Published in final edited form as:

N Engl J Med. 2009 August 20; 361(8): 818–820. doi:10.1056/NEJMe0905480.

Increasing Options for the Treatment of Osteoporosis

Sundeep Khosla, M.D.

Endocrine Research Unit, College of Medicine, Mayo Clinic, Rochester, MN.

More than a decade ago, receptor activator of nuclear factor- κ B ligand (RANKL) was identified as the key molecule mediating osteoclast development, activity, and survival.¹ Since osteoporosis results, in part, from increased osteoclastic bone resorption, the inhibition of RANKL activity has been an obvious therapeutic target. In this issue of the *Journal*, two articles^{2,3} report pivotal studies that reflect more than 10 years of drug development and that establish the efficacy of a human monoclonal antibody to RANKL, denosumab, in reducing fractures.

Cummings et al.² enrolled 7868 postmeno-pausal women with osteoporosis and randomly assigned them to receive either 60 mg of denosumab or placebo subcutaneously every 6 months for 3 years. As compared with placebo, denosumab reduced the 3-year incidence of new vertebral fractures from 7.2% to 2.3% (a 68% decrease), of hip fractures from 1.2% to 0.7% (a 40% decrease), and of all nonvertebral fractures from 8.0% to 6.5% (a 20% decrease). In a smaller study of elderly men undergoing androgen deprivation for prostate cancer, Smith et al.³ randomly assigned 1468 men to a similar regimen of denosumab or placebo. At 36 months, patients in the denosumab group had a 1.5% incidence of new vertebral fractures, as compared with 3.9% in the placebo group (a 62% decrease).

Both randomized, controlled trials use the primary clinical end point of fracture. As the basic biology of RANKL predicted, the neutralization of RANKL was an effective treatment for osteoporosis. If the drug goes on to be approved by the Food and Drug Administration (FDA), what effect will it have on the care of patients with osteoporosis?

A growing number of FDA-approved drugs are currently available for the treatment of osteoporosis (Table 1) — predominantly antiresorptive drugs, which inhibit bone resorption with a subsequent reduction in coupled bone formation. These drugs increase bone mineral density largely by promoting the refilling of bone-remodeling cavities and thereby increasing mineralization density. The only currently approved anabolic agent for treating osteoporosis is teriparatide (human parathyroid hormone 1–34), which stimulates new bone formation.

Fortunately for our patients, but perhaps less so for the pharmaceutical industry, the field of antiresorptive drugs is fairly crowded. The predominant competitors for denosumab are the four bisphosphonates, which have varying routes and frequencies of administration. Costs of these drugs also vary widely, with average wholesale prices ranging from approximately \$2,000 per year for intravenous ibandronate every 3 months to as little as approximately \$100 per year for generic oral alendronate. Since denosumab will be entering this possibly saturated antiresorptive-drug market, where will it fit in terms of clinical use?

As with any new drug, the answer depends on efficacy, patient adherence, treatment risks, and cost. In the absence of head-to-head comparator trials, it is difficult to compare the antifracture efficacy of the various drugs. Nonetheless, the magnitude of risk reduction for vertebral fractures with denosumab appears to be similar to that reported for intravenous zoledronic acid⁴ or teriparatide⁵ and perhaps somewhat greater than that seen with oral bisphosphonates.⁶ Risk reductions for nonvertebral fractures appear to be in the same range for all these agents.⁶ Thus, denosumab seems at least as efficacious as the best of the currently approved alternatives.

Studies examining patients' adherence to osteoporosis therapies report disappointing findings: less than half of patients who are prescribed these medications are compliant after 1 year.⁷ Such studies have mainly included the oral medications that need to be taken daily, weekly, or monthly, so perhaps increasing the use of once-yearly intravenous zoledronic acid would improve compliance rates. Since denosumab is given subcutaneously twice yearly and could be self-administered, obviating the need for a clinic visit for an intravenous infusion, it is possible that patients taking denosumab would have higher compliance rates.

Potential adverse events associated with long-term bisphosphonate use, including osteonecrosis of the jaw⁸ and atypical femoral subtrochanteric fracture,⁹ have attracted recent attention. Although these complications appear to be rare, there is concern that increasing use of bisphosphonates may uncover a growing number of affected patients. To the extent that either of these complications is unique to bisphosphonate use, rather than a consequence of the suppression of bone turnover, there might be an advantage (albeit small, given the rarity of these events) to the use of denosumab. Moreover, since bisphosphonates are cleared by the kidney and contraindicated in patients with renal insufficiency, denosumab (which is cleared by nonrenal metabolism) may prove to be a safe drug in these patients, although studies that directly address this issue need to be done.

Perhaps the major concern about long-term use of denosumab relates to its possible effects on the immune system, since RANKL is expressed not just on bone cells but also on immune cells.¹ Neither Cummings et al. nor Smith et al. observed an increased rate of serious infections related to denosumab. However, as compared with placebo, Cummings et al. reported significant increases in rates of eczema and hospitalizations for cellulitis. Previously, McClung and colleagues reported that in a study involving 314 patients who were treated with denosumab, neoplasms developed in 6 patients and serious infections in 3, whereas none of the 46 patients in the placebo group had such complications.¹⁰ Although not statistically significant, such findings support ongoing surveillance of patients receiving denosumab, particularly when the drug is used in the community setting in patients with coexisting illnesses that might have excluded them from participating in clinical trials.

Finally, cost is increasingly relevant. The average wholesale price for the most direct competitor for denosumab, zoledronic acid, is approximately \$1,300 per year. Given the relatively marginal clinical differences between these two drugs, a higher cost of denosumab would considerably limit its use.

The real need in osteoporosis treatment is for additional anabolic agents. The use of teriparatide leads to new bone formation, but not all patients have a response to treatment, and the skeletal response wanes over time, limiting its anabolic effect.¹¹ Fortunately, a number of anabolic drugs are in development, and an increasing number of treatment options will be available. Beyond the science driving new drug development, however, will remain the art of being a physician. Specifically, our success or failure in combating osteoporosis increasingly depends not so much on the drugs available to us but rather on our ability to engage our patients and ensure that they take the medications we prescribe.

References

1. Lacey DL, Timms E, Tan HL, et al. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. *Cell*. 1998; 93:165–176. [PubMed: 9568710]
2. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med*. 2009; 361:756–765. [PubMed: 19671655]
3. Smith MR, Egerdie B, Hernandez Toriz N, et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med*. 2009; 361:745–755. [PubMed: 19671656]
4. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med*. 2007; 356:1809–1822. [PubMed: 17476007]
5. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med*. 2001; 344:1434–1441. [PubMed: 11346808]
6. Russell RGG, Watts NB, Ebetino FH, Rogers MJ. Mechanisms of action of bisphosphonates: similarities and differences and their potential influences on clinical efficacy. *Osteoporos Int*. 2008; 19:733–759. [PubMed: 18214569]
7. Siris ES, Selby PL, Saag KG, Borgstrom F, Herings RMC, Silverman SL. Impact of osteoporosis treatment adherence on fracture rates in North America and Europe. *Am J Med*. 2009; 122(Suppl 2):S3–S13. [PubMed: 19187810]
8. 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; 22:1479–1491. [PubMed: 17663640]
9. Lenart BA, Lorch DG, Lane JM. Atypical fractures of the femoral diaphysis in postmenopausal women taking alendronate. *N Engl J Med*. 2008; 358:1304–1306. [PubMed: 18354114]
10. McClung MR, Lewiecki EM, Cohen SB, et al. Denosumab in postmenopausal women with low bone mineral density. *N Engl J Med*. 2006; 354:821–831. [PubMed: 16495394]
11. Khosla S, Westendorf JJ, Oursler MJ. Building bone to reverse osteoporosis and repair fractures. *J Clin Invest*. 2008; 118:421–428. [PubMed: 18246192]

Table 1

Drugs Approved by the Food and Drug Administration for the Prevention or Treatment of Osteoporosis.

Drug	Dose
Antiresorptive	
Bisphosphonate	
Alendronate	10 mg/day or 70 mg/wk orally
Risedronate	5 mg/day or 35 mg/wk orally
Ibandronate	2.5 mg/day or 150 mg/mo orally or 3 mg intravenously every 3 mo
Zoledronic acid	5 mg intravenously every 12 mo
Raloxifene	60 mg/day orally
Estrogen	Variable doses and routes (oral and transdermal)
Calcitonin	200 IU/day intranasally
Anabolic	
Teriparatide	20 µg/day subcutaneously