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Review Article

Denosumab for the treatment of osteoporosis

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Abstract

Denosumab, a specific inhibitor of RANK ligand, is a novel therapy for postmenopausal osteoporosis and related disorders. An extensive clinical development program has evaluated the clinical efficacy and safety of denosumab with several thousand patients being followed for up to 10 years. Combined with more than six years of postmarketing experience, these studies provide substantial confidence that denosumab is a convenient and appropriate treatment for patients, including Asians, at high risk for fracture. This review will summarize the clinical development of denosumab and lessons learned since its approval for clinical use in 2010.

Keywords: Denosumab; RANK ligand; Osteoporosis; Fracture; Drug safety

1. Introduction

Fractures related to osteoporosis are a major and increasing global health concern. Because the risk of fracture increases with advancing age, the burden of osteoporosis will progressively increase as populations continue to age, especially in Asia where the percentage of the population age 65 years and older is projected to be 9.3% in 2025, an increase of 75% over 1995 [1].

Osteoporosis is the consequence of an imbalance in bone remodeling with resorption exceeding formation, resulting in bone loss, damage to skeletal microarchitecture and impaired bone strength. Rates of bone loss are relatively high in the first year following menopause and in elderly men and women. Therapies that decrease osteoclastic bone resorption such as estrogen and bisphosphonates are known to slow or prevent bone loss and to decrease the risk of osteoporotic fracture in postmenopausal women [2,3].

The discovery and elucidation of the pivotal role played by the receptor activator of nuclear factor-kappa B (RANK) ligand pathway in the regulation of osteoclast activity provided new targets for osteoporosis therapy [4]. The interaction of RANK ligand, an osteoblast-derived growth promoter, with its receptor RANK on pre-osteoclasts is required for the differentiation and proliferation of osteoclasts. Absence of RANK ligand in human and in animal models results in low bone resorption and a phenotype of high bone mass [5,6]. Osteoprotegerin (OPG) is a soluble RANK receptor and is also expressed by osteoblasts. By binding to RANK ligand, OPG inhibits the activation of osteoclasts, reduces bone resorption and increases bone mass in rats and monkeys [7,8]. Based on this understanding and a very strong preclinical platform, denosumab emerged as the first inhibitor of RANK ligand (RANKL) to be registered as a treatment for osteoporosis [9]. This article will review the clinical development of denosumab and studies pertaining to its use in clinical practice.

2. Clinical development

Denosumab is a fully human IgG_2 antibody that avidly and very specifically binds RANKL [9]. In a Phase 1 study, single

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doses of denosumab ranging from 0.01 to 3 mg/kg, were administered to healthy postmenopausal women [10]. Non-linear pharmacokinetics were observed; larger doses were cleared more slowly than smaller doses. As with other human antibodies, clearance is by the reticuloendothelial system, and there is no renal excretion. The acute effects on bone resorption, as measured by reduction in urinary N-telopeptide (NTX), were similar among all doses with decreases of about 80% occurring within 24 h of dosing. The duration of the inhibition of bone resorption was dose-dependent with effects of doses of 60 mg and higher persisting for at least six months. These data confirmed that denosumab functions like OPG to reduce bone resorption by inhibiting the actions of RANKL.

In a Phase 2 dose-ranging study, denosumab was administered subcutaneously range from doses of 6 mg every 3 months to 210 mg every six months (Q6M) to women with low bone mineral density (BMD) [11]. Significant increases in BMD occurred with all doses. With all but the smallest doses, the BMD response in the lumbar spine with denosumab was similar to the response seen in women who had been randomized to receive alendronate 70 mg each week. The increases in BMD in the proximal femur and mid-radius were modestly greater with denosumab than with alendronate. All doses of denosumab resulted in a similar prompt and marked decrease in serum C-telopeptide (CTX) (a marker of bone resorption), decreasing by 85% at three days after dosing with the nadir of the effect occurring at about one month. Again, the duration of the effect on bone resorption was dose-related. Upon dosing with 60 mg denosumab, Q6M, serum CTX gradually increased during the 6 months between doses, reaching a level similar to that observed in women receiving continuous alendronate therapy. Markers of bone formation decreased after 2−3 months of treatment, and the response to denosumab paralleled that seen with alendronate therapy. Similar effects on bone remodeling markers were observed over 8 years of dosing with 60 mg denosumab Q6M [12−15]. The results of the Phase 2 study led to the choice of 60 mg Q6M as the clinical dose to be evaluated in subsequent studies evaluating the effectiveness and safety of denosumab for treatment of postmenopausal osteoporosis.

The pivotal Phase 3 fracture endpoint trial, called the Fracture Reduction Evaluation of Denosumab in Osteoporosis (FREEDOM) study, enrolled 7808 healthy postmenopausal women with osteoporosis who were randomly assigned to receive placebo or denosumab 60 mg subcutaneously Q6M [16]. All received calcium and vitamin D. The average age of subjects in FREEDOM was 72.3 years; 23% had one mild vertebral fracture at baseline. After three years of treatment, the incidence of new morphometric vertebral fractures decreased from 7.2% with placebo to 2.3% with denosumab (68% relative reduction, 95% confidence interval (CI) 59%,74%). A decrease of at least 60% was also seen at the 1 and 2-year time points. The incidence of hip and nonvertebral fracture was 1.2% and 8.0%, respectively, in subjects receiving placebo, and was 0.7% and 6.5%, respectively, in the denosumab group, resulting in a relative risk reduction of hip fracture of 40% (CI 3%,63%) and 20% (CI 5%,33%) for nonvertebral fracture. As was observed in the Phase 2 study, significant increases in BMD were noted in the lumbar spine (9.2%), total hip (6%) and distal radius (3.2%) with denosumab compared to placebo at 3 years [16,17] (Table 1). In FREEDOM, the change in total hip BMD from baseline to 36 months with denosumab accounted for 35% and 87% of the reduction in risk of vertebral and non-vertebral fractures, respectively [18].

The effectiveness of denosumab was evaluated in predefined subgroups of baseline age, body mass index, geography, BMD, fracture status and renal function [19]. The effect of therapy on vertebral fractures did not significantly differ for any of the subgroups analyzed ($p > 0.09$ for all potential interactions). The risk of non-vertebral fracture was statistically significantly reduced in women with a baseline femoral neck BMD T-score ≤ -2.5 but not in those with a T-score > -2.5; in those with a body mass index (BMI) ≤ 25 kg/m^2 but not >25 kg/m^2; and in those without but not with a prevalent vertebral fracture. The effects of denosumab on increasing bone density and decreasing the incidence of vertebral fracture were similar across the spectrum of baseline renal function [20]. This included a total of 2817 women with estimated glomerular filtration rate (GFR) between 30 and 59 mL per minute and 73 women with estimated GFR or 15−29 mL per minute. The efficacy and safety of denosumab therapy in patients with renal failure on dialysis have not been adequately studied.

The incidence of new morphometric vertebral and hip fractures in the placebo group of FREEDOM was substantially lower than observed in pivotal trials of other drugs approved for osteoporosis treatment, likely the consequence of the entry criteria of FREEDOM that excluded women with T-score values of <-4 or with more than one mild vertebral deformity

Table 1
Effects of denosumab therapy on fracture risk in FREEDOM.

Fracture	Placebo (%) $N = 3906$	Denosumab (%) $N = 3902$	Absolute risk reduction (%)	Relative risk reduction (%)	P value
Vertebral	7.2%	2.3%	4.9%	68%	<0.001
Non-vertebral	8.0%	6.5%	1.5%	20%	0.01
Hip	1.2%	0.5%	0.5%	40%	0.04
≥ age 75	2.3%	0.9%	1.4%	62%	0.007
Femoral neck T-score ≤ −2.5	2.8%	1.4%	1.4%	47%	0.02
Wrist	2.9%	2.5%	0.9%	15%	0.21
Femoral neck T-score ≤ −2.5	4.0%	2.4%	1.6%	40%	0.03

or with any moderate or severe vertebral fracture at baseline [16]. Post-hoc analyses evaluated the effects of denosumab therapy in high risk subgroups in FREEDOM defined as age >75 years, baseline femoral neck T-score ≤ -2.5 and baseline vertebral fracture status [21]. Vertebral and hip fracture risk was significantly reduced in all high risk subgroups. Notably, hip fracture risk was 0.9% over 3 years with denosumab compared to 2.3% with placebo (relative risk reduction 62%) in patients aged 75 years and older (Table 1). At baseline, the median 10-year probability of a major osteoporotic fracture, as assessed with the FRAX tool, was approximately 15% and for hip fracture was about 5% in both treatment groups [22]. In accord with the subgroup analyses, the reduction in clinical fracture risk was greater in patients at moderate to high risk of fracture and was independent of prior fracture, paternal history of hip fracture or secondary causes of osteoporosis while low body mass index was associated with greater efficacy.

3. Effects in Asian populations

The effects of denosumab 60 mg Q6M for 6–12 months on BMD and bone turnover markers in small cohorts of Indian (n = 225) [23] and South Korean (n = 132) [24] women were similar to the responses observed in FREEDOM which was comprised primarily of Caucasian women. The pharmacokinetics of denosumab in Japanese adults [25] and the BMD and bone marker responses in postmenopausal Japanese women [26] were similar to the results observed in Caucasians. In a study of 1262 Japanese postmenopausal women with osteoporosis, denosumab 60 mg Q6M for 24 months reduced new and worsening vertebral fracture incidence by 65.7% (incidence 10.3% with placebo vs 3.6% with denosumab) [27]. No difference in the overall incidence of non-vertebral fractures was observed between patients receiving denosumab or placebo. In that study, alendronate reduced the incidence of new and worsening vertebral fracture risk in patients randomized to receive open label alendronate 35 mg weekly was 7.2%. These results provide confidence that the effects of denosumab observed in American and European populations should be applicable to Asian patients.

4. Denosumab with or following other osteoporosis therapies

Many patients who are considered candidates for denosumab will have been previously treated with bisphosphonates. In women who had taken alendronate for at least 12 months (median duration of therapy was 36 months), the increase in BMD at the lumbar spine and total hip was statistically greater after 12 months in those randomized to switch to denosumab compared to those who continued alendronate [28]. Denosumab also resulted in greater increases in BMD compared to risedronate [29,30], ibandronate [30,31] and zoledronic acid [32] in patients who had previously received bisphosphonate therapy. Significant increases in BMD and reductions in biochemical markers of bone turnover were observed with denosumab in patients previously treated with zoledronic acid [33]. These results are in contrast to the observation that transitioning from alendronate to zoledronic acid resulted in no additional increase in BMD over 12 months [34].

The effects of following therapy with the anabolic agent teriparatide with denosumab have been studied in women with postmenopausal osteoporosis. After two years of teriparatide therapy, during which lumbar spine and total hip BMD increased by about 8% and 2%, respectively, from baseline, lumbar spine increased by an additional 10% and total hip BMD by 4.6% during an additional 24 months of denosumab therapy [35].

There is no pharmacological or clinical justification for combining denosumab and bisphosphonate therapies. However, using denosumab to inhibit the RANK ligand-mediated increase in bone resorption that accompanies teriparatide therapy has intellectual appeal. In the Denosumab and Teriparatide Administration (DATA) study, treatment with a combination of teriparatide and denosumab resulted in more rapid and greater increases in BMD over 12 months than did either drug alone [36]. The advantage of combination therapy was maintained but did not increase further compared to monotherapy during a second year of treatment [37]. Whether combined therapy results in faster or greater reduction in fracture risk could not be evaluated in that study.

5. Effects on skeletal structure

New imaging techniques have been used to assess the effects of denosumab therapy on skeletal structure and architecture. From computed tomography (CT) scans acquired in a subset of patients in FREEDOM, it was shown that denosumab therapy increased bone mass in both the cortical and trabecular compartments [38,39]. Cortical thickness but not cortical diameter of the radius increased, suggesting that denosumab reduced endocortical porosity, resulting in recovery of previously trabecularized cortical bone [38]. Using a unique cortical mapping protocol for CT scans, Poole and colleagues demonstrated significant increases in cortical mass and thickness in the proximal femur in response to denosumab [40]. Estimated vertebral bone strength, based on finite element analysis (FEA) of CT scans increased by 30% after 36 months of denosumab therapy while total hip strength increased by 9% from baseline [41]. Using a different FEA model, Zysett and colleagues also observed that denosumab treatment increased vertebral and femoral strength progressively over 3 years of treatment [42]. Analyses of high-resolution peripheral QCT (HRpQCT) scans of the radius and tibia confirm that cortical thickness increases and cortical porosity deceases with denosumab therapy [43]. In a head-to-head comparison with alendronate, denosumab reduced cortical porosity significantly more over 12 months than did alendronate [44]. In the DATA study, HRpQCT analyses demonstrated increases in volumetric BMD, cortical thickness and FEA estimates of bone strength at the radius and tibia with denosumab while there were no changes or decreases with teriparatide [45,46]. Radial and tibial cortical porosity increased by 20.9% and 5.6%, respectively, in patients receiving teriparatide but did not change with denosumab treatment [45].

6. Longer term therapy

From the initial planning, a long-term follow-up of FREEDOM was planned. In the FREEDOM Extension, about 4500 women who had completed the 3 year placebo controlled trial agreed to take open label denosumab 60 mg Q6M for up to ten years [47]. In women who received denosumab during the first three years of FREEDOM, continued treatment has resulted in progressive increases in BMD in the spine and total hip, reaching changes from baseline of 18.4% and 8.3%, respectively, after 8 years [48]. These results were similar to the BMD changes observed in a smaller group of women in the Extension of the Phase 2 study who received denosumab therapy for 8 years [15]. In FREEDOM Extension, the annualized incidence of vertebral fracture remained stable during the 8 years of therapy despite the aging of the cohort [48] (Fig. 1). The annual incidence of non-vertebral fracture has also remained stable or has possibly decreased with long-term therapy [49]. Pre-dosing levels of bone turnover markers were persistently reduced with no evidence of loss of treatment effectiveness during the 8 years of treatment. A preliminary report suggests that these effects continue out to 10 years of therapy [50].

7. Effects of discontinuing denosumab

Consistent with the pharmacology of denosumab and the lack of binding of the drug to skeletal tissues, the inhibitory effects of denosumab on bone remodeling disappear quickly upon withdrawal of therapy [13,51]. The average serum level of CTX returns to baseline values 9 months following the previous dose of denosumab (e.g., 3 months after missing a dose), and BMD values fall toward baseline within 12 months of stopping therapy. When therapy was re-started 12 months after stopping, the bone loss that had occurred since stopping treatment was restored within 12 months [13]. These results are very similar to the loss of BMD and fracture protection that occurs upon stopping other non-bisphosphonate drugs such as estrogen [52,53]. No increases in fracture risk have been observed in the small groups of patients in the discontinuation studies or in a review of patients who had discontinued placebo or denosumab during the FREEDOM study [54]. However, recent reports of multiple and/or severe vertebral fractures occurring within months of discontinuing denosumab therapy have raised the possibility of a rebound in vertebral fracture risk when treatment is stopped [55,56].

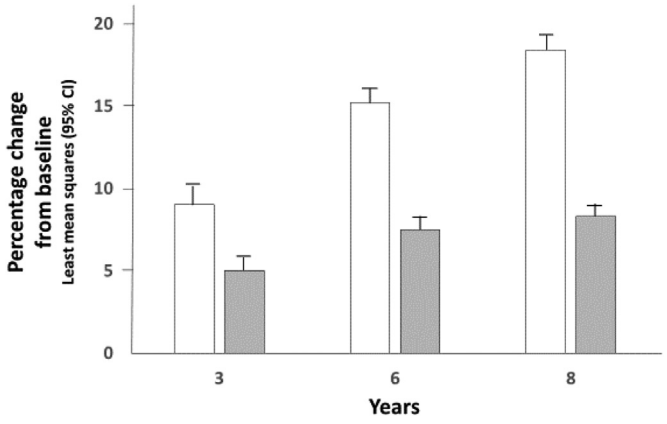

Fig. 1. Changes in BMD in the lumbar spine and total hip to denosumab 60 mg every 6 months in the FREEDOM study and Extension. Adapted from Ref. [16, 47,48].

8. Adherence

Therapies are only effective in patients who take them consistently, and poor adherence is a well recognized component of oral osteoporosis therapies [57]. With Q6M subcutaneous dosing by a healthcare professional, persistence with denosumab therapy is higher than with other osteoporosis treatments [58–62]. In a head-to-head crossover study, adherence during the first 12 months was 88% with denosumab and 76% with alendronate [63]. After switching therapies, adherence was 92.5% and 63.5% with denosumab and alendronate, respectively, during the second year. More than 90% of patients preferred the Q6M dosing regimen over the once weekly alendronate dosing schedule.

9. Safety

In FREEDOM, the proportions of patients in the denosumab and placebo group who experienced adverse events or serious adverse events was balanced [16] (Table 2). Ninety of the 3906 patients in the placebo group died as did 70 of 3902 patients in the denosumab group (P value = 0.06). Skin rash, including eczema, usually mild and self-limited, occurred more commonly with denosumab than with placebo. Cellulitis associated with hospitalization occurred in 12 patients who received denosumab and in one who received placebo P value = 0.002). The skin disorders were not related to the injection site (usually upper extremity) or the time of the injection. For unexplained reasons (perhaps chance), falls not resulting in fracture and concussions occurred less commonly with denosumab than with placebo.

Because RANK ligand is expressed in some T lymphocytes, concern existed about a possible inhibition of immune function with denosumab therapy [64]. Markers of cellular immunity, assessed monthly in the phase 2 study, revealed no signal of immune dysfunction [11]. Adverse events categorized as “infections” occurred numerically more often with denosumab then with placebo in FREEDOM (Table 2). This accounting included cases of appendicitis, diverticulitis, labyrinthitis and rare cases of endocarditis and pancreatitis. In neither FREEDOM nor other studies was there evidence of an increased risk of opportunistic infections. Watts and colleagues have provided a detailed review of all the adverse events related to infections in FREEDOM [65]. Reassuringly, denosumab therapy was not associated with an increased risk of serious infection compared to zoledronic acid therapy (hazard ratio 0.81, CI 0.55, 1.21) in postmenopausal women with osteoporosis [66], and the rate of infection associated with hospitalization among patients with rheumatoid arthritis receiving denosumab concurrently with biologic agents for

Table 2
Adverse events in FREEDOM.

	Placebo (%) $N = 3876$	Denosumab (%) $N = 3886$
Adverse events	93.1	92.8
Skin rash, eczema	1.7	3.0
Falls not associated with fracture	5.7	4.5
Serious adverse events	25.1	25.8
Cellulitis	<0.1	0.3
Infections	3.4	4.1
Cancer	3.2	3.7
Mortality	2.3	1.8
Most common AEs		
Back pain	34.6	34.7
Pain in extremity	11.1	11.7
Musculoskeletal pain	7.5	7.6
Hypercholesterolemia	6.1	7.2
Cystitis	5.8	5.9

RA was not increased compared to those receiving zoledronic acid [67]. The incidence of malignancy was also numerically but not statistically greater with denosumab than with placebo in FREEDOM [16] (Table 2). This was not explained by an increase in any particular tumor type, and there was no evidence of an increased risk of immune-related neoplasms such as lymphoma.

During the eight years of denosumab therapy in the long term treatment arm of FREEDOM Extension, no other new safety signals were observed [48]. The incidence of skin disorders, infections and malignancy did not change with longer duration of therapy. In the crossover arm of FREEDOM Extension, no increased risk of skin rash or infection, malignancy or serious infection was noted after denosumab therapy was begun in patients who had received placebo during the three years of FREEDOM.

As with all potent anti-remodeling agents, serum calcium levels decreased transiently when denosumab therapy was started, accompanied by a physiologic increase in serum parathyroid hormone [11]. No cases of symptomatic hypocalcemia were observed in the denosumab arm of FREEDOM [16]. During the Extension study, hypocalcemia was noted very rarely [48]. In postmarketing reports, cases of severe hypocalcemia have been noted, especially in patients with severe renal impairment, hypoparathyroidism or vitamin D deficiency [68–71].

Subcutaneous injections of denosumab are well-tolerated, and injection site reactions are very uncommon [14,48]. Rare patients develop denosumab-binding antibodies, detected with very sensitive assays. No patients developed antibodies with neutralizing activity during 4 years of therapy in the Phase 2 study [14] or in FREEDOM [48]. The frequency of binding antibody formation does not increase with long-term denosumab therapy, and the presence of antibodies has not been associated with skin reactions or loss of effectiveness. Very rare cases of hypersensitivity reactions or anaphylaxis have been described with denosumab in postmarketing reports [72].

FREEDOM was the first large osteoporosis study in which special committees prospectively adjudicated cases of osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFF). No cases of AFF or ONJ were observed in FREEDOM [16]. During the first 5 years of FREEDOM Extension (up to 8 years exposure to therapy), 8 patients had oral adverse events is consistent with ONJ, 5 in the long-term group and 3 in the cross-over arm [48]. These cases improved or resolved with conservative therapy, often while the patient remained on therapy. Two of 7 cases of subtrochanteric or femoral shaft fractures were consistent with AFF [47,48]. One occurred in the long-term treatment arm after 14 doses of denosumab, the other in the cross-over arm after 6 doses. Both fractures ultimately healed following surgical therapy, even while treatment was continued in the first case. There are several case reports of patients treated with denosumab in the clinical setting experiencing femoral fractures with atypical features, most often in patients who had received previous bisphosphonate therapy [73,74]. Denosumab had no appreciable effects on fracture healing [75], and the number of cases of impaired healing or delayed union were similar in the denosumab and placebo groups of FREEDOM [16].

In regulatory documents, the most common adverse reactions with denosumab are listed as back pain, pain in extremity, hypercholesterolemia, musculoskeletal pain, and cystitis [76]. As noted in Table 2, those were also the most common adverse events observed with placebo treatment. The increased frequency of hypercholesterolemia reported as an adverse event with denosumab likely reflects more patients on denosumab being started on cholesterol-lowering therapy by their personal physicians, counter to the observation that serum lipid levels are not affected by denosumab therapy [77]. No effect of denosumab on progression of aortic calcification or incidence of cardiovascular adverse events was observed over 3 years of therapy in FREEDOM [78], and no effect of denosumab therapy on glucose tolerance was observed in non-diabetic adults [77]. An active, on-going postmarketing pharmacoepidemiology study is continuing to monitor the long-term safety of denosumab [79].

10. Bone histology and histomorphometry

Transiliac crest bone biopsy specimens were obtained from 92 postmenopausal women with osteoporosis at either month 24 and/or month 36 (53 specimens in denosumab group, 62 specimens in placebo group) [80]. Qualitative histological assessment of biopsies from denosumab treated patients showed normally mineralized lamellar bone with normal architecture and quality. Double tetracycline labeling, indicative of active bone remodeling, was present in 94% evaluable biopsies from patients treated with placebo but in only 19% of denosumab treated patients in FREEDOM. The markedly reduced indices of remodeling, both resorption and formation, were consistent with histomorphometric studies in cynomolgus monkeys demonstrating virtually absent bone remodeling but preserved modeling-based bone formation with denosumab therapy [81]. These histologic and histomorphometric findings remained stable over 5 years of therapy [82] and returned to normal levels, with tetracycline labels

observed in all patients, within an average of 25 months (range 21−29 months) in 15 patients who had discontinued denosumab treatment [83].

11. Denosumab for other form of osteoporosis

In addition to the clinical development of higher doses of denosumab for the treatment of metastatic bone disease [84], the dose of the drug used for the treatment of postmenopausal osteoporosis has been evaluated is several other groups of patents. In men with low bone mass [85,86], women receiving aromatase inhibitors for non-metastatic breast cancer [87,88], and men with non-metastatic prostate cancer receiving androgen deprivation therapy [89], denosumab increases BMD is a pattern similar to that observed in FREEDOM. Over 3 years, vertebral fracture risk was reduced from 3.9% with placebo to 1.5% with denosumab (risk reduction 62%) in the androgen deprivation study [89]. These studies have resulted in regulatory approval for the use of denosumab in these groups of patients. Increases in BMD in response to denosumab therapy, similar to that observed in patents with postmenopausal osteoporosis, have also been reported in postmenopausal women with low bone mass [90]; patients with rheumatoid arthritis [91,92], Paget's disease of bone [93], renal transplantation [94], beta-thalassemia [95] or Hajdu Cheney syndrome [96] and children with osteogenesis imperfecta [97] or fibrous dysplasia [98]. In patients with rheumatoid arthritis, denosumab also prevents the progression of or partially heals juxta-articular bone erosions more effectively than does alendronate [99,100]. Results of a study evaluating the BMD effect of denosumab in patients receiving glucocorticoids will be available soon.

12. Summary

By inhibiting RANKL and bone resorption, denosumab is a unique strategy to treat osteoporosis. In postmenopausal women with osteoporosis, denosumab effectively and quickly reduces the risk of important fractures related to osteoporosis, and that fracture protection persists as long as treatment is given, at least to 10 years. The safety profile of therapy is excellent. Theoretical concern about impaired immune function have not materialized, and no other important or unexpected safety signals have become evident. Too few cases of ONJ and femoral fractures with atypical features have been reported to date to assess whether these are related to the duration of denosumab therapy or to exposure to the drug at all. On the basis of the large and well-designed FREEDOM fracture endpoint study, denosumab was approved in 2010 for the treatment of postmenopausal women with osteoporosis. Subsequently, regulatory approval has been granted for treating men with osteoporosis and men and women receiving hormone deprivation therapy for prostate or breast cancer.

As with all osteoporosis drugs, the clinical efficacy and the benefit:risk relationship is optimized when patients at high risk are treated. In the absence of contraindications (hypocalcemia, sensitivity to IgG_2 antibodies, pregnancy), denosumab is an appropriate treatment for most patients with osteoporosis. Adequate intakes of calcium and vitamin D should be assured before and during treatment to minimize the risk of hypocalcemia.

Because of its Q6M subcutaneous dosing regimen, denosumab is particularly attractive for patients who are intolerant or in whom there is concern about gastrointestinal absorption of oral agents, for elderly patients taking many other medications and for patients known to be poorly compliant with osteoporosis drugs. Denosumab has a special niche as a treatment for patients with significantly impaired renal function, although added attention to vitamin D status is required in these patients. Until its role in treating the skeletal complications of renal dialysis is known, denosumab should be used with great caution, if at all, in this setting. Treatment with denosumab is also appropriate in patients whose BMD is still in the osteoporosis range after several years of bisphosphonate therapy or who have completed a course of teriparatide therapy.

No side effect of denosumab has been shown to increase in frequency with longer duration of therapy. As a result, there is no safety reason to limit the duration of denosumab therapy. Since, unlike bisphosphonates, the skeletal effects of denosumab, including protection from vertebral fracture, are quickly and completely reversible, the Q6M dosing regimen must be strictly and consistently adhered to. There is no justification for a temporary interruption of therapy (so-called “drug holiday”) with denosumab. If therapy is discontinued, either because of intolerance or the patient having met a treatment goal, it would be very prudent to take pharmacological measures to prevent the rapid bone loss and the return of fracture risk.

The availability of denosumab broadens and enhances our menu of osteoporosis treatment options. It has already found its place among the important treatments for osteoporosis in postmenopausal women and older men, and it will likely be very useful in treating other forms of bone diseases associated with increased bone remodeling. Used alone, it effectively, quickly and persistently reduces the risk of important osteoporotic fractures. In already has a role as follow-on therapy for patients who have received maximal benefit from bisphosphonate therapy or who have completed a course of anabolic therapy. There will likely never be a more potent anti-remodeling agent. Denosumab will be an important component of pharmacological management of osteoporosis as the treatment paradigm shifts toward sequential or combined therapy.

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Conflict of interest

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