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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-

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ceptor activator of nuclear factor kappa B ligand (RANKL) inhibitor (denosumab) [1].

Bisphosphonates (BPs) are currently the most widely used antiresorptive therapies [1,2]. They act by binding the mineral component of bone and interfere with the action of osteoclasts. The nitrogen-containing bisphosphonates, such as alendronate, act as inhibitors of farnesyl-pyrophosphate synthase, which leads to inhibition of the prenylation of many intracellular signaling proteins [3].

Denosumab (60 mg of Prolia® or 120 mf of Xgeva®, Amgen Inc., Thousand Oaks, CA) is a fully human monoclonal antibody (IgG_2) that binds the RANKL and blocks the binding of the RANKL to the RANK. It finally inhibits the formation, function, and survival of osteoclasts, decreases bone resorption, and increases bone density, mass, and strength, similar to the endogenous effects of osteoprotegerin (OPG) [4-6].

This narrative review examines when this novel immune-related antiresorptive agent, denosumab, is indicated or may be substituted for current anti-osteoporotic drugs, based on its mechanism of action and adverse events compared with other drugs [7].

MAIN BODY

1. History for approved indications

The U.S. Food and Drug Administration (FDA) approved denosumab for the treatment of postmenopausal women with osteoporosis at high risk for fracture on June 1, 2010 after a study entitled Fracture Reduction of Denosumab in Osteoporosis Every 6 Months (FREEDOM) [6].

It also approved new indications for denosumab for the treatment of bone loss in patients with prostate or breast cancer undergoing hormone ablation therapy on September 19, 2011, for the treatment of bone loss in men with osteoporosis at risk for fracture on September 21, 2012, and for the treatment of adults and skeletally mature adolescents with a giant cell tumor of the bone that is unresectable or where surgical resection is likely to result in severe morbidity on June 13, 2013 (**Table 1**) [8,9].

The representative bone metastasis symptoms are called skeletal-related events (SREs). They are a devastating consequence of bone metastasis due to radiation of the bone, pathologic fracture, bone surgery, or spinal cord compression due to metastasis, producing intolerable pain, devastating physical and emotional burdens, longer hospital stays, and increased mortality [10-13]. Bone-targeted agents, such as BPs and denosumab, offer both pain reduction and SREs in the metastatic bone diseases [14].

2. Mechanism of action matching with bone remodeling cycle

Bone is a dynamic tissue that undergoes continual adaptation through remodeling to maintain its integrity. Old bone is resorbed by the osteoclasts (bone-resorbing cells) and is replaced with new osteoids which are secreted by the osteoblasts (bone-forming cells). It is similar to the process of pavement in road repair. These clusters of osteoblasts and osteoclasts are arranged within temporary anatomical structures, basic multicellular units (BMUs), which are responsible for bone remodeling, which requires about 4 months (16 weeks including 3 weeks for osteoclastic activity and 13 weeks for osteoblastic activity) [15,16].

The bone remodeling cycle is categorized into at least 6 steps: 1) the resting (quiescence) phase, 2) the activation

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

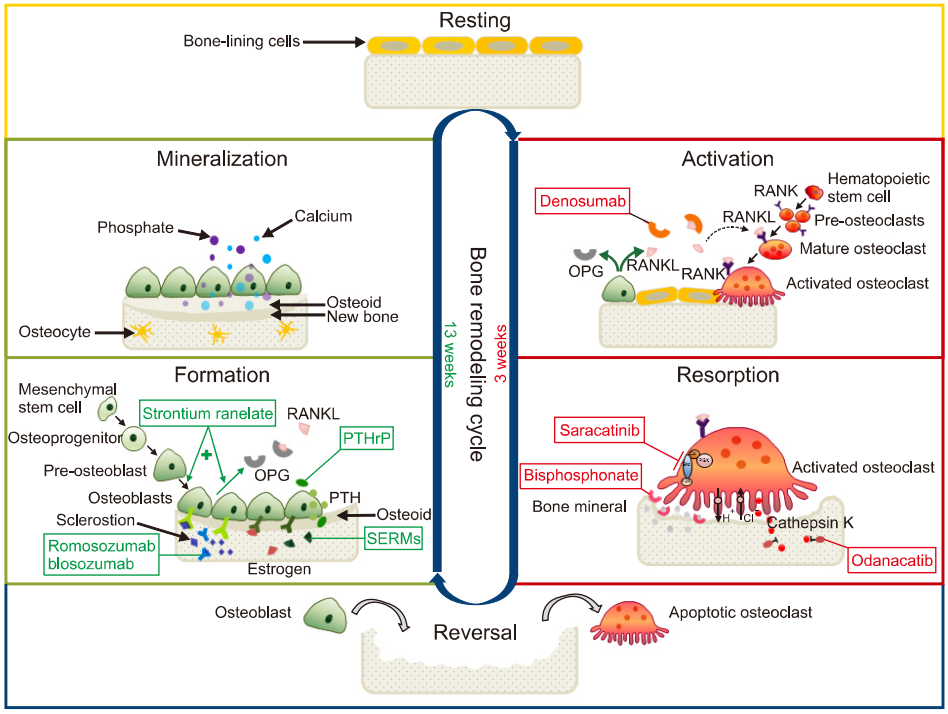

Fig. 1. Bone remodeling cycle and medications for the treatment of osteoporosis. Bone remodeling cycle consists of at least 6 different phases: 1. resting, 2. activation, 3. resorption, 4. reversal, 5. formation, and 6. mineralization. Drugs for the treatment or prevention of osteoporosis act on different 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-osteoblasts 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 blosozumab*, 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 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.

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 1 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 1 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/m or receiving dialysis), frequent monitoring of calcium and other electrolytes is required.

2) Complications

The known complications related to denosumab are

hypersensitivity, hypocalcemia and mineral metabolism abnormality, osteonecrosis of the jaw, atypical femoral fractures, serious infections such as cellulitis, musculoskeletal pain, and suppression of bone turnover [28].

The risk of osteonecrosis of the jaw (ONJ) may increase in invasive dental procedures with duration of exposure to denosumab. Atypical subtrochanteric and diaphyseal fractures were also reported in patients receiving denosumab.

Serious skin, abdomen, urinary tract, or ear infections were frequently reported in denosumab-treated patients. It is important to consider the risk of serious infections in patients with immunosuppressed states or on concomitant immunosuppressant agents. The incidence of dermatologic adverse reactions, including dermatitis, eczema, and rashes, increased.

Musculoskeletal pain, such as bone, joint, and/or muscle pain, has been reported from 1 day to several months after taking denosumab.

The most common adverse reactions leading to discontinuation of denosumab in patients with postmenopausal osteoporosis have been back pain and constipation.

6. Preparation and administration methods

Denosumab (60 mg/1 ml of Prolia® or 120 mg/1.7 ml of Xgeva®) is a clear, colorless to pale yellow (not discolored or cloudy) solution, however, it may contain some trace of translucent and white proteinaceous particles. Before administration, it should be kept at room temperature for 15 to 30 minutes after removal from the refrigerator. This single-use prefilled syringe with a green safety guard has a 27-gauge needle with a cap [29].

A subcutaneous injection, not into the skin or muscle, should be given into the upper anterior thigh, arm, or abdomen every 6 months. It is recommended that all patients receive 1000 mg of calcium and at least 400 IU of vitamin D daily [30].

7. Future development in the use of denosumab

It would be ideal to develop a hybrid molecule in which BPs may serve as a vehicle for the delivery of denosumab selectively to the bone in order to reduce the effect on the immune system along with an increased antiresorptive activity [31].

It is promising to use denosumab in rheumatoid arthri-

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 Inhibition of FFP for nitrogen bisphosphonates
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 antiresorptive 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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REFERENCES

1. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, et al. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int 2014; 25: 2359-81.
2. Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. Mayo Clin Proc 2008; 83: 1032-45.
3. Baron R, Ferrari S, Russell RG. Denosumab and bisphosphonates: different mechanisms of action and effects. Bone 2011; 48: 677-92.
4. McClung MR, Lewiecki EM, Cohen SB, Bolognese MA, Woodson GC, Moffett AH, et al. Denosumab in postmenopausal women with low bone mineral density. N Engl J Med 2006; 354: 821-31.
5. Cheung AM, Frame H, Ho M, Mackinnon ES, Brown JP. Bone strength and management of postmenopausal fracture risk with antiresorptive therapies: considerations for women's health practice. Int J Womens Health 2016; 8: 537-47.
6. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 2009; 361: 756-65.
7. Khosla S. Increasing options for the treatment of osteoporosis. N Engl J Med 2009; 361: 818-20.
8. Rizzoli R, Yasothan U, Kirkpatrick P. Denosumab. Nat Rev Drug Discov 2010; 9: 591-2.
9. Zaheer S, LeBoff M, Lewiecki EM. Denosumab for the treatment of osteoporosis. Expert Opin Drug Metab Toxicol 2015; 11: 461-70.
10. Janjan N. Bone metastases: approaches to management. Semin Oncol 2001; 28: 28-34.
11. Weinfurt KP, Li Y, Castel LD, Saad F, Timbie JW, Glendenning GA, et al. The significance of skeletal-related events for the health-related quality of life of patients with metastatic prostate cancer. Ann Oncol 2005; 16: 579-84.
12. Yong M, Jensen AÖ, Jacobsen JB, Nørgaard M, Fryzek JP, Sørensen HT. Survival in breast cancer patients with bone metastases and skeletal-related events: a population-based cohort study in Denmark (1999-2007). Breast Cancer Res Treat 2011; 129: 495-503.
13. Cassinello Espinosa J, González Del Alba Baamonde A, Rivera Herrero F, Holgado Martín E; SEOM (Spanish Society of Clinical Oncology). SEOM guidelines for the treatment of bone metastases from solid tumours. Clin Transl Oncol 2012; 14: 505-11.
14. von Moos R, Costa L, Ripamonti CI, Niepel D, Santini D. Improving quality of life in patients with advanced cancer: targeting metastatic bone pain. Eur J Cancer 2017; 71: 80-94.
15. Raggatt LJ, Partridge NC. Cellular and molecular mechanisms of bone remodeling. J Biol Chem 2010; 285: 25103-8.
16. Proff P, Römer P. The molecular mechanism behind bone remodelling: a review. Clin Oral Investig 2009; 13: 355-62.
17. Ghayor C, Weber FE. Epigenetic regulation of bone remodeling and its impacts in osteoporosis. Int J Mol Sci 2016; 17: E1446.
18. Crockett JC, Rogers MJ, Coxon FP, Hocking LJ, Helfrich MH. Bone remodelling at a glance. J Cell Sci 2011; 124: 991-8.
19. Miller SC, de Saint-Georges L, Bowman BM, Jee WS. Bone lining cells: structure and function. Scanning Microsc 1989; 3: 953-60.
20. Hanley DA, Adachi JD, Bell A, Brown V. Denosumab: mechanism of action and clinical outcomes. Int J Clin Pract

2012; 66: 1139–46.
21. Xing L, Xiu Y, Boyce BF. Osteoclast fusion and regulation by RANKL-dependent and independent factors. World J Orthop 2012; 3: 212–22.
22. Martin TJ. Paracrine regulation of osteoclast formation and activity: milestones in discovery. J Musculoskelet Neuronal Interact 2004; 4: 243–53.
23. Clarke BL. Anti-sclerostin antibodies: utility in treatment of osteoporosis. Maturitas 2014; 78: 199–204.
24. Boivin G, Farlay D, Bala Y, Doublier A, Meunier PJ, Delmas PD. Influence of remodeling on the mineralization of bone tissue. Osteoporos Int 2009; 20: 1023–6.
25. Bone HG, Bolognese MA, Yuen CK, Kendler DL, Wang H, Liu Y, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women. J Clin Endocrinol Metab 2008; 93: 2149–57.
26. Sohn W, Simiens MA, Jaeger K, Hutton S, Jang G. The pharmacokinetics and pharmacodynamics of denosumab in patients with advanced solid tumours and bone metastases: a systematic review. Br J Clin Pharmacol 2014; 78: 477–87.
27. Miller PD. A review of the efficacy and safety of denosumab in postmenopausal women with osteoporosis. Ther Adv Musculoskelet Dis 2011; 3: 271–82.
28. Martin M, Bell R, Bourgeois H, Brufsky A, Diel I, Eniu A, et al. Bone-related complications and quality of life in advanced breast cancer: results from a randomized phase III trial of denosumab versus zoledronic acid. Clin Cancer Res 2012; 18: 4841–9.
29. Kendler DL, Roux C, Benhamou CL, Brown JP, Lillestol M, Siddhanti S, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women transitioning from alendronate therapy. J Bone Miner Res 2010; 25: 72–81.
30. Fizazi K, Carducci M, Smith M, Damião R, Brown J, Karsh L, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet 2011; 377: 813–22.
31. Anastasilakis AD, Polyzos SA, Anastasilakis CD, Toulis KA, Makras P. Denosumab and bisphosphonates: rivals or potential "partners"? A "hybrid" molecule hypothesis. Med Hypotheses 2011; 77: 109–11.
32. Chiu YG, Ritchlin CT. Denosumab: targeting the RANKL pathway to treat rheumatoid arthritis. Expert Opin Biol Ther 2017; 17: 119–28.
33. Tsai JN, Uihlein AV, Lee H, Kumbhani R, Siwila-Sackman E, McKay EA, et al. Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomised trial. Lancet 2013; 382: 50–6.