

Safety and tolerability of denosumab for the treatment of postmenopausal osteoporosis

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Abstract: Denosumab is a fully human monoclonal antibody to receptor activator of nuclear factor kappa-B ligand (RANKL), a cytokine member of the tumor necrosis factor family that is the principal regulator of osteoclastic bone resorption. Postmenopausal osteoporosis (PMO) is a systemic skeletal disease associated with high levels of RANKL, resulting in a high rate of bone remodeling and an imbalance of bone resorption over bone formation. By inhibiting RANKL in women with PMO, denosumab reduces the rate of bone remodeling, thereby increasing bone mineral density, improving bone strength, and reducing the risk of fractures. In clinical trials of women with osteoporosis and low bone mineral density, denosumab has been well tolerated, with overall rates of adverse events and serious adverse events in women treated with denosumab similar to those receiving placebo. In the largest clinical trial of denosumab for the treatment of women with PMO, there was a significantly greater incidence of cellulitis reported as a serious adverse event, with no difference in the overall incidence of cellulitis, and a significantly lower incidence of the serious adverse event of concussions with denosumab compared with placebo. The evidence supports a favorable balance of benefits versus risks of denosumab for the treatment of PMO. Assessments of the long-term safety of denosumab are ongoing. Denosumab 60 mg subcutaneously every 6 months is an approved treatment for women with PMO who are at high risk for fracture.

Keywords: denosumab, osteoporosis, safety, risk, benefit, FDA

Introduction

Osteoporosis is a skeletal disease characterized by low bone mineral density (BMD) and poor bone quality that reduces bone strength and increases the risk of fractures.¹ It is a major public health concern, with more than 200 million men and women reported to have osteoporosis worldwide,² including about 75 million individuals in Europe, Japan, and the USA.³ Approximately one-third of postmenopausal women in Europe and the USA have osteoporosis, with about 40% of them expected to have at least one fragility fracture during their remaining lifetimes.⁴ Any fracture may be painful and disabling. Hip fractures and vertebral fractures are associated with an increased risk of death.^{5,6}

Osteoporosis is diagnosed by measuring BMD with dual-energy X-ray absorptiometry. In patients with osteoporosis, many pharmacological agents, including the bisphosphonates (eg, alendronate, risedronate, ibandronate, zoledronic acid), raloxifene, salmon calcitonin, strontium ranelate, teriparatide, parathyroid hormone (PTH) 1–84, and denosumab have been shown to reduce fracture risk with generally favorable safety profiles, with other compounds for the treatment of osteoporosis

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being investigated.⁷ There is accumulating evidence that by preventing fractures, particularly fractures of the hip, drug therapy can lower mortality rates.^{8–11} However, despite these advances, the care of osteoporosis in clinical practice has been disappointing. Osteoporosis is underdiagnosed¹² and undertreated;¹³ when treatment is prescribed, compliance and persistence (collectively called adherence) is often poor,¹⁴ resulting in higher fracture risk¹⁵ and greater health care costs than in patients with good adherence.¹⁴ While many factors have been associated with poor adherence to osteoporosis therapy, side-effects, fear of side-effects, and poor understanding of the balance between the expected benefits and potential risks of therapy are important considerations.¹⁶ More effective risk communication and shared decision making offer the potential of improving clinical outcomes by enhancing patient understanding of the balance of benefits and risks and improving adherence to therapy.^{17,18}

Denosumab (Prolia[®], Amgen Inc, Thousand Oaks, CA) is a compound with a novel mechanism of action that is approved for the treatment of postmenopausal women with osteoporosis at high risk for fracture, treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer, and treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer. It is administered by a health care professional as a 60 mg subcutaneous (SC) injection every 6 months (Q6M). The same drug, used with a higher dose (120 mg) and shorter interval between doses (every 4 weeks [Q4W]), is approved as Xgeva[™] (Amgen Inc) for the prevention of skeletal-related events in patients with bone metastases from solid tumors.

This review focuses on the safety and tolerability of denosumab in treating women with postmenopausal osteoporosis (PMO).

Methodology

Randomized controlled clinical trials of denosumab were selected from a PubMed search for matches with “denosumab.” US regulations on safety reporting in clinical trials and safety reports for denosumab were obtained from the website of the US Food and Drug Administration (FDA). Additional information on denosumab safety was selected from abstracts and oral presentations at recent scientific congresses.

Bone remodeling

The pathophysiology of PMO and the mechanism of action of the drugs used to treat osteoporosis, including denosumab,

involve alterations of bone remodeling. The adult skeleton undergoes a lifelong process of resorption and formation in numerous localized areas called “bone multicellular units” (BMUs), with each BMU having an estimated volume of about 0.025 mm³ and a lifespan of about 6–9 months, resulting in a turnover of approximately 10% of the entire skeleton each year.¹⁹ BMUs can be identified microscopically as tiny pits on the surface of trabecular bone (the type of bone in the interior of vertebral bodies and inside the ends of long bones) and tunnels (Haversian systems) in cortical bone, the exterior envelope around all bones. Bone remodeling may be “targeted” at repairing areas of microdamage that occur from normal physical activities as well as with severe repetitive microtrauma, or may be “nontargeted” when it occurs at apparently random locations on bone to maintain mineral homeostasis, keeping extracellular calcium levels within a very narrow range.²⁰ In healthy premenopausal women, there is a low rate of remodeling and an even balance between bone resorption and formation. With declining estrogen levels in perimenopausal and postmenopausal women, the remodeling rate is accelerated and unbalanced, with bone resorption being greater than formation. As a consequence, there is a degradation of microarchitectural elements that may eventually result in measurable bone loss, increased skeletal fragility, and high fracture risk.

The cells involved in the highly coordinated process of bone remodeling are osteoclasts (bone resorbing cells), osteoblasts (bone forming cells), and osteocytes (mechanosensory cells). Receptor activator of nuclear factor kappa-B ligand (RANKL), a member of the tumor necrosis family of proteins that is expressed by cells of the osteoblast lineage, has been identified as the principal regulator of osteoclastic bone resorption.²¹ When RANKL binds to its receptor, RANK, on the cell membrane of osteoclasts and preosteoclasts,²² it stimulates their formation, activity, and survival, thereby increasing the rate of bone resorption.²³ Osteoprotegerin (OPG), also expressed by osteoblasts, is a counter-regulatory nonsignaling “decoy receptor” for RANKL. The binding of RANKL to OPG reduces the amount of RANKL available for binding to RANK, resulting in a decrease in osteoclast formation, activity, and survival. The balance between RANKL and OPG is thought to be a major determinant of the rate of bone resorption, with an abundance of RANKL favoring more bone resorption and, conversely, an abundance of OPG favoring less bone resorption. The decline of estrogen in postmenopausal women leads to an excess of RANKL over OPG²⁴ and an increase in bone resorption. The discovery that high levels of RANKL were

associated with increased bone resorption and bone loss suggested that inhibition of RANKL might be an effective treatment for osteoporosis and other skeletal diseases characterized by high bone turnover.

Early studies of RANKL inhibition

In vitro studies have shown that recombinant OPG inhibits osteoclast differentiation in a dose-dependent manner.²⁵ Recombinant OPG prevents bone loss in ovariectomized rats²⁵ and causes nonlethal osteopetrosis in normal mice.²⁵ In young male rats, RANKL inhibition increases bone mineralization and improves mechanical strength in the femur.²⁶ These preclinical studies and others with similar findings paved the way for the study of RANKL inhibition in humans.

The first clinical trial of RANKL inhibition was a Phase I randomized, double-blind, placebo-controlled, sequential dose-escalation study of OPG-Fc, a fusion molecule of recombinant OPG with the Fc fragment of immunoglobulin G, in 52 healthy postmenopausal women.²⁷ Administration of a single SC dose of OPG-Fc resulted in a rapid, reversible, and dose-dependent suppression of bone resorption, and was not associated with serious adverse events or identification of neutralizing antibodies. The results of this study led to further clinical investigation of RANKL inhibition with denosumab, a fully human monoclonal antibody to RANKL that acts similarly to OPG-Fc, with the additional advantages of having greater antiresorptive potency, a longer duration of action, and avoidance of the potential risk of an OPG molecule generating anti-OPG antibodies that might cross-react with endogenous OPG.

Pharmacodynamics and pharmacokinetics of denosumab

Bone turnover markers (BTMs) such as N-telopeptide (NTX) and C-telopeptide, markers of bone resorption, and bone-specific alkaline phosphatase (BSAP), a marker of bone formation, have been used to assess the effect of denosumab on the rate of bone turnover. Changes in NTX and BSAP were measured in a Phase I randomized, placebo-controlled, double-blind, single-dose, dose-escalation study of SC denosumab (0.01 to 3.0 mg/kg) in 49 healthy postmenopausal women followed for up to 9 months. Treatment with denosumab was followed by a rapid (within 12 hours of dosing) dose-dependent decrease in urinary NTX, with a maximum decrease of 84% at 3 months and a rise in NTX levels at the end of the observational period.²⁸ Decreases in BSAP occurred later and were less pronounced than NTX.

In the same study, the pharmacokinetics of denosumab was nonlinear with dose, as reported with other fully human monoclonal antibodies. Serum profiles were characterized by three phases: (1) a prolonged absorption phase with maximum serum concentration (C_{max}) observed 5–21 days postdose, with the C_{max} increasing as dose increased; (2) a prolonged β -phase, with serum half-life as long as 32 days with the maximum dose; and (3) a rapid terminal phase with serum concentration dropping below 1000 ng/ml.

Efficacy of denosumab

The rapid, profound, sustained, and reversible decrease of NTX in the Phase I study of denosumab²⁸ supported further investigation of the efficacy and safety of this antiresorptive compound as a potential treatment for osteoporosis. A Phase II randomized, placebo-controlled, dose-ranging study evaluated the effects of denosumab in postmenopausal women with low BMD, defined as a lumbar spine T-score of -1.8 to -4.0 or total hip or femoral neck T-score of -1.8 to -3.5 , with an initial enrollment of 412 subjects. The findings of this study have been reported for the time points of 1 year,²⁹ 2 years,³⁰ 4 years,³¹ 6 years,³² and 8 years.³³ Subjects received either denosumab 6, 14, or 30 mg every 3 months; 14, 60, 100, or 210 mg Q6M, open-label oral alendronate 70 mg once weekly; or placebo for the first 24 months of study. The primary endpoint was change in lumbar spine BMD compared with baseline at 12 months. It was found that lumbar spine BMD increased significantly at 12 months by 3.0%–6.7% with SC denosumab doses of 6, 14, or 30 mg every 3 months or 14, 60, 100, or 210 mg Q6M, with smaller but significant increases at other measured skeletal sites, including total hip and one-third radius ($P < 0.001$ for all).²⁹ BTMs decreased in a dose-dependent manner. Continuous treatment in 80 subjects who received denosumab for 8 years, with a dose of 60 Q6M (the dose that was later approved for osteoporosis treatment) after 24 months, was associated with progressive gains in BMD: a mean increase of 16.8% at the lumbar spine and 6.9% at the total hip compared with baseline.³³ Reductions in C-telopeptide and BSAP levels were sustained for the entire time of treatment.

The Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 Months (FREEDOM) trial was an international 3-year, randomized, double-blind, placebo-controlled Phase III study in 7868 women with PMO. This was the pivotal fracture trial to determine the efficacy of denosumab in reducing fracture risk. Subjects were randomized to receive SC denosumab 60 mg ($n = 3902$) or placebo ($n = 3906$) Q6M.³⁴ The primary efficacy endpoint

was new vertebral fractures at 36 months, with secondary endpoints that included time to first hip fracture and non-vertebral fractures. Baseline T-score at the lumbar spine or total hip ranged from less than -2.5 to greater than or equal to -4.0 . Approximately 23% of subjects had at least one baseline prevalent vertebral fracture. Subjects were excluded from participation for any severe prevalent vertebral fracture or more than two moderate prevalent vertebral fractures. Treatment with denosumab was associated with a statistically significant 68% decrease in the risk of new vertebral fractures compared with placebo (2.3% denosumab versus 7.2% placebo, $P < 0.0001$), a 40% decrease in the risk of hip fractures (0.7% denosumab versus 1.2% placebo, $P = 0.036$), and a 20% decrease in the risk of nonvertebral fractures (6.5% denosumab versus 8.0% placebo, $P = 0.011$).³⁴

Other Phase III studies have been conducted to evaluate the efficacy and safety of denosumab in a variety of circumstances that could provide guidance to physicians considering the use of this agent in clinical practice. Denosumab Fortifies Bone Density (DEFEND) was a 2-year randomized, double-blind, placebo-controlled Phase III study of denosumab in 332 postmenopausal women with low BMD, defined as lumbar spine T-score between -1.0 and -2.5 .³⁵ This study evaluated the efficacy of denosumab to stabilize or increase BMD in postmenopausal women with osteopenia. Subjects were randomized to receive SC denosumab 60 mg Q6M or placebo, with a primary efficacy endpoint of percentage change of lumbar spine BMD at 24 months compared with placebo. Denosumab significantly increased BMD at the lumbar spine compared with placebo (denosumab 6.5% versus placebo -0.6% , $P < 0.0001$), with significant BMD increases at other measured skeletal sites as well ($P < 0.0001$). Denosumab significantly reduced levels of BTMs compared with placebo.

Determining Efficacy: Comparison of Initiating Denosumab versus Alendronate (DECIDE) was a 1-year randomized, double-blind, double-dummy Phase III noninferiority study in 1189 postmenopausal women with lumbar spine or total hip T-score of -2.0 or less.³⁶ DECIDE was a head-to-head comparison of the effects of denosumab and alendronate, the most commonly prescribed bisphosphonate for the treatment of osteoporosis. Subjects were randomized to receive SC denosumab SC 60 mg Q6M plus weekly oral placebo or oral alendronate 70 mg weekly plus placebo SC injections Q6M. The primary efficacy endpoint was the percentage change from baseline of total hip BMD after 12 months of treatment with denosumab compared with alendronate. It was found that subjects treated with denosumab had a significantly

greater BMD increase at the total hip (denosumab 3.5% versus alendronate 2.6%, $P < 0.0001$) and at all other measured skeletal sites at 12 months compared with alendronate. Reductions in BTM levels were significantly greater with denosumab than alendronate.

The Study of Transitioning from Alendronate to Denosumab (STAND) addressed the response to treatment with denosumab in women previously treated with alendronate. This was a 1-year double-blind, active-controlled, double-dummy Phase III study in 504 postmenopausal women treated with alendronate for at least the past 6 months (median 36 months, range 6–192 months) and having a baseline lumbar spine or total hip T-score of -2.0 to -4.0 .³⁷ Subjects were randomized to either switching from alendronate to SC denosumab 60 mg Q6M or continuing oral alendronate 70 mg weekly. The primary efficacy endpoint was the percentage change in total hip BMD at 12 months in subjects switched to denosumab compared with those who continued alendronate. A significantly greater total hip BMD increase was reported in subjects switched to denosumab (denosumab 1.90%, alendronate 1.05%, $P < 0.0001$). BMD increases with denosumab were also greater at the lumbar spine, and distal one-third radius ($P < 0.0125$ for all).

These clinical trials show that denosumab is associated with a reduction in BTM levels, increase in BMD, and, in women with postmenopausal osteoporosis, a decrease in the risk of vertebral fractures, nonvertebral fractures, and hip fractures.

Denosumab safety reporting in clinical trials and postmarketing surveillance

Safety has been evaluated in all of the denosumab clinical trials and their extensions. Postmarketing safety data are collected through reports submitted to Amgen Medical Information,³⁸ the Amgen Post-marketing Active Safety Surveillance Program³⁹ (available to enrolled physicians), and the MedWatch Program of the FDA.⁴⁰ The denosumab Risk Evaluation and Mitigation Strategy (REMS)⁴¹ is a strategy to manage known or potential risks associated with denosumab to ensure that the benefits of treatment outweigh the risks. The REMS program includes methods for communicating risks to health care professionals and patients in the form of “Prescribing Information,”⁴² a “Medication Guide,”⁴³ and “Dear Healthcare Professional” letters,⁴⁴ all of which are accessible through the Prolia product website⁴⁵ and the REMS website.⁴¹

The required terminology for premarketing safety reporting of investigational new drugs is defined by the US

Code of Federal Regulations (CFR), recently updated in the Federal Food, Drug and Cosmetic Act (21 CFR Parts 312 and 320) (Table 1).⁴⁶ A reported untoward (unfavorable, negative, or harmful) medical occurrence is designated as an adverse “event” or “reaction” that may be modified by the terms “serious,” “life-threatening,” “suspected,” or “unexpected.” When an untoward occurrence is reported as an adverse “event,” there may or may not be a causal relationship with the drug. When reported as an adverse “reaction” without a modifier, there is reason to conclude that the drug caused the event. The modifier “suspected” with “reaction” is intended to mean that there is a reasonable possibility that the drug caused the event – that is, a lesser degree of certainty than without the modifier.

The implementation of this terminology may help to resolve some of the uncertainty and confusion generated from earlier definitions that might mislead patients and physicians regarding safety and causality with denosumab. For example, the FDA stated⁴⁷ that “An adverse drug reaction, also called a side effect, is any undesirable experience associated with the use of a medicine in a patient.” There is no mention of causality, despite designating “side effect” as synonymous with “adverse drug reaction.” The use of “side effect” in this fashion is contrary to common usage and quite different from the dictionary definition of “side effect,” which clearly recognizes a causal relationship between the drug and the untoward occurrence.⁴⁸ The distinction between an

untoward occurrence that is caused by a drug and one that is likely to be a consequence of the disease state being studied (eg, a fracture with osteoporosis) or one that commonly occurs in the population being studied (eg, back pain in the elderly) is an important one.

A “Medication Guide” is a paper handout or pamphlet for distribution of FDA-approved information to patients for medications that the FDA determines pose a serious and significant public health concern. US federal regulations (21 CFR 208.20) state that it “shall be scientifically accurate and shall be based on, and shall not conflict with, the approved professional labeling for the drug product under 201.57;”⁴⁹ 21 CFR 201.57 defines adverse reactions as “only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.”⁵⁰ However, the Medication Guide for Prolia[®] in use at the time of writing lists the most common “side effects” as back pain, arm and leg pains, high cholesterol, muscle pain, and bladder infections.⁴³ While these untoward medical occurrences were commonly reported in FREEDOM trial subjects, the differences in incidence between those receiving denosumab and placebo were trivial (Table 2). The Medication Guide for Prolia[®] does not provide information on the frequency of these occurrences with treatment compared with placebo and does not state whether there is a clinically or statistically significant difference in these events in subjects taking denosumab

Table 1 Safety reporting terminology for investigational new drugs (INDs)⁴⁶

Reporting term	Definition
Adverse event	Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related
Adverse reaction	Any adverse event caused by a drug
Life-threatening adverse event or life-threatening suspected adverse reaction	An adverse event or suspected adverse reaction is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death
Serious adverse event or serious suspected adverse reaction	An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect
Suspected adverse reaction	Any adverse event for which there is a reasonable possibility that the drug caused the adverse event
Unexpected adverse event or unexpected suspected adverse reaction	An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended

Notes: The US Code of Federal Regulations defines the terms used for identifying unfavorable, negative, or harmful medical occurrences in clinical trials of INDs and bioavailability and bioequivalence studies. An “adverse event” is an untoward medical occurrence in any clinical trial subject (eg, receiving study drug or placebo) regardless of causality, while an “adverse reaction” is an untoward medical occurrence that is caused by a drug. All definitions are from: US Food and Drug Administration. Investigational new drug safety reporting requirements for human drug and biological products and safety reporting requirements for bioavailability and bioequivalence studies in humans. *Federal Register*. 21 CFR Parts 312 and 320. 2010;75(188):59935–59963. Available from: http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=2010_register&docid=fr29se10-3.pdf. Accessed September 2, 2011.

Table 2 The five most common “adverse reactions” of denosumab from the pivotal fracture trial in women with postmenopausal osteoporosis that occurred in 2% or more of patients treated with denosumab and were more frequent than in placebo-treated subjects⁴²

Adverse reaction	Denosumab (n = 3886)	Placebo (n = 3876)
Back pain	1347 (34.7%)	1340 (34.6%)
Pain in extremity	453 (11.7%)	430 (11.1%)
Musculoskeletal pain	297 (7.65)	291 (7.5%)
Hypercholesterolemia	280 (7.2%)	236 (6.1%)
Cystitis	228 (5.9%)	225 (5.8%)

Notes: These are listed as “side effects” of denosumab in the Prolia® medication guide⁴³ without explanation regarding statistical significance, causality, or clinical relevance. These untoward medical occurrences are those that are common in elderly populations, with the differences in incidence between the two groups being very small.

and those on placebo; there is no mention of severity, causality, or biological plausibility.

Safety concerns

At a meeting of the Advisory Committee for Reproductive Health Drugs held on August 13, 2009, the FDA safety analysis identified the following as “adverse events of special interest”: infection, new malignancy, tumor progression, dermatologic events, hypocalcemia, osteonecrosis of the jaw (ONJ), bone histomorphometry findings, hypersensitivity/immunogenicity, cardiovascular adverse events, pancreatitis, and ocular adverse events.⁵¹ For some of these categories, biological plausibility was clearly present, while others appeared to be listed due to unexpected clinical trial findings. After consideration of the efficacy and safety data available at that time, the committee voted unanimously that the benefit of treatment with denosumab is likely to outweigh the risks in women with PMO at high risk for fracture.⁵² This ultimately led to FDA approval for this indication.

The biological plausibility for possible increased risk of infections, new malignancies, and tumor progression with denosumab is derived from what is known about the role of the RANKL/RANK/OPG signaling pathway with the immune system. RANKL plays an essential role in the development and maturation of the immune system in rodents,⁵³ is expressed by activated T cells,⁵⁴ and is an activator of dendritic cells, monocytes, and macrophages.^{55,56} OPG is expressed by mature B cells.⁵⁷ However, a small permissive level of RANKL and RANK in transgenic rats is associated with normal lymph node development^{58,59} and inhibition of RANKL in adult humans has not been shown to adversely affect measured parameters of immune function.^{27,28}

Carcinogenicity studies were not performed with denosumab, since it is an antibody specific to human and nonhuman primate RANKL and is not active in the rodent. Potential adverse effects of denosumab on immunity continue to be assessed in clinical trials and postmarketing surveillance.

RANK and RANKL are expressed in normal human skin. Preclinical studies have shown that RANKL is a regulator of epidermal dendritic cell function and T cell activity in the skin.⁶⁰ The finding that cutaneous RANKL expression suppresses inflammation of the skin in mice⁶¹ suggests the possibility that RANKL inhibition in humans might lead to an enhanced inflammatory response, providing a rationale for the observation of some of the dermatological untoward occurrences reported with denosumab.³⁴

Hypocalcemia, usually subclinical but sometimes symptomatic, with associated increases in serum PTH levels, has been observed with the use of potent antiresorptive agents, including bisphosphonates⁶² and denosumab.²⁹

Denosumab is a robust antiresorptive agent, as demonstrated by the magnitude of reduction in BTMs^{28–34} and the results of histomorphometry in bone biopsy substudies in clinical trials.⁶³ There has been concern that prolonged treatment with drugs that inhibit bone remodeling might cause oversuppression of bone turnover⁶⁴ that could impair the healing of microcracks, possibly leading to reduced bone strength with unusual fractures,⁶⁵ impairment of fracture healing,⁶⁶ or ONJ.⁶⁷

There is a potential for any therapeutic protein, including denosumab, to elicit an immune response. Most clinical studies with denosumab included evaluations of immunogenicity with a screening immunoassay to detect binding antibodies, a second immunoassay to confirm binding antibodies, and a cell-based bioassay to evaluate for neutralizing antibodies.^{28–34}

Cardiovascular concerns with denosumab have been raised since RANKL, RANK, and OPG are expressed by vascular endothelial cells, and studies in humans have shown an association of elevated OPG levels with cardiovascular endpoints, such as coronary artery disease,⁶⁸ stroke,⁶⁹ progression of atherosclerosis,⁷⁰ vascular calcification,⁷¹ and mortality.⁷² However, it now appears that increased OPG levels are a compensatory response to vascular disease rather than a causal factor, and that OPG may inhibit vascular calcification by reducing bone turnover.⁷³ An increased risk of atrial fibrillation as a serious adverse event has been reported in a single randomized, placebo-controlled trial of zoledronic acid,⁷⁴ another potent antiresorptive agent, suggesting the possibility that this might be a class effect of bisphosphonates

or all antiresorptive drugs. After a review of all available data, the FDA found that there was insufficient evidence to conclude that bisphosphonates caused atrial fibrillation and that physicians should not change prescribing habits due to this concern.⁷⁵

FDA concerns regarding pancreatitis focused on a numerical imbalance in reported events in denosumab-treated subjects compared with those receiving placebo in pooled PMO studies. There was also a numerical imbalance of an ocular adverse event (cataracts) in a trial of denosumab in men with prostate cancer but not in PMO studies.⁷⁶ There is no clear rationale for a causal relationship between denosumab and either of these adverse events.

As with the study of any investigational new drug, adverse effects that are very uncommon or ones that do not emerge until treatment has been continued for many years may not be recognized in clinical trials. The reasons that clinical trials fail to identify all adverse drug effects include the relatively small number of subjects compared with the total number of patients eventually exposed to the drug, the homogeneity of the study population compared with patients in clinical practice, and the limited duration of observation during studies compared with a much longer time of treatment for many clinical practice patients. For these reasons, postmarketing surveillance for the safety of approved medications is appropriate and necessary.

Safety data

In the report of the Phase I study of denosumab in healthy postmenopausal women, there were no related serious adverse events and no discontinuations from the study due to adverse events.²⁸ Mild transient dose-dependent decreases in albumin-adjusted serum calcium and corresponding increases in serum intact PTH levels were observed. Infectious adverse events were similar with the combined denosumab dosing groups (38%) and placebo (33%). Two subjects treated with denosumab had mild injection-site reactions. There were no changes in white blood cell counts, T-, B-, or NK-cell counts, immunoglobulins, or coagulation parameters associated with denosumab treatment.

Safety data for subjects in the Phase II study of denosumab in postmenopausal women with low BMD have been incrementally reported for time points beginning at 1 year and progressing most recently to 8 years.^{29–33} At 4 years, all adverse events, including infections, and all serious adverse events, including malignancies, were similar in groups receiving denosumab, alendronate, and placebo.³¹ Most patients reported an adverse event at some stage during the 4 years,

the most common events being an upper respiratory tract infection, arthralgia, and back pain. Infections requiring hospitalization were reported in 3.2% of subjects treated with denosumab and none of those receiving placebo or alendronate. The infections were typical community-acquired infections that responded appropriately to conventional antibiotic therapy. No opportunistic infections suggestive of impaired immune function were reported. Serum calcium levels remained stable and within the normal range with denosumab, with no patient having symptomatic hypocalcemia. No patient developed neutralizing antibodies to denosumab. Of the 262 subjects who completed the 4-year parent study, 200 enrolled in the 4-year single-arm study extension, with all receiving open-label SC denosumab 60 mg Q6M; 116 completed the extension and 80 of these received 8 years of continuous denosumab treatment. The adverse event profile at 6 years³² and 8 years³³ was similar to what was reported after 1–4 years of drug exposure, with no report of increased frequency of any specific event over time.

FREEDOM, the largest of the denosumab clinical trials, provides the single most robust database for evaluation of safety endpoints, with 3-year data published in a peer-reviewed journal³⁴ and more detailed information presented to the FDA as a report to the Advisory Committee for Reproductive Health Drugs.⁷⁷ After 3 years of observation, there were no significant differences in the total incidence of adverse events or serious adverse events in subjects receiving denosumab or placebo. There was no evidence of hypersensitivity or allergic drug reactions. Neutralizing antibodies to denosumab were not detected in any of the clinical trial subjects. The overall risk of infections, opportunistic infections, cardiovascular events, atrial fibrillation, stroke, cataracts, hypocalcemia, malignancies, and death was similar in subjects receiving denosumab or placebo. In pooled data from FREEDOM and other studies in women with PMO ($n = 4050$ for denosumab-treated subjects, $n = 4041$ for placebo-treated subjects), pancreatitis was reported in eight subjects on denosumab and four subjects on placebo; cataracts were reported for 232 subjects on denosumab and 253 subjects on placebo.⁵¹

In a prespecified analysis, complications in the healing of nonvertebral fractures were evaluated.⁷⁸ Complications associated with the fracture or its surgical repair occurred in 1.7% of denosumab subjects and 5.7% of placebo subjects ($P < 0.01$). There were two reports of delayed union with denosumab and four with placebo, and one nonunion with placebo. There was no signal for impaired fracture healing with denosumab. There were no reports of atypical femur fractures or ONJ in denosumab-treated subjects.

Assessment of adverse events showed that eczema and flatulence were significantly more common with denosumab, while falling was less common with denosumab; with serious adverse events, cellulitis was significantly more common with denosumab, although there was no significant difference in the incidence of cellulitis overall, and concussions were less common with denosumab (Table 3). Skin infections were not related to the injection site or to the timing of the injection. Denosumab was well tolerated with no reported injection-site reactions. Local reactions after injection occurred in 0.8% of subjects in the denosumab group and 0.7% in the placebo group.

The quality of bone with denosumab treatment and the mechanism of action of denosumab have been evaluated in bone biopsy substudies of FREEDOM and STAND. Transiliac bone biopsies with a standardized double-tetracycline labeling procedure were obtained at 24 and/or 36 months in FREEDOM (47 women on denosumab, 46 on placebo) and at 12 months in STAND (15 women on denosumab after alendronate, 21 continuing alendronate).⁶³ Qualitative bone histology was unremarkable in all women treated with denosumab, showing normal lamellar bone, normal mineralization, and the absence of marrow fibrosis. Data from FREEDOM biopsies at 24 and 36 months were not significantly different and were therefore combined to provide greater statistical power. In the FREEDOM substudy, double tetracycline labeling was observed in trabecular or cortical bone in all biopsies of subjects on placebo, while for subjects treated with denosumab, 40% had double label, 25% had single label only, and 36% had no label. There was no correlation between BTM levels and the presence or absence of labeling. Nine subjects in the substudy had fractures: six in the placebo group (all with double labels) and three in the denosumab group (one with single labels and two with no labels), with no reports of impaired fracture healing.

Structural indices measured by histomorphometry and microcomputed tomography were consistent with reduced bone turnover in the denosumab group. Reduced cortical porosity and increased cortical volumetric BMD were observed in the denosumab group with microcomputed tomography at 24 months. In the STAND substudy, indices of bone turnover tended to be lower in the denosumab group than the alendronate group; double labeling was observed in trabecular or cortical bone in all biopsies of subjects in the alendronate group, while for subjects switched to denosumab, 60% had double label, 20% had single label only, and 20% had no label. These bone biopsy substudies confirmed that denosumab is a robust inhibitor of bone remodeling. The clinical relevance and long-term safety of such a low level of remodeling with a reduction or absence of detectable tetracycline labeling in a substantial number of subjects is unknown. Reversibility of the antiresorptive effects of denosumab has been demonstrated by changes in BTMs and BMD in subjects discontinuing denosumab in the Phase II study.³¹ Reversibility was confirmed in a bone biopsy study in 15 women who had been treated with denosumab and discontinued treatment an average of 2 years before a double tetracycline-labeled bone biopsy was done.⁷⁹ These biopsies showed normal histology and bone remodeling similar to untreated women with postmenopausal osteoporosis.

A detailed analysis of adverse events and serious adverse events of specific types of infections reported in the 3-year FREEDOM dataset has recently been released.⁸⁰ The incidence of serious adverse events of infections did not change with increasing duration of denosumab exposure. The incidence of serious adverse events of opportunistic infections was low and similar in both groups, with no temporal relationship between administration of drug and the onset of infection. Serious adverse events of skin infections in denosumab-treated subjects were mostly cellulitis and clinically diagnosed erysipelas

Table 3 Adverse events and serious adverse events in the FREEDOM trial³⁴

Type of event	Denosumab (n = 3886)	Placebo (n = 3876)	P value
Adverse events occurring in at least 2% of subjects in either group with $P \leq 0.05$			
Eczema	118 (3.0%)	65 (1.7%)	<0.001
Falling	175 (4.5%)	219 (5.7%)	0.02
Flatulence	84 (2.2%)	53 (1.4%)	0.008
Serious adverse events occurring in at least 0.1% of subjects in either group with $P \leq 0.01$			
Cellulitis (including erysipelas)	12 (0.3%)	1 (<0.1%)	0.002
Concussion	1 (<0.1%)	11 (0.3%)	0.004
All adverse events and serious adverse events	3605 (92.8%)	3607 (93.1%)	0.91
All serious adverse events	1004 (25.8%)	972 (25.1%)	0.61

Notes: Five events were identified as being statistically significantly different between subjects treated with denosumab and placebo. Three of these (eczema, flatulence, cellulitis) favored placebo while two (falling, concussions) favored denosumab. There was no difference in total adverse events or serious adverse events.

in the lower extremities (unrelated to the injection site) that resolved with the use of common antibiotics. Preexisting risk factors of venous ulcers and skin wounds were reported in five of the twelve denosumab-treated subjects with these infections. There was no temporal relationship between administration of drug and the onset of skin infections. Serious adverse events of urinary tract infections were reported in 29 (0.7%) of denosumab-treated subjects and 20 (0.5%) of those receiving placebo; these were typically caused by *Escherichia coli* or other common Gram-negative bacteria. Endocarditis, without identification of a causative organism, was reported in three subjects in the denosumab group and none in the placebo group. Two of the subjects with reported endocarditis underwent echocardiography and were treated, while the third subject had suspected acute bacterial endocarditis associated with fatal multiorgan failure, but no further details were available and no autopsy was performed. Neutrophil, lymphocyte, and monocyte counts were similar in both groups with no change in cell counts with increased duration of exposure to denosumab.

Of the 6468 women who completed the 3-year study, 4550 enrolled in the 7-year extension (total of 10 years) to receive open-label SC denosumab 60 mg Q6M. Preliminary data are available for the first 2 years of the extension, with 2343 women in the group with 5 years of continuous exposure to denosumab ("long-term group") and 2207 in the group receiving placebo for 3 years followed by denosumab for 2 years ("cross-over group").^{81,82} The yearly incidence rates for serious adverse events of infections, including cellulitis and erysipelas, and adverse events of malignancies for the long-term and cross-over groups in the first 2 years of the extension were similar to or lower than the observed yearly rates in the FREEDOM placebo group. The imbalances in serious adverse events of skin infections in the FREEDOM trial were not observed in the extension study. One reported case of oral osteomyelitis and one case of oral bone necrosis in the cross-over group were adjudicated as consistent with ONJ.

In DEFEND,³⁵ DECIDE,³⁶ and STAND,³⁷ total adverse events and serious adverse events were similar among groups. Differences reported for some categories of adverse events and serious adverse events. In DEFEND, there were more reports of rashes, sore throats, and infections treated in hospital in the denosumab group (8.5%, 9.1%, and 4.9%, respectively) than placebo (3.0%, $P=0.035$; 3.0%, $P=0.022$; and 0.6%, $P=0.020$, respectively). Adverse events of infections in the denosumab (60%) and placebo groups (61%) were similar, and there was no significant difference among groups in the incidence of neoplasms. In DECIDE and

STAND, there were no significant differences among groups in the incidence of adverse events or serious adverse events of infections or neoplasms.

A meta-analysis⁸³ evaluated the efficacy and safety of denosumab in 8864 subjects with low bone mass or osteoporosis in four randomized placebo-controlled trials.^{30,34,35,84} The analysis was dominated by the large number of subjects (7868) in FREEDOM and included one study of 252 women with nonmetastatic breast cancer on aromatase inhibitor therapy. The risk ratio for all serious adverse events, serious adverse events of infections, serious adverse events of neoplasms, and adverse events leading to study discontinuation was not statistically significantly different for women receiving denosumab and placebo. A sensitivity analysis excluding the study in cancer patients made little difference in the findings.

In three large clinical trials in cancer patients, SC denosumab 120 mg every Q4W was compared with intravenous zoledronic acid 4 mg adjusted for creatinine clearance Q4W.^{85–87} The primary endpoint was time to first on-study skeletal-related event, defined as radiation therapy to alleviate pain or prevent fracture, surgery to bone to treat or prevent fractures, pathologic fracture, and spinal cord compression that can result in paresthesias, incontinence, and paralysis. While the safety data from these cancer studies are not directly applicable to women treated with denosumab for osteoporosis, it may be noteworthy that no increase in the incidence of skin reactions (eg, eczema or cellulitis as a serious adverse event) was reported in denosumab-treated cancer subjects, despite the use of a higher dose and shorter dosing interval than in FREEDOM.

Patient-focused perspectives

The Denosumab Adherence, Preference, Satisfaction (DAPS) study evaluated patient perspectives with SC denosumab 60 mg Q6M compared with oral alendronate 70 mg weekly in 250 women with PMO.⁸⁸ In this randomized, open-label, 2-year cross-over study, the primary study endpoint was adherence at 1 year. It was reported that adherence, defined as meeting study criteria for both compliance and persistence, was significantly greater with denosumab (87.3%) than alendronate (76.6%). Subject ratings for treatment preference and satisfaction were also significantly greater for denosumab than alendronate. Adverse events were similar with both drugs. In the second 12 months of the DAPS study, with each treatment group crossing over to the other, serious adverse events were reported in 3.5% of subjects receiving denosumab and 3.9% of those receiving alendronate.⁸⁹

Role of denosumab in clinical practice

Denosumab is indicated for the treatment of women with PMO who are at high risk for fracture, defined by the FDA as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy. The focus on treating women “at high risk for fracture” is generally consistent with current clinical practice guidelines, although different definitions of “high risk” have been used. The National Osteoporosis Foundation in the USA, for example, considers a postmenopausal woman to be at sufficiently high risk for fracture to initiate pharmacological therapy, including denosumab, under any of the following conditions:⁹⁰ (1) T-score of -2.5 or below at the femoral neck or lumbar spine (without the need for additional risk factors); (2) T-score between -1.0 and -2.5 at the femoral neck or lumbar spine with a FRAX (World Health Organization fracture risk assessment tool) 10-year probability of major osteoporotic fracture $\geq 20\%$ or 10-year probability of hip fracture $\geq 3\%$ (without the need for a densitometric classification of osteoporosis); or (3) previous hip or vertebral fracture. Denosumab, as well as alendronate, risedronate, and zoledronic acid, is recommended by the American Association of Clinical Endocrinologists as a first-line agent for the treatment of PMO.⁹¹ Denosumab is distinguished by: its infrequent injectable administration, which avoids issues of malabsorption and gastrointestinal intolerance, and may improve long-term adherence to therapy compared with oral bisphosphonates; its SC method of injection, which is less disruptive to the office routine of most physicians than intravenous bisphosphonates and expands the potential number of facilities willing to administer the drug compared with intravenous bisphosphonates; the absence of restrictions on its usage in patients with severe chronic kidney disease; and by reversibility of antiresorptive effect soon after the 6-month dosing period has passed, which may be reassuring to patients who are concerned with the long skeletal half-life of bisphosphonates. Treatment decisions should be made after an evaluation for secondary causes of osteoporosis has been conducted. The expected benefit and potential risks with each medication under consideration should be discussed with the patient prior to starting treatment.⁹²

Conclusion

Denosumab is a fully human monoclonal antibody to RANKL associated with a rapid, sustained, and reversible reduction in BTM levels, an increase in BMD, and decrease in the risk of vertebral fractures, hip fractures, and

nonvertebral fractures in women with PMO. Compared with alendronate, denosumab is associated with a greater increase in BMD and, in women previously treated with alendronate, switching to denosumab increases BMD more than continuing alendronate. It is well tolerated with total adverse events and serious adverse events generally similar to placebo. Differences between denosumab and placebo have been reported for some individual safety endpoints. The evidence supports a favorable balance between the expected benefit and potential risks with the use of denosumab for the treatment of PMO.

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Disclosure

The author reports no conflicts of interest in this work.

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