Can denosumab be a substitute, competitor, or complement to bisphosphonates?

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Osteoblasts, originating from mesenchymal cells, make the receptor activator of the nuclear factor kappa B ligand (RANKL) and osteoprotegerin (OPG) in order to control differentiation of activated osteoclasts, originating from hematopoietic stem cells. When the RANKL binds to the RANK of the pre-osteoclasts or mature osteoclasts, bone resorption increases. On the contrary, when OPG binds to the RANK, bone resorption decreases. Denosumab (AMG 162), like OPG (a decoy receptor), binds to the RANKL, and reduces binding between the RANK and the RANKL resulting in inhibition of osteoclastogenesis and reduction of bone resorption. Bisphosphonates (BPs), which bind to the bone mineral and occupy the site of resorption performed by activated osteoclasts, are still the drugs of choice to prevent and treat osteoporosis. The merits of denosumab are reversibility targeting the RANKL, lack of adverse gastrointestinal events, improved adherence due to convenient biannual subcutaneous administration, and potential use with impaired renal function. The known adverse reactions are musculoskeletal pain, increased infections with adverse dermatologic reactions, osteonecrosis of the jaw, hypersensitivity reaction, and hypocalcemia. Treatment with 60 mg of denosumab reduces the bone resorption marker, serum type 1 C-telopeptide, by 3 days, with maximum reduction occurring by 1 month. The mean time to maximum denosumab concentration is 10 days with a mean half-life of 25.4 days. In conclusion, the convenient biannual subcutaneous administration of 60 mg of denosumab can be considered as a first-line treatment for osteoporosis in cases of low compliance with BPs due to gastrointestinal trouble and impaired renal function. (Korean J Pain 2017; 30: 86-92)

Key Words: Bisphosphonates; Bone mineral density; Bone resorption; Denosumab; Hypocalcemia; Monoclonal antibodies; Osteoclast; Osteoporosis; Osteoprotegerin; RANK ligand.

INTRODUCTION

The U.S. Food and Drug Administration (FDA)-approved pharmacologic options for osteoporosis include bisphosphonates (zoledronate, alendronate, ibandronate, and risedronate, in order of affinity for binding to the bone mineral matrix), calcitonin, estrogen agonist/antagonist (raloxifene), estrogens and/or hormone therapy, tissue-selective estrogen complex (conjugated estrogen/bazedoxifene), human parathyroid hormone 1–34 (teriparatide), and the re-
Table 1. The U.S. Food and Drug Administration (FDA)-Approved Indications for Denosumab (Prolia® and Xgeva®)

| Approved indications for 60 mg of Prolia® | Date       | Approved indications for 120 mg of Xgeva® | Date       |
|------------------------------------------|------------|------------------------------------------|------------|
| Postmenopausal women with osteoporosis at high risk for fracture | June 1, 2010 | Bone metastasis from solid tumors | November 18, 2010 |
| Bone loss in patients with prostate or breast cancer undergoing hormone ablation therapy | September 19, 2011 | Giant cell tumor of bone | June 13, 2013 |
| Bone loss in men with osteoporosis at risk for fracture | September 21, 2012 | Adults and skeletally mature adolescents with giant cell tumor of the bone that is unresectable or where surgical resection is likely to result in severe morbidity | June 13, 2013 |
phase (activation of pre-osteoclasts), 3) the resorption phase (resorption by the activated osteoclasts), 4) the reversal phase (the transition from bone resorption to bone formation), 5) the formation phase (bone formation by the osteoblasts), and 6) the mineralization phase (Fig. 1) [15–18].

1) During the resting phase, the bone surface is covered with flattened bone-lining cells (inactive non-remodeling forms of osteoblasts). The osteoblasts are destined to become osteocytes, bone lining cells, or undergo apoptosis [19].

2) In the activation phase, pre-osteoclasts from the hematopoietic cells differentiate into activated osteoclasts via mature osteoclasts under the influence of the RANKL and OPG, secreted from the osteoblasts. Denosumab, like OPG (a decoy receptor produced by osteoblasts), binds the RANKL and prevents the RANKL from binding to the

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**Fig. 1.** Bone remodeling cycle and medications for the treatment of osteoporosis. Bone remodeling cycle consists of at least 6 different phases: 1) resting, 2) activation, 3) resorption, 4) reversal, 5) formation, and 6) mineralization. Drugs for the treatment or prevention of osteoporosis act on different phases. In the activation phase, *denosumab*, like OPG (a decoy receptor produced by osteoblasts), binds the RANKL and blocks the RANKL from binding to the RANK, inhibits the differentiation steps from pre-osteoclasts via mature osteoclasts to activated osteoclasts, and finally reduces bone resorption. In the resorption phase, *bisphosphonates* bind to the bone mineral and take the space where activated osteoclasts attach at sites of bone resorption. *Odanacatib*, a cathepsin K inhibitor, inhibits the osteoclastic enzyme that degrades collagens. *Saracatinib*, a c-src inhibitor, inhibits osteoclastic activation. Selective estrogen receptor modulators (*SERMs*) and hormone (estrogen) replacement therapy interfere with various osteoblast-derived factors that stimulate osteoclasts. In the formation phase, *strontium ranelate* stimulates pre-osteoblasts to differentiate into osteoblasts, and stimulates osteoblasts to secrete OPG in order to prevent pre-osteoclasts from becoming activated osteoclasts via mature osteoclasts, as well. *Parathyroid hormone (PTH)* analogues and PTH-related protein (PTHrP) analogues increase the number and activity of osteoblasts. *Romosozumab* (*AMG 785*) and *bisphosphonate,* anti-sclerostin monoclonal antibodies, bind to the sclerostin (a glycoprotein inhibitor of osteoblast Wnt signaling produced by osteocytes) and inhibit its action. Cbl: Casitas B-lineage lymphoma, FAK: focal adhesion kinase, OPG: osteoprotegerin, PI3k: phosphoinositide 3-kinase, PTH: parathyroid hormone, PTHrP: PTH-related protein, RANK: the nuclear factor kappa B, RANKL: RANK ligand, SERMs: selective estrogen receptor modulators, Src: Src family kinase (a group of non-receptor tyrosine kinases). Modified from Connelly D. Osteoporosis: moving beyond bisphosphonates. *Pharmaceutical Journal* 2016 Nov [2016 Nov 23]. Available at http://www.pharmaceutical-journal.com/news-and-analysis/infographics/osteoporosis-moving-beyond-bisphosphonates/20201978.article.
RANK, inhibits the differentiation steps from pre-osteoblasts via mature osteoclasts to activated osteoclasts, and finally reduces bone resorption [20,21].

3) In the resorption phase, activated osteoclasts break down the old bone mineral and matrix in order to create an erosion cavity. This phase ranges from the time of osteoclast adherence to the bone to the release of calcium and phosphate ions into the blood stream. This osteoclastic bone resorption is controlled by 4 main hormones: calcitonin, parathyroid hormone, vitamin D3, and estrogen [22]. BPs bind to the bone mineral and take the space where activated osteoclasts attach at sites of bone resorption. Even though the disabled osteoclasts survive, they cause loss of resorptive function [3]. Odanacatib, a cathepsin K inhibitor, inhibits the osteoclastic enzyme that degrades collagen, Saracatinib, a c-src inhibitor, inhibits osteoclastic activation. Selective estrogen receptor modulators (SERMs) and hormone (estrogen) replacement therapy interfere with various osteoblast-derived factors that stimulate osteoclasts.

4) In the reversal phase (from bone resorption to formation), mesenchymal stem cells prepare the bone surface for new osteoblasts (with several steps from osteoprogenitors via pre-osteoblasts to osteoblasts) to start building bone.

5) In the (bone) formation phase, mature osteoblasts synthesize new bone matrix. Strontium ranelate stimulates pre-osteoblasts to differentiate into osteoblasts, and stimulates osteoblasts to secrete OPG in order to prevent pre-osteoclasts from becoming activated osteoclasts via mature osteoclasts, as well. Parathyroid hormone (PTH) analogues and PTH-related protein (PTHrP) analogues increase the number and activity of osteoblasts. Romosozumab (AMG 785) and blosozumab, anti-sclerostin monoclonal antibodies, bind to the sclerostin (a glycoprotein inhibitor of osteoblast Wnt signaling produced by osteocytes) and inhibit its action [23].

6) In the mineralization phase, the newly deposited osteoid is mineralized. Calcium and phosphate, with the aid of vitamin D, make hydroxyapatite to increase the mechanical strength and hardness of the bone through the primary and secondary mineralization phases [15,24].

3. Pharmacodynamics

After subcutaneous administration of 60 mg of denosumab, the bone resorption marker, serum type I C-telopeptide (CTX), reduced approximately 85% after 3 days, with maximal reductions occurring at 1 month. The level decreased below the limit of assay quantitation (0.049 ng/ml) in 39% to 68% of patients in 1 to 3 months. It maintained a decreased state of a maximal reduction of 45% to 80% 6 months after administration, and returned to baseline within 12 months. The degree of inhibition of CTX in re-initiation of denosumab was similar to that of its initial use [25].

Consistent with the physiological coupling of bone formation and resorption in bone remodeling, the bone formation markers, such as osteocalcin and procollagen type I N-terminal peptide (PINP), are also reduced subsequently.

4. Pharmacokinetics

After a single subcutaneous injection of 60 mg of denosumab in healthy volunteers, the mean maximal serum concentration was reached at 10 days, and the mean half-life was 25.4 days, and declined over a period of 4 to 5 months [9]. There was no accumulation or change in the pharmacokinetics of denosumab over time in those who take it every 6 months. It did not show any differences in pharmacokinetics related to age, race, body weight, or hepatorenal function. Carcinogenesis, mutagenesis, or impaired fertility has not reported [26].

5. Precautions related to contraindications and complications

1) Contraindications

The known common contraindications of denosumab are hypocalcemia, pregnancy, and hypersensitivity to denosumab, such as anaphylaxis, facial swelling, and urticaria [27].

Hypocalcemia should be corrected before using denosumab, because it exacerbates preexisting hypocalcemia for weeks or months. If hypocalcemia persists, intravenous or oral calcium with/without vitamin D should be supplied. Therefore, monitoring of calcium with phosphorus and magnesium levels is strongly recommended.

In addition, in cases of mineral metabolism disturbances, such as a history of hypothyroidism, thyroid surgery, parathyroid surgery, malabsorption syndrome, excision of the small intestine, or severe renal impairment (creatinine clearance < 30 ml/min or receiving dialysis), frequent monitoring of calcium and other electrolytes is required.

2) Complications

The known complications related to denosumab are
Table 2. Differences between Denosumab and Bisphosphonates

|                        | Denosumab | Bisphosphonates |
|------------------------|-----------|-----------------|
| **Chemistry**          | Monoclonal antibody | Chemical agent |
| **Targets**            | Selectively binds the RANKL, similar to the OPG | Selective uptake by hydroxyapatite |
| **Distribution**       | Circulating in the blood and extracellular fluid | Bone mineral surface |
| **Major bone target cells** | Pre-osteoclasts via mature osteoclasts to activated osteoclasts | Activated osteoclasts |
| **Mechanism of action** | It prevents the RANKL from binding to its receptor, the RANK, and inhibits the development, activation, and survival of osteoclasts. | They bind the bone mineral and inhibit the resorptive function of the osteoclasts at the site of bone resorption. |
| **Mode of administration** | Subcutaneous (60 mg biannually) | Oral (daily, weekly, or monthly) or intravenous (quarterly or yearly) |
| **Onset of action (serum CTX)** | Faster | Slower |
| **Inhibition of bone resorption (serum CTX)** | Greater | Lesser |
| **Effect on BMD** | Greater | Lesser |
| **Serum calcium monitoring** | Essential | Sometimes |
| **Reversibility of effect after stopping treatment** | Fully reversible and relatively rapid offset of action | Slow offset of action |

BMD: bone mineral density, CTX: C-terminal telopeptide, FPP: farnesyl pyrophosphate, OPG: osteoprotegerin, RANK: receptor activator of the nuclear factor kappa B, RANKL: receptor activator of the nuclear factor kappa B ligand. Modified from Baron R, Ferrari S, Russell RG. Denosumab and bisphosphonates: different mechanisms of action and effects. Bone 2011; 48: 677-92.
tis with focal pathologic bone resorption due to excessive activity of the osteoclasts, combined with an anti–tumor necrosis factor (TNF) agent or with disease modifying anti–rheumatic drugs (DMARDs) [32].

**CONCLUSIONS**

Denosumab prevents the RANKL from binding to its receptor, the RANK, thereby inhibiting the development, activation, and survival of osteoclasts; however, the familiar antiresorptive agents, BPs, bind to the bone mineral and inhibit the resorptive function of osteoclasts by being taken up by osteoclasts at the site of resorption, though the disabled osteoclasts may persist. The two anti–resorptive agents are unlikely to be used in combined treatment due to the inhibitory action of osteoclasts in the same pathway. It is more reasonable to use combined anabolic and anti–catabolic treatment [33].

Therefore, even though denosumab has better compliance (a single subcutaneous injection every 6 months) with rapid onset, strong inhibition of osteoclastic activity, reversibility of its action after discontinuance, and advantages to patients with gastrointestinal trouble and impaired renal function, the economic status and cost/benefit comparison, the immune status with infection susceptibility, and compliance with taking calcium/vitamin D supplements and frequent monitoring of calcium or other minerals should be considered (Table 2).

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