Therapeutics and Clinical Risk Management

Dovepress

open access to scientific and medical research

Open Access Full Text Article

REVIEW

Long-term treatment of osteoporosis: safety and efficacy appraisal of denosumab

Therapeutics and Clinical Risk Management downloaded from https://www.dovepress.com/
For personal use only.

This article was published in the following Dove Press journal:
Therapeutics and Clinical Risk Management
15 June 2012
Number of times this article has been viewed

Athanasios D Anastasilakis[1]
Konstantinos A Toulis[1]
Stergios A Polyzos[2]
Chrysostomos D Anastasilakis[3]
Polyzois Makras[4]

[1]Department of Endocrinology, 424 General Military Hospital, [2]Second Medical Clinic, Medical School, Aristotle University of Thessaloniki, Ippokration Hospital, [3]Department of Pharmacology, 424 General Military Hospital, Thessaloniki; [4]Department of Endocrinology and Diabetes, 251 Hellenic Air Force and VA General Hospital, Athens, Greece

Abstract: Denosumab is a fully human monoclonal antibody to the receptor activator of nuclear factor-κB ligand (RANKL), a member of the tumor necrosis factor receptor superfamily essential for osteoclastogenesis. Denosumab treatment is associated with a rapid, sustained, and reversible reduction in bone turnover markers, a continuous marked increase in bone mineral density at all sites, and a marked decrease in the risk of vertebral, hip, and nonvertebral fractures in women with postmenopausal osteoporosis. Therefore, it could be considered as an effective alternative to previous bisphosphonate treatment as well as first-line treatment of severe osteoporosis. Cost-effectiveness studies support this suggestion. In addition, denosumab seems to be the safest treatment option in patients with impaired renal function. Denosumab is characterized by reversibility of its effect after treatment discontinuation, in contrast with bisphosphonates. Large-scale clinical trials, including the extension of FREEDOM trial for up to 5 years, are reassuring for its safety. However, given its brief post-market period, vigilance regarding adverse events related to putative RANKL inhibition in tissues other than bone, as well as those related to bone turnover oversuppression, is advised.

Keywords: adverse event, denosumab, efficacy, fracture, osteoporosis, safety

Introduction

Osteoporosis is the most common bone disease, caused by a relatively increased rate of bone resorption by osteoclasts that exceeds the rate of bone formation by osteoblasts, resulting in net loss of bone mass. Osteoporosis affects a significant proportion of postmenopausal women and its incidence increases with advancing age.[1] Considering that the mean age of menopause is around 50 years and the life expectancy for women is currently over 80 years in Western countries (http://en.wikipedia.org/wiki/List_of_countries_by_life_expectancy) and continues to grow, many women are going to spend a long period of their lives being postmenopausal and potentially osteoporotic. Therefore, the need for antiosteoporotic agents that can be administered for prolonged periods of time with both efficacy and safety is mandatory.

Unfortunately, many currently available treatments have a limited duration of safe administration in humans. For example, anabolic agents, such as teriparatide, the 1–34 amino-terminal fraction of natural parathyroid hormone, and synthetic parathyroid hormone 1–84 are given for a maximum of two years. Prolonged administration of bisphosphonates, currently representing the medications most commonly used for osteoporosis, has raised concerns about rare but serious adverse events, such as osteonecrosis of the jaw, atypical fractures, and esophageal cancer.[2] Therefore, a drug holiday after 5–10 years of bisphosphonate treatment is advised.[2] Thus, a medication

Correspondence: Athanasios D Anastasilakis
Soulini 4, 566 25 Sykies, Greece
Tel +30 23 1038 1697
Fax +30 23 1038 1010
Email anastath@endo.gr

© 2012 Anastasilakis et al, publisher and licensee Dove Medical Press Ltd. This is an Open Access article which permits unrestricted noncommercial use, provided the original work is properly cited.

that could safely treat osteoporosis in the long term would be welcome. Could denosumab, an antibody against human RANKL, be that medication?

Denosumab

The receptor activator of nuclear factor-κB ligand (RANKL) is a member of the tumor necrosis factor (TNF) receptor superfamily, essential for osteoclastogenesis. RANKL is expressed by activated T cells and B cells, marrow stromal cells, osteoblasts, lining cells, osteocytes, and chondrocytes. Alternative splicing of RANKL mRNA allows expression of a type II transmembrane glycoprotein or a soluble ligand. Soluble RANKL can also be released from its membrane-bound state by metalloproteinases. RANKL binds to its receptor, RANK, on the surface of osteoclast precursors and enhances their differentiation, survival, and fusion, while activating mature osteoclasts and inhibiting their apoptosis. The natural compensatory mechanism against RANKL is another member of the TNF receptor superfamily, osteoprotegerin, a decoy receptor, produced locally in the bone microenvironment by mature osteoblasts.[3] Osteoprotegerin binds to RANKL, thereby blocking the RANKL-RANK interaction and thus osteoclast differentiation and activation.[4]

Derangement of the balance in RANKL/osteoprotegerin action is implicated in the pathophysiology of metabolic bone diseases, including osteoporosis,[5] and several current antiosteoporotic therapies are thought to act, at least in part, through modification of the RANKL/osteoprotegerin expression.[5] Denosumab (AMG-162) is a fully human monoclonal IgG2 antibody against human RANKL that specifically binds and neutralizes RANKL in order to decrease bone resorption and subsequent bone loss.

Pharmacology, mode of action, and pharmacokinetics

Denosumab is composed of amino acids and carbohydrates as natural immunoglobulin and its stereotactic configuration resembles that of the natural IgG2 immunoglobulin. Limited pharmacokinetic/pharmacodynamic analyses of denosumab using noncompartmental approaches have been reported. Because rodent RANKL is not recognized by this drug, preclinical data have been limited to studies conducted in cynomolgus monkeys.[6]

Pharmacodynamics

Denosumab binds to RANKL with high specificity and affinity (K_d approximately 10^{-12} M).[6] Therefore, it is more potent and acts for longer than natural osteoprotegerin or even the initially tested recombinant osteoprotegerin or RANK molecules that were constructed by removing different domains of the molecule and fusing the remaining peptide to the Fc domain of human immunoglobulin G1 (osteoprotegerin-Fc, Fc-osteoprotegerin, RANK-Fc).[7–10] The result is a more prolonged suppression of osteoclasts.[11,12] Another limitation of the abovementioned recombinant molecules has been a lack of specificity for RANKL (they also react with other members of the TNF family, including TNF-related apoptosis-inducing ligand [TRAIL]) which seems to be overcome with denosumab.

The effect of denosumab appears to be primarily antiresorptive. A single subcutaneous dose of denosumab results in a dose-dependent, rapid (within 12 hours), profound (up to 84%), and sustained (up to 6 months) decrease in bone resorption markers (N-telopeptide and C-telopeptide of type 1 collagen) and a subsequent decrease in bone formation markers (bone-specific alkaline phosphatase and N-propeptide of procollagen type 1) due to a coupling effect, leading to a decrease in bone turnover.[11–13] Decreases in bone-specific alkaline phosphatase occur later and are less pronounced than for N-telopeptide.[11] The decreases are maximal at three months (70%–90% for resorption and 55%–75% for formation markers) and remain for as long as treatment is continued.[5,14] After discontinuation of denosumab, bone markers rise to above pretreatment levels[14–16] within 12 months. Levels of the markers return towards baseline in the second year of discontinuation, even with no further therapy.[16] The rebound rise of bone markers above baseline after cessation of denosumab is similar to the pattern seen after cessation of estrogen therapy, although rebound occurs earlier with denosumab. The implication of this rebound effect on clinical outcomes is not clear.

Differences in the level and pattern of serum collagen type 1 C-telopeptide decreases have been observed between denosumab and alendronate, that are possibly due to the distinct mechanisms by which the two agents inhibit bone resorption.[12,13]

Following injection of denosumab, albumin-adjusted serum calcium levels decrease in a dose-dependent manner. The decrease is early but modest (does not exceed 10%). Serum phosphate levels also decrease in a manner similar to that of calcium because of the antiresorptive effect of denosumab. Intact parathyroid hormone levels increase up to three-fold after a few days and slowly return towards baseline after several months.[11]

The denosumab dose for treatment of osteoporosis in adults is 60 mg subcutaneously once every 6 months.

A 60 mg dose provides RANKL inhibition similar to that achieved by equivalent body-weight-based dosing; therefore, there seems to be no need for dose adjustment based on patient demographics. The effects of age and race on the area under the serum concentration-time curve for denosumab were less than 15% over the range of covariate values evaluated.[17] Administration of denosumab does not require adjustment in patients with renal impairment, and its use in patients with severe hepatic impairment has not been studied.[18,19]

To maintain the stability and pharmaceutical activity of denosumab, the drug must be stored protected from direct light and exposure to temperatures >25°C, usually at 2°C–8°C but not under 0°C, and definitely used within 14 days after removal from the refrigerator. Vigorous treatment and shaking should be avoided.[18]

Pharmacokinetics

The pharmacokinetics of subcutaneously administered denosumab in postmenopausal women are nonlinear with dose,[11,20] and because of this, the mean serum residence time increases with dose from 12 to 46 days. The nonlinearity in denosumab pharmacokinetics is probably due to RANKL binding.[17]

Specifically, three distinct phases have been observed,[11] ie, a prolonged absorption phase, which results in maximum serum concentration (C_{max}) in 5–21 days after administration, with the C_{max} to increase disproportionally (2.6-fold larger) to the increase in dose, and be reached in approximately 10 days at the 60 mg dose;[18] a prolonged β-phase, characterized by dose-dependent increases in the half-life to a maximum of 32 days, with the half-life of a 60 mg subcutaneous dose of denosumab being approximately 25–32 days;[18] and a more rapid terminal phase, evident at concentrations <1000 ng/mL, with a dose-dependent increase in half-life from 5 to 10 days.

The bioavailability of denosumab after subcutaneous administration has been reported to be 61%–64%,[17,21] with a k(a) of 0.00883 h-1. The baseline RANKL level, quasi-steady-state constant and RANKL degradation rate were 614 ng/mL, 138 ng/mL, and 0.00148 h-1, respectively.[17]

Characterization of other monoclonal antibodies indicates that absorption is probably mediated by the lymphatic system and that clearance may occur via the reticuloendothelial system because renal excretion is not expected.[22,23] The central volume of distribution and linear clearance are 2.49 L/66 kg and 3.06 mL/hour/66 kg, respectively.[17]

In conclusion, osteoclastic activity is profoundly suppressed while denosumab is in the circulation, which is for a prolonged period based on its pharmacokinetic profile. However, this effect is reversible,[11,24] as indicated by the return of N-telopeptide levels to baseline when denosumab is cleared from the circulation.[11]

Efficacy in postmenopausal osteoporosis

Preclinical studies

Denosumab inhibited bone resorption and increased bone density in knock-in mice that expressed chimeric (murine/human) RANKL.[25] In ovariectomized primates, denosumab significantly increased cortical and trabecular bone mineral content and bone mineral density (BMD) and improved biomechanical parameters of bone strength.[26,27]

Clinical studies

As mentioned above, subcutaneous administration of denosumab every 6 months has led to rapid and remarkable decreases in bone turnover markers, which are at least comparable with the most potent bisphosphonates[28] and remain for as long as treatment is continued.[5,29,30] These decreases result in a significant increase in BMD at both predominantly trabecular and predominantly cortical sites and a consequent reduction in fracture risk[30,31] (Table 1).

In particular, BMD continues to increase as long as treatment is continued, for at least up to 5–6 years.[14,30] Data from the FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 Months) trial, a three-year Phase III study of the effect of denosumab in postmenopausal women with osteoporosis, showed significant increases in BMD at the lumbar spine, hip, and distal radius.[31] The mean increase in lumbar spine BMD in the denosumab trials ranged between 3.0%–5.3% at 12 months, 6.5%–7.7% at 24 months, and 8.2%–10.1% at 36 months of treatment. The mean increase in total hip BMD was 1.6%–3.6% at 12 months, 3.4%–5.1% at 24 months, and 5.2%–6.7% at 36 months.[31] The mean increase in distal radius BMD was 1.1%–1.3% at 12 months[13,32] and 0.3%–1.4% at 24 months, compared with a 2.1% reduction in the placebo group.[30,33] These increases are significantly greater when compared directly with those achieved with alendronate[13] and at least similar when compared indirectly with those achieved with other bisphosphonates.[28]

The extension of the FREEDOM trial is currently ongoing in an open-label design for an additional 7 years, for a total of 10 years, aiming to evaluate the long-term efficacy and safety of denosumab. Data from the first 2 years of the extension trial were recently published.[30] According to these data,

Table 1 Studies of denosumab in postmenopausal women with low bone mass

Study	Duration	Extent of bone disease	Total study size (plc) [60 mg/6 months]	Results	
				Fractures	% BMD [% change versus plc]
McClung et al[32]	12 months	Osteopenia or osteoporosis (T-score < –1.8)	412 (46) [47]	No difference in the sum of denosumab groups compared with plc (3.8% versus 2.2%)*	LS: 4.6 [5.4] Hip: 3.6 [4.2]
Lewiecki et al[84] (one-year extension of study by McClung et al)	24 months	Osteopenia or osteoporosis (T-score < –1.8)	412 (46) [47]	Increased clinical (6.7% versus 2.2%) and osteoporotic (3.8% versus 0.0%) fractures in the sum of denosumab groups compared with plc*	LS: 7.4 [8.6] Hip: 5.1 [NR]
Miller et al[85] (2-year extension of study by Lewiecki et al)	48 months	Osteopenia or osteoporosis (T-score < –1.8)	412 (46) [231]	No difference in clinical (10.5% versus 10.9%) and osteoporotic (7.0% versus 8.7%) fractures compared with plc*	LS: 9.4 –11.8 [11.8–14.2] Hip: 4.0–6.1 [7.5–9.6] Distal radius: 1.0–1.7 [5.7–6.4]
Miller et al[14] (2-year extension of study by Miller et al in 2008)	72 months	Osteopenia or osteoporosis (T-score < –1.8)	124 [124]	4.5% (no plc group for comparison)*	LS: 13.3 Hip: 6.1 Distal radius: 1.9
Bone et al[33]	24 months	Osteopenia or osteoporosis	332 (166) [166]	Decreased vertebral (0% versus 0.6%) and nonvertebral (1% versus 4%) fractures compared with plc *	LS: 6.5 [7.1] Hip: 3.4 [4.5] Distal radius: 1.4 [3.5]
Cummings et al[31] (FREEDOM trial)	36 months	Osteoporosis (T-score ≤ –2.5)	7868 (3906) [3902]	New vertebral fractures: 2.3% versus 7.2% in the plc group (68% reduction, $P < 0.0001$) [at 12 months 61%, at 24 months 78% reduction] New nonvertebral fractures: 6.5% versus 8.0% in the plc group (20% reduction, $P < 0.011$) Hip fractures: 0.7% versus 1.2% in the plc group (40% reduction, $P < 0.036$)	LS: NR [9.2 (8.2–10.1)] Hip: NR [6.0 (5.2–6.7)]
Papapoulos et al[30] (2-year extension of FREEDOM trial)	60 months	Osteoporosis (T-score ≤ –2.5)	2343 [2343]	New vertebral fractures: year incidence 1.4% versus 2.2% in the virtual plc New nonvertebral fractures: year incidence 1.1% versus 2.6% in the virtual plc	LS: 13.7 Hip: 7.0 Distal radius: 2.3
Brown et al[13]	12 months	Low bone mass (T-score ≤ –2)	1189 (594) [595]	No difference in overall (4.0% versus 3.2%, $P = 0.54$) and osteoporotic (3.0% versus 2.2%, $P = 0.37$) fractures compared with alendronate*	LS: 5.3 Hip: 3.5 Distal radius: 3.1

Note: *Fractures reported as adverse events (not as endpoints of the study).
Abbreviations: plc, placebo; NR, not reported; BMD, bone mineral density (measured by dual energy X-ray absorptiometry); LS, lumbar spine; hip, total hip.

during years 4 and 5 of treatment, BMD increased further at all sites (by 1.9% and 1.6%, respectively, at the lumbar spine; by 0.8% and 0.6%, respectively, at the total hip; by 0.9% and 0.4%, respectively, at the femoral neck; and by 0.6% and −0.3%, respectively, at the distal radius).[30] The total increase in BMD over the 5 years of continuous treatment reached 13.7% in the lumbar spine, 7.0% in the total hip, 6.1% in the femoral neck, and 2.3% in the distal radius.[30]

Discontinuation of denosumab results in loss of gains in BMD; in both the Phase III[33] and Phase II[15] trials, BMD at the spine and total hip returned to pretreatment levels within 12 months of discontinuation. Surprisingly, in the Phase II trial, BMD remained below baseline for a further 12 months in those who remained off treatment, and then returned to baseline levels at month 36–48 without additional medication. In contrast, after one year of retreatment with denosumab (following 12 months of discontinuation) BMD increased again, and more rapidly than the first time, at both the spine and hip to levels comparable with those achieved after the first 24 months of treatment.[33]

In the FREEDOM trial, a significant reduction in both vertebral and nonvertebral fractures, at least equal to those achieved by bisphosphonates, was observed.[31] More specifically, a reduction by 68% for new vertebral fractures, 20% for new nonvertebral fractures, and 40% for hip fractures compared with placebo at 36 months was reported. In the 2-year extension of FREEDOM, fracture incidence rates remained low and below those observed in the core trial placebo group. They were also below the estimated fracture incidence rates of a "virtual untreated twin" cohort (twin-estimated placebo). More specifically, the annual incidence of a new vertebral fracture for years 4 and 5 of treatment was 1.4% compared with 2.2% for the twin-estimated placebo; the annual incidence of a nonvertebral fracture for years 4 and 5 of treatment was 1.4% and 1.1%, respectively, compared with 2.6% for the twin-estimated placebo.

In a recent meta-analysis, denosumab was associated with odds ratios of 0.33, 0.50, and 0.74 for vertebral, hip, and nonvertebral fractures, respectively, compared with placebo.[34] Treatment with denosumab for over 3 years was associated with a 32% decrease in clinical osteoporotic fractures.[35]

Reduction in fracture risk with denosumab has been reported to be independent of age, prior fracture, parental history of hip fracture, baseline femoral neck BMD, or secondary causes of osteoporosis,[35] and greater in those at moderate to high risk of fracture assessed by FRAX®.[35] On the other hand, in another analysis of the same study population, the reduction in the risk of nonvertebral fracture was statistically significant only in women with a baseline femoral neck BMD T-score ≤ -2.5 but not in those with a T-score > -2.5.[36,37] A low body mass index has been associated with greater efficacy of denosumab,[35,36] and this could be attributed to the lower estradiol levels observed in women with lower body mass index which result in higher bone turnover and fracture risk. Another reason could be the proportionally greater drug amount per kilogram, and therefore greater tissue exposure of subjects with lower body mass index to denosumab. However, this is unlikely, given that the pharmacokinetics of denosumab are not notably affected by body weight, as evidenced by its consistent pharmacodynamic effect across a wide range of weights.[35]

Furthermore, denosumab is effective among patients with impaired kidney function.[38] More specifically, the magnitude of fracture risk reduction and the increases in both spine and hip BMD associated with denosumab treatment seem to be unaffected by the level of kidney function, even in patients with a moderate to severe decrease in glomerular filtration rate.

In a post hoc analysis of the Phase II study of denosumab, improved mechanical properties at the proximal femur compared with placebo were observed at 12 and 24 months of denosumab treatment using hip structural analysis software to evaluate cross-sectional geometry parameters and derived strength indices.[39] Even when compared directly with alendronate, the effects of denosumab were greater at the intertrochanteric and shaft sites.[39]

Long-term safety and tolerability

Osteoporosis is a chronic condition, so safety and tissue specificity are prerequisites for any novel treatment, especially one that affects molecular signaling pathways.[40] This is the case for denosumab and it comes as no surprise that safety issues have attracted particular attention early in the development of the drug.[5,28]

The safety profile of denosumab can largely be summarized as a putatively increased serious infection risk (those that require hospitalization), nonspecific dermatologic reactions and hypocalcemia, all of which, among others, are detailed in the summary of product characteristics for Prolia®.[18] Herein, the safety concerns for denosumab will be classified into two groups on a pathophysiologic basis, ie, those related to suboptimal tissue specificity (otherwise, unsatisfactory selectivity of effect on bone) and refer to concerns about increased risk of serious infections, cancers (including breast), eczema and nondermatologic reactions, and vascular calcifications, and those related to an "exaggerated" effect on bone tissue,

namely oversuppression of bone remodeling, hypocalcemia, decreased or delayed fracture healing, and osteonecrosis of the jaw (Table 2). Of note, many of the safety issues listed above remain hypothetical and, thus, caution and an evidence-based approach are essential.

To begin with, RANKL and RANK are expressed in cells of the immune system, including activated T lymphocytes, B cells, and dendritic cells,[41,42] and RANK activation by RANKL is also essential for the growth of T cells and function of dendritic cells,[3,43] and is considered to play a key role in the development of lymph nodes. RANKL also enhances the survival of dendritic cells and antigen presentation, implying that inhibition of RANKL by denosumab might alter immune function or even cause susceptibility to infections.[44] Despite ample preclinical (in vitro and in vivo in rodents and monkeys) evidence of such an effect, it appears that RANKL pathway might have a secondary role within the immune system in humans,[45] potentially through an effect on the intensity of the inflammatory response.[46] Corroborating evidence in support of a modest effect on the immune system in humans may be found in osteoclast-poor osteopetrosis due to absence of RANKL, in which individuals did not show any obvious defects in immunologic parameters[47] and in a Phase I trial of denosumab, in which no significant changes in B or T cells and lymphocyte counts were noted.[11] Using best available evidence from a meta-analysis of randomized, placebo-controlled trials, including the large FREEDOM registration trial, it has been suggested that denosumab was associated with a borderline increased risk of serious infections (risk ratio 1.25, 95% confidence interval 1.00–1.54) in women with postmenopausal osteoporosis when intention-to-treat analysis was used,[48] and with a nonsignificant risk ratio of 2.1 when per protocol analysis was used.[49]

Table 2 Safety concerns in postmenopausal women with osteoporosis treated with denosumab

Suboptimal tissue specificity		**Bone turnover oversuppression**	
SIR	**Rare**	**Hypocalcemia**	**Rare**
Infections:		ONJ*	Very rare
Urinary, upper respiratory,	Uncommon		
gastrointestinal tract, ear	Rare		
Rashes/dermatitis	Uncommon	Delayed fracture	Controversial
Eczema	Rare	healing	
Cataracts	Uncommon	"Frozen bone"	Controversial
Hypercholesterolemia	Uncommon	Atypical fragility	Controversial
Vascular calcifications	Controversial		
Malignancies	Controversial		

Notes: Classification was based on the following conventions: common (>10%), uncommon (1%–10%), rare (0.1%–1%), very rare (<0.1%) and controversial based on one-year event rates. *Etiopathogenesis not fully elucidated yet and thus classification is conventional.

Abbreviations: SIR, serious infection risk, requiring hospitalization or resulting in death, (erysipelas, cellulitis); ONJ, osteonecrosis of the jaw.

In a recent post hoc analysis of serious infection risk using data from the FREEDOM trial, it was suggested that serious adverse events of infections, namely referring to the skin infections of erysipelas and cellulitis, events of diverticulitis and other gastrointestinal tract, ear, renal and urinary infections, and endocarditis, were numerically higher in the denosumab group compared with the placebo group, yet the number of events was small. Moreover, no relationship was observed between serious adverse events of infections and timing of administration or duration of exposure to denosumab,[46] which may be interpreted as indirect evidence against a causal relationship. Finally, the two-year extension results from the FREEDOM trial (five years of denosumab administration in total for the denosumab group and a cross-over group with two years of denosumab exposure) indicated that infectious events did not increase nor decrease with long-term administration of denosumab.

Suboptimal tissue specificity may also raise concerns for cancer. In fact, osteoprotegerin binding to TRAIL, which is a survival factor for tumor cells, may interfere with a natural defense mechanism against tumorigenesis.[50,51] However, although mimicking the effect of osteoprotegerin in human RANKL, denosumab does not bind to human TRAIL. Notably, expression of RANKL and RANK has been shown in mammary cells, along with reduction in tumorigenesis upon RANKL inhibition.[52] In randomized, placebo-controlled trials comparing denosumab with placebo, numerically more cases of neoplasms, including those of the breast, ovary and gastrointestinal tract, have been reported in the denosumab group compared with placebo by McClung et al[32] (1.9% versus 0%), Bone et al[33] (2.4% versus 0.6%), and in the FREEDOM trial[31] (4.8% versus 4.2%). However, meta-analyses of randomized, placebo-controlled trials failed to detect a statistically significant difference.[28,49] Data from the extension of FREEDOM are also reassuring so far.[30] Long-term use of denosumab in a large post-marketing base would clarify this putative risk.

Suboptimal tissue specificity may also be the case for eczema and allergic skin reactions, including dermatitis and rashes. RANKL is expressed in keratinocytes of inflamed skin[53] and Langerhans cells express RANK. Their coordination on the skin epithelium results in activation of T regulatory cells and control over contact hypersensitivity

and autoimmune response. The deranging effect of RANKL inhibition by denosumab could amplify cutaneous allergic and inflammatory responses and lead to skin hypersensitivity. In the FREEDOM trial, a small but significantly higher risk of eczema was recorded,[31] with a 10.8% combined incidence of eczema, dermatitis, and rashes. In the first 2 years of FREEDOM extension, rates of skin-related events were similar to or lower than those in the denosumab group during the core trial.[30]

More controversial than the latter issue of tissue specificity is the effect of denosumab on vascular calcification. It is an issue of significant concern, because abdominal aortic calcification detected on lateral spine images from a bone densitometer was found to predict incident myocardial infarction and stroke in older women.[54] In preclinical models, it was reported that doses of osteoprotegerin that inhibit bone resorption can potently inhibit calcification of arteries induced by warfarin or vitamin D treatment[55] and that RANKL inhibition by denosumab reduced vascular calcium deposition in glucocorticoid-induced osteoporosis.[56] In humans, serum osteoprotegerin levels were found to be associated with the presence and severity of coronary artery disease, suggesting that osteoprotegerin may be involved in the progression of coronary artery disease,[57,58] cardiovascular mortality,[59] and the onset of cardiovascular disease,[60] findings not confirmed in a study of patients with peripheral artery disease.[61] Of note, hypercholesterolemia, a well established risk factor for atherosclerosis and vascular calcification, was reported as an adverse event in 7.2% of patients on denosumab in the FREEDOM trial. Unfortunately, pharmacologic manipulation of osteoprotegerin levels by denosumab in humans has not been extensively investigated and no evidence regarding this effect on vascular calcification has been published to date.

As previously specified, the second class of safety concerns largely results from an exaggerated effect of denosumab on bone remodeling. Denosumab is a potent antiosteoclastic agent, as documented by the rapid and persistent suppression of bone markers after its subcutaneous administration at low and even undetectable levels. Hypocalcemia was reported as an adverse event in 1.7% of the denosumab group in the FREEDOM trial, and more women were reported to have a calcium concentration below 8.5 mg/dL compared with the placebo arm at the one-month assessment (1.7% versus 0.4%),[31] reflecting the acute effect of denosumab on osteoclast functionality. It is worth stating that patients with impaired renal function were at an increased risk for this effect. Aside from the acute effects, oversuppression of bone turnover, in proportion to that reported with potent bisphosphonates,[2,62] might lead to diminished repair and microdamage accumulation due to "frozen bone" and potentially to an increased risk of atypical fragility and/or osteonecrosis of the jaw, a condition that has never been reported to be associated with other pharmaceutical agents, except for bisphosphonates.[63] No cases of atypical fractures have been reported in the trials after continuous administration of denosumab for up to 5 years.[30] On the other hand, although extremely rare, the potential risk of osteonecrosis of the jaw is a major concern in patients treated with denosumab.[64,65] Apart from several reports of denosumab-related osteonecrosis of the jaw in the literature, a pooled analysis in cancer patients with bone metastases quantified denosumab-related osteonecrosis of the jaw with a similar incidence (1.5%) to that of zoledronic acid[66] and calculated the number needed-to-harm at approximately 70. In the recent FREEDOM extension trial, two patients with osteoporosis from the crossover group (0.09%) but none from the long-term denosumab group have been reported as cases of osteonecrosis of the jaw.[30] Interestingly, these cases were not cancer patients and were treated with denosumab for less than two years. Overall, it appears that the attributable risk is extremely low, at least for patients with osteoporosis. It is worth stating that the pathogenesis of osteonecrosis of the jaw is not straightforward, and several hypotheses, implicating also a role of macrophages,[67] vascularity, and bacterial infection of the area have been proposed. Furthermore, denosumab discontinuation is reported to restore bone markers rapidly to pretreatment levels, while in both the FREEDOM trial[31] and its two-year extension,[30] the increases in bone markers at the end of the dosing interval appeared to increase with time in the study. Thus, osteonecrosis of the jaw cannot be classified with certainty into the "exaggerated" bone remodeling effect or "suboptimal tissue specificity" class.

This is not the case for the concern regarding the effect of denosumab on fracture healing, a concern that was raised early in the development of pharmacologic RANKL inhibition. The question concerning whether coupling and osteoclast depletion via RANK blockade would affect callus formation and maturation and matrix remodeling was tested early using RANK-Fc therapy in mice, and no adverse effects on fracture healing were observed when therapy was discontinued.[68] These findings were confirmed in a study in which RANK-Fc administration did not adversely affect the mechanical properties of healing bone in mice with osteogenesis imperfecta and was associated with increased strength in wild-type mice.[69] In osteoprotegerin-deficient mice, accelerated cartilage resorption by chondroclasts was

observed during bone fracture healing.[70] Finally, denosumab was found to delay removal of cartilage and remodeling of the fracture callus without diminishing the mechanical integrity and stiffness in male human-RANKL knock-in mice.[71] Similarly, in a subset of 199 patients with incident nonvertebral fractures from the FREEDOM trial, use of denosumab was not associated with delayed healing or with any complications following fracture surgical management.[72] To our knowledge, there are no studies on denosumab and implant fixation (ie, osseointegration) to date.

In summary, it appears that denosumab is a rather safe choice for all subgroups of patients with postmenopausal osteoporosis, with the exception of those with chronic kidney disease stage 5 and hepatic dysfunction. However, given the lack of pharmacovigilance data for this agent as yet[64,73] and its brief post-marketing presence, it would be prudent to be vigilant for issues relevant to "suboptimal tissue specificity" as well as those regarding "bone turnover oversuppression".

Place in osteoporosis treatment

As mentioned before, denosumab is an antiresorptive compound with anti-fracture efficacy at all skeletal sites and, although direct comparative studies with fracture endpoints are lacking, completed trials with established surrogates suggest an effect at least similar to that of zoledronic acid. Therefore, it could be used as first-line antiresorptive treatment in patients with severe newly diagnosed osteoporosis. However, it is likely that most patients with severe osteoporosis have already been treated with another antiresorptive agent; thus, denosumab could be considered in cases of previous antiresorptive treatment failure. Additionally, denosumab could be used as an alternative treatment option in patients with intolerance of oral bisphosphonates. Furthermore, given that osteoporosis is a chronic condition, and prolonged administration of bisphosphonates has raised concerns about rare but serious adverse events limiting their safe use at 5–10 years,[2] denosumab represents an alternative with the potential for more prolonged administration than bisphosphonates, even if they are effective and well tolerated. Finally, given that antiresorptive treatment following parathyroid hormone (teriparatide [PTH 1-34] or full-length PTH 1-84) treatment[74] preserves or further increases BMD, denosumab could be used sequential to synthetic parathyroid hormone.

The cost-effectiveness of denosumab has been evaluated by estimating the cost per quality-adjusted life-year gained. Analyses have shown that denosumab is cost-effective in postmenopausal women with low bone mass compared with no treatment[75] or treatment with oral bisphosphonates,[76] and therefore has the potential to be a first-line treatment for postmenopausal women with osteoporosis. As expected, the cost-effectiveness of denosumab is favorable, particularly in patients at high risk of fracture or with low expected adherence to oral treatments.[77]

Although both denosumab and bisphosphonates share a similar effect on bone turnover, namely interference with the osteoclast and suppression of bone resorption, there are certain characteristics that clearly separate denosumab from the bisphosphonates. First, denosumab represents a distinct class of antiresorptives because it inhibits osteoclast maturation in the early stages of development and osteoclast activity, rather than impairing viability of osteoclasts. Second, it is not incorporated into bone mineral. Therefore, the mode of action of denosumab is mainly characterized by reversibility of its effect after cessation of treatment, in contrast with bisphosphonates which can exert an antifracture effect for several years after their discontinuation.[78] This could be regarded as a disadvantage in terms of rapid BMD reduction and putative fracture risk increase after discontinuation of denosumab, rendering a drug holiday prohibitive; on the other hand, the same characteristic could be an asset in patients at risk for bone turnover oversuppression and its consequences (atypical fractures, osteonecrosis of the jaw) due to long-term antiresorptive treatment. Third, denosumab is metabolized via the reticuloendothelial system and not through the kidneys. Thus, no adjustment is required in subjects with renal impairment, although there is a greater risk of hypocalcemia among patients with severe renal insufficiency (creatinine clearance <30 mL/minute) and those on hemodialysis. Therefore, in patients with severe kidney dysfunction, particular attention should be paid to ensuring that patients are calcium-replete and vitamin D-replete prior to treatment initiation and supplementing with calcium and vitamin D during treatment. In addition, patients with severe kidney disease may also have metabolic bone diseases that mimic osteoporosis clinically but be other forms of renal bone disease (renal osteodystrophy), where a different management strategy may be required. Finally, gastrointestinal side effects, one of the most common causes for poor compliance with oral bisphosphonates, are lacking with denosumab.[79]

A practical advantage of denosumab over current therapies is its convenient biannual administration. Thus, denosumab has a likelihood of long-term adherence similar to that of the intravenous bisphosphonates.

Because of the risk of decreased concentrations of serum calcium, denosumab is contraindicated in patients with hypocalcemia.[19] Therefore, careful monitoring is required

in patients at high risk of hypocalcemia, such as those with hypoparathyroidism (primary or post-surgical) or malabsorption syndromes. Prior to starting denosumab, patients with hypocalcemia must have their calcium levels corrected because they could severely worsen with denosumab, particularly in case of concomitant renal impairment.

Comprehensive assessment of the immune status of patients on denosumab (white cell count, and T cell, B cell, and natural killer cell numbers)[80] as well as comparison of patients versus controls regarding infections in the FREEDOM study revealed no alarming side effects of denosumab. With both the reported increased risk of infections requiring hospitalization[32] and biologic plausibility (inhibition of RANKL, RANKL in B and T cell differentiation, and RANKL involvement in dendritic cell survival), patients on concurrent immunosuppressive agents, with pre-existing immunosuppression, or who developed severe infection during therapy should undergo a complete evaluation of the benefits and risks of treatment prior to use of denosumab.[19] There are currently no reports of denosumab interfering with the metabolism of other compounds. However, it is wiser to avoid the concurrent use of immunosuppressants and immune modulators due to the possible increased risk of infection.

In addition, and in order to minimize further the already low risk of osteonecrosis of the jaw, patients scheduled to undergo invasive dental procedures, those with poor oral hygiene, those with malignancy and/or other additional systemic (glucocorticoids, chemotherapy) or local (radiation, dental diseases) risk factors should either avoid or postpone administration of denosumab.[19,81] In these patients, a comprehensive dental examination is mandatory prior to consideration of denosumab.

In conclusion, denosumab is a novel treatment option which can help the clinician to choose the right therapy for each osteoporotic patient. Although there are no established protocols by which to choose a particular drug, decisions regarding the onset, type, and duration of treatment are currently based on the need to reduce fracture risk. According to this approach and based on the properties of denosumab and its mode of action, it can be considered in: patients at high risk of fractures, particularly of the hip; patients who cannot tolerate oral bisphosphonates and are not willing to receive intravenous bisphosphonates; patients who do not want or are unable to follow complex dosing regimens; patients with renal insufficiency; and nursing home patients.[82] However, denosumab can also be involved in sequential treatment plans of other patients based on the fact that pharmacologic treatment should not be static and must change over the patient's lifetime to adapt the clinical and metabolic needs of each time period.[83] In all cases, the clinician should keep in mind the reversibility of the effect of denosumab following discontinuation of treatment and act accordingly.

Conclusion

Osteoporosis is a major growing public health issue and represents the most common bone disease in humans. With the variety of antiosteoporotic compounds available as well as multiple novel therapies in advanced clinical trials, the trend of the therapeutic approach is towards individualized treatment. The properties of the ideal osteoporosis treatment include: antifracture efficacy at various skeletal sites, including the spine, nonvertebral sites, and hip; a high skeletal and extraskeletal safety margin; mode of administration and treatment interval compatible with patient adherence; compatibility with concomitant treatment for other medical conditions; and affordable cost.[81] Because denosumab seems to meet the above criteria to a satisfactory degree, it could be considered both as an effective alternative to previous bisphosphonate treatment as well as first-line treatment of newly diagnosed osteoporosis. Furthermore, it seems to be the treatment of choice in patients with some degree of kidney dysfunction.

The mode of action of denosumab is characterized by reversibility of its effect after treatment discontinuation, in contrast with bisphosphonates which are retained in the bone and exert a long-term antifracture effect.[78] This could be a disadvantage, rendering a denosumab holiday prohibitive; on the other hand, it could be an advantage in patients at risk for oversuppression of bone turnover.

It appears that denosumab is reasonably safe for all subgroups of patients with postmenopausal osteoporosis, with the exception of those with hepatic or stage 5 renal insufficiency. However, given the lack of pharmacovigilance data for this agent as yet and its brief post-marketing period, it would be prudent to be vigilant for adverse events related to the putative effect of RANKL inhibition in tissues other than bone, as well as those related to bone turnover oversuppression.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Ahlborg HG, Rosengren BE, Järvinen TL, et al. Prevalence of osteoporosis and incidence of hip fracture in women – secular trends over 30 years. *BMC Musculoskelet Disord*. 2010;11:48.
2. Watts NB, Diab DL. Long-term use of bisphosphonates in osteoporosis. *J Clin Endocrinol Metab*. 2010;95(4):1555–1565.

3. Kong YY, Yoshida H, Sarosi I, et al. OPGL is a key regulator of osteoclastogenesis, lymphocyte development and lymph-node organogenesis. *Nature*. 1999;397(6717):315–323.
4. Simonet WS, Lacey DL, Dunstan CR, et al. Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. *Cell*. 1997; 89(2):309–319.
5. Anastasilakis AD, Toulis KA, Polyzos SA, Terpos E. RANKL inhibition for the management of patients with benign metabolic bone disorders. *Expert Opin Investig Drugs*. 2009;18(8):1085–1102.
6. Kostenuik PJ. Osteoprotegerin and RANKL regulate bone resorption, density, geometry and strength. *Curr Opin Pharmacol*. 2005;5: 618–625.
7. Bekker PJ, Holloway D, Nakanishi A, Arrighi M, Leese PT, Dunstan CR. The effect of a single dose of osteoprotegerin in postmenopausal women. *J Bone Miner Res*. 2001;16(2):348–360.
8. Body JJ, Greipp P, Coleman RE, et al. A Phase I study of AMGN-0007, a recombinant osteoprotegerin construct, in patients with multiple myeloma or breast carcinoma related bone metastases. *Cancer*. 2003;97(Suppl 3):887–892.
9. Morony S, Lu J, Capparelli C, Dunstan CR, Lacey DL, Kostenuik PJ. Osteoprotegerin (OPG) prevents bone loss in a rat model of glucocorticoid-induced osteopenia. *J Bone Miner Res*. 2001;16: S148.
10. Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. *Nature*. 2003;423(6937):337–342.
11. Bekker P, Holloway D, Rasmussen A, 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(7): 1059–1066.
12. Kearns AE, Khosla S, Kostenuik PJ. Receptor activator of nuclear factor kappaB ligand and osteoprotegerin regulation of bone remodeling in health and disease. *Endocr Rev*. 2008;29(2):155–192.
13. 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(1):153–161.
14. Miller PD, Wagman RB, Peacock M, et al. Effect of denosumab on bone mineral density and biochemical markers of bone turnover: six-year results of a phase 2 clinical trial. *J Clin Endocrinol Metab*. 2011;96(2):394–402.
15. 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;96:972–980.
16. Boonen S, Ferrari S, Miller PD, et al. Postmenopausal osteoporosis treatment with antiresorptives: effects of discontinuation or long-term continuation on bone turnover and fracture risk-a perspective. *J Bone Miner Res*. 2012;27(5):963–974.
17. Sutjandra L, Rodriguez RD, Doshi S, et al. Population pharmacokinetic meta-analysis of denosumab in healthy subjects and postmenopausal women with osteopenia or osteoporosis. *Clin Pharmacokinet*. 2011; 50(12):793–807.
18. Amgen Inc. Prolia (denosumab) package insert. Thousand Oaks, CA: Amgen Inc; 2010.
19. Bridgeman MB, Pathak R. Denosumab for the reduction of bone loss in postmenopausal osteoporosis: a review. *Clin Ther*. 2011;33(11): 1547–1559.
20. Body JJ, Facon T, Coleman RE, et al. A study of the biological receptor activator of nuclear factor K-B ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastasis from breast cancer. *Clin Cancer Res*. 2006;12:1221–1228.
21. Rodriguez RD, Sutjandra L, Peterson MC, Jang GR, Perez Ruixo J. Population pharmacokinetic meta-analysis of denosumab in healthy and cancer subjects and postmenopausal women with osteopenia or osteoporosis. *AAPS J*. 2009;11:S1.
22. Lobo ED, Hansen RJ, Balthasar JP. Antibody pharmacokinetics and pharmacodynamics. *J Pharm Sci*. 2004;93(11):2645–2668.
23. Lewiecki EM. Denosumab – an emerging treatment for postmenopausal osteoporosis. *Expert Opin Biol Ther*. 2010;10(3):467–476.
24. Wang J, Lee J, Burns D, et al. "Fit-for-purpose" method validation and application of a biomarker (C-terminal telopeptides of type 1 collagen) in denosumab clinical studies. *AAPS J*. 2009;11(2):385–394.
25. Kostenuik PJ, Nguyen HQ, McCabe J, et al. Denosumab, a fully human monoclonal antibody to RANKL, inhibits bone resorption and increases BMD in knock-in mice that express chimeric (murine/human) RANKL. *J Bone Miner Res*. 2009;24:182–195.
26. Ominsky MS, Schroeder J, Smith SY, Farrell DJ, Atkinson JE, Kostenuik PJ. Denosumab (AMG 162), a fully human RANKL antibody, improves cortical and cancellous bone mass and bone strength in ovariectomized cynomolgus monkeys. *J Bone Miner Res*. 2007;22:S23.
27. Ominsky MS, Schroeder J, Smith SY, Farrell JP, Kostenuik PJ, Atkinson JE. Denosumab (AMG 162, a fully human RANKL antibody) increases cortical and cancellous bone mass in aged ovariectomized cynomolgus monkeys. *J Bone Miner Res*. 2006;21:S72.
28. Anastasilakis AD, Toulis KA, Goulis DG, et al. Efficacy and safety of denosumab in postmenopausal women with osteopenia or osteoporosis: a systematic review and a meta-analysis. *Horm Metab Res*. 2009; 41(10):721–729.
29. Eastell R, Christiansen C, Grauer A, et al. Effects of denosumab on bone turnover markers in postmenopausal osteoporosis. *J Bone Miner Res*. 2011;26(3):530–537.
30. 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(3):694–701.
31. 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(8):756–765.
32. McClung M, Lewiecki E, Cohen S, et al. Denosumab in postmenopausal women with low bone mineral density. *N Engl J Med*. 2006;354(8): 821–831.
33. Bone H, Bolognese M, Yuen C, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women. *J Clin Endocrinol Metab*. 2008;93(6):2149–2157.
34. Murad MH, Drake MT, Mullan RJ, et al. Comparative effectiveness of drug treatments to prevent fragility fractures: a systematic review and network meta-analysis. *J Clin Endocrinol Metab*. March 30, 2012. [Epub ahead of print.]
35. McCloskey EV, Johansson H, Oden A, et al. Denosumab reduces the risk of osteoporotic fractures in postmenopausal women, particularly in those with moderate to high fracture risk as assessed with FRAX®. *J Bone Miner Res*. March 10, 2012. [Epub ahead of print.]
36. McClung M, Boonen S, Törring O, et al. Effect of denosumab treatment on the risk of fractures in subgroups of women with postmenopausal osteoporosis. *J Bone Miner Res*. October 4, 2011. [Epub ahead of print.]
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(6): 1727–1736.
38. 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(8):1829–1835.
39. Beck TJ, Lewiecki EM, Miller PD, et al. Effects of denosumab on the geometry of the proximal femur in postmenopausal women in comparison with alendronate. *J Clin Densitom*. 2008;11(3):351–359.
40. Toulis KA, Anastasilakis AD, Polyzos SA, Makras P. Targeting the osteoblast: approved and experimental anabolic agents for the treatment of osteoporosis. *Hormones (Athens)*. 2011;10:174–195.
41. Anderson DM, Maraskovsky E, Billingsley WL, et al. A homologue of the TNF receptor and its ligand enhance T-cell growth and dendritic-cell function. *Nature*. 1997;390(6656):175–179.
42. Bachmann MF, Wong BR, Josien R, Steinman RM, Oxenius A, Choi Y. TRANCE, a tumor necrosis factor family member critical for CD40 ligand-independent T helper cell activation. *J Exp Med*. 1999;189(7): 1025–1031.

43. Wong B, Josien R, Lee SY, et al. TRANCE (tumor necrosis factor [TNF]-related activation induced cytokine), a new TNF family member predominantly expressed in T cells, is a dendritic cell-specific survival factor. *J Exp Med*. 1997;186(12):2075–2080.
44. Schwartzman J, Yazici Y. Denosumab in postmenopausal women with low bone mineral density. *N Engl J Med*. 2006;354(22): 2390–2391.
45. Ferrari-Lacraz S, Ferrari S. Do RANKL inhibitors (denosumab) affect inflammation and immunity? *Osteoporos Int*. 2010;22:435–446.
46. Watts NB, Roux C, Modlin JF, et al. Infections in postmenopausal women with osteoporosis treated with denosumab or placebo: coincidence or causal association? *Osteoporos Int*. 2012;23(1):327–337.
47. Sobacchi C, Frattini A, Guerrini MM, et al. Osteoclast-poor human osteopetrosis due to mutations in the gene encoding RANKL. *Nat Genet*. 2007;39(8):960–962.
48. Toulis KA, Anastasilakis AD. Increased risk of serious infections in women with osteopenia or osteoporosis treated with denosumab. *Osteoporos Int*. 2010;21(11):1963–1964.
49. von Keyserlingk C, Hopkins R, Anastasilakis A, et al. Clinical efficacy and safety of denosumab in postmenopausal women with low bone mineral density and osteoporosis: a meta-analysis. *Semin Arthritis Rheum*. 2011;41(2):178–186.
50. Emery JG, McDonnell P, Burke MB, et al. Osteoprotegerin is a receptor for the cytotoxic ligand TRAIL. *J Biol Chem*. 1998;273: 14363–14367.
51. Wiley SR, Schooley K, Smolak PJ, et al. Identification and characterization of a new member of the TNF family that induces apoptosis. *Immunity*. 1995;3(6):673–682.
52. Gonzalez-Suarez E, Jacob AP, Jones J, et al. RANK ligand mediates progestin-induced mammary epithelial proliferation and carcinogenesis. *Nature*. 2010;468(7320):103–107.
53. Loser K, Mehling A, Loeser S, et al. Epidermal RANKL controls regulatory T-cell numbers via activation of dendritic cells. *Nat Med*. 2006;12(12):1372–1379.
54. Schousboe JT, Taylor BC, Kiel DP, Ensrud KE, Wilson KE, McCloskey EV. Abdominal aortic calcification detected on lateral spine images from a bone densitometer predicts incident myocardial infarction or stroke in older women. *J Bone Miner Res*. 2008;23:409–416.
55. Price PA, June HH, Buckley JR, Williamson MK. Osteoprotegerin inhibits artery calcification induced by warfarin and by vitamin D. *Arterioscler Thromb Vasc Biol*. 2001;21(10):1610–1616.
56. Helas S, Goettsch C, Schoppet M, et al. Inhibition of receptor activator of NF-kappaB ligand by denosumab attenuates vascular calcium deposition in mice. *Am J Pathol*. 2009;175(2):473–478.
57. Jono S, Ikari Y, Shioi A, et al. Serum osteoprotegerin levels are associated with the presence and severity of coronary artery disease. *Circulation*. 2002;106(10):1192–1194.
58. Schoppet M, Sattler AM, Schaefer JR, Herzum M, Maisch B, Hofbauer LC. Increased osteoprotegerin serum levels in men with coronary artery disease. *J Clin Endocrinol Metab*. 2003;88(3):1024–1028.
59. Browner WS, Lui LY, Cummings SR. Associations of serum osteoprotegerin levels with diabetes, stroke, bone density, fractures, and mortality in elderly women. *J Clin Endocrinol Metab*. 2001;86(2): 631–637.
60. Kiechl S, Schett G, Wenning G, et al. Osteoprotegerin is a risk factor for progressive atherosclerosis and cardiovascular disease. *Circulation*. 2004;109(18):2175–2180.
61. Pennisi P, Signorelli SS, Riccobene S, et al. Low bone density and abnormal bone turnover in patients with atherosclerosis of peripheral vessels. *Osteoporos Int*. 2004;15(5):389–395.
62. Visekruna M, Wilson D, McKiernan F. Severely suppressed bone turnover and atypical skeletal fragility. *J Clin Endocrinol Metab*. 2008;93(8):2948–2952.
63. Kyrgidis A, Triaridis S, Vahtsevanos K, Antoniades K. Osteonecrosis of the jaw and bisphosphonate use in breast cancer patients. *Expert Rev Anticancer Ther*. 2009;9:1125–1134.
64. Rizzoli R, Reginster JY, Boonen S, et al. Adverse reactions and drug-drug interactions in the management of women with postmenopausal osteoporosis. *Calcif Tissue Int*. 2011;89(2):91–104.
65. Kyrgidis A, Tzellos TG, Toulis K, Antoniades K. The facial skeleton in patients with osteoporosis: a field for disease signs and treatment complications. *J Osteoporos*. 2011;16:147689.
66. Kyrgidis A, Toulis KA. Denosumab-related osteonecrosis of the jaws. *Osteoporos Int*. 2011;22(1):369–370.
67. Pazianas M. Osteonecrosis of the jaw and the role of macrophages. *J Natl Cancer Inst*. 2011;103(3):232–240.
68. Flick LM, Weaver JM, Ulrich-Vinther M, et al. Effects of receptor activator of NFkappaB (RANK) signaling blockade on fracture healing. *J Orthop Res*. 2003;21(4):676–684.
69. Delos D, Yang X, Ricciardi BF, Myers ER, Bostrom MP, Camacho NP. The effects of RANKL inhibition on fracture healing and bone strength in a mouse model of osteogenesis imperfecta. *J Orthop Res*. 2008;26(2):153–164.
70. Ota N, Takaishi H, Kosaki N, et al. Accelerated cartilage resorption by chondroclasts during bone fracture healing in osteoprotegerin-deficient mice. *Endocrinology*. 2009003B150(11):4823–4834.
71. Gerstenfeld LC, Sacks DJ, Pelis M, et al. Comparison of effects of the bisphosphonate alendronate versus the RANKL inhibitor denosumab on murine fracture healing. *J Bone Miner Res*. 2009;24(2):196–208.
72. Adami S, Adachi J, Boonen S, et al. Denosumab administration is not associated with fracture healing complications in postmenopausal women with osteoporosis: results from the FREEDOM trial. *J Bone Miner Res*. 2010;25 Suppl 1:MO0405.
73. Rizzoli R, Yasothan U, Kirkpatrick P. Denosumab. *Nat Rev Drug Discov*. 2010;9(8):591–592.
74. Rittmaster R, Bolognese M, Ettinger M, et al. Enhancement of bone mass in osteoporotic women with parathyroid hormone followed by alendronate. *J Clin Endocrinol Metab*. 2000;85(6):2129–2134.
75. Hiligsmann M, Reginster JY. Potential cost-effectiveness of denosumab for the treatment of postmenopausal osteoporotic women. *Bone*. 2010;47(1):34–40.
76. Hiligsmann M, Reginster JY. Cost effectiveness of denosumab compared with oral bisphosphonates in the treatment of post-menopausal osteoporotic women in Belgium. *Pharmacoeconomics*. 2011;29(10): 895–911.
77. Jönsson B, Ström O, Eisman JA, et al. Cost-effectiveness of denosumab for the treatment of postmenopausal osteoporosis. *Osteoporos Int*. 2011;22(3):967–982.
78. Black DM, Schwartz AV, Ensrud KE, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. *JAMA*. 2006; 296(24):2927–2938.
79. Makras P, Vaiopoulos G, Lyritis GP. 2011 guidelines for the diagnosis and treatment of osteoporosis in Greece. *J Musculoskelet Neuronal Interact*. 2012;12(1):38–42.
80. Stolina M, Kostenuik PJ, Dougall WC, Fitzpatrick LA, Zack DJ. RANKL inhibition: from mice to men (and women). *Adv Exp Med Biol*. 2007;602:143–150.
81. Rachner TD, Khosla S, Hofbauer LC. Osteoporosis: now and the future. *Lancet*. 2011;377(9773):1276–1287.
82. Silverman S, Christiansen C. Individualizing osteoporosis therapy. *Osteoporos Int*. 2012;23(3):797–809.
83. Palacios S. Bazedoxifene acetate for the management of postmenopausal osteoporosis. *Drugs Today (Barc)*. 2011;47(3):187–195.
84. Lewiecki EM, Miller PD, McClung MR, et al. Two-year treatment with denosumab (AMG 162) in a randomized phase 2 study of postmenopausal women with low BMD. *J Bone Miner Res*. 2007;22(12): 1832–1841.
85. 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(2): 222–229.

Therapeutics and Clinical Risk Management

Dovepress

Publish your work in this journal

Therapeutics and Clinical Risk Management is an international, peer-reviewed journal of clinical therapeutics and risk management, focusing on concise rapid reporting of clinical studies in all therapeutic areas, outcomes, safety, and programs for the effective, safe, and sustained use of medicines. This journal is indexed on PubMed Central, CAS, EMBase, Scopus and the Elsevier Bibliographic databases. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: http://www.dovepress.com/therapeutics-and-clinical-risk-management-journal