Beyond Bisphosphonates: Denosumab and Romosozumab for Osteoporosis

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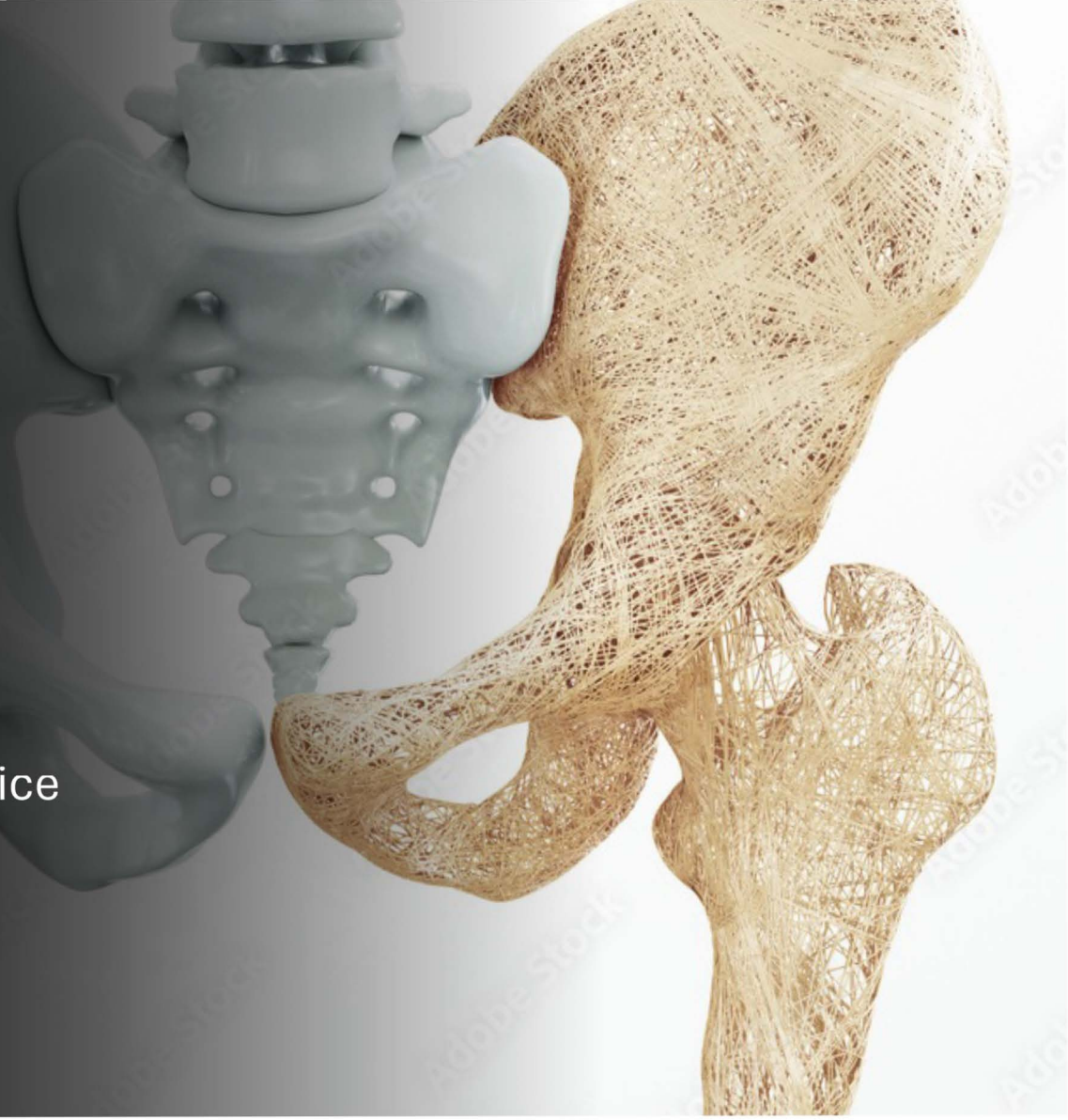
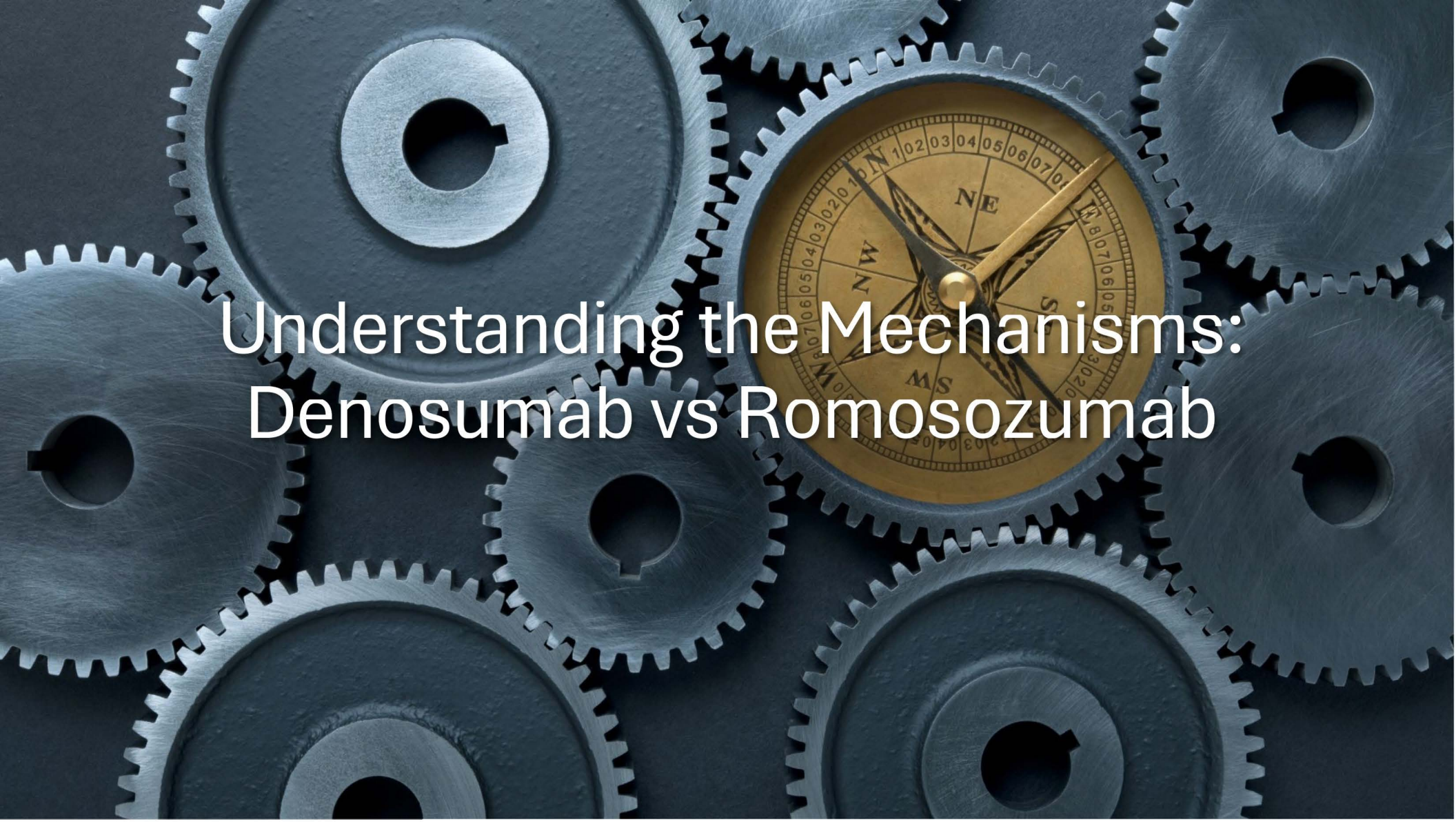


Learning Objectives

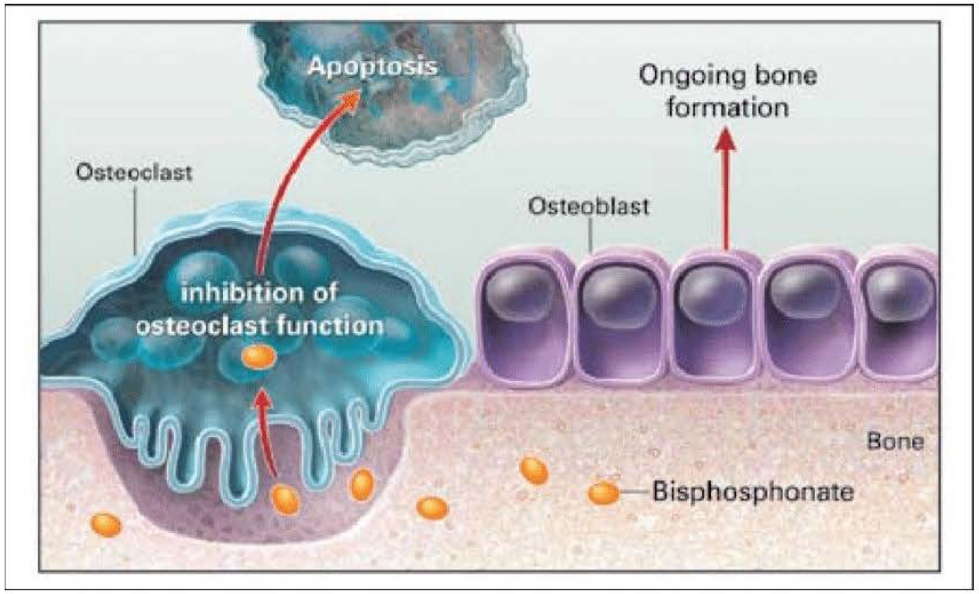
- Describe the mechanisms of action for denosumab and romosozumab and how they differ from bisphosphonates
- Evaluate the clinical trial evidence supporting the efficacy and safety of denosumab and romosozumab in reducing fracture risk.
- Identify appropriate patient populations for treatment with denosumab and romosozumab
- Analyze potential safety concerns and contraindications associated with denosumab and romosozumab.



Understanding the Mechanisms: Denosumab vs Romosozumab

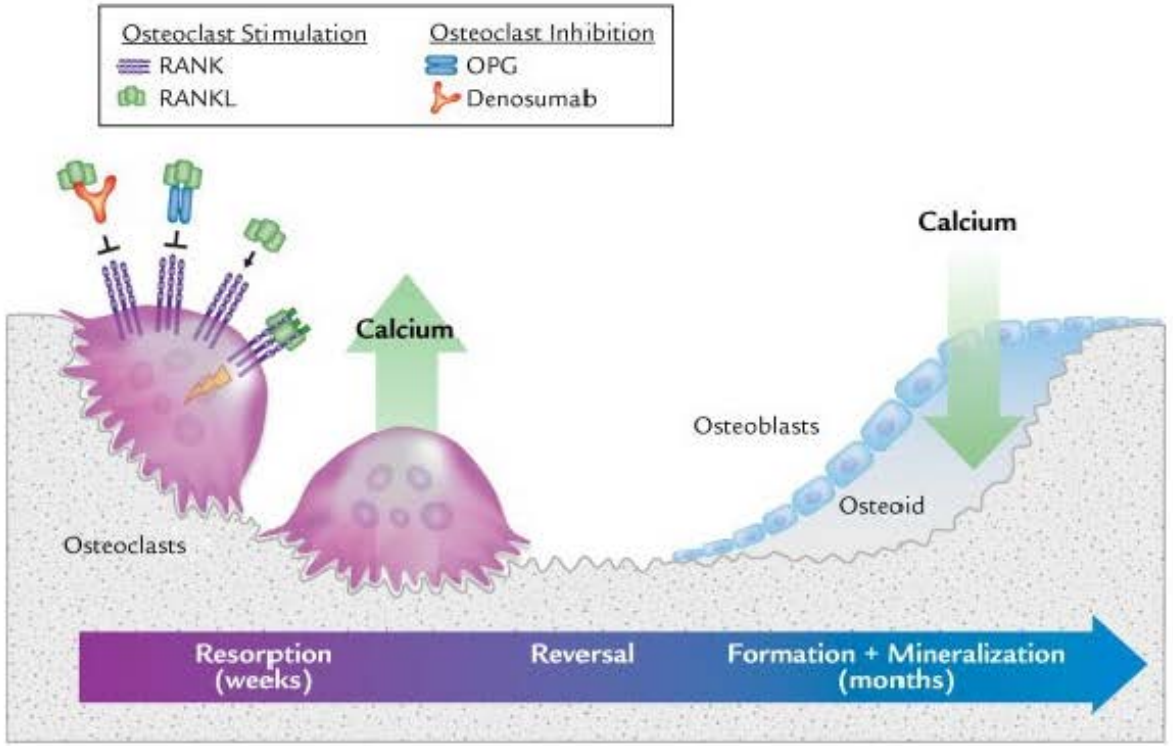
Bisphosphonates

- Inhibit osteoclastic bone resorption
- Attach to the hydroxyapatite binding sites on bony surfaces.
- Osteoclasts begin to resorb bone impregnated with bisphosphonate, the bisphosphonate reduces osteoclast activity



Solomon, Caren G. "Bisphosphonates and osteoporosis." *New England Journal of Medicine* 346.9 (2002): 642-642.

Denosumab



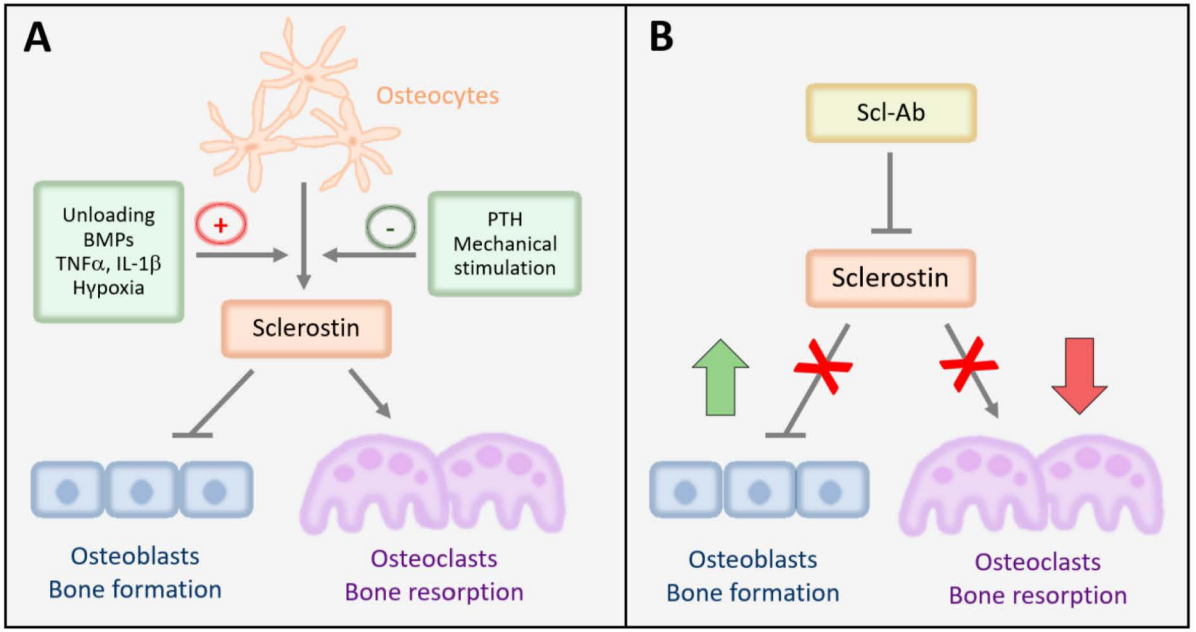
David W. Dempster, Cheryl L. Lambing, Paul J. Kostenuik, Andreas Grauer, Role of RANK Ligand and Denosumab, a Targeted RANK Ligand Inhibitor, in Bone Health and Osteoporosis: A Review of Preclinical and Clinical Data,Clinical Therapeutics,Volume 34, Issue 3,2012,Pages 521-536,

Denosumab (Prolia)

- Fully humanized monoclonal antibody that binds to and inhibits the action of (Receptor Activator of Nuclear factor-Kappa B Ligand) RANKL
  - Inhibit osteoclast formation and activity
- At least as effective as bisphosphonates
- Dose:
  - Denosumab 60 mg subcutaneously every 6 months
- Note different brand name for different indication
  - Prolia – Osteoporosis
  - XGEVA – Prevent fracture in oncology
- Adverse effects:
  - **Immunologic:** Immune cells express RANKL - blocking RANKL on immune cells may increase risk of infection
  - **Bone:** Suppression of bone turnover – potential risk of osteonecrosis of the jaw and subtrochanteric fractures (like bisphosphonates)
  - **Calcium:** Transient hypocalcemia especially in patients with renal disease – monitor calcium
  - Does not result in death of osteoclasts (unlike bisphosphonates), so if therapy is stopped a surge of bone resorption can occur.

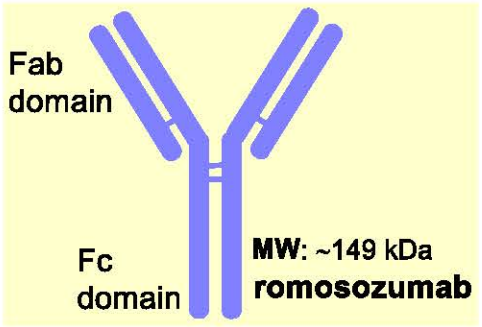
Sclerostin Regulation and Effect of Bone Cells

- Produced by the osteocytes
- Inhibitor of bone formation



Rauner M, Taipaleenmäki H, Tsourdi E, Winter EM. Osteoporosis Treatment with Anti-Sclerostin Antibodies—Mechanisms of Action and Clinical Application. *Journal of Clinical Medicine*. 2021; 10(4):787. https://doi.org/10.3390/jcm10040787

Romosozumab



- Antibody against sclerostin
  - Suppresses osteoclast activity
- Therapeutic Use
  - Anabolic agent that promotes new bone formation and inhibits bone resorption
- Dose
  - Romosozumab 210 mg subcutaneously once monthly x 1 year
    - Given as (2) consecutive injections of 105 mg each
- Adverse effect
  - Neuro: Stroke
  - CV: Increased risk of myocardial infarction, CV death
- Black Box Warning – Contraindicated in patient with previous MI or stroke in the past year

Clinical Trial Data

ORIGINAL ARTICLE

Denosumab for Prevention of Fractures in Postmenopausal Women with Osteoporosis

Steven R. Cummings, M.D., Javier San Martin, M.D., Michael R. McClung, M.D., Ethel S. Siris, M.D., Richard Eastell, M.D., Ian R. Reid, M.D., Pierre Delmas, M.D., Ph.D., Holly B. Zoog, Ph.D., Matt Austin, M.S., Andrea Wang, M.A., Stepan Kutilek, M.D., Silvano Adami, M.D., Ph.D., Jose Zanchetta, M.D., Cesar Libanati, M.D., Suresh Siddhanti, Ph.D., and Claus Christiansen, M.D., for the FREEDOM Trial*

ABSTRACT

BACKGROUND

Denosumab is a fully human monoclonal antibody to the receptor activator of nuclear factor-κB ligand (RANKL) that blocks its binding to RANK, inhibiting the development and activity of osteoclasts, decreasing bone resorption, and increasing bone density. Given its unique actions, denosumab may be useful in the treatment of osteoporosis.

METHODS

We enrolled 7868 women between the ages of 60 and 90 years who had a bone mineral density T score of less than −2.5 but not less than −4.0 at the lumbar spine or total hip. Subjects were randomly assigned to receive either 60 mg of denosumab or placebo subcutaneously every 6 months for 36 months. The primary end point was new vertebral fracture. Secondary end points included nonvertebral and hip fractures.

RESULTS

As compared with placebo, denosumab reduced the risk of new radiographic vertebral fracture, with a cumulative incidence of 2.3% in the denosumab group, versus 7.2% in the placebo group (risk ratio, 0.32; 95% confidence interval [CI], 0.26 to 0.41; P<0.001) — a relative decrease of 68%. Denosumab reduced the risk of hip fracture, with a cumulative incidence of 0.7% in the denosumab group, versus 1.2% in the placebo group (hazard ratio, 0.60; 95% CI, 0.37 to 0.97; P=0.04) — a relative decrease of 40%. Denosumab also reduced the risk of nonvertebral fracture, with a cumulative incidence of 6.5% in the denosumab group, versus 8.0% in the placebo group (hazard ratio, 0.80; 95% CI, 0.67 to 0.95; P<0.01) — a relative decrease of 20%. There was no increase in the risk of cancer, infection, cardiovascular disease, delayed fracture healing, or hypocalcemia, and there were no cases of osteonecrosis of the jaw and no adverse reactions to the injection of denosumab.

CONCLUSIONS

Denosumab given subcutaneously twice yearly for 36 months was associated with a reduction in the risk of vertebral, nonvertebral, and hip fractures in women with osteoporosis. (ClinicalTrials.gov number, NCT00089791.)

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*Investigators for the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial are listed in the Appendix.

This article (10.1056/NEJMoa0809493) was published on August 11, 2009, and was updated on November 4, 2009, at NEJM.org.

N Engl J Med 2009;361:756-65.

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Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis

Kenneth G. Saag, M.D., Jeffrey Petersen, M.D., Maria Luisa Brandi, M.D., Andrew C. Karaplis, M.D., Ph.D., Mattias Lorentzon, M.D., Ph.D., Thierry Thomas, M.D., Ph.D., Judy Maddox, D.O., Michelle Fan, Ph.D., Paul D. Meisner, Pharm.D., and Andreas Grauer, M.D.

ABSTRACT

BACKGROUND

Romosozumab is a monoclonal antibody that binds to and inhibits sclerostin, increases bone formation, and decreases bone resorption.

METHODS

We enrolled 4093 postmenopausal women with osteoporosis and a fragility fracture and randomly assigned them in a 1:1 ratio to receive monthly subcutaneous romosozumab (210 mg) or weekly oral alendronate (70 mg) in a blinded fashion for 12 months, followed by open-label alendronate in both groups. The primary end points were the cumulative incidence of new vertebral fracture at 24 months and the cumulative incidence of clinical fracture (nonvertebral and symptomatic vertebral fracture) at the time of the primary analysis (after clinical fractures had been confirmed in ≥330 patients). Secondary end points included the incidences of nonvertebral and hip fracture at the time of the primary analysis. Serious cardiovascular adverse events, osteonecrosis of the jaw, and atypical femoral fractures were adjudicated.

RESULTS

Over a period of 24 months, a 48% lower risk of new vertebral fractures was observed in the romosozumab-to-alendronate group (6.2% [127 of 2046 patients]) than in the alendronate-to-alendronate group (11.9% [243 of 2047 patients]) (P<0.001). Clinical fractures occurred in 198 of 2046 patients (9.7%) in the romosozumab-to-alendronate group versus 266 of 2047 patients (13.0%) in the alendronate-to-alendronate group, representing a 27% lower risk with romosozumab (P<0.001). The risk of nonvertebral fractures was lower by 19% in the romosozumab-to-alendronate group than in the alendronate-to-alendronate group (178 of 2046 patients [8.7%] vs. 217 of 2047 patients [10.6%]; P=0.04), and the risk of hip fracture was lower by 38% (41 of 2046 patients [2.0%] vs. 66 of 2047 patients [3.2%]; P=0.02). Overall adverse events and serious adverse events were balanced between the two groups. During year 1, positively adjudicated serious cardiovascular adverse events were observed more often with romosozumab than with alendronate (50 of 2040 patients [2.5%] vs. 38 of 2014 patients [1.9%]). During the open-label alendronate period, adjudicated events of osteonecrosis of the jaw (1 event each in the romosozumab-to-alendronate and alendronate-to-alendronate groups) and atypical femoral fracture (2 events and 4 events, respectively) were observed.

CONCLUSIONS

In postmenopausal women with osteoporosis who were at high risk for fracture, romosozumab treatment for 12 months followed by alendronate resulted in a significantly lower risk of fracture than alendronate alone. (Funded by Amgen and others; ARCH ClinicalTrials.gov number, NCT01631214.)

From the University of Alabama, Birmingham (K.G.S.); Amgen, Thousand Oaks, CA (J.P., J.M., M.F., A.G.); University of Florence, Florence, Italy (M.L.B.); McGill University, Montreal (A.C.K.); University of Gothenburg and Sahlgrenska University Hospital, Mölndal, Sweden (M.L.); Centre Hospitalier Universitaire de Saint-Etienne and INSERM Research Unit 1059, University of Lyon, Saint-Etienne, France (T.T.); and UCB Pharma, Brussels (P.D.M.). Address reprint requests to Dr. Saag at the Division of Clinical Immunology and Rheumatology, University of Alabama, Faculty Office Tower, Suite 820, 510 20th St. South, Birmingham, AL 35294-3408.

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Denosumab (FREEDOM trial)

- 7868 postmenopausal women (60 – 90 years of age) with osteoporosis (T-scores between -2.5 and -4.0 at the lumbar spine (LS) or total hip (TH))
- Randomized to denosumab 60 mg q6 months or placebo
- Efficacy: after three years
  - Lower rate of new vertebral fractures (2.3% vs 7.2%; RR 0.32, 95% CI 0.26-0.41)
  - Lower rate of hip (0.7% vs 1.2%) and nonvertebral (6.5% vs 8.5%) fractures
  - Improvement in BMD of LS (9.2% vs 0%) and TH (4% vs -2%) compared with placebo
- Conclusion: Denosumab given subcutaneously twice yearly after 36 months was associated with a reduction in the risk of vertebral, nonvertebral, and hip fractures in women with osteoporisis

Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, Delmas P, Zoog HB, Austin M, Wang A, Kutilek S, Adami S, Zanchetta J, Libanati C, Siddhanti S, Christiansen C; FREEDOM Trial. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009 Aug 20;361(8):756-65. doi: 10.1056/NEJMoa0809493.

Denosumab vs Alendronate

- 1189 postmenopausal women with low BMD (T-score $\leq$ at the lumbar spine or hip)
- Randomized to denosumab (60 mg sq q6months) plus oral placebo or oral alendronate (70 mg qweek) plus subcutaneous placebo injection q6months
- Efficacy after 1 year, BMD increase at the total hip (3.5% vs 2.6%), femoral neck (2.4% vs 1.8%), and lumbar spine (5.3% vs 4.2%)
- Conclusion: slightly but significantly greater with denosumab. Trial design was not designed to assess fracture reduction.

Brown JP, Prince RL, Deal C, Recker RR, Kiel DP, de Gregorio LH, Hadji P, Hofbauer LC, Alvaro-Gracia JM, Wang H, Austin M, Wagman RB, Newmark R, Libanati C, San Martin J, Bone HG. Comparison of the effect of denosumab and alendronate on BMD and biochemical markers of bone turnover in postmenopausal women with low bone mass: a randomized, blinded, phase 3 trial. J Bone Miner Res. 2009 Jan;24(1):153-61. doi: 10.1359/jbmr.0809010. PMID: 18767928.

Romosozumab vs Alendronate (ARCH trial)

- 4093 postmenopausal women with osteoporosis and prior fragility fracture
  - mean T-scores of -2.96 (lumbar spine), -2.80 (total hip), and -2.90 (femoral neck)
- Randomized to romosozumab (210 mg) or weekly alendronate (70mg) for 12 months. All patients subsequently got alendronate weekly.
- Efficacy after 24 months
  - Radiographic vertebral fractures occurred in the romosozumab to alendronate group than the alendronate-to-alendronate group
    - 6.2% vs 11.9%, RR 0.52, 95% CI 0.40 – 0.66
  - Risk of clinical fractures (9.7% vs 13%), nonvertebral fractures (8.7% vs. 10.6%), or hip fractures (2.0% vs. 3.2%) was lower in the romosozumab group.
- Conclusion - Romosozumab followed by alendronate appears more effective than alendronate alone in post menopausal women with established osteoporosis.

Saag KG, Petersen J, Brandi ML, Karaplis AC, Lorentzon M, Thomas T, Maddox J, Fan M, Meisner PD, Grauer A. 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.

Patient Selection and ACP 2023 Guidelines

CLINICAL GUIDELINE

ACP American College of Physicians® Leading Internal Medicine, Improving Lives

Pharmacologic Treatment of Primary Osteoporosis or Low Bone Mass to Prevent Fractures in Adults: A Living Clinical Guideline From the American College of Physicians

Amir Qaseem, MD, PhD, MHA; Lauri A. Hicks, DO; Itziar Etxeandia-Ikobaltzeta, PharmD; Tatyana Shamliyan, MD, MS; and Thomas G. Cooney, MD; for the Clinical Guidelines Committee of the American College of Physicians*

Description: This guideline updates the 2017 American College of Physicians (ACP) recommendations on pharmacologic treatment of primary osteoporosis or low bone mass to prevent fractures in adults.

Methods: The ACP Clinical Guidelines Committee based these recommendations on an updated systematic review of evidence and graded them using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system.

Audience and Patient Population: The audience for this guideline includes all clinicians. The patient population includes adults with primary osteoporosis or low bone mass.

Recommendation 1a: *ACP recommends that clinicians use bisphosphonates for initial pharmacologic treatment to reduce the risk of fractures in postmenopausal females diagnosed with primary osteoporosis (strong recommendation; high-certainty evidence).*

Recommendation 1b: *ACP suggests that clinicians use bisphosphonates for initial pharmacologic treatment to reduce the risk of fractures in males diagnosed with primary osteoporosis (conditional recommendation; low-certainty evidence).*

Recommendation 2a: *ACP suggests that clinicians use the RANK ligand inhibitor (denosumab) as a second-line pharmacologic treatment to reduce the risk of fractures in postmenopausal females diagnosed with primary osteoporosis who have contraindications to or experience adverse effects of bisphosphonates (conditional recommendation; moderate-certainty evidence).*

Recommendation 2b: *ACP suggests that clinicians use the RANK ligand inhibitor (denosumab) as a second-line pharmacologic treatment to reduce the risk of fractures in males diagnosed with primary osteoporosis who have contraindications to or experience adverse effects of bisphosphonates (conditional recommendation; low-certainty evidence).*

Recommendation 3: *ACP suggests that clinicians use the sclerostin inhibitor (romosozumab, moderate-certainty evidence) or recombinant PTH (teriparatide, low-certainty evidence), followed by a bisphosphonate, to reduce the risk of fractures only in females with primary osteoporosis with very high risk of fracture (conditional recommendation).*

Recommendation 4: *ACP suggests that clinicians take an individualized approach regarding whether to start pharmacologic treatment with a bisphosphonate in females over the age of 65 with low bone mass (osteopenia) to reduce the risk of fractures (conditional recommendation; low-certainty evidence).*

Ann Intern Med. 2023;176:224-238. doi:10.7326/M22-1034 **Annals.org**
For author, article, and disclosure information, see end of text.
This article was published at Annals.org on 3 January 2023.

Primary osteoporosis (osteoporosis that is not secondary to a separate condition or medication) is characterized by decreasing bone mass and density and reduced bone strength leading to a higher risk for fracture (**Appendix Table 1**, available at Annals.org) (1, 2). Fractures can occur in any bone, but hip and spine fractures are most common, accounting for 42% of all osteoporotic fractures. Fractures are associated with serious morbidity and mortality, and people with prevalent fractures are at much higher risk for future fractures (3–5). Overall, an estimated 10.2 million persons aged 50 years or older in the United States have osteoporosis, and about 43.3 million persons (>40% of older U.S. adults) have low bone mass associated with a high risk for progression to osteoporosis (6).

The clinical and economic burden of osteoporotic fractures is increasing over time in certain racial and ethnic

See also:

Related article 182
Summary for Patients I-24

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Supplement

* This article, written by Amir Qaseem, MD, PhD, MHA; Lauri A. Hicks, DO; Itziar Etxeandia-Ikobaltzeta, PharmD; Tatyana Shamliyan, MD, MS; and Thomas G. Cooney, MD, was developed for the Clinical Guidelines Committee of the American College of Physicians. Individuals who served on the Clinical Guidelines Committee from initiation of the project until its approval were Timothy J. Wilt, MD, MPH‡ (Chair); Carolyn J. Crandall, MD, MS‡ (Vice Chair); Devan Kansagara, MD, MCR‡ (Past Vice Chair); Pelin Batur, MD, NCMP‡; Thomas G. Cooney, MD†; J. Thomas Cross Jr., MD, MPH†; Nick Fitterman, MD†; Lauri A. Hicks, DO†; Jennifer S. Lin, MD, MCR†; Michael Maroto, JD, MBA†§; Reem A. Mustafa, MD, PhD, MPH‡; Adam J. Obley, MD†; Douglas K. Owens, MD, MS‡; Jeffrey A. Tice, MD†; Janice E. Tufte†§; Sandeep Vijan, MD, MS‡; and John W. Williams Jr., MD, MHS‡. Kate Carroll, MPH, was a nonauthor contributor from ACP staff. Approved by the ACP Board of Regents on 25 April 2022.
† Author.
‡ Nonauthor contributor.
§ Nonphysician public representative.

Who Benefits Most? Integrating ACP Recommendations

- 2023 ACP Guidelines
  - **Bisphosphonates** for initial pharmacologic treatment to reduce risk of fractures in post menopausal females diagnosed with primary osteoporosis (*strong recommendation*)
    - Males (*conditional recommendation*)
  - **Denosumab** as second-line pharmacologic treatment to reduce the risk of fractures in postmenopausal females and males diagnosed with primary osteoporosis who have contraindication to or experience adverse effects of bisphosphonates (*conditional recommendation*)
  - **Romosozumab,** a sclerostin inhibitor followed by a bisphosphonate to reduce the risk of fractures only in females (romosozumab not FDA approved for men) with primary osteoporosis with very high risk of fracture (*conditional recommendation*)

Questions