*Michał Wąsowski, Magdalena Proniewska-Sadowska, Urszula Budzińska

Bisphosphonates and denosumab – the efficacy in the fracture prevention

Bisfosfoniany i denosumab – skuteczność w zapobieganiu złamaniom

Department of Geriatrics, Internal Medicine and Metabolic Bone Diseases, Centre of Postgraduate Medical Education, Warsaw
Head of Department: Associate Professor Marek Tałałaj, MD, PhD

Keywords

bisphosphonates, denosumab, fracture prevention, osteoporosis

Słowa kluczowe

bisfosfoniany, denosumab, prewencja złamań, osteoporoza

S u m m a r y

During one's expected remaining lifetime, 1 in 2 postmenopausal women and 1 in 5 older men are at risk for an osteoporosis-related fracture. Osteoporotic fractures are the most devastating complications of osteoporosis, especially those of the hip. The osteoporosis and the consequent fractures are associated with increased morbidity and mortality. The aim of the therapy is to diminish the rate of bone loss, to increase bone strength, and to reduce the risk of low energy fractures. Bisphosphonates (BPs), together with calcium and vitamin D supplementation, have been considered for many years, as a first line therapy for the prevention and treatment of osteoporosis. They are able to bind strongly and selectively to bone mineral and to inhibit the activity of bone resorbing cells – osteoclasts. Denosumab is a fully human monoclonal antibody that can bind receptor activator of nuclear factor kappaB ligand (RANKL) secreted by osteoblasts, bone marrow stromal cells, and T cells. Reduced stimulation of RANK receptors, presented on mature osteoclasts and their precursors, results in inhibition of migration, differentiation, and fusion of hematopoietic cells of the osteoclast lineage as well as in decreased activity and survival of mature osteoclasts. It was documented that bisphosphonates and denosumab are effective in fracture prevention among patients with osteoporosis and/or prevalent vertebral fracture, decreasing the incidence of vertebral fractures by more than 50%, non-vertebral fractures by 20-25% and hip fractures by 40-50%. The choice of the treatment among osteoporotic patients should consider not only their effectiveness and safety but also such important factors as compliance and adherence to the drug.

S t r e s z c z e n i e

W oczekiwanym okresie życia 1 na 2 kobiety po menopauzie i 1 na 5 mężczyzn w starszym wieku są narażeni na wystąpienie złamania w przebiegu osteoporozy. Złamania osteoporotyczne są najgroźniejszymi powikłaniami osteoporozy, zwłaszcza zlokalizowane w bliższej części kości udowej. Osteoporoza i wikłające ją złamania związane są ze zwiększoną chorobowością i śmiertelnością. Celem leczenia jest zmniejszenie tempa utraty kości, zwiększenie jej wytrzymałości oraz redukcja ryzyka złamań niskoenergetycznych. Bisfosfoniany (BPs) łącznie z suplementacją wapnia i witaminą D przez wiele lat stanowiły podstawową terapię w prewencji i leczeniu złamań ostoporotycznych. Silnie i wybiórczo wiążą się one z tkanką kostną hamując aktywność komórek kościogubnych – osteoklastów. Denosumab jest ludzkim przeciwciałem monoklonalnym wiążącym ligand receptora jądrowego czynnika kappaB (RANKL) wytwarzanym przez osteoblasty, komórki szpiku kostnego oraz limfocyty T. Zmniejszona stymulacja receptora RANK, obecnego na dojrzałych osteoklastach i ich prekursorach, powoduje zarówno zahamowanie migracji, różnicowania oraz fuzji prekursorowych komórek hemopoetycznych linii osteoklastycznej, jak i aktywności oraz przeżycia dojrzałych osteoklastów. Udokumentowano, że bisfosfoniany i denosumab są skuteczne w prewencji złamań u pacjentów z osteoporozą i/lub przebytymi złamaniami kręgów, zmniejszając ryzyko złamań kręgosłupa o więcej niż 50%, ryzyko złamań pozakręgowych o 20-25% i złamań biodra o 40-50%. Wybór rodzaju terapii u pacjentów z osteoporozą powinien uwzględniać nie tylko jej skuteczność i bezpieczeństwo, ale także wpływ na systematyczność jej stosowania.

Conflict of interest
Konflikt interesów

None
Brak konfliktu interesów

Address/adres:

*Michał Wąsowski
Department of Geriatrics,
Internal Medicine and Metabolic Bone Diseases
Centre of Postgraduate Medical Education
ul. Czerniakowska 231, 00-416 Warszawa
tel. +48 (22) 584-11-47
kl.geriatrii@szpital-orlowskiego.pl

INTRODUCTION

Low energy fractures are the most devastating complications of osteoporosis. They occur most often at the hip, spine and forearm but may occur throughout the whole skeleton. Osteoporotic fractures especially those of the hip and spine appear most often in elderly people and are associated with increased morbidity and mortality (1, 2).

The main goal of treatment of osteoporosis is to prevent low energy fractures or at least significantly reduce the risk of their incidence. Current osteoporosis therapies have been developed to decrease bone resorption and/or to increase bone formation. Most often used medications are powerful inhibitors of bone resorption: bisphosphonates and denosumab (3).

BISPHOSPHONATES AND DENOSUMAB – DIFFERENT MOLECULES, DIFFERENT ACTIONS

Bisphosphonates (BPs), together with calcium and vitamin D supplementation, have been considered for many years, as a first line therapy for the prevention and treatment of osteoporosis. BPs are able to bind strongly and selectively to bone mineral and to inhibit the activity of bone resorbing cells – osteoclasts. BPs influence mainly trabecular bone turnover, because they are primarily located across bone surfaces, especially those with adjacent bone marrow, such as endocortical and trabecular surfaces.

Bisphosphonates have to be internalized to act upon osteoclasts (4, 5). BPs suppress the birth of new remodeling units, with fewer and shallower resorption cavities, and maintain bone structure with more complete mineralization. Nitrogen-containing BPs, such as alendronate, risedronate, ibandronate and zoledronic acid, cause long-term inhibition of the mevalonate pathway in osteoclasts, and accelerate their apoptosis (6).

Based on the results of randomized controlled trials (RCTs) all nitrogen containing BPs have been accepted for the prevention and treatment of postmenopausal osteoporosis. Alendronate, risedronate and zoledronic acid were also accepted for osteoporosis in men as well as for prevention and treatment of glucocorticoid-induced osteoporosis.

RCTs are performed for daily oral formulations of the drugs. The other formulations, once weekly or monthly, were granted on the basis of bone mineral density bridging studies and pharmacokinetic measurements.

All BPs are contraindicated in patients with hypocalcemia. Oral formulations should be avoided in patients with abnormalities of the esophagus which delay its emptying, and used with caution in persons with upper gastrointestinal diseases and in individuals unabled to stand or sit upright for at least 30 minutes. The drugs are not recommended in patients with renal impairment with glomerular filtration rate (GFR) < 30-35 ml/min (7).

Side-effects include upper gastrointestinal symptoms, bowel disturbances, headaches and musculoskeletal pains, while intravenous administration may be associated with an acute phase reaction, characterized by an influenza-like illness, which is generally short-term and typically occurs mainly after the first injection.

The intestinal absorption of BPs is extremely poor (between 1 and 3%) and bioavailability of the drugs can vary considerably. Absorption of the oral BPs occurs rapidly, with maximum serum concentrations reached in 30-60 minutes but is substantially reduced and delayed if the drugs are taken with meals, especially rich in calcium.

Virtually the whole absorbed dose is either taken up into bone tissue or eliminated with urine. BPs have a high affinity for exposed hydroxyapatite surfaces ready for or undergoing bone resorption and they are selectively bound with mineralized bone tissue. It was found that approximately 50-60% of the absorbed oral dose of risedronate and alendronate is taken up by the bones. Following the administration of a 10 mg dose of intravenous radiolabeled alendronate the serum concentration of the drug declined by over 95% within 6 hours and was undetectable after 15 hours. Risedronate was found to be eliminated from the circulation with serum half-life of 1.5 hours (8).

The first generation bisphosphonates such as etidronate and clodronate decrease bone resorption by reversing pyrophosphorylytic reactions catalyzed by aminoacyl-tRNA synthetases. The activity of the nitrogenated BPs seems to result mainly from their capacity of inhibiting farnesyl pyrophosphate synthase (FPPS) activity in the mevalonate pathway. The bisphosphonate concentration to inhibit 50% of enzyme activity was found to be 500 nM for pamidronate, 460 nM for alendronate, and 3.9 nM for risedronate. It was documented that the potency for inhibiting human FPP synthase *in vitro* was highly correlated with antiresorptive potency *in vivo*. The order of potency at inhibiting the enzyme: zoledronic acid > risedronate > ibandronate > alendronate > pamidronate matched closely the order of antiresorptive potency of BPs, suggesting that FPP synthase is a major pharmacologic target for BPs (8).

Strong affinity for bone tissue provides bisphosphonates with the capacity of remaining embedded in bone matrix for a long time, thus making possible weekly, monthly or even yearly regimens (8).

BPs remain sequestered in bone tissue for extended time, then they are gradually released to the circulation depending on the rate of bone turnover. In healthy human volunteers, the plasma terminal elimination half-life following a single oral dose of 30 mg risedronate was 224 hours, and increased to 480 hours following multiple doses of the drug. The terminal half-life of zoledronic acid was found to be 146 hours and of ibandronate was estimated for 10-60 hours (8).

Inhibition of bone resorption by BPs was dependent on the dose and dosing interval with intermittent administration. In patients treated with BPs bone resorption was found not to become progressively lower but

reached a new steady level, suggesting that, despite accumulation of BPs in the skeleton, bone turnover still continues, thought at a slower rate (9).

Denosumab is a fully human monoclonal antibody that can bind receptor activator of nuclear factor kappaB ligand (RANKL) secreted by osteoblasts, bone marrow stromal cells, and T cells (10, 11). Reduced stimulation of RANK receptors, present on mature osteoclasts and their precursors, results in inhibition of migration, differentiation, and fusion of hematopoietic cells of the osteoclast lineage as well as in decreased activity and survival of mature osteoclasts (12).

Denosumab is administered subcutaneously every 6 months. Following the infusion the drug circulates in the blood and extracellular fluid reaching both trabecular and cortical bone tissue including intracortical sites (3). Therapy with denosumab results in significant inhibition of bone resorption and bone turnover that resolves within 1 year after stopping treatment (4, 5, 13).

BISPHOSPHONATES IN FRACTURE PREVENTION

All BPs accepted for the prevention and treatment of osteoporosis were found to reduce significantly the incidence of skeletal fractures.

Alendronate, given orally at the dose of 10 mg daily or 70 mg once weekly, was proved to reduce the risk of vertebral, non-vertebral and hip fractures in postmenopausal women with osteoporosis (7).

Risedronate, given orally at a dose of 5 mg daily or 35 mg once weekly, was shown to reduce the incidence of both vertebral and non-vertebral fractures, and in elderly women with low bone mineral density (T-score < -2.5) to decrease the risk of hip fractures as well (14, 15).

Ibandronate is the only BP that can be given orally at the doses of 2.5 mg daily or 150 mg once monthly or as an intravenous injection given every 3 months at a dose of 3 mg. In women treated with the drug at a dose of 2.5 mg daily significant reduction in a vertebral fracture rate was demonstrated, while in a post hoc analysis of high risk women with extremely low bone mineral density (BMD) – femoral neck T-score < -3.0 – a significant reduction in non-vertebral fractures was shown as well (16, 17).

Zoledronic acid given intravenously at the dose of 5 mg once a year was proved to reduce the incidence of vertebral, non-vertebral and hip fractures in postmenopausal women with osteoporosis and to reduce the risk of clinical fractures and attendant mortality when given to patients shortly after their first hip fractures (18-21).

The systematic review of randomized, placebo-controlled trials published by MacLean et al. concluded that there were good-quality evidence that alendronate, risedronate, ibandronate, and zoledronic acid reduced the risk of osteoporotic fractures, although not all of them were able to prevent hip fractures (22).

Bisphosphonates used in the prevention and treatment of osteoporotic fracture are characterized by long-term skeletal retention and persistence of antiresorptive effect after therapy discontinuation. Due to possible serious adverse effects of long-term bisphosphonate therapy, such as osteonecrosis of the jaw (ONJ) and atypical femur fractures (AFF), the risk-benefit ratio of treatment continuation should be reviewed at the regular intervals. Based on the available data, the review of therapy with alendronate, risedronate or ibandronate after 5 years and with zoledronic acid after 3 years has been recommended, and the concept of bisphosphonate "holidays" has been suggested (23).

A recent FDA review revealed that the rate of vertebral and nonvertebral fractures in patients who had received BPs for more than 6 years was from 9.3 to 10.6% compared with 8.0 to 8.8% in patients who had been switched to placebo. Therefore the last FDA conclusion stated that "these data raised the question of whether continued bisphosphonate therapy imparted additional fracture-prevention benefit, relative to cessation of therapy after 5 years" (14, 24, 25).

DENOSUMAB IN FRACTURE PREVENTION

Denosumab has been shown to be associated with a significant reduction in the risk of vertebral, hip, and nonvertebral fractures compared to placebo in postmenopausal women with osteoporosis (20). The results of FREEDOM trial revealed that three-year treatment of postmenopausal women aged 60-90 years, with low BMD, with denosumab at the dose of 60 mg every 6 months caused significant risk reduction of vertebral fractures (by 68%), hip fractures (by 40%), and non-vertebral fractures (by 20%) compared to placebo (tab. 1) (26).

The FREEDOM extension study showed that denosumab therapy lasting up to 10 years resulted in cumulative gain in BMD of 21.7% at the lumbar spine and 9.2% at the total hip, compared with baseline (tab. 1). The annual rates of new vertebral and nonvertebral fractures remained low throughout the whole study period (27). Bone histomorphometry evaluation of transiliac bone biopsies revealed normal bone quality and dynamic parameters of low bone turnover (26). It can be concluded, that denosumab treatment over 10 years led to a persistent reduction of bone turnover with continuing progressive increases in BMD with no therapeutic plateau and a persisted low fracture incidence (27).

ADAMO study comparing the efficacy and safety of the treatment with denosumab in males aged 30-85, with osteoporosis, at high risk for fractures, resulted in increases of BMD by 5.7% at the lumbar spine, by 2.4% at the total hip, and by 2.1% at the femoral neck after 12 months of the therapy (tab. 1) (28).

BISPHOSPHONATES AND DENOSUMAB – COMPARATIVE EFFECTIVENESS

Head-to-head comparative effectiveness studies assessing fracture outcomes are rare. They seldom

Tab. 1. Selected Phase III and post-marketing clinical trials of denosumab (26)

Study	Description	Primary endpoint	Number of subjects	Efficacy results
FREEDOM	Treatment of postmenopausal osteoporosis (denosumab vs. placebo)	New vertebral fractures at 36 months	7868	Denosumab reduced vertebral fracture risk
FREEDOM extension	5 years of extension data beyond the 3-year FREEDOM trial	Efficacy and safety	2678 at 8 years of therapy	Continued reduction of vertebral and non-vertebral fracture risk
ADAMO	Treatment of osteoporosis in males (denosumab vs. placebo)	Change in LS BMD at 12 months	242	Greater BMD increase with denosumab
HALT	Treatment of bone density loss in men undergoing androgen-deprivation therapy for non-metastatic, hormone-sensitive prostate cancer (denosumab vs. placebo)	Change in LS BMD at 24 months	1468	Greater BMD increase with denosumab. Decreased incidence of new vertebral fractures at 36 months
Denosumab in women receiving adjuvant aromatase inhibitors for non-metastatic breast cancer	Treatment of bone density loss in women with hormone receptor-positive non-metastatic breast cancer treated with adjuvant aromatase inhibitor (denosumab vs. placebo)	Change in LS BMD at 12 months	252	Greater BMD increase with denosumab
DATA	Treatment of post-menopausal osteoporosis (teriparatide vs. denosumab vs. combination)	Change in LS BMD at 24 months	94	Greater BMD increase with combination therapy compared to single therapy
DAPS	Patient satisfaction and adherence to treatment in post-menopausal women (denosumab vs. alendronate)	Proportion of subjects adherent to treatment at 1 year	221	Greater patient adherence to and satisfaction with denosumab

ADAMO – study to compare the efficacy and safety of denosumab versus placebo in males with osteoporosis; BMD – bone mineral density; HALT – denosumab hormone ablation bone loss trial; DAPS – denosumab adherence preference satisfaction; DATA – denosumab and teriparatide administration study; FREEDOM – fracture reduction evaluation of denosumab in osteoporosis every 6 months; LS – lumbar spine

report statistical testing and fracture outcomes between examined therapies or analyze the comparisons on a per-protocol differences rather than an intention-to-treat basis (fig. 1) (29).

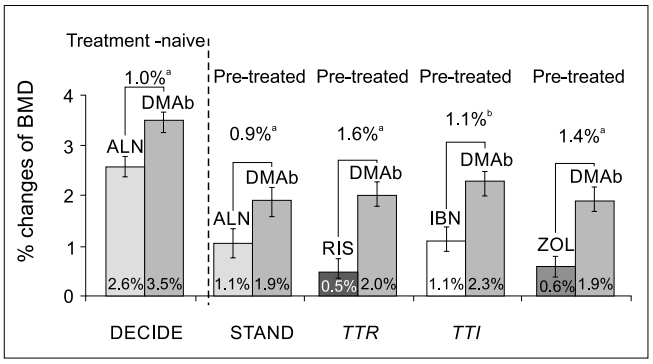

Fig. 1. The influence on BMD in the hip in head-to-head study (DMAb vs. BP) (20, 21, 25, 42, 43)
ALN – alendronate, DMAb – denosumab, RIS – risendronate, IBN – ibandronate, ZOL – zoledronic acid; a $p < 0.0001$, b $p < 0.001$

Several attempts have been made to estimate comparative effectiveness using network meta-analyses and indirect (ITC) or mixed treatment comparisons (MTC). A recent network meta-analysis of 116 placebo-controlled or head-to-head trials assessing alendronate, risedronate, ibandronate, zoledronic acid and denosumab concluded that each of the drugs were likely more effective than vitamin D or calcium. The differences in a vertebral and nonvertebral fracture risk reduction among BPs, denosumab and teriparatide were, however, not consistent or statistically significant (29).

Other network meta-analyses by Hopkins et al. including 30 randomized controlled trials and by Freemantle et al. including 21 RCTs, found no significant differences in nonvertebral risk of fractures among alendronate, risedronate, ibandronate, zoledronic acid and denosumab. It was noted, however, that ibandronate had no effect on a nonvertebral fractures reduction relative to placebo (29). A meta-analysis, that included 9 RCTs and reported both clinical and morphometric vertebral fractures, with treatment period of at least 3 years, revealed no statistically significant differences among alendronate, risedronate, ibandronate, zoledronic acid, and denosumab in the mixed treatment comparisons (29).

All of these network meta-analyses are limited by the dearth of head-to-head studies, but their conclusions are relatively consistent and suggest that the differences in comparative effectiveness among drugs are insignificant. Hopkins et al. tried to assess the relative efficacy of 9 osteoporosis medications in the reducing the rate of fractures in postmenopausal women. For vertebral fractures teriparatide, zoledronic acid and denosumab were likely to have the highest probability

Tab. 2. Comparison of major characteristics of bisphosphonates (alendronate and zoledronic acid) versus denosumab (18, 32, 33)

Drugs	Alendronate	Zoledronic acid	Denosumab
Efficacy	Vertebral and hip fracture reduction: ~ 50% (STAND and DECIDE trials comparing alendronate to denosumab showed greater BMD gains with denosumab at 12 months)	Vertebral fracture reduction: 70% Hip fracture reduction: 41% (ongoing trial comparing efficacy of ZA vs. denosumab)	Vertebral fracture reduction: 68% Hip fracture reduction: 40%
Pivotal Trial	FIT	HORIZON-PFT	FREEDOM
Safety	Risk for AFF and ONJ with prolonged exposure	Risk for AFF and ONJ with exposure to high doses and/or prolonged exposure	Risk for AFF and ONJ. Increased risk of serious skin infections

AFF – atypical femur fractures; ONJ – osteonecrosis of the jaw; FIT – fracture intervention trial; HORIZON-PFT – health outcomes and reduced incidence with zoledronic acid once yearly-pivotal fracture trial; FREEDOM – fracture reduction evaluation of denosumab in osteoporosis every six months; STAND – study of transitioning from alendronate to denosumab; DECIDE – the determining efficacy: comparison of initiating denosumab versus alendronate

of being most efficacious. These drugs had also the lowest number needed to treat compared with other BPs. For the hip only alendronate revealed a significant reduction in relative rate of fractures. No data are available for denosumab, ibandronate or zoledronic acid as far as wrist fractures are considered (30). The results of meta-analysis by Zhang et al. indicated that teriparatide and denosumab were more effective than alendronate and risedronate for reducing vertebral fractures (31).

The studies comparing influence of denosumab and oral bisphosphonates on BMD revealed additional benefit with denosumab compared with BPs. Denosumab, given at the dose of 60 mg q 6 months, resulted in significantly greater BMD increase at the total hip compared to alendronate (3.5 vs. 2.6%), with treatment difference of 0.6% at femoral neck, and 1.1% at lumbar spine over 12 months of the treatment (tab. 2) (18, 32, 33). Comparison of denosumab and risedronate in postmenopausal women previously treated with suboptimal doses of alendronate showed greater BMD gains in denosumab group at total hip (2.0 vs. 0.5%), femoral neck (1.4 vs. 0%), and lumbar spine (3.4 vs. 1.1%) after 12 months of the therapy. Analogous comparison of denosumab and ibandronate revealed greater BMD increases in denosumab treated women at total hip (2.3 vs. 1.1%), femoral neck (1.7 vs. 0.7%), and lumbar spine (4.1 vs. 2.0%) after 12 months of treatment (26, 30, 34-37).

Observed differences in the skeletal response among the same category of antiresorptive drugs can not be easily explained. Perhaps a better understanding of the drug influence on bone metabolism allows to find an answer (23, 38).

CONCLUSIONS

According to the current data alendronate, risedronate, ibandronate, zoledronic acid and denosumab have a broad spectrum of fracture prevention in patients with osteoporosis and/or prevalent vertebral fracture. The decrease of the vertebral fracture incidences exceed 50%, of non-vertebral fracture reach 20-25% and of hip fracture 40-50% (39). Denosumab treatment continued for up to 10 years is associated with progressive BMD gain, low fracture rate, and a consistent safety profile. The incidence of the adverse events do not increase over the time (40, 41).

The choice of the treatment among osteoporotic patients should consider not only their effectiveness and safety but also such important factors as compliance and adherence to the drug.

BIBLIOGRAPHY

1. Sambrook P, Cooper C: Osteoporosis. Lancet 2006; 367(9527): 2010-2018.
2. Johnell O, Kanis JA: An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int 2006; 17(12): 1726-1733.
3. Muschitz Ch, Fahrleitner-Pammer A, Huber J et al.: Update on denosumab in postmenopausal osteoporosis – recent clinical data. Wiener Med Wochenschr 2012; 162: 374-379.
4. Baron R, Ferrari S, Russell RGG: Denosumab and bisphosphonates: different mechanisms of action and effects. Bone 2011; 48(4): 677-692.
5. Russell RGG, Xia Z, Dunford JE et al.: Bisphosphonates: an update on mechanisms of action and how these relate to clinical efficacy. Ann NY Acad Sci 2007; 1117: 209-257.
6. Grey A, Bolland M, Mihov B et al.: Duration of antiresorptive effects of low-dose zoledronate in osteopenic postmenopausal women: a randomized, placebo-controlled trial. J Bone Miner Res 2014; 29: 166-172.
7. 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: 2927-2938.
8. Licata AA: Discovery, clinical development, and therapeutic uses of bisphosphonates. Ann Pharmacother 2005; 39: 668-677.
9. Hampson G, Fogelman I: Clinical role of bisphosphonate therapy. Int J Womens Health 2012; 4: 455-469.
10. Tsourdi E, Rachner TD, Rauner M et al.: Denosumab for bone diseases: translating bone biology into targeted therapy. Eur J Endocrinol 2011; 165: 833-840.
11. Moen MD, Keam SJ: Denosumab: a review of its use in the treatment of postmenopausal osteoporosis. Drugs Aging 2011; 28: 63-82.
12. Biju B, Mridula Ambwani B, Myint S et al.: Review on the comparison of effectiveness between denosumab and bisphosphonates in post-menopausal osteoporosis. Osteoporos Sarcopenia 2016; 2(2): 77-81.
13. Miller PD, Bolognese MA, Lewiecki EM et al.; Amg Bone Loss Study Group: Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinded phase 2 clinical trial. Bone 2008; 43: 222-229.
14. Mellstrom D, Sorensen O, Goemaere S et al.: Seven years of treatment with risedronate in women with postmenopausal osteoporosis. Calcif Tissue Int 2004; 75: 462-468.
15. Watts N, Chines A, Olszynski W et al.: Fracture risk remains reduced one year after discontinuation of risedronate. Osteoporos Int 2008; 19: 365-372.

16. Delmas PD, Recker RR, Chesnut CH 3rd et al.: Daily and intermittent oral ibandronate normalize bone turnover and provide significant reduction in vertebral fracture risk: results from the BONE study. Osteoporos Int 2004; 15: 792-798.
17. Delmas PD, Adami S, Strugala C et al.: Intravenous ibandronate injections in postmenopausal women with osteoporosis: one year results from the dosing intravenous administration study. Arthritis Rheum 2006; 54: 1838-1846.
18. Black DM, Delmas PD, Eastell R et al.: Once yearly zoledronic acid for treatment of postmenopausal osteoporosis. New Engl J Med 2007; 356: 1809-1822.
19. Black DM, Reid IR, Boonen S et al.: The effect of 3 versus 6 years of zoledronic acid treatment in osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). J Bone Miner Res 2012; 27: 243-254.
20. National Institute for Health and Clinical Excellence: Appraisal Consultation Document. Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women. NICE, London Feb 2007.
21. National Institute for Health and Clinical Excellence: Final appraisal determination. Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. NICE, London June 2007.
22. 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: 197-213.
23. Lewiecki EM, Binkley N: What we don't know about osteoporosis. J Endocrinol Investig 2016; 39(5): 491-493.
24. Schwartz AV, Bauer DC, Cummings SR et al.; FLEX Research Group: Efficacy of continued alendronate for fractures in women with and without prevalent vertebral fracture: the FLEX trial. J Bone Miner Res 2010; 25: 976-982.
25. Whitaker M, Guo J, Kehoe T et al.: Bisphosphonates for osteoporosis – where do we go from here? N Engl J Med 2012; 366: 2048-2051.
26. Zaheer S, LeBoff M, Lewiecki EM: Denosumab for the Treatment of Osteoporosis. Expert Opin Drug Metab Toxicol 2015; 11(3): 461-470.
27. Bone HG: Late-Breaking Abstract Presentations. Ten Years of Denosumab Treatment in Postmenopausal Women With Osteoporosis: Results From the FREEDOM Extension Trial. Presented at: American Society for Bone and Mineral Research (ASBMR) 2015 Annual Meeting Oct. 9-12, 2015; Seattle.
28. Orwoll E, Teglbjærg C, Langdahl B et al.: A randomized, placebo-controlled study of the effects of denosumab for the treatment of men with low bone mineral density. J Clin Endocrinol Metab 2012; 97(9): 3161-3169.
29. Crandall CJ, Newberry SJ, Diamant A et al.: Comparative Effectiveness of Pharmacologic Treatments to Prevent Fractures: An Updated Systematic Review. Ann Intern Med 2014; 161: 711-723.
30. Hopkins RB, Goeree R, Pulenayegume E et al.: The relative efficacy of nine osteoporosis medications for reducing the rate of fractures in post-menopausal women. BMC Muscloskelet Dis 2011; 12: 209.
31. Zhang L, Pang Y, Shi Y et al.: Indirect comparison of teriparatide, denosumab, and oral bisphosphonates for the prevention of vertebral and nonvertebral fractures in postmenopausal women with osteoporosis. Menopause 2015; 22(9): 1021-1025.
32. Cummings SR, San Martin J, Mcclung MR et al.: Denosumab for prevention of fractures in postmenopausal women with osteoporosis. NEJM 2009; 361(8): 756-776.
33. Black D, Cummings S, Karpf D et al.: Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996; 348(9041): 1535-1541.
34. Brown J, Prince R, Deal C et al.: Comparison of the effect of denosumab and alendronate on BMD and biochemical markers of bone turnover in postmenopausal women with low bone mass: a randomized, blinded, phase 3 trial. J Bone Miner Res 2009; 24(1): 153-161.
35. Kendler D, Roux C, Benhamou C et al.: Effects of denosumab on bone mineral density and bone turnover in postmenopausal women transitioning from alendronate therapy. J Bone Miner Res 2009; 25(1): 72-81.
36. Roux C, Hofbauer L, Ho P et al.: Denosumab compared with risedronate in postmenopausal women suboptimally adherent to alendronate therapy: efficacy and safety results from a randomized open-label study. Bone 2014; 58: 48-54.
37. Recknor C, Czerwinski E, Bone H et al.: Denosumab compared with ibandronate in postmenopausal women previously treated with bisphosphonate therapy: a randomized open-label trial. Obstet Gynecol 2013; 121(6): 1291-1299.
38. McClung MR, Lewiecki EM, Geller ML et al.: Effect of denosumab on bone mineral density and biochemical markers of bone turnover: 8-year results of a phase 2 clinical trial. Osteoporos Int 2013; 24: 227-235.
39. Murad MH, Drake MT, Mullan RJ: Clinical review. Comparative effectiveness of drug treatments to prevent fragility fractures: a systematic review and network meta-analysis. J Clin Endocrinol Metab 2012; 97: 1871-1880.
40. Min Y-K: Update on denosumab treatment in postmenopausal women with osteoporosis. Endocrinol Metab 2015; 30(1): 19-26.
41. Freemantle N, Satram-Hoang S, Tang ET et al.; DAPS Investigators: Final results of the DAPS (Denosumab Adherence Preference Satisfaction) study: a 24-month, randomized, crossover comparison with alendronate in postmenopausal women. Osteoporos Int 2012; 23: 317-326.
42. Miller PD, Pannacciulli N, Brown JP et al.: Denosumab or Zoledronic Acid in Postmenopausal Women With Osteoporosis Previously Treated With Oral Bisphosphonates. J Clin Endocrinol Metab 2016; 101(8): 3163-3170.
43. Sheedy K, Maria Camara M, Camacho P: Comparison of the Efficacy, Adverse Effects, and Cost of Zoledronic Acid and Denosumab in the Treatment of Osteoporosis. Endocrine Practice 2015; 21(3): 275-279.

received/otrzymano: 07.12.2016
accepted/zaakceptowano: 28.12.2916