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# Denosumab: A novel antiresorptive drug for osteoporosis

## ABSTRACT

Denosumab is a novel antiresorptive drug that has been approved for use as a first-line drug for primary and secondary prevention of osteoporotic fractures. The authors discuss the mechanism of action of denosumab, review the evidence for its efficacy and safety in patients with osteoporosis, and offer recommendations for its use in clinical practice.

## KEY POINTS

Denosumab is a fully human monoclonal antibody that targets the receptor activator of nuclear factor kappa B ligand, a key mediator of osteoclastic bone resorption.

Compared with placebo, denosumab has been shown to significantly reduce the risk of vertebral, nonvertebral, and hip fractures in postmenopausal women with osteoporosis.

Patients taking denosumab are more adherent, compliant, and persistent with therapy than those taking alendronate. Denosumab is also superior to alendronate in improving bone mineral density at all skeletal sites.

Denosumab is safe, with safety data now available for up to 8 years of exposure.

A 68-year-old white woman presents with mid-thoracic back pain. Plain radiographs reveal a compression fracture of the 10th thoracic vertebra. She is diagnosed with osteoporosis on the basis of dual energy x-ray absorptiometry (DXA) scans that show T scores of  $-2.9$  in her lumbar spine and  $-2.6$  in her left femoral neck. Her 10-year probability of fracture is estimated as 23% for major osteoporotic fracture and 5.9% for hip fracture (based on the World Health Organization's absolute fracture risk assessment tool, adapted for the United States, and available at [www.shef.ac.uk/FRAX](http://www.shef.ac.uk/FRAX)).

After excluding common secondary causes of osteoporosis, her physician recommends a bisphosphonate to reduce her risk of fracture, but she develops upper-gastrointestinal adverse effects with both alendronate and risedronate despite correctly following the instructions for oral administration.

What should her physician consider next?

## ■ OSTEOPOROSIS IS A MAJOR PROBLEM

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, predisposing to an increased risk of fragility fractures, particularly of the spine, hip, and wrist.

It is a major public health problem, affecting 200 million people throughout the world, with 9 million osteoporotic fractures reported in the year 2000.<sup>1</sup> The incidence of hip fracture alone is predicted to rise to 2.6 million by the year 2025, and to 4.5 million by the year 2050.<sup>2</sup> In the United States, the total burden was estimated to be about 2 million incident fractures in the year 2005, projected to rise by another 50% by the year 2025,<sup>3</sup> primarily because of the aging of the population. Population studies have indeed suggested that about 40% of white women and 13% of white men

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**Consequences  
of osteoporotic  
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over the age of 50 are at risk of sustaining an osteoporotic fracture during the remainder of their lifetime.<sup>4</sup>

The consequences of osteoporotic fractures can be devastating. Hip fractures are associated with a risk of death ranging from 8.4% to 36% during the first year after fracture.<sup>5</sup> One-fifth of patients who sustain a hip fracture require long-term nursing home care, and more than half of the survivors do not regain their previous level of independence.

Patients with vertebral fractures are also at increased risk of death, although the results of some studies suggest that this could be the result of comorbid factors.<sup>6-9</sup> Vertebral fractures can result in chronic back pain, loss of height from spinal deformity, reduced mobility, loss of self-esteem, and in severe cases, respiratory and digestive problems because of contact between the lower ribs and pelvis.

A person with one vertebral compression fracture is five times more likely to have another vertebral fracture,<sup>10</sup> and a person with two or more compression fractures is 12 times more likely.<sup>11</sup>

The costs of treating osteoporotic fractures are greater than those of treating myocardial infarction or stroke<sup>12,13</sup>; they include not only direct costs incurred in treating the fracture, but also indirect societal costs owing to the long-term morbidity associated with the fracture. In the United States, the total cost of treating osteoporotic fractures was estimated at \$19 billion in the year 2005.<sup>3</sup> By 2025, the annual costs are projected to rise by almost 50%.<sup>3</sup>

■ **A NEED FOR MORE OPTIONS**

Until fairly recently, bisphosphonates were the only drugs of first choice, but adherence to oral bisphosphonate therapy is generally poor (< 50% at 1 year),<sup>14</sup> most commonly because of dyspepsia,<sup>15</sup> and poor adherence has been shown to be associated with increased fracture risk.<sup>16,17</sup> Hence the need for additional therapeutic options.

In this review, we discuss denosumab, an antiresorptive drug approved by the US Food and Drug Administration (FDA) in 2010. First, we discuss its mechanism of action, efficacy, and safety, and then we offer recommendations for its use in clinical practice.

■ **WHAT IS DENOSUMAB  
AND HOW DOES IT WORK?**

Bone remodeling is a dynamic process involving a balance between bone resorption by osteoclasts on the one hand and new bone formation by osteoblasts on the other. A net gain in bone occurs when the activity of osteoblasts exceeds that of osteoclasts, and bone loss occurs when there is increased osteoclast activity or reduced osteoblast activity, or both. The activities of osteoblasts and osteoclasts are tightly coupled because of the opposing effects of two sets of proteins, namely, receptor activator of nuclear factor kappa b ligand (RANKL) and osteoprotegerin.

Both RANKL and osteoprotegerin are produced by osteoblasts. RANKL binds to its receptor (RANK) on preosteoclasts and osteoclasts and induces their differentiation and activation, respectively. Osteoprotegerin is the decoy receptor and natural antagonist for RANKL. By binding with RANKL, it blocks its interaction with RANK.<sup>18</sup> In healthy individuals, a fine balance between RANKL and osteoprotegerin ensures that bone remodeling is regulated.

In postmenopausal women, estrogen deficiency leads to an imbalance between RANKL and osteoprotegerin (increased RANKL and reduced osteoprotegerin), resulting in net bone loss. This imbalance is also a feature of rheumatoid arthritis, myeloma bone disease, and osteolytic metastatic bone disease; it also occurs in those receiving androgen deprivation therapy for prostate cancer or aromatase inhibitors for breast cancer.

Denosumab is a fully human monoclonal antibody that targets RANKL.<sup>19</sup> By binding to RANKL, this drug prevents the maturation and differentiation of preosteoclasts and promotes apoptosis of osteoclasts. Bone resorption is therefore slowed. It was parenteral osteoprotegerin that was initially developed by denosumab's manufacturer,<sup>20</sup> but this approach failed because neutralizing antibodies developed to osteoprotegerin, rendering it ineffective. Development of neutralizing antibodies has thus far not been a problem with denosumab.

Denosumab, with its property of RANKL inhibition, has also been used to prevent skeletal events in patients with bone metastases

from solid tumors and to treat unresectable giant cell tumors of the bone (both FDA-approved indications) and hypercalcemia of malignancy. There is limited clinical experience in Paget disease of the bone as well.<sup>21–23</sup> These other potential uses of denosumab are beyond the scope of this review.

## ■ HOW WELL DOES DENOSUMAB WORK FOR OSTEOPOROSIS?

Several phase 2 and phase 3 randomized controlled trials have evaluated the efficacy of denosumab, but only one, the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial, included fracture reduction as the primary outcome measure. The rest evaluated changes in bone mineral density or in markers of bone turnover, or both.

**FREEDOM** was a double-blind, randomized controlled trial in 7,808 postmenopausal women with T scores between  $-2.5$  and  $-4.0$  at the lumbar spine or hip.<sup>24</sup> Twenty-four percent of the patients had vertebral fractures at baseline. Patients were randomized to receive either denosumab 60 mg ( $n = 3,902$ ) or placebo ( $n = 3,906$ ) every 6 months for up to 36 months. All patients also received adequate calcium and vitamin D supplementation.

At 36 months, compared with those who were randomized to receive placebo, those who were randomized to denosumab had lower incidence rates of:

- New vertebral fracture (2.3% vs 7.2%, risk ratio 0.32, 95% CI 0.26–0.41,  $P < .001$ )
- Nonvertebral fracture (6.5% vs 8.0%, risk ratio 0.80, 95% CI 0.67–0.95,  $P = .01$ )
- Hip fracture (0.7% vs 1.2%, risk ratio 0.60, 95% CI 0.37–0.97,  $P = .04$ ).

Increases in bone mineral density at the lumbar spine and hip, and decreases in bone turnover markers were also significantly greater in the denosumab group. The number needed to treat to prevent one new fracture over 3 years was 21 for vertebral fracture, 67 for nonvertebral fracture, and 200 for hip fracture, reflecting the relatively low event rate in the study.

In an open-label extension of the FREEDOM trial, the fracture incidence rates among participants who continued to receive denosumab for an additional 5 years remained low, and still below those projected for a “virtual placebo cohort” (total duration of exposure of 8 years). The rates among participants who switched from placebo to denosumab were similar to those of the denosumab group from the parent trial.<sup>25,26</sup>

A subgroup analysis of the FREEDOM trial suggested that denosumab reduced the risk of new vertebral fractures irrespective of age, body mass index, femoral neck bone mineral density, prevalent vertebral fractures, or prior nonvertebral fractures (risk ratio 0.32; 95% CI 0.26–0.41,  $P < .001$ ), whereas the risk of nonvertebral fractures was only reduced in those women with body mass indices less than 25 kg/m<sup>2</sup>, femoral neck bone mineral density T scores less than  $-2.5$ , and in those without a prevalent vertebral fracture.<sup>27</sup>

A post hoc analysis revealed that denosumab significantly reduced the risk of new vertebral and hip fractures even in subgroups of women at higher risk of fracture.<sup>28</sup> At 10% fracture probability (as estimated by the FRAX risk calculator), denosumab reduced the fracture risk by 11% ( $P = .629$ ), whereas at 30% probability (moderate to high risk), the reduction was 50% ( $P = .001$ ).<sup>29</sup>

Other phase 2 and phase 3 trials, in postmenopausal women with low bone mineral density, demonstrated that compared with placebo, denosumab significantly increased bone mineral density at all skeletal sites, increased volumetric bone mineral density at the distal radius, improved hip structural analysis parameters, and reduced bone turnover markers.<sup>30–33</sup> Increases in bone mineral density and reductions in bone turnover markers with denosumab have been shown in men as well.<sup>34</sup>

In a randomized controlled trial,<sup>35</sup> improvement in bone mineral density was better in those who received the combination of denosumab and teriparatide than in those who received either drug on its own.

Denosumab has also been shown to reduce the incidence of new vertebral fractures and improve bone mineral density in men receiving androgen-deprivation therapy for nonmetastatic prostate cancer,<sup>36</sup> and to improve bone

**Denosumab is a fully human monoclonal antibody that targets RANKL**

**TABLE 1**

**Antifracture efficacy of osteoporosis drugs relative to placebo**

Drug	Relative risk (95% confidence interval)			
	Hip fracture	Vertebral fracture	Wrist fracture	Other fractures
<b>Alendronate</b>	0.62 (0.40–0.98)	0.56 (0.46–0.68)	0.67 (0.34–1.31)	0.81 (0.68–0.97)
<b>Risedronate</b>	0.74 (0.59–0.93)	0.61 (0.50–0.75)	0.68 (0.43–1.08)	0.76 (0.64–0.91)
<b>Strontium ranelate</b>	0.85 (0.61–1.19)	0.60 (0.53–0.69)	Not assessed	0.84 (0.73–0.97)
<b>Raloxifene</b>	1.13 (0.66–1.96)	0.65 (0.53–0.79)	0.89 (0.68–1.15)	0.92 (0.79–1.07)
<b>Denosumab</b>	0.60 (0.37–0.97)	0.32 (0.26–0.41)	Not assessed	0.80 (0.67–0.95)

DATA FROM NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE (NICE). NICE TECHNOLOGY APPRAISAL GUIDANCE: TA161. ALENDRONATE, ETIDRONATE, RISEDRONATE, RALOXIFENE, STRONTIUM RANELATE AND TERIPARATIDE FOR THE SECONDARY PREVENTION OF OSTEOPOROTIC FRAGILITY FRACTURES IN POSTMENOPAUSAL WOMEN (AMENDED). [HTTP://PUBLICATIONS.NICE.ORG.UK/ALENDRONATE-ETIDRONATE-RISEDRONATE-RALOXIFENE-STRONTIUM-RANELATE-AND-TERIPARATIDE-FOR-TA161](http://publications.nice.org.uk/alendronate-etidronate-risedronate-raloxifene-strontium-ranelate-and-teriparatide-for-ta161). ACCESSED NOVEMBER 5, 2014.

mineral density in women with metastatic breast cancer and low bone mass who were receiving adjuvant aromatase inhibitor therapy.<sup>37</sup>

**■ HOW DOES DENOSUMAB COMPARE WITH OTHER OSTEOPOROSIS DRUGS?**

A double-blind randomized controlled trial in postmenopausal women with low bone mass demonstrated that denosumab was superior to alendronate in improving bone mineral density at all skeletal sites (3.5% vs 2.6% for total hip bone mineral density,  $P < .0001$ ).<sup>38</sup>

Another double-blind trial demonstrated that in patients previously treated with alendronate, switching to denosumab resulted in significantly greater increases in bone mineral density at all skeletal sites compared with continuing with alendronate ( $P < .0001$ ).<sup>39</sup>

Denosumab has also been shown to be superior to alendronate in improving cortical bone mineral density, as measured by quantitative computed tomography.<sup>40</sup>

No trial has directly compared the efficacy of denosumab with other osteoporosis drugs in reducing fracture risk, but a systematic literature review of multiple databases,<sup>41</sup> comparing the antifracture efficacy of nine osteoporosis drugs, concluded that teriparatide, zoledronic acid, and denosumab had the highest probabilities of being most efficacious for nonvertebral and vertebral fractures, with the greatest effect sizes. Indirect comparisons of the relative risk of fracture with denosumab (based on the

results of FREEDOM), alendronate, risedronate, raloxifene, and strontium (based on a meta-analysis of randomized controlled trials) are presented in **TABLE 1**.<sup>42</sup>

A 2-year randomized, open-label, crossover study<sup>43</sup> randomized patients to receive either denosumab followed by alendronate or alendronate followed by denosumab over successive 12-month periods. The results suggested that postmenopausal women with osteoporosis were more adherent, compliant, and persistent with denosumab therapy (a subcutaneous injection every 6 months) than with alendronate therapy in the form of oral tablets, self-administered weekly (7.5% nonadherence vs 36.5% at the end of 2 years). After receiving both treatments, women reported greater satisfaction with denosumab, with 92.4% preferring it over oral alendronate. Bone mineral density remained stable when patients were switched from denosumab to alendronate, but improved further when they were switched from alendronate to denosumab.

**■ HOW SAFE IS DENOSUMAB?**

The most frequent adverse events with denosumab reported in the long-term extension of one phase 2 study were upper respiratory tract infections (13.5%), arthralgia (11.5%), and back pain (9.0%).<sup>30</sup>

Increased risk of infection, cancer, and dermatologic reactions has been a concern, as RANKL and RANK are expressed by a wide

**Denosumab  
dosage: 60 mg  
subcutaneously  
every 6 months**



variety of cells, including T lymphocytes, B cells, and dendritic cells.<sup>44</sup> However, there were no significant differences in the overall incidences of adverse events between patients who received denosumab and those who received placebo or alendronate in any of the phase 2, phase 3, or extension studies.

In the FREEDOM trial,<sup>24</sup> there was no significant difference between the two groups in the overall incidence of infection (52.9% with denosumab vs 54.4% with placebo,  $P = .17$ ), or serious infection (4.1% with denosumab vs 3.4% with placebo,  $P = .14$ ), although the incidence of “serious” cellulitis requiring hospitalization was higher in the denosumab group (0.3% vs < 0.1%,  $P = .002$ ). There were more serious infections involving the gastrointestinal system, urinary tract, and ear and cases of endocarditis in the denosumab group, but the number of events was small, and there was no relationship with the timing of administration or duration of exposure to denosumab.<sup>45</sup> Eczema was more common in the denosumab than in the placebo group (3.0% vs 1.7%,  $P < .001$ ), but the extension data from the first 3 years did not provide any evidence for an increased risk of cellulitis or eczema with denosumab.<sup>26</sup>

Although randomized controlled trials reported more cases of neoplasms in the denosumab than in the placebo groups, meta-analyses have failed to detect a statistically significant difference (risk ratio 1.11, 95% CI 0.91–1.36).<sup>46</sup> The overall incidence of adverse and serious adverse events reported in the 8-year extension of FREEDOM were consistent with data reported in the previous extension studies.<sup>25</sup>

In the FREEDOM extension trial, four events in the long-term group ( $n = 2,343$ ), and two in the crossover group ( $n = 2,207$ ) were adjudicated as being consistent with osteonecrosis of the jaw.<sup>26</sup> One mid-shaft fracture in the crossover group was adjudicated as an atypical femoral fracture. There were, however, no reports of osteonecrosis of the jaw or atypical femoral fracture in the long-term phase 2 trial after 8 years of follow-up.<sup>30</sup> By September 2013, postmarketing safety surveillance data for denosumab (estimated exposure of 1.2 million patient-years) had recorded four cases of atypical femoral fracture. All four patients had pre-

viously been on bisphosphonates. There were also 32 reports of osteonecrosis of the jaw.<sup>47</sup>

Denosumab’s manufacturer aims to communicate the risks of treatment to health care professionals and patients. Information is available online at [www.proliahcp.com/risk-evaluation-mitigation-strategy/](http://www.proliahcp.com/risk-evaluation-mitigation-strategy/).

## ■ WHAT ARE THE PRECAUTIONS?

Several precautions need to be taken when considering treatment with denosumab.

Antiresorptives can aggravate hypocalcemia by inhibiting bone turnover. Serum calcium should therefore be checked and preexisting hypocalcemia should be corrected before starting denosumab.<sup>48</sup>

Denosumab is contraindicated in women who are pregnant or are planning to become pregnant, as fetal loss and teratogenicity have been reported in animal experiments. (Denosumab is unlikely to be used in premenopausal women, as it is not approved for use in this group.)

There are no data on excretion of denosumab in human milk, so it should not be given to nursing mothers.

Renal impairment is not a contraindication, and no dose adjustment is necessary (even for patients on renal replacement therapy), as denosumab, being an antibody, is eliminated through the reticuloendothelial system.<sup>49,50</sup> However, in practice, any antiresorptive agent should be used with caution in patients with severe renal impairment because of the possible presence of adynamic bone disease. Further reduction of bone turnover would be detrimental in such patients. Also, severe hypocalcemia has been reported in patients with a creatinine clearance rate less than 30 mL/min and in those receiving dialysis.<sup>51,52</sup> Postmarketing surveillance data have reported eight cases of severe symptomatic hypocalcemia, of which seven were in patients with chronic kidney disease.<sup>47</sup>

The manufacturer suggests that patients receive a dental examination with appropriate preventive dentistry before starting denosumab to reduce the incidence of osteonecrosis of the jaw, despite the lack of evidence in support of this strategy. The American Dental Association recommends regular dental vis-

**Check serum calcium and correct hypocalcemia before starting denosumab**

its and maintenance of good oral hygiene for patients already established on antiresorptive therapy.<sup>53,54</sup>

### ■ SHOULD PATIENTS ON DENOSUMAB BE OFFERED A DRUG HOLIDAY?

A drug holiday (temporary discontinuation of the drug after a certain duration of treatment) has been proposed for patients receiving bisphosphonates because of the risk of atypical femoral fracture and osteonecrosis of the jaw (although small) consequent to long-term continuous suppression of bone turnover.<sup>55</sup> The antifracture efficacy of bisphosphonates is likely to persist for an unknown length of time after discontinuation because of their long skeletal half-life, while the risks gradually diminish.

By contrast, denosumab targets RANKL in the extracellular fluid and does not become embedded within the bone tissue.<sup>56</sup> Pharmacokinetic studies have shown that denosumab has a rapid offset of action, with a half-life of only 26 days and biological activity lasting only 6 months.<sup>57</sup> The results of a phase 2 extension study suggest that bone mineral density starts to decline and bone turnover markers start to rise within 12 months of discontinuing denosumab.<sup>58</sup>

Although fracture risk did not increase in those who were randomized to stopping the treatment and bone mineral density increased further when treatment was restarted, a drug holiday cannot presently be recommended for patients receiving denosumab because of the lack of supportive data.

### ■ HOW COST-EFFECTIVE IS DENOSUMAB?

The wholesale acquisition cost is \$825 per 60-mg prefilled syringe of denosumab, although this may vary depending on where the drug is obtained. This does not include physician-related service costs associated with administration of denosumab.

Cost-effectiveness analyses conducted in the United States, the United Kingdom, and Sweden have all concluded that denosumab would offer a cost-effective alternative to other osteoporosis medications for primary prevention and secondary prevention of fractures.<sup>59–61</sup> The Swedish study also incorporated

adherence in the cost-effectiveness model and showed that denosumab was a cost-effective alternative to oral bisphosphonates, particularly for patients who were not expected to adhere well to oral treatments.<sup>61</sup>

### ■ WHICH OSTEOPOROSIS PATIENTS ARE CANDIDATES FOR DENOSUMAB?

The FDA has approved denosumab for the treatment of postmenopausal women and men at high risk of fracture (defined as having a history of osteoporotic fracture or multiple risk factors for fracture), or in those who cannot tolerate other osteoporosis medications or for whom other medications have failed.

Denosumab is also approved for men at high risk of fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer, and for women at high risk of fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.

### ■ WHAT DO THE GUIDELINES RECOMMEND?

The National Osteoporosis Foundation guidelines recommend pharmacologic treatment for patients with hip or vertebral fractures (clinical or asymptomatic); T scores lower than  $-2.5$  at the femoral neck, total hip, or lumbar spine; and those with a 10-year probability of hip fracture of more than 3% or of a major osteoporotic fracture more than 20% based on the US-adapted FRAX calculator.<sup>62</sup> The American College of Endocrinology guidelines have proposed similar thresholds for pharmacologic treatment, and they recommend alendronate, risedronate, zoledronate, and denosumab as first-line agents.<sup>63</sup>

The 2010 Osteoporosis Canada guidelines recommend denosumab, alendronate, risedronate, and zoledronate as first-line therapies for preventing hip, nonvertebral, and vertebral fractures in postmenopausal women (grade A recommendation).<sup>64</sup> The National Institute of Health and Clinical Excellence in England and Wales, on the other hand, recommends denosumab only for patients who are unable to take a bisphosphonate.<sup>65</sup>

### ■ PRACTICAL PRESCRIBING TIPS

The patient described at the beginning of this article has already sustained a vertebral com-

**Denosumab costs about \$825 per dose, but may be cost-effective**

pression fracture, and her DXA scan shows T scores in the osteoporotic range. She is therefore at increased risk of another fragility fracture (with a fivefold higher risk of another vertebral fracture). Pharmacologic therapy should be considered. In addition, she should be encouraged to adhere to lifestyle measures such as a healthy diet and regular weight-bearing exercise, her risk of falling should be assessed, and adequate calcium and vitamin D supplementation should be given.

Secondary causes of osteoporosis are present in about 30% of women and 55% of men who have vertebral fractures.<sup>66</sup> A complete blood count, erythrocyte sedimentation rate, bone biochemistry, 25-hydroxyvitamin D, thyroid-stimulating hormone, and renal and liver function tests should be requested in all patients. Further tests should be considered depending on the clinical evaluation and results of initial investigations.

Because this patient cannot tolerate oral bisphosphonates, she could be offered the option of annual intravenous zoledronic acid infusions or 6-monthly subcutaneous denosumab injections. In clinical trials, gastrointestinal adverse effects were noted with intravenous bisphosphonates as well, but the adverse effects reported were no different than those with placebo. The potential advantages with denosumab include better bone mineral density gains, adherence and patient satisfaction compared with oral bisphosphonates, convenient twice-yearly administration, safety in patients with renal impairment, and absence of gastrointestinal effects.

Raloxifene, a selective estrogen receptor modulator, has estrogen-like action on the bone and antiestrogen actions on the breast and uterus. Unlike standard hormone replacement therapy, raloxifene can therefore increase bone mineral density without increasing the risk of breast and endometrial cancers. However, it has only been shown to reduce the risk of vertebral fracture, not hip fracture. Hence, it would be a more appropriate choice for younger postmenopausal women. Moreover, it may cause troublesome menopausal symptoms.

Teriparatide, the recombinant parathyroid hormone, is an anabolic agent. It is very expensive, and because of this, guidelines in sev-

eral countries restrict its use to women with severe osteoporosis and multiple fractures who fail to respond to standard treatments. It cannot be used for longer than 2 years because of its association with osteosarcoma in rats.

If our patient prefers denosumab, therapy should be initiated after appropriate counseling (see precautions above). The dose is 60 mg, given subcutaneously, once every 6 months.

### Monitoring

There is no consensus regarding the optimal frequency for monitoring patients on treatment, owing to the lack of prospective trial data. The National Osteoporosis Foundation recommends repeating the bone mineral density measurements about 2 years after starting therapy, and about every 2 years thereafter.<sup>62</sup> Some studies suggest that changes in bone mineral density correlate with reduction in fracture risk.<sup>67,68</sup> A change in bone mineral density is considered significant when it is greater than the range of error of the densitometer (also known as the least significant change).<sup>69</sup> If the bone mineral density is stable or improving, therapy could be continued, but if it is declining and the decline is greater than the least significant change, a change in therapy should be considered if no secondary causes for bone loss are evident (but see **WHAT ARE THE AREAS OF UNCERTAINTY?** below).

The National Osteoporosis Foundation also recommends measuring a bone turnover marker at baseline and then 3 to 6 months later, as its suppression predicts greater bone mineral density responses and fracture risk reduction.<sup>70</sup> If there is a decrease of more than 30% in serum carboxy-terminal collagen crosslinks (CTX) or more than 50% in urinary N-telopeptide (NTX),<sup>71</sup> the patient can be reassured that the next bone mineral density measurement will be stable or improved. In patients on oral bisphosphonates, measurement of bone turnover markers also provides evidence of compliance.

Clinical trials suggest that a numerical increase in bone mineral density can be expected in most patients on treatment, though this depends on the measurement site and the length of time between examinations. In one phase 3 trial of denosumab in postmenopausal women, only 5% of the participants had unchanged or

**Secondary causes of osteoporosis are present in about 30% of women and 55% of men who have a vertebral fracture**

diminished bone mineral density at the lumbar spine, and 8% at the hip, after 36 months of treatment.<sup>72</sup> However, the CTX levels fell to below the lower limit of the reference interval as early as 1 month after commencing treatment in all denosumab-treated patients.<sup>68</sup>

Hence, bone turnover markers may be a more sensitive indicator of treatment effect than bone mineral density, but this would ultimately need to be evaluated against fracture rates in a real-world setting.

### ■ WHAT ARE THE AREAS OF UNCERTAINTY?

There are currently no guidelines for long-term management of patients on denosumab, and also no data to suggest whether patients should be switched to a weaker antiresorptive drug after a certain number of years in order to reduce the possible risk of atypical femoral fracture or osteonecrosis of the jaw.

No head-to-head trials have directly compared the antifracture efficacy of denosumab with that of other standard osteoporosis therapies. The antifracture efficacy and safety of combination therapies involving denosumab are also uncertain. For adherent patients who have a suboptimal response, there is no evidence to guide the further course of action. The International Osteoporosis Foundation guidelines suggest replacing a stronger antire-

sorptive with an anabolic agent, but acknowledge that this is only based on expert opinion.<sup>71</sup>

The very-long-term effects (beyond 8 years) of continuous denosumab administration on increasing the risk of atypical femoral fracture, osteonecrosis of the jaw, malignancy, or infection or the duration after which risks would start to outweigh benefits is not known. However, postmarketing safety data continue to be collected through the voluntary Postmarketing Active Safety Surveillance Program (for prespecified adverse events) in addition to the FDA's MedWatch program.

### ■ CASE PROGRESSION

*The patient described in the vignette is presented with two options—zoledronate and denosumab. She chooses denosumab. Her renal function and serum calcium are checked and are found to be satisfactory. She undergoes a dental examination, which is also satisfactory. She is counseled about the possible increased risk of infection, and then she is started on 60 mg of denosumab subcutaneously, once every 6 months.*

*When reviewed after 2 years, she reports no further fractures. Her bone mineral density remains stable compared with the values obtained before starting treatment. She reports no adverse effects and is happy to continue with denosumab.* ■

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