Postmenopausal Osteoporosis Treatment: PTH analogs, Denosumab, Romosozumab

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Disclosures

• I have no relevant financial disclosures.

• No off-label/investigational use of commercial products/devices will be discussed.

This lecture will focus on *postmenopausal osteoporosis* (PMO)

Male Osteoporosis:

Glucocorticoid-induced osteoporosis:
Learning Objectives

1. Utilize pharmacologic and non-pharmacologic treatments for PMO.

2. Identify the risks and benefits of newer pharmacotherapies for PMO to help educate patients and select the appropriate medication.

3. Assess response to osteoporosis treatment and know what constitutes a “treatment failure”.
Outline

• Treatment options for postmenopausal osteoporosis
  – Non-pharmacologic aspects of treatment
  – Newer prescription medications

• Assessing response to treatment
Case #1

- 65 yo F with a h/o hypothyroidism presents for discussion of newly diagnosed osteoporosis.
  - Lowest T-score -2.5 at right femoral neck on screening DXA
  - No secondary causes of osteoporosis identified
  - Plan to initiate alendronate 70mg PO qweek
  - She asks what else she could be doing to treat her osteoporosis
Which of the following are important components of osteoporosis treatment?

a) Physical activity with weight bearing exercise
b) Adequate calcium and vitamin D
c) Adequate dietary protein intake
d) Fall prevention
e) All of the above
Which of the following are important components of osteoporosis treatment?

- Physical activity with weight bearing exercise
- Adequate calcium and vitamin D
- Adequate dietary protein intake
- Fall prevention
- All of the above
Non-Pharmacologic Treatments of Osteoporosis

- Physical Activity including weight-bearing exercise & balance training
Exercise for Bone Health

• Weight-Bearing Exercise: Walking, jogging, Tai Chi, stair climbing, dancing, etc.
  – NOT biking or swimming

• Should be done throughout life +/- resistance training and posture/balance exercises

• Has small improvements in BMD (2% at L-spine) & helps slow bone loss in older groups
  – Greater impact on decreasing fall risk

Non-Pharmacologic Treatments of Osteoporosis

- Physical Activity including weight-bearing exercise & balance training
- Fall prevention
- Smoking cessation
- Weight maintenance*
- Avoid bone-harming medications, if possible
- Avoid excess alcohol and caffeine
- Adequate calcium/vitamin D/protein
Calcium Recommendations

- Calcium 1,200mg/day, including and preferably via diet
  - 1 serving = 200-300mg of Calcium

*Non-dairy sources available (www.nof.org)*

Images courtesy of www.express.co.uk; eintimex.org; newsroom.heart.org
Calcium Supplement Formulations

• Calcium Carbonate
  – Take WITH food

• Calcium Citrate
  – Take with OR without food
  – More expensive
  – Better absorbed in some conditions
“Natural” Sources of Vitamin D

• Sun
  – 5-10 minutes on a bright summer day = 3,000 IU
  – Lots of variation (winter) & has other risks

• Food

Images courtesy of www.benekeith.com; http://www.slideshare.net/pm18aug/vitamins-minerals-52217779; LiveStrong.com
Bikle S et al. Vitamin D: Production, Metabolism, Mechanism of Action and Clinical Requirements. Primer on the Metabolic Bone Diseases. 8th Ed.
Vitamin D Supplements

• Different Supplement Formulations:
  – D₂ (Ergocalciferol) = Plant based
  – D₃ (Cholecalciferol) = Animal based (more effective)

• Can be taken on an empty stomach or with food

• Goal 25OHD > 30 ng/mL
  – Avoids treatment-related hypocalcemia
  – Optimizes pharmacologic treatments
  – Fat Soluble Vitamin (more is NOT better)

Swanson, CM et al. *Higher 25(OH)D₂ is Associated with Lower 25(OH)D₃ and 1,25(OH)₂D₃*. JCEM 2014
Romagnoli E et al. *Short and long-term variations in serum calcitropic hormones after a single very large dose of ergocalciferol or cholecalciferol in the elderly*. JCEM 2008.
Nimitphong H et al. *Changes in circulating 25OHD according to VDBP genotypes after vitamin D3 or D2 supplementation*. Nutr J 2013.
Bikle S et al. *Vitamin D: Production, Metabolism, Mechanism of Action and Clinical Requirements*. Primer on the Metabolic Bone Diseases. 8th Ed.
Calcium & Vit D Are Still Good!

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trials (No. participants)</th>
<th>Risk Ratio, M-H, Random, 95% CI</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td><strong>Coronary heart disease</strong></td>
<td></td>
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<tr>
<td>Overall</td>
<td>5 (48,460)</td>
<td>1.02 (0.96-1.09)</td>
<td>0.51</td>
</tr>
<tr>
<td>Calcium alone</td>
<td>3 (4,128)</td>
<td>1.15 (0.88-1.50)</td>
<td>0.30</td>
</tr>
<tr>
<td>Calcium with D</td>
<td>4 (45,062)</td>
<td>1.01 (0.95-1.08)</td>
<td>0.69</td>
</tr>
<tr>
<td>Calcium with D + WHI (NPS)*</td>
<td>4 (24,082)</td>
<td>0.95 (0.86-1.04)</td>
<td>0.23</td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td></td>
<td></td>
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<tr>
<td>Overall</td>
<td>17 (62,383)</td>
<td>0.96 (0.91-1.02)</td>
<td>0.18</td>
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<tr>
<td>Calcium alone</td>
<td>7 (6,933)</td>
<td>1.03 (0.88-1.21)</td>
<td>0.68</td>
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<tr>
<td>Calcium with D</td>
<td>12 (56,180)</td>
<td>0.95 (0.89-1.01)</td>
<td>0.11</td>
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<tr>
<td>Calcium with D + WHI (NPS)*</td>
<td>12 (35,200)</td>
<td>0.97 (0.91-1.04)</td>
<td>0.41</td>
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<tr>
<td><strong>Myocardial infarction</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Overall</td>
<td>7 (51,111)</td>
<td>1.08 (0.93-1.25)</td>
<td>0.32</td>
</tr>
<tr>
<td>Calcium alone</td>
<td>5 (6,333)</td>
<td>1.37 (0.98-1.92)</td>
<td>0.07</td>
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<tr>
<td>Calcium with D</td>
<td>5 (45,796)</td>
<td>1.03 (0.91-1.16)</td>
<td>0.65</td>
</tr>
<tr>
<td>Calcium with D + WHI (NPS)*</td>
<td>5 (24,816)</td>
<td>1.07 (0.90-1.26)</td>
<td>0.45</td>
</tr>
</tbody>
</table>

**Fig. 5.** Sensitivity analyses based on type of supplementation. *Post hoc subgroup analysis of the Women's Health Initiative (WHI) in participants with no personal supplements at baseline (NPS) using the trial investigators' internal data set.\(^{28}\) M-H = Mantel-Haenszel. This method estimates the amount of between-study variation by comparing each study's result with a Mantel-Haenszel fixed-effect meta-analysis result.
Case #2

- 79yo F with a h/o MI 6 months ago and severe osteoporosis presents to discuss medication options after completing a 2-year course of teriparatide (2019-2021)
  - Right hip fracture s/p ground level fall 2019
  - No secondary causes of osteoporosis identified on 2019 evaluation
  - Asymptomatic vertebral compression fracture (VCF) identified 2019
  - T-score improved from -3.5 to -3.0 on teriparatide with no fractures while on therapy
What medication would you recommend for this woman?

a) Denosumab 60mg SQ q6months (Prolia)
b) Denosumab 120mg SQ qmonth (Xgeva)
c) Alendronate 70mg PO qweek
d) Abaloparatide 80 mcg SQ daily
e) Romosozumab 210mg SQ monthly x 1 year
What medication would you recommend for this woman?

A. Denosumab 60mg SQ q6months (Prolia)
B. Denosumab 120mg SQ qmonth (Xgeva)
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D. Abaloparatide 80 mcg SQ daily
E. Romosozumab 210mg SQ monthly x 1 year
Who Gets Pharmacologic Treatment?

- Fragility (hip or vertebral) fracture
- T-score ≤ -2.5
- Osteopenia + FRAX score
  - ≥ 3% (hip) and/or
  - ≥ 20% (major osteoporotic fracture)
- Consider tx for those with rapid, excess (non-physiologic) bone loss
  - Glucocorticoids, aromatase inhibitors, etc.

Camacho et al. AACE Guidelines for Dx & Tx of Postmenopausal Osteoporosis. Endocrine Practice 2020.
FDA-Approved Medications for PMO

- Oral Bisphosphonates*
  - Alendronate (Fosamax) 70mg PO qweek
- IV Bisphosphonate (Zoledronic Acid 5mg annually)*
- Denosumab (Prolia) 60mg SQ injection q6months
- Teriparatide (Forteo) 20mcg daily SQ injection
- Abaloparatide (Tymlos) 80mcg daily SQ injection x 2 yrs
- Romosozumab (Evenity) 210mg SQ injection monthly x 12 months

* Requires renal adjustment; only meds that don’t need to be followed by subsequent therapy.
Osteoporosis Treatment
(Pharmacologic)

Anti-Resorptives

- Estrogen/SERMs (Raloxifene)
- Bisphosphonates (Alendronate, Zoledronic Acid)
- RANKL Inhibitor (Denosumab aka Prolia)
Denosumab (aka Prolia)
Progressive BMD Gains Out to 10 years with Densoumab

Lumbar Spine 21.7%
Total Hip 9.2%

Medication Sequence Matters!

Figure 1: DATA-Switch study design

Medication Sequence Matters!

Figure 3: Mean percent change (SEM; error bars) in bone mineral density from baseline to 48 months in the lumbar spine, 1/3 distal radius, femoral neck, and total hip.

* p<0.01 versus both other groups. † p<0.05 versus both other groups. ‡ p<0.0005 versus both other groups.

Denosumab – Adverse Events

• Similar to bisphosphonates:
  – Hypocalcemia
  – Osteonecrosis of the Jaw (ONJ)
  – Atypical Femur Fracture (AFF)
Osteonecrosis of the Jaw (ONJ)

- Risk Factors:
  - Concurrent glucocorticoids/chemotherapy
  - Invasive dental procedures (extractions, implants)


www.nof.org
Subtrochanteric Atypical Femur Fractures

• What to Look For?
  – Thigh/groin ache
  – Get xray +/- MRI and refer to ortho

• Incidence:
  – May be duration related - rise in age-adjusted incidence rates from 1.8/100,000 per year with a 2-year exposure to 113/100,000 per year with exposure from 8 to 9.9 years.
  – Risk decreases 70%/year since last bisphosphonate use

Fig. 1. Risks associated with bisphosphonate use and other health outcomes. The likelihood of suffering fractures and other adverse events in adults is shown. For fractures, the risk of fractures on BP therapy and for stroke on aspirin therapy is illustrated. Fracture incidence rates are age-standardized, whereas for others they represent crude rates in the US. For atypical femoral fracture, the risks represent those reported while on BP therapy for 5 and 10 years. For osteonecrosis of the jaw, a single risk estimate is reported because of the paucity of evidence for a duration effect.
Denosumab – Adverse Events

• Similar to bisphosphonates:
  – Hypocalcemia
  – ONJ
  – AFF

• Infection/skin reactions?
• Injection-site reaction
• Musculoskeletal pain
• Rapid offset of fracture protection
“Cancel the Denosumab Holiday”


Slides courtesy of E. Michael Lewiecki “Long-Term Treatment” MBDS 2016.
Vertebral Fractures After Stopping Denosumab

• 24 women with 112 fractures occurred 8-16 months after last denosumab injection
  – Majority had multiple vertebral fractures
    • More in those getting vertebroplasty
  – Risk factors (not age):
    • Prevalent Fracture
    • Treatment duration > 2 years
    • Treatment naïve
    • Within 1st year after stopping denosumab
    • Aromatase Inhibitor Use

Anastasilakis et al. Clinical features of 24 Patients With Rebound-Associated Vertebral Fractures After Denosumab Discontinuation: Systematic Review & Additional Cases. JBMR 2017
Case #3

- 68yo F with h/o PMO s/p 10 years of denosumab therapy (with 5 years of BP prior to denosumab initiation)
  - No h/o fracture
  - Lowest T-score now -1.1 at left femoral neck
Does she need ongoing therapy?
If yes or no, what medication?

a) Yes – continue denosumab to target a T-score in the normal range
b) No – stop denosumab with no subsequent therapy
c) No – stop denosumab and transition to alendronate or zoledronate
d) No – stop denosumab and transition to teriparatide
Does she need ongoing therapy? If yes or no, what medication?

Yes – continue denosumab to target a T-score in the normal range

No – stop denosumab with no subsequent therapy

No – stop denosumab and transition to alendronate or zoledronate

No – stop denosumab and transition to teriparatide
Total Hip BMD & Non-Vertebral Fracture Risk on 10 yrs of Denosumab

Ferrari et al. Relationship Between BMD T-score and Nonvertebral Fracture Risk Over 10 Years of Denosumab Treatment. JBMR 2019.
Transitioning Off Denosumab

- Consider exit plan *prior to* denosumab initiation

- Alternative anti-resorptive therapy should be initiated 6 months after final denosumab injection

Transitioning Off Denosumab

1. Young patient with low risk of fracture
   - Denosumab treatment is generally not recommended

2. Denosumab treatment for short duration [i.e. up to 2.5 years] and low fracture risk
   - Switch to oral BPs for 12-24 months or administer zoledronate for 1-2 years depending on re-evaluation of BTMs and BMD

3. Denosumab treatment for long duration [i.e. more than 2.5 years] and/or high fracture risk
   - Continue denosumab for up to 10 years [Individualized decision after that timepoint]
   - Switch to zoledronate:
     - Begin 6 months after last denosumab injection and measure BTMs 3 and 6 months later. Consider repeated infusion of zoledronate in case of persistently increased BTMs
     - In case BTMs are not available administer zoledronate 6 and 12 months after last denosumab injection
     - If zoledronate is not an option due to availability, patient preference or intolerance: treat with oral BPs for 12-24 months depending on re-evaluation of BTMs and BMD

Transitioning Off Denosumab

- Avoid vertebroplasty and/or monotherapy with teriparatide

  - Prompt re-initiation of denosumab

    - or

    - Treat with i.v. zoledronate or oral BPs

    - or

    - Consider combination of denosumab and teriparatide for 2 years followed by zoledronate

VFx occurring within 1-2 years after denosumab discontinuation

Case #4

• 70yo F with a h/o GERD with esophagitis presents to discuss therapy options for newly diagnosed severe PMO.
  – Vertebral compression fracture while lifting her grandson → DXA with T-score -3.2 at L-spine
  – MI 6 months ago
  – No history of radiation
  – Anticipating tooth extraction soon
  – Travels frequently to see family
  – Negative evaluation for secondary causes
Which medication is the best option?

a) Zoledronate 5mg IV annually for 3 years
b) Teriparatide 20 mcg SQ daily x 2 years
c) Abaloparatide 80 mcg SQ daily x 2 years
d) Romosozumab 210mg SQ monthly x 1 year
Which medication is the best option?

A. Zoledronate 5mg IV annually for 3 years

B. Teriparatide 20 mcg SQ daily x 2 years

C. Abaloparatide 80 mcg SQ daily x 2 years

D. Romosozumab 210mg SQ monthly x 1 year
Osteoporosis Treatment
(Pharmacologic)

**Anti-Resorptives**
- Bisphosphonates (Alendronate, Zoledronic Acid)
- RANKL Inhibitor (Denosumab aka Prolia)
- Estrogen/SERMs (Raloxifene)

**Anabolics**
- PTH Analog (Teriparatide aka Forteo)
- PTH-rp Analog (Abaloparatide aka Tymlos)
- Sclerostin Ab (Romosozumab aka Evenity)

**OC**
(Bone Resorption)

**OB**
(Bone Formation)
Teriparatide (Forteo)

- PTH 1-34
- Daily subcutaneous injection
- Increases BMD 10% at L-spine and 2-3% at total hip
- Decreased fracture risk at spine (65-80%) and non-vertebral sites (30-48%)
- Only use for 2 years?? - must use anti-resorptive afterwards to maintain BMD

- Side Effects:
  - Hypercalemia/hypercalciuria
  - Myalgias/Arthralgias
  - Osteosarcoma (not really)
Teriparatide (Forteo) Label Change

- Nov 2020: FDA approved removal of 2-year lifetime treatment limitation and boxed warning about the potential risk of osteosarcoma.
- New label: Teriparatide use 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.

**Features of patients who may benefit from long-term teriparatide use**

- Very high fracture risk, unable to come off glucocorticoid therapy
- High fracture risk, with P1NP level that remains high after 2 years on teriparatide
- High fracture risk, with multiple vertebral compression fractures at baseline but none while on teriparatide
- Adynamic renal bone disease
- Severe chronic obstructive pulmonary disease and vertebral compression fractures

P1NP = procollagen type 1 N-terminal propeptide

Abaloparatide (Tymlos)

- PTH-rp analog
- FDA Approved 4/2017 for postmenopausal osteoporosis
- Daily subcutaneous injection
- Increases BMD 11% at L-spine, 4% at hip
- Decreased vertebral and non-vertebral fractures over 18 months by 86% and 43%, respectively
- Must be followed by anti-resorptive agent
- 2 year total duration of teriparatide/abaloparatide

Abaloparatide vs. Teriparatide

• Different labels with regards to osteosarcoma risk and duration of use (for now)

• Similar side effects

• Abaloparatide does not require refrigeration for up to one month once opened

• 30 injections/pen vs. 28 injections/pen

• Good for SEVERE osteoporosis (T-score <-3.0; vertebral fracture) or in those who fail bisphosphonate therapy

Why not romosozumab? What is romosozumab? How do you say romosozumab?
Romosozumab (Evenity)

- **210mg SQ monthly injection**
  - Requires two SQ injections to administer the 210mg dose
  - Injected in thigh, abdomen or upper arm
  - No dose CKD adjustment – higher risk of hypocalcemia

- **Adverse events:**
  - Hypocalcemia
  - Headache
  - Arthralgia
  - Hypersensitivity
  - ONJ
  - AFF
  - Injection site rxn
  - CV Events*

*Cannot give within 12 months of MI/CVA

Evenity Prescriber Information
Fig. 1. Photos of the skull of a patient with sclerosteosis (A) and an individual without bone disease (B). From the collection of the University of Pretoria, South Africa.
Sclerostin

Image Courtesy of Padhi et al Pharmacokinetics & Pharmacodynamics 2013.

Figure 1. Proposed effects of Wnt signaling, sclerostin binding to LRP5/6, and a sclerostin antibody (romosozumab) on osteoblast formation. Lrp, lipoprotein receptor-related protein coreceptor; PINP, serum type I aminoterminal propeptide; OC, osteocalcin; BSAP, bone-specific alkaline phosphatase; sCTx, serum C-telopeptide.
### Which Medication to Choose? Fracture Relative Risk Reduction*

<table>
<thead>
<tr>
<th></th>
<th>Vertebral Fx</th>
<th>Hip Fx</th>
<th>Non-vertebral Fx</th>
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</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>35-65%</td>
<td>45-55%</td>
<td>23%</td>
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<tr>
<td>Zoledronate</td>
<td>70%</td>
<td>41%</td>
<td>25%</td>
</tr>
<tr>
<td>Denosumab</td>
<td>68%</td>
<td>40%</td>
<td>20%</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>65%-80%</td>
<td>**</td>
<td>40%</td>
</tr>
<tr>
<td>Abaloparatide</td>
<td>86%</td>
<td>--</td>
<td>43%</td>
</tr>
<tr>
<td>Romosozumab</td>
<td>73%</td>
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</table>

*For post-menopausal osteoporosis vs. placebo
**Numerically fewer hip fractures in TPTD group vs. placebo

Source: Primer for Metabolic Bone Diseases and Disorders of Mineral Metabolism 8th Edition. 2013; ACTIVE Trial; FRAME Study
Which Medication to Choose?

Which Medication to Choose?

AACE/ACE 2020 POSTMENOPAUSAL OSTEOPOROSIS TREATMENT ALGORITHM

Lumbar spine or femoral neck or total hip T-score of ≤-2.5, a history of fragility fracture, or high FRAX fracture probability*

Evaluate for causes of secondary osteoporosis

Correct calcium/vitamin D deficiency and address causes of secondary osteoporosis

• Recommend pharmacologic therapy
  • Education on lifestyle measures, fall prevention, benefits and risks of medications

High risk/no prior fractures**

• Alendronate, denosumab, risendronate, zoledronate***
  • Alternate therapy:ibandronate, raloxifene

Reassess yearly for response to therapy and fracture risk

Increasing or stable BMD and no fractures

Consider a drug holiday after 5 years of oral and 3 years of IV bisphosphonate therapy

Resume therapy when a fracture occurs, BMD declines beyond LSC, BTM’s rise to pretreatment values or patient meets initial treatment criteria

Progression of bone loss or recurrent fractures

• Assess compliance
  • Re-evaluate for causes of secondary osteoporosis and factors leading to suboptimal response to therapy

• Switch to injectable antiresorptive if on oral agent
  • Switch to abaloparatide, romosozumab, or teriparatide if on injectable antiresorptive or at very high risk of fracture
  • Factors leading to suboptimal response

Very high risk/prior fractures**

• Abaloparatide, denosumab, romosozumab, teriparatide, zoledronate***
  • Alternate therapy: Alendronate, risendronate

Reassess yearly for response to therapy and fracture risk

Denosumab
  • Continue therapy until the patient is no longer at high risk and ensure transition with another antiresorptive agent

Romosozumab for 1 year
  • Sequential therapy with oral or injectable antiresorptive agent

Abaloparatide or teriparatide for up to 2 years
  • Sequential therapy with oral or injectable antiresorptive agent

Zoledronate
  • If stable, continue therapy for 6 years****
  • If progression of bone loss or recurrent fractures, consider switching to abaloparatide, teriparatide or romosozumab

ABBREVIATIONS GUIDE
BMD – bone mineral density
LSC – least significant change
BTM – bone turnover marker

* 10-year major osteoporotic fracture risk ≥20% or hip fracture risk ≥3%. Non-US countries/regions may have different thresholds.
** Indicators of very high fracture risk in patients with low bone density would include advanced age, frailty, glucocorticoids, very low T scores, or increased fall risk.
*** Medications are listed alphabetically.
**** Consider a drug holiday after 6 years of IV zoledronate. During the holiday, an anabolic agent or a weaker antiresorptive such as raloxifene could be used.

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Which Medication to Choose?

Alendronate

Zoledronate
Denosumab?
Teriparatide
Abaloparatide
Romosozumab

Teriparatide
Abaloparatide
Romosozumab
Zoledronate
Denosumab?

Images courtesy of BethanyLuthernVillage.org; empr.com;
Figure 2. The declining proportion of patients receiving registered pharmacological therapy for osteoporosis after hospitalization for a hip fracture (3).
Monitoring on Treatment

• Fracture incidence
• Bone Turnover Markers (BTMs)
  – Preferred markers:
    • CTX (bone resorption)
    • P1NP (bone formation)
  – Morning, fasted blood draw
• DXA q1-2 years at SAME facility on SAME machine
  – Monitor BMD (NOT T-score) at L-spine and Total Hip
  – BMD stable/improving = good
  – BMD declining → consider treatment failure
Treatment “Failure”

• Significant BMD loss despite treatment
• 2+ fractures while on treatment
• Lack of response in bone turnover markers to anti-resorptive therapy

• What to do?
  – Assess adherence/proper administration
  – Malabsorption?
  – Evaluate for secondary causes of osteoporosis/BMD loss (ensure adequate calcium/vitamin D)
  – Consider change in therapy

Camacho et al. AACE Guidelines for Dx & Tx of Postmenopausal Osteoporosis. Endocrine Practice 2020.

Summary

• Non-pharmacological therapy is an important part of osteoporosis treatment

• All osteoporosis meds except bisphosphonates need subsequent therapy
  – Critical for denosumab

• For individuals at high fracture risk:
  – Sequential therapy is best but any med is better than no med

• Stable BMD is an adequate response to therapy
Thank you!