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CLINICAL USE OF PINP AND βCTX AS BONE TURNOVER MARKERS IN NOVEL TREATMENT OF OSTEOPOROSIS

KLINIČKA UPOTREBA MARKERA KOŠTANOG PROMETA PINP I βCTX U SAVREMENOJ TERAPIJI OSTEOPOROZE

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Key words

osteoporosis, bone turnover markers, P1NP, βCTX, teriparatide, denosumab, romosozumab, blosozumab, odanacatib

Ključne reči

osteoporoza, markeri koštanog prometa, P1NP, βCTX, teriparatid, denosumab, romosozumab, blosozumab, odanacatib

Abstract

Bone turnover markers (BTMs) are increasingly being evaluated for their role in detection of bone loss, assesment of fracture risk, selecting the most appropriate therapy, assessment and following of therapeutic response. During the last decade several new remedies with special mechanisms of action, as denosumab, cathepsin K inhibitors and anti-sclerostin therapy, have been tested in the treatment of osteoporosis. The clinical challenge will be to select medications with different effects on bone resorption and formation, alone or in combination, in order to treat osteoporosis patients most effectively. Therefore, the aim of our analysis of recently published clinical trials was quantifying differences between teriparatide and new remedies (denosumab, romosozumab, blosozumab, odanacatib) effects on bone mineral density and the most widely used BTMs such as procollagen type I N propeptide (PINP) and β croos-linked C-telopeptides (βCTX). Founded differences may contribute not only to better understanding of relationship between various mechanisms of action of these drugs and their influence on the level of BTMs, but also to their more appropriate choice in the treatment of osteoporosis.

INTRODUCTION

Osteoporosis is a global healthcare problem due to an ageing population and raising life expectancy, resulting in higher morbidity and mortality. Criteria for making diagnosis of osteoporosis is based on bone mineral density (BMD) of the spine and proximal femur, but there are limitations of BMD measurements such as small annual changes and poor treatment response. However, biochemical bone turnover markers (BTMs) may be used to provide missing information on bone remodeling. They play an important role in detection of bone loss, assesment of fracture risk and represent potential improvement of clinical drug development [1].

Bone turnover markers and their role in therapy of osteoporosis

BTMs have been purposed to be useful in selecting the most appropriate therapy, than for the assessment and following up the therapeutic response. Changes in BTMs and subsequent changes in BMD, depend on mechanism of action of antiresorptive agent, size of change in bone turnover rate, and route of drug administration[2]. Currently, treatment strategies include antiresorptive drugs (biphosphonates and novel drug denosumab, as the most prescribed), osteoanabolic drugs (teriparatide) and few new potential drugs (cathepsin K inhibitors and anti-sclerostin therapy) [3].

Therefore, the aim of this paper is better understanding of reference bone turnover markers and their utilization in clinical settings. Pubmed was searched for randomised controlled trials of new therapies for osteoporosis with complete data about drug, its dosage, administration, duration of therapy and changes in BTMs and BMD. According to clinical trials included in this paper, the most widely used markers are N- terminal propeptide ot type I collagen (PINP) as formation marker and breakdown products of type I collagen, C- terminal cross-linked telopeptide (βCTX) as marker

of resorption. During the extracellular processing of type I procollagen, PINP is enzymatically released, and reflects the rate of collagen synthesis. β CTX is generated by cathepsin K and represents breakdown of aged collagen[4].

The new antiosteopototic drugs, bone mineral density and bone turnover markers

Teriparatide (recombinant human parathyroid hormone-PTH [1-34]) is the only widely available anabolic agent used for osteoporosis[3]. Teriparatide increases bone formation on bone surfaces, bone mass and strength and shows reduction of the risk of vertebral and nonvertebral fractures. This is reflected in an elevation of BMD, PINP at peak level and simultaneous, but smaller increasing of βCTX[5]. So, when bone remodeling is stimulated, there is still greater bone formation than bone resorption. Some recent, the most informative studies about teriparatide are presented in Table 1.

Table 1 near here

Therefore, the additional anabolic agents would be a welcome option to improve managing patients with osteoporosis. In that sence, romosozumab and blosozumab are monoclonal antibodies that bind to and inhibit sclerostin, so they initiate a signaling cascade that stimulates osteoblast activation, differentiation, and bone formation. Also, they decrease bone resorption, and leed to rapid and marked increases in BMD[23]. But they are still in trial stage. BTMs and BMD are changed in dose-dependent manner and the magnitude of BMD improvements at the lumbar spine and total hip with multiple doses were similar to those reported previously in a single dose studies (Table 1) [12]. Decreased bone resorption is reflected in decrease of βCTX level.

Denosumab, a fully human IgG_2 monoclonal antibody that binds to and neutralizes the activity of receptor activator of nuclear factor-kB ligand, is a novel antiresorptive treatment. Although it is not as the first-line pharmacological treatment of osteoporosis, but can be initiated as a first-line choice for treatment of osteoporosis in certain patients who are intolerant to other antiresorptive drugs or have renal failure. Denosumab inhibits osteoclast differentiation, activity, survival, and consequently, results in decreased bone resorption and increased BMD. Continued, long-term therapy is required to maintain the anti-fracture benefit[17] (Table 1). There is trend of sustained reductions in βCTX and PINP. If > 30% decrease for serum βCTX, drug is having desired effect, therefore this antiresorptive agent is beneficial[24].

There is a special group of antiresorptive agents, cathepsin K inhibitors, with unique mechanism of altering bone metabolism. However, their development has been abandoned due to significant side effects, but only odanacatib as attractive pharmacological treatment still remains at a significant stage of development in osteoporosis. Odanacatib inhibits cathepsin K in osteoclasts and reduces resorption efficiency of osteoclasts, but preserves their differentiation, migration, polarization and survival. Odanacatib is a potent inhibitor of osteoclastic resorption, but with relative maintenance of bone formation and elevation of BMD in dose-dependent fashion[25]. Decrease in βCTX is greater than 30% which is confirmation of drug efficiency. Otherwise, at the end of therapy bone formation markers reach values near baseline.

Relationship between osteoporosis therapy and main bone turnover markers

During the last decade these several new remedies with different mechanisms of action have been tested clinically in the treatment of osteoporosis. Therefore, the aim of our analysis of recently published original papers was to compare teriparatide's influence on changes in BMD and BTMs with such changes of the new remedies in order to quantify the differences. Found differences may contribute not only to better understanding of relationship between various mechanisms of action of these drugs and their influence on the level of BTMs, but also to their more appropriate choice in the treatment of osteoporosis.

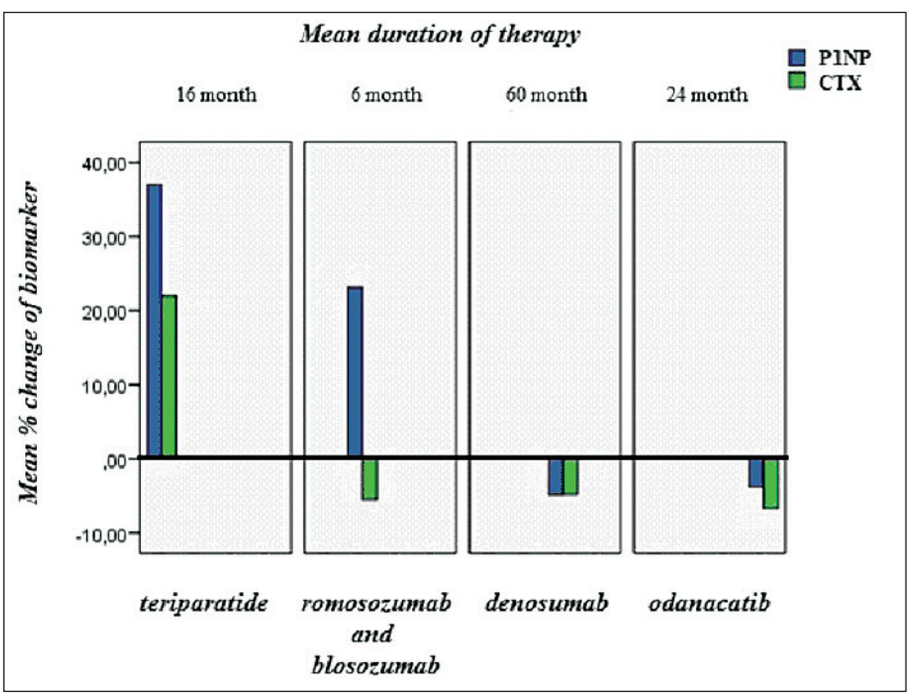

Figure 1. near here

Figure 1*. P1NP and CTX mean procentual changes from baseline for 1 % of change in BMD*

According to Table 1. behavior of mean BMD at lumbar spine ($BMD_{lumbar\ spine}$) depends on choice of drug and treatment duration. Consequently, mechanisam of action of drug, its dosage and route of administration have great impact, too. Maximum change of mean $BMD_{lumbar\ spine}$ is 13,0 % with long-term denosumab therapy which is in correlation with maximum decreasing of βCTX.

Figure 1. demonstrates PINP and βCTX responses to the different drugs, as ratio of their mean percentage changes from baseline for 1 % of change in $BMD_{lumbar\ spine}$. It is obvious that the greatest antiresorptive activity belongs to

denosumab. Minimum change of BMD $_{\text{lumbar spine}}$ achieve odanacatinb and teriparatide, 6,4 % and 6,5 %, respectively. Teriparatide as anabolic drug shows the biggest elevations in PINP, but in same time, the biggest elevation in βCTX, which can be a reason of smaller then expected BMD gain. Odanacatib and anti-sclerostin drugs decrease βCTX in a similar extent and confirm their antiresorptive roles. But, romosozumab and blosozumab show greater increase in mean $BMD_{\text{lumbar spine}}$ than odanacatib (8,4% and 6,4%, respectively). It can be because these anti-sclerostin antibodies as teriparatide exhibit anabolic activity with consequent, great elevations in PINP for 1% $BMD_{\text{lumbar spine}}$. In this sence, the increase in formation marker is associated with improvement of BMD, and decrease in bone resorption marker is evidence of successful antiresorptive treatment.

CONCLUSION

BTMs have significant role in clinical drug trials and provide valuable information on the assessment of therapeutic response. BTMs can also be used to predict patients with greatest benefits from treatment and therefore promote treatment adherence. PINP as bone forming and βCTX as bone resorption marker hold the promise of monitoring new forms of treatment. In order to treat osteoporosis patients the most effectively, the clinical challenge is selecting medications with different effects on bone resorption and formation and their possible combining.These new approaches to the treatment of osteoporosis give wider perspectives for individualized and targeted fracture prevention.

Table 1. *Percentage changes in BMD and BTMs acording to following therapy*

Study	Drug	Mean duration of therapy	Mean % change of BMDL1-L4 and BMD TOTAL HIP	BTM	Mean % change of biomarker
Moore AEB et.al.2012 (6) Frost et al.2013(7) Yu EW et al.2014(8) Muschitz C et al.2014(9)	teriparatide	16 month	6,5/2	P1NP CTX	241,2 142,3
Padhi et al.2011(10) McClung et al.2014(11) Padhi et al.2014(12) McColm et al.2014(13) Recker et al.2015(14)	romosozumab &blosozumab	6 month	8,4/3,3	P1NP CTX	194 -46.5
Gatti et al.2012(15) Papapoulos et al.2012(16) Mc Clung et al.2013(17) Bone et al.2013(18) Papapoulos et al.2015(19)	denosumab	60 month	13.0/6,1	P1NP CTX	-63,3 -62,8
Bone et al 2010(20) Eisman et al.2011(21) Nakamura et al.2014(22)	odanacatib	24 month	6,4/4	P1NP CTX	-24,3 -42,6

p values < 0.05 from baseline

Sažetak

Biomarkeri koštanog prometa se sve vise proučavaju zbog svoje uloge u proceni gubitka koštane mase i rizika od frakture kostiju, zatim učestvuju prilikom izbora odgovarajuće terapije i tokom praćenja terapeutskog odgovora. U poslednjoj deceniji, nekoliko novih lekova sa specifičnim mehanizmom delovanja kao što su denosumab, katepsin K inhibitori i anti-sklerostin terapija, testirani su u tretmanu osteoporoze. Klinički izazov predstavlja odabir pojedinačnih lekova ili njihovih kombinacija za efikasan tretman pacijenata obolelih od osteoporoze zbog njihovog različitog delovanja na procese formiranja i razgradnje kostiju. Cilj našeg proučavanja nedavno objavljenih kliničkih studija bilo je određivanje razlika između teriparatida i novijih lekova (denosumaba, romosozumaba, blosozumaba, odanacatiba), kao i njihovog uticaja na gustinu kostiju i markere koštanog prometa, kao što su N-terminalni propeptid kolagena tipa I (eng. procollagen type I N propeptide-PINP) i C-terminalni telopeptid kolagena tipa I (β croos-linked C-telopeptides-βCTX). Pronađene razlike mogu doprineti, kako boljem razumevanju odnosa između različitih mehanizama dejstva proučavanih lekova i njihovog uticaja na koncetraciju markera koštanog prometa, tako i na primenu odgovarajućeg tretmana u lečenju osteoporoze.

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