The FREEDOM trial

Is family medicine ready for biologic therapies?

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Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 2009;361(8):756-65.

Research question

Can administration of a monoclonal antibody directed against receptor activator of nuclear factor-κB ligand (RANKL), a cytokine necessary for osteoclast formation, function, and survival, reduce fragility fractures in postmenopausal women with osteoporosis.

Study design

The FREEDOM study was a 3-year international multicentre trial with a placebo-controlled, randomized, double-blind design.

Relevance to family medicine

Postmenopausal osteoporosis is a common clinical problem managed by family physicians. It is associated with enormous societal costs and a substantial burden of illness, affecting quality of life and mortality.[1-3] In conjunction with bone hygiene advice and calcium and vitamin D supplementation, oral bisphosphonates are the agents most commonly used to treat osteoporosis. Unfortunately, adherence to these drugs is known to be poor, regardless of whether daily, weekly, or monthly dosing strategies are used, with approximately 50% of patients discontinuing therapy within 1 year.[4] Further, the drugs must be taken in a fasting state and apart from the necessary coadministration of calcium. It has also been demonstrated that no fracture risk reduction occurs with compliance rates below 50%, and rates approaching 80% are needed for substantial reductions.[4] Zoledronic acid, an intravenous (IV) bisphosphonate with demonstrated safety and efficacy when administered yearly by IV infusion,[5] addresses some of the adherence issues. However, patients are reluctant to accept medication by infusion, and family physicians face considerable logistical barriers to administering such therapy.

Denosumab is a fully human monoclonal antibody directed against RANKL, which acts by binding RANK on the surface of osteoclasts and their precursors, a necessary process for bone resorption. It is administered by subcutaneous injection every 6 months. Broadly speaking, this monoclonal antibody is a member of a class of treatments referred to as biologic therapies. These large molecules act by specifically targeting known cellular and extracellular pathways to achieve a desired clinical response. They have been in clinical use for decades, although specificity of indications, administration, complex monitoring, and potential side effects have largely limited use to specialist care in oncology, rheumatology, respirology, and gastroenterology. Denosumab, however, is well-suited for use in primary care.

Overview of the study and outcomes

The FREEDOM study was an international randomized, placebo-controlled trial designed to test the effect of denosumab on fracture risk in postmenopausal women during a 3-year follow-up period. Improvements in bone mineral density with denosumab have been reported in previous studies.[6] Women

BOTTOM LINE

There is a considerable care gap in osteoporosis treatment, and adherence to oral bisphosphonates is poor. The FREEDOM trial demonstrated that denosumab, a monoclonal antibody, is efficacious in vertebral, hip, and nonvertebral fracture reduction in postmenopausal osteoporosis. No direct comparisons are available, but denosumab appears to provide greater reduction in fragility fractures than oral bisphosphonates do. Although rare, a statistically increased rate of cellulitis requiring hospitalization was observed with denosumab compared with placebo. No other serious infectious or neoplastic events have been seen. Ongoing monitoring is required. Family physicians provide most osteoporosis care. They might be hesitant to embrace a new biologic therapy; however, monoclonal antibodies and other biologics represent a targeted approach to disease and will likely become a mainstay of treatment in many therapeutic areas.

POINTS SAILLANTS

Il y a d'importantes lacunes dans le traitement de l'ostéoporose, et la conformité aux ordonnances de diphosphonates par voie orale est faible. L'étude FREEDOM a démontré que le dénosumab, un anticorps monoclonal, est efficace pour réduire les fractures vertébrales, de la hanche et non vertébrales chez les femmes atteintes d'ostéoporose après la ménopause. Il n'existe pas de comparaisons directes, mais le dénosumab semble procurer une plus grande réduction des fractures de fragilité par rapport aux diphosphonates par voie orale. Bien que rares, on a signalé un taux statistiquement plus élevé de cas de cellulite exigeant une hospitalisation avec le dénosumab qu'avec un placebo. Aucun signe d'autres infections graves ou de néoplasie n'a été relevé. Il faut une surveillance continue. Les médecins de famille sont les principaux dispensateurs de soins pour l'ostéoporose. Ils hésiteront peut-être à adopter une nouvelle thérapie biologique; par ailleurs, les anticorps monoclonaux et d'autres agents biologiques représentent des approches ciblées à la maladie et vont probablement demeurer un soutien principal dans de nombreux domaines thérapeutiques.

were eligible for the FREEDOM trial if they were between 60 and 90 years of age and had bone mineral density T scores of less than -2.5 at the lumbar spine or total hip. Owing to concerns about fracture risk in this placebo-controlled trial, women were excluded if hip or spine T scores were less than -4.0, or if there was 1 severe or more than 2 moderate vertebral fractures at baseline. All subjects received at least 1000 mg of calcium and 400 IU of vitamin D supplementation daily. The primary end point was new vertebral fracture, defined radiographically using a semiquantitative grading scale,[7] on annual lateral spine radiographs. Secondary end points included time to first hip fracture and time to first nonvertebral fragility fracture. Other end points included clinically defined vertebral fracture, multiple new vertebral fractures on x-ray scan, changes in bone mineral density, and markers of bone turnover.

The strengths of the study include its robust power to detect treatment benefit; its clinically relevant primary and secondary end points of vertebral fracture and other fractures; its reporting of other important surrogate outcomes including bone mineral density and bone turnover markers; the adequate 3-year follow-up period for fracture events; a long, open-label follow-up period subsequent to the main trial; and its similar design to previous oral and IV bisphosphonate trials.

The study is limited by having no active comparator and by differences in the study population from previous bisphosphonate trials, which limit treatment comparisons.

Results

A total of 7868 women were randomized to denosumab or placebo and followed for 36 months. Baseline characteristics between the study groups were similar. Mean lumbar and total hip T score values were -2.8 and -1.9, respectively.

Approximately 25% of participants had vertebral fractures at baseline. A total of 1390 women were lost to follow-up.

The primary end point of new vertebral fracture occurred in 7.2% of those in the placebo group and 2.3% of those receiving denosumab (risk ratio 0.32, 95% confidence interval [CI] 0.26 to 0.41, $P<.001$). This effect was observed in similar magnitude in each trial year. Cumulative incidence of hip (1.2% vs 0.7%; hazard ratio 0.60, 95% CI 0.37 to 0.97, $P=.04$) and nonvertebral (8.0% vs 6.5%; hazard ratio 0.80, 95% CI 0.67 to 0.95, $P=.01$) fragility fracture was significantly reduced in the denosumab group, with separation of the curves evident at 12 months. Whereas bone mineral density remained stable in the placebo group, there was an increase of 9.2% and 6.0% in the denosumab group at the lumbar spine and total hip, respectively.

Rates of all adverse events were similar between the study groups. There was no excess of serious or fatal adverse events in the denosumab group. During the 3-year follow-up period, rates of infection, cancer, and cardiovascular events were not different. Although rates of cellulitis were similar between the groups, cellulitis requiring hospitalization occurred statistically more frequently in the denosumab group (0.3% vs <0.1%). Eczema (3.0% vs 1.7%) and flatulence (2.2% vs 1.4%) also occurred more commonly with denosumab ($P<.05$). There were no cases of osteonecrosis of the jaw.

Analysis of methodology

Vertebral fractures are the most common osteoporotic fracture; however, unlike fragility fractures involving the hip or limbs, they are often clinically silent and occur without antecedent trauma.[8] Thus, careful assessment of vertebral fracture rate is a sensitive means of demonstrating efficacy of osteoporosis treatment. The primary study outcome was the development of vertebral fracture, defined using a semiquantitative radiographic approach.[7] Although severe vertebral fractures are easy to identify, there is no radiographic consensus on distinguishing vertebral deformity from more subtle fracture. Visual inspection of x-ray scans (ie, qualitative analysis) alone is associated with high intraobserver variability, and vertebral morphometry (ie, quantitative analysis) is plagued by high rates of false-negative and false-positive results.[9] A hybrid, semiquantitative approach was proposed by Genant et al[7] in 1993, which has since become the standard for defining vertebral fractures in clinical trials because of its clinical significance and simplicity. This approach was used in the trials of bisphosphonates and in the FREEDOM study. Radiographs were read in a centralized fashion by radiologists blinded to treatment arm.

Application to clinical practice

Osteoporosis affects approximately 1.4 million Canadians, including 1 in 4 women older than 50 years of age.[10] Fragility fractures substantially affect quality of life and result in considerable morbidity and even mortality. About 40% of patients are unable to walk independently following hip fracture.[11] Data from the Canadian Multicentre Osteoporosis Study indicate that barely 50% of Canadian women suffering fragility fracture subsequently receive osteoporosis treatment.[12] Denosumab might offer a new option to address the treatment gap. However, a paradigm change in family medicine—the adoption of a biologic therapy—will be necessary for this to occur. New forms of therapy have had unexpected consequences in the past, so adoption of a new biologic might be viewed with a wary eye.

Because the RANK-RANKL pathway is involved in other cell signaling pathways, including immune surveillance, there is a theoretical increased risk of cancer or infections. Although an increased rate of cellulitis requiring hospitalization was seen in the FREEDOM study, the overall rate of cellulitis was not different from placebo. No increased rates of cancer or other infections were seen in the trial, nor has there been a signal of such in the entire clinical development program. Subjects taking continuous denosumab therapy for up to 6 years have demonstrated persistence of effect on bone density and bone turnover markers.[13] In studies of osteoporosis, there have been no published cases of jaw osteonecrosis, atypical femoral fractures, or impaired fracture healing.

The results of the FREEDOM trial are consistent with previous research using surrogate end points. Brown et al demonstrated significantly greater increases in bone density after 1 year in postmenopausal osteoporosis patients at the lumbar spine, total hip, and femoral neck with denosumab compared with oral alendronate ($P<.001$).[14] Miller et al demonstrated that the effect of denosumab is fully reversible following discontinuation of treatment.[15]

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Competing interests

Dr Alan Bell has received speaker honoraria and consultancy fees from the following organizations: Osteoporosis Canada, Sanofi-Aventis, Amgen, and Bristol-Myers Squibb. **Dr Benjamin Bell** has no conflicts of interest to declare.

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