CMRO

Current Medical Research & Opinion Vol. 29, No. 3, 2013, 205–216

0300-7995
doi:10.1185/03007995.2013.763779

Article RT-0376.R1/763779

Brief review

Denosumab, a new pharmacotherapy option for postmenopausal osteoporosis

Robert Josse
St Michael's Hospital, University of Toronto, Toronto, ON, Canada

Aliya Khan
McMaster University, Hamilton, ON, Canada

Daniel Ngui
University of British Columbia, Vancouver, BC, Canada

Marla Shapiro
University of Toronto Department of Family and Community Medicine, Toronto, ON, Canada

Address for correspondence:
Dr Robert Josse, St Michael's Hospital Health Centre, 61 Queen Street East, Toronto, ON M5C 2T2, Canada.
Tel.: 416 867 7476; Fax: 416 867 3696;
josserg@smh.ca

Key words:
Bisphosphonates – Bone mineral density – Denosumab – Fracture – Osteoporosis – Postmenopausal

Accepted: 3 January 2013; published online: 25 January 2013
Citation: Curr Med Res Opin 2013; 29:205–16

Abstract

Background:

According to the 2010 Osteoporosis Canada Clinical Practice Guidelines, denosumab is a first-line option for the pharmacological management of postmenopausal osteoporosis (PMO), along with several therapeutics that may be more familiar to family practice doctors: bisphosphonates, raloxifene, teriparatide, and hormone therapy. Denosumab is indicated for postmenopausal patients at high risk for fracture or others who have failed, or are intolerant to, other osteoporosis therapies.

Scope:

We undertook a review of the efficacy and safety of denosumab in PMO, searching the English-language literature on this drug via PubMed queries as of July 2012.

Findings:

Although established treatments reduce fracture risk among osteoporotic postmenopausal women in trials, their effectiveness in clinical practice is limited by patient adherence. Twice-yearly denosumab treatment is associated with markedly improved bone mineral density (BMD) and cortical and trabecular bone strength, and significantly reduced osteoporotic fracture. Inhibition of bone resorption is fully reversible following discontinuation. Placebo-controlled and open-label extension studies showed similar adverse event (AE) and serious AE rates, relative to placebo, over up to 5 years. Data indicate a potential advantage of denosumab over the bisphosphonate alendronate for BMD and patient adherence and preference.

Conclusion:

Owing to its efficacy, safety, and potential to improve adherence rates, denosumab is an appropriate first-line pharmacologic option for PMO management.

Case description

Mrs W. is 70 and still works as a high school librarian. She is new to your office and has come in for an annual assessment. She has no history of broken bones since childhood. She is relatively sedentary and has a BMI of 27 (height 166 cm; weight 75 kg). A DXA study yielded femoral neck and lumbar spine (L1–4) T-scores of −3.4 and −2.5, respectively. From Canadian Association of Radiology, Osteoporosis Canada (CAROC) fracture risk assessment tables[1], Mrs W. is considered to be at high fracture risk (>20% 10 year fracture probability), and by Canadian FRAX[2] she has a 19% 10 year probability of major fracture and a 7.4% 10 year probability of hip fracture. She is knowledgeable and interested, and you discuss her treatment options to help her prevent fragility fractures.

Introduction

An estimated one in four Canadian women over the age of 50 has osteoporosis[3]. In this population, osteoporosis accounts for approximately 80% of all fractures[4]. Pain, reduced mobility, and long-term disability are common sequelae of osteoporotic fragility fractures[5], and individuals who have suffered a fracture are at greater risk of a subsequent fracture compared to those with no such history[6]. Hip and vertebral fractures can be particularly devastating, with 23.5% and 15.7% of patients dying within 5 years of experiencing these respective types of fractures[7]. The consequences of osteoporosis also place a significant economic burden on the Canadian health-care system, with costs associated with hip fractures alone expected to reach $2.4 billion by 2041[8]. Unfortunately, osteoporosis is still not being identified or treated in the majority of individuals at risk of fracture, including those who have already suffered a fragility fracture and have received fracture care in a clinic in Canada. One study of Ontario fracture clinic patients estimated that less than 20% of osteoporotic women were examined for signs of the disease or questioned about a history of fragility fractures[9]. More recent evidence suggests that only 15% of women who experienced a fragility fracture received pharmacologic treatment within 6 to 8 months of the event, in order to prevent further fractures[4].

According to the 2010 Osteoporosis Canada Clinical Practice Guidelines[1], written by a panel of bone specialists and family physicians, all Canadian women over 50 years of age should be screened for osteoporosis and fracture risk. As shown in Figure 1, patients deemed to have a low 10 year risk of fracture (<10%) are not likely to benefit from pharmacotherapy and should instead receive counseling on exercise, fall prevention, optimization of calcium and vitamin D intake, and smoking cessation[1]. Conversely, patients with a moderate (10–20%) 10 year fracture risk, among whom the greatest absolute number of fragility fractures occur[10], should be assessed further to determine whether pharmacologic treatment should be offered[1]. Finally, patients with a high (>20%) 10 year fracture risk, those who have experienced a fragility fracture of the hip or spine, or more than one fragility fracture, or those on long-term glucocorticoid therapy, should receive pharmacologic intervention. Therapeutic options supported by high-level evidence include bisphosphonates, selective estrogen receptor modulator (SERM), hormone therapy, teriparatide, and most recently, denosumab, a RANK (receptor activator of nuclear factor κB) ligand inhibitor.

Physicians, including primary care physicians, consistently overestimate patients' adherence to osteoporosis medications, relative to the adherence patterns identified from pharmacy records[11]. While pharmacologic agents are efficacious in reducing fracture risk in clinical trials[12], their real-world effectiveness is often limited by poor patient adherence[13]. For instance, the most widely prescribed first-line agents, the oral bisphosphonates, are not taken as directed by one-third to one-half of patients, and drug refill studies suggest half of patients discontinued therapy within 184 days of treatment initiation[13–15]. Indeed, a recent analysis of Ontario Drug Benefit pharmacy claims showed that 10% of patients filled only a single bisphosphonate prescription, and less than half of patients remained fully compliant and persistent after 2 years. Treatment gaps of at least 60 days were common even in the first year of treatment, with 22% of patients going off therapy one or more times during this period[16]. These observations are important, given that oral bisphosphonates' effectiveness is severely compromised in patients with reduced adherence[17], with a 28–43% higher risk of hip and vertebral fractures in non-adherent, compared to adherent, patients. Poor adherence, defined by being in possession of an oral bisphosphonate for ≤50% of the period over which it is prescribed, does not appear to confer any protection from incident fractures[17]. Thus, there is a clear need for additional treatment options that combine efficacy with greater patient adherence and use.

In August 2010, denosumab was approved by Health Canada for the treatment of postmenopausal women with a high risk of osteoporotic fracture, as well as those who have failed or are intolerant to other therapeutic options[18]. Denosumab, administered subcutaneously twice yearly, is a novel anti-resorptive drug, differing in its mode of action from the more familiar anti-resorptive treatments such as bisphosphonates and SERMs. Long-term safety and efficacy of denosumab continue to be evaluated in a study of patients receiving twice-yearly injections over up to 10 years (NCT00523341). Data for up to 6 years have been reported to date[19].

The objective of the current paper is to provide an up-to-date review of the literature on denosumab, the newest entry into the field of PMO therapeutics, and to consider its current standing in Canadian primary care for osteoporosis.

Methods

The authors reviewed published, English-language papers identified in a PubMed search on the terms 'denosumab' and 'osteoporosis', up to July 2012. Phase 2 and phase 3 clinical trials were considered. Public records of conference proceedings were also queried via Web of Science, in order to examine non-peer-reviewed secondary analyses and updates of the key denosumab studies. Pivotal studies reporting on functional outcomes with other therapeutics were identified as those that were cited in the product monograph. An additional PubMed search was done for systematic reviews on the efficacy and safety of PMO therapeutics.

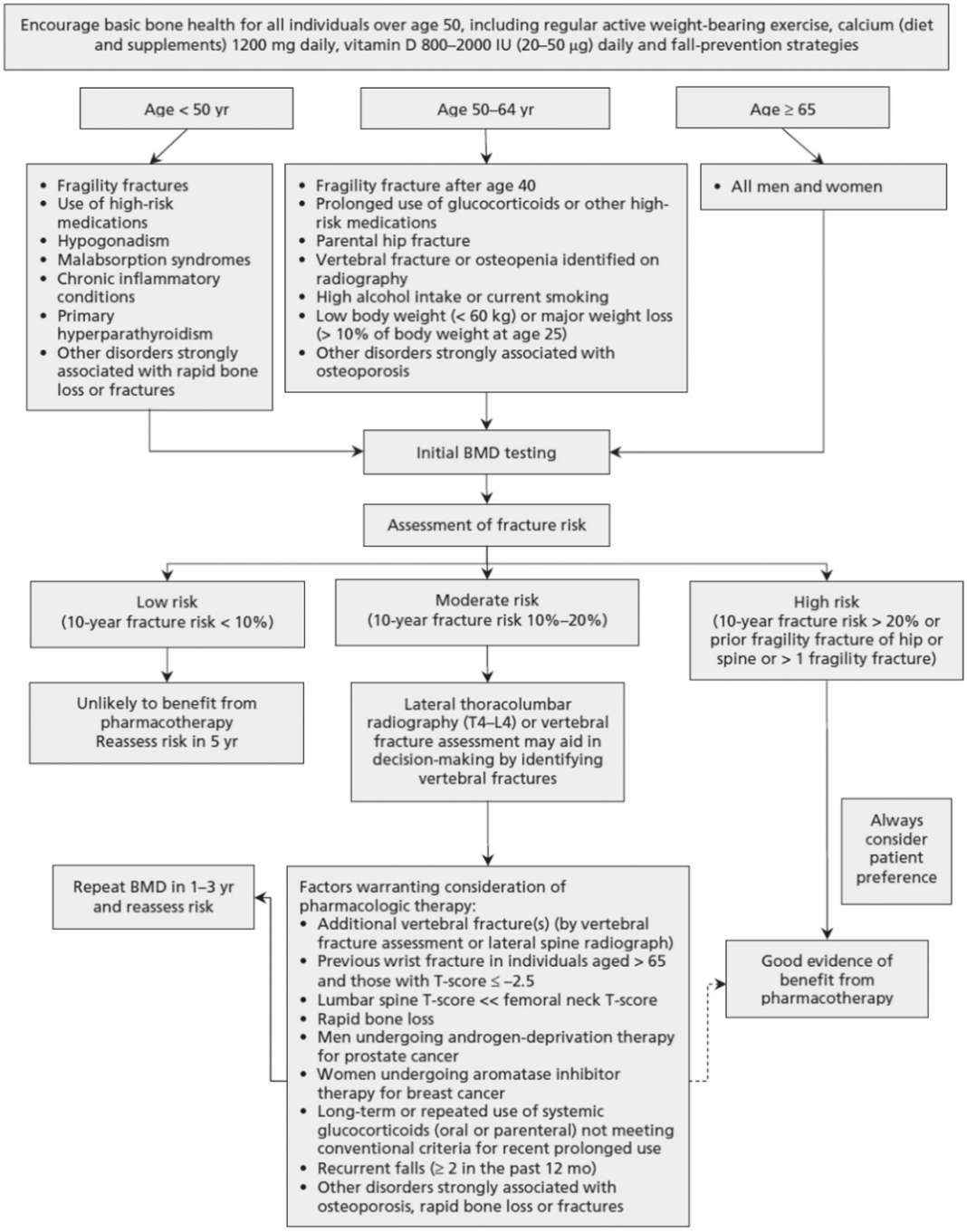
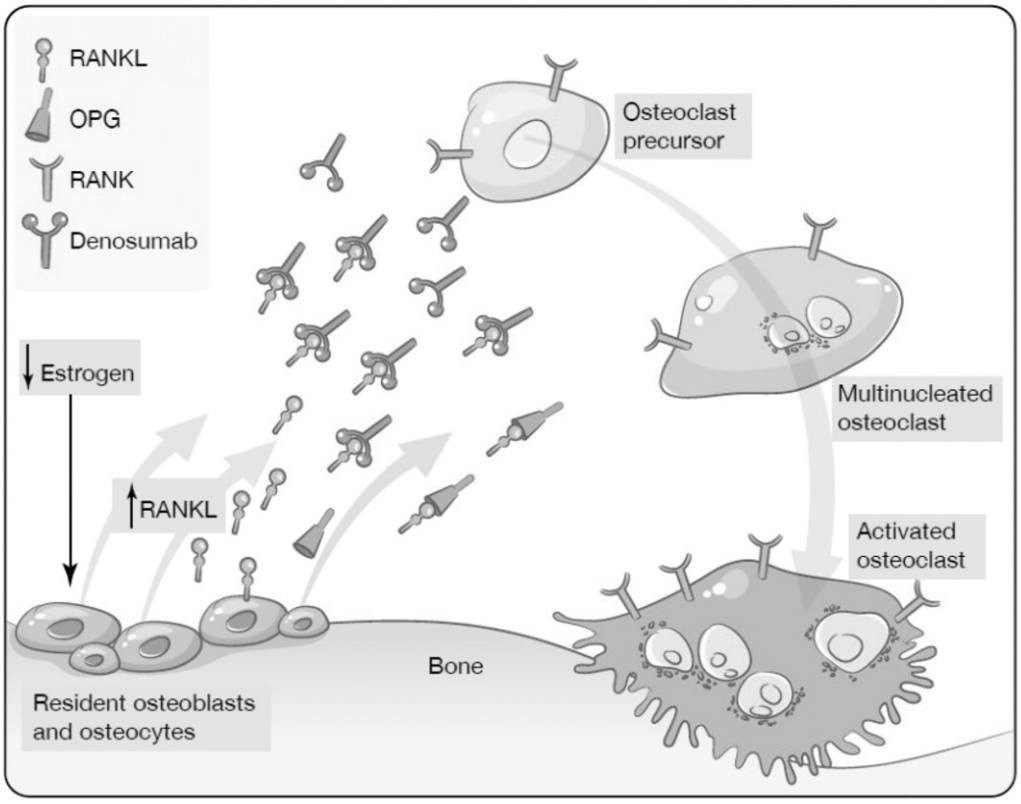


Figure 1. Integrated approach to management of patients who are at risk for fracture. Reprinted from Alexandra Papaioannou, Morin, Cheung *et al.* 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary, Figure 2: integrated approach to management of patients who are at risk for fracture. Can Med Assoc J 2010;182:1870. © Canadian Medical Association, 2010. This work is protected by copyright and the making of this copy was with the permission of the Canadian Medical Association Journal (www.cmaj.ca) and Access Copyright. Any alteration of its content or further copying in any form whatsoever is strictly prohibited unless otherwise permitted by law.

Results

Denosumab in the treatment of PMO: mechanism, indications, and dosing

Denosumab is a human monoclonal antibody that binds RANK ligand (RANKL), preventing this protein from activating RANK, its receptor, on the osteoclast surface[20]. The RANK–RANKL interaction is under dynamic regulation at a number of levels, both in healthy bone and in disease states such as osteoporosis. Thus, the endogenous protein osteoprotegerin (OPG) serves as a decoy receptor for RANKL, blocking the RANK–RANKL interaction



OPG—osteoprotegerin, RANK—receptor activator of nuclear factor kappa, RANKL—RANK ligand.

Figure 2. The role of denosumab in inhibiting bone resorption and opposing the effects of reduced estrogen levels. Inspired by Singer and Grauer (2010)[22].

and helping maintain a physiologic balance of bone turnover[21]. For a comprehensive discussion of osteoporosis pathophysiology and the effects of denosumab on this process, readers are encouraged to consult recent reviews[21–23].

Like endogenous OPG, denosumab inhibits the activation of RANK on osteoclast precursors and thereby diminishes osteoclast formation, differentiation and survival[24]. The resulting inhibition of bone resorption can be therapeutically useful in the postmenopausal state, where decreasing estrogen levels lead to an increase in RANKL expression[21]. Thus, as illustrated in Figure 2, denosumab effectively inhibits the effects of estrogen decline on bone turnover.

Denosumab 60 mg is given as a single subcutaneous injection every 6 months. It is approved for use in postmenopausal women and should be given with appropriate calcium and vitamin D supplementation[25]. According to the Osteoporosis Canada Clinical Practice Guidelines, denosumab is one of several first-line options for the pharmacological management of PMO, along with several bisphosphonates, raloxifene, teriparatide, and hormone replacement therapy.

As shown in Table 1, all of these first-line options have been shown to reduce risk of incident fractures by 30–68%, depending on the agent and the site of fracture (vertebral, non-vertebral or hip)[1]. Pivotal trial data for denosumab and the bisphosphonate zoledronic acid indicate that these two agents significantly reduce risk of all three classes of fracture, with the greatest absolute risk reduction seen with vertebral fractures. For hip fractures, while the primary study on risedronate did not report hip data[26], another prospective study reported specifically on this outcome[27]. Because head-to-head fracture trials have not been conducted, quantitative comparisons of fracture risk reduction with the various treatments cannot be made, as there are differences in study population and trial design[28].

A recent comprehensive meta-analysis reports that for denosumab and the three bisphosphonates shown in Table 1, there is high-level evidence supporting a reduced risk of fracture at all sites (hip, non-vertebral and vertebral)[29]. For vertebral fractures, several other agents, including teriparatide and raloxifene, were supported by high-level evidence[29].

Denosumab and fracture risk

The international, placebo-controlled **F**racture **RE**duction **E**valuation of **D**enosumab in **O**steoporosis

Table 1. Pivotal trial evidence of fracture risk reduction in postmenopausal women for first-line therapies identified in the 2010 Osteoporosis Canada Guidelines.

Medication	Pivotal Trial Name, Reference	Relative Fracture Risk Reductions vs. Control (Absolute Risk Reduction)*		
		Vertebral	Non-vertebral	Hip
Alendronate	FIT I[30]	47% (7%)	NS	51% (1.1%)
	FIT II[31]	44% (1.7%)	NS	NS
Risedronate	VERT NA[26]	41% (5%)	39% (3%)	NR
	HIP[27]	NR	20% (1.7%)	28% (1.1%)
Zoledronic acid	HORIZON[32]	70% (7.6%)	25% (2.7%)	41% (1.1%)
Raloxifene	MORE[33]	41% (1.3%)	NS	NS
Estrogen replacement therapy	WHI[34]	34% (6%)	NR	34% (5%)
Teriparatide	FPT[35]	65% (9%)	53% (2.9%)	NR
Denosumab	FREEDOM[36]	68% (4.9%)	20% (1.5%)	40% (0.5%)

NS = not significant; NR = not reported.
*Relative and absolute risk reduction data are shown if statistically significant vs. control in the pivotal trial ($p < 0.05$ or better). Note that these results cannot be directly compared across studies due to differences in study populations and methods.

every 6 Months (FREEDOM) trial assessed the effect of 36 months of twice-yearly 60 mg denosumab treatment on new vertebral fracture risk in 7868 postmenopausal women with osteoporosis (with T-scores <−2.5 at the lumbar spine or total hip, but not <−4.0 at both sites)[36]. As depicted in Figure 3, 36 months of denosumab treatment was associated with a 68% reduction in the relative risk of new radiographic vertebral fractures compared to placebo (cumulative incidence 7.2% vs 2.3%; $p < 0.001$). Reduced risk was evident after 12 months of denosumab treatment; within the first year of the study, a 61% reduction of new vertebral fracture rate was evident among denosumab-treated patients (0.9% vertebral fracture incidence for denosumab-treated vs 2.2% for placebo-treated; $p < 0.001$). Denosumab treatment was also associated with a 40% ($p = 0.04$) and 20% ($p = 0.01$) relative decrease in hip and non-vertebral fractures, which were followed as secondary endpoints. Over 3 years, the number needed to treat (NNT) to prevent one new vertebral and one hip fracture, respectively, were 21 and 232. Absolute risk reduction was greater (and NNT correspondingly smaller) in women with multiple risk factors, such as prior fracture plus low baseline femoral neck BMD[37].

FREEDOM patients from both study arms were eligible to participate in an open-label extension study of denosumab treatment for up to seven additional years. Data from the 2 year extension suggest that 5 years of treatment leads to continued protection from vertebral and non-vertebral fractures. In patients who crossed over to denosumab from the placebo group, findings at 2 years were similar to those in the group originally randomized to denosumab[38].

A post-hoc analysis of data from the FREEDOM study evaluated the effect of denosumab treatment among women judged to be at higher risk of new vertebral and hip fractures because of their prior fracture history, age, or BMD[37]. In women with baseline femoral neck T-scores of −2.5 or lower, incidences of new vertebral and hip fracture over the 36 month study were 9.9% and 2.8%, respectively, among placebo-treated patients. As would be expected, these values were higher than the corresponding incidences in the placebo group of the FREEDOM study overall (7.2% and 1.2%, respectively). With 36 months of denosumab treatment in this same group of higher-risk women, the new vertebral and hip fracture relative risk significantly reduced by 69% ($p < 0.001$) and 47% ($p = 0.02$). Absolute risk reduction among women with baseline femoral neck BMD T-score of <−2.5 or lower was 6.8% and 1.4% for new vertebral and hip fractures, respectively, corresponding to a NNT of 15 and 71 for each of these outcomes.

Safety and tolerability of denosumab treatment

During 3 years of the FREEDOM study, incidences of all, serious, and fatal AEs among denosumab-treated patients were similar to those of placebo-treated patients (Table 2)[36]. While the overall incidence of infection was similar between the denosumab and placebo groups (52.9% vs 54.4%; p = NS), skin infections (predominantly cellulitis/erysipelas) requiring hospitalization, although uncommon, were significantly more common in the former group (0.3% vs <0.1%; $p = 0.002$)[36]. The incidence of epidermal and dermal AEs (e.g., dermatitis, eczema, and rashes), as well as flatulence, was also higher among denosumab-treated patients[25,36]. Denosumab treatment for osteoporosis was not associated with any cases of atypical femoral fractures, detection of neutralizing antibodies against denosumab, hypocalcemia, or osteonecrosis of the jaw (ONJ) in the pivotal fracture trial[36].

Adverse event incidences were not significantly different between study arms and were consistent in the higher- and lower-risk study groups and in the FREEDOM study overall[36,37]. As would be anticipated[7,39], patients at higher risk of new vertebral and hip fracture showed increased mortality over the course of the study. There were numerically fewer fatal AEs among subjects treated with

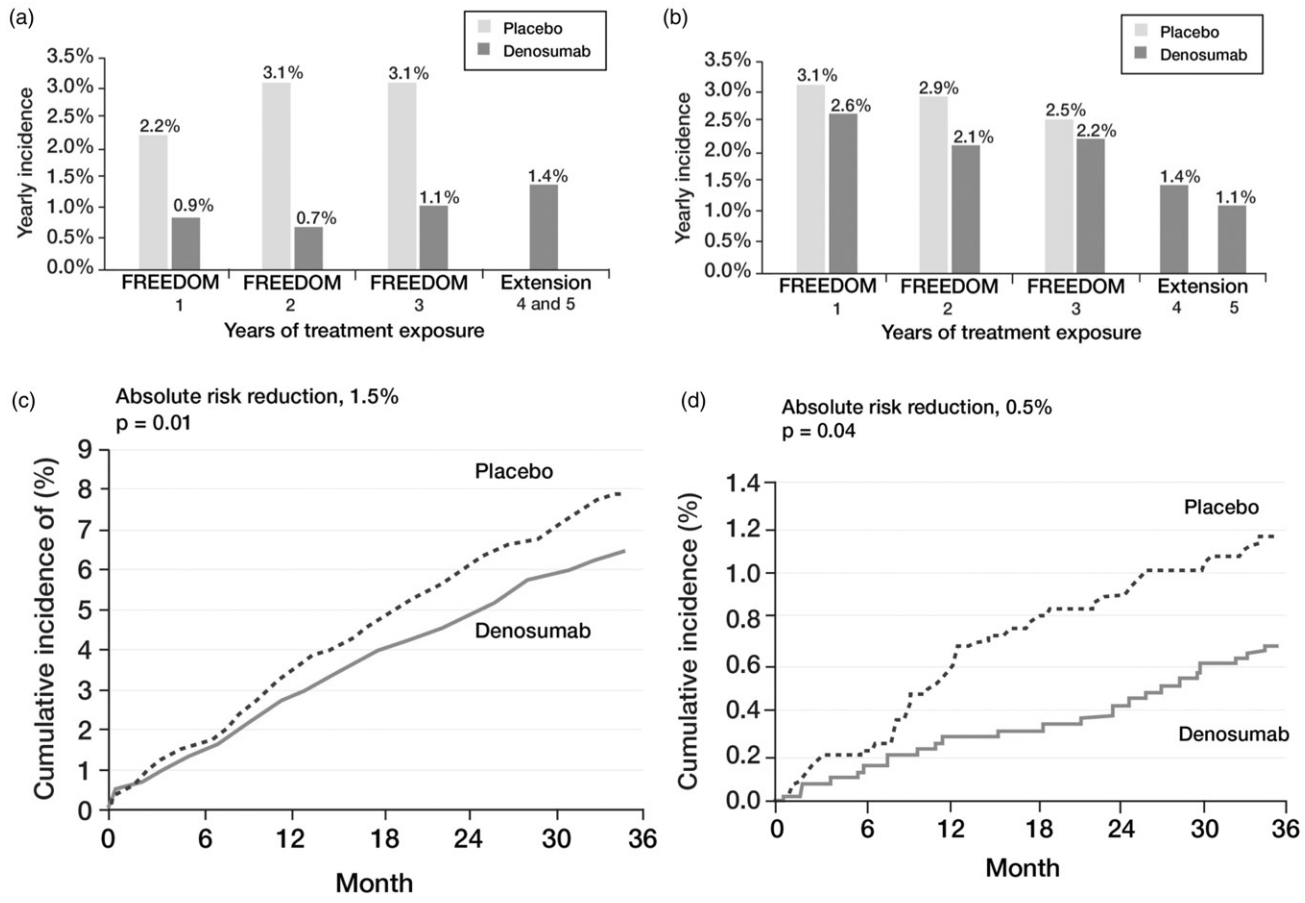


Figure 3. Incidence of new vertebral fracture in postmenopausal women with osteoporosis receiving denosumab or placebo for up to 5 years. New vertebral fracture incidence (a) and non-vertebral fracture incidence (b) in the 3 year placebo-controlled FREEDOM study and 2 years of the open-label FREEDOM Extension study. Time to first non-vertebral (c) and hip (d) fracture over 36 months in the original FREEDOM study. (a) Adapted from: Papapoulos S, Chapurlat R, Libanati C *et al.* Five years of denosumab exposure in women with postmenopausal osteoporosis: results from the first two years of the FREEDOM extension. J Bone Mineral Res 2011:694-701. Copyright© 2011. Used with permission from John Wiley and Sons. (b) Adapted from: Papapoulos S, Chapurlat R, Libanati C *et al.* Five years of denosumab exposure in women with postmenopausal osteoporosis: results from the first two years of the FREEDOM extension. J Bone Mineral Res 2011:694-701. Copyright© 2011. Used with permission from John Wiley and Sons. (c) From: Cummings SR, San Martin J, McClung MR *et al.* Denosumab for prevention of fractures in postmenopausal women with osteoporosis. New Engl J Med 2009;361:756-65. Copyright © (2009) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. (d) From: Cummings SR, San Martin J, McClung MR *et al.* Denosumab for prevention of fractures in postmenopausal women with osteoporosis. New Engl J Med 2009;361:756-65. Copyright © (2009) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Table 2. Adverse events during 36 months of placebo or denosumab treatment of postmenopausal women with osteoporosis. Adapted from Cummings *et al.* (2009)[36].

Event	Denosumab (*N* = 3886)	Placebo (*N* = 3876)	*P* Value
All	92.8%	93.1%	0.91
Serious	25.8%	25.1%	0.61
Fatal	1.8%	2.3%	0.08
Leading to study discontinuation	2.4%	2.1%	0.39
Leading to discontinuation of a study drug	4.9%	5.2%	0.55

N = number of subjects who received at least one dose of investigational product.

denosumab in the overall FREEDOM population; this difference in mortality was significant in patients at higher risk of new vertebral fractures (those with prevalent vertebral fractures and low femoral neck BMD)[37].

In the FREEDOM extension study, incidences of AEs and of serious or fatal AEs over the first 2 years of the extension period were similar to or lower than those observed in the core study in the placebo and denosumab groups[38]. Rates of skin infection were low in the long-term group during the first 2 years of the extension (representing 5 years of denosumab exposure). Adjudicated cases of ONJ have been reported in this extension trial, but it appears that ONJ is rare among patients receiving denosumab

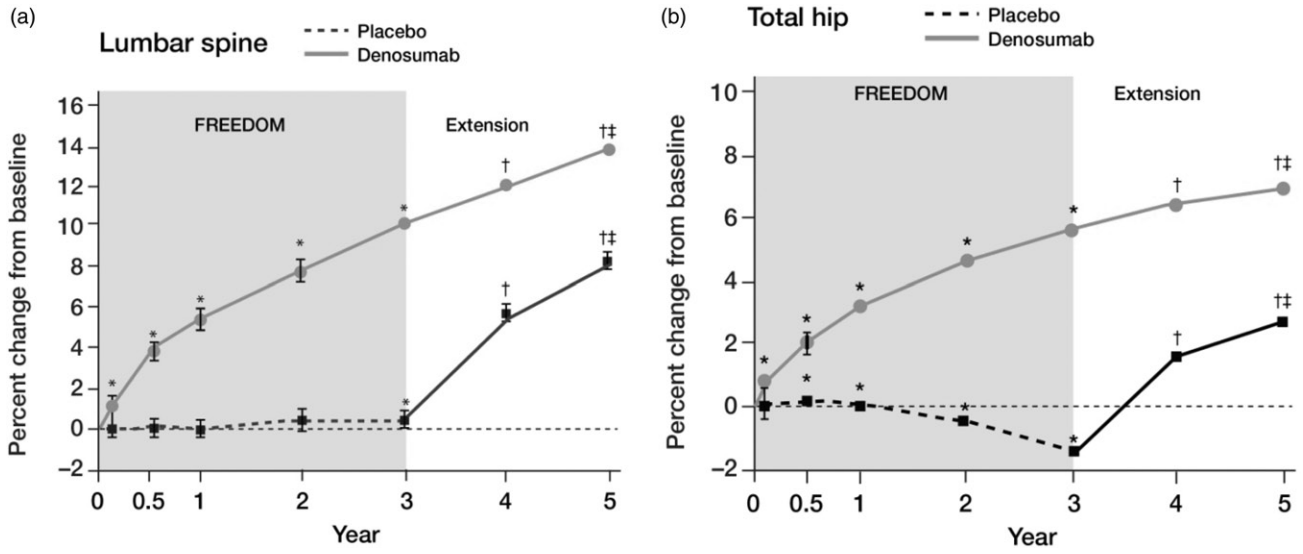


Figure 4. Changes in lumbar spine (a) and total hip (b) BMD in response to up to 5 years of denosumab in postmenopausal women with osteoporosis. Patients crossing over from placebo to active treatment in the Extension phase received 2 years of denosumab treatment. $^{*}p<0.05$ compared with baseline; $^{\dagger}p<0.05$ compared with FREEDOM baseline and Extension baseline; $^{\ddagger}p<0.05$ compared with year 4. Adapted from: Papapoulos S, Chapurlat R, Libanati C *et al.* Five years of denosumab exposure in women with postmenopausal osteoporosis: results from the first two years of the FREEDOM extension. J Bone Mineral Res 2011;694-701. Copyright © 2011. Used with permission from John Wiley and Sons.

for PMO[25]. Similarly, ONJ appears to be rare in osteoporosis patients on bisphosphonates, with an estimated incidence of less than 1 case per 100,000 person-years of exposure[40]. A dental exam and preventative dentistry prior to denosumab treatment should be considered for patients at risk of ONJ, and good oral hygiene practices should be maintained during treatment[25]. There have been reports of ONJ in clinical studies in patients with advanced cancer treated with denosumab (120 mg administered every 4 weeks) or zoledronic acid (4 mg every 4 weeks) at much higher doses than recommended for osteoporosis. A recent integrated analysis of three phase III trials in cancer patients demonstrated an incidence of 1.3% in patients treated with zoledronic acid and 1.8% in patients treated with denosumab ($p=0.13$)[41]. Adjudicated cases of atypical femoral fractures have been reported in the FREEDOM extension study[42]. It appears that these events are very rare among patients receiving denosumab in bone loss studies. Similarly, thus far atypical femoral fracture is rare among osteoporotic patients receiving other anti-resorptive therapy. The estimated incidence of atypical femoral fracture has been calculated in several populations. Meier et al estimated 0.32 atypical fractures/10,000 subject-years in individuals 50 years and older[43]. Such fractures have been reported in patients who have received or never received bisphosphonates[43–46]. The difference in the risk of atypical fracture between users and nonusers of bisphosphonates has been estimated at 5 cases/10,000 patient-years[44]. During osteoporosis treatment, patients should be advised to report new or unusual thigh, hip, or groin pain[47]. Patients presenting with such symptoms should be evaluated for an incomplete femoral fracture, and the contralateral femur should also be examined[47].

Effect of denosumab on BMD, bone turnover markers, and bone architecture

Denosumab treatment significantly reduces bone turnover markers (BTMs) and increases BMD at all measured sites, including the lumbar spine, femoral neck and total hip, and distal radius, compared to placebo[24,36,48–54]. While rarely evaluated in primary care, BTMs offer useful surrogate endpoints in many clinical studies; the degree of BTM suppression achieved during the early stages of denosumab treatment positively predicts the subsequent degree of improvement in BMD[48]. In the FREEDOM study, the magnitude of denosumab's impact on BMD was also directly related to treatment duration (Figure 4). Thus, the 9.2% and 6.0% increases in lumbar spine and total hip BMD documented in that study ($p<0.001$ for both, relative to placebo) occurred progressively over the 36 months of denosumab treatment[36]. FREEDOM extension data suggest a further 4.5% and 1.0% increase in lumbar spine and total hip BMD ($p<0.0001$ for all), respectively, over the following 2 years of denosumab treatment, for a total increase of 13.7% and 7% increase in lumbar spine and total hip BMD, respectively, relative to baseline values[38].

In addition to improving BMD, denosumab treatment results in gains in the estimated mechanical strength of bone[53,54], with improvements seen in cortical as well as trabecular bone tissue[54]. Quantitative computed tomography data from the 24 month, randomized, and placebo-controlled **DE**nosumab **F**ortifi**E**s Bo**N**e **D**ensity

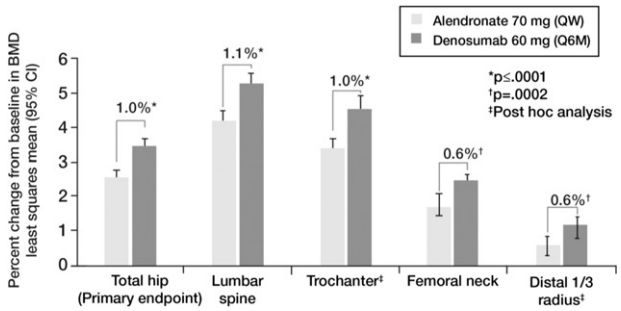


Figure 5. The efficacy of 12 months denosumab versus alendronate treatment in increasing BMD at various sites among postmenopausal women with low BMD randomized to active treatment with either alendronate or denosumab. Adapted from Brown *et al.* (2009)[55].

(DEFEND) trial indicate significant increases in the BMD of cortical (1.7%; $p<0.001$) and trabecular (9.4%; $p<0.05$) bone along the radius with denosumab treatment[53]. The improvement in cortical bone density is of interest because it is not reliably seen in response to bisphosphonate treatment, and most osteoporotic fractures occur at skeletal sites comprising predominantly cortical bone[53,54].

Denosumab versus alendronate in the treatment of PMO

In the head-to-head **D**etermining **E**fficacy: **C**omparison of **I**nitiating **D**enosumab versus Al**E**ndronate (DECIDE) study, 1189 postmenopausal women with low BMD were randomized to active treatment with either subcutaneous twice-yearly 60 mg denosumab or 70 mg weekly oral alendronate for 12 months[55]. The primary endpoint was change in total hip BMD; a double-blind/double-dummy design was used to ensure blinding despite the differences in dosing and administration for these two agents. Denosumab treatment resulted in significantly greater BMD increases in the hip and all other sites measured (Figure 5) and significantly greater reductions in BTMs compared with alendronate, with a similar AE profile[55]. A smaller, phase 2 study also showed that denosumab increased cortical BMD at the distal radius ($p=0.023$) and tibia ($p<0.001$) after 12 months of treatment, and compared with alendronate, led to a greater increase in estimated bone strength ($p<0.001$)[54].

The effect of transitioning from oral bisphosphonate to denosumab therapy was investigated in STAND (**S**tudy of **T**ransitioning from **A**le**N**dronate to **D**enosumab), which included 504 postmenopausal women with low BMD who had been receiving alendronate for ≥6 months[52]. The primary endpoint in STAND was change in hip BMD over 12 months of treatment. Compared with women who continued on alendronate therapy, those who transitioned to denosumab experienced a significantly greater increase in BMD at all sites (total hip, lumbar spine, femoral neck, and one-third radius) within 6 to 12 months (Figure 6), and superior suppression of BTMs within 1 month[52]. Both groups experienced similar rates of AEs, suggesting that transitioning from alendronate to denosumab can be done safely[52]. Patients participating in the phase 3 head-to-head trials described above also reported significantly greater satisfaction and preference for the twice-annual injection regimen of denosumab versus weekly oral alendronate[56].

In the **D**enosumab **A**dherence **P**reference **S**atisfaction (DAPS) study, 250 treatment-naïve postmenopausal osteoporotic women were randomized to 12 months of either denosumab or alendronate treatment, followed by crossover to the other treatment for another 12 months[57]. As illustrated in Figure 7, time to non-adherence was greatly extended in patients receiving denosumab versus alendronate treatment. Adherence rates differed significantly over the first year of the study (88.1% vs 76.6%)[58] and also differed in the second year (92.5% vs 63.5%)[57]. Most patients (91.2%) also indicated preference for denosumab as a long-term treatment option[57].

Reversibility of denosumab treatment upon discontinuation

Denosumab discontinuation resulted in a decline in BMD at all sites during the first 12 months, followed by BMD stabilization during the following 12 months. Interestingly, despite the initial loss following treatment discontinuation, BMD at all sites measured remained significantly higher than in placebo patients, who had never received denosumab[51]. In women discontinuing denosumab for 21 to 29 months, bone histomorphometry results were consistent with those seen in a postmenopausal population with osteoporosis. The effects of denosumab were fully reversible over this time span, with no deleterious effect on bone micro-architecture[59].

Following 12 months of discontinuation, denosumab treatment re-initiation was associated with BMD increases at all sites to levels achieved during 24 months of initial treatment, as well as a return of BTM levels to below baseline[24]. Thus, interruption and re-initiation are feasible for patients on denosumab. Nevertheless, because osteoporosis is a chronic condition, individuals at high risk of fracture should maintain osteoporosis treatment without drug holidays, as recommended in the 2010 Osteoporosis Canada guidelines[1].

Denosumab treatment of specific patient populations

Denosumab metabolism does not depend on renal clearance, and it appears to be safe and effective in reducing

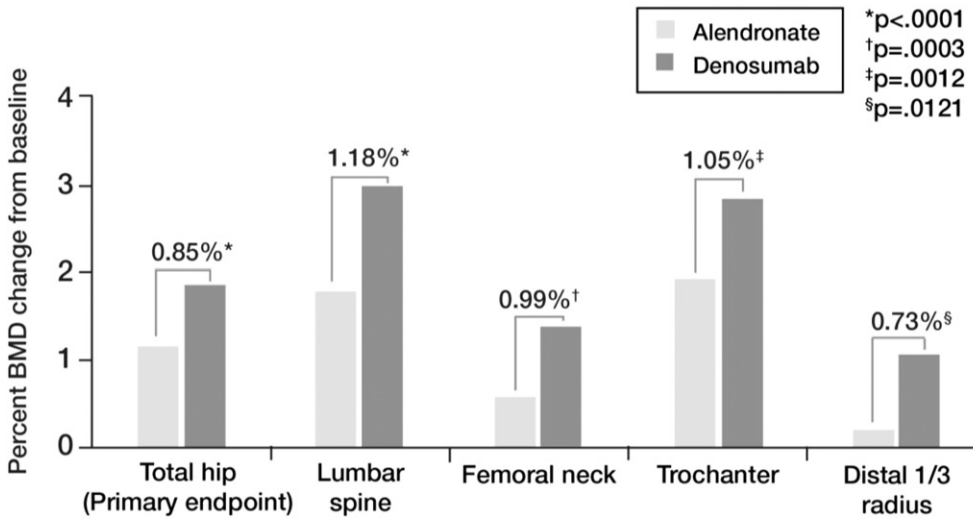


Figure 6. Percentage change from baseline in BMD at various sites in subjects transitioning to denosumab or continuing on alendronate therapy. Adapted from Kendler *et al.* (2010)[52].

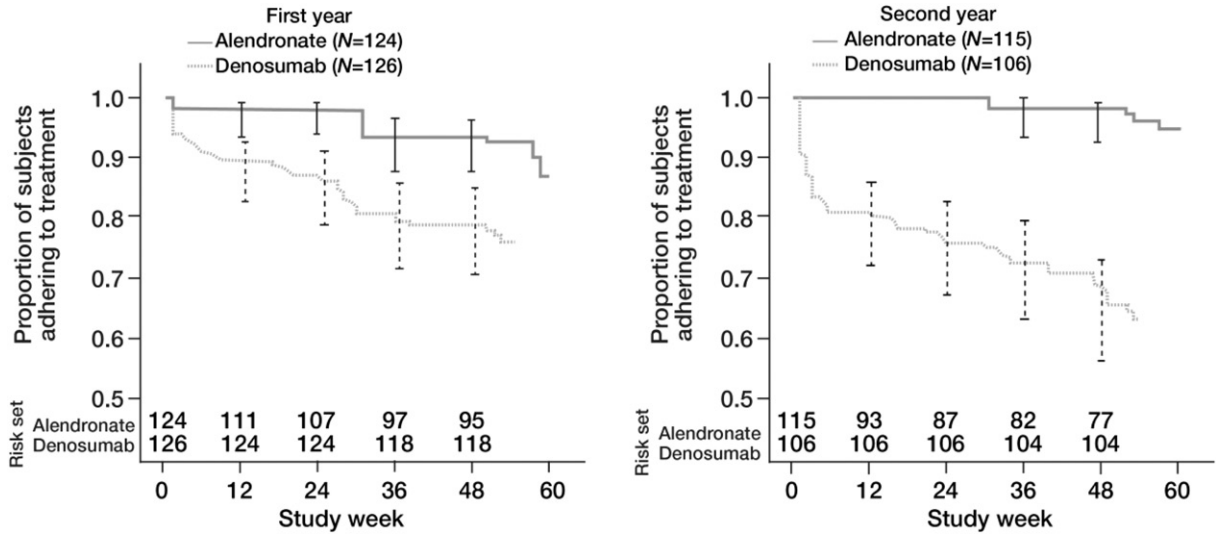


Figure 7. Time to non-adherence to denosumab or alendronate treatment over 12 months in postmenopausal osteoporotic women. Non-adherence to alendronate could begin at any time, while the time to denosumab non-adherence was defined as failure to take an injection within 4 weeks of the scheduled date. Adapted from Freemantle *et al.* (2011)[57]. With kind permission from Springer Science + Business Media: Freemantle N, Satram-Hoang S, Tang ET *et al.* Final results of the DAPS (Denosumab Adherence Preference Satisfaction) study: a 24-month, randomized, crossover comparison with alendronate in postmenopausal women. Osteoporos Int 2011;23:317-26, figure 2, and with any original (first) copyright notice displayed with material.

fracture risk and improving BMD at all sites among patients with normal to severely reduced kidney function, i.e. stage 1–4 chronic kidney disease (only a small number of patients with stage 4 disease, $N = 73$)[60]. No dose adjustment of denosumab is required for patients with renal impairment; however, it is important to maintain adequate and appropriate intake of calcium and vitamin D in this population. For patients with severe renal impairment (estimated glomerular filtration rate per Cockcroft-Gault <30 mL/min) or those receiving dialysis, specialist advice should be obtained to help determine the appropriate therapy. Anti-resorptive treatment is contraindicated in the presence of adynamic bone disease associated with renal failure.

Case resolution

Based on her individualized absolute risk factor assessment using the CAROC and Canadian FRAX tools, Mrs W.

would appear to be at high fragility fracture risk in the next 10 years. She should be counseled on calcium/vitamin D supplementation (according to Guideline recommendations) and the need for weight-bearing exercise. Pharmacological management is a reasonable option as well, depending on her preference and willingness to take regular treatment. Given a specific concern about possible hip fracture, the first-line alternatives for Mrs W. to consider would include any of three bisphosphonates (alendronate, risedronate, and zoledronic acid) or denosumab. You should present Mrs W. with information on the differences between these options, including features that may affect her ability to persist with therapy, such as route of administration, frequency of dosing and side-effect profile.

Conclusion

Although established pharmacologic agents have shown efficacy in reducing fracture risk among osteoporotic postmenopausal women in clinical trials, their value in practice may be limited by poor patient adherence, resulting in suboptimal outcomes[13,17]. The 2010 Osteoporosis Canada guidelines identify denosumab as a first-line therapy for preventing hip, non-vertebral, and vertebral fractures among postmenopausal women[1]. Ongoing denosumab treatment in PMO is associated with marked improvements in BMD and mechanical strength of cortical and trabecular bone, as well as a significant reduction in the risk of osteoporotic fractures at all sites studied. Based on surveillance for up to 6 years of ongoing treatment, denosumab also appears to have a favorable safety and tolerability profile. Benefits of denosumab treatment appear to be independent of renal function and prior bisphosphonate therapy. Available data also suggest a superiority of denosumab over bisphosphonate therapy in terms of BMD improvement and patient adherence and preference.

These conclusions echo those of other, systematic reviews and meta-analyses of treatment efficacy in PMO[29,61]. Crandall *et al.* recently reported that alendronate, risedronate, zoledronic acid, teriparatide and denosumab were all effective in reducing fracture risk in PMO. They also noted high-level evidence for poor adherence to bisphosphonates and for an association between frequent dosing and lower adherence[29]. No systematic review has yet compared adherence between denosumab and other treatments; the only published data on this issue appear to be from the clinical trials discussed above, suggesting significantly extended time to non-adherence in patients receiving denosumab, relative to those on alendronate[56,57]. A meta-analysis by Lin *et al.* showed that clinical fracture risk and safety concerns did not differ significantly between denosumab and alendronate, although denosumab was significantly more effective than this bisphosphonate at restoring bone mass over 1 year of treatment[61].

Owing to the favorable combination of treatment efficacy, safety, and patient adherence, the introduction of denosumab has the potential to markedly improve management of PMO in primary care.

Transparency

Declaration of funding

Amgen Canada supported this project from its inception. The opinions and analysis presented here are solely those of the authors.

Declaration of financial/other relationships

R.J. is an Advisory board member for and has received speaker honoraria and/or clinical research grants from: Amgen, Eli Lilly, Novartis, Warner Chilcott, Merck, GSK, Astra Zeneca, Osteoporosis Canada, International Osteoporosis Foundation. A.K. has received consulting fees, honoraria or research grants from Amgen, Alliance, Merck, Novartis, Eli Lilly, and NPS. D.N. has participated in National Advisory Boards and Speakers Bureau for Amgen Canada, Merck and Novartis and is a member of the Executive Editorial Board for Guidelines and Advisory Board for Primary Care Research with Amgen/Osteoporosis Canada. M.S. has received speaker honoraria from and is an advisory board member for Amgen, Pfizer, Merck, NovoNordisk, Bayer, GSK, Warner Chilcott, AstraZeneca and Eli Lilly.

Acknowledgments

Writing assistance was provided by John Ashkenas PhD (SCRIPT, Toronto Ontario) and Peter Janiszewski PhD (SCRIPT, Toronto Ontario), funded by Amgen Canada.

References

1. Papaioannou A, Morin S, Cheung AM, et al. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. CMAJ 2010;182:1864-73
2. WHO Fracture Risk Assessment Tool: Canada Available at: http://www.shef.ac.uk/FRAX/tool.jsp?country=19 [Last accessed January 2012]
3. Hanley DA, Josse RG. Prevention and management of osteoporosis: consensus statements from the Scientific Advisory Board of the Osteoporosis Society of Canada. 1. Introduction. CMAJ 1996;155:921-3
4. Bessette L, Ste-Marie LG, Jean S, et al. The care gap in diagnosis and treatment of women with a fragility fracture. Osteoporos Int 2008;19:79-86
5. Papaioannou A, Kennedy CC, Ioannidis G, et al. The impact of incident fractures on health-related quality of life: 5 years of data from the Canadian Multicentre Osteoporosis Study. Osteoporos Int 2009;20:703-14
6. Kanis JA, Johnell O, De Laet C, et al. A meta-analysis of previous fracture and subsequent fracture risk. Bone 2004;35:375-82
7. Ioannidis G, Papaioannou A, Hopman WM, et al. Relation between fractures and mortality: results from the Canadian Multicentre Osteoporosis Study. CMAJ 2009;181:265-71
8. Wiktorowicz ME, Goeree R, Papaioannou A, et al. Economic implications of hip fracture: health service use, institutional care and cost in Canada. Osteoporos Int 2001;12:271-8

9. Hajcsar EE, Hawker G, Bogoch ER. Investigation and treatment of osteoporosis in patients with fragility fractures. CMAJ 2000;163:819-22
10. Leslie WD, Berger C, Langsetmo L, et al. Construction and validation of a simplified fracture risk assessment tool for Canadian women and men: results from the CaMos and Manitoba cohorts. Osteoporos Int 2011; 22:1873-83
11. Copher R, Buzinec P, Zarotsky V, et al. Physician perception of patient adherence compared to patient adherence of osteoporosis medications from pharmacy claims. Curr Med Res Opin 2010;26:777-85
12. MacLean C, Newberry S, Maglione M, et al. Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. Ann Intern Med 2008;148:197-213
13. Imaz I, Zegarra P, Gonzalez-Enriquez J, et al. Poor bisphosphonate adherence for treatment of osteoporosis increases fracture risk: systematic review and meta-analysis. Osteoporos Int 2010;21:1943-51
14. Kothawala P, Badamgarav E, Ryu S, et al. Systematic review and meta-analysis of real-world adherence to drug therapy for osteoporosis. Mayo Clin Proc 2007;82:1493-501
15. Adachi JD, Josse RG, Russell RG. If you don't take it – it can't work: the consequences of not being treated or nonadherence to osteoporosis therapy. Ther Clin Risk Manag 2011;7:181-98
16. Burden AM, Paterson JM, Solomon DH, et al. Bisphosphonate prescribing, persistence and cumulative exposure in Ontario, Canada. Osteoporos Int 2012; 23:1341-7
17. 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
18. Osteoporosis Canada. Health Canada approves PROLIA™ (denosumab) as new choice in osteoporosis therapy. 2010. Available at: http://www.osteoporosis.ca/index.php/ci_id/10046/la_id/1.htm [Last accessed 26 September 2011]
19. Brown JP, Chapurlat R, Franchimont N, et al. Six Years of Denosumab Treatment in Postmenopausal Women with Osteoporosis: Results From the First Three Years of the FREEDOM Extension ACR/ARHP Scientific Meeting. Chicago, 2011
20. Bekker PJ, Holloway DL, Rasmussen AS, et al. A single-dose placebo-controlled study of AMG 162, a fully human monoclonal antibody to RANKL, in postmenopausal women. J Bone Miner Res 2004;19:1059-66
21. Baron R, Ferrari S, Russell RG. Denosumab and bisphosphonates: different mechanisms of action and effects. Bone 2011;48:677-92
22. Singer A, Grauer A. Denosumab for the management of postmenopausal osteoporosis. Postgrad Med 2010;122:176-87
23. Hanley DA, Adachi JD, Bell A, Brown V. Denosumab: mechanism of action and clinical outcomes. Int J Clin Pract 2012;266:1139-46
24. Miller PD, Bolognese MA, Lewiecki EM, et al. Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinded phase 2 clinical trial. Bone 2008;43:222-9
25. Amgen Canada Inc. PROLIA Product Monograph 2011. Available at: http://www.amgen.ca/Prolia_PM.pdf [Last accessed 26 September 2011]
26. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA 1999;282:1344-52
27. McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med 2001;344:333-40
28. Hopkins RB, Goeree R, Pullenayegum E, et al. The relative efficacy of nine osteoporosis medications for reducing the rate of fractures in post-menopausal women. BMC Musculoskelet Disord 2011;12:209
29. Crandall C, Newberry SJ, Diament A, et al. Treatment To Prevent Fractures in Men and Women With Low Bone Density or Osteoporosis: Update of a 2007 Report. Comparative Effectiveness Review No. 53. (Prepared by Southern California Evidence-based Practice Center under Contract No. HHSA-290-2007-10062-I). Rockville, MD: Agency for Healthcare Research and Quality, 2012
30. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996;348:1535-41
31. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998;280:2077-82
32. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007;356:1809-22
33. Apo-Raloxifene Product Monograph. Apotex Inc. March 24, 2006
34. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002; 288:321-33
35. Forteo Product Monograph. Eli Lilly Canada Inc. February 9, 2009
36. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 2009;361:756-65
37. Boonen S, Adachi JD, Man Z, et al. Treatment with denosumab reduces the incidence of new vertebral and hip fractures in postmenopausal women at high risk. J Clin Endocrinol Metab 2011;96:1727-36
38. Papapoulos S, Chapurlat R, Libanati C, et al. Five years of denosumab exposure in women with postmenopausal osteoporosis: results from the first two years of the FREEDOM extension. J Bone Miner Res 2012;27:694-701
39. Cooper C, Atkinson EJ, Jacobsen SJ, et al. Population-based study of survival after osteoporotic fractures. Am J Epidemiol 1993;137:1001-5
40. Khan AA, Sandor GK, Dore E, et al. Bisphosphonate associated osteonecrosis of the jaw. J Rheumatol 2009;36:478-90
41. Saad F, Brown JE, Van Poznak C, et al. Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases. Ann Oncol 2012;23:1341-7
42. Franchimont N, Bone H, Brown J, et al. Six Years of Denosumab Treatment in Postmenopausal Women With Osteoporosis: Results From the First Three Years of the FREEDOM Extension. American Association of Nurse Practitioners, 27th National Conference. Orlando, Florida, USA, June 20–24, 2012
43. Meier RP, Perneger TV, Stern R, et al. Increasing occurrence of atypical femoral fractures associated with bisphosphonate useatypical femoral fractures and bisphosphonate use. Arch Intern Med 2012;172:930-6
44. Schilcher J, Michaelsson K, Aspenberg P. Bisphosphonate use and atypical fractures of the femoral shaft. N Engl J Med 2011;364:1728-37
45. Girgis CM, Seibel MJ. Bisphosphonate use and femoral fractures in older women. JAMA 2011;305:2068; author reply 9
46. Lenart BA, Neviaser AS, Lyman S, et al. Association of low-energy femoral fractures with prolonged bisphosphonate use: a case control study. Osteoporos Int 2009;20:1353-62
47. Shane E, Burr D, Ebeling PR, et al. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 2010;25:2267-94
48. Eastell R, Christiansen C, Grauer A, et al. Effects of denosumab on bone turnover markers in postmenopausal osteoporosis. J Bone Miner Res 2011;26:530-7
49. 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
50. McClung MR, Lewiecki EM, Cohen SB, et al. Denosumab in postmenopausal women with low bone mineral density. N Engl J Med 2006;354:821-31
51. Bone HG, Bolognese MA, Yuen CK, et al. Effects of denosumab treatment and discontinuation on bone mineral density and bone turnover markers in postmenopausal women with low bone mass. J Clin Endocrinol Metab 2011;96:972-80

52. 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;25:72-81
53. Genant HK, Engelke K, Hanley DA, et al. Denosumab improves density and strength parameters as measured by QCT of the radius in postmenopausal women with low bone mineral density. Bone 2010;47:131-9
54. Seeman E, Delmas PD, Hanley DA, et al. Microarchitectural deterioration of cortical and trabecular bone: differing effects of denosumab and alendronate. J Bone Miner Res 2010;25:1886-94
55. Brown JP, Prince RL, Deal C, et al. 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;24:153-61
56. Kendler DL, Bessette L, Hill CD, et al. Preference and satisfaction with a 6-month subcutaneous injection versus a weekly tablet for treatment of low bone mass. Osteoporos Int 2010;21:837-46
57. Freemantle N, Satram-Hoang S, Tang ET, et al. Final results of the DAPS (Denosumab Adherence Preference Satisfaction) study: a 24-month, randomized, crossover comparison with alendronate in postmenopausal women. Osteoporos Int 2012;23(1):317-26
58. Kendler DL, McClung MR, Freemantle N, et al. Adherence, preference, and satisfaction of postmenopausal women taking denosumab or alendronate. Osteoporos Int 2011;22:1725-35
59. Brown JP, Dempster DW, Ding B, et al. Bone remodeling in postmenopausal women who discontinued denosumab treatment: off-treatment biopsy study. J Bone Miner Res 2011;26:2737-44
60. Jamal SA, Ljunggren O, Stehman-Breen C, et al. Effects of denosumab on fracture and bone mineral density by level of kidney function. J Bone Miner Res 2011;26:1829-35
61. Lin T, Wang C, Cai XZ, et al. Comparison of clinical efficacy and safety between denosumab and alendronate in postmenopausal women with osteoporosis: a meta-analysis. Int J Clin Pract 2012;66:399-408

