Monitoring Postmenopausal Osteoporosis: Which Modalities and How Often?

Orlando, FL

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Disclosure and Conflicts of Interest

I serve on Advisory Boards of Amgen, Merck and Radius

and

have received honoraria from Amgen and Merck

Michael McClung, MD          2016
Objectives

• Highlight the 2015 ASBMR Task Force and 2016 AACE Osteoporosis Clinical Practice Guidelines
• Monitoring during treatment – what modalities and how often?
• Monitoring during drug holiday – what modalities and how often?
• Defining treatment “failures”
**Background**

A systemic condition of decreased bone mass and microarchitectural deterioration resulting in impaired bone strength and increased risk for fractures\(^1\)

- **Objectives of therapy**
  - improve bone strength
  - reduce risk of fractures

- Several treatments have been documented to effectively reduce the risk of serious fractures in patients with postmenopausal osteoporosis

Images courtesy of Dr David Dempster

Objectives of Monitoring

1. To determine if drug is having an effect. If not, why?
   a) poor absorption
   b) poor compliance
   c) resistance

2. To guide long-term therapy
   a) continue, change or stop treatment
   b) risk of complications
Mechanisms of Fracture Risk Reduction

Anti-resorptive Therapy

Reduces bone turnover:
resorption faster than formation

Reduces "stress risers"
Closes remodeling space
Increases bone density

Preserves microarchitecture
Increases mineralization

Increases bone strength
Reduces fracture risk

**Mechanisms of Fracture Risk Reduction**

- **Anabolic Therapy**
  - Increases bone turnover: formation > resorption
  - New bone formation
  - Increases cortical porosity
  - Decreases mineralization
  - Improves trabecular microarchitecture
  - Increases bone density
  - Increases bone strength
  - Reduces fracture risk

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Tools to Monitor Therapy

- Bone mineral density
  - By DXA of lumbar spine and/or total hip
- Markers of bone turnover
- Estimates of fracture risk — FRAX
DXA Measurements of Spine and Hip

Lumbar spine

Proximal femur

Femoral neck

Total hip
The relationship between BMD and fracture risk varies with age.

Kanis et al, *Osteopor Int* 2001
Alendronate: BMD Response

*Patients: Low bone mass without vertebral fractures*

Lumbar spine BMD

Femoral neck BMD

Liberman et al, *NEJM* 1995
Average BMD Responses to Therapy: Clinical Trials in Women with Osteoporosis

% Change from Baseline at 2 Years

Lumbar spine

Femoral neck

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OOC
Spine BMD Responses in EPIC Study: Placebo

373 women ages 45-59 followed for 4 years

Number of Patients

% Change from Baseline to 4 Years

Precision error
Spine BMD Responses in EPIC Study: Treated

373 women ages 45-59 followed for 4 years

Precision error

4.8% would be observed to “lose” BMD

44% had “no change”

Treatment: alendronate 5 mg daily

51% had significant increase in BMD

Average increase is 4% vs baseline and 6% vs placebo

Number of Patients

% Change from Baseline to 4 Years
Monitoring Therapy with DXA

- Quality assurance of acquisition and analysis is crucial
- Changes occur slowly
  - 1 or 2 years is a substantial time delay before discovering that the patient has had a disappointing response to drug therapy.
- Changes are relatively small with current therapies
  - After 2 years of therapy, many patients do not exhibit a significant change in BMD in spine and almost none have a change in hip BMD greater than the least significant change (LSC) of the test. However, most of these patients are benefiting from the medication.
  - Post hoc analyses of clinical trials show that individuals whose bone mass does not change on drug therapy have a lower fracture risk than those assigned to placebo.

Schousboe JT and Bauer DC. *Curr Osteopor Rep* 2012; 10: 56–63
Monitoring Therapy with DXA

- Magnitude of gain inconsistently correlated with reduction in fracture risk
  - Greater gains in spine density with alendronate or teriparatide did not result in greater reduction in spine fracture risk
- Significance of loss is unknown
  - Randomized controlled trials
  - Randomized controlled trials suggest that very few individuals lose sufficient bone on drug therapy to be confidently detected by bone densitometry.
  - Observing a loss does not always mean ineffective treatment
  - There is no published evidence to demonstrate that management can be improved when those individuals who experience bone loss are correctly identified.

Schousboe JT and Bauer DC. *Curr Osteopor Rep* 2012; 10: 56–63
FNIH Meta-regression
Change in Total Hip BMD vs Reduction in Hip Fracture

MORE (RAL)
FIT II (ALN)
HIP (RIS)
FREEDOM (DMAB)
Clodronate

Bubble size ~ to n fractures in study

Courtesy of Dr D Black et al, ASBMR 2015

+1% BMD change = -11.11% in RR (95% CI -14.54% to -7.54%, p = 0)
Treatments for Osteoporosis are Based on Bone Remodeling
Osteoclasts remove old bone, osteoblasts make new bone & osteocytes sense mechanical stress and direct the activity of ‘clasts & ‘blasts.

Seeman E and Delmas PD; *N Engl J Med* 2006;354:2250-61
Markers of Bone Turnover

Entities that reflect but do not regulate bone remodeling

Marker Responses to Therapy

Vasikaran S et al. for the IOF-IFCC Bone Marker Standards Working Group.
Osteoporos Int 2011;22:391–420
Monitoring Osteoporosis Therapy

**Bone Turnover Markers**

- Changes in resorption markers predict change in forearm BMD relatively well, hip density less well and spine density not at all
- Change in serum P1NP predicts change in BMD moderately well
  - *NOTE: baseline BTM value a better predictor of increase in BMD than is change in BTM with therapy*
- Changes in markers correlate modestly with fracture risk reduction with bisphosphonates but not with other agents
- Effects of monitoring markers on persistence is inconsistent – and no better than follow-up call from office nurse
- Markers are NOT predictive of risks of ONJ or atypical femoral fracture

2. Bruýere O et al. *Best Practice Res Clin Endo & Metabolism* 2014;28:835e841
IOF-IFCC Bone Marker Standards Working Group

- “...their (markers) clinical value for monitoring is limited by inadequate appreciation of the sources of variability, by limited data for comparison of treatments using the same BTM and by inadequate quality control.”

## Monitoring: Bone Density vs Bone Marker

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<th>Hip BMD</th>
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<td>to predict change in BMD</td>
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<td>to determine whether to stop therapy</td>
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* BTM = bone turnover marker
Using BMD Testing to Monitor Therapy

- **Advantages**
  - Results are familiar to patients and clinicians
  - Can identify the non-responders with spine BMD after 1-2 years
  - Changes in hip BMD may predict non-vertebral fracture risk reduction
  - Hip BMD Good understanding of QC and LSC

- **Disadvantages**
  - Response occurs slowly
  - Short-term changes correlate poorly with objective of treatment
Using Bone Markers to Monitor Therapy

- **Advantages**
  - Response occurs quickly
  - Reflects the mechanism of action of drugs
  - Correlates with fracture protection in patients with osteoporosis

- **Disadvantages**
  - Requires referral laboratory
  - Instability of the assays in clinical laboratories
  - Information about lab QC and LSC often unavailable
Highlight 2016 AACE Clinical Guidelines
Guidelines for Frequency of Repeat DXA Testing to Monitor Therapy

- **ISCD 2007**
  - Intervals between BMD testing should be determined according to each patient's clinical status: typically one year after initiation or change of therapy is appropriate, with longer intervals once therapeutic effect is established.

- **NOF 2010**
  - Repeat BMD measurements should generally agree with Medicare guidelines of every 2 years but testing more frequently may be warranted in certain clinical situations.


How Is Treatment Monitored?

- R28. Obtain a baseline DXA, and repeat DXA every 1 to 2 years until findings are stable. Continue with follow-up DXA every 2 years or at a less frequent interval (Grade B; BEL 2).

- R29. Monitor changes in spine or total hip bone mineral density (BMD) (Grade C; BEL 2).

- R30. Follow-up of patients should be in the same facility, with the same machine, and, if possible, with the same technologist (Grade B; BEL 2).

- R31. Bone turnover markers may be used at baseline to identify patients with high bone turnover and can be used to follow the response to therapy (Grade C; BEL 2).

AACE Treatment Algorithm - 2016

A

No prior fracture or lower fracture risk

↓

alendronate, risedronate, zoledronic acid, denosumab

↓

Reassess at least yearly for response to therapy and fracture risk

Progression of bone loss or recurrent fractures

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

Resume therapy when a fracture occurs, BMD declines beyond LSC, or patient meets original treatment criteria

Switch to injectable antiresorptive if on oral agent; switch to teriparatide if on injectable antiresorptive or at very high fracture risk

Increasing or stable BMD, no fractures, T-score > -2.5

Consider a bisphosphonate holiday in 3-5 years

Resume therapy when a fracture occurs, BMD declines beyond LSC, or patient meets original treatment criteria

Camacho P and Petak SM. Draft of 2016 CPG.
AACE Treatment Algorithm - 2016

B

Prior fragility fractures or indicators of high fracture risk

teriparatide, zoledronic acid, denosumab

Reassess at least yearly for response to therapy and fracture risk

Termiparatide for up to 2 years

Sequential therapy with oral or injectable antiresorptive agent

Denosumab and zoledronic acid

Continue therapy or switch to teriparatide if on injectable antiresorptive or at very high fracture risk

Monitoring During Treatment
What Modalities and How Often? - Summary

- DXA of spine and/or total hip
- First test 1-2 years after therapy
- If stable or increasing, measure next
  - if changes in clinical status (including fractures) occur
  - when change in therapy is contemplated
- Measurement of P1NP 3-6 months after beginning teriparatide provides assurance of response
- Measurement of markers may be of value in selected patients
Monitoring for Risk of Atypical Femoral Fracture

- At least 70% of patients have prodromal thigh pain weeks to months before complete fracture occurs.
- Periosteal stress reaction may be evident on DXA scan even in patients without symptoms.

68 year old woman treated for “osteopenia” with alendronate for 10 years.
Atypical Femoral Fracture: Management Tips

- At least 70% of patients have prodromal thigh pain weeks to months before complete fracture occurs
- Periosteal stress reaction may be evident on DXA scan even in patients without symptoms

In patients on therapy for 3 years or more,
  - counsel to report new thigh pain
  - consider extending DXA scan further down the femoral shaft
Monitoring During Drug Holiday
What Modalities and How Often?
Drug Holiday: FDA

• “There are no substantial data available to inform decisions regarding the initiation or duration of a drug holiday.”

Background Document for Meeting of Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee. September 7, 2011

FDA “Guidance”

• Reassess need for treatment after 3-5 years.
  • for lower risk patients, consider a drug holiday
  • for patients at high risk of (spine) fracture, there is benefit in continuing therapy

Highlight 2015 ASBMR Task Force Recommendations

Post-menopausal women treated with oral (≥ 5 yrs) or IV (≥ 3 yrs) BPs

Hip, spine or multiple other osteoporotic fractures before or during therapy

Yes

Reassess benefits/risks
Consider continue BP (1) or change to alternative therapy (2)
Reassess every 2-3 years

No

Hip BMD T-Score ≤ -2.5 (3)
OR
High fracture risk (4)

Yes

Reassess benefits/risks
Consider continue BP for up to 10 yrs (1)
or change to alternative therapy (2)
Reassess every 2-3 years

No

Consider drug holiday
Reassess every 2-3 years (5)

Bisphosphonate “Drug Holiday”

- An “opportunity” – not a necessity
  - Protection from fragility fracture persists 1-2 years upon stopping therapy
  - Risk of atypical fracture appears to decrease quickly (70% per year) when treatment stopped

There is no evidence that a “drug holiday” reduces the risk of any complication of bisphosphonate therapy

No justification for a “drug holiday” with non-bisphosphonate therapies
921 women received IV zoledronic acid 5 mg annually for 5 years.

Randomly assigned to stop or continue for 3 more years.

921 women received IV zoledronic acid 5 mg annually for 5 years.

Randomly assigned to stop or continue for 3 more years.

In FLEX study, markers after stopping alendronate did not identify those patients who experienced a fracture.

Monitoring During Drug Holiday
What Modalities and How Often?

- BMD by DXA
  - after 3-5 years of bisphosphonate therapy
    - to decide if a “holiday” is appropriate
  - at 1-3 years after stopping therapy
    - If BMD declines, consider re-starting therapy

- Bone turnover markers
  - not recommended
  - rarely increase substantially before the “holiday” is over
  - not effective in identifying patients who fracture off therapy
Define Treatment “Failures”
What is Successful Treatment of Osteoporosis?

- R32. BMD is stable or increasing, and no fractures are present (Grade B; BEL 2).
- R33. For patients taking antiresorptive agents, bone turnover markers at or below the median value for premenopausal women are achieved (see section 4.9) (Grade B; BEL 2).
- R34. One fracture is not necessarily evidence of failure. Consider alternative therapy or reassessment for secondary causes of bone loss for patients who have recurrent fractures.
What is Treatment Failure

- International Osteoporosis Foundation
  
  In the face of limited evidence, failure of treatment may be inferred when
  
  a) two or more incident fractures have occurred during treatment
  
  b) serial measurements of bone remodelling markers are not suppressed by anti-resorptive therapy
     
     *value should be below median premenopausal value*

  c) bone mineral density continues to decrease

Diez-Perez A et al. *Osteoporos Int* 2012;23:2769-74
Monitoring Patients with Osteoporosis

The Near Future
Monitoring Patients with Osteoporosis

The Near Future

- New drugs
  - For patients with severe osteoporosis, a sequential treatment regimen will be used
    - Finite interval of anabolic agent followed by an anti-remodeling drug

Anabolic agent → Anti-remodeling Drug → Anabolic agent → Anti-remodeling Drug
6-12 months → 6-12 months → 6-12 months → 6-12 months
Monitoring Patients with Osteoporosis

The Near Future

- New drugs
  - Large, progressive increases in BMD

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FREEDOM FREEDOM Extension

- Total Hip BMD
  - Placebo
  - Denosumab 60 mg QM
  - Odanacatib 50 mg QW

- Femoral Neck BMD
  - Placebo
  - Denosumab 60 mg QM
  - Odanacatib 50 mg QW

Percentage Change From Baseline

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Percentage Change From Baseline

Month
Monitoring Patients with Osteoporosis

*The Near Future*

- Treat to Target
  - Treatment success will not be defined as a mere change in BMD or bone turnover
  - Rather we will choose and change therapies to achieve a specific treatment target
Relationship Between Total Hip T-score on Therapy and Non-vertebral Fracture Risk

Ferrari S et al. ASBMR 2015
Monitoring Patients with Osteoporosis

*The Near Future*

- New Endpoint – **Bone Strength**
  - Finite element analysis (FEA) of routine CT scans provides accurate estimate of bone strength
  - I predict that this will become the treatment “target”
Hip FEA: Denosumab

Monitoring Patients with Osteoporosis

**Summary**

- At present time, BMD of the proximal femur (total hip) remains the best tool to monitor treatment response.
- Markers of bone turnover have a limited role – but may be useful to address specific clinical questions.
- How we monitor – and what our targets become – will change in the near future.
- Both then as well as now, decisions about monitoring must be individualized.
Thank you

Working to prevent

Bone Attacks

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