

Osteoporosis –Sequential Drug Therapy

Daniel L. Hurley, MD FACE
Mayo Clinic, Rochester MN
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Disclosures

- **Industry support**
 - None
- **Off label drug use**
 - None



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Objectives

At the end of the presentation, the attendee will have reviewed:

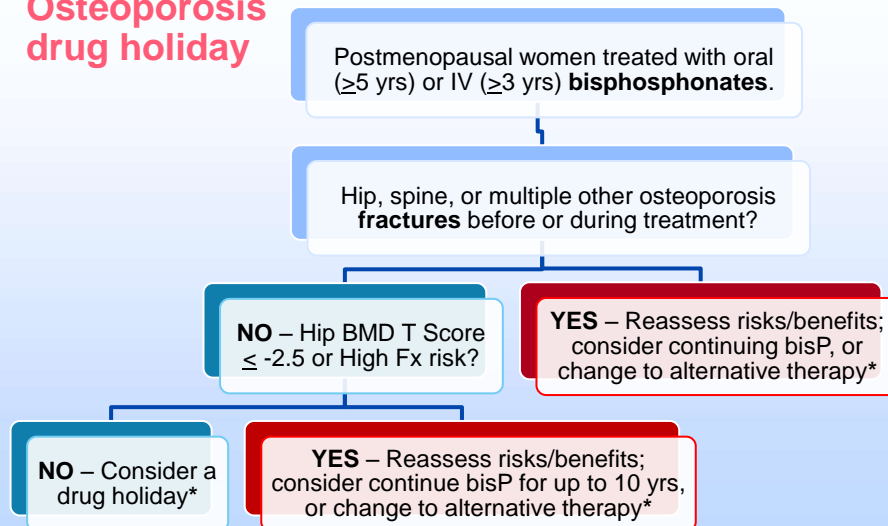
- Drug differences in the duration of skeletal antiresorptive effects during a 'drug holiday'
- Use of antiresorptive and anabolic drugs in sequential or combination therapy for postmenopausal osteoporosis



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ASBMR 2015 Task Force Recommendations

Osteoporosis drug holiday



* Reassess every 2 to 3 years.

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Objectives

2015 ASBMR Task Force recommendations for an osteoporosis-related 'drug holiday'

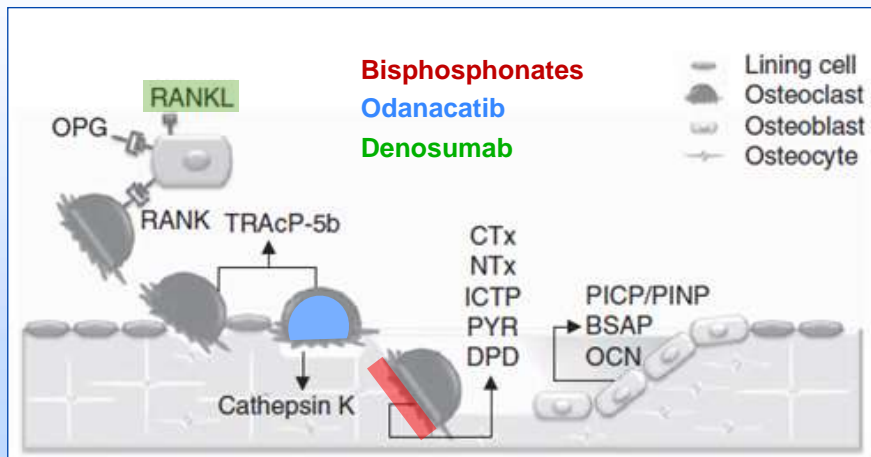
- Drug differences in duration of skeletal antiresorptive effects during a 'drug holiday'



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Bone Remodeling and Bone Turnover Markers (BTMs)

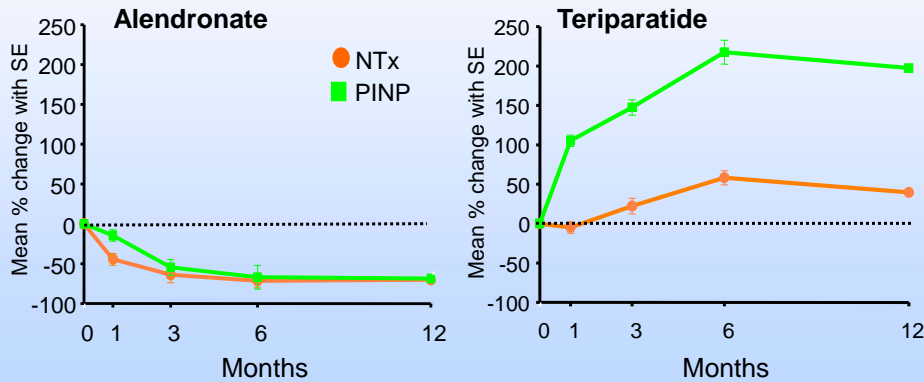
Relationship of BTMs to their origins of bone resorption or bone formation during bone remodeling



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Antiresorptive vs Anabolic Therapy

- The '*anabolic window*' is the time between onset of bone formation to subsequent onset of bone resorption



McClung, et al, ASBMR 2003

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Antiresorptive Therapy and 'Drug Holidays'

Effect on BMD and BTMs during & after 2-years Rx

| Bauer DC. <i>JBMR</i> 2011;26(2):239 | Alendronate, 5–10 mg/day ^b (n = 437) ⁽¹³⁾ | Risedronate, 5 mg/day (n = 398) ⁽¹⁴⁾ | Denosumab, 60 mg/6 month (n = 128) ⁽¹⁵⁾ | Odanacatib, 50 mg/week (n = 20) ⁽⁶⁾ |
|--|---|---|--|--|
| Effects on bone mass^c | | | | |
| 0- to 24-month change on active treatment | | | | |
| Lumbar spine | 6.0%* | 5.0%* | 6.5% ^d | 6%* |
| Femoral neck | 3.0%* | 2.0%* | NA | 3% |
| Total hip | 2.5%* | NA | 3.4% ^d | 1.5% |
| 12-month change after discontinuation ^c | | | | |
| Lumbar spine | -1.3% | -0.8%** | -6.5% ^d | -4.3%** |
| Femoral neck | -0.8% | -1.2%** | NA | -1.4% |
| Total hip | -1.3% | NA | -3.5% ^d | -2.7%** |
| Effects on bone turnover^c | | | | |
| 0- to 24-month change on active treatment | | | | |
| NTX | -65%* | -55%* | NA | -60% ^d |
| sCTX | NA | NA | -65%* | -50% ^d |
| PINP | NA | NA | -70%* | -25% ^d |
| 12-month change after discontinuation | | | | |
| NTX | 23%** | 67%** | NA | 230%** |
| sCTX | NA | NA | 40% ^d | 98%** |
| PINP | NA | NA | 40% ^d | 46% |



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Objectives

2015 ASBMR Task Force recommendations for an osteoporosis-related 'drug holiday'

- Drug differences in duration of skeletal antiresorptive effects during a 'drug holiday'
- **Use of antiresorptive and anabolic drugs in sequential and combination therapy for postmenopausal osteoporosis**
 - **Switch** sequential regimen – to alternate drug
 - **Add** combination regimen – to present drug
 - **Simultaneous** combination regimen – at onset



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Sequential Antiresorptive – Anabolic Rx: Switch regimen

- Alternate drug treatment after ALN or RIS
 - **PubMed search**, from 11 studies prospectively assessing treatment after ALN or RIS in PMO
 - No study had power to assess Fx efficacy
 - All studies \leq 24 mos duration
 - **BMD outcomes – sequential therapy**
 - BMD **maintained** with ALN **switch** to → RAL, RIS, IBN, or ZOL*
 - BMD **improved** with ALN or RIS **switch** to → denosumab* or teriparatide

* Drug switch resulted in significant decline in BTM.



ALN, alendronate. IBN, ibandronate. RIS, risedronate. ZOL, zoledronate. RAL, raloxifene. PMO, postmenopause osteoporosis. P Eiken, *Osteoporos Int* 05 Oct 2015 [Epub. ahead of print].

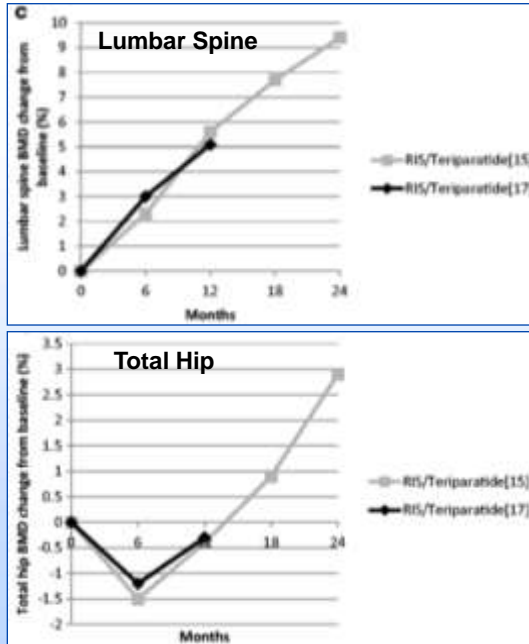
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Sequential PMO Therapy: Switch regimen

Switch from risedronate (RIS) to teriparatide

Figures: BMD (%) change from baseline

2 prospective studies assessing treatment after RIS in women with postmenopausal OP; 12 and 24 mos. duration



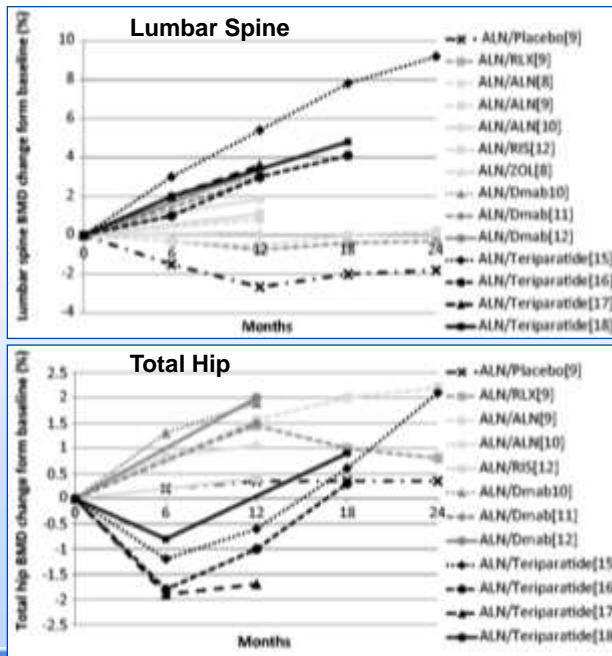
TPTD, teriparatide. PMO, postmenopausal osteoporosis. BMD, bone mineral density. P Eiken, *Osteoporos Int* 05 Oct 2015 [Epub. ahead of print].

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Sequential PMO Therapy: Switch regimen

Switch from alendronate (ALN) to alternate drug therapy

9 prospective studies assessing treatment after ALN in women with postmenopausal OP; 12, 18, 24 mos. duration



OP, osteoporosis. IBN, ibandronate. RIS, risedronate. ZOL, zoledronate. Dmab, denosumab. RAL, raloxifene. BMD, bone mineral density. P Eiken, *Osteoporos Int* 05 Oct 2015 [Epub. ahead of print].

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Combination Antiresorptive – Anabolic Rx Add Teriparatide (TPTD) regimen

- **Change in BMD**
 - Significant BMD ↑ with TPTD **added** to:
 - Prior estrogen Rx¹
 - Prior alendronate Rx²
 - Prior risedronate Rx³

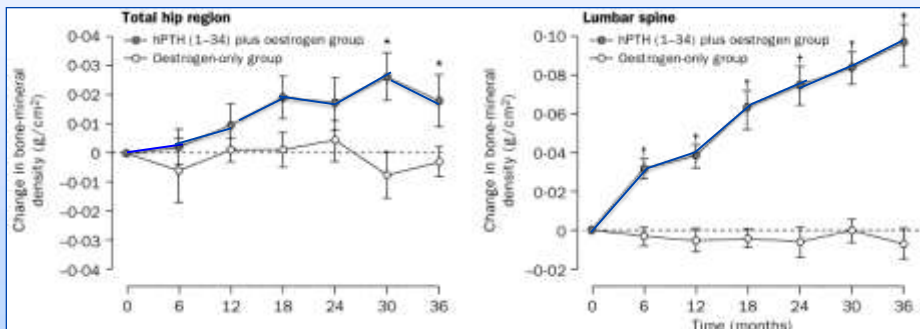


¹Lancet 1997;350(9077):550-5. ²NEJM 2005;353(6):566-75. ³JCEM 2009;94(10):3772-80.

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Combination Antiresorptive – Anabolic Rx Add Teriparatide to estrogen

- TPTD (25 ug/d, 1-34 hPTH) **added** to estrogen
 - RCT for 3-years, n=17
 - **Significant ↑ in BMD and ↓ in vertebral fractures**



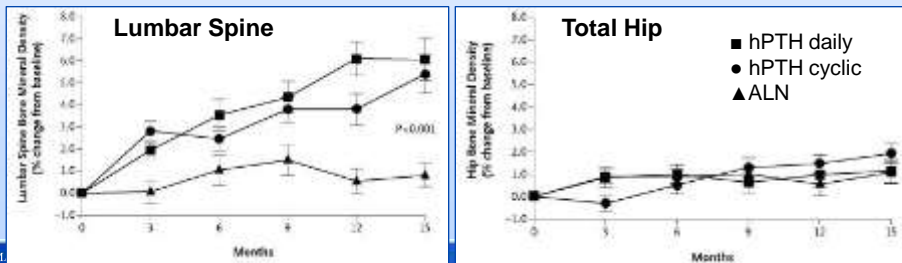
Lindsay R, et. *Lancet* 1997; 350(9077):550-5.

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Combination Antiresorptive – Anabolic Rx Add Teriparatide to Alendronate (ALN)

- TPDT (20 ug, 1-34 hPTH) **added** to ALN

| Treatment | hPTH daily, n=43 | hPTH cyclic, n=40 | ALN only, n=43 |
|---------------|------------------|-------------------|----------------|
| Age | 67 ± 7 | 67 ± 8 | 71 ± 7 |
| Years ALN use | 2.8 | 3.5 | 3.0 |
| T-score Lsp | -2.9 ± 0.9 | -2.8 ± 0.8 | -2.9 ± 0.8 |
| T-score Thip | -2.0 ± 0.9 | -2.1 ± 0.7 | -1.9 ± 0.8 |
| Prevalent VFx | 51% | 45% | 49% |



Cosman F, et al. *N Engl J Med* 2005;353:566-575

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Osteoporosis Antiresorptive – Anabolic Rx Add versus switch to TPTD regimen

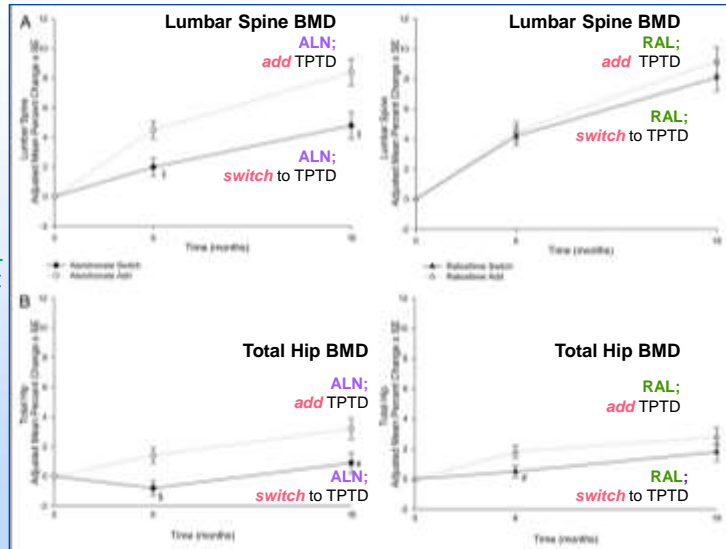
- **Effect on BTMs**
 - BTMs ↑ more with **switch** to TPTD from prior RAL or ALN therapy
 - vs TPTD **add** to RAL or ALN
- **Effect on BMD**
 - BMD ↑ may be greater with TPTD **add** on regimen,
 - due to a greater '*anabolic window*' effect?

Add vs switch to TPTD – from prior ALN or RAL

BMD Change
Randomized open label study in PM women with OP

Alendronate - ALN
Raloxifene - RAL

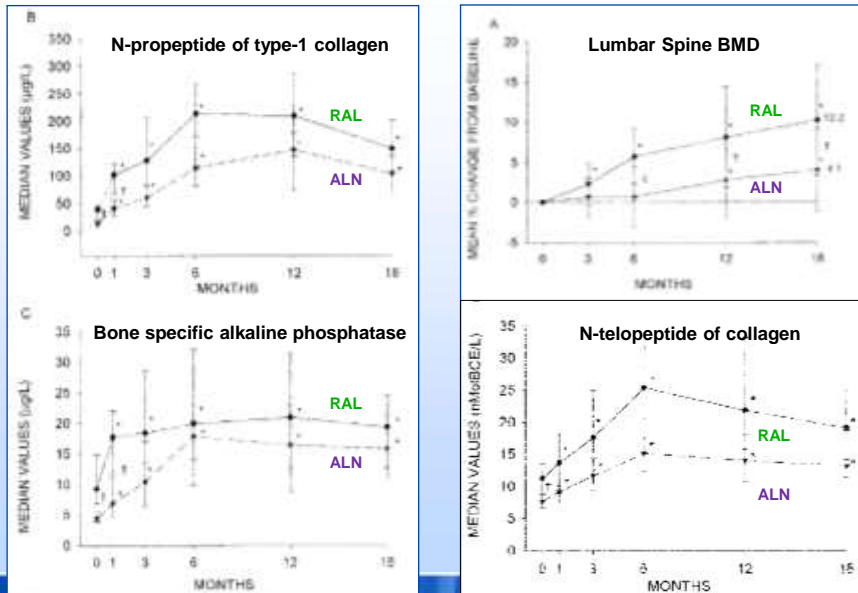
Both ALN and RAL therapy for at least 18 mos prior to TPTD



PM, postmenopausal. OP, osteoporosis. AR, antiresorptive. Cosman F, *JCEM* 2009; 94(10):3772-80

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Switch to TPTD – from prior ALN or RAL



*p<0.05 from baseline. †p<0.05 between Rx's. TPTD, teriparatide. RAL, raloxifene. ALN alendronate. Ettinger B, *JBMR* 2004;19(5):745

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Combination Antiresorptive – Anabolic Rx *Simultaneous onset of TPTD + antiresorptive Rx*

- Studies
 - Teriparatide + raloxifene¹
 - Teriparatide + alendronate^{2,3}
 - Teriparatide + zoledronate⁴
 - Teriparatide + denosumab⁵
- Outcomes
 - **Primary outcome** is change in L-spine BMD
 - *No fracture data*
 - *Studies of short (1-year) duration*



TPTD, teriparatide. BMD, bone mineral density. ¹*JBMR* 2005; 20:1905-11. ²*NEJM* 2003; 349:1207-15. ³*NEJM* 2003;349:1216-26. ⁴*JBMR* 2011;26:503-11. ⁵*Lancet* 2015;386:1147-55.

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Combination Antiresorptive – Anabolic Rx *Simultaneous onset of TPTD + antiresorptive Rx*

- **Change in BMD**
 - Teriparatide + raloxifene (RAL)¹
 - BMD ↑ **greater** at Total-hip vs TPTD alone
L-spine and femur-neck BMD change ns



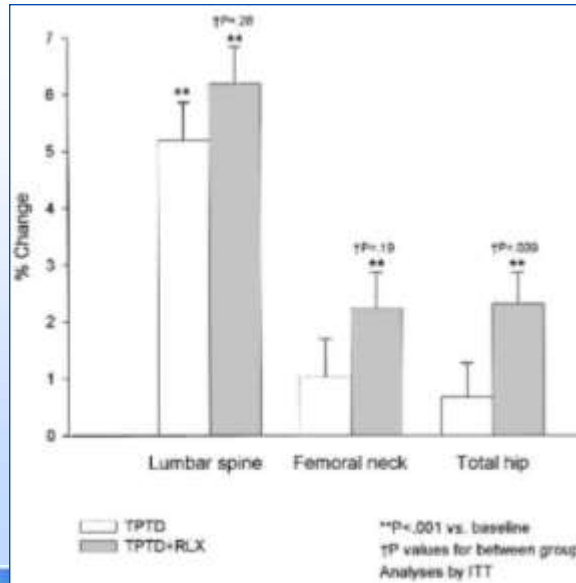
TPTD, teriparatide. BMD, bone mineral density. ¹*JBMR* 2005; 20:1905-11. ²*NEJM* 2003; 349:1207-15. ³*NEJM* 2003;349:1216-26. ⁴*JBMR* 2011;26:503-11. ⁵*Lancet* 2015;386:1147-55.

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Simultaneous onset – teriparatide + raloxifene

RCT to compare
TPTD+RAL (n=69) vs
TPTD alone (n=68)

- **BMD increase** over 6 mos.
 - L-sp ↑ in both groups
 - Hip ↑ only in the TPTD+RAL group
 - **Combined TPTD+RAL with a greater ↑ at the T-hip than TPTD alone**
- **BTM change** over 6 mos.
 - **P1NP** ↑ similar in both groups
 - **CTX** ↑ significantly less with TPTD+RAL



Cosman F, et al. *N Engl J Med* 2005;353:566-575

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Combination Antiresorptive – Anabolic Rx Simultaneous onset of TPTD + antiresorptive Rx

- **Change in BMD**
 - Teriparatide + raloxifene¹
 - BMD ↑ **greater** at Total hip vs TPTD alone
 - Teriparatide + alendronate (ALN)^{2,3}
 - BMD ↑ **variable** vs TPTD alone at the hip
 - TPTD alone with BMD ↓ at cortical bone
 - ALN as 1st line Rx appears to be equal to or better than TPTD alone or TPTD+ALN



TPTD, teriparatide. BMD, bone mineral density. ¹*JBMR* 2005; 20:1905-11. ²*NEJM* 2003; 349:1207-15. ³*NEJM* 2003;349:1216-26. ⁴*JBMR* 2011;26:503-11. ⁵*Lancet* 2015;386:1147-55.

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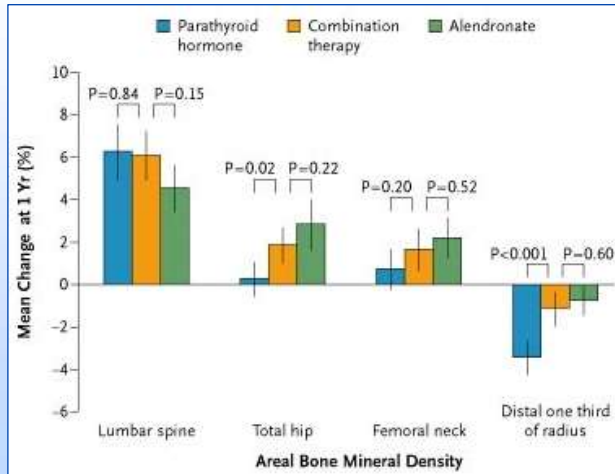
Alendronate + Teriparatide in PM Women *Simultaneous onset of TPTD and ALN*

238 PM women w/o prior bisphosphonate + low hip or spine BMD

- (T score < -2.5, or T score < -2.0 with another OP risk factor)

Randomly assigned to daily treatment

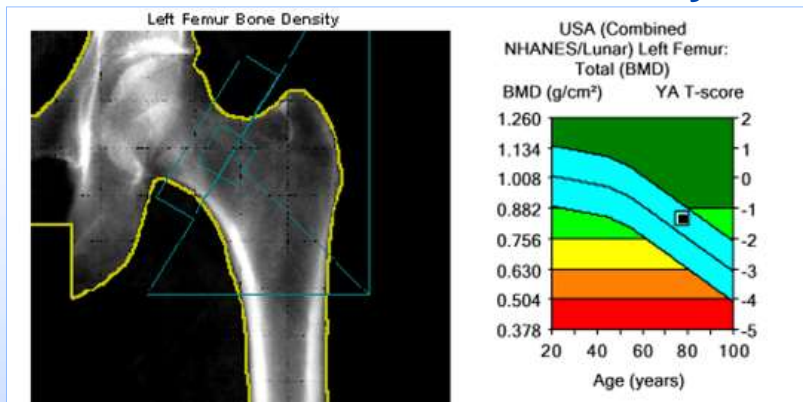
- rhPTH (1-84) (100 µg; n=119), alendronate (10 mg; n=60), or both (n=59) and followed for 12 months
- Spine and hip BMD assessed by DXA and quantitative CT scan



BMD, bone mineral density. OP, osteoporosis. PM, postmenopausal. DXA, dual x-ray absorptiometry. rhPTH, recombinant hormone parathyroid hormone. Black DM, *NEJM* 2003; 349(13):1207-15.

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Femur Bone Structure and Density



| Region | BMD (g/cm ²) | Young-Adult T-score | Age-Matched Z-score |
|------------|--------------------------|---------------------|---------------------|
| Neck Left | 0.827 | -1.5 | 0.5 |
| Total Left | 0.840 | -1.3 | 0.6 |



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Combination Antiresorptive – Anabolic Rx

Simultaneous onset of TPTD + antiresorptive Rx

• Change in BMD

- Teriparatide + raloxifene¹
 - BMD ↑ **greater** at Total hip vs TPTD alone
- Teriparatide + alendronate^{2,3}
 - BMD ↑ **variable** vs TPTD alone at the hip
- Teriparatide + Zoledronate (ZOL)⁴
 - BMD ↑ **greater** vs TPTD alone
 - Better than TPTD alone at the hip
 - Equal to TPTD alone at the spine
 - Better than ZOL alone at the spine

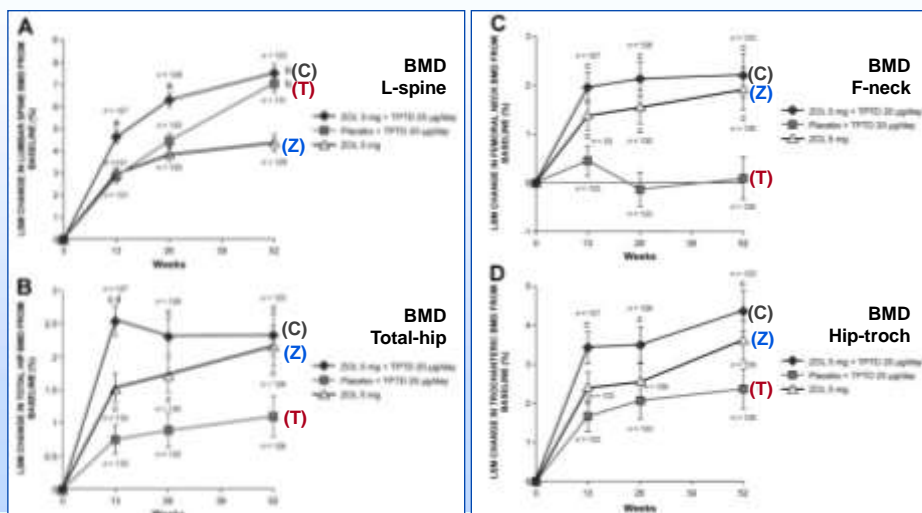


TPTD, teriparatide. BMD, bone mineral density. ¹JBM 2005; 20:1905-11. ²NEJM 2003; 349:1207-15. ³NEJM 2003;349:1216-26. ⁴JBM 2011;26:503-11. ⁵Lancet 2015;386:1147-55.

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Combination Antiresorptive – Anabolic Rx

Simultaneous onset of TPTD and ZOL



TPTD, teriparatide; ZOL, zoledronic acid. Cosman F, *JBM* 2011; 26(3):503

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Combination Antiresorptive – Anabolic Rx

Simultaneous onset of TPTD + antiresorptive Rx

• Change in BMD

- Teriparatide + raloxifene¹
 - BMD ↑ **greater** at Total hip vs TPTD alone
- Teriparatide + alendronate^{2,3}
 - BMD ↑ **variable** vs TPTD alone at the hip
- Teriparatide + Zoledronate⁴
 - BMD ↑ **greater** vs TPTD alone
- Teriparatide + Denosumab⁵
 - BMD ↑ **best** with combination therapy, or TPTD to Dmab; vs Dmab to TPTD switch



TPTD, teriparatide. BMD, bone mineral density. ¹JBM 2005; 20:1905-11. ²NEJM 2003; 349:1207-15. ³NEJM 2003;349:1216-26. ⁴JBM 2011;26:503-11. ⁵Lancet 2015;386:1147-55.

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Denosumab + Teriparatide in PM Women

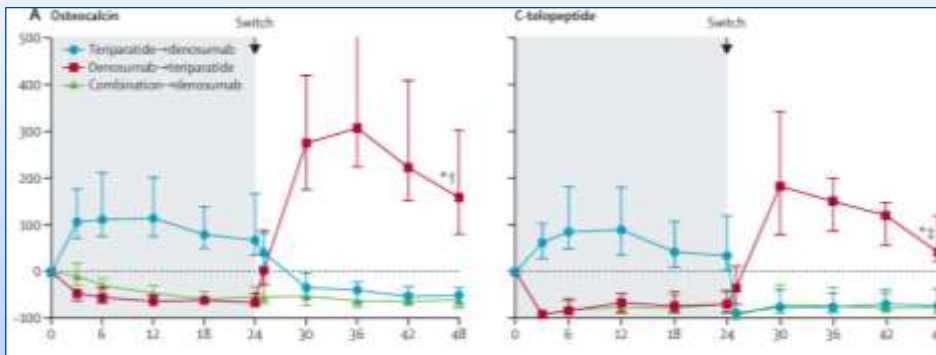
The DATA-Switch study

Figures: Change in BTMs

Osteocalcin (bone formation)

C-telopeptide (bone resorption)

| Years 1-2 | Years 3-4 |
|--------------------|--------------|
| Teriparatide, n=27 | Denosumab |
| Denosumab, n=27 | Teriparatide |
| Combination, n=23 | Denosumab |



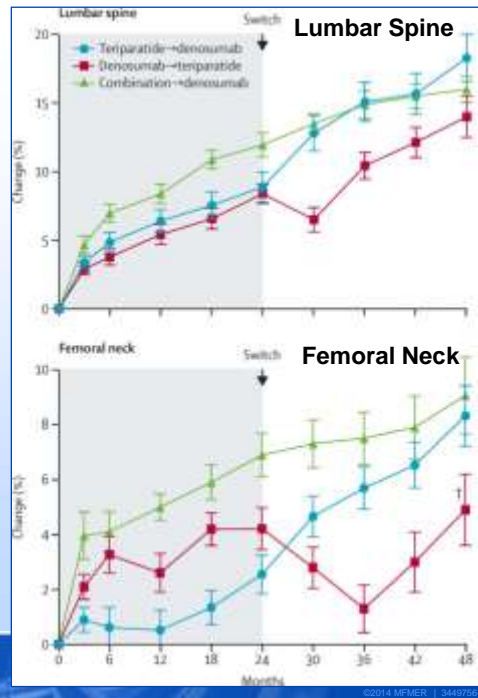
Leder B, Lancet 2015;386:1147.

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Denosumab plus Teriparatide

| Years 1-2 | Years 3-4 |
|--------------------|----------------|
| Teriparatide, n=27 | ► Denosumab |
| Denosumab, n=27 | ► Teriparatide |
| Combination, n=23 | ► Denosumab |

Figures: BMD change (%)



Leder B, *Lancet* 2015;386:1147

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Conclusions

Osteoporosis-related 'drug holiday'

- Based on **FLEX** and **HORIZON** trials
 - **After 3-5 yrs**, management based on Fx risk, to include Fx history and BMD
 - **After 10-yrs**, management in high risk patients as per clinical judgment
- Study limitations
 - Based on ALN and ZOL only
 - Based on VFx reduction
 - In Caucasian women only



ALN, alendronate, ZOL, zoledronic acid. VFx, vertebral fracture.

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Conclusions

Sequential/combination therapy

- With prior **ALN** or **RIS** antiresorptive (AR) therapy
 - BMD **maintained** with ALN *switch* to → RAL, RIS, IBN, or ZOL
 - BMD **improved** with ALN or RIS *switch* to → denosumab or teriparatide
- With **Teriparatide** use
 - **Add** on to prior AR builds BMD better than *switch*, especially for short half-life drugs (RAL, Dmab)
 - AR **switch** to TPTD builds BMD at spine >> hip
 - **Combination** therapy ensures best overall BMD gain at both spine and hip sites, if drug naïve



RAL, raloxifene. Dmab, denosumab. ALN, alendronate. IBN, ibandronate. RIS, risedronate. ZOL, zoledronic acid. TPTD, teriparatide. VFX, vertebral fracture.

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Thank You !

hurley.daniel@mayo.edu



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