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PHARMACOTHERAPY OF OSTEOPOROSIS IN MALES

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Abstract. *The article deals with the problems of osteoporosis (OP) treatment in male patients in whom the disease often remains undiagnosed and untreated despite the progress made in understanding the mechanisms of development, principles of diagnostics, prevention and treatment of OP. Medications used for the treatment and prevention of OP represent a large and diverse group of drugs according to their mechanism of action. A common property, allowing to combine these drugs in one pharmaceutical group, is their predominant influence on bone remodeling processes, as well as calcium homeostasis. In this article the results of clinical trials were examined according to the evaluation of the effectiveness of antiosteoporotic drugs in males with OP. Men with an increased risk of fractures should be recommended antiosteoporotic drugs, for which the evidence of efficacy in clinical trials in relevant cohorts of patients has been obtained.*

Keywords: *osteoporosis, osteoporosis in males, treatment, antiosteoporotic drugs.*

Despite the progress made in understanding of the mechanisms of development, principles of diagnostics, treatment and prevention of osteoporosis (OP), the disease often remains undiagnosed and untreated, especially in males [1]. At the same time prevalence of OP in males increases with the growth of the duration of life, the detection rate of reduction of bone mineral density (BMD) on examination for back pains, and perhaps due to the change in diet and lifestyle, having negative impact on calcium and bone tissue metabolism.

In accordance with the recommendations of the American Association of Clinical Endocrinologists [21], pharmacotherapy of OP is indicated to the males with high risk of fractures. This group includes patients with risk factors shown below (but not limited to them):

– men who have had hip fractures or vertebral fractures, not connected with serious injuries (1; moderate) [1];

– men who did not have any fractures of the spine or cervical hip, but who had BMD values of the spine, cervical hip and / or the whole hip below the mean values for healthy young white race males for at least 2.5 standard deviations (SD) (1; low);

– men with a T-score between – 1.0 and – 2.5 for the spine, femoral neck or the whole hip with 10-year risk of any fractures and 10-year hip fracture risk on the scale of evaluation of the Fracture Risk Assessment Tool (FRAX) equal ≥ 20% and ≥ 3 respectively (in the USA). To determine the appropriate levels of intervention on the basis of fracture risk assessments using other algorithms, further research is required. In other regions local instructions on this problem should be taken into account (1, low);

– men taking long-acting glucocorticoids in pharmacological doses (e.g. prednisolone or its equivalent in a dose > 7.5 mg / day) in accordance with the recommendations of the American Society of Clinical Rheumatologists (2010) (1; low).

[1] – The strength and level of evidence of the recommendations are evaluated with the GRADE system: 1 – strong recommendation, 2 – weak recommendation; levels of evidence: very low, low, moderate and high.

Medications used for the treatment and prevention of OP represent a large and diverse group according to the mechanism of drug action. General property, allowing to combine these drugs into one pharmacotherapeutic group, is their predominant influence on the processes of bone remodeling, as well as the calcium homeostasis closely related to it (Table 1).

Table 1. Classification of modern antiosteoporotic drugs [20]

Group	Characteristics of main properties	Subgroup	Main drugs

Anti-catabolic drugs	↓ of increased bone resorption, ↓ of bone remodeling, Prevent disturbances of the microarchitecture of bone tissue and injuries of the trabecula and bone porosity. Although the drugs may moderately ↑ bone mass and promote its mineralization, these properties are not compulsory	A. Bisphosphonates B. RANKL antagonists B. Calcitonins G. SERM D. HRT medications	Alendronate, risedronate, zoledronic acid, ibadronat and others. Denosumab Salmon Calcitonin Raloxifene, lazoxifene Estrogens, testosterone and others.
Anabolic drugs	↑ of bone strength by increasing its mass due to the prolongation of bone formation and cell activity of osteoblastic line within the remodeling processes	The parathyroid hormone (PTH)	Teriparatide, semiparatide
Anti-catabolic and anabolic drugs with additional properties	Rebalancing between resorption and formation phases in the process of bone remodeling, intensification and acceleration of mineralization of the newly formed bone, healing of microfractures	A. The active metabolite of vitamin D and its analogues B. Strontium salts	Calcitriol, Alfacalcidol Strontium ranelate

Notes: ↓ – decrease; ↑ – increase; HRT – hormone replacement therapy; SERM – selective estrogen receptor modulators; RANKL – receptor activator of nuclear factor kappa-B ligand (RANK).

Bisphosphonates is the most studied group of drugs for the treatment of OP. The ability of bisphosphonates to inhibit abnormal bone resorption of bone tissue and stimulate bone formation determines their therapeutic effect in OP. In clinical studies it was shown that bisphosphonates are effective in males with primary and secondary OP, including hypogonadism and glucocorticoid-induced OP.

Alendronate. In a double-blind placebo-controlled study [14] 2-year therapy with alendronate (at a dose of 10 mg / day) resulted in an increase in BMD of the lumbar spinal region, femur and reduction of the incidence of vertebral fractures in males with OP.

In another study [12] it was shown that the prescription of alendronate at a dose of 70 mg once a week was an efficient and convenient alternative to a daily intake of the drug in the treatment of male OP with a good safety and tolerability profile.

Risedronate. It was established that an intake of risedronate at a dose of 35 mg once a week lead to a significant increase in BMD at the lumbar region of the spine by 4.5% (in 95% CI from 3.5% to 5.6%, $p < 0.001$) compared with placebo. There were no significant differences between the groups observed in the frequency of fracture development. Then in the open phase of the study, risedronate was prescribed to all the patients in a dose of 35 mg once a week for the next two years. A significant increase in BMD in the lumbar region of the spine has been demonstrated in the group of previously treated patients and those who just started the treatment (by 7.87% and 6.27%) compared with the original data [3].

Zoledronic acid (ZA). In a comparative 2-year study including males with primary OP and OP associated with hypogonadism [15] it was noted, that according to the effect on BMD, bone biochemical markers and therapy safety, ZA (at a dose of 5 mg once a year) is similar to alendronate (70 mg once a week).

In a double-blind placebo-controlled trial HORIZON-RFT (The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Recurrent

Fracture Trial) [10] ZA was introduced during the first 90 days after surgical treatment of fractures of the proximal part of the femur and then every 12 months. The average term of the study was 1.9 years. The primary endpoint was the rate of new clinical fractures. It was demonstrated that intravenous administration of ZA in the first 90 days after the surgical treatment of proximal femur fractures is associated with a reduced incidence of new clinically apparent fractures and the number of lethal outcomes.

In a multicenter double-blind placebo-controlled study [4] the effectiveness of treatment with ZA (intravenously at a dose of 5 mg once a year) for the reduction of the risk of vertebral fractures in males with OP was studied. The primary point of the study was the number of patients with one or more new vertebral fractures according to morphometric data for 24 months. It was noted that the ZA treatment resulted in a statistically significant reduction of the risk of new vertebral fractures.

Ibandronate is highly active, nitrogen-containing bisphosphonate, positively proven in the treatment of postmenopausal OP in females. At the same time, there is not enough data on administration of ibandronate in males with OP. In a double-blind, placebo-controlled study STRONG (The Study Researching Osteoporosis in Guys) [16], which included males with reduced BMD, it was shown that under the influence of ibandronate a significant increase of BMD in the region of lumbar spine was observed compared with placebo (3, 5% versus 0.9%, respectively; $p<0.001$). Also in the main group BMD increased in the region of hip, femoral neck and the region of trochanter compared to placebo. Ibandronate effectively inhibited bone resorption, what resulted in a significant decrease of bone turnover markers together with good tolerability.

RANKL antagonists

Denosumab. Denosumab is a fundamentally new antiresorptive drug having a direct impact on the key system RANK / RANKL / OPG, regulating bone resorption. Denosumab is a completely human monoclonal antibody (IgG2),

having high affinity and specificity for receptor activator of nuclear factor kappa-B ligand (RANKL). Thereby it prevents the activation of the single receptor RANKL – activator of nuclear factor kB (RANK) located on osteoclast surface and their precursors. Thus prevention of RANKL / RANK interaction inhibits the formation, activation and duration of existence of osteoclasts. As a result, denosumab reduces bone resorption and increases weight and strength of the cortical and trabecular bone layers.

In a multicenter randomized double-blind placebo-controlled study ADAMO [17] the efficacy and safety of denosumab was studied in males with OP. It was shown that treatment with denosumab (at a dose of 60 mg subcutaneously every 6 months during 1 year) resulted in a significant increase in BMD at the lumbar region of the spine compared with placebo (5.7% vs 0,9%, $p < 0,0001$). This effect did not depend on age, testosterone level, BMD status and set fracture risk. The frequency of adverse effects did not differ among the groups.

Anabolic drugs

Teriparatide. Physiological effect of parathyroid hormone (PTH) lies in the stimulation of bone tissue formation by direct impact on osteoblasts. PTH indirectly stimulates the intestinal absorption and tubular reabsorption of calcium as well as the excretion of phosphates [11]. Introduction of teriparatide stimulates new bone tissue formation in connection with primary stimulation of osteoblasts in comparison to osteoclasts.

The positive effect of three drugs on the base of parathormone was observed on bone: PTH 1-34 (teriparatide) [13], PTH 1-84 and analogue of PTH-related peptide (Semiparatide) [5]. At the same time, in clinical studies the evidence of efficiency is obtained only for PTH 1-34, recombinant human teriparatide produced by Escherichia coli. It was established that teriparatide is effective for increasing of BMD in males with primary and hypogonadal OP with high risk of fractures and treatment of glucocorticoid-associated OP in males with high risk of fractures.

The most reliable research for the effectiveness of teriparatide treatment of OP in males was a double-blind placebo-controlled study [18], which included 437 males randomized into 3 groups: placebo injections (147 persons), 20 mcg of teriparatide (151 persons) and 40 mcg of teriparatide (139 persons). After 11 months spinal BMD increased by 5.9% in patients receiving 20 mg / day and by 9.0% in patients who were administered 40 g / day of teriparatide femoral BMD increased by 1.5% and 2.9% respectively.

The patients treated with teriparatide, showed dose-dependent increase in the markers of bone formation and bone resorption. After 18 months after completion of treatment with teriparatide 355 males were re-examined [7]. In patients treated with teriparatide there was no reduction in BMD after completion of treatment, moreover, there was a tendency for an increase of BMD (it should be noted, that patients could receive antiresorptive therapy after the end of the study). Also after 18 months it was shown that the incidence of severe fractures and moderately severe fractures was significantly lower (by 83%) in the group receiving teriparatide [54].

Treatment with testosterone

In the clinical studies [1, 2] it was found that, testosterone replacement therapy in males with hypogonadism prevents bone loss and increases BMD, but main problem is still the lack of long-term investigations and the data on the influence on the risk of fractures. At the same time, the American Association of Clinical Endocrinologists recommends the therapy with testosterone for males with high risk of fractures and testosterone level <200 ng / dL (6.9 mmol / l) in the absence of standard indications for testosterone therapy, but having contraindications for approved medications for the treatment of OP (2, low).

Strontium ranelate

Strontium ranelate has a unique combined action, inhibiting bone resorption and, at the same time, stimulating its formation. The experiment indicated that strontium ranelate stimulates replication of osteoblast precursors, collagen

synthesis and formation of bone in bone tissue culture, inhibits differentiation and osteoclast activity, thus reducing bone resorption [6]. It was established that in men with primary OP the intake of strontium ranelate at a dose of 2 g / day for 2 years led to a greater increase in BMD in the lumbar spinal region, femoral neck and entire hip (all $p < 0.001$) in comparison with placebo. In assessment of the dynamics of bone markers against a background of the treatment with strontium ranelate the increased levels of markers of bone formation and reduced indicators of bone resorption were observed [8]. In an open prospective controlled 12-month study [19] the effect of strontium ranelate (2 g / day) or alendronate (70 mg / week) on the BMD in 152 males with primary OP were compared. An increase in BMD in the lumbar spinal region and entire hip in both therapy groups was observed. However, in the group of strontium ranelate an increase of BMD in the lumbar spinal region by 22% ($p = 0.033$) and entire hip by 23% ($p = 0.002$) was greater than in the alendronate group. Side effects were observed in 28 (37%) and 38 patients (50%) in the strontium ranelate and alendronate groups respectively.

Thus, it is desirable to recommend antiosteoporotic drugs for the males with increased risk of fractures, for which the evidence of efficacy in clinical trials in the relevant cohorts of patients was obtained. When choosing a drug, it is necessary to find an individual approach and consider such factors as past history of fractures, severity of OP (by T-score), the risk of hip fractures, the pattern of BMD of cortical and cancellous bones, concomitant diseases, expenses for treatment and others.

Литература

1. *Amory J.K., Watts N.B., Easley K.A.* et al. Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. J Clin Endocrinol Metab 2004; 89: 503-510

2. *Benito M., Vasilic B., Wehrli F.W.* et al. Effects of testosterone replacement on trabecular architecture in hypogonadal men // J Bone Miner Res.- 2005.- Vol. 20.- P. 1785-1791

3. *Boonen S, Orwoll ES, Wenderoth D.* et al. Once-weekly risedronate in men with osteoporosis: results of a 2-year, placebo-controlled, double-blind, multicenter study // J Bone Miner Res.- 2009.- Vol.24.-P.719–25

4. *Boonen S, Lorenc RS, Wenderoth D.* et al. Evidence for safety and efficacy of risedronate in men with osteoporosis over 4 years of treatment: Results from the 2-year, open-label, extension study of a 2-year, randomized, double-blind, placebo-controlled study // Bone. -2012.- Vol. 51(3).-P.383-8.

5. *Gallagher J.C., Semparatide Investigators*. PTHrP (1-34) analog, semparatide acetate (RS-66271) causes sustained increases BMD in spine in postmenopausal osteoporotic women: two randomised placebo-controlled trials // Program and abstract of the J. Bone and Miner. Res. Annual Meeting. September 30-0ctober4 1999; St.Louis, Mo.Abstr.1018.

6. *Grynpas M.D.., Hamilton E., Cheung R.* et al. Strontium increases vertebral bone volume in rats at a low dose that does not induce detectable mineralization defect // Bone. – 1996.– Vol. 18. – P. 253–259.

7. *Kaufman J.M., Orwoll E., Goemaere S.* et al. Teriparatide effects on vertebral fractures and bone mineral density in men with osteoporosis: treatment and discontinuation of therapy // Osteoporos Int.- 2005.- Vol.16.-P.510–16.

8. *Kaufman JM., Audran M., Bianchi G.* et al. Efficacy and safety of strontium ranelate in the treatment of osteoporosis in men // J Clin Endocrinol Metab. – 2013.- Vol.98(2).-P.592-601.

9. *Kovalenko V.N., Povoroznyuk V.V., Bortkiewicz O.P.* et al. Recommendations for diagnosis, prevention and systemic treatment of osteoporosis in postmenopausal women // Ukr. revmatol. zhurn.-2009.- №3 (37) .- S. 23-39.

10. *Lyles K.W., Colon-Emeric C.S., Magaziner J.S.* et al. Zoledronic acid and clinical fractures and mortality after hip fracture // N Engl J Med.- 2007.- Vol.357.-P.1799–1809.

11. *Mazurenko S.O.* Diagnosis and treatment of osteoporosis in general clinical practice. - St. Petersburg, 2010. - 51 p.

12. *Miller P.D., Schnitzer T., Emkey R.* et al. Weekly oral alendronic acid in male osteoporosis // Clin Drug Investig. 2004;24(6):333–41.

13. *Neer R.M., Arnaud C.D., Zanchetta J.R.* et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis // England J. Medicine.- 2001.- Vol.35.- P.1434-1441.

14. *Orwoll .E, Ettinger M., Weiss S..* et al. Alendronate for the treatment of osteoporosis in men // N Engl J Med. – 2000.- Vol. 343(9).-P.604-10.

15. *Orwoll E.S., Miller P.D., Adachi J.D.* et al. Efficacy and safety of a once-yearly i.v. Infusion of zoledronic acid 5 mg versus a once-weekly 70-mg oral alendronate in the treatment of male osteoporosis: a randomized, multicenter, double-blind, active-controlled study // J Bone Miner Res. – 2010.- Vol.25.- P.2239–50

16. *Orwoll E.S., Binkley N.C., Lewiecki E.M.* et al. Efficacy and safety of monthly ibandronate in men with low bone density // Bone.- 2010.- Vol.46(4).- P.970-6.

17. *Orwoll E., Teglbjærg C.S., Langdahl B.L.* et al. A randomized, placebo-controlled study of the effects of denosumab for the treatment of men with low bone mineral density // Clin Endocrinol Metab. – 2012.- Vol.97(9).-P.3161-9.

18. *Orwoll E.S., Scheele W.H., Paul S.* et al. The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis // J Bone Miner Res. – 2003.- Vol.18.- P.9–17.

19. *Ringe J.D., Dorst A., Farahmand P.* Efficacy of strontium ranelate on bone mineral density in men with osteoporosis // Arzneimittelforschung.- 2010.- Vol.60.-P.267–72.

20. *Schwartz G.J.* Modern combination pharmacotherapy for osteoporosis // RMZH.- 2011.- № 13.- S. 842

21. *Watts N.B., Adler R.A., Bilezikian J.P.* et al. Osteoporosis in Men: An Endocrine Society Clinical Practice Guideline // J. Clin. Endocrinol. Metab.- 2012.- Vol.97(6).- P.1802–1822.

Фармакотерапия остеопороза у мужчин

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Аннотация. *Несмотря на достигнутый прогресс в понимании механизмов развития, принципов диагностики, профилактики и терапии остеопороза (ОП), заболевание зачастую остается не диагностированным и не лечится, особенно у мужчин Лекарственные средства, применяемые для лечения и профилактики ОП – большая и разнородная по механизму действия группа препаратов. Общим свойством, позволяющим объединить эти препараты в общую фармакотерапевтическую группу, является их преимущественное влияние на процессы костного ремоделирования, а также тесно связанный с ним гомеостаз кальция. В представленной статье рассмотрены результаты клинических исследований по оценке эффективности антиостеопоретических препаратов у мужчин с ОП. Мужчинам с повышенным риском переломов целесообразно рекомендовать*

антиостеопоретические препараты, для которых получены доказательства эффективности в клинических исследованиях в соответствующих когортах пациентов.

Ключевые слова: *остеопороз, остеопороз у мужчин, лечение, антиостеопоретические препараты*

Фармакотерапія остеопорозу у чоловіків

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Анотація. *Незважаючи на досягнутий прогрес в розумінні механізмів розвитку, принципів діагностики, профілактики і терапії остеопорозу (ОП), захворювання часто залишається не діагностованим і не лікується, особливо у чоловіків Лікарські засоби, що використовуються для лікування і профілактики ОП, – велика і різнорідна по механізму дії група препаратів. Загальною властивістю, що дозволяє об'єднати ці препарати в загальну фармакотерапевтичну групу, є їх переважний вплив на процеси кісткового ремоделювання, а також тісно пов'язаний з ним гомеостаз кальцію. У представленій статті розглянуті результати клінічних досліджень по оцінці ефективності антиостеопоретичних препаратів у чоловіків з ОП. Чоловікам з підвищеним ризиком переломів доцільно рекомендувати антиостеопоретичні препарати, які підтвердили ефективність в клінічних дослідженнях у відповідних когортах пацієнтів.*

Ключові слова: *остеопороз, остеопороз у чоловіків, лікування, антиостеопоретичні препарати*