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celiac disease</td>
<td>IgA transglutaminase (tTGA), endomysial antibodies</td>
</tr>
<tr>
<td>Cushing syndrome</td>
<td>Urinary free cortisol</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>Intact PTH</td>
</tr>
<tr>
<td>Rickets, osteomalacia</td>
<td>Vitamin D</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Rheumatoid factor</td>
</tr>
</tbody>
</table>

Assessing the Cause of BMD Deterioration: Conclusions

► Since her BMD loss is not due to secondary causes, treatment failure or compliance problems are likely
  ● The patient has suggested that she has been taking her medication as prescribed

Case Dilemma

► Patient presentation and history
► Patient evaluation
► Assessing the cause of BMD deterioration
► Treatment plan
After continued BMD losses over 2 years, what would you do?

A. Stop medication
B. Switch medication
C. Add another medication

How long would you continue treatment with a BMD loss before considering changing/stopping medication?

A. 6–12 months
B. 1–2 years
C. >2 years
If you were to switch medication, what would you switch to?

A. Alternative oral bisphosphonate with extended dosing interval
B. Alternative weekly oral bisphosphonate with Vit D
C. IV bisphosphonate
D. Denosumab every 6 months sc
E. Teriparatide

What factors would you consider most important when choosing next medication?

A. Prevention of near-term fractures
B. Prevention of mid- to long-term future fractures
C. Increased BMD
D. Long-term Safety and tolerability
E. Optimal adherence to oral/IV formulation
The treatment plan

Treatment Plan: Nutrition, Physical Activity and Mobility

- The patient is taking 1000mg calcium and 800IU vitamin D per day\(^1\)
- The patient's 24h urinary calcium normal and 25-hydroxyvitamin D measurements is nearly normal
- No additional supplements are recommended except could > Vit D.
- This patient would benefit from weight-bearing exercise, if possible\(^1\)

Treatment Plan: Points to Consider

► At the age of 71, in view of her previous fracture, treatment should be maintained over the long term

► Clinical trial evidence for fracture reduction following the switching or adding of treatments is currently lacking

► The patient tolerates oral bisphosphonate therapy but had lost significant BMD

► The reasons for BMD loss cannot be certain (ineffective treatment/non-adherence?)

Treatment Plan: Medication

► After discussion with the patient, an extended dosing drug, denosumab, administered sc, was considered the treatment of choice
An 80-year-old woman with a perception of height loss was noted to have a compression fracture at T12 on lateral X-ray of the thoracolumbar spine. The lumbar spine T-score was -2.3, and her hip T-score was -1.7. The following is true regarding the diagnosis of osteoporosis.

1) The patient should be diagnosed as having osteopenia
2) The patient should be diagnosed as having osteoporosis
3) The compression is normal at the patients age and no diagnosis of osteoporosis is required
A initial and repeat (after 2 years) bone mineral density (BMD) measurement at the lumbar spine (L1-L4) in a 56 year-old otherwise healthy patient on adequate calcium and vitamin D supplementation showed the following:

- Initial: 0.650 g/cm²
- 2 years later: 0.620 g/cm²
- The least significant change (LSC) of the machine is 0.02g/cm²
- The following is correct regarding the decline in the patient’s BMD.

1) There has been a significant decline as the change in BMD in g/cm² is greater than the LSC
2) The BMD does not show a significant decline as it is not greater than 10% over 2 years
3) More information, including a change in T-scores, is required before a judgment can be made
The following is NOT a risk factor included in FRAX:

1) Age
2) Prior history of fracture
3) Bone mineral density at femoral neck (T-score)
4) Bone turnover markers
The following statement is NOT correct about denosumab:

1) It is a human monoclonal antibody against RANK-L that suppresses bone resorption
2) It is an anabolic agent that builds bone
3) It has been approved for use in women with postmenopausal osteoporosis who are at a high risk of fracture
4) It can be used safely in patients with renal impairment
For a patient who is on a PPI for recurrent GERD, which type of calcium should be used:

1) Calcium carbonate
2) Calcium citrate
3) Any calcium pills
4) Calcium should not be given