Clinical Question 10

- How long do osteoporosis patients need to be treated?

1

Learning Objectives

Upon completion of this module, participants will be better able to:

- Incorporate the history of prior fractures in determining future risk
- Assess the risk of falls as a major and independent risk for fractures
- Consider patient preference when selecting long term treatment
- Explain the importance of adherence including avoidance of drug holidays in high risk individuals

2

Clinical Question 10

How long do osteoporosis patients need to be treated?

Osteoporosis is a chronic disease requiring a long-term strategic approach to maintain protection from fragility fractures which otherwise increases with aging. Sequential therapy with consideration of all available anabolic and antiresorptive therapies should be planned at the time patients are first diagnosed. Osteoporosis therapy should not be discontinued after an arbitrary length of time but rather continued as long as patients remain at risk of fragility fractures. Clinical trials confirm the long-term efficacy and safety of osteoporosis treatments.

3

Osteoporosis is a Chronic Disease Requiring Life-long Strategies to Reduce Fracture Risk

- Oral BP: up to 10 years of treatment maintains fracture risk reduction similar to the 3-year registration trials
  - → Increasing but low risk of atypical femoral fractures (AFF) with increasing duration of BP therapy
  - → Risk of AFF increases to about 11.3/ per 10,000 patients after 8-10 yrs of treatment
- Denosumab: 10 years of therapy provides fracture risk reduction similar to or better than that observed in the 3-year registration trial
- Antifracture benefits of long-term therapy with BPs and denosumab in appropriately selected patients outweigh the risk of rare side effects

BP = bisphosphonate

Hanley DA, Writing Group for the Western Osteoporosis Alliance. Am J Med. 2017;130(7):862.

4

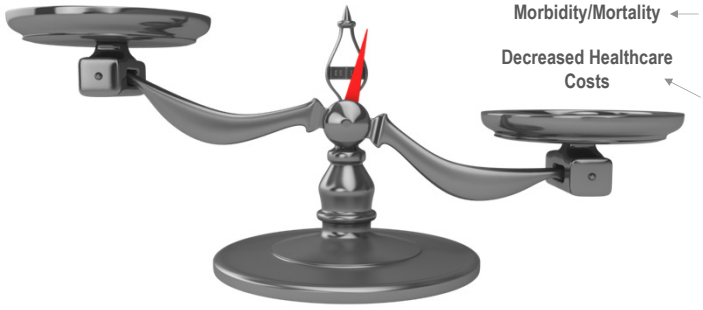
Weighing the Benefits of OP Therapy

RISK

- ONJ — Risk of ONJ from BP use: 1.03*[1]
- Atypical Femoral Fracture — Risk of atypical fracture from BP use: 2 (2 yrs of use)**[1], 78 (8 yrs of use)**[1]

BENEFIT

- Fraction Risk Reduction — Reduces vertebral fracture risk by 30-70%[2]
- Independent Living — In women with hip fracture: 24% enter LTC[3]
- Decreased Morbidity/Mortality — Prevent nonvertebral and/or hip fractures and reduce mortality among individuals at high risk by 11%[2,4]
- Decreased Healthcare Costs — Acute Care Costs associated with fracture $1.5 billion[5]



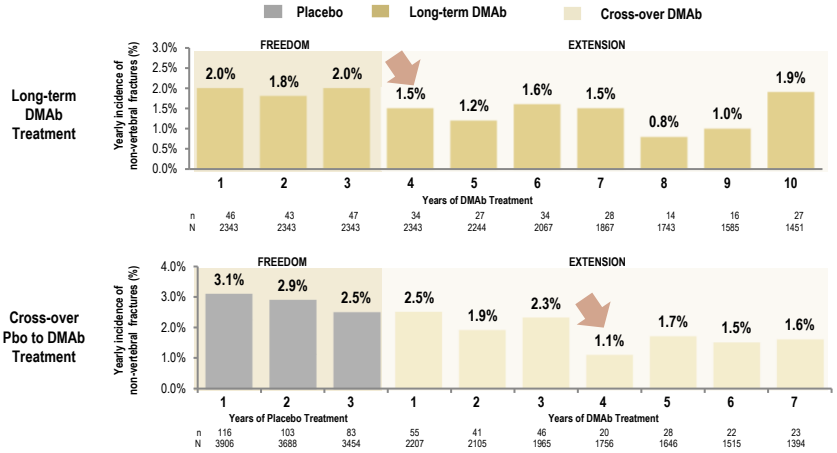
*Incidence per 100,000 people **Incidence per 100,000 patient-years

1. Brown J.P., et al *Can Fam Physician.* 2014;60(April):324-333.; 2. Papaioannou, A., et al. *CMAJ.* 2010;182:1864-1873.; 3. Nikitovic, M., et al. *Osteoporos Int.* 2013;24:659-669.; 4. Bolland, M.J., et al. *J Clin Endocrinol Metab.* 2010;95:1174–1181.; 5. Hopkins, R.B., et al. *Osteoporos Int.* 2016;DOI: 10.1007/s00198-016-3631-6.

5

Long-term Reduction in Bone Remodeling with Denosumab: Associated with Continued Low Fracture Incidence[1]

Yearly Non-vertebral Fracture Incidence With Denosumab Treatment for Up to 10 Years[1]

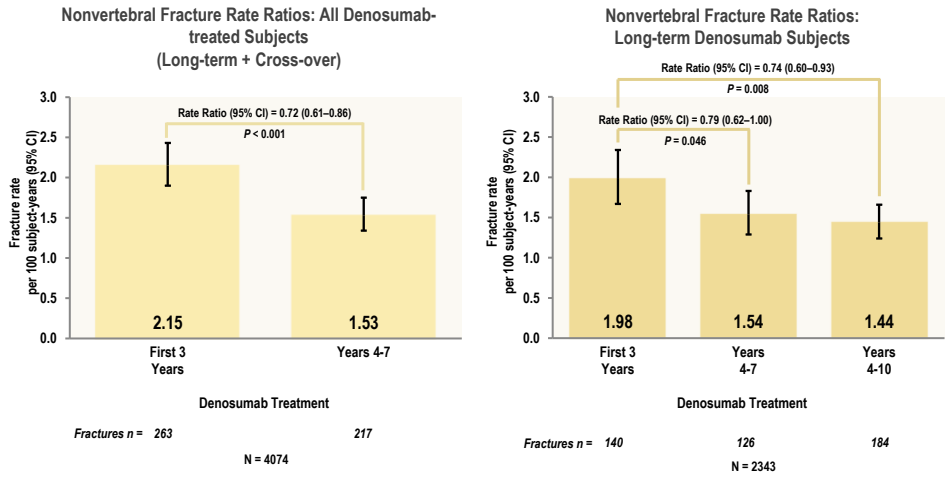


n = number of subjects who have ≥ 1 nonvertebral fracture. N = number of enrolled subjects who remained in the study at the beginning of each year. Percentages for nonvertebral fractures are Kaplan-Meier estimates.

1. Ferrari S, et al. ASBMR (oral presentation). 2017; Abstract 1073; 2. Bone, H.G., et al. *Lancet Diabetes Endocrinol.* 2017;5(7):513-523.

6

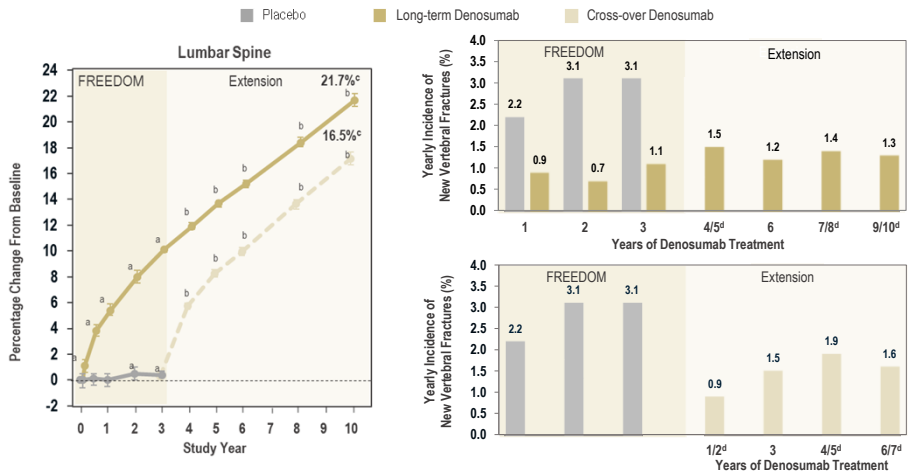
Comparison of Nonvertebral Fracture Rates with up to 10 Years of Denosumab Treatment



N = number of subjects who did not miss > 1 dose of DMAb during the first 3 years of FREEDOM or the extension.
Ferrari S, et al. ASBMR (oral presentation). 2017; Abstract 1073.

7

Effects of Denosumab Treatment on Lumbar Spine BMD and New Vertebral Fractures Through 10 Years



BMD data are LS means and 95% confidence intervals. [a]P < 0.05 vs FREEDOM baseline. [b]P < 0.05 vs FREEDOM and Extension baselines. [c]Percentage change while on denosumab treatment. [d]Annualized incidence: (2-year incidence) / 2. Lateral radiographs (lumbar and thoracic) were not obtained at years 4, 7, and 9 (years 1, 4, and 6 of the Extension).

Adapted from Bone HG, et al. (2017). *Lancet Diabetes Endocrinol*. Published Online May 22, 2017 http://dx.doi.org/10.1016/ S2213-8587(17)30138-9.

8

Long-Term Use of BP Therapy Prevents Bone Loss and Reduces Vertebral Fractures

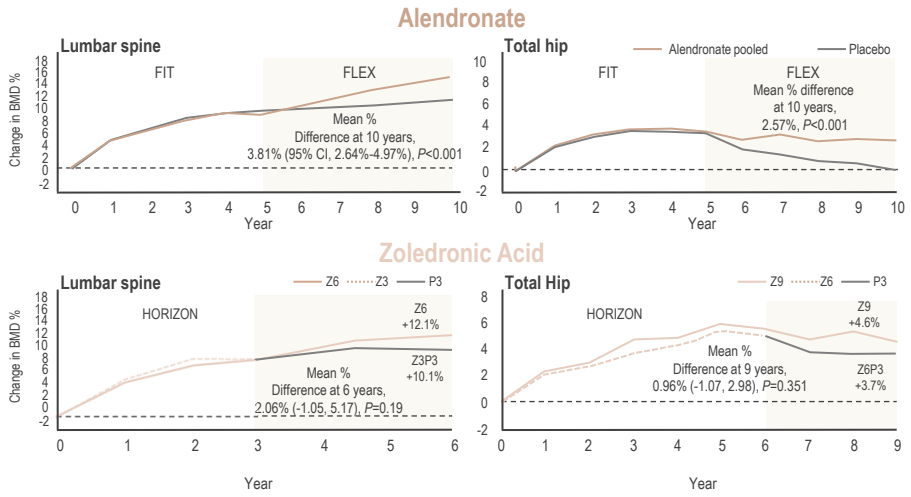
- Long-term BP therapy (ALN 10 years, ZOL 6 years) prevented bone loss at multiple skeletal sites and reduced vertebral fractures compared with stopping ALN after 5 years or ZOL after 3 years
- Greatest benefit with long-term ALN or ZOL therapy were high risk patients with:
  - → Persistent low T-score at hip (≤ -2.5 for total hip or femoral neck T-score (HORIZON) and > -2.5 to ≤ -2 for femoral neck (FLEX)
  - → Incident fracture during the core study
  - → Prevalent vertebral fracture (at entrance to HORIZON extension)
- Continued ALN resulted in a lower risk of clinical vertebral fractures; ZOL resulted in a lower risk of morphometric vertebral fractures

ALN = alendronate; ZOL = zoledronic

Adler RA, et al. *J Bone Miner Res*. 2016;31(1):16-35.

9

BMD is Sustained With Long-Term Bisphosphonate Therapy

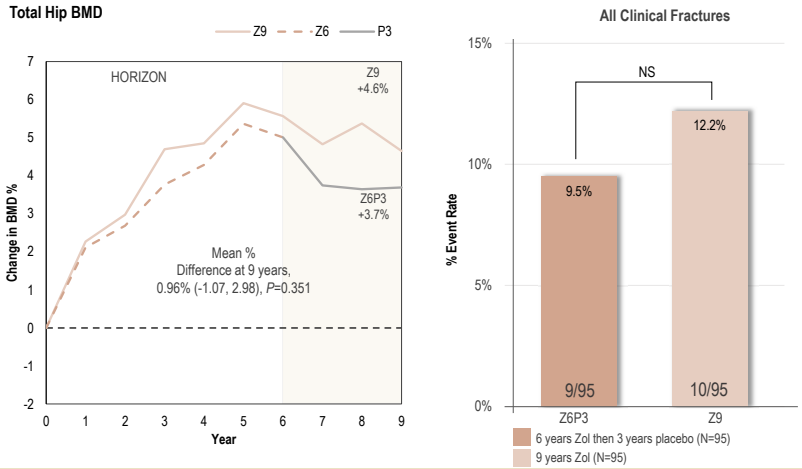


Adapted from: Black, D.M., et al. *JAMA*. 2006;296:2927-2938.; Black, D.M., et al. *J Bone Miner Res*. 2012;27:243-254.; Black, D.M., et al. *J Bone Miner Res*. 2014;30(5):934-44. DOI: 10.1002/jbmr.2442.

10

No Significant Difference in Risk of Fracture Between Year 6 and 9 on Zoledronic Acid

Results show continued efficacy in both groups, yet did not provide evidence of benefit from continuing ZOL infusions for more than 6 years



NS: not significant
Black, D.M., et al. *J Bone Miner Res*. 2015;30(5):934-44.

11

Management of Postmenopausal Women on Long-Term Bisphosphonate Therapy

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

Continue BP[1] or change to alternative anti-fracture therapy[2] (e.g. teriperatide or denosumab)

Reassess every 2-3 years

NO

Hip BMD T-Score ≤ -2.5[3]
OR
High Fracture Risk

YES

Continue BP for up to 10 yrs[1] or change to alternative anti-fracture therapy[2] (e.g. teriparatide or denosumab)

NO

Consider BP drug holiday

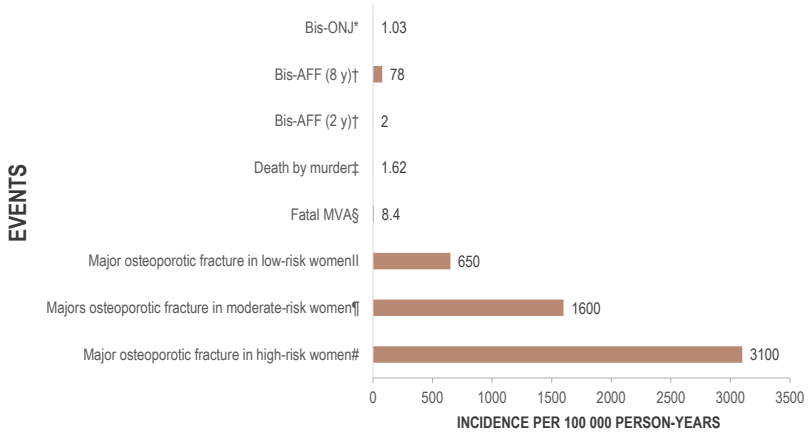
Reassess every 2-3 years

- Decision to stop therapy should be made on individual basis, based on informed choice of benefits/risks

1. Brown, J.P., et al. *Can Fam Physician*. 2014;60:324-333.; 2. Silverman, S.L., et al. *Osteoporos Int*. 2016;27:849-852.; 3. McClung, M., et al. *Am J Med*. 2013;126:13-20.

12

Risks of Major Osteoporotic Fracture and Other Rare Events



Brown, J.P., et al. *Can Fam Physician*. 2014;60:324-333

13

No Holiday with Denosumab

Loss of benefit and increased risk of vertebral fractures

+

- No clear signal of any risk associated with the duration of therapy (up to 10 yrs continuous therapy)
- Patients have not been refractory to therapy
- Intolerance is uncommon

−

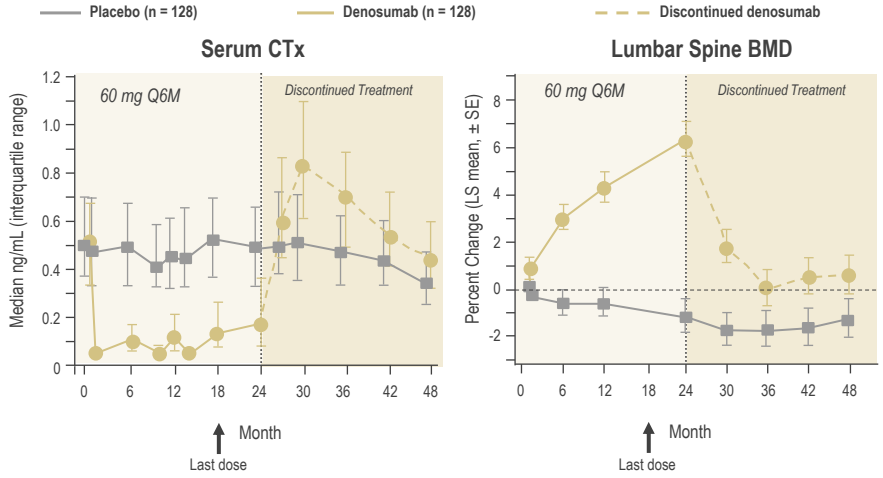
- Possible increase in fracture risk (to level observed in untreated person) with increase in bone remodelling and bone loss

If denosumab is discontinued, steps must be taken to prevent rapid bone loss; biologic therapies (due to half-life) only control the disease process for as long as drug taken.

McClung, M.R. *Osteoporos Int*. 2016;27(5):1677-82. DOI: 10.1007/s00198-016-3553-3; Cummings, S.R., et al. *J Bone Miner Res*. 2018;33(2):190-198.

14

Effect of Denosumab Discontinuation
DEFEND

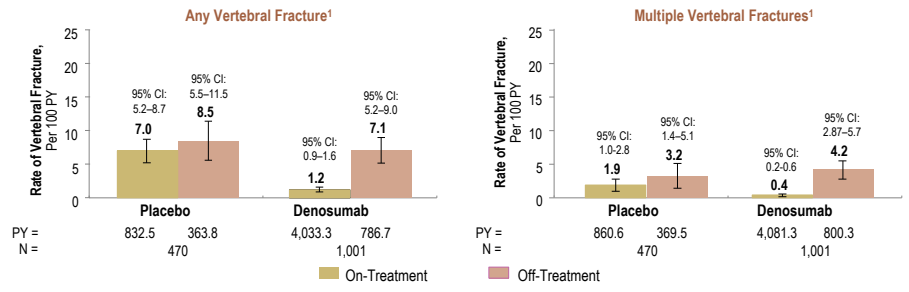


Results from a follow-up to a 2-year phase 3 trial of denosumab in postmenopausal women with low bone mass (DEFEND, N = 332). Off-treatment phase of the trial included 256 women.
Adapted from Bone HG, et al. *J Clin Endocrinol Metab*. 2011;96:972-980.

15

On- vs Off-Treatment Vertebral Fracture Rate:
All Patients FREEDOM and Extension Study – Analysis of MVF

- During treatment, the rate of new vertebral fractures was lower in patients receiving denosumab compared to placebo (1.2 versus 7.0 per 100 patient-years)
- After discontinuation of denosumab, the rate of vertebral fractures increased relative to the on-treatment period and became similar to that of patients discontinuing placebo (7.1 versus 8.5 per 100 patient-years)
- The rate of multiple vertebral fracture was slightly higher in patients discontinuing denosumab compared to discontinuing placebo (4.2 versus 3.2 per 100 patient-years)



*PY = patient-years; CI = confidence interval
Journal of Bone and Mineral Research, Vol. 33, No. 2, February 2018, pp 190–198 DOI: 10.1002/jbmr.3337.

16

Significant Predictors of Off-Treatment MVF

- Prior vertebral fracture is the strongest predictor of off-treatment vertebral fractures
- Other predictors of MVF were time off-treatment and rate of off-treatment total hip BMD loss

Significant Covariates	772 Patients Included† OR (95% CI)	1,471 Patients Included* OR (95% CI)
Prior VFx‡ (yes vs no)	3.6 (1.8–7.1)	3.9 (2.1–7.2)
Off-treatment duration (per year)	1.4 (1.1–1.7)	1.6 (1.3–1.9)
Annualized off-treatment total hip BMD loss§ (per 1%)	1.2 (1.1–1.3)	NA

*1,471 patients included 470 patients who discontinued placebo and 1,001 patients who discontinued denosumab; †772 patients included 307 patients who discontinued placebo and 465 patients who discontinued denosumab, and had available off-treatment annualized total hip BMD change assessments; ‡"Prior VFx" includes any VFx sustained before or during treatment; §"Off-treatment annualized total hip BMD loss" was defined as annualized percent change in total hip BMD after treatment discontinuation, ie, between the last on- and off-treatment BMD assessments.
BMD = bone mineral density; CI = confidence interval; NA = not applicable; OR = odds ratio; VFx = vertebral fracture

Adapted from: Cummings SR, et al. *J Bone Miner Res.* 2017; [Published only ahead of print November 4, 2017]. 10.1002/jbmr.3337.

17

Discussion: Clinical Takeaways

- There is no arbitrary time limit to osteoporosis therapy[1]
- In high risk patients, switching therapy from bisphosphonate to non-bisphosphonate antiresorptive or anabolic therapy may be rational[1]
- No drug holiday for HRT, SERMs, teriparatide and denosumab[1,2]
- Drug holiday (not retirement) is feasible with ALN, RIS and ZOL after 3-5 years if patient at moderate or low risk[3]
- If bisphosphonate interrupted, reassess risk (and BMD) after:[2,3]
  - → 1 yr for risedronate, 2 yrs for alendronate, 3 yrs for zoledronic acid
- Long-term adverse effects of osteoporosis therapies are offset in high risk patients by the benefits of long-term reduction in fractures[1,3]

HRT: hormone replacement therapy; SERMs: selective estrogen receptor modulators.
1. Papaioannou, A., et al. *CMAJ.* 2010;182:1864-1873.; 2. Silverman, S.L., et al. *Osteoporos Int.* 2016;27:849-852.; 3. Brown, J.P., et al. *Can Fam Physician.* 2014;60:325-333.

18