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Review article ■

New Drugs for Osteoporosis Therapy: A Review of the Clinical Trials Phase 2 and 3

Ivana Tadić[1], Ljiljana Tasić[1], Nada Vujasinović Stupar[2], Katarina Ilić[3], Dejan Stevanović[4]

[1]*University of Belgrade, Faculty of Pharmacy, Department of Social Pharmacy and Pharmaceutical Legislation, Serbia*

[2]*University of Belgrade, School of Medicine, Institute of Rheumatology, Serbia*

[3]*University of Belgrade, Faculty of Pharmacy, Department of Pharmacology, Serbia*

[4]*Department of Psychiatry, General Hospital Sombor, Serbia*

SUMMARY

Osteoporosis is a chronic disease with increasing incidence that predominantly occurs in female population. There are evidences that bisphosphonates, selective estrogen receptor modulators, denosumab, teriparatide and strontium renalate, prevent vertebral fractures while alendronate, risedronate, zoledronic acid, denosumab and strontium renalate prevent hip fractures. Although these drugs are effective in osteoporosis treatment, their use is limited by their side-effects and low-adherence. The aim of this review article was to compare efficacy of new drugs for osteoporosis currently in phase 2 and 3 clinical trials. After reviewing 57 articles available on PubMed and Scopus databases that evaluated efficacy of osteoporosis medications, 10 papers, that fulfilled the review criteria, were selected for the analysis. Finally, the efficacy of five drugs was compared. Efficacy was evaluated by the values of bone mineral density (BMD) and bone turnover markers (BTM). In all the analyzed articles the BMD increased and changes of BTM were noted. The highest increase of lumbar BMD from the baseline values was achieved after six months of subcutaneous application of 20 μg/day teriparatide (11.3%). The lowest increase of BMD in the same region was recorded after six months of risedronate therapy 100 mg per os once monthly (2.1%). From ten selected articles, only one has reported data about fracture risk.

Keywords: **osteoporosis, therapy, efficacy, clinical trials phase 2 and 3**

Corresponding author:

Ivana Tadić •

phone: +381 11 3951 206•

e-mail: ivana.tadic@pharmacy.bg.ac.rs •

INTRODUCTION

Osteoporosis is a chronic disease that predominantly occurs in the ageing female population (1-3). About 30% of postmenopausal women have osteoporosis (3). It is estimated that consequently the number of females older than 50 years until the year 2050 will increase by 26% (4). Therefore, an increased incidence of osteoporosis among females is expected (4-7). The main goal of the prevention and therapy of osteoporosis is to prevent fractures, which otherwise can easily occur when the bones lose their strength and density (8). The cost of treatment of incident osteoporosis fractures is similar to other chronic diseases such as stroke or heart disease (9). It is estimated that by the year 2025 the direct treatment cost of osteoporotic fractures will reach approximately $25.3 billion per year (10).

Discovery of detailed bone structure, roles of bone cells and pathogenesis of osteoporosis enabled development of new therapeutic agents. The theories about bone remodeling, the roles of bone cells (osteoclasts, osteoblasts and osteocytes) and bone remodeling mediators (such as endocrine, paracrine, autocrine mediators, growth factors, immune mediators and eicosanoids) were quite developed during the past decade (11, 12).

The main classification of osteoporosis drugs into antiresorptive and anabolic medications is based on their mechanism of action. The antiresorptive medications include the following drugs: bisphophonates, hormones, selective estrogen receptor modulators (SERMs), bazedoxifene and denosumab (11). The second class includes anabolic medication teriparatide (TPTD) that stimulates bone formation as parathyroid hormone analogs (PTH) (4, 11). Strontium ranelate has an unclear mechanism of action and could be classified as both anabolic and antiresorptive agent (4, 13). Nevertheless, there are several therapeutic groups under investigation: wingless signaling (Wnt) pathway proteins, cathepsin K inhibitors, cell adhesion molecules (CAMs), L-carnitine derivates, calcitonin homologs, growth hormones, and cultures of Streptomyces (14).

This review is required because of expansion of new drugs which are currently in clinical trial phases 2 or 3. Therefore, health care professionals need more information about coming drugs in order to improve treatment of osteoporotic patients. Also, there are no sufficient reviews that outline comparisons of new therapeutic agents' efficiency.

The aims of this review were to evaluate new drugs for osteoporosis in clinical trial phases 2 and 3, and to assess their efficacy and fracture risk according to published data.

METHODOLOGY

Search Strategy

The primary literature search was conducted during August and September 2011 and followed by an update performed from December to January 2012. Articles reviewed in this paper were identified through two electronic databases, PubMed and Scopus by combining the following MeSH terms: "osteoporosis", "therapy" and "clinical trials phase (CTP) 2 and 3". Only articles published in English after 2007 available as a full paper were considered for the review. The general inclusion criterion was human study population aged 45 years or more. Database PubMed allowed fine filter according to the search criteria. For Scopus the authors needed to match the key words with the inclusion criteria. Screening and selection of the articles were performed according to the Centre for Reviews and Dissemination guidance for undertaking reviews in health care, and Preferred Reporting Items for Systematic reviews and Meta-Analyses statement (15, 16).

After the initial selection of the papers, the authors reviewed every title and abstract to identify if a study meets the specified criteria. For the articles unavailable in full length the corresponding authors were contacted. All collected articles were included into further analysis.

Selection of studies

Only articles that published the results of the CTP 2 and CTP3 were included in the review process. Studies comparing an intervention to placebo or to another intervention were eligible for inclusion. The studies were selected if they met the endpoints, measurement of bone mineral density (BMD) and/or bone turnover markers (BTM). The articles which did not measure BMD and/or percentage change of BMD compared to baseline values as an endpoint were excluded. Also, studies that examined drug efficacy in patients with secondary osteoporosis (breast, ovarian or prostate cancer) were excluded. There were no limits regarding the patient's gender, duration or type of the study, and pharmacological classification of drug for osteoporosis treatment.

Types of outcome measures

Studies that reported values of BMD and BTM were considered for this review. Studies that measured BMD by Dual-energy x-ray absorptiometry (DXA) on the total hip (TH), femoral neck (FN), lumbar spine (region L1-L4) (L), and forearm (distal radius) and presented BMD change in g/cm^2 or as a percentage change (a difference between the values of BMD at the end of the study versus baseline value) were included.

Bone turnover is associated with the low BMD and high fracture risk (5). BMD changes in a short-term period can be well predicted by changes of biochemical markers (17). Changes in bone metabolism can be faster assessed by measuring of BTM than BMD. Therefore, early assessment of efficacy of osteoporosis therapy should be followed by the values of BTM (18). Two groups of well-known BTM are used: bone formation and bone resorption markers. Frequently used biochemical bone formation markers are specific for collagen formation (osteocalcin (OC), bone-specific alkaline phosphatise (BSAP) and amino-terminal propeptide of type 1 collagen (PI NP)). Mostly used resorption markers are deoxypyrolidinoline, amino- and carboxy–terminal cross-linked telopeptides of type 1 collagen (NTX, CTX) (19). BTM can be measured in serum (BSAP, OC, CTX, PINP) or urine (NTX, Urinary deoxypyridinoline (DPD)) according to the reference methods.

Efficacy evaluation

Efficacy of medicines for osteoporosis treatment was examined as the percentage change of BMD or/and change in BTM (decrease during the therapy with antiresorptive agents or increase during the therapy with anabolic agents). The fracture risk, if reported, was also examined in all selected articles.

RESULTS

After the initial search of the PubMed and Scopus databases, 57 articles were identified. Forty-two articles were excluded by the title after abstract review or because they did not meet the required criteria. Nine articles were not available in full text format, however, four of them were obtained from the corresponding authors. The final review included 10 articles (Figure 1).

In selected articles, all studies recruited postmenopausal women for the analysis except one (20). Half of the articles published the results of multicenter international clinical trials. Measurement of BMD on L spine was performed in all the studies, and in some of them BMD was additionally measured on the forearm (F), proximal femur (PF), TH and/or trochanter (Trc). In all the studies, patients were taking additional supplements of calcium and/or vitamin D. Selected articles examined efficacy of five different drugs: denosumab, TPTD, arzoxifene, risedronate and bazedoxifene (Table 1).

Value of BMD at the end of the study versus baseline value is a useful indicator of medication efficacy, but only one article presented both values. All other studies showed their results as BMD percentage change without specifying what was the BMD value at the end of the study (21). Studies' aims, main results, baseline BMD and percentage of its change at the end of the study were presented in Table 1.

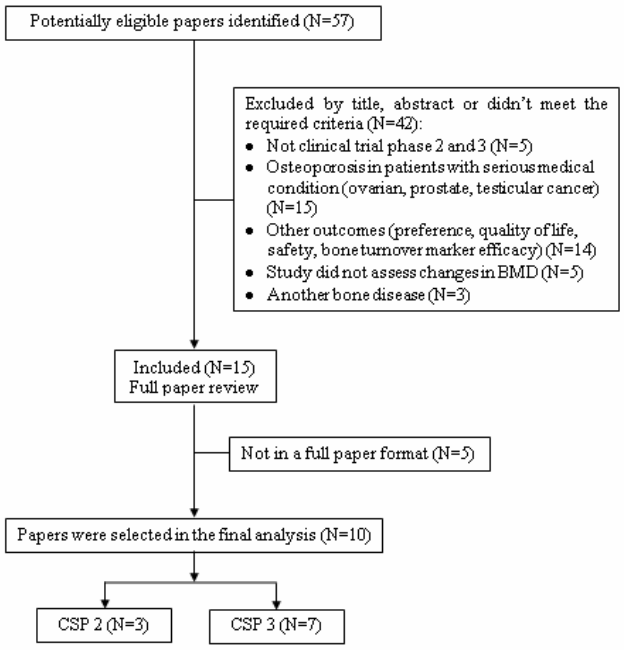

Figure 1. *Article selection*

In the analyzed articles, all five drugs increased L BMD in the range from 2.1% (risedronate 100 mg per os, once monthly during 6 months) (22) to 11.3% (TPTD 20 μg daily subcutaneous injection during 6 months) (Table 1) (20, 22, 23).

Two studies demonstrated that after one-year treatment with denosumab (60mg subcutaneous (sc) injection every 6 months) the increase of BMD was the highest in L spine in comparison with other skeletal sites (21, 24). One-year treatment study conducted by Kendler et al. showed that the improvement of BMD after denosumab treatment was significantly higher (3%, $p<0.05$) at the L site, as well as at the TH site (1,9%, $p<0.001$) in comparison to alentronate (70 mg once weekly) (24). Miller et al. showed a constant increase of the L BMD with the same doses of denosumab therapy during the two-year extension study (BMD T-score - 2,14 in the beginning and -1,55 in the end of the study, without specified level of significance) (21).

All three articles that described TPTD efficacy showed significant increase only for L spine (20, 23, 25). As TPTD is a peptide hormone, it cannot be given orally and currently can only be administered as a daily sc injection. A new transdermal administration of TPTD made its application more convenient. Increase of TH BMD was significant ($p<0.05$) after 6-month administration of 40 μg daily TPTD transdermal-patch (1.33% change) in comparison to placebo-patch (-0.63% change), and 20 μg daily TPTD sc injection (0.09% change). Other daily TPTD transdermal-patch doses (20 μg and 30 μg), did not show significant improvement of BMD at TH region, unlike L region where all examined TPTD transdermal-patch doses showed significant improvement (~3% for dose of 20 μg; ~3.5% for dose of 30 μg; ~5% for

dose of 40 μg, p<0.001) in comparison to baseline values and placebo (25). Another study showed better results of daily sc. injection form of TPTD in TH region. Increase of BMD at the TH (2.66%, p<0.001) was statistically significant after first 12 months of therapy in comparison to baseline. Follow-up therapy (from 12 to 24 months), showed continuous but not statistically significant increase of TH BMD (20).

New monthly oral therapeutic regiment of risedronate was also examined as a more convenient way of application. Doses of 100, 150 or 200mg once a month showed efficacy similar to standard 5 mg daily dose after a 6-month therapy. Percentage changes of L BMD was not significantly different between applications of risedronate daily regimen (~3%) and monthly regimens: ~2% (100 mg monthly); ~3% (150 mg monthly); ~3,4% (200 mg monthly) (22). Investigation of new therapeutic regimen of risedonate therapy of 75 mg at two consecutive days a month showed similar efficacy (L BMD+3,4%) to standard daily dose (L BMD+3,6%) after one year of application (26).

Arzoxifene (20 mg/daily, per os, during two years of application) showed a significant increase of BMD at the level of p<0.001 at the L and TH region (2.92%, 2.19%, p<0.001) compared with placebo (27).

Bazedoxifene (20 mg/daily and 40 mg/daily, per os, during 3 years of application) showed a similar efficacy as raloxifene 60mg compared with placebo (percentage change in L spine was 2.21%, 2.38%, 2.96, p <0.001 respectively; percentage change in TH was 0.27 %, 0.50%, 0.90, p<0.001, respectively) (27, 28).

From 10 selected articles only one reported data about fracture risk. Silverman et al. have reported that bazedoxifene (20mg, 40mg daily) and raloxifene significantly reduced the risk of new vertebral fractures after 36 months of therapy compared to placebo (42%, 37%, 42%, respectively) (28).

DISCUSSION

This review presented efficacy of osteoporosis drugs that are currently in clinical trials phase 2 and 3. Beside efficacy of new drugs, some of the studies tested new dosing regimens, or new ways of application of existing drugs. All the reviewed studies showed that the examined drugs increased more BMD in L spine region than in the hip region.

Denosumab has high specificity and affinity for RANKL (6, 11, 29), and pharmacokinetic properties that allow its application once per every six months (11). This dosing regimen enables better adherence. Denosumab therapy (60 mg sc every 6 months) showed a modest efficacy. After six years of therapy with denosumab, the improvement in BMD was about 3% in L spine and 1% in TH region (21). In the study conducted by McClung et al. denosumab applied in different therapeutic regimens (6, 14 or 30 mg sc every three months or 14, 60, 100, or 210 mg sc every six months) after 12 months of therapy showed a similar efficacy (L spine: 3.0-6.7%, TH: 1.9-3.6%) (30). The study conducted by Kendler et al. showed that after switching therapy from alendronate (70 mg weekly, per os) to denosumab (60 mg/6 months, sc), increase of BMD in L and TH was significantly (p<0.0001) higher during the 12-month therapy (BMD % change in L spine: 1.85%, 3.03%, respectively; and TH region: 1.05%, 1.90%, respectively). After switching, the adherence was better with 60mg/6 months denosumab therapy. The interesting fact was that BTM at the end of the study reached almost the baseline value in subjects continuing on alendronate but not in the denosumab group (24). Study conducted by Miller et al. examined effects of denosumab discontinuation after a two-year treatment (210 mg/6months, sc). Discontinuation period lasted one year. At the end of that period BMD decreased by 6.6% at the L spine and 5.3% at the TH. After discontinuation period, retreatment was continued with denosumab sc 60 mg/6 months dose for a period of one year. At the end of retreatment period, BMD was increased by 9% in L spine and 3.9% in the total hip compared to the baseline values (31).

TPTD daily sc application, showed the best efficacy in BMD improvement in all measured skeletal regions (LS, TH and FN) in comparison to all examined drugs in this review (20, 25). Study conducted by Miyauchi et al. demonstrated that treatment with TPTD 20 μg/day sc. inj constantly improved BMD during the two-year study period compared to baseline values (20). TPTD daily sc application was uncomfortable, thus a *new formulation* of TPTD as transdermal patches was developed. The best results were achieved with 40 μg TPTD patch at the L spine (improvement about 5%) (25).

Review study published in 2006 by Cramer et al. indicated that a half of the patients treated with bisfosfonates on a daily bases discontinued treatment after one year of therapy (32). Poor adherence could be the main reason for such early discontinuation of treatment with bisfosfonates (33). Values of BTM are in correlation with adherence (34).

Similar to daily bisphosphonates, 5 mg daily dose regime of risedronate could lead to low patients' adherence (33). Delmas et al. showed that the efficacy of risedronate 75 mg orally in two consecutive days a month was similar to daily regimen in all studied skeletal regions (35). For the L region, monthly risedronate regimen with doses 100 mg and 150 mg showed slightly lower, but 200 mg higher efficacy than risedronate 5mg/daily. This study explored efficacy only at L spine (22). One more study presented similar efficacy in L spine of weekly (35 mg and 50 mg) risedronate treatment compared to 5 mg daily regimen (36).

Selective estrogen receptor modulators (SERMs) or estrogen agonists/antagonists demonstrated positive effects on both fracture reduction and breast cancer risk reduction (2), but negative effects on endometrial sti-

mulation (37, 38). Second class of SERM, arzoxifene, lasofoxifene and bazedoxifene had positive effects on bone formation and a little effect on uterine stimulation (39-41). Published results showed positive effects of arzoxifene on BMD and no significant side effects on uterus and endometrium (27). Different doses of bazedoxifene showed higher percentage change of BMD on L than on thoracic spine. Efficacy of basedoxifene was slightly lower than efficacy of raloxifene. Bazedoxifene have shown similar incidence of adverse events as placebo. Deep vein thrombosis, vasodilatation, leg cramps and breast cysts/fibrocystic breast disease were less common than with raloxifene therapy (28).

Fracture risk is one of the most important outcomes of efficacy evaluation. It is necessary for further studies to display accurate information on fracture risks.

Limitations

Several limitations were noted during the study review: a) only one study presented numerical values of BMD at the beginning and at the end of the study (21). Other studies presented graphical increase of BMD from the baseline values (without specified values) and percent change of BMD at the end of the study. This might lead to conclusion bias: a) only one study that examined efficacy of basedoxifene and arzoxifene was considered in the review b) duration of reviewed studies was different, thus comparing the results could be inadequate; c) although the most of the analyzed studies had as a second aim the analysis of drug safety, in this paper we reviewed only efficacy of the drugs; d) only articles published in English were included in the review.

According to this analysis, almost all reviewed drugs, with exception of TPTD, showed similar efficacy at the L skeletal region. The best results at all skeletal sites were achieved with TPTD. Efficacy of all examined drugs was less in hip than in L spine. Taking into account the cost and complications during the treatment of patients with TH fractures, the search for a new potential drugs/way of application need to be continued. The main goal of new treatment should be improved efficacy in all skeletal regions especially in TH region. Also, when considering the efficacy of drugs, it is necessary to consider the cost-effectiveness of potential treatments and fracture risk assessment.

Table 1. *A brief review of basic information and main results of selected clinical studies phase 2 and 3*

Authors, year of publication, country [ref]	Study period, country and duration of study	Drug/supplements (dose)	Study design/ drugs to compare, measurements	Study population, inclusion criteria	BMD T-score (SD) baseline or in comparable/placebo group	Change (%) of BMD vs. comparator, BTM changes
Miller PD, et al., 2010 (21)	NA, USA, 2 years extension of a 4-year study (6 years in total)	Denosumab (60mg every 6 months, sc)/ Calcium (≥500mg) daily PO, Vitamin D (≥400IU) daily PO	Open-label, single-arm, M: BMD (L, TH, 1/3R, FN), BTM (BSAP, CTX)	N (f): 200, MA (y): 66.10 PSMW (aged up to 80 yr), BMD (L) -4.0≤T-score ≤-1.8, BMD (FN, TH) -3.5≤T-score ≤-1.8	At the end of 1-4yr: L: -2.14 (0.77) TH: -1.42 (0.69) FN: -1.86 (0.67) 1/3R: -1.48 (1.18)	L: 2.9† TH: 1.1† FN: 1.2† 1/3R: 1.0† ↓ CTX , BSAP in all measured time points
Cosman F, et al., 2010 (25)	NA, USA, Argentina, Mexico, 6-months	Teriparatide (20, 30, 40μg 30min wear time daily, TP)	R, PC, positive control / DTC: TPTD 20μg SC, Pb-patch M: BMD (L, left TH, FN, left F), BTM (P1NP, CTX, total serum calcium)	N (f): 165, MA (y): 64.06 PSMW (aged 50–81yr), BMD according to WHO criteria	L: -3.2 (0.7) TH: -1.6 (0.7)	L: 2.96** (TPTD-P 20μg) L: 3.47** (TPTD-P 30μg) L: 4.97** (TPTD-P 40μg) L: 3.55** (TPTD-Inj 20μg) TH:1.33* (TPTD-P 40μg) TH: 0.09 † (TPTD-Inj 20μg) No stat. sign. diff. for FN. F Pb-patch ↑ P1NP, CTX significantly different vs. Pb-patch group for all treatment groups
Ste-Marie LG, et al., 2009 (22)	April 2004 – June 2005, international , 6-months	Risedronate (100mg; 150mg; 200 mg monthly, PO) / Calcium (≥1000mg) daily, Vitamin D (≥400IU) daily	R, DB, active-controlled, dose-ranging / DTC: Risedronate 5mg/daily, PO M: BMD, BTM (CTX, NTX, BSAP)	N (f): 370, MA (y): 65,74 PSMW (at least 5 yr), age 50 to 85yr, BMI:18-32kg/m^2, BMD (L) T- score≤ - 2.0	5 mg/day; 100mg monthly; 150mg monthly; 200 mg monthly; L: -3.11 (0.87) / -3.12 (0.82) / -2.93 (0.81) / -2.98 (0.83)	L: 3.05*** (5 mg/day) L: 2.10*** (100mg monthly) L: 2.99*** (150mg monthly) L: 3.38*** (200 mg monthly) C: baseline ↓ BTM sign. from bv.
Miyauchi A, et al., 2010 (20)	NA, Japan, 2 years	Teriparatide (20 μg/day, sc) / Calcium (≥610mg), Vitamin D (400IU) daily PO	R, DB, PC, open-label / Administration: The 1st 12 months: case group used TPTD and control	N (f/m): 136 TPTD group (127/9) and 67 placebo group (62/5); MA (y): TPTD group: 69.2;	NA	At the end of 12M;18M;24M L: 10,23**; 12,38†; 13,96†

			used Pb; the 2nd 12 months: all subjects used TPTD M: BMD (L, FN, TH), BTM (P1NP, BSAP, CTX), new fractures	Placebo group: 70.4 PSMW (≥5 yr), man and women ≥55 yr: BMD (L2–L4)<80% of YAM + min. one vertebral fracture; BMD (L2–L4)<70% + age≥65; BMD (L2–L4)<65% + age≥55		TH: 2,66**; 3,23†; 3,69 † FN: 2,24‡; 2,92†; 3,25† C: Pb ↑P1NP, CTX sign. from bv. ↓ BSAP sign. from bv.
Sethi BK, et al., 2008 (23)	12.2005 – 08. 2007, India, 6-months	Teriparatide (20 μg/day, sc) / Calcium (1000mg), Vitamin D (500IU) daily PO	R, multicentre, prospective, open-label, controlled M: BMD and BMC (L, TH, FN); BTM (BSAP, OC, DPD)	N (f): 41 TPTD and 41 placebo group, MA (y): 62.0PSMW (≥3 yr), age 45 to 75yr, T-score (L, FN, TH) ≤-2.5	L: -3.40 ± 0.87 TH: - 1.99 ± 0.57 FN: -2.49 ± 0.55	Teriparatide: L: 11.30 ** TH: 8.12† FN: 4.87† C: baseline ↑BTM, BRM from bv.
Delmas PD, et al. 2008 (26)	NA, international , 1 year	Risedronatee (75mg on 2 consecutive days a month, PO)/ Calcium (1000mg), Vitamin D (400-800IU) daily PO	R, DB, active-controlled, parallel-group / DTC: Risedronate 5mg/day, PO, M: BMD (L, TH, FN, Trh), BTM (NTX, BSAP)	N (f): 1229, MA (y): ≈ 64.65 PSMW (≥5 yr), age ≥50 yr, BMD according to WHO criteria	75mg/2 days a month / 5mg/day L:-3.16 (0.54) / -3.17 (0.56) TH: -1.91 (0.77) / -1.86 (0.78) FN: -2.09 (0.61) / -2.05 (0.64)	75mg/2 days a month / 5mg/day L: 3.4*** / 3.6*** TH: 2.1† / 1.9† FN: 1.6 †/ 1.2† Trh: 3.0 †/ 3.0† C: baseline
Välimäki MJ, et al., 2007 (42)	NA, international , 2 years	Risedronate (5mg/day, PO) / Calcium (1000mg), Vitamin D (400IU) daily PO	R,DB, PC, parallel-group /DTC: Pb, M: BMD (L, PF); BTM (NTX, BSAP)	N (f): 171, MA (y): 65.9 Healthy, ambulatory, PSMW (≥5 yr), BMD (L) -2.5 ≤T-score ≤-1.0; BMD (TH) T-score ≤-1, or the presence of ≥1 risk factor for osteoporosis	Risedronate: L: -1.81 FN: -1.29	Risedronate: L: 4.49* FN: 2.04* C: baseline ↓ BTM sign. from bv. and Pb
Kendler DL, et al., 2010 (24)	10. 2006 – 03. 2008, international 1 year	Denosumab (60mg once every 6 months, sc) / Calcium (1000mg/d) Vitamin D (400IU) daily PO	R, DB, double-dummy study / DTC: Alendronate (Fosamax) 70mg once weekly PO, M: BMD (L, PF, FN, D1/3R), BTM (P1NP, CTX)	N (f): 504, MA (y): 67.6 PSMW, age ≥ 55yr, BMD T-score ≤ -2.0 or less; BMD T-score ≥-4.0 who had been receiving alendronate for at least 6 months	Denosumab / Alendronate: L: - 2.64 (0.75) / -2.62 (0.79) TH: -1.79 (0.82) / -1.81 (0.74)	Denosumab / Alendronate: L: 3.03† / 1.85† TH: 1.90†/ 1.05† C: baseline ↓ CTX sign. at all measurement points between treatment groups (higher decrease in denosumab group)
Bolognese M et al., 2009 (27)	NA, NA, 2 years	Arzoxifene (20 mg/day, PO) / Calcium (500mg/d)	Multicenter, R, placebo-controlled / DTC: Pb, M: BMD (L, TH), BTM (P1NP, CTX), mammogram, gynecological procedures	N (f): 331, MA (y): 54,69 PSMW (at least 2 yr), age 45 - 60yr, BMD (L, FN) -2.5 ≤T-score ≤0; no vertebral fracture	Arzoxifene / Pb L: 0.95 ± 0.12 / 0.96 ± 0.12 TH: 0.886 ± 0.09 / 0.894 ± 0.10	Arzoxifene / Pb L: 2.92** TH: 2.19** C: Pb

Silverman SL, et al., 2008 (28)	NA, international 3 years	Bazedoxifene (20mg, 40 mg daily, PO) / Calcium (1200mg/d), Vitamin D (400-800IU) daily PO	R, DB, placebo- and active-controlled / DTC: Raloxifene 60mg/day PO, Pb, M: RM of vertebral fractures (T4–L4); BMD (L, TH, FN), BTM (CTX, OC)	N (f): 7492, MA (y): 66.4 PSMW (at least 2 yr), age 55 - 85 yr, osteoporosis; BMD (L, FN) -4.0≤T-score ≤-2.5, no prevalent vertebral fracture	Bazedoxifene 20mg/40mg/Raloxifene 60mg/Pb L: -2.4 (1.2) / -2.4 (1.2) / -2.4 (1.2) / -2.4 (1.2) FN: -1.7 (0.9) / -1.7 (0.9) /-1.7 (0.9) / -1,8 (0,9)	Bazedoxifene 20mg/40mg/Raloxifene 60mg/Pb L: 2.21** /2.38** / 2.96** TH: 0.27 ** / 0.50** / 0.90** C: Pb ↓ OC, CTX sign. from Pb

R – Randomized
C - Placebo - controlled
DB - Double-blind
DTC - Drugs to compare
N – Number
f- female
m- male
MA - Mean age
M - Measurements
BTM - Bone Turnover Markers
BMC – Bone Mineral Content
P1NP - Terminal propeptide of type I procollagen
CTX – Serum C-telopeptide type I
OC – Serum osteocalcin
NTX – Urinary N-telopeptide fragment of type I collagen
BSAP – Bone specific alkaline phosphatase
DPD – Urinary deoxypyridinoline
TP – Transdermal Patch
PO – Per Os
Sc – Sub Cutaneus
RM: radiographycally measurement
PSMW- Post-menopausal women
Bv. – Baseline value
C – Comparator
F - forearm
PF - proximal femur
TH - total hip
Trc - trochanter
L - lumbar spine
1/3R - one third radius
Pb - placebo
NA – not available (not presented in article)
* Significant difference at the level 0.05
** Significant difference at the level 0.001
*** Significant difference is noted but the level is not specified
† Significance level not specified
‡ Not significant difference
WHO Criteria: BMD (L, FN or TH) T-score ≤ - 2.5, BMD (L) T-score ≤ -1; or BMD (L, FN or TH) T-score ≤ - 2.0 with a prevalent vertebral fracture
CG – control group

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NOVI LEKOVI U TERAPIJI OSTEOPOROZE: pregled 2. i 3. faze kliničkih istraživanja

Ivana Tadić[1], Ljiljana Tasić[1], Nada Vujasinović Stupar[2], Katarina Ilić[3], Dejan Stevanović[4]

[1]Univerzitet u Beogradu, Farmaceutski fakultet,
Katedra za socijalnu farmaciju i farmaceutsko zakonodavstvo, Srbija
[2]Univerzitet u Beogradu, Medicinski fakultet, Institut za reumatologiju, Srbija
[3]Univerzitet u Beogradu, Farmaceutski fakultet, Katedra za farmakologiju, Srbija
[4]Odeljenje za psihijatriju, Opšta bolnica Sombor, Srbija

Sažetak

Osteoporoza je hronična bolest koja je sve više zastupljena i to pretežno kod osoba ženskog pola. Postoje dokazi da bisfosfonati, selektivni modulatori estrogenskih receptora, denosumab, teriparatid i stroncijum ranelat mogu da preveniraju prelom kuka. Iako su ovi lekovi efikasni u lečenju osteoporoze, njihova upotreba je ograničena usled ispoljavanja neželjenih reakcija, a time i postojanja niske adherencije bolesnika. Cilj ovog preglednog rada bio je upoređivanje efikasnosti novih lekova za lečenje osteoporoze koji su trenutno u 2. i 3. fazi kliničkih istraživanja. Nakon pregleda 57 originalnih radova koji su imali za cilj da pokažu efikasnost lekova u lečenju osteoporoze, dostupnih na PubMed i Scopus bazi, za analizu je odabrano 10 radova koji su zadovoljili kriterijume za pretraživanje. Na kraju analize, poređena je efikasnost pet lekova. Efikasnost je evaluirana na osnovu vrednosti mineralne koštane gustine (BMD) i koštanih markera (BTM). Povećanje BMD vrednosti i promene u vrednostima BTM zabeležene su u svim radovima. Najveće povećanje BMD (za 11,3%) lumbalnog skeletnog regiona postignuto je nakon šestomesečne subkutane terapije teriparatidom u dozi 20 μg dnevno. Najmanje povećanje BMD (za 2,1%) istog skeletnog regiona zabeleženo je nakon šestomesečne per os terapije risedronatom u dozi od 100 mg jednom mesečno. Od deset analiziranih studija, samo je jedna prikazala podatke o riziku od frakture.

Ključne reči: **osteoporoza, terapija, efikasnost, 2. i 3. faza kliničkih istraživanja**