Osteoporosis: How to Manage Long-Term Use of Bisphosphonates

AKA – Now What?

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Introduction

• A fracture due to OP occurs every 3 seconds around the world.
• 1 in 3 older women; 1 in 5 older men
  – Will experience fragility fx after age 50.
• Solid evidence from randomized placebo-controlled trials of 3-4 years duration, supports use of BPs in decreasing risk:
  – Of vertebral Fx’s (by 40-70%)
  – Of hip Fx’s (by 20-50%)
  – Of non-vert Fx’s (by 15-39%)
## Fracture Risk Reduction in RCTs

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Background

• Bisphosphonates (BPs) have dominated the landscape of osteoporosis therapies for the last 2 decades!
  – Between 2005-2009, approximately 150 million Rx’s were dispensed in the US for oral BPs.
  – 5.1 million patients over 55 received a Rx in 2008.

• Increasing evidence for an effect of prolonged BP use on rare adverse events (AEs), namely Atypical Femoral Fractures (AFF) and Osteonecrosis of the Jaw (ONJ), have raised serious concerns.
Fearing Drugs’ Rare Side Effects, Millions Take Their Chances With Osteoporosis

CT scans show the progression of one patient’s vertebra over a six- to eight-year period, from normal bone density to moderate osteoporosis and severe osteoporosis. A. Boyde and P.D. Miller
Background

- The long term retention of BPs on bone, albeit with a differential temporal profile, and the AEs, led to the concept of drug holiday, to maximize benefits and minimize harms.
Background

• American Society for bone and Mineral Research (ASBMR) – convened a multidisciplinary international task force to address the topic of “Managing Osteoporosis Patients after Long-term Bisphosphonate (BPs) Treatment”

• Started in 2013, published in 2016
Task Force Charges

• Provide *guidance* on duration of BP therapy in patients with postmenopausal osteoporosis, developing an algorithm that incorporates risk assessment (efficacy)

• Determine how potential harms may affect duration of therapy (safety), with a risk benefit perspective.
Basis

• BP Long Term Randomized Trials reviewed.

• *Only 2* randomized, double-blind discontinuation trials in US/Europe that supported long-term BP therapy beyond 5 years!
  
  – Extension Studies
    • FLEX (Alendronate)
    • HORIZON EXTENSION (Zoledronic acid)
Design of FLEX (Alendronate) Trial

- Extension of the FIT trial which randomized roughly 3,000 people to get PBO vs. ALN
- FLEX was a 5 year PBO vs. ALN 5/10mg extension trial with roughly 1100 people
  - Of those, about 660 people got ALN.
FLEX (Alendronate) characteristics

- Age – 73 +/- 5.7 years
- 96% caucasian
- T-score T hip (mean): -1.9
- T-score FN (mean): -2.2
- % prevalent VFx (already suffered VFx): 34%
- % Clinical Fx history after age 45: 60%
- Outcomes: 1) Change in FN BMD, 2) BMD others sites, BTMs
• Roughly 7700 randomized to either ZOL vs PBO for 3 year
• Extension was ZOL vs PBO for another 3 years with roughly 1200 participants; split almost evenly
HORIZON characteristics

- Age 75 +/- 5.5 years
- 80% white/16% South Am, 4% Asia
- T-score FN (mean): -2.6
- Prevalent VFx at entry into extension: 60%
- Outcomes: 1) change in FN BMD, 2) BMD other sites, BTMs, Fractures, Safety
Conclusions
Long Term BP vs Switch to PBO

• FLEX demonstrated that ALN 10 years
  – Maintained BMD at all sites versus loss in PBO, p<0.001
  – Reduced risk of clinical vertebral fractures: RR=0.45 (0.24-0.85)
• HORIZON extension demonstrates that ZLN for 6 years
  – Maintained BMD at all sites versus loss in PBO, p<0.001
  – Reduced risk of morphometric vertebral fractures: RR=0.51 (0.26-0.95)

Black et al. *J Bone Miner Res.* 2012 Feb
FLEX

Clinical Vertebral Fractures

Cumulative Incidence, %

RR, 0.45 (95% CI, 0.24-0.86)

Time to First Fracture, mo

No. at Risk
Placebo 437 428 429 421 417 414
Alandronate 662 659 657 654 650 646

HORIZON

Morphometric Vertebral Fractures

Patients with New Vertebral Fracture (%)

Odds Ratio = 0.51
95% CI (0.26, 0.95)

Extension Study (Year 3-6)

30/456 14/469
Put another way

**Reductions (RR) for Fractures for Continuing BPs ALN and ZOL**

- **FLEX (Aln) 5/5 years**
  - Clinical Fracture: 1.00 (0.8, 1.3)
  - Vertebral FX (clinical): 0.45 (0.2, 0.85)

- **Horizon Ext (ZOL) 3/3 years**
  - Clinical Fracture: 0.99 (0.7, 1.5)
  - Vertebral FX (morphometric): 0.48 (0.3, 0.9)

Relative Hazard (± 95% CI)
- Favors Bisphosphonate
- Favors Placebo

Courtesy of Dina Black, Ph.D.
Differences Among Bisphosphonates

• Elevated BTMs have been associated with low BMD and increased fracture risk in untreated postmenopausal women.
• In pivotal studies of BPs, a significant decrease in BTMs has been demonstrated.
• Persistence of low BTMs may be a potential indication of continued beneficial effects after discontinuation of long-term BP use.
Differences Among Bisphosphonates

• Withdrawal of BP treatment is associated with decreases in BMD and increases in bone turnover, changes which differ among BPs.
  – Beneficial effects of ALN persist for 2-3 years
  – And possibly 1-2 years for ibandronate/risedronate
  – For ZOL, effects may persist for 3 more years.
  – These findings are consistent with the relative binding affinities of BPs for hydroxyapatite and human bone tissue.
Looking Further

- Identify high risk subjects when therapy is stopped (ie. PBO Arm)
- **Who are the people who continue fracturing?**
  - In FLEX, age was a RR
  - FN or Hip T-score ≤ -2.5
    - Clinical VFx risk: FLEX 2 fold increase
    - Morphometric VFx risk: HORIZON 3-4 fold increase
  - Incident Fractures during Core study in HORIZON
    - Morph VFx increased risk of incident morph VFx 5 fold
    - Non-VFx increased risk of incident Non-VFx 2.5 fold
  - Risk Factors: in HORIZON increased number of risk factors (Low T-score, prevalent fractures, incident fractures) increased fracture risk
Looking Further
Continued BP vs PBO

• **Who are patients to benefit from continued therapy?**
  – Continued ALN for 10 years reduced risk of clinical fractures
    • If FN BMD T-score > -2.5 to ≤ -2.0, RR=0.22 (0.05-0.74)
  – Continued ZLN for 6 years reduced risk of morphometric VFx
    • If Total hip T-score ≤ -2.5, RR=0.26 (0.08-0.69)
    • If FN BMD T-score ≤ -2.5, RR=0.36 (0.15-0.77)
  – In HORIZON subjects with incident morphometric VFx during core study, these patients benefitted most from continued therapy.
Looking Further
Continued BP vs PBO

– In low risk subjects, vertebral fracture rates were low and there was no increased risk of nonvertebral fractures after therapy discontinuation: for up to 5 years FU (after 5 years of ALN), and for up to 3 years FU (after 3 years ZLN).
Looking Further

• **Summary**: Based on these findings, continued BP therapy should be considered beyond 3 years with ZOL and beyond 5 years with ALN in *high risk individuals*, based on evidence for reductions in the risk of vertebral fractures only.

• In lower risk patients, and in light of lack of evidence for fracture reduction with long-term therapy, discontinuation of treatment beyond 3-5 years, with monitoring, seems prudent.
Risk of ONJ
ONJ

- 1st report in 2003, in patients with metastatic cancer receiving high-dose IV BP therapy.
  - Although ONJ 1st described 160 years ago.
- Pathogenesis remains unclear.
- In patients receiving BP therapy for OP, current estimates of the incidence of ONJ range from about 1/10,000 to 1/100,000 patient treatment years.
ONJ

• Potential mechanisms:
  – Over-suppression of bone remodeling
  – Infection
  – Inhibition of angiogenesis
  – Soft tissue toxicity
  – Immune dysfunction
• Risk factors for BP-treated patients:
  – Poor oral hygiene
  – Smoking
  – Diabetes mellitus
  – Concomitant glucocorticoid and/or chemo use
  – Invasive dental procedures (extractions/implants)
  – Incidence may be higher in Asians (?) Genetics

Atypical Femoral Fractures (AFFs)

• Relationship between AFFs and BPs was 1st reported in 2008 in patients receiving oral BPs for OP.
• In large retrospective analysis of > 1.8 million adults, including about 10% who had been treated with BPs, 142 AFF were identified, including 128 in subjects with prior BP exposure.
• Analysis suggests AFF risk increases with prolonged duration of BP Tx.
“Atypical” Femoral Shaft Fractures

Prodromal symptom of dull or aching pain in the groin or thigh
May be bilateral

Theory: Prolonged absence of osteoclast activity, which has tight coupling activity with osteoblasts results in a subsequent inability of osteoblasts to repair microdamage

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

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

Yes

Continue BP\(^{(1)}\) or change to alternative anti-fracture therapy\(^{(2)}\)
Reassess every 2-3 years

No

Hip BMD T-Score ≤ -2.5\(^{(3)}\)
OR
high fracture risk\(^{(4)}\)

Yes

Continue BP for up to 10 yrs\(^{(1)}\) or change to alternative anti-fracture therapy\(^{(2)}\)

No

Consider drug holiday
Reassess every 2-3 years\(^{(5)}\)
Limitations of Evidence and Algorithm

• Methodological Issues:
  – Studies are underpowered
  – Fractures were secondary or exploratory, post-hoc exploratory nature for many analyses

• Both FLEX and HORIZON extension demonstrate a reduction in vertebral fractures with continued BP therapy: Morph vs. Clinical VFx

• No data for other BPs
• No adequate data on non-vertebral fracture reduction
• Data from FLEX and HORIZON: do not provide evidence to advocate use of markers today.
Limitations of Evidence and Algorithm

• Algorithm does not cover management of patients on BPs beyond 10 years
• The T-score cut-off of -2.5 is applicable to Caucasian subjects and may not be applicable to other ethnic groups or populations
• No adequate data for use of FRAX in patients on therapy
• No trials demonstrating that re-starting BP or switching to alternate therapies results in fewer fractures
• No fracture data with prolonged BP therapy in men or GIOP
Bone Turnover Markers

• No evidence to support the measurements of BTMs to assess fracture risk after long term BPs therapy or in offset periods

• Some experts use BTMs to determine whether a discontinued BP is still exerting its effect, and resume therapy when they exceed the lower half of the premenopausal range.
Knowledge Gaps/Research Agenda

• Validate FRAX in patients on BP therapy
  – To identify patients at high fracture risk after therapy discontinuation
  – To identify patients who respond best to continued therapy
• Investigate additional predictors to identify high risk individuals who benefit most from continued BP therapy
• Identify monitoring parameters for patients off therapy
Thoughts/Opinion

• Not at all sure that there is a right answer
• Data regarding risk/benefit ratio of long term treatment are suboptimal
• Better data are not coming soon (if at all)
We seem to know...

• Short-term BP Treatment cuts fracture risk – in half

• No doubt virtually that this benefit outweighs rare risks for the 1st 3-5 years of treatment

• Question is do we continue longer??
Benefit vs. Risk

• Benefits: Decreased Fractures, Decreased Mortality, Maintained QOL

• Risks: GI, ONJ, AFF, Nephrotoxicity, eye problems, musculoskeletal pain, esophageal cancer? A-fib?
How might long-term BPs treatment improve skeletal status?

• Increase BMD
• Reduce bone turnover
• Alter bone material properties
• Reduce fracture risk
The FLEX and Horizon trials demonstrate that long-term BP Rx produces slightly higher BMD and persistent BTM suppression.

- Is stable to slight BMD increase good?
- Is a slight BMD decrease after stopping bad?
- Is long-term turnover suppression good?
- Is slight turnover increase after stopping bad?
How do BP’s Increase BMD?

• Much of the increase in BMD is due to filling in of open remodeling space. Could they be anabolic? It was determined “no”.

• 3 years of ALN or ZOL does not alter wall thickness (BPs are not anabolic).

• 3 key material properties are altered.
  – Mineralization
  – Collagen cross linking
  – Microdamage
• Women at high risk, for example, older women, those with a low hip T-score or high fracture risk score, those with prior major osteoporotic fracture or who fracture on therapy, continuation of TX, with periodic evaluation should be considered.

• The risk of AFF and maybe ONJ increases with BP therapy duration, but such rare events are outweighed by vertebral fx risk reduction in high risk patients.

• For women not at high fracture risk after 3-5 years of BP treatment, a drug holiday of 2-3 years can be considered.
ASBMR Algorithm

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

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

Yes → Continue BP (1) or change to alternative anti-fracture therapy (2) → Reassess every 2-3 years

No → Hip BMD T-Score ≤ -2.5 (3) OR high fracture risk (4)

Yes → Continue BP for up to 10 yrs (1) or change to alternative anti-fracture therapy (2)

No → Consider drug holiday → Reassess every 2-3 years (5)
My Opinion (Shaped from others)

• Inform patients that they have a disease that may adversely affect quality/quantity of life
• Strongly encourage treatment of high risk individuals (prior fx/FRAX over thresholds)
• Plan on ≈ 4-5 years oral/3 years IV BP
• If doing “well” (stable or increased BMD), and no fractures, then drug holiday. (almost always)
• If still high risk, consider teriparatide.
• If tx failure, consider teriparatide.
• Monitor holiday with BTMs and DXA every other year (no data to support this)
• Be aware that not all BPs are the same
Benefits and Risks – Final Thoughts

There are about 2.3 million adults treated in ERs each year for injuries related to MVAs.
There are about 2 million osteoporotic fractures each year.

The **risk** of seat belt injuries and serious side effects from OP Tx **is very small in proportion to benefits**. Data from multiple sources.

ISCD CME; www.iscd.org
References

- ISCD Website CME Program – “Long Term Bisphosphonate Therapy” - Ghada Fuleihan, MD, MPH, CCD and Neil Binkley, MD, CCD.