New drugs for osteoporosis

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Contents

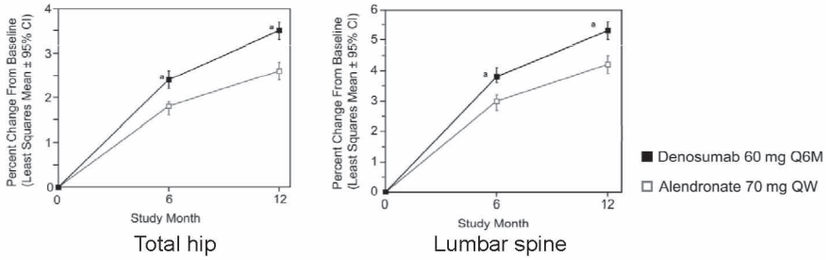
- **Denosumab**
- **Odanacatib**
- **PTH 1-84**
- **Calcium sensing receptor antagonist**

Denosumab

- Human monoclonal Ab with high affinity and specificity for RANKL
- By reducing RANKL, binding to the osteoclast receptor RANK, there is decrease in differentiation, activity, and survival of osteoclast.

Phase III trial compared with Alendronate

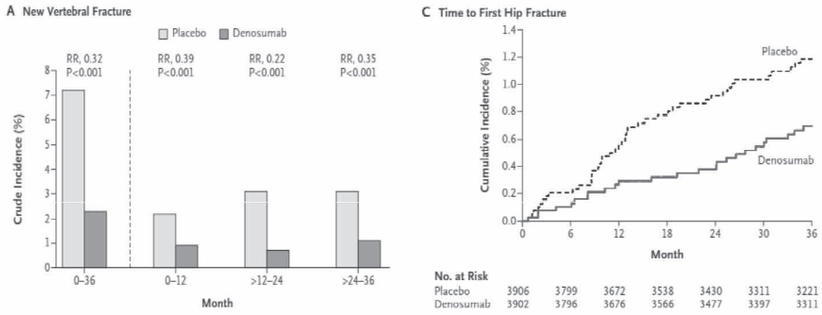
- N=1189
- Postmenopausal women with T-score ≤-2.0 at lumbar spine or total hip
- BMD change after 1yr
- At all site, denosumab showed significantly greater increases in BMD and siginificantly greater reduction of bone turnover markers.
- Safety profile was similar for both Tx



Brown JP, J Bone Miner Res, 2009

Anti-Fracture efficacy – FREEDOM trial

- N=7868, PM women (60~90yrs), BMD T-score <-2.5 but not <-4.0

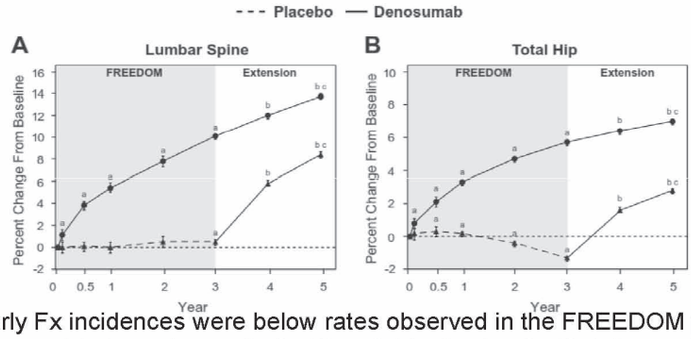


- Non-vertebral Fx: HR, 0.80, 95% CI, 0.67-0.95
- Hip Fx: HR, 0.60, 95% CI, 0.37-0.97

Cummings SR, NEJM, 2009

FREEDOM Extension – after 5 yrs

- To continue the evaluation of denosumab efficacy and safety for up to 10 yrs
- 2,343 long-term group (5yrs of denosumab) and 2,207 cross-over group (3yrs of placebo and 2yrs of denosumab)

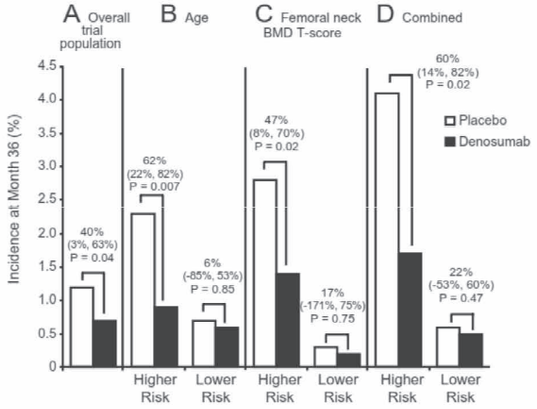


- Yearly Fx incidences were below rates observed in the FREEDOM placebo group and below rates projected for a “virtual untreated twin” cohort

Papapoulos S, J Bone Miner Res, 2012

FREEDOM trial – post hoc analysis

- RRR in hip Fx with denosumab for 36 months



- B: Age ≥75 yrs
- C: FN BMD ≤-2.5
- D: age and BMD

Boonen S, J Clin Endocrinol Metab, 2011

- Suspected cases of ONJ in pts. on denosumab

Aghaloo T, J Oral Maxillofac Surg, 2010

Taylor KH, Br J Oral Maxillofac Surg, 2010

- Rapid reversibility of its anti-resorptive effect

Bone HG, J Clin Endocrinol,Metab, 2011

- Greater adherence (subcutaneous injection every 6 months) over weekly alendronate at 12 months (p=0.043)

Kendler DL, Osteoporos Int, 2010

- Gains in total hip BMD explain a considerable proportion of the fracture risk reductions observed with denosumab. (New vertebral Fx 35%, nonvertebral Fx 87%) – FREEDOM trial

Austin M, J Bone Miner Res, 2012

Differences between Denosumab and Bisphosphonate

Denosumab	Bisphosphonates
Biological	Nonbiological
Inhibits receptor activated nuclear factor kB	Inhibit mevalonate pathway
Prevents osteoclast formation	Decrease osteoclast function and survival
Subcutaneous	Oral, intravenous
Twice a year	Weekly, monthly, yearly
Half-life short, not bound to skeleton	Prolonged half-life, accumulate in the skeleton
Efficacy reduces vertebral, nonvertebral, and hip Fx	Efficacy on Fx reduction is agent dependent
Safety, possible increase in serious infections such as cellulitis	Safety bone selective, oral BP associated with GI intolerability
Suppression of bone remodeling marked but potentially reversible	Suppression of bone remodeling protracted
Not cleared by the kidneys	Cleared by kidneys

Canalis E, Endocr Pract, 2010

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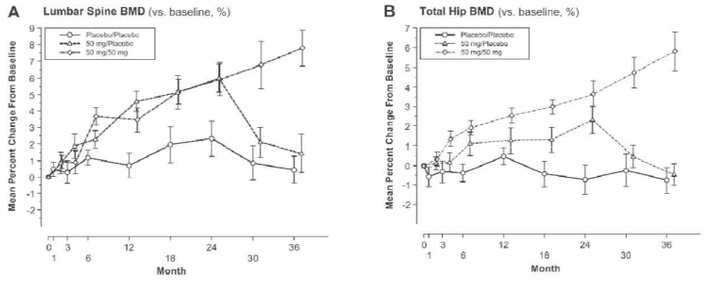
Odanacatib

- Cathepsin K: a lysosomal protease, expressed in osteoclasts that contributes to the breakdown of bone matrix (Type I collagen)
- Odanacatib – 2yrs of phase II trial with 1yr extension



- Greater gain of BMD after 5 yrs of ODN

Eisman JA, J Bone Miner Res, 2011

Langdahl B, J Bone Miner Res, 2012

Odanacatib- safety

- Back pain (10.1%)
- Arthralgia (7.9%)
- Pain in an extremity (8.5%)
- Nasopharyngitis (9.5)
- Urinary tract infection or cystitis

- No clinically important changes in serum Ca level or mineral homeostasis
- Not significant skin reaction

Advantages and disadvantages of Cathepsin K inhibitors

Advantages	Disadvantages
Oral bioavailability	Potential targeting of nonskeletal cathepsins leading to adverse effects
Weekly administration	Fx reduction efficacy unknown
Do not accumulate in skeletal tissue	Long-term safety and efficacy unknown
Good effect on BMD	Increased bone fragility in pycnodysostosis and cathepsin K null mouse models
Bx suggest bone safety	

Canalis E, Endocr Pract, 2010

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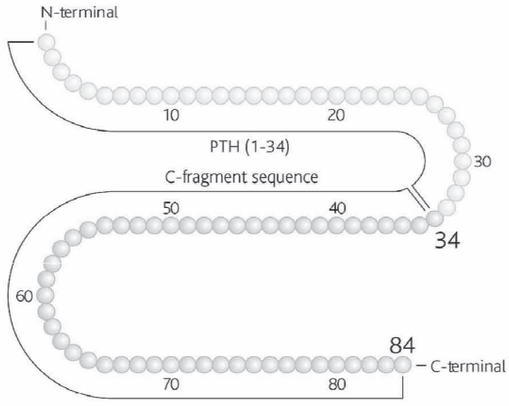
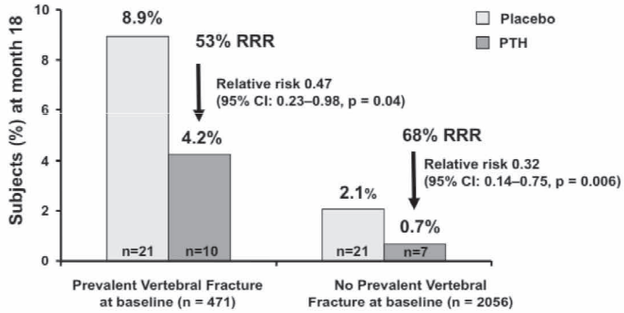
PTH (parathyroid hormone) 1-84



TOP (Treatment of Osteoporosis) study

- 2,532 postmenopausal women
- 45-54YO with T-score ≤-3 or with T-score ≤ -2.5 and vetebral Fx (+)
- >55YO with T-score ≤ -2.5 or ≤ -2.0 with vertebral Fx
- 100 μg of PTH 1-84 daily s.c. injection for 18 months



Greenspan SL, Ann Intern Med, 2007

- OLES study (open-label extension of the TOP study)
  - 781 women continued Tx with PTH 1-84 for an extra time of 6 months
  - Lumbar spine, hip BMD increased and the reduction in vertebral Fx risk was sustained

Roux C, Calcif Tissue Int, 2007

- Effects of PTH 1-84 on Fx healing
  - Accelerated fracture healing after PTH

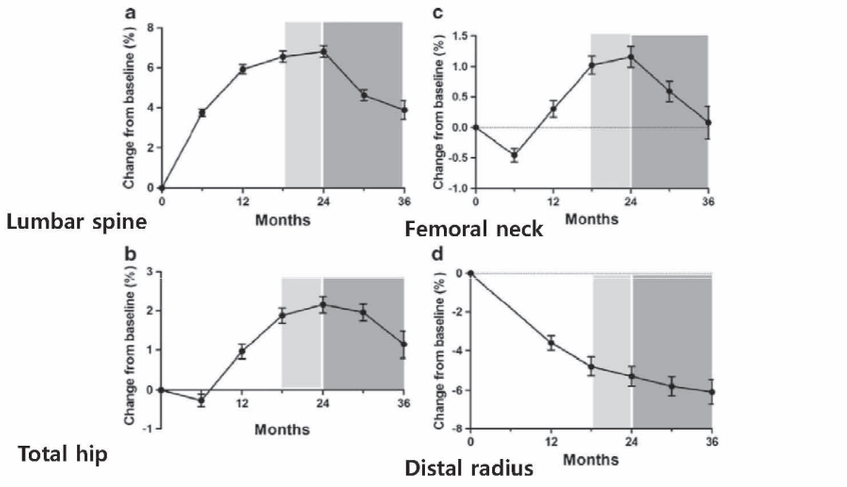
Peichi P, J Bone Joint Surg Am, 2011

	PTH 1-84 treatment group (n = 21)	Placebo group (n = 44)	P value
Rate of fracture healing			
Week 4	4.8%	0%	0.145
Week 8	100%	9.1%	<0.001
Week 12	100%	68.2%	0.004
Mean visual analog scale score for pain (VAS)			
basal	7.6 ± 1.1	7.7 ± 1.1	0.743
Week 8	3.2 ± 7.7	6.5 ± 0.9	<0.001

- Effects of PTH on Quality of Life
  - Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO) total score improved siginificantly.
  - Decreased pain, improved mobility

Moricke R, Clin Drug Investig, 2011

12 months f/u after OLES for 24 months



Black DM, Osteoporos Int, 2012

Contents

- **Bazedoxifene**
- **Lasofoxifene**
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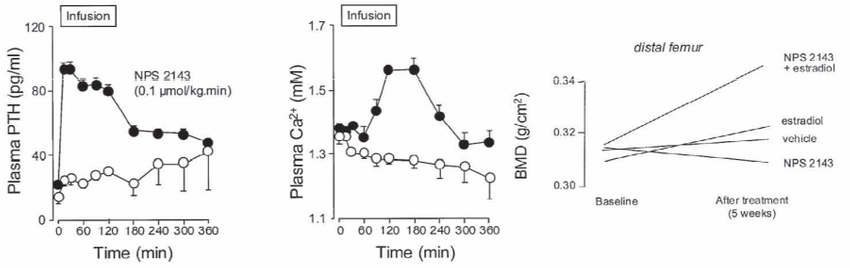
Action mechanism

- Circulating Ca^{2+} is a primary regulator of bone homeostasis through its action on PTH secretion
- pulsatile PTH could be achieved by acutely stimulating the release of endogenous PTH by inhibiting the calcium-sensing receptor (CaSR)
- Short-term antagonist of the CaSR
- NPS 2143 in normal rats



Nemeth EF, J Mol Endocrinol, 2002

Ronacaleret

- N=528
- Lumbar spine: lower BMD gain at 12 months than teriparatide or alendronate
- BMD decreased in total hip, femoral neck, and trochanter at 12 months.
- PTH elevation with ronacaleret were prolonged relative to those previously reported with teriparatide.

Fitzpatrick LA, J Clin Endocrinol Metab, 2011