Shoring Up Osteoporosis Management: A Fresh Start?

Noah Furr, MD, Ansley Ulmer, MD, and Brock Cardon, MD

Anabolic bone agents, such as parathyroid hormone receptor agonists (teriparatide and abaloparatide) and sclerostin-inhibiting monoclonal antibody (romosozumab), are superior at preventing clinically significant fractures and/or vertebral fractures in women with and without severe osteoporosis compared with bisphosphonates. (J Am Board Fam Med 2024;37:490–493.)

Keywords: **Anabolic Bone Agents, Bisphosphonates, Fracture Prevention, Osteoporosis**

Strength of Recommendation: A

Based on a single systematic review with meta-analysis and meta-regression analysis.[1]

Illustrative Case

A 67-year-old-woman with moderate osteoarthritis presents for follow up from her recent annual preventative medicine examination. A recent dual energy Radiograph absorptiometry (DEXA) scan was diagnostic for osteoporosis with T-scores of −2.8 in her L-spine and −2.4 in bilateral hips. Her calculated Fracture Risk Assessment Tool (FRAX) score predicts a 10-year risk of major osteoporotic fracture of 8.2%. After discussing osteoporosis treatment options, she agrees to pharmacologic treatment. In addition to conservative treatments and nutritional supplementation, what pharmacologic intervention will best reduce the risk for future osteoporotic fractures in this postmenopausal patient?

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From the Nellis Family Medicine Residency, Nellis AFB, Las Vegas, NV.
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FPIN Editor: Rebecca Mullen, MD, MPH, University of Colorado Program, Denver, CO.
Corresponding author: Brock Cardon, MD, Mike O'Callaghan Military Medical Center Family Medicine Residency, 4700 N. Las Vegas Blvd, Nellis AFB, NV 89191 (E-mail: brock.e.cardon.mil@health.mil).

Clinical Context

Osteoporosis is the most prevalent metabolic bone disease worldwide and in the US, claiming fragility fractures in approximately 50% of all women and 20% of all men >50 years of age within the US within their lifetime.[2] Approximately 54 million individuals were affected by low bone mass and osteoporosis in the US in 2010, estimated only to increase as the US population ages, with costs associated with osteoporosis projected to be upward of $25.3 billion in 2025 alone.[3,4]

The World Health Organization (WHO) defines osteoporosis via a DEXA measurement of bone mineral density (BMD) of either the hip or the spine ≥2.5 standard deviations below that of healthy sex-adjusted younger adults. This can then be subdivided into primary and secondary causes, primary being menopause and age as main contributors, and secondary stemming from a clear alternate etiology. Considering the subtle and insidious development of osteoporosis, asymptomatic screening is essential in preventing significant morbidity and disability from fragility fractures.[5] The US Preventative Services Task Force (currently under review for edits) recommends all women ≥65 and all women ≤65 "at increased risk of osteoporosis" be screened with DEXA imaging with a "Grade B" recommendation, but insufficient data to recommend globally screening men as of 2018.[6]

The 2 main categories of osteoporotic pharmacotherapies are antiresorptive medications (to include

bisphosphonates, denosumab, estrogen replacement therapy, and selective estrogen receptor modulators such as raloxifene hydrochloride) and anabolic agents (such as parathyroid receptor agonists and the sclerostin inhibitor, romosozumab).[7] In addition to increasing BMD, treatment is aimed at preventing osteoporotic fragility fractures. Treatment should also be initiated after an osteoporotic fragility fracture occurs, a point of care which primary care physicians seldom initiate.[8]

In women at very high risk of fracture, anabolic agents show improved fracture risk reduction compared with antiresorptive medications.[7] In contrast to this emerging evidence, for average risk patients, current clinical practice guidelines of various organizations either support use of bisphosphonates as first-line therapy for primary osteoporosis followed by denosumab, or recommend individualized care within available evidence-based medications.[2,9,10] As such, anabolic agents are only explicitly recommended conditionally in the context of women with primary osteoporosis who are considered "very high-risk" for fracture.[10]

This systematic review, network meta-analysis, and meta-regression analysis compares the safety and efficacy of current osteoporosis therapies to each other and placebo, with evidence to extend anabolic agent use to include all postmenopausal women with osteoporosis regardless of baseline risk factors.[1] This analysis is germane to family physician as we screen for osteoporosis and often initiate pharmacotherapy for fragility fracture prevention.

Methods

This article was identified as a potential PURL through the standard systematic methodology.[11] An additional literature search was conducted by searching UpToDate and USPSTF with the terms "osteoporosis" and "osteoporosis treatment guidelines" to find additional literature to place this research into the context of current clinical practice.

Study Summary

This 2023 systematic review, network meta-analysis and meta-regression analysis (69 trials, n > 80,000) assessed the comparative effectiveness of osteoporosis treatments on reducing fracture risk in postmenopausal women. Included studies were randomized controlled trials that included interventions with antiresorptive and anabolic agents. Studies with postmenopausal women, without age restriction, that measured bone mineral density or fractures were included in the analysis. Studies comparing effects with placebo or with an active comparator met eligibility criteria. Trials with sequential treatment or combination treatment were considered and concomitant use of calcium and vitamin-D supplementation was allowed. No restrictions were set on dose or duration of treatment. However, studies completed in exclusively Asian settings were excluded due to differences in dosing guidelines in Asia from the rest of the world. The primary outcome was incidence of all clinical fractures (excluding fingers and toes). Secondary outcomes were vertebral, nonvertebral, hip, and major osteoporotic fractures, as well as all-cause mortality, adverse events, and serious cardiovascular events.

Results illustrated benefit with bisphosphonates (absolute risk reduction [ARR], 14 per 100; 95% CI 7 to 21), parathyroid hormone receptor agonists (PTHRa) (ARR, 35 fewer per 1000; 95% CI, 3 to 39) and romosozumab (ARR, 9 per 1000; 95% CI, 3 to 13) compared with placebo for reducing clinical fractures but did not demonstrate benefit for denosumab or selective estrogen receptor modulators. Network meta-analysis illustrated that bisphosphonates were less effective at reducing clinical fractures compared with PTHRa (odds ratio [OR], 1.5; 95% CI, 1.1 to 2). Denosumab was less effective at reducing clinical fracture risk than PTHRa (OR, 1.9; 95% CI, 1.2 to 2.9) and romosozumab (OR, 1.6; 95% CI, 1 to 2.4).

Secondary outcomes demonstrated that all treatments had protective effects compared with placebo for vertebral fractures. However, in head-to-head comparisons, denosumab (OR, 1.8; 95% CI, 1.1 to 2.9), PTHRa (OR, 2.5; 95% CI, 1.8 to 3.5), and romosozumab (OR, 2.1; 95% CI, 1.4 to 3.0) were more effective than oral bisphosphonates in preventing vertebral fractures. Romosozumab was the only agent more effective than bisphosphonates at preventing hip fracture (OR, 1.6; 95% CI, 1.1 to 2.4). Antiresorptive treatments showed greater reduction of clinical fractures compared with placebo with increasing mean age (studies = 17;

$\beta = 0.98$, 95% CI 0.96-0.99); otherwise, baseline risk indicators did not affect treatment efficacy. Network analysis could not be completed for nonvertebral fractures.

What Is New

Current clinical guidelines recommend initial pharmacologic treatment to reduce the risk of fractures in postmenopausal women with primary osteoporosis. Guidelines suggest the use of anabolic agents, followed by bisphosphonate therapy, to reduce the risk of fractures only in women with primary osteoporosis and very high risk of fracture. This study's findings suggest using anabolic agents as initial therapy for osteoporosis in postmenopausal women is more effective at preventing clinical or vertebral fractures, regardless of baseline risk indicators. From a clinical standpoint, this systematic review does not support limiting anabolic agents to only patients at very high risk of fractures.

Caveats

This study relied on published mean baseline characteristics rather than individual patient data which may increase the risk of aggregation bias. Network meta-analysis and meta-regression analysis were limited due to a large amount of missing data on outcomes and baseline risk indicators and overlap of outcomes and treatment groups. Exclusion of all studies conducted in exclusively Asian settings may affect the generalizability of these recommendations to postmenopausal Asian women. Lastly, assessment of denosumab's effectiveness may be limited by exclusion of the FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months) trial, which ostensibly brought denosumab into broad clinical practice and FDA approval, due to it not meeting this meta-analysis's inclusion criteria.

Challenges to Implementation

Current first line treatments for postmenopausal women with nonsevere osteoporosis, such as bisphosphonates, cost significantly less and have more long-term safety data than anabolic agents. Though this systematic review does not support limiting anabolic agents to only patients at very high-risk of fractures, these factors will need to be considered by physicians and researchers and may slow implementation of these findings. Direct cost-comparison analyses with current pharmaceutical prices are needed.

To see this article online, please go to: http://jabfm.org/content/37/3/490.full.

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