RhAPP

RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

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Individualizing Osteoporosis Treatment

Eileen Lydon, MSN, ANP
NYU Langone Orthopedic Hospital

Patty Travis, MSN, A/GNP
Cleveland Clinic

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Objectives

- Identify the most appropriate osteoporosis treatment selection based on case presentation
- Discuss possible adverse effects of various osteoporosis medications, weight the risks and benefits of treatment for specific patients and discuss perceived risks of rare major adverse effects of medications
- Communicate the imminent risk of future fractures in those with recent fragility fracture

Case #1

S.L. 57 yo female presents for an osteoporosis evaluation:

- Recent BMD
  - Femoral Neck T score -2.3
  - Lumbar Spine -2.7.
- FRAX Hip 1.3%, Major 7.3%
- No h/o fracture or falls
- No previous OP treatment
- Menarche 13, menopause 48
- No hot flashes
- Never used HRT
- No FH osteoporosis or parental hip fracture
- Mother with a hx. of breast cancer
- Daily milk drinker as a child
- No tobacco use , Social ETOH
- Denies hx of steroid use, thyroid disease, breast cancer or kidney stones.
- Takes calcium and vitamin d.

Case #1 – S.L., 57yo

Medical History

- PMH
  - Insomnia
  - GERD
- PSH
  - Denies
- Medications
  - Ambien PRN
  - Pepcid 20 mg daily

Workup

Labs

- PTH 30, Calcium 10
- Vitamin d 25 47
- C-telopeptide 186
- SPEP normal
- Creatinine 0.9
- Urine Calcium 100
- TSH – WNL

Discussion

- Should this patient be treated?
- If so, what are her treatment options?
- What plan would you discuss with this patient?

Raloxifene

Estrogen agonist/ antagonist

- Selective estrogen effect on the skeleton
- Anti-estrogenic effect on the breast
  - Decreases risk for breast cancer
- No increased risk of uterine cancer

MORE Trial

- Randomized 7705 women to PBO, Raloxifene 60 mg or 120mg for 3 years
- 30-50% reduction vertebral fracture risk
- No effect against non-vertebral fracture

Ettinger B et al. JAMA 1999; 282:637-645

Raloxifene (possible side effects)

- 3-fold increased risk of DVT/PE
- Increased mortality in women with stroke
  - No increased incidence of stroke or coronary events
- Increased hot flashes and night sweats

Ettinger B et al. JAMA 1999; 282:637-645

Case #1

- S.L. now age 68, continues on Raloxifene 60 mg daily. Her most recent bone density revealed RFN -2.7, Spine -2.7, c/w previous RFN T score -2.3, and Spine -2.7. She continues without falls or fractures, and no new medications or medical conditions. FRAX; Major osteoporotic 13%, Hip 3.5%

- Would you keep the same regimen?
- If change is made, what are your options?
- What is your treatment plan or this patient?

Bisphosphonates

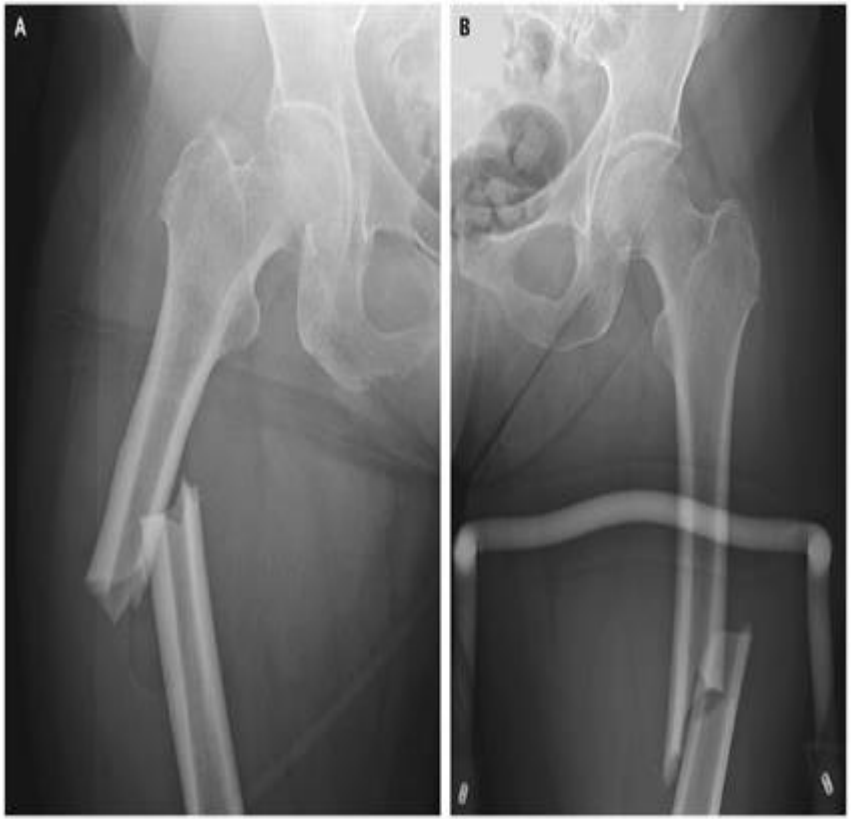
- Bisphosphonates inhibit bone resorption
- Alendronate, Risendronate, Ibandronate and Zolendronic acid
- Reduction of vertebral fracture; 40-70%, non vertebral 20-35%, hip fracture 30-50%
  - Ibandronate reduces risk for vertebral fractures only
- Zolendronic acid given after hip fracture is associated with a 35% RR of new clinical fractures, and improved survival.

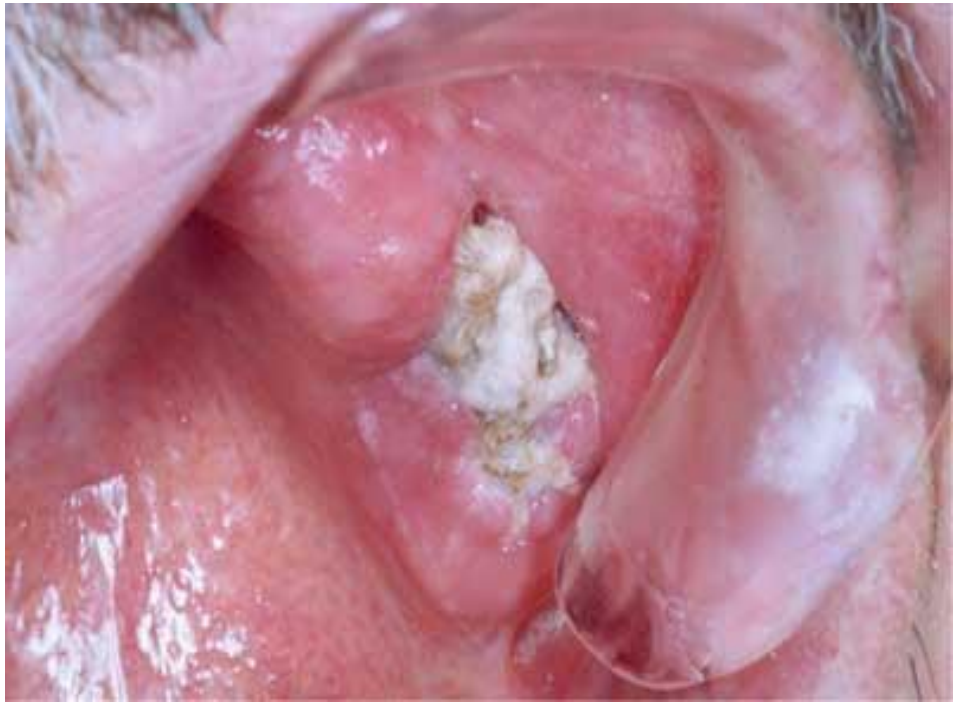
Lyles KW et at NEJM 2007;357:1799-1809

Bisphosphonates: Safety issues

- Contraindications
  - Hypocalcemia
  - Impaired renal function (GFR <30-35 ml/min)
  - If unable to take while fasting in AM, or able to wait upright for 30-60 minutes before eating (oral formulations only)
  - Esophagitis
- Zolendronic acid may cause acute phase reactions in up to 30% with first IV

What could go wrong?





Rare safety concerns

- Atypical femur fracture
  - Associated with long term use, higher in Asian population
- Osteonecrosis of the jaw
  - Less clear if duration dependent

- How do you educate your patients on these rare safety concerns ? Do you ever get resistance to start treatment due to these concerns?

Case #2

K.K. is a 55 yo female with PMH of uncontrolled diabetes, CAD, s/p MI 3/2022 (stent x 2), presented for a osteoporosis evaluation, s/p R THA 1/2023 due to hip fracture. She fell and fractured after slipping on a wet floor. This is her only known fracture, and she never took any bone strengthening medication.

- Bone density 1/2023 Spine -3.2, L hip – 2.7.
- Menarche age 14, Menopause age 53. G 13, P 9, Ab 4, and breast fed 12 of her children.
- Denies h/o steroid use, thyroid disease, kidney stones or breast cancer.
- Denies family history of osteoporosis or parental hip fracture.
- Takes supplemental calcium and vitamin D

Case #2 – K.K., 55yo

Medical History

- PMH
  - Uncontrolled DM
  - HL
  - CAD (MI, s/p stent x2)
- PSH
  - R THA
- Meds
  - Atorvastatin, clopidogrel, ASA, metoprolol,emaglutide, empagliflozin, metformin

Workup

- Vitamin d 25 - 52.5
- PTH – 57
- SPEP – WNL
- C-telopeptide – 234
- Calcium 10.1
- Creatinine 0.67
- Urine calcium 13.1
- IPEP – no monoclonal bands
- TSH 1.20

Discussion

- What are your thoughts about her fracture risk?
- What medication(s) would you discuss with this patient and why?

Who are the highest risk of fracture?

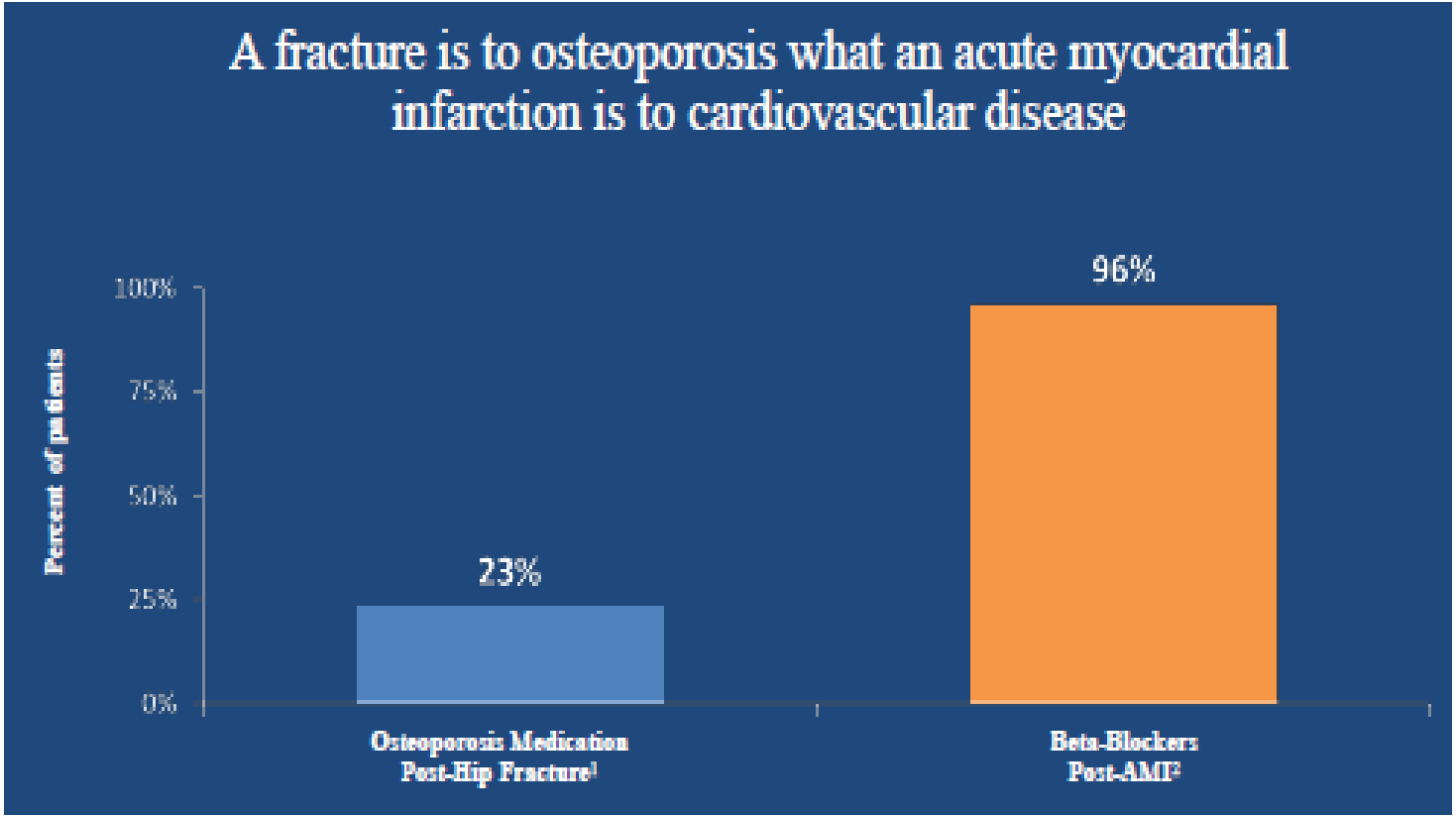
- Patients with recent clinical or new radiographic vertebral fracture
- Patients with a history of multiple fractures
- Patients with T score ≤ -3
  - Especially with other risk factors
  - Starting glucocorticoids

Imminent risk of a fracture, after prior fracture

- Incidence of imminent fracture after a prior fragility fracture was 7.58% in the first year and 11.58% in the first 2 years.
- Approximately half of re-fractures occurred in the first 2 years after a fragility fracture
- Older patients that have suffered from a fragility fracture should be treated promptly, to prevent the imminent risk of a fracture

Osteoporosis International (2022)

Only 23% of patients receive osteoporosis medication after a hip fracture



Yusuf A, et al. Present at: ASBMR annual meeting. October 9-12, 2015; Seattle, WA. Abstract M00350

Faridi KF, et al. "Timing of First Postdischarge Follow-up and Medication Adherence After Acute Myocardial Infarction." JAMA Cardiol 2016;1 147-155

Treatment gap

- Treatment gap approximately 80% worldwide
- Morbidity, mortality, and health care costs of subsequent fx is higher than initial
- Studies show that patient's perceived risk of fracture low
- Important for HCP to initiate the conversation to counsel
- Fracture liaison services have been developed to better manage treatment

How to treat the very high risk

- Want to treat those with a recent fracture with agents that have the most rapid effect on fracture prevention

- Anabolic agents have a more rapid and greater fracture risk reduction compared with antiresorptive medications, especially in those at very high fracture risk

Cosman F. Endo Practice 2020; 26;777-786
Bouxsein M, et al, JBMR 2019; 32; 632-642
Black DM, et al. Lancet Diab Endo 220; 8;672-682

Anabolic Agents

- Which one would you choose and why?
  - Teriparatide
  - Abaloparatide
  - Romosozumab

Teriparatide and Abaloparatide

- Safety issues:
  - Rodent osteosarcoma – Boxed warning and 24 month cumulative use restriction removed form PI
  - Hypercalcemia (transient), and hypercalciuria (minimal)
  - Orthostatic hypotension – dizziness, tachycardia, nausea
  - Erythema at injection site
  - Leg cramps/musculoskeletal pains/fatigue

Case Study #3 – H.G.

- 48 yo female, BMD 5/2023
  - LS (L1-L4) T-score -2.2
  - L total hip T-score -2.3
  - L fem neck T-score -2.9

New OP. No previous treatment.

What's your first thought on treatment?

What do you want to know?

Case Study #3 – H.G., 48 yo

Clinical Pearl: Steepest decline in bone loss the first 5 yrs after menopause

- Key History
  - Works as OT
  - No falls or fx
  - No smoking or etoh use
  - No transplant hx
  - Good dentition
- OP Risk Factors
  - Wt <127, Ht 4’ 11”
  - FHx +OP (mother)
  - Menarche, 13
  - Menopause, **47**
  - G 4, P 4, Ab 0 (youngest 8yo & 10yo)

Any changes to your treatment plan?

Case Study #3 – H.G.

- 48 yo female, BMD 5/2023
  - LS (L1-L4) T-score -2.2; SS interval decrease -8.1%
  - L total hip T-score -2.3; SS -10.5%
  - L fem neck T-score -2.9; SS -11.4%

Osteopenia a year ago. Thoughts?

- BMD 5/2022
  - LS (L1-L4) T-score -1.5
  - L total hip T-score -1.7
  - L fem neck T-score -2.3

What else do you want to know?

Case Study #3 – H.G.

PMH – no CV hx

- Epilepsy
  - anti-convulsants since age 18
- GERD
  - Famotidine PRN
- UCTD
  - HCQ & MTX, 2019
  - Limited pred since 2019 (dose pack, 5mg PRN)
- Breast CA, 2020
  - Bilat mastectomy, Jan
  - Chemo & Radiation
  - Tamoxifen (SERM), Aug
- Total Hysterectomy, 12/2021
  - Tamoxifen changed to Anastrazole (AI), May 2022

Benefits of Treatment Choice

Anabolic

Significant BMD advantage
- PTH underestimated by DXA
- Romo 1-yr hip +6%

Clear fracture advantage
- Vertebral
- Non-vertebral and hip

Morphometric
- Cortical thickening
- Trabecular connectivity

Foundational effect
- Lower fx rates with AR agent after anabolic

Antiresoptive

Easy to use

Less expensive

No 2-year limitation

Extention trials
- 10 yrs denosumab
- 10 yrs for alendronate

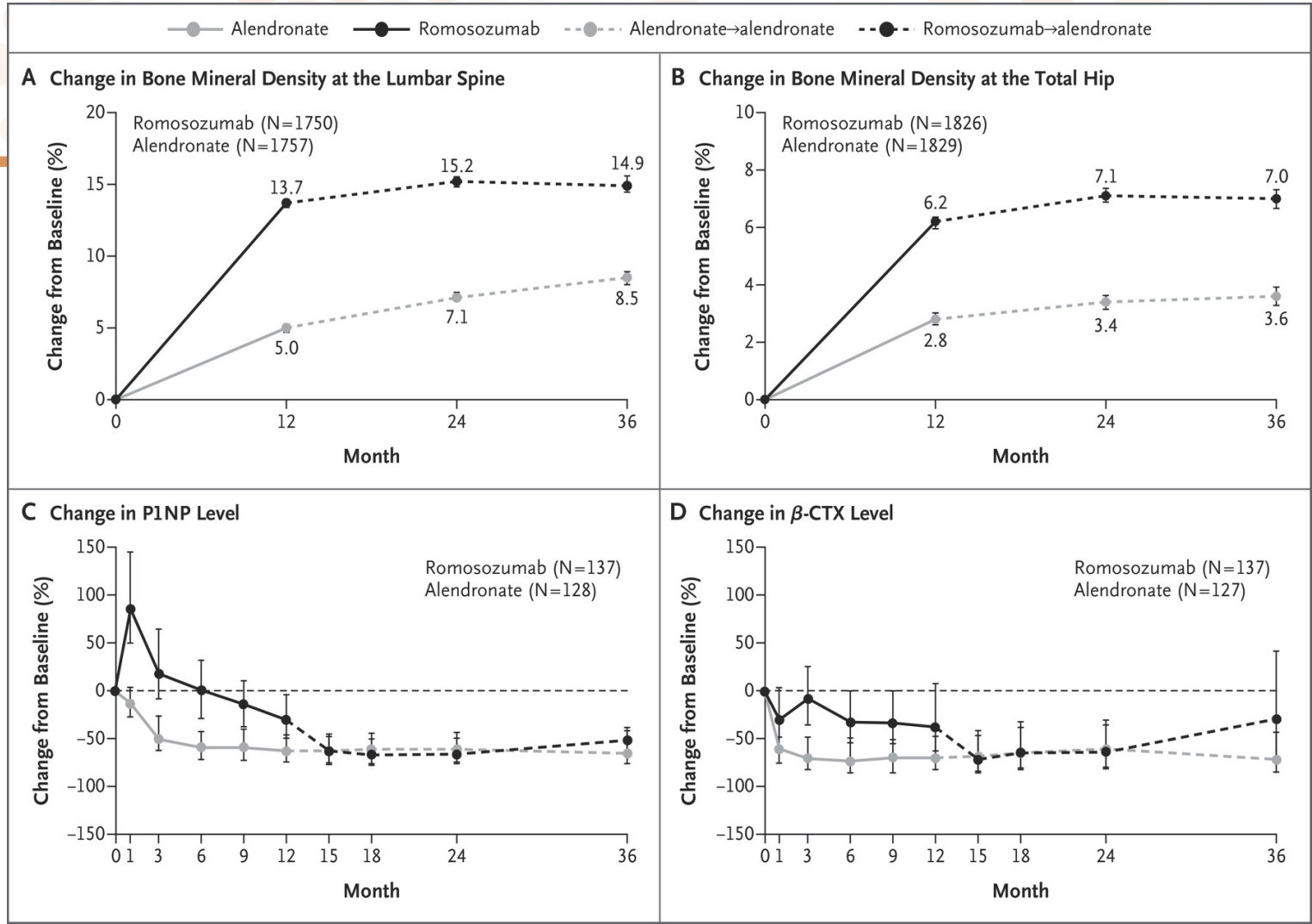
Duration
- 3-10 yrs, holiday, retreat

Romosozumab Background

- Monoclonal antibody that binds and inhibits sclerostin
- Sclerostin inhibition has dual effect on bone
  - Stimulates bone formation by promoting osteoblast number and activity
  - Reduces bone resorption by inhibiting RANK ligand expression
  - Increases BMD markedly
- Phase 3 Trials
  - FRAME: randomized, blinded, placebo-controlled for 1 year followed by denosumab for 1 year in all[1]
  - ARCH: randomized, blinded romosozumab vs alendronate for 1 year followed by alendronate for all[2] (black box warning on CV events from this study)
  - STRUCTURE: alendronate treated women randomized to romosozumab vs teriparatide[3]

1. Cosman F, et al. *N Engl J Med*. 2016;375:1532-1543.
2. Saag K, et al. *N Engl J Med* 2017;377:1417-1427.
3. Langdahl B, et al. Lancet 2017

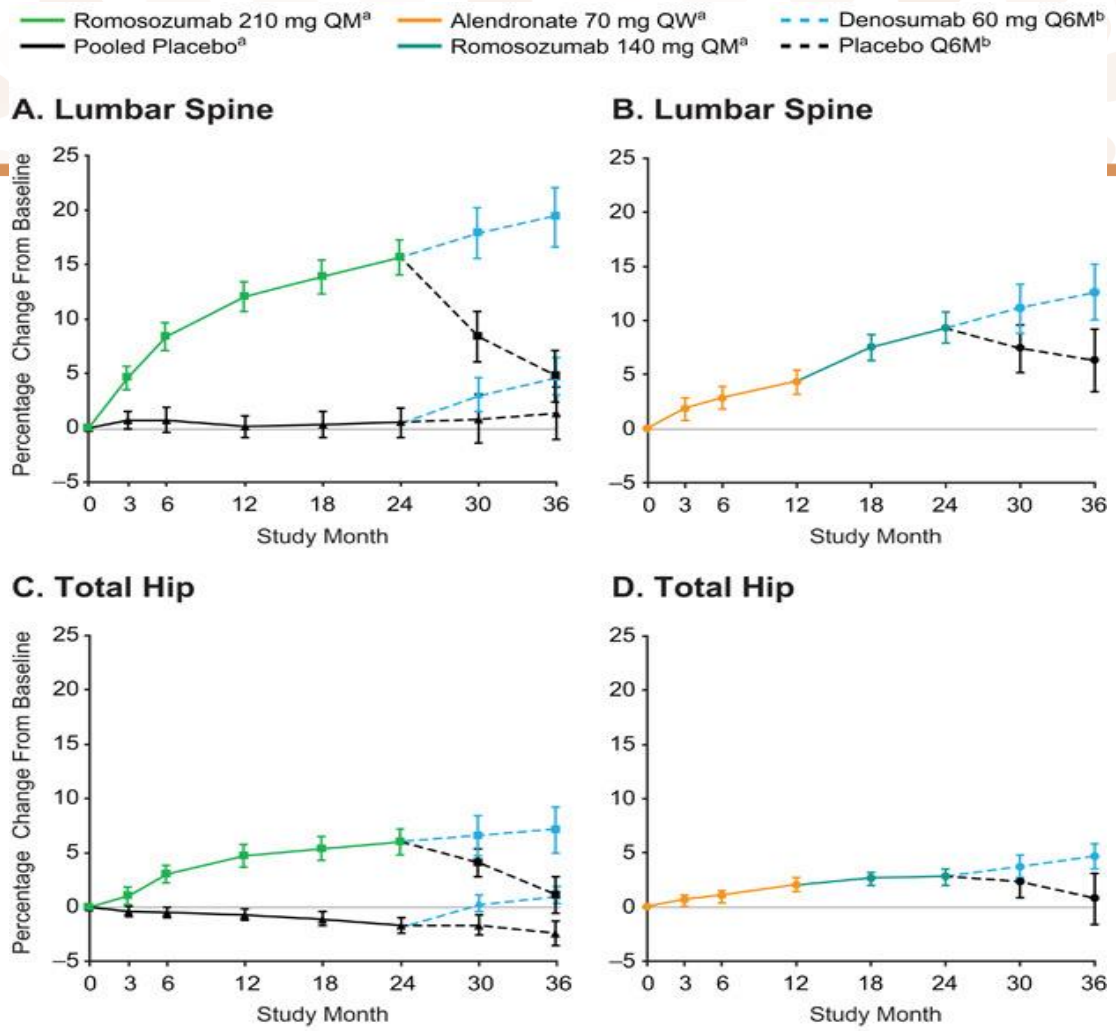
Treatment Sequencing Matters ARCH Trial



Saag KG, et al. Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis. N Engl J Med. 2017 Oct 12;377(15):1417-1427. doi: 10.1056/NEJMoa1708322. Epub 2017 Sep 11. PMID: 28892457.

Antiresorptive after Anabolics

Percentage change from baseline in BMD at the lumbar spine (*A*, *B*) and total hip (*C*, *D*) through month 36.



McClung MR, et al. Effects of 24 Months of Treatment With Romosozumab Followed by 12 Months of Denosumab or Placebo in Postmenopausal Women With Low Bone Mineral Density: A Randomized, Double-Blind, Phase 2, Parallel Group Study. J Bone Miner Res. 2018 Aug;33(8):1397-1406. doi: 10.1002/jbmr.3452. Epub 2018 May 22. PMID: 29694685.

Safety Considerations for Anabolic Agents

Teriparatide/Abaloparatide

- Rodent osteosarcoma (no increase in 15 year follow up with teriparatide)
- Hypercalcemia and hypercalciuria
- Orthostatic hypotension-dizziness, tachycardia, nausea
- Erythema at injection site
- Leg cramps/musculoskeletal pains/fatigue

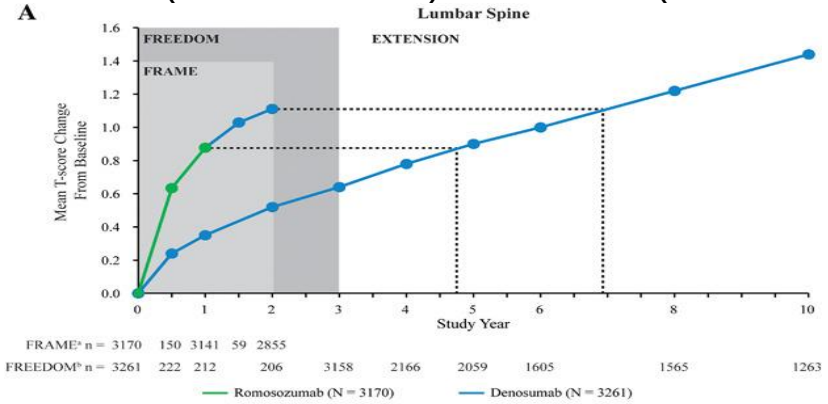
Romosozumab

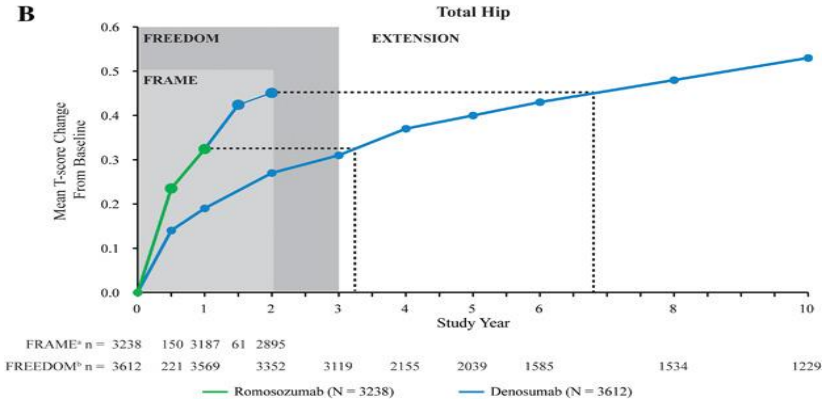
- Injection site reactions
- Hypersensitivity
- Hypocalcemia
- MI, CVA, CV Death Imbalance in ARCH but not FRAME

BMD Increases

Clinical Pearl: Gains lost if not followed up with antiresorptive

FRAME (Romozosumab) vs Freedom (Denosumab)





BMD increases

BMD Changes LS

Romo	1 years
Dmab	>4.5 years

BMD Changes LS

Romo-Dmab	2 years
Dmab alone	7 years

BMD Changes Hip

Romo-Dmab	2 years
Dmab alone	>6.5 years

Cosman F. *JBMR*. 2018;33(7):1219

Case #4

Clinical Pearl: OP with/ from PHPT, preferentially seen in the distal forearm, which is rich in cortical bone

78 yo female with PMH of DM2, CHF, COPD on 3L O2, h/o lung carcinoid s/p resection 2009, CKD 3-4, HLD, thyroid cancer s/p TT 2009, postoperative hypothyroidism, OSA, HPT

- BMD 4/2022
  - L Fem Neck: T-Score -2.8; L Hip: T-Score -2.0
  - Distal 1/3 R Forearm: T-Score -3.0

Denosumab administered
- **5/3/22**
- **11/2/22**
- **5/3/23**

Bone Labs	2/24/2022	5/26/2022	6/21/2022	9/8/2022	2/3/2023	5/26/2023
PTH, Intact	299 (H)	1,081 (H)	214 (H)	240 (H)	250 (H)	514 (H)
Vitamin D25	21.2 (L)		20.5 (L)	38.0	22.5 (L)	29.6 (L)
Vit D1,25					47.1	71.8

Calcium			
Pre-Dmab	10.8 (4/22)	10.3 (10/22)	10.0 (5/23)
Post-Dmab	8.6 (5/22)	9.3 (11/15/22)	8.1 (6/9/23)
Post-post-Dmab		10.9 (11/30/22)	10.8 (7/18/23)

Wood K, et al. Oncologist. 2012;17(3):322-5.

Discussion

- Why was denosumab chosen for this pt
- How to manage hypocalcemia in the setting of CKD
- How long to expect hypocalcemia

* Clinical Pearl
PTH in CKD
Stage 3: 35-70
Stage 4: 70-110
Stafe 5: 150-300

Eremkina A, et al Endocr Connect. 2020 Oct;9(10):1019-1027.

Denosumab Considerations

* Clinical Pearl
ONJ statistically the same as being killed by lightning

- Significantly reduces the risk of vertebral and nonvertebral fractures
- Patients who discontinue denosumab are at increased risk for rebound vertebral fractures, often multiple fx & can occur as soon as 8 months after the last injection
- Providers should consider the patient's ability to adhere to regular, timely dosing and counsel the pt about possibility of rebound fx & against discontinuation without medical consultation
- Possible rare risk of ONJ and AFF

Symonds C, Kline G. CMAJ. 2018 Apr 3;190(16):E485-E486.

Transitioning from Denosumab to Bisphosphonate

Summary of Recommendations Regarding the Discontinuation of Denosumab

- If long-term denosumab is stopped, patients should be transitioned to a bisphosphonate, with either
  - a single-dose of zoledronic acid 6 months from the last denosumab dose, or
  - a short course (at least 1 year) of oral alendronate

Monitor serum CTX or urine NTX and BMD and re-dose if bone turnover markers are persistently elevated or if BMD shows a significant decline

Tay WL, Tay D. Endocrinol Metab (Seoul). 2022 Apr;37(2):183-194.

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