Denosumab: A new injectable treatment for postmenopausal osteoporosis

Anne Marie Whelan, BScPharm, PharmD, FCSHP; Lalitha Raman-Wilms, BScPhm, PharmD, FCSHP

A.M. Whelan

L. Raman-Wilms

Patients with osteoporosis are commonly prescribed bisphosphonates. With the increase in the number of adverse events and adherence concerns reported with these agents, as well as the contraindication for these agents in those with renal impairment, we wished to assess the role of denosumab in the management of postmenopausal osteoporosis.

On prescrit souvent des bisphosphonates aux patients atteints d'ostéoporose. Compte tenu de l'augmentation du nombre d'effets indésirables et des problèmes d'observance du traitement signalés avec ces agents, et de leur contre-indication en cas de déficience rénale, il nous a paru utile d'évaluer le rôle du denosumab dans la prise en charge de l'ostéoporose post-ménopausique.

Abstract

Background/Introduction: Osteoporosis results in a significant increase in fractures, leading to morbidity and mortality. Adherence is a concern with commonly used antiresorptive agents, the bisphosphonates. Denosumab, which inhibits bone resorption by a different mechanism and is administered subcutaneously every 6 months, may provide an advantage in decreasing fracture risk in those with osteoporosis.

Objective: To review the available data with respect to the mechanism of action, efficacy and safety of denosumab for the management of postmenopausal osteoporosis.

Methods: Several databases were searched to identify phase III randomized controlled trials (RCT) that examined the effect of denosumab on bone mineral density (BMD) and/or fracture rate and the safety of denosumab in the management of postmenopausal osteoporosis.

Results: In 2 of the 4 trials identified, denosumab was significantly better than placebo at increasing BMD, and in 1 trial reduced the risk of vertebral, nonvertebral and hip fractures. No head-to-head trials comparing fracture risk reduction of denosumab to bisphosphonates were found, however, 2 trials did report increased BMD with denosumab compared to alendronate. In the 4 studies reviewed, adverse effects reported more frequently with denosumab included rash and eczema, as well as bronchitis and influenza-like illness. There is potential for an increased risk of other infections and malignancies.

Conclusions: The results of RCT trials suggest that denosumab is effective at maintaining or increasing BMD compared to placebo or alendronate in women with either osteopenia or osteoporosis and in 1 trial demonstrated a significant reduction in fracture rate compared to placebo. Overall, denosumab appeared to be well tolerated in the studies reviewed. Continued monitoring is needed to determine long-term safety and efficacy. *Can Pharm J* 2011;144:72-78.

Introduction

Osteoporosis affects about 1 in 4 women and 1 in 8 men over the age of 50 in Canada,[1] with a 20% prevalence rate of vertebral fractures in this age group.[2] This common bone disorder is characterized by compromised bone strength, resulting in a fragile skeleton that is vulnerable to fractures. Bone strength is determined by both bone quality and quantity. Bone quantity is measured by bone mineral density (BMD).

Osteoporosis results in significant morbidity, as well as mortality. Individuals with osteoporosis can suffer from chronic disabling pain and loss of height from vertebral fractures. In severe cases, kyphosis (curvature of the spine, or hunching) can cause shortness of breath and dysphagia. In individuals who have sustained a hip fracture, the mortality in the first year has been reported to be

as high as 20%.[3] The Canadian Multicentre Osteoporosis Study (CaMos) evaluated the relationship between fractures and mortality in those over 50 years of age. This study demonstrated that both men and women with hip or vertebral fractures were more likely to die during 5 years of follow-up compared to those without such fractures.[4]

All individuals either at risk for or with osteoporosis require adequate daily calcium and vitamin D intake. Current antiresorptive options available for the prophylaxis and/or treatment of osteoporosis include bisphosphonates, raloxifene and calcitonin. Follow-up studies indicate that at least 50% of patients prescribed oral bisphosphonates stop therapy within a year of receiving the prescription.[5] Teriparatide, a newer anabolic agent administered subcutaneously, is an option reserved for those with severe osteoporosis. However, teriparatide is currently recommended for use up to 18 months only, due to concerns of osteosarcoma with long-term use in animal studies.[6]

Denosumab is a human monoclonal antibody (IgG2) that inhibits bone resorption by a different mechanism than current agents. In August 2010, it was approved in Canada for the treatment of osteoporosis in postmenopausal women at high risk for fracture.[7] In clinical trials of postmenopausal osteoporosis, 60 mg of denosumab was administered subcutaneously every 6 months.

The objective of this review is to provide a summary of the available data with respect to the mechanism of action, efficacy and safety of denosumab for the management of postmenopausal osteoporosis.

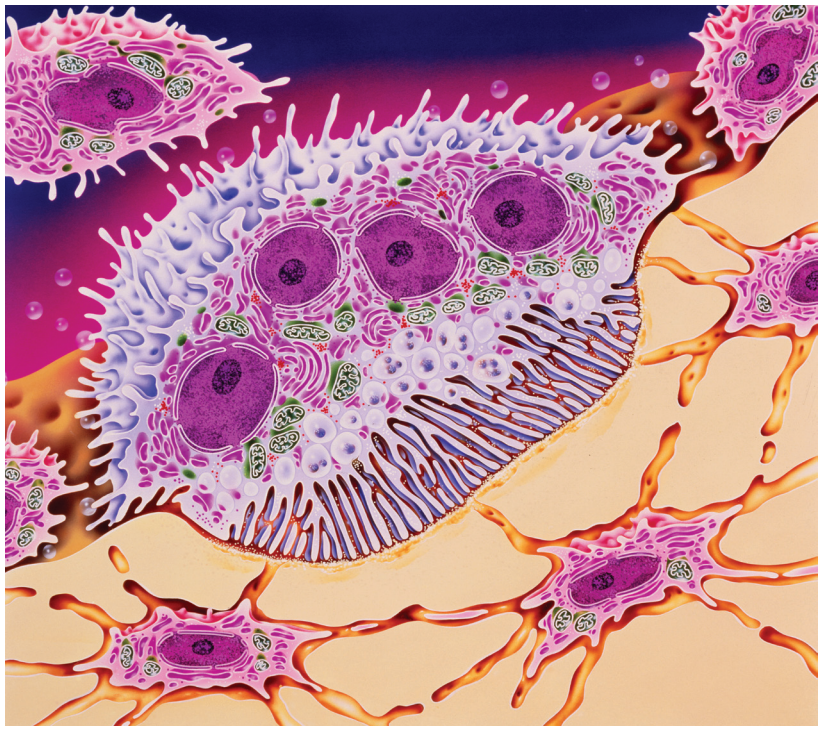
Does denosumab work the same as currently available medications for postmenopausal osteoporosis?

Bone is continuously being broken down by osteoclast cells (bone resorption), which results in cavities that are filled in with new bone by osteoblast cells (bone formation). Most of the prescription medications for the management of osteoporosis currently available in Canada are antiresorptive drugs. In general, these medications work by preventing the resorption of bone.[8] Teriparatide is the only available drug that actually stimulates new bone formation.

In the 1990s, the receptor activator of nuclear factor κB ligand (RANKL) was identified. This molecule is important in osteoclast development, activity and survival.[9] It is believed that free RANKL binds to the RANK receptor found on the surface of osteoclasts and its precursors. This stimulates the production of osteoclasts, which then results in bone resorption. Osteoprotegerin (OPG), a member of the tumour necrosis family, is produced by osteoblasts and can also bind RANKL. When OPG binds to RANKL, osteoclast production and activity are inhibited, resulting in less bone resorption. Denosumab binds to RANKL (mimicking the activity of OPG), thus preventing RANKL from binding to the RANK receptor and resulting in decreased proliferation and activity of osteoclasts.[10] In summary, denosumab is similar to most of the currently available medications in that it is also an antiresorptive drug; however, it works by a different mechanism than currently available options. As the binding of denosumab to RANKL appears to result in substantial and prolonged inhi-

Knowledge into practice

- Denosumab is a biologic agent, recently approved in Canada for the treatment of postmenopausal osteoporosis in women at high risk of fracture (e.g., those with a history of osteoporotic fractures or with multiple risk factors for fracture) or women who have failed or are unable to tolerate other therapies.
- Denosumab has been shown to increase bone mineral density in women with postmenopausal osteoporosis.
- Limited data have shown that denosumab is effective at decreasing the risk of vertebral, nonvertebral and hip fractures in women with postmenopausal osteoporosis.
- Overall, adverse event rates with denosumab have been reported to be similar to both placebo and alendronate.
- Because of potential effects on the immune system, postmarketing surveillance will be important to better determine the long-term effects of denosumab.



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Process of osteoporosis. An osteoclast bone cell in action during removal of bone tissue. An osteoclast (purple, centre) is a giant multinucleated cell that normally breaks down the calcified matrix of bone (beige) during bone growth and formation. In the disease of osteoporosis, the imbalance between bone resorption and formation causes bones to become brittle and less dense, increasing their susceptibility to fracture.

bition of bone resorption with greater increases in BMD, the drug may, over time, offer advantages over current antiresorptive medications.[11]

Is denosumab effective for postmenopausal osteoporosis?

PubMed, Embase, International Pharmaceutical Abstracts, the Cochrane Library and reference lists of screened articles were searched to identify phase III randomized controlled trials (RCTs), considered the gold standard in terms of evidence, that examined the effect of denosumab on BMD and/or fracture rate and the safety of denosumab compared to placebo or active treatment in the management of postmenopausal osteoporosis. Databases were searched from time of inception to February 2010 using terms such as "denosumab," "osteoporosis," "osteopenia" and "postmenopausal." Searches were limited to humans and English language. Over 120 articles were identified; however, all but 4 (Table 1) were excluded as they were duplicate articles, were not RCTs or did not evaluate the use of denosumab in postmenopausal osteoporosis.

Denosumab vs placebo

In the FREEDOM trial, Cummings et al. examined the effect of denosumab in postmenopausal women with osteoporosis as defined by a BMD T-score between −4.0 and −2.5 at the lumbar spine or hip.[12] They found that denosumab not only significantly increased BMD at measured sites as compared to placebo, but it also reduced the risk of vertebral, nonvertebral and hip fractures. A second study, DEFEND, was conducted in postmenopausal women who had low bone mass (osteopenia) as defined by a BMD T-score between −2.5 and −1.0 at the lumbar spine.[13] In this study, BMD was significantly increased at all sites compared to placebo. This study was not designed to examine differences in the occurrence of fracture rates; however, it was noted that there were only 2/142 (1.4%) fractures reported in the denosumab group compared to 7/144 (4.8%) in the placebo group.

Denosumab vs alendronate

In the DECIDE study, Brown et al. compared the effect of denosumab to alendronate in postmeno-

TABLE 1 Denosumab in the management of postmenopausal osteoporosis: Summary of phase III randomized controlled trials

Study design, participants and interventions	Summary of results	Summary of adverse events
Denosumab versus placebo		
FREEDOM trial[12] Cummings et al., 2009		
Design: DB, PC, 36 months **Participants**: 7868 postmenopausal women enrolled with BMD T-score between −4.0 and −2.5 at lumbar spine or hip; mean age ± SD in denosumab group was 72.3±5.2 years; mean age ± SD in placebo group was 72.3±5.2 years **Interventions**: • Denosumab 60 mg SC every 6 months (n = 3702 completed) • Placebo injection SC every 6 months (n = 3691 completed) All participants received 1000 mg calcium plus 400–800 IU vitamin D per day. Primary outcome: New vertebral fractures.	**BMD**: Denosumab significantly ($p < 0.001$) increased BMD at lumbar spine (+9.2%) and hip (+6.0%) compared to placebo **Fractures**: Denosumab significantly reduced risk of fracture in spine (↓ 68%; $p < 0.001$), nonvertebral sites (↓ 20%; $p = 0.01$) and hip (↓ 40%; $p = 0.04$) compared to placebo **Adherence**: Injections administered at study site; 5979/7869 (76%) received all injections	AEs reported more commonly with denosumab: • Eczema (3% vs 1.7%; $p < 0.001$) • Flatulence (2.2% vs 1.4%; $p = 0.008$) • Serious AE of cellulitis (0.3% or 12 individuals vs < 0.1% or 1 individual; $p = 0.002$)
DEFEND trial[13] Bone et al., 2008		
Design: DB, PC, 24 months **Participants**: 332 postmenopausal women enrolled with low bone mass (osteopenia) defined as BMD T-score between −2.5 and −1.0 at lumbar spine; mean age ± SD in denosumab group was 59.8±7.4 years; mean age ± SD in placebo group was 58.9±7.5 years **Interventions**: • Denosumab 60 mg SC every 6 months (n =142 completed) • Placebo injection SC every 6 months (n = 144 completed) All participants received ≥ 1000 mg calcium plus 400–800 IU vitamin D per day. Primary outcome: Percent change in lumbar spine BMD at 24 months with denosumab compared to placebo.	**BMD**: Denosumab significantly ($p < 0.0001$) increased BMD of spine (+6.5%), total hip (+3.4%), femoral neck (+2.8%), trochanter (+5.2%), one-third radius (+1.4%) and total body regions (+2.4%) compared to placebo **Fractures**: Study not designed to examine differences in fracture rates but occurrence was recorded: 7/144 (4.9%) nonvertebral fractures in placebo group compared to 2/142 (1.4%) with denosumab **Adherence**: 86% completed the 24 months of treatment	AEs reported more commonly with denosumab: • Constipation (11% vs 4.8%) • Sore throat (9.1% vs 3%) • Rash (8.5% vs 3%) • Serious infections requiring hospitalization (8 individuals or 4.9% vs 1 individual or 0.6%)

pausal women with a BMD T-score of ≤−2.0 at the lumbar spine or total hip.[14] Approximately 40% of women in each group had osteoporotic fractures at baseline. BMD was significantly increased in the denosumab group compared to the alendronate group. The occurrence of fractures was documented in this study as an adverse effect, with a nonsignificant difference ($p = 0.37$) in the denosumab group (18/593, 3%) and alendronate group (13/586, 2.2%). In the STAND trial, postmenopausal women with a BMD T-score between −4.0 and −2.0 at the lumbar spine or total hip who had been receiving alendronate for at least 6 months were randomized to either alendronate or denosumab.[15] Again, the denosumab group had greater increases in BMD than the alendronate group. This study was not designed to examine differences in the incidence of fractures; however, it was noted that there was a nonsignificant difference ($p = 0.3820$), with 8/253 (3.2%) fractures reported in the denosumab group and 4/249 (1.6%) in the alendronate group.

TABLE 1 Denosumab in the management of postmenopausal osteoporosis: Summary of phase III randomized controlled trials – cont'd

Study design, participants and interventions	Summary of results	Summary of adverse events
Denosumab versus alendronate		
DECIDE trial[14] Brown et al., 2009		
Design: DB, PC, 12 months **Participants**: 1189 postmenopausal women enrolled with low bone mass defined as BMD T-score ≤ −2.0 at lumbar spine or total hip; mean age ± SD in denosumab group was 64.1±8.6 years; mean age ± SD in alendronate group was 64.6±8.3 years **Interventions**: • Denosumab 60 mg SC every 6 months plus placebo tablet once weekly ($n = 561$ completed); 40% had osteoporotic fractures at baseline • Alendronate 70 mg weekly plus placebo injection every 6 months ($n = 563$ completed); 41% had osteoporotic fractures at baseline All participants received ≥ 500 mg calcium plus 400–800 IU vitamin D per day. Primary outcome: Percent change in total hip BMD at 12 months with denosumab compared to alendronate.	**BMD**: Denosumab significantly increased BMD compared to alendronate at total hip (+3.5% vs +2.6%; $p < 0.0001$), trochanter (+4.5% vs +3.4%; $p < 0.0001$), one-third radius (+1.1% vs +0.6%; $p < 0.0001$), femoral neck (+2.4% vs +1.8%; $p = 0.0001$) and lumbar spine (+ 5.3% vs +4.2%; $p < 0.0001$) **Fractures**: Study not designed to examine differences in fracture rates, but occurrence was documented as part of adverse reaction recording: no significant difference ($p = 0.37$), with 18/593 (3%) occurring in denosumab group and 13/586 (2.2%) in alendronate group **Adherence**: Injections administered at study site: 1124/1189 (94.5%) completed study; 93% of denosumab group and 91% of alendronate group were compliant with treatment (received all injections and took ≥ 80% of tablets)	AEs reported more commonly with denosumab: • Nonsymptomatic, transient decrease in serum calcium reported with denosumab at 1 month; this was normal at 12 months • Serious AEs: denosumab 5.7% vs alendronate 6.3%
STAND trial[15] Kendler et al., 2009		
Design: DB, PC, 12 months **Participants**: 504 postmenopausal women enrolled with BMD T-score between −4.0 and −2.0 at the lumbar spine or total hip who had been receiving alendronate for at least 6 months; mean age ± SD in denosumab group was 66.9±7.8 years; mean age ± SD in alendronate group was 68.2±7.7 years **Interventions**: All participants received alendronate (open label) 70 mg once weekly for 1 month then randomized to: • Denosumab 60 mg SC every 6 months plus placebo tablet weekly ($n = 243$ completed) • Alendronate 70 mg once weekly plus placebo injection every 6 months ($n = 238$ completed) All participants supplied with 1000 mg elemental calcium plus 400 IU vitamin D per day. Primary outcome: Percent change in total hip BMD at 12 months with denosumab compared to alendronate.	**Design**: Denosumab significantly increased BMD compared to alendronate at total hip (+1.9% vs +1.05%; $p < 0.0001$), lumbar spine (+3.03% vs +1.85%; $p < 0.0001$), as well as femoral neck and one-third radius ($p \leq 0.0121$) **Fractures**: Study not designed to examine differences in fracture rates, but occurrence was recorded: 8/253(3.2%) in denosumab group and 4/249 (1.6%) in alendronate group ($p = 0.3820$) **Adherence**: 481/504 (95.4%) completed study; 94% of subjects in both groups group were compliant with treatment (received all injections and took ≥ 80% of tablets)	AEs reported more commonly with denosumab: • Nasopharyngitis (13.4% vs 10.8%) • Bronchitis (6.3% vs 5.6%) Other events: • Back pain (10.7% vs 11.6%) • Pain in extremity (4.7% vs 8.4%)

AE = adverse event; BMD = bone mineral density; DB = double-blind; PC = placebo-controlled; SC = subcutaneous; SD = standard deviation.

La connaissance en pratique

• Le denosumab est un agent biologique récemment approuvé au Canada pour le traitement de l'ostéoporose postménopausique chez les femmes à haut risque de fractures (p. ex., en cas d'antécédents de fractures ostéoporotiques ou de multiples facteurs de risque de fractures), ou en cas d'échec des autres traitements ou d'intolérance aux autres traitements.

• Les études ont montré que le denosumab permettait d'accroître la densité minérale osseuse des femmes atteintes d'ostéoporose postménopausique.

• Il existe un nombre limité de données montrant l'efficacité du denosumab pour réduire les risques de fracture de la hanche et de fractures vertébrales et non vertébrales chez les femmes atteintes d'ostéoporose postménopausique.

• Dans l'ensemble, le denosumab présente des taux d'effets indésirables du même ordre que le placébo et l'alendronate.

• En raison de l'action potentielle du denosumab sur le système immunitaire, il sera important d'effectuer une surveillance après la mise en marché afin de mieux déterminer ses effets à long terme.

Although all the studies reviewed above were sponsored by Amgen Inc. (the manufacturer of denosumab), they appeared, in general, to be well designed as they were all randomized, double-blinded and placebo-controlled. Studies ranged in length from 12 to 36 months, adequate durations to measure the intended outcomes. It should be noted that in all the trials, participants took calcium and vitamin D supplements. The results of these 4 trials suggest that denosumab is effective at maintaining or increasing BMD at all sites as compared to placebo or alendronate in women with either osteopenia or osteoporosis.[12-15] The primary clinical outcome of interest, fracture rate, is less well studied. The only trial designed to measure this outcome did find a significant reduction in fracture rates with denosumab as compared to placebo in postmenopausal women with osteoporosis.[12]

Is denosumab safe to use for postmenopausal osteoporosis?

Overall, denosumab has been shown to be well tolerated in the phase III trials evaluating its use in postmenopausal osteoporosis. Since RANKL and RANK are expressed by a variety of cell types (e.g., endothelial, bone marrow and immune cells, as well as osteoclasts and osteoblasts), there is concern regarding the potential effect of denosumab in increasing the risk of infections and neoplasms.[16] Additionally, phase I studies reported mild, transient, dose-dependent decreases in serum calcium.[17] Therefore, phase III studies have carefully monitored adverse effects, development of specific antibodies to denosumab and biochemical markers.

Denosumab vs placebo

No significant difference in overall adverse events was reported in the FREEDOM trial.[12] As noted in Table 1, a few events, such as eczema and flatulence, were reported more frequently in the treatment group. The trial reported no significant difference in the overall incidence of cancer, cardiovascular events or serious infections. Patients were tested for hypocalcemia and for denosumab-specific antibodies prior to each injection (at baseline and 6, 12, 24 and 36 months). Hypocalcemia was not reported in the treatment group, with 3 reports in the placebo group. No antibodies to denosumab developed in any of the subjects. Local reactions at the site of injection occurred in 0.8% of individuals in the denosumab group and 0.7% in the placebo group.

In the DEFEND trial, the most commonly reported adverse events were arthralgia, nasopharyngitis, back pain and headache in both groups (not significant).[13] Individuals in the treatment group reported constipation, sore throat and rash more frequently (see Table 1). The authors did not consider the rashes to be a drug reaction and they reported that no specific pattern with respect to location or onset was identifiable. The overall incidence of infections was similar in both groups; however, the incidence of serious infections requiring hospitalization was reported to be higher in the denosumab group. These infections included pneumonia, appendicitis, sepsis, pyelonephritis, diverticulitis and cellulitis; all were treated successfully with standard antibiotics. Neoplasms were reported in 4 individuals in the denosumab group and 1 individual in the placebo group, but the authors indicated that none were considered to be related to the study drug. The neoplasms included breast cancer in situ, mycosis fungoides, ovarian cancer and uterine cancer in the treatment group and B cell lymphoma in the placebo group. A transient decrease in calcium levels, with no reported symptoms of hypocalcemia, was identified at the 1-month follow-up after the dose of denosumab; calcium levels then returned to normal and were stable thereafter. Denosumab-binding antibodies were identified in 3 women in the placebo group (2%) and 2 women in the treatment group (1%).

Denosumab vs alendronate

Safety was monitored in the DECIDE trial using serum chemistry and hematology assessments (at baseline and 1, 6 and 12 months), as well as adverse events (at baseline and 1, 3, 6, 9 and 12 months).[14] Overall, adverse events reported to be related to the treatments were similar between the 2 groups (17% for denosumab vs 18.3% for alendronate). Two serious adverse events, vaginal neoplasm and severe arthralgia, were reported in the alendronate

group. The incidence and types of infection were similar in the 2 groups and included nasopharyngitis, influenza, upper respiratory infection, bronchitis and urinary tract infection. Serious adverse events related to infections were similar in both groups and included diverticulitis and pneumonia. Benign and malignant neoplasms were reported to be similar in both groups. There was a transient decrease in serum calcium at 1 month in the denosumab group, which was reported to be normal at 12 months. No antibodies to denosumab developed in any of the subjects.

Overall, in the STAND trial there was no significant difference in the adverse events reported between the 2 groups (see Table 1).[15] Adverse events were recorded at each study visit, while serum chemistry assessments (at baseline and 1, 6 and 12 months) and anti-denosumab antibodies (at baseline and 6 and 12 months) were screened periodically. Nasopharyngitis, back pain, bronchitis, arthralgia, constipation and pain in the extremity were most commonly reported. Serious adverse events included infections and neoplasms and were similar in both groups. The authors did not report the types of infections or neoplasms that occurred. Mean serum calcium levels remained in the normal range in both groups and no subjects developed anti-denosumab antibodies.

In summary, adverse effects experienced by individuals taking denosumab have been reported to be similar to those taking placebo. Trials have reported a transient decrease in calcium levels at 1 month after the start of denosumab, with no symptoms and a return to normal shortly thereafter. Only 1 study reported development of anti-denosumab antibodies; however, the authors noted that there was no evidence of any impact of these antibodies on the safety, efficacy or pharmacokinetics of denosumab.[13] Overall, the rates of infection in these studies are similar, although infections requiring hospitalization were reported to be higher with denosumab. Also, the incidence of eczema (FREEDOM)[12] and rashes (DEFEND)[13] has been reported to be higher in those taking denosumab.

As mentioned previously, based on the mechanism of action of denosumab and its potential effect on the immune system, the risk of malignancy has been raised as a concern. However, results of the phase III studies in postmenopausal women for the management of osteoporosis report no increase in neoplasms in those using denosumab vs placebo or alendronate. However, these trials may not be of sufficient duration (only up to 3 years) to clearly assess this potential adverse outcome. It should also be noted that the suppression of bone turnover may have negative consequences, such as osteonecrosis of the jaw, atypical fractures and delayed fracture healing.[18] Osteonecrosis of the jaw has already been reported in trials of denosumab being evaluated for cancer.[18] Postmarketing follow-up of this drug will help better identify and address these concerns.

What is the role of denosumab in the management of postmenopausal osteoporosis?

Denosumab is approved in Canada for the treatment of postmenopausal osteoporosis in women at high risk of fracture.[7] Women at high risk were defined as those with a history of osteoporosis-related fractures or those with multiple risk factors for fracture. Additionally, the drug was approved for use in those who have failed or are unable to tolerate other osteoporosis therapies.[7] The 2010 Canadian clinical practice guidelines for osteoporosis management recommend denosumab as first-line therapy for the prevention of hip, nonvertebral and vertebral fractures in menopausal women needing treatment for osteoporosis.[19] Other experts have proposed that denosumab may also be an alternative for those who cannot take or who demonstrate poor adherence to oral therapies.[12,20] As denosumab is not cleared by the kidneys, it may be useful for patients with renal insufficiency; however, this has not yet been proven in clinical studies.[8] An expert has suggested that because denosumab does not persist in the bones as long as many bisphosphonates, its actions might be potentially reversible, which may be of benefit to any patient experiencing an adverse effect.[20]

Denosumab is given as an injection every 6 months. It is available in a single-use, prefilled syringe (containing 1 mL of 60 mg/mL solution) and should be administered subcutaneously in the upper arm, thigh or abdomen.[21] As it is a biologic product, cost may limit its use.[8] It is anticipated that in Canada the annual cost will be approximately $710, comparable to that of brand name bisphosphonates (Aclasta costs approximately $720 per year), but more expensive than generic bisphosphonates (generic alendronate costs approximately $310 per year).[18] Denosumab is contraindicated in those with uncorrected hypocalcemia.[21]

Conclusion

Denosumab is a new drug that has a different mechanism of action than other medications currently used in the management of postmenopausal osteoporosis. It is administered every 6

months and no dose adjustment is necessary in patients with renal impairment. Patients taking denosumab should receive the recommended amount of calcium and vitamin D from the diet and/or supplements. Monitoring of serum calcium is recommended in those with a history of or predisposition to hypocalcemia and in anyone with signs or symptoms of hypocalcemia. Overall, denosumab appeared to be well tolerated in the studies reviewed. Patients should be made aware of common adverse effects. Adverse events reported more often with denosumab included nasopharyngitis, bronchitis, upper respiratory infection, influenza-like illness, rash and eczema. There is the potential for an increased risk of malignancies and infections; therefore, continued monitoring is needed to determine if these adverse effects are of major concern when denosumab is used to treat postmenopausal osteoporosis. Patients should be advised to seek medical attention if they develop signs or symptoms of a serious infection (e.g., fever, severe abdominal pain, or red, swollen skin). Data from trials 3 years in duration suggest that denosumab is effective at increasing BMD and reducing the incidence of vertebral, nonvertebral and hip fractures. Additional comparison trials with other osteoporosis therapies as well as post-marketing surveillance will be useful to provide more data regarding the drug's long-term safety and efficacy. ■

From the College of Pharmacy and the Department of Family Medicine (Whelan), Dalhousie University, Halifax, Nova Scotia; and the Leslie Dan Faculty of Pharmacy, University of Toronto and The Anne Johnston Health Station (Raman-Wilms), Toronto, Ontario. Contact anne.marie.whelan@dal.ca.

References

1. Hanley DA, Josse RG. Prevention and management of osteoporosis: consensus statements from the Scientific Advisory Board of the Osteoporosis Society of Canada. *Can Med Assoc J* 1996;155:921-3.

2. Jackson SA, Tenenhouse A, Robertson L. Vertebral fracture definition from population-based data: preliminary results from the Canadian Multicentre Osteoporosis Study (CaMos). *Osteoporos Int* 2000;11:680-7.

3. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis and Therapy. Osteoporosis prevention, diagnosis and therapy. *JAMA* 2001;285:785-95.

4. Ioannidis G, Papaioannou A, Hopman WM, et al. Relation between fractures and mortality: results from the Canadian Multicentre Osteoporosis Study. *Can Med Assoc J* 2009;181:247-8.

5. Siris ES, Harris ST, Rosen CJ, et al. Adherence to bisphosphonate therapy and fracture rates in osteoporotic women: relationship to vertebral and nonvertebral fractures from 2 US claims databases. *Mayo Clin Proc* 2006;81:1013-22.

6. Forteo [product monograph]. eCPS. Ottawa (ON): Canadian Pharmacists Association; 2010. Available: www.e-cps.ca (accessed March 7, 2010).

7. Prolia (denosumab) receives approval in Switzerland and Canada. Amgen. August 6, 2010. Available: www.amgen.com/media/prolia_approval_switzerland_canada.html (accessed August 27, 2010).

8. Khosla S. Increasing options for the treatment of osteoporosis. *N Engl J Med* 2009;361(8):818-20.

9. Lacey DL, Timms E, Tan HL, et al. Osteoprotegerin ligand is a cytokine that regulates osteoclastic differentiation and activation. *Cell* 1998;93:165-76.

10. Geusens P. Emerging treatments for postmenopausal osteoporosis — focus on denosumab. *Clin Interv Aging* 2009;4:241-50.

11. Burkiewicz JS, Scarpace SL, Bruce SP. Denosumab in osteoporosis and oncology. *Ann Pharmacother* 2009;43:1445-55.

12. Cummings SR, Martin JS, McClung MR, et al. for the FREEDOM Trial. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 2009;361:756-65.

13. Bone HG, Bolognese MA, Yuen CK, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women. *J Clin Endocrinol Metab* 2008;93:2149-57.

14. Brown JP, Prince RL, Deal C, et al. Comparison of the effect of denosumab and alendronate on BMD and biochemical makers of bone turnover in postmenopausal women with low bone mass: a randomized, blinded, phase 3 trial. *J Bon Miner Res* 2009;24:153-61.

15. Kendler DL, Roux C, Benhamou CL, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women transitioning from alendronate therapy. *J Bone Miner Res* 2010 Jan;25(1):72-81.

16. Lewiecki EM. Denosumab in postmenopausal osteoporosis: what the clinician needs to know. *Ther Adv Musculoskel Dis* 2009;1(1):13-26.

17. Lewiecki EM. Denosumab: an investigational drug for the management of postmenopausal osteoporosis. *Biologics* 2008;2(4):645-53.

18. New drug: Prolia (denosumab). *Pharm Lett/Prescr Lett* 2010;26(9):260919.

19. Papaioannou A, Morin S, Cheung AM, et al. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. *CMAJ* 2010;182(17):1864-73.

20. Gever J. Denosumab a winner in phase III osteoporosis trials. MedPage Today. August 11, 2009. Available: www.medpagetoday.com/tbprint.cfm?tbid=15474 (accessed December 2, 2009).

21. Prolia [product monograph]. Mississauga (ON): Amgen Canada Inc.; August 2010.