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Original Research Article

Romosozumab: A New Drug for Osteoporosis

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Abstract: Osteoporosis is a chronic, progressive skeletal disorder characterized by reduced bone mass, deteriorated bone microarchitecture, and an elevated risk of fragility fractures. While antiresorptive therapies have long formed the treatment backbone, new osteoanabolic agents offer the potential for faster and greater improvements in bone strength. Romosozumab, a first-in-class sclerostin inhibitor, has emerged as a potent and innovative therapy, capable of both stimulating bone formation and reducing bone resorption. This article reviews romosozumab's mechanism of action, pivotal clinical trial data, efficacy, safety, real-world experience, and best practices for its integration into osteoporosis management.

Keywords: Romosozumab, Osteoporosis, Sclerostin inhibitor, Bone formation, Fracture risk reduction.

INTRODUCTION

Osteoporosis affects over 200 million people worldwide and leads to significant morbidity, mortality, and healthcare costs due to fractures. Despite existing treatment options, many patients remain at high risk for subsequent fractures. Romosozumab (brand name: Evenity®) represents a major advance, targeting a novel pathway for bone anabolism and providing meaningful clinical benefits to those at highest fracture risk[1][2][3].

MECHANISM OF ACTION

Romosozumab is a humanized monoclonal IgG2 antibody that binds to and inhibits sclerostin, a glycoprotein secreted by osteocytes that restricts bone formation by inhibiting Wnt signaling in osteoblasts[2][4][5]. Sclerostin blockade simultaneously unleashes two reciprocal effects:

- **Increases bone formation:** Promotes osteoblast proliferation and activity via activation of Wnt/β-catenin signaling.
- **Reduces bone resorption:** Indirectly suppresses osteoclastogenesis by reducing RANKL expression, limiting bone breakdown.

This dual effect sets romosozumab apart from traditional therapies (e.g., bisphosphonates, denosumab) that act primarily by inhibiting bone resorption.

Pharmacology and Administration

- **Dosing:** 210mg subcutaneously (administered as two 105mg injections) once monthly for 12 months[6][7].
- **Pharmacokinetics:** Peak serum levels in 5 days; half-life 6–7 days; subcutaneous bioavailability 50–70%.
- **Supplementation:** Adequate calcium and vitamin D during therapy is necessary.

- **Sequence:** Therapy typically limited to 12 months due to waning anabolic effect. Transition to antiresorptive treatment (e.g., bisphosphonates, denosumab) is recommended to preserve BMD gains[3][8].

CLINICAL EFFICACY

Pivotal Trials

1. FRAME Study

- **Population:** Postmenopausal women with osteoporosis.
- **Results:** Romosozumab for 12 months reduced the risk of new vertebral fractures by 73% (0.5% vs. 1.8%) compared to placebo[3][9].
- **Bone Mineral Density (BMD) increases:** Lumbar spine +13%, total hip +6% vs. placebo at 12 months[2][9].

2. ARCH Study

- **Population:** Postmenopausal women with osteoporosis at high risk for fracture.
- **Results:** Compared to alendronate, romosozumab followed by alendronate resulted in:
  - Lower risk of vertebral (HR 0.63) and nonvertebral fractures (HR 0.81).
  - Greater BMD gains and earlier reduction in fracture risk[3].

3. BRIDGE Study (men with osteoporosis)

- **Results:** Greater increase in lumbar spine BMD (12.1% vs. 1.2%) and total hip BMD (2.5% vs. -0.5%) at 12 months vs. placebo[10][11].

Meta-Analysis (2024, 6 RCTs, n=7,990)

Outcome	Effect Size (vs. placebo)
Lumbar spine BMD	+12.7%
Total hip BMD	+4.4%
Major osteoporotic fractures	Risk ratio (RR) 0.37 (63% reduction)
Falls	RR 0.80 (20% reduction)
Injection-site reactions	RR 1.83 (increased, but mostly mild)
Cardiovascular events	No significant increase at 12 months[9]

Visual: Relative Changes in BMD at Different Skeletal Sites

A bar graph can demonstrate mean percentage increases in BMD at the spine, total hip, and femoral neck after 12 months of romosozumab compared to placebo[11][9].

Real-World Effectiveness

Recent observational studies in large cohorts confirm clinical trial findings:

- **BMD increases:** Mean +7.7% at lumbar spine, +1.8% at total hip after 12 months.
- **Fracture incidence:** New fractures in 3%; lower in primary osteoporosis than in secondary.
- **Greatest benefit:** Patients naïve to prior antiosteoporotic therapy; less robust BMD increases in those switching from denosumab or bisphosphonates[12][13][14].

Safety Profile

- **Injection-site reactions:** Most frequent, generally mild.
- **Hypocalcemia:** Rare, risk increased in renal insufficiency; monitor serum calcium.
- **Cardiovascular events:** Slightly higher (non-significant) rates observed in some studies; FDA issued black box warning contraindicating use in people with recent myocardial infarction or stroke[3][8][9].
- **Other:** No significant difference in general adverse events, including infections or malignancy, compared to placebo.

Table: Common Adverse Events with Romosozumab (12 months)	
Injection site reactions	2–5%
Arthralgia and muscle pain	2–4%
Cardiovascular events	1–2% (caution: high-risk pts)

Hypocalcemia	<1% (supplement calcium/vit D)

Patient Selection and Guidelines

Romosozumab is indicated for patients at high risk for fracture, including:

- History of osteoporotic fracture
- Multiple risk factors (very low BMD, frailty, falls)
- Failure or intolerance to prior osteoporosis therapies

Not recommended for patients with high baseline cardiovascular risk (recent MI or stroke)[8][15].

- **Duration:** Up to 12 months, then transition to antiresorptive agent.
- **Monitoring:** BMD (spine and hip), calcium, vitamin D, cardiovascular status[6][8].

DISCUSSION

Romosozumab's unique dual anabolic and antiresorptive effects address key limitations of prior therapies. Its rapid, robust improvement in BMD and fracture risk reduction, especially in the initial months, make it well-suited to those with imminent fracture risk. Careful patient selection and a treatment sequence that preserves gains are essential for maximizing benefit and minimizing risks[1][2][3][8].

CONCLUSION

Romosozumab is an effective, first-in-class sclerostin inhibitor for osteoporosis in high-risk patients. It rapidly increases BMD and significantly reduces fracture risk. Its approved use as a 12-month, once-monthly injection followed by antiresorptive therapy represents an important option for postmenopausal women and some men with osteoporosis, with appropriate attention to cardiovascular safety.

Table: Summary of Romosozumab in Osteoporosis

Aspect	Clinical Effect/Recommendation
Mechanism	Sclerostin inhibition, dual anabolic/anti-resorptive
Dosing	210mg s.c. monthly, 12 months
Major BMD gain (12mo)	Spine: ~13%; Hip: ~6% vs. placebo
Fracture reduction	Vertebral: up to 73% at 12mo
Major side effects	Injection reactions, possible CV risk
Sequence	12mo then antiresorptive agent

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