

# Clinical utility of denosumab for treatment of bone loss in men and women

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**Abstract:** While most older patients with osteoporosis are treated with antiresorptive bisphosphonates such as alendronate, risedronate, ibandronate, and zoledronic acid, such drugs have side effects, remain in bone for extended periods, and lead to poor adherence to chronic treatment. Denosumab is a humanized monoclonal antibody and antiresorptive agent that works by decreasing the activity of the receptor activator of nuclear factor kappa B ligand. In major trials in postmenopausal women, denosumab increased bone mineral density by dual energy x-ray absorptiometry in the spine, hip, and distal third of the radius and decreased vertebral, nonvertebral, and hip fractures. Denosumab is administered by subcutaneous injection every six months, suggesting that adherence may be improved with such therapy. In addition, pharmacokinetic studies measuring bone turnover markers imply that the antiresorptive effect diminishes more quickly over time. Whether these properties will lead to fewer long-term side effects needs to be proven. Denosumab has also been studied in men with prostate cancer treated with androgen deprivation therapy. These men, at high risk for fracture, also have increases in spine, hip, and forearm dual energy x-ray absorptiometry, as well as fewer morphologic vertebral fractures on x-ray. Denosumab is approved for postmenopausal women with osteoporosis in the US and Europe and for men on androgen deprivation therapy in Europe.

**Keywords:** osteoporosis, fracture, denosumab, bisphosphonates, dual energy x-ray absorptiometry, androgen deprivation therapy, osteonecrosis of the jaw

## Introduction

Osteoporosis remains an important problem in older adults in spite of the fact that generally safe and effective therapies are available. Bisphosphonates, including the oral bisphosphonates, ie, alendronate, risedronate, and ibandronate, and intravenous bisphosphonates, including ibandronate and zoledronic acid, are indicated for many patients with osteoporosis. These drugs, while usually well tolerated, have been associated with side effects, such as osteonecrosis of the jaw,<sup>1</sup> atrial fibrillation,<sup>2</sup> and atypical fractures of the femoral shaft.<sup>3,4</sup> In addition, oral bisphosphonates have been reported to be associated with an increased risk of esophageal carcinoma.<sup>5,6</sup> While the connection between these side effects and bisphosphonates may not be fully established, and indeed a recent study<sup>7</sup> from Korea suggests that atrial fibrillation may occur less often in patients on bisphosphonates, the incidence of side effects is quite low. Thus, one reason to identify alternative antiresorptive drugs for osteoporosis would be to eliminate or decrease side effects. The mechanism of action and pharmacokinetics of an alternative antiresorptive might also mitigate the side effects. As recently reviewed,<sup>8</sup> studies of bisphosphonates have shown a decrease in fractures of 30%–50% in three-year

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studies, but other evidence shows that some bisphosphonates appear safe and effective for 5–10 years. Nonetheless, the optimal length of bisphosphonate treatment remains to be established. It is interesting that while increasing age is a major risk factor for fracture, most bisphosphonate studies did not include the “old old”.

Most bisphosphonates are oral preparations, usually taken weekly or monthly. Because of poor gut absorption, oral bisphosphonates must be taken fasting with only water. Other medications and nutrients must be postponed for at least half an hour. Zoledronic acid is administered as a yearly intravenous infusion. While zoledronic acid is convenient, some patients will have an acute-phase reaction, particularly with the first dose. Perhaps more importantly, adherence to oral bisphosphonates has been poor,<sup>9–11</sup> whereas long-term adherence to intravenous bisphosphonates has yet to be determined. Patients must take approximately 80% of oral bisphosphonate doses in order to have decreased fracture risk.<sup>12,13</sup> For the elderly patient with a heavy pill burden, the extra work involved with oral bisphosphonate ingestion may lead to poor adherence. Therefore, alternative antiresorptives that are more likely to result in better treatment persistence are very appealing.

Denosumab is a humanized monoclonal antibody directed against the receptor activator of nuclear factor kappa B ligand (RANKL).<sup>14</sup> Normally, RANKL is produced by osteoblasts and acts through the receptor activator of nuclear factor kappa B (RANK) found on osteoclasts and preosteoclasts.<sup>15</sup> RANKL interacts with RANK to stimulate activation of osteoclasts, leading to augmented bone resorption.<sup>16</sup> Interestingly, there is a decoy receptor, known as osteoprotegerin, that prevents RANKL from interacting with RANK, thus leading to less osteoclast activation.<sup>17</sup> In some clinical situations, such as postmenopausal osteoporosis, the relation of RANKL to osteoprotegerin is such that osteoclast activity increases, leading to bone loss.<sup>18</sup> Denosumab acts like osteoprotegerin, diminishing osteoclast activity.<sup>19</sup> Unlike bisphosphonates, denosumab does not become incorporated into bone, yielding a much shorter terminal half-life.<sup>20</sup> Therefore, denosumab presents a potential advantage and a potential disadvantage. For the patient who has a side effect from therapy, denosumab will be no longer active six months after the last dose. On the other hand, if patients are not receiving denosumab regularly, the patient’s fracture risk might increase after the dose “wears off”. The ramifications of this property and some specific examples are discussed in the following.

## Denosumab in women with postmenopausal osteoporosis

Postmenopausal osteoporosis is the most common type of osteoporosis, resulting in the largest number of fractures each year. As the population ages, the number of fractures is predicted to rise dramatically.<sup>21</sup> In addition to the pain, decreased mobility, and cost, hip fractures, and to a lesser extent vertebral fractures, lead to increased mortality in women and men.<sup>22,23</sup> Hence, treatments that decrease fracture risk improve and extend the lives of patients at risk. As stated earlier, antiresorptive bisphosphonates have been the most commonly used medications in patients with osteoporosis. Bisphosphonates decrease fracture risk by about 40%–50% over the short term (three years or so). While there is controversy about whether the various bisphosphonates differ in their effectiveness, there are no head-to-head studies that demonstrate better fracture risk reduction by a given bisphosphonate.<sup>24,25</sup> For this reason, weekly generic alendronate is usually the first treatment of choice because of its low cost. On the other hand, there is some evidence that a monthly bisphosphonate preparation or an annual intravenous preparation may improve persistence with therapy. Denosumab has the potential to improve adherence to therapy because it is administered as a subcutaneous injection every six months, thus not adding to the pill burden of older patients.

Denosumab has been tested in four Phase III studies in postmenopausal women. The registration trial called FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months) is the largest and most important. In this trial, almost 8000 women were randomized to receive either denosumab 60 mg or placebo by subcutaneous injection every six months for three years.<sup>26</sup> To be included in the study, women aged 60–90 years had to have a bone density T score < –2.5 in the lumbar spine or total hip. Exclusion criteria included a T score < –4, one severe or two moderate prevalent fractures on spine x-ray, or recent exposure to oral glucocorticoids or hormone replacement therapy. All subjects received calcium and vitamin D supplements. The primary outcome was a new vertebral fracture diagnosed by spine x-ray. At three years, 2.3% of the women in the active drug group had a new vertebral fracture compared with 7.2% of placebo subjects. This was a statistically significant 68% relative risk reduction and an almost 5% absolute risk reduction. Clinical vertebral fractures were reduced to approximately the same extent. Nonvertebral fractures were also reduced, ie, by 6.5% versus 8.0%,  $P = 0.01$ ). The time to first hip fracture was

significantly shorter in the placebo group. Bone mineral density increased relative to the placebo group by 9.2% (spine) and 6% (total hip). Bone turnover markers reflecting both osteoclastic and osteoblastic activity were suppressed by denosumab compared with placebo. Adverse events included local injection site reactions (0.8% denosumab, 0.7% placebo), eczema (3% denosumab, 1.7% placebo,  $P < 0.001$ ), and cellulitis (0.3% denosumab,  $<0.1\%$  placebo,  $P = 0.002$ ). No cases of osteonecrosis of the jaw were found, and the overall rates of infection and cancer as adverse events were the same in the active drug and placebo groups.<sup>26</sup>

A recent post hoc analysis of the FREEDOM trial evaluated fracture incidence in women with known risk factors for fractures, including multiple and/or moderate or severe prevalent vertebral fractures, age 75 years or older, and/or having a femoral neck bone mineral density T score  $\leq -2.5$ .<sup>27</sup> Compared with placebo, denosumab significantly reduced the risk of new vertebral fractures in women with multiple and/or severe vertebral fractures (7.5% denosumab versus 16.6% placebo,  $P < 0.001$ ). Similarly, denosumab significantly reduced the risk of hip fractures in subjects aged 75 years or older (0.9% denosumab versus 2.3% placebo,  $P < 0.01$ ) or with a baseline femoral neck bone mineral density T score  $\leq -2.5$  (1.4% denosumab versus 2.8% placebo,  $P = 0.02$ ). These risk reductions in higher-risk individuals were consistent with those seen in patients at lower risk of fracture.

Osteoporosis is a chronic disorder, and most experts recommend at least five years of bisphosphonate treatment, based on relatively limited data.<sup>8,28</sup> The pivotal fracture trial for denosumab described earlier is being followed by a longer-term extension study. In the meantime, there are now some data on up to six years of denosumab treatment. In an extension of a Phase II study, some postmenopausal women have been treated with continuous denosumab or have started denosumab after 1–4 years of placebo treatment (with some subjects having received some years of denosumab or alendronate therapy).<sup>29</sup> From the relatively small number of subjects studied, it can be concluded that continuous denosumab leads to further gains of bone mineral density (lumbar spine 2.9%, total hip 1.1%, femoral neck 1.2%, distal third of radius 1% over the two-year extension).<sup>29</sup> Bone resorption markers continued to be at about half the level at the original baseline. Without a full placebo group for the two-year extension it is difficult to determine the importance of the adverse events reported. Upper respiratory infections, arthralgias, and back pain were the most common adverse events reported during the extension.

Another study compared the bone density changes over one year in postmenopausal women randomized to denosumab or alendronate.<sup>30</sup> At baseline, the women had a T score at the spine or total hip  $\leq -2$ . Women receiving denosumab had increased bone density at the total hip, femoral neck, lumbar spine, and distal third of radius of 3.5%, 2.4%, 5.3%, and 1.1%, respectively, all significantly greater than the changes measured in the women on weekly alendronate (2.6%, 1.8%, 4.2%, and 0.6%, respectively). There were no differences in adverse events between the two treatment groups, although this was only a one-year study with approximately 1200 participants. There is controversy over whether a greater improvement in bone density translates into a greater decrease in fracture risk.<sup>31,32</sup> Nonetheless, the robust increase in bone density by denosumab and the fracture decrease reported in the registration trial strengthen the conclusion that denosumab is efficacious.

## Denosumab in androgen deprivation therapy

Prostate cancer is very common in aging men, and androgen deprivation therapy (ADT) is used in many cases. A man with localized prostate cancer on ADT is at great risk for fracture, as high as 20% over five years, despite having a good overall survival outlook.<sup>33–35</sup> Hip fracture in older men has particularly severe consequences. Men aged 75–84 years have a one in three chance of dying by one year after a hip fracture.<sup>36</sup> Thus, treatment of older men on ADT might lead to both decreased fracture risk and decreased mortality. Bisphosphonates have been used successfully in men on ADT, but the same potential problems of adherence to therapy may actually be exaggerated in men on ADT.<sup>37</sup> After all, they have a cancer, and are affected by the other side effects of ADT.<sup>38</sup> Treatment of osteoporosis in such men has no impact on how they feel, unless the treatment prevents a fracture. Convincing a man on ADT to be concerned about his bones is challenging, and persistence in taking a weekly or even monthly oral bisphosphonate will likely not be good. While yearly intravenous zoledronic acid works well in such patients, denosumab is also attractive because it can be given subcutaneously at every other administration of ADT therapy, which is usually a gonadotropin hormone-releasing hormone analog provided every three months.<sup>39,40</sup> In a study of about 1400 men on ADT, denosumab increased bone density at the spine, hip, and forearm over three years.<sup>41</sup> At two years, ie, the primary analysis endpoint, denosumab increased lumbar spine density by 5.6% compared with a

loss of 1% in the placebo group. This 6.7% difference between the active drug and placebo was similar in the total hip (4.8% difference), femoral neck (3.9%), and distal third of radius (5.5%). The difference in the distal third of radius is of particular interest because loss of forearm bone density is common in men on ADT.<sup>42</sup> There has been one small study of treatment with denosumab in men with primary osteoporosis, the results of which have not been published yet.

## Place of denosumab in osteoporosis treatment

### Approved uses

Denosumab appears to have some potential benefits, only some of which have been studied. First, it is given as a subcutaneous injection in a physician's office. Thus, for the approved use in postmenopausal women in the US and Europe, it is an attractive drug that might lead to better adherence to therapy. In a study of women treated with denosumab for two years, three months after discontinuation of therapy there was a rise of bone turnover markers above the baseline.<sup>43</sup> It is likely that to continue the therapeutic effect would require the patient to return to the clinician's office for another injection every six months. However, even two years after discontinuation of denosumab, bone mineral density was still higher than in placebo-treated patients.

In Europe, denosumab is approved for men on ADT for prostate cancer. For this indication, the drug is attractive because most of the men on ADT are returning to clinicians' offices to receive gonadotropin hormone-releasing hormone analog treatment every three months. Hence, treatment of their osteoporosis risk can conveniently be done by denosumab injection every other visit.

### Unapproved uses

The following scenarios are potential uses for denosumab. These are not approved by government agencies, but might be considered for specific patients. For example, a young woman with asthma requiring glucocorticoids and already having suffered a fragility fracture is at high risk for another fracture.<sup>44</sup> While bisphosphonates are used commonly in glucocorticoid-induced osteoporosis, a woman who retains reproductive potential should generally avoid bisphosphonates because they stay in the skeleton, are recirculated, and their effect on the fetal skeleton is unknown. Teriparatide might be considered because it does not linger in the skeleton after treatment.<sup>45</sup> Denosumab might also be considered in this situation as well. There is only minimal evidence that denosumab works in glucocorticoid-induced osteoporosis, but it

is likely that there will be more studies.<sup>46</sup> Another potential patient is a man who has had an allergic reaction to bisphosphonates and is not a candidate for teriparatide. Some patients refuse to take a daily subcutaneous injection. Others may have a contraindication to teriparatide, such as a history of radiation to bone. There are a few patients who have had severe acute-phase reactions to intravenous zoledronic acid and may refuse another infusion. For such patients, offlabel use of denosumab might be considered. It is hoped that more studies of denosumab will be published, so that there will be guidance for the clinician faced with a patient who does not fit into the categories of those studied so far.

### Side effects of denosumab

As stated earlier, the side effect profile of denosumab has been encouraging from the major published studies. However, the same could be said for the early bisphosphonate trials, and many side effects were only noted after thousands of patients had used bisphosphonates. For example, the original studies of alendronate did not identify any patients with osteonecrosis of the jaw, but of course this has become a well known if unusual side effect. In the registration trial of denosumab, osteonecrosis of the jaw was not seen, but it has been reported in osteoporosis patients.<sup>26</sup> In addition, denosumab has been used to decrease skeletal events in patients with metastatic cancers, and osteonecrosis of the jaw has been reported more commonly in a similar proportion of patients as with zoledronic acid.<sup>47</sup> Hence, we can expect that as many more osteoporosis patients are treated with denosumab, there will be more reports of osteonecrosis of the jaw. The incidence will need to be assessed in comparison with that of other antiresorptive agents. Eczema was noted to occur more frequently in the denosumab subjects (3%) compared with placebo subjects (1.7%) in the pivotal fracture trial.<sup>26</sup> Cellulitis was also more common in subjects receiving denosumab (0.3% versus 0.1%).<sup>26</sup> In other Phase III studies, infections and neoplasms reported as adverse events were about the same in the active drug and placebo groups. Esophageal carcinoma, which may or may not be associated with oral bisphosphonates, is unlikely to be a problem because denosumab is not an oral medication. Atypical fractures of the femoral shaft have been more recently reported in patients taking long-term bisphosphonates for osteoporosis.<sup>3,4</sup> While the mechanism of these fractures, the true incidence, and specific patient susceptibility to them have not been established, it is possible that such atypical fractures will also be found in patients taking long-term denosumab. As with any new medication, postmarketing



surveillance will be important to determine if there are any unexpected side effects.

## Conclusion

Denosumab is potentially a very useful medication for osteoporosis because of the convenience of receiving a subcutaneous injection every six months. It appears to be well tolerated overall, and may be more potent than bisphosphonates, but longer-term studies will be necessary to determine long-term safety. Efficacy in the registration trial is impressive, and short-term safety appears to be acceptable. The long-term effect on bone and fracture risk requires continued vigilance. In addition, long-term studies will be needed to show that the apparent convenience of subcutaneous injection every six months leads to better treatment persistence than present bisphosphonate use.

## Disclosure

The authors report no conflicts of interest in this work.

## References

- Khosla S, Burr D, Cauley J, et al. Bisphosphonate-associated osteonecrosis of the jaw: Report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res*. 2007;22(10):1479–1491.
- Abrahamsen B. Adverse effects of bisphosphonates. *Calcif Tissue Int*. 2010;86(6):421–435.
- Shane E, Burr D, Ebeling PR, et al. Atypical subtrochanteric and diaphyseal femoral fractures: Report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res*. 2010;25(11):2267–2294.
- Rizzoli R, Akesson K, Bouxsein M, et al. Subtrochanteric fractures after long-term treatment with bisphosphonates: A European Society on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis, and International Osteoporosis Foundation Working Group report. *Osteoporos Int*. 2011;22(2):373–390.
- Green J, Czanner G, Reeves G, Watson J, Wise L, Beral V. Oral bisphosphonates and risk of cancer of esophagus, stomach, and colorectum: Case-control analysis within a UK primary care cohort. *BMJ*. 2010;1:341.
- Cardwell CR, Abnet CC, Cantwell MM, Murray LJ. Exposure to oral bisphosphonates and risk of esophageal cancer. *JAMA*. 2010;304(6):657–663.
- Rhee CW, Lee J, Oh S, Choi NK, Park BJ. Use of bisphosphonates and risk of atrial fibrillation in older women with osteoporosis. *Osteoporos Int*. March 24, 2011. [Epub ahead of print].
- Watts NB, Diab DL. Long-term use of bisphosphonates in osteoporosis. *J Clin Endocrinol Metab*. 2010;95(4):1555–1565.
- Silverman SL, Schousboe JT, Gold DT. Oral bisphosphonate compliance and persistence: A matter of choice? *Osteoporos Int*. 2011;22(1):21–26.
- Wilkes MM, Navickis RJ, Chan WW, Lewiecki EM. Bisphosphonates and osteoporotic fractures: A cross-design synthesis of results among compliant/persistent postmenopausal women in clinical practice versus randomized controlled trials. *Osteoporos Int*. 2010;21(4):679–688.
- Petkov VI, Williams MI. Adherence, compliance, and persistence with osteoporosis therapies. In: Adler RA, editor. *Osteoporosis Pathophysiology and Clinical Management*. 2nd ed. New York, NY: Humana Press; 2010.
- Siris ES, Pasquale MK, Wang Y, Watts NB. Estimating bisphosphonate use and fracture reduction among US women aged 45 years and older. *J Bone Miner Res*. 2011;26(1):3–11.
- Hadji P, Claus V, Ziller V, Intorcchia M, Kostev K, Steinle T. GRAND: The German retrospective cohort analysis on compliance and persistence and the associated risk of fractures in osteoporotic women treated with oral bisphosphonates. *Osteoporos Int*. February 10, 2011. [Epub ahead of print].
- Kostenuik PJ, Nguyen HQ, McCabe J, et al. Denosumab, a fully human monoclonal antibody to RANKL, inhibits bone resorption and increases BMD in knock-in mice that express chimeric (murine/human) RANKL. *J Bone Miner Res*. 2009;24(2):185–195.
- Eghbali-Fatourehchi G, Khosla S, Sanyal A, Boyle WJ, Lacey DL, Riggs BL. Role of RANK ligand in mediating increased bone resorption in early postmenopausal women. *J Clin Invest*. 2003;111(8):1221–1230.
- Li J, Sarosi I, Yan XQ, et al. RANK is the intrinsic hematopoietic cell surface receptor that controls osteoclastogenesis and regulation of bone mass and calcium metabolism. *Proc Natl Acad Sci U S A*. 2000;97(4):1566–1571.
- Ross AB, Bateman TA, Kostenuik PJ, et al. The effects of osteoprotegerin on the mechanical properties of rat bone. *J Mater Sci Mater Med*. 2001;12(7):583–588.
- Hofbauer LC, Khosla S, Dunstan CR, Lacey DL, Spelsberg TC, Riggs BL. Estrogen stimulates gene expression and protein production of osteoprotegerin in human osteoblastic cells. *Endocrinology*. 1999;140(9):4367–4370.
- Lewiecki EM. Treatment of osteoporosis with denosumab. *Maturitas*. 2010;66(2):182–186.
- Baron R, Ferrari S, Russell RG. Denosumab and bisphosphonates: Different mechanisms of action and effects. *Bone*. 2011;48(4):677–692.
- Durge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005–2025. *J Bone Miner Res*. 2007;22(3):465–475.
- Morin S, Lix LM, Azimae M, Metge C, Caetano P, Leslie WD. Mortality rates after incident non-traumatic fractures in older men and women. *Osteoporos Int*. December 16, 2010. [Epub ahead of print].
- Haentjens P, Magaziner J, Colon-Emeric CS, et al. Meta-analysis: Excess mortality after hip fracture among older women and men. *Ann Intern Med*. 2010;152(6):380–390.
- MacLean C, Newberry S, Maglione M, et al. Systematic review: Comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. *Ann Intern Med*. 2008;148(3):197–213.
- Rizzoli R. Bisphosphonates for post-menopausal osteoporosis: Are they all the same? *QJM*. 2011;104(4):281–300.
- Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med*. 2009;361(8):756–765.
- Boonen S, Adachi JD, Man Z, et al. Treatment with denosumab reduces the incidence of new vertebral and hip fractures in postmenopausal women at high risk. *J Clin Endocrinol Metab*. March 16, 2011. [Epub ahead of print].
- Black DM, Schwartz AV, Ensrud KE, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-Term Extension (FLEX): a randomized trial. *JAMA*. 2006;296(24):2927–2938.
- Bone HG, Bolognese MA, Yuen CK, et al. Effects of denosumab treatment and discontinuation on bone mineral density and bone turnover markers in postmenopausal women with low bone mass. *J Clin Endocrinol Metab*. 2011;96(4):972–980.
- Brown JP, Prince RL, Deal C, et al. Comparison of the effect of denosumab and alendronate on bone mineral density and biochemical markers of bone turnover in postmenopausal women with low bone mass: A randomized, blinded, phase 3 trial. *J Bone Miner Res*. 2009;14:1–34.

31. Hochberg MC, Greenspan S, Wasnich RD, Miller P, Thompson DE, Ross PD. Changes in bone density and turnover explain the reductions in incidence of nonvertebral fractures that occur during treatment with antiresorptive agents. *J Clin Endocrinol Metab.* 2002;87(4):1586–1592.
32. Eastell R, Vrijens B, Cahall DL, Ringe JD, Garnero P, Watts NB. Bone turnover markers and bone mineral density response with risedronate therapy: Relationship with fracture risk and patient adherence. *J Bone Miner Res.* February 1, 2011. [Epub ahead of print].
33. Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med.* 2005;352(2):154–164.
34. Lu-Yao GL, Albertsen PC, Moore DF, et al. Survival following primary androgen deprivation therapy among men with localized prostate cancer. *JAMA.* 2008;300(2):173–181.
35. Adler RA. Management of osteoporosis in men on androgen deprivation therapy. *Maturitas.* 2011;68(2):143–147.
36. French DD, Bass E, Bradham DD, Campbell RR, Rubenstein LZ. Rehospitalization after hip fracture: Predictors and prognosis from a national veterans study. *J Am Geriatr Soc.* 2008;56(4):705–710.
37. Greenspan SL, Nelson JB, Trump DL, Resnick NM. Effect of once-weekly oral alendronate on bone loss in men receiving androgen deprivation therapy for prostate cancer: A randomized trial. *Ann Intern Med.* 2007;146(6):416–424.
38. Kim HS, Freedland SJ. Androgen deprivation therapy in prostate cancer: Anticipated side-effects and their management. *Curr Opin Support Palliat Care.* 2010;4(3):147–152.
39. Smith MR. Androgen deprivation therapy for prostate cancer: New concepts and concerns. *Curr Opin Endocrinol Diabetes Obes.* 2007;14(3):247–254.
40. Smith MR. Androgen deprivation therapy and risk for diabetes and cardiovascular disease in prostate cancer survivors. *Curr Urol Rep.* 2008;9(3):197–202.
41. Smith MR, Egerdie B, Hernandez Toriz N, et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med.* 2009;361(8):745–755.
42. Bruder JM, Ma JZ, Basler JW, Welch MD. Prevalence of osteopenia and osteoporosis by central and peripheral bone mineral density in men with prostate cancer during androgen-deprivation therapy. *Urology.* 2006;67(1):152–155.
43. Bone HG, Bolognese MA, Yuen CK, et al. Effects of denosumab treatment and discontinuation on bone mineral density and bone turnover markers in postmenopausal women with low bone mass. *J Clin Endocrinol Metab.* 2011;96(4):972–980.
44. Grossman JM, Gordon R, Ranganath VK, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Care Res.* 2010;62(11):1515–1526.
45. Hansen KE, Fink H, Minisola S, Wilson HA, Zapalowski C, Adler RA. Uncertainties in the prevention and treatment of glucocorticoid-induced osteoporosis. *J Bone Miner Res.* 2011. In press.
46. Dore RK, Cohen SB, Lane NE, et al. Effects of denosumab on bone mineral density and bone turnover in patients with rheumatoid arthritis receiving concurrent glucocorticoids or bisphosphonates. *Ann Rheum Dis.* 2010;69(5):872–875.
47. Stopeck AT, Lipton A, Body JJ, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: A randomized, double-blind study. *J Clin Oncol.* 2010;28(35):5132–5139.

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