Combination and Sequential Therapy for the Treatment of Osteoporosis

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Current pharmacologic management of osteoporosis
• Antiresorptive agents:
  • Hormone/estrogen therapy
  • Selective estrogen receptor modulators
  • Conjugated estrogen/bazedoxifene complex
  • Oral bisphosphonates
    – Alendronate, risedronate, ibandronate
  • Intravenous zoledronic acid
  • Subcutaneous denosumab
• Anabolic agents:
  • Parathyroid hormone analogs
    – PTH 1-84
    – Teriparatide (PTH 1-34)
Choosing anabolic vs. antiresorptive therapy

- As first-line therapy
  - No consensus or guidelines
  - Use in highest risk patients:
    - Patient with recent fracture (within the year)
    - Patients with history of multiple fractures
- As second-line therapy
  - Sometimes mandated by reimbursement
  - Response to anabolic medication different in patients who have already been treated with potent antiresorptive therapy (bisphosphonates and denosumab)
  - No fracture data in this group

Combination therapy rarely used

- Cost and potential for additional side effects/adverse events
- Belief that combination therapy provides no benefit and might even be inferior to TPTD monotherapy
  - In part based on results of the PaTH trial \(^1\)
    - Women randomized to receive PTH monotherapy, alendronate monotherapy or PTH plus alendronate combination therapy

PaTH 12 month changes with PTH1-84 in DXA BMD

- PTH-alendronate combination group showed no greater improvement in spine BMD – a disappointment
- The combination therapy did produce a superior effect on hip and radius BMD
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Caveats in generalizability of PaTH trial

- Daily not weekly alendronate
  - Small uptake into osteoblasts with each dose
- Alendronate is different from other bisphosphonates and other antiresorptives
- PaTH utilized PTH 1-84 (not 1-34)
  - Possible differences in skeletal response
- Study performed in treatment naïve women
  - Results may not apply to treatment experienced women, particularly those on the most potent antiresorptive therapies

Response to TPTD different in treatment naïve and treatment experienced

- Much larger active bone surface in treatment naïve individuals
- In treatment naïve, with acute administration of potent antiresorptive agents
  - Increase in endogenous PTH for up to 12 months
    - Might produce a different response to exogenously administered PTH
- Perhaps unique effects on osteoclasts and/or osteoblasts in treatment experienced individuals

Images used with permission by Dr. Dempster 31 May 2013
Dempster, et al., ASBMR 2007
Re-evaluating the potential role for combination and sequential therapy

- In treatment naïve women
  - Concomitant treatment with intravenous zoledronic acid and TPTD\(^1\)
  - Concomitant treatment with subcutaneous denosumab and TPTD\(^2\)

2. Tsai et al., Lancet 2013
3. Leder et al., JCEM 2014

Treatment naïve: IV zoledronic acid and daily TPTD study overview

- 412 treatment naïve postmenopausal women
  - T score ≤−2.5 at any site or T score ≤−2.0 plus ≥1 op-related fracture
  - Age range 45-87 years, mean 65
  - Mean spine T-score spine -2.9, Hip -1.9
  - Randomized to one of 3 active treatment groups
    - IV ZOL 5 mg
    - IV ZOL 5 mg + Subcut TPTD 20 μg/day
    - IV PBO + TPTD 20 μg/day
  - One-year follow-up


Treatment naïve women: IV Zol and daily TPTD changes in serum β–CTx and PINP

- Graph showing changes in serum biomarkers over time for different treatment groups:
  - ZOL + TPTD
  - TPTD alone
  - ZOL alone


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**Treatment naïve women: IV Zol and daily TPTD**

**percent changes in lumbar spine BMD**

- Mean % change in BMD:
  - ZOL + TPTD
  - TPTD alone
  - ZOL alone

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**Treatment naïve women: IV Zol and daily TPTD**

**percent changes in lumbar spine BMD (2)**

- Mean % change in BMD:
  - Total hip BMD
  - Femoral neck BMD

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**Treatment naïve women: IV Zol and daily TPTD - summary**

- With combination (ZOL+TPTD) therapy:
  - Spine BMD increase similar to TPTD alone
    - Combination >ZOL alone but not greater than TPTD alone
  - Hip BMD increase similar to ZOL alone
    - Combination >TPTD alone
  - Considering hip and spine BMD outcomes together, combination therapy provided the overall largest and fastest BMD outcome

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DATA trial: teriparatide or Dmab monotherapy vs. combination

- 94 postmenopausal women at high risk of fracture (age 51-91)
- 12 month open label randomized controlled trial with three treatment groups:
  - Teriparatide (TPTD) 20 μg SC daily (n=31)
  - Denosumab (DMAB) 60 mg SC Q6 mo (n=33)
  - Both medications (n=30)

Teriparatide or Denosumab monotherapy vs. combination therapy

Teriparatide or Denosumab monotherapy vs. combination therapy (2)
Teriparatide or Denosumab monotherapy vs. combination therapy (3)

Gray bars: BMD gain year 3
Yellow bars: BMD gain year 2

Summary: combination therapy in treatment naïve women
- Combination therapy: all studies consistent with superior BMD gain in the hip compared to TPTD/PTH monotherapy
  - Teriparatide with zoledronic acid
  - Teriparatide with denosumab
  - PTH with alendronate
- Combination therapy superior for BOTH spine and hip BMD gain
  - Teriparatide with denosumab

Teriparatide in the treatment experienced woman: teriparatide monotherapy or combination therapy?
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Teriparatide after prior bisphosphonate treatment

• ADD vs. Switch Studies
  ▪ Spine BMD may not be affected substantially when switching to teriparatide monotherapy compared to adding teriparatide to ongoing antiresorptive
  ▪ Hip BMD routinely declines in Switch Studies over 6-12 months
  ▪ Hip BMD does not decline when TPTD is added to ongoing BP

References:

TPTD after raloxifene or alendronate: effect on total hip BMD

![Graph showing mean % change in total hip BMD over months.](image)

Total hip BMD percent changes from baseline
Completer population

• Hip bone density declined substantially within the first six months, and was still below baseline at the end of the year-long study (residronate or alendronate switch to PTH monotherapy)

References:
Adjusted mean BMD changes from baseline
Total hip

- When women were switched to teriparatide:
  - Hip bone density declined significantly in both groups within the first six months
  - It remained below baseline for the entire first whole year of treatment

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Switch to teriparatide in patients experienced on prior denosumab treatment

- Patients randomized to denosumab arm in DATA trial
  - After 2 years of denosumab alone, switched to teriparatide

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Switch to teriparatide in patients experienced on prior antiresorptive treatment

- Hip BMD declines consistently in all studies in patients on potent antiresorptive agents (alendronate, risedronate, denosumab)
  - Magnitude of BMD decline might be related to potency of antiresorptive effect
- No fracture data available to determine if this decline is associated with a detrimental effect on fracture occurrence
  - Studies small
  - An approach to prevent this BMD decline would be preferable in patients at high risk for hip and other cortical bone fractures.

Teriparatide in treatment experienced: monotherapy vs. combination therapy

- Objective: to compare the effect of adding vs. switching to TPTD in women on prior aln or rlx in a randomized trial
- Subjects: postmenopausal women ≥ 50 years of age on weekly aln (n=102) or daily rlx (n=96) for ≥ 18 months
  - Average treatment duration >4 years
  - Mean age 68
- Protocol: randomize to
  - Continue Aln/Rlx and add TPTD (combination therapy)
  - Stop Aln/Rlx and switch to TPTD (monotherapy)
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**TPTD in treatment experienced switch vs. add:**
bone turnover markers: PINP

P < 0.05; §, P < 0.01; and †, P < 0.001 for percentage change difference between groups within the alendronate or raloxifene stratum

Cosman F, et al., JCEM 2009; 94: 3772–3780

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**TPTD in treatment experienced switch vs. add:**
bone turnover markers: CTX

P < 0.05; §, P < 0.01; and †, P < 0.001 for percentage change difference between groups within the alendronate or raloxifene stratum

Cosman F, et al., JCEM 2009; 94: 3772–3780

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**Teriparatide in treatment experienced switch vs. add: BMD at 6 months**

*P<0.05 within group from baseline
+P<0.05 between treatment groups within each treatment stratum

Cosman F, et al., JCEM 2009; 94: 3772–3780

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**Teriparatide in treatment experienced switch vs. add: BMD at 18 months**

- ALN
- RLX

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**Spine volumetric BMD**

- Add group
- Switch group

Values are medians (IQR range)

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**Estimated spine strength**

- Add group
- Switch group

Values are medians (IQR range)

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*P < 0.01 vs. baseline
p-values for differences between add vs. switch groups are shown above each pair of bars

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**Hip volumetric BMD**

- Add group
- Switch group

Values are medians (IQR range)

*P<0.01 vs. baseline
p-values for differences between add vs. switch groups are shown above each pair of bars


**Estimated hip strength**

- Add group
- Switch group

Values are medians (IQR range)

*P<0.01 vs. baseline; †P<0.05 vs. baseline
p-values for differences between add vs. switch groups are shown above each pair of bars


**Alendronate stratum**

*P<0.01 vs. baseline
p-values for differences between add vs. switch groups are shown above each pair of bars

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Alendronate stratum
Estimated hip strength, month 18

Values are medians (IQ range)

*P<0.01 vs. baseline
p values for differences between add vs. switch groups are shown above each pair of bars

CONFORS trial: TPTD alone for 9 months followed by combination
• 125 women
  • 90% had history of prior AR therapy
    – 70% history of alendronate exposure
• All women received TPTD alone for 9 months
• After 9 months TPTD, randomized to:
  • Continued TPTD alone (n=47)
  • Continued TPTD + ALN 70 mg/wk (n=41)
  • Continued TPTD + RLX 60 mg/day (n=37)
for 9 additional months

Bone turnover


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**Summary**

**Combination therapy studies**

In both treatment naïve as well as in women who have been on prior bisphosphonates, hip BMD increments are superior with combination treatment compared to teriparatide/PTH monotherapy.

**Possible role of combination Rx**

- **Treatment naïve patients:**
  - In general, anabolic therapy should be used alone followed by potent AR
  - Limited role for combining anabolic and AR agents in patients at highest risk for fractures
    - Patients with acute hip or spine fractures
    - Patients with multiple fractures
- **Bisphosphonate/denosumab treated patients:**
  - Bigger role for combination Rx esp in pts with acute hip fracture or very low hip BMD
    - Add TPTD to ongoing AR (possibly switch to most potent AR)
    - Switch to TPTD for 6-9 months followed by re-addition of potent AR
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