# ПРИМЕНЕНИЕ ДЕНОСУМАБА ПРИ РАЗЛИЧНЫХ ВАРИАНТАХ ТЕЧЕНИЯ ОСТЕОПОРОЗА

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В статье представлено описание трех клинических случаев успешного применения таргетного препарата для лечения остеопороза – деносумаба – у пациентов с различными формами остеопороза: постменопаузальным остеопорозом при неэффективности бисфосфонатов, остеопорозом смешанного генеза на фоне супрессивной терапии тиреоидными гормонами и ингибиторами ароматазы, остеопороз у мужчины на фоне первичного гиперпаратиреоза. Механизм действия деносумаба отличен от такового у бисфосфонатов: связываясь с лигандом рецептора активатора ядерного фактора каппа бета (RANKL), деносумаб предотвращает дифференцировку остеокластов из преостеокластов, и, тем самым, подавляет резорбцию костной ткани. В клинических исследованиях было показано, что деносумаб способствует дальнейшему приросту минеральной плотности костной ткани после лечения бисфосфонатами. Деносумаб применяется в России с 2012 года. Клиническая эффективность и безопасность применения позволяют отнести деносумаб к препаратам первой линии лечения остеопороза.

КЛЮЧЕВЫЕ СЛОВА: *Остеопороз; деносумаб; RANKL; денситометрия; клинический случай;*

# DENOSUMAB TREATMENT IN PATIENTS WITH DIFFERENT COURSES OF OSTEOPOROSIS

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We present three clinical cases of successful osteoporosis treatment with denosumab in patients with different courses of osteoporosis: postmenopausal with bisphosphonates ineffectiveness, osteoporosis of mixed etiology in patient on thyroid stimulating hormone suppression and aromatase inhibitor therapy and a case of osteoporosis in a male caused by primary hyperparathyroidism. Mechanism of denosumab action is different from bisphosphonates: denosumab prevents osteoclast differentiation by binding to receptor activator of nuclear factor kappa-B ligand (RANKL) and thus suppressing bone resorption. Clinical trials showed that denosumab promotes further increase of bone mineral density after bisphosphonate treatment. Denosumab has been used in Russian Federation since 2012. Clinical effectiveness and safety profile make denosumab one of the first-line drugs for osteoporosis treatment.

KEYWORDS: *Osteoporosis; denosumab; RANKL; DXA; case report;*

## BACKGROUND

Denosumab (DMB) is the first developed and applied into clinical practice targeted therapy for osteoporosis (OP). DMB is a fully human monoclonal antibody to the receptor activator of nuclear factor-κB ligand (RANKL), which is the key molecule inosteoblast maturation, function and survival [1]. Regarding DMB effect on bone metabolism, it is classified as antiresorptive treatment The mechanism of action of DMB differs from that of bisphosphonates (BF), as DMB inhibits octeoclasts' formation from pre-osteoclasts without influence on mature cell function, the effect is reversible and the drug does not accumulate in bone tissue [2]. DMB has been applied into clinical practice in Russian Federation since 2012.

Numerous studies have shown that DMB suppresses biochemical markers of bone metabolism and improves bone mineral density (BMD) [3]. The ten-year treatment period has shown that DMB is effective for the prevention of hip and vertebral fractures, as well as extra-vertebral fractures in women with postmenopausal OP [4]. DMB also has proved to be effective in treatment of senile OP in men [5].

DMB prevents BMD loss and improves it in men receiving androgen deprivation therapy for prostate cancer [6] and in women receiving aromatase inhibitors for breast cancer [7].

Compared with alendronate, DMB treatment of postmenopausal OP leads to better BMD improvement, measured by dual energy X-ray absorptiometry (DEXA), quantitative computed tomography and high resolution computed tomography [8,9]. Transition to DMB after alendronate, ibandronate and zoledronic acid treatment results in further improvement of BMD [10]. Above mentioned DMB features, its clinical effectiveness and safety lets to consider DMB as a first-line treatment of postmenopausal, senile OP, and OP developed as a result of androgen depriving therapy and aromatase inhibitors.

We have the experience of DMB treatment of more than 170 patients with OP for a follow-up period of 2 – 5 years.

## CASE REPORT 1

Patient T., a 78-year old woman, admitted to the outpatient department of Endocrinology Research Centre in 2013 complaining of back pain, and gradual height loss


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of 7 cm. According to medical history, menopause started at the age of 42, father had a hip fracture at the age of 82. Osteoporosis was diagnosed when patient was 68 years old. Patient had right radius fracture at the age of 70 and humerus fracture at 75. During medical examination at 75 years of age, X-ray scan revealed vertebral compression fracture of Th12 (grade 2) and L1 (grade 3). BMD data in 2006: lumbar vertebrae T-score (L1-L4) -3,5 SD, femur neck T-score -3,0SD. Before admission to Endocrinology Research Centre the patient was treated with alendronate 70 mg once a week per os for 3 years and with ibandronate 3 mg intravenously once in 3 months for 3 years. During the first years of treatment, BMD improvement in vertebrae was +4%, in the hip – up to +2,5% (table 1a). In 2012 vitamin D (25OHD) was measured for the first time, it was decreased to 10,6 ng/ml (30-60), which required colecalciferol therapy. In 2013, already recieving treatment patient suffered low traumatic left radius fracture. According to DEXA, the patient had BMD loss: -6% in femur neck, -2% in L1-L4. The patient underwent further examination in Endocrinology Research Centre: calcium (Ca), phosphorus (P), alkaline phosphatase (AP), 24-hours urine calcium levels were normal. Serum 25OHD level was 18,2 ng/ml (30-60), collagen type 1 C-telopeptide (CTx) was 0,654 ng/ml (upper quartile of reference interval), osteocalcin (OC) – 32,4 ng/ml (upper quartile of reference interval). X-ray scan revealed progression of Th12 fracture to grade 3.

Based on the medical history and current observations, the diagnosis was made: «Severe form of progressive postmenopausal osteoporosis, with Th12 and L2 compression fractures, both radius fractures, humerus fracture, negative BMD and Th12 compression dynamics on bisphosphonates therapy».

Despite ibandronate treatment CTx was not suppressed. Besides,vitamin D deficiency remained. Consequently, the patient had following indications for treatment change: development of new fractures, absence of bone resorption marker suppression, decrease in femur neck BMD by 6%. In 2013 the following treatment was prescribed: colecalciferol 50000 IU per week for 6 weeks, with further decrease to 15000 IU per week, calcium carbonate 500 mg after dinner. Two weeks after colecalciferol dosage was increased, we initiated DMB treatment: 60 mg subcutaneously once per 6 months.

Three months after the first DMB injection, CTx level was 0,08 ng/ml (decreased by 78%), 25OHD – 31 ng/ml; Ca, creatinine, P, AP were normal. No adverse effects were registered. Additionally, we recommended the patient to start therapeutic exercises, and walking 3000-5000 steps per day. After six months of treatment, the patient reported general health improvement, back pain disappearance, increased physical activity, absence of falling. After 1 year of DMB treatment, 25OHD remained normal, CTx suppressed to 0,09 ng/ml. L1-L4 BMD improvement +3,2%, hip BMD improvement +3,4%. There were no new fractures or height loss, physical activity further increased. After 4 years of DMB treatment – no new fractures or height loss. Vitamin D – 34,2 ng/ml, CTx 0,11 ng/ml. Estimated vertebral BMD improvement +8,4%, femoral BMD +4,7% (table 1 and 1a). DMB treatment 60 mg once per 6 months, colecalciferol 15000 IU once a week, calcium 500 mg after dinner daily were continued. In addition to treatment, movement exercises and walking 5000-7000 steps every day were recommended.

The key points of this clinical case: severe progressive osteoporosis with fractures, bisphosphonates ineffectiveness after 5 years of treatment, vitamin D deficiency. Initiation of DMB after six years of bisphosphonates treatment showed good results according not only to indirect parameters, such as BMD improvement in all skeletal sights, appropriate suppression of bone resorption marker and vitamin D level elevation, but also to clinical features: absence of new fractures for 4 years, quality of life improvement, increase in physical activity.

## CASE REPORT 2

Patient Sh., a 76 year-old male, admitted to outpatient department of Endocrinology Research Centre in 2011 complaining of hip joints pain, and leg weakness. Concomitant diseases: coronary artery disease, unstable angina, two coronary artery stent placements (in1999 and 2012), stage 2 hypertension, spondyloarthropathy with radicular syndrome; coxarthrosis. In 2011, osteoporosis was diagnosed: decrease in femur neck BMD to -2,8 SD T-score, in L1-L4 -1,3 SD and -3,6 SD in radius. Further examination in Endocrinology Research Centre revealed hypercalcemia up to 2,6-2,75 mmol/l (2,15-2,55), PTH elevation to 180 ng/ml (15-65); CTx 0,94 ng/ml (reference interval below 0,63), osteocalcin 56 ng/ml (reference interval below 43), hypercalciuria 8,6 mmol/24h (2,5-7,5). Parathyroid

**Table 1.** Vitamin D and bone metabolism marker changes in patient T.

| Parameter / year | 2012 | 3 months after Denosumab injection | 2013 | 2017 | Reference range |
|---|---|---|---|---|---|
| 25(OH)D (ng/ml) | 18,2 | 31,0 | - | 34,2 | 30-100 |
| β-cross laps (ng/ml) | 0,654 | 0,08 | 0,09 | 0,11 | 0.01-0.69 |

**Table 1a.** BMD change in patient T.

| Skeletal site/year | 2006 | 2012, bisphosphonates treatment | 2013, bisphosphonates treatment | 2014, first year of DMB treatment | 2017, 4 years of DMB treatment |
|---|---|---|---|---|---|
| L1-L4 | -3,5 SD | +4% | -6% | +3,2% | +8,4% |
| Femoral neck | -3,0 SD | +2,5% | -2% | +3,4% | +4,7% |

ultrasound showed hyperplasia of three parathyroid glands: from 0,9x0,7 cm. to 1,2x0,9 cm. in size. According to renal ultrasound, patient had renal concrements up to 0,6 cm, but no clinical signs of kidney stones.

The diagnosis was made: «Primary hyperparathyroidism. Multiple parathyroid gland enlargement. Hypercalcemia, hypercalciuria. Osteoporosis of mixed etiology (senile, hyperparathyroid)».

The patient refused suggested surgical treatment. In 2011, for osteoporosis and hypercalcemia treatment, we initiated intravenous injections of zoledronic acid 5 mg yearly. One year after zoledronic acid injection, femoral BMD improved by 4% with no change in lumbar spine and radius. Serum calcium level varied from 2,6 to 2,7 mmol/l, hypercalciuria up to 8,0 mmol/24h, we observed no nephrolithiasis progression. These findings suggested stabilization of hyperparathyroidism. In 2014, after three zoledronic acid injections we observed decrease in BMD: femur neck T-score -5,2%, radius -2,4%. Six months after the last zoledronic acid injection, bone resorption marker was not suppressed (CTx 0,68 ng/ml), serum 25OHD was 21,8 ng/ml. Serum calcium level ranged from 2,68-2,67 to 2,71 mmol/l, PTH level was 208-230 pg/ml (7,6-69). Due to decreased influence of bisphosphonate treatment on BMD, absence of CTx suppression, persistent mild hypercalciemia, in March 2014 we initiated DMB treatment 60 mg subcutaneously once per 6 months and colecalciferol 10000 IU weekly. In case of persistent hypercalcemia, we planned the addition of cinacalcet. However, after DMB injection serum calcium level decreased to 2,54-2,6 mmol/l, CTx got suppressed to 0,1 ng/ml. To the present day, eight DMB injections were made, the last one in September 2017. In September 2017, serum calcium level was 2,55 mmol/l, PTH 166 ng/ml, phosphorus 1,01 mmol/l, CTx – 0,069 ng/ml, osteocalcin – 14 ng/ml, 24-hour urine calcium level 8,0 mmol/24h, 25OHD – 35 ng/ml, creatinine – 88 µmol/L , GFR – 64 ml/min/1,73m2, alkaline phosphatase – 59 U/l. DEXA: L1-L4 -0,8 SD (+9,4%), femur neck -2,4 SD (+5,6%), radius -3,3 SD (+2,6%) (table 2). Parathyroid ultrasound showed no change in parathyroid size. During the observation no fractures or falling occurred. We are planning to continue the treatment for at least two years.

The key points of this clinical case are: DMB prescription to an elderly patient with primary hyperparathyroidism, OP of mixed etiology (senile and as the result of hyperparathyroidism) and mild hypercalcemia, patient refusal of surgical treatment. It is known, that besides good anti-osteoporotic effect in men with senile OP [11], DMB also has a hypocalcemic effect [12]. There are several case reports of DMB use for hypercalcemia treatment [13]. As the result of DMB and colecalciferol treatment, our patient achieved BMD improvement in femur to osteopenia level, significant improvement in radius BMD. We also managed to keep calcium level on upper limits of the reference interval and to suppress the bone resorption activity. Taken together, these effects lead to fracture prevention in this patient.

## CASE REPORT 3

Patient A., a 58 year-old female, admitted to Endocrinology Research Centre with hypothyroidism. According to medical history, the patient underwent thyroidectomy and radioactive iodine treatment for papillary thyroid cancer in 2011. Until 2016, the patient was treated with suppressive doses of levothyroxine, prior to admission she started to receive a replacement therapy with levothyroxine, 125 µg daily. Menopause since 50 years (since 2005). In 2013, the patient was diagnosed with breast cancer (T2, N1, M0) and underwent right breast mastectomy, treatment with radiation therapy with further aromatase inhibitor (anastrozole) treatment. In January 2014, she developed low trauma left radius fracture. Examination in Endocrinology Research Centre in 2014: serum Ca – 2,31 mmol/l (2,15-2,55), 25OHD – 17,1 ng/ml, creatinine – 55 µmol/L, TSH 0,009 mU/l (0,35-4,0), free T4 16 pmol/l, thyroglobulin 0,1 ng/ml, CTx – 0,74 ng/ml (reference interval below 0,63), 24-hour urine Ca 3,69 mmol/24h (2,5-7,5). DEXA: L1-L4 T-score BMD -3,2 SD, femoral neck -1,9 SD, radius BMD -2,9 SD. The patient reported no height loss. According to lateral X-ray scan, no vertebral height loss occurred.

We revealed the following risk factors for osteoporosis and fractures: low body weight, low calcium intake,

**Table 2.** Calcium metabolism, bone metabolism marker changes and BMD improvement in patient Sh.

| Parameter | 2011 | 2012, 1 year after ZA injection | 2014, 3 years after ZA injection | 2017, 3 years after DMB injection | Reference range |
|---|---|---|---|---|---|
| Serum calcium (mmol/l) | 2,75 | 2,70 | 2,71 | 2,55 | 2.15-2.55 |
| 24-hour urine calcium (mmol/24h) | 8,6 | 8,0 | - | 8,0 | 2.5-8.0 |
| Parathyroid hormone (ng/ml) | 180 | - | 230 | 166 | 15-65 |
| β-cross laps (ng/ml) | 0,94 | - | 0,68 | 0,069 | 0.01-0.69 |
| | | | DEXA BMD change | | |
| L1-L4, T-score | -1,3 SD | No dynamics | No dynamics | +9,4% | |
| Femoral neck, T-score | -2,8 SD | +4% | -5,2% | +5,6% | |
| Middle third of the radius, T-score | -3,6 SD | No dynamics | -2,4% | +2,6% | |

Note: ZA – zoledronic acid, DMB – denosumab

**Table 3.** Calcium metabolism, bone metabolism marker changes and BMD improvement in patient A.

| Parameter | 2014, initial data | 2017, after 3 years of DMB treatment | Reference range |
|---|---|---|---|
| Serum calcium (mmol/l) | 2,31 | 2,42 | 2.15-2.55 |
| 24-hour urine calcium (mmol/24h) | 3,69 | 6,6 | 2.5-8.0 |
| β-cross laps (ng/ml) | 0,94 | 0,06 | 0.01-0.69 |
| DEXA BMD improvement | | | |
| L1-L4, T-score | -3,2SD | -2,6SD | - |
| Femoral neck, T-score | -1,9SD | -1,6SD | |
| Radius, T-score | -2,9SD | -2,7SD | |

levothyroxine suppressive therapy, estrogen sensitive breast cancer therapy by aromatase inhibitor.

The diagnosis of this patient: «Postoperative hypothyroidism after thyroidectomy and radioactive iodine treatment of thyroid papillary cancer. Right breast mastectomy and radiotherapy of estrogen sensitive breast cancer, aromatase inhibitor therapy. Osteoporosis of mixed etiology, maximum BMD loss in L1-L4 to -3,2 SD T-score and low-trauma left radius fracture in 2014; vitamin D deficiency».

Since March 2014, the patient has been treated with decreased levothyroxine dosage (88 µg per day) and DMB treatment was initiated (until September 2017, 6 injections have been made). In addition, calcium 1000 mg daily and colecalciferol 50000 IU once per week for 6 weeks were prescribed with further correction of colecalciferol to 15000IU weekly. According to the follow-up data in May 2017: Ca 2,42 mmol/l, creatinine 67 µmol/L, 25OHD 34,8 ng/ml, CTx 0,06 ng/ml, TSH 0,9 mU/l, free T4 15,3 pmol/l, PTH 36,5 pg/ml, 24-hour urine calcium 6,6 mmol/24h. DEXA: L1-L4 BMD changed from -3,2 SD to -2,9 SD, in femur neck from -1,9 SD to -1,6 SD, in right radius BMD changed from -2,9 to -2,7 by T-score (table 3). We decided to continue DMB treatment until aromatase inhibitor discontinuation and L1-L4 BMD improvement up to osteopenia level. As the result of levothyroxine 88 µg and colecalciferol 15000 IU per week treatment, target TSH and 25OHD levels were achieved.

The key points of this clinical case are: mixed etiology of osteoporosis (postmenopausal and iatrogenic as the result of levothyroxine and aromatase inhibitor treatment) in a 58 year-old woman with multiple risk factors for osteoporosis and fractures.

For many decades, tamoxifen remained the main medication for estrogen sensitive breast cancer treatment [14]. Aromatase inhibitors showed better efficacy in tumor relapse prevention [15], they are often included in standard breast cancer therapy protocols [16]. However, their use is complicated with increased bone turnover, which leads to BMD loss and increased rate of fractures [18]. Clinical studies proved DMB efficacy in prevention of BMD loss and fractures in this cohort of patients [19-20]. DMB is indicated to patients recieving aromatase inhibitors' therapy. Considering all mentioned factors, our patient had indications for antiresorptive treatment, particularly DMB. Three years of the follow-up showed therapeutic efficacy.

## DISCUSSION

Clinical cases presented in the article demonstrate efficacy and safety of DMB in cases of severe postmenopausal OP with bisphophonates therapy failure; OP of mixed etiology with concomitant suppressive levothyroxine and aromatase inhibitors treatment; in a patient with OP and primary hyperparathyroidism, where DMB demonstrates mild hypocalcemic effect. In all presented cases there were no side effects.

## CONCLUSION

DMB is a target therapy for osteoporosis treatment, which can be used in postmenopausal OP, OP in women being treated with aromatase inhibitors and in men being treated with androgen deprivation therapy. DMB is characterized by mild hypocalcemic and profound antiresorptive effects and can be used in women with postmenopausal OP and in men with senile OP and primary hyperparathyroidism [21].

DMB has proved its efficacy and good long-term safety profile according to results of longstanging patients' follow-up.

## ADDITIONAL INFORMATION

**Conflict of interests**. Authors declare no explicit and potential conflicts of interests associated with the publication of this article

**The patient's informed consent**. Patients signed the informed consent form for anonymous personal medical data publication in «Osteoporosis and osteopathy» medical journal.

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