Bone markers and osteoporosis therapy

Marcadores de turnover ósseo e tratamento da osteoporose

Francisco Bandeira¹, Aline G. Costa², Manoel Anderson Soares¹, Larissa Pimentel¹, Lourena Lima¹, John P. Bilezikian²

ABSTRACT

Several factors are involved in determining bone quality including bone density, bone turnover, the extent of trabecular bone connectivity, cortical porosity and geometry. Metabolically active and in a continuous process of remodeling, approximately 20% of bone tissue is renewed annually. Bone turnover markers (BTM) are frequently used in clinical trials and to provide valid information about the effectiveness of osteoporosis treatment, reflecting the state of bone metabolism and its response to treatment, although they are not useful alone to estimate bone loss. In this review the behavior of BTM from different clinical trials or different osteoporotic drugs will be addressed. Arq Bras Endocrinol Metab. 2014;58(5):504-13

Keywords
Bone markers; osteoporosis; bone density

INTRODUCTION

Bone is a specific type of tissue composed primarily of type I collagen impregnated with minerals in the form of hydroxyapatite crystals. Several factors are involved in determining bone quality including bone density, bone turnover, the extent of trabecular bone connectivity, cortical porosity and geometry (Figure 1) (1). Metabolically active and in a continuous process of remodeling, approximately 20% of bone tissue is renewed annually (2). This complex process begins at birth and is maintained throughout life. The active cellular participants in this process, often configured as multiple multicellular units, are osteoclasts, osteoblasts and osteocytes.

The system is highly regulated by many factors. For example, osteoprotegerin (OPG) (osteoprotegerin), receptor activator of NF-kappaB (RANK) and its cognate ligand, (RANKL), form a metabolic regulatory system focused upon bone resorption (3). Additionally there are other factors that influence bone turnover, such as parathyroid hormone (PTH), 1,25-dihydroxyvitamin D (calcitriol), prostaglandin E2 and interleukins (4). The process of bone turnover leads to the release of factors that give highly relevant information on rates of bone formation and resorption (Figure 2).
Osteoporosis can be primary or secondary to various conditions such as hypogonadism, hyperthyroidism, skeletal metastases, multiple myeloma, anticonvulsants, corticosteroids, and alcohol abuse (Table 1). The prevalence of osteoporosis increases with age and is accelerated in women by the menopause (5). The aging process is associated with bone loss even before the menopause sets in, suggesting that factors related to cellular aging, apart from estrogen deficiency, are important (6). In assessing the dynamics of bone loss and, with therapy, bone gain, bone resorption and bone formation markers can be used, alone or together (7). In clinical practice, for reasons of cost, sometimes a single marker will be used. Since in most cases bone formation mirrors bone resorption, and vice versa, a single bone turnover marker could be used. With regard to bone formation, the production phase of the collagen matrix coincides with increased alkaline phosphatase activity, while mineralization process coincides closely with osteocalcin (Tables 2 and 3). In contrast, bone turnover markers (BTM) are frequently used in clinical trials and to provide valid information about the effectiveness of osteoporosis treatment, reflecting the state of bone metabolism and its response to treatment, although they are not useful alone to estimate bone loss (8).

The aim of this work is to provide an available literature from PubMed that reports bone markers data in response to osteoporosis therapy.

**CHANGES IN BTM WITH BISPHOSPHONATE TREATMENT**

In regard to alendronate, the Fracture Intervention Trial (FIT) showed that the group treated with alendronate had a mean decrease in urinary NTX by 41.9% and 52.4% in CTX after 3 years of treatment (9,10). Likewise, in a post-hoc analysis of the alendronate FIT, osteoporotic women with higher baseline levels of N-terminal propeptide of procollagen type 1 (PINP) showed greater reduction in risk of nonvertebral fractures in response to alendronate than those with low BTM and osteoporosis therapy.
Table 1. Causes of osteoporosis

<table>
<thead>
<tr>
<th>Primary causes</th>
<th>Secondary causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenopausal</td>
<td>Hyperthyroidism, hyperparathyroidism, Cushing’s syndrome, diabetes mellitus, acromegalay, adrenal insufficiency</td>
</tr>
<tr>
<td>Senile osteoporosis</td>
<td>Anorexia nervosa, bulimia nervosa, athelete’s amenorrhea, hyperprolactinemia, panhypopituitarism</td>
</tr>
<tr>
<td>Idiopathic osteoporosis</td>
<td>Osteogenesis imperfecta, Gaucher’s disease, hemochromatosis, homocystinuria, Marfan syndrome, Ehlers-Danlos syndrome, porphyria, Turner syndrome, Klaineleffel syndrome, Menkes syndrome</td>
</tr>
<tr>
<td>Idiopathic juvenile osteoporosis</td>
<td>Inflammatory bowel disease, malabsorption syndromes, celiac disease, primary biliary cirrhosis, gastrectomy, total parenteral nutrition, bariatric surgery</td>
</tr>
<tr>
<td>Multiple myeloma, leukemia, lymphoma, sickle cell anemia, thalassemia, hemophilia, mastocytosis, polycythemia</td>
<td></td>
</tr>
<tr>
<td>Calcium, magnesium, phosphorus and vitamin D deficiency</td>
<td></td>
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<tr>
<td>Use of corticosteroids, excess thyroid hormones, heparin, warfarin, chemotherapy, methotrexate, anticonvulsants, lithium, aluminum hydroxide, GnRH analogues, anti-retrovirals</td>
<td></td>
</tr>
<tr>
<td>Prolonged immobilization, reflex sympathetic dystrophy, rheumatoid arthritis, systemic lupus, ankylosing spondylitis, pregnancy, chronic renal failure</td>
<td></td>
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<tr>
<td>Renal tubular acidosis, COPD, chronic liver disease, sarcoidosis, amyloidosis, transplantation, excessive alcohol intake</td>
<td></td>
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</tbody>
</table>

Table 2. Main bone formation markers

<table>
<thead>
<tr>
<th>Marker</th>
<th>Source</th>
<th>Action</th>
<th>Assay type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone-specific alkaline phosphatase</td>
<td>Enzymes in the osteoblast plasma membrane</td>
<td>Degradation of the alkaline pyrophosphate mineralization inhibitor</td>
<td>Serum immunoassay and EDTA plasma</td>
</tr>
<tr>
<td>Osteocalcin</td>
<td>Non-collagen proteins of bone produced by osteoblasts during bone formation and connected to hydroxyapatite</td>
<td>Influences in osteoid mineralization. Works with negative feedback during the process of bone remodeling</td>
<td>Immunoassay and EDTA plasma</td>
</tr>
<tr>
<td>Aminoterminal propeptide of type I collagen (PINP)</td>
<td>Specific product proliferation of osteoblasts and fibroblasts</td>
<td>Cleavage of pro collagen type 1 protease during the process of formation of collagen type 1</td>
<td>Immunoassay, intact serum fraction, EDTA plasma</td>
</tr>
</tbody>
</table>

Table 3. Main bone resorption markers

<table>
<thead>
<tr>
<th>Marker</th>
<th>Source</th>
<th>Action</th>
<th>Assay type</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-telopeptide (CTX)*</td>
<td>Isomerization of aspartyl beta that occurs in mature collagen</td>
<td>Cleavage of type 1 collagen by Cathepsin K in bone resorption</td>
<td>Immunoassay, measurable serum/urine, EDTA plasma</td>
</tr>
<tr>
<td>N-telopeptide amino-terminal portion of type 1 collagen</td>
<td>Bone collagen type 1</td>
<td>Cleavage of type 1 collagen by Cathepsin K in bone resorption</td>
<td>Immunoassay, urine, serum, EDTA plasma</td>
</tr>
<tr>
<td>Receptor activator Kappa-B ligand (RANKL)</td>
<td>Produced by osteoblasts, activated by B and T cells</td>
<td>Binds to RANK, which is expressed on osteoclasts and their precursors, stimulating their differentiation and activation</td>
<td>Immunoassay or soluble forms in serum</td>
</tr>
<tr>
<td>Osteoprotegerin</td>
<td>Secreted by osteoblasts</td>
<td>RANKL receptor, reduces bone resorption by binding to RANK and prevents osteoclastogenesis</td>
<td>Immunoassay in serum</td>
</tr>
<tr>
<td>Sclerostin</td>
<td>Secreted mainly by osteocytes</td>
<td>Antagonist of Wnt signaling, inhibits bone formation</td>
<td>Immunoassay in serum or plasma</td>
</tr>
</tbody>
</table>

* Beta CTX more useful in osteoporosis.

levels of P1NP (9). However, this association was not found for vertebral fractures. Similar results were found using collagen type I c-telopeptide (CTX) and bone-specific alkaline phosphatase (BSAP). These results suggest that baseline BTM levels can influence the effectiveness of treatment with alendronate, especially at non-vertebral sites. Among patients without osteoporosis, higher baseline levels of the 3 BTMs were associated with a greater increase in hip bone mineral density (BMD) after treatment; in those with osteoporosis, higher baseline levels of P1NP were associated with a greater increase in vertebral BMD (10).

Using data from FIT, Bauer and cols. reported that in women treated with alendronate, large reductions
in one or more BTMs were associated with large reductions in vertebral, non-vertebral and hip fractures. The greater the reduction in BTM, the lower the risk of fracture. This study showed that women in the alendronate group with a reduction of at least 30% of BSAP, had a lower risk of non-vertebral and hip fractures. This effect was as strong as the anti-fracture effect observed with changes in BMD in 1 year (11).

In the Vertebral Efficacy with Risedronate Therapy (VERT) study, it was observed that BSAP levels decline and reach a nadir of -33% from baseline values by year 3 (12). Postmenopausal women with at least one vertebral fracture who showed reductions in urinary CTX (mean -60%) and NTX (mean -51%) at 3 and 6 months of treatment with risedronate, were significantly associated with reduction of vertebral and non-vertebral fractures risk after 3 years (12). In a subanalysis of the MOVER (MONTHLY intraVenous ibandronatE versus daily oral Risedronate) study, it was observed that the relative change in mean CTX and collagen type I cross-linked N-telopeptide (NTX) levels, in relation to the baseline, was similar with ibandronate 1 mg and risedronate, with a decrease in these levels at 3 months which remained below baseline levels by the end of the study. After 6 months, the mean reduction using 1 mg ibandronate was -67 and -53% for CTX and NTX, respectively (13).

Regarding zoledronic acid, data from the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) study demonstrated that serum CTX, BSAP and urinary NTX levels were 59%, 30% and 58% lower, respectively, in the group treated with zoledronic acid compared to placebo. The effects of zoledronic acid on BTMs were similar to the other bisphosphonates (14).

In a study of postmenopausal women with low bone mass, using a different doses of zoledronic acid, there was a nadir in bone resorption markers in 1 month, with an average decrease of 65-83% in serum CTX and 50-69% in urinary NTX (15). These decreases tend to be dose-dependent, in agreement with previous reports that higher doses of bisphosphonates increase the duration of drug action. The reduction in BTMs remained at the end of the study (month 12), with an average decrease of 49-52% in CTX and 54-65% in NTX. Serum osteocalcin and BSAP showed similar responses without strong apparent decline in one month, but with persistent suppression at the end of the study.

**Changes in BTM with Strontium Ranelate**

There is much controversy about BTMs during treatment with strontium ranelate (SR) (16, 17). In fact, the mechanism of action of SR is unknown. Although the presence of SR itself on bone matrix, leading to preservation of some determinants of bone material quality influencing the intrinsic properties on bone tissues and an effect on the calcium-sensing receptor have all been proposed (18). In a recent post-hoc analysis of the core studies with SR, involving 2,373 women with postmenopausal osteoporosis treated with SR or placebo, after 3 months of treatment, BSAP increased by 9.6%, serum C-propeptide of type I collagen (PICP) in 9.9%, s-CTX was reduced by 5.9%. Considering the technical and biological variability of BTM measurements, these changes could not be ascertained as significant in a given patient. On the other hand, the increments in BMD may be remarkable. After 3 years, mean BMD increased by 14.4% in the lumbar spine, 5.5% at the femoral neck and 7.1% at total hip. Multiple regression analysis showed that changes in bone formation markers (PICP and BSAP), but neither in s-CTX nor u-NTX I, were significantly associated with increased BMD at the lumbar spine and femoral neck (19). The responses of BTM in women previously treated with long term bisphosphonates have been evaluated in recent studies and compared to those women who never took any osteoporosis medication before SR. Middleton and cols. (20) showed a positive, although delayed, responses after 2 years which were more pronounced in women previously treated with a bisphosphonate: serum CTX +61%, serum P1NP +55% and serum BSAP +46%. This data are in accordance with our own data on short-term changes and long-term changes in BMD in response to SR in postmenopausal women previously treated with long-term bisphosphonates. We observed a mean increase of 53.7% in serum CTX and 30.7% in osteocalcin levels and these changes were associated with a mean increase in lumbar spine BMD of 4.8% after 2.5 years of treatment with SR (21,22).

The study by Recker and cols. showed that mineralization surfaces (MS/BS %) at the trabecular level were 7.73 ± 1.48% for tereparatide and 5.25 ± 1.15% SR (p = 0.219) and the endocortical level were 17.22 ± 3.06% and 9.70 ± 2.07%, respectively (p = 0.052). Cortical porosity was 5.40 ± 0.41% in the tereparatide and 4.14 ± 0.40% in the SR group (p = 0.037). They were increased both with SR and tereparatide. Although
more pronounced with tereparatide. Likewise, cortical porosity was also improved with both agent. Serum PINP increased at first month with tereparatide, but it wasn’t measured at this time in SR group. As expected for bisphosphonate-naive patients bone turnover markers decreased 3 and 6 months in the SR group (23).

**CHANGES IN BTM WITH DENOSUMAB**

Denosumab is a human monoclonal antibody with high affinity and specificity for human RANK-L. By binding to RANK-L, denosumab prevents the interaction of RANK-L with RANK and, thus, inhibits bone resorption. The reduction in resorption markers CTX, NTX and formation markers P1NP and BSAP is expected to occur as with any other potent anti-resorptive agent.

In the FREEDOM (Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months) study, a clinical trial of postmenopausal women using Denosumab (60 mg every 6 months for 3 years) or placebo, there was a suppression of BTM within 12 hours after administration of the drug which persists until the next dose. Denosumab reduced bone resorption by an average of 86% within 1 month, which is a greater reduction than with other anti-resorptive drugs. The decrease in serum CTX was more pronounced and faster than the decreases in serum P1NP and BSAP. There was a significant correlation between serum CTX reduction and increased BMD (24).

In FREEDOM, the median values for serum CTX were 0.049 g/mL (−90%) at day 10 and 0.131 ng/mL at month 6, after the first extension dose (the seventh dose of denosumab). For serum P1NP, median values were 19.0 µg/L (−51%) at day 10 and 13.0 µg/L at month 6. In the 6 years of denosumab treatment without discontinue the drug, the median BTM values remained below the median values observed at FREEDOM baseline (25).

Taken together, these data suggest that biochemical markers of bone turnover are useful tools to assess the therapeutic effects of anti-catabolic or anti-resorptive osteoporosis medications and that serial measurements can help to decide whether a patient is responding or not to a specific treatment.

**CHANGES IN BTMS WITH OSTEOANABOLIC THERAPY**

Anabolic agents represent an important approach to the treatment of osteoporosis. They target bone formation which distinguishes them from the mechanism of action of most of the drugs that we have available which have their primary action to inhibit bone resorption. Parathyroid hormone (PTH) is currently the only approved osteoanabolic therapy for osteoporosis. It is available as the full-length molecule PTH (1-84) in Europe and as the recombinant amino-terminal fragment PTH (1-34) (teriparatide) worldwide. Another promising therapeutic osteoanabolic class is targeted against sclerostin. Monoclonal antibodies against sclerostin, romosozumab and blosozumab, are currently being developed and have advanced to clinical trials.

**PTH**

Both teriparatide and PTH (1-84) are administered by subcutaneous daily injection for up to a 2-year course for the treatment of osteoporosis in postmenopausal women and in men with osteoporosis who are at high risk for fracture. In Japan, a weekly regimen of teriparatide is also approved to treat osteoporosis (26). In contrast to antiresorptive therapies, teriparatide and PTH (1-84) directly stimulate processes associated with bone accrual. Virtually all clinical studies with PTH therapy show an interesting discordance in the timing of the increase in bone formation and bone resorption markers. Bone formation markers increase first followed subsequently by an increase in resorption markers. In the teriparatide studies, the bone formation markers, BSAP and PICP increase by 1 month of therapy (27,28). It was observed an increase of 67% in PICP in the first month and serum CTX increased 88% in the sixth month (27). The increase in bone resorption markers, NTX and deoxypyridinoline (DPD), is delayed, relative to the increase in the bone formation markers, and is not of the same magnitude (27,28). A subanalysis of The Fracture Prevention Trial showed that changes in PICP at 1 month and P1NP at 3 months are sensitive and accurate predictors of the lumbar spine BMD response at 18 months (27). The changes noted in BTMs also reflect the histomorphometric findings of an effect of PTH to increase processes associated with bone formation first before there is any evidence for bone resorption (29). This period of time when PTH stimulates bone formation directly, without any evidence for bone remodeling, has been called the “anabolic window” (30). This concept also suggests that during this period of time, when only bone formation is ongoing, the primary anabolic mechanism is bone modeling. The
The pattern of change in bone turnover markers with weekly teriparatide (56.5 μg/week) appears to be different from daily use of the drug. While changes in bone formation markers with weekly teriparatide are similar to the daily regimen (32,33), the u-NTX, reflecting bone resorption falls, after an initial tendency to rise. Black and cols. have reported similar results using weekly PTH (1-84) (34).

Many patients who are switched to PTH therapy have been taking an antiresorptive agent. A subgroup analysis of the EUROpean Study of FORSteo (EUROFORS) stratified patients by previous antiresorptive therapy (alendronate, risedronate, etidronate and non-bisphosphonate) before the switch to teriparatide. Regardless of previous antiresorptive use, bone formation markers P1NP and BSAP increased in all groups after 1 month of teriparatide treatment and continued to rise through 6 months, although the increment change varied according to previous antiresorptive treatment (35). In another study, Miller and cols. compared the effect of previous exposure to risedronate or alendronate in terms of subsequent effects of teriparatide (36). The hypothesis of this study was that the more potent effects of alendronate on bone turnover markers would lead to a slower onset of effect on bone formation markers, in comparison to risedronate. The results of this trial were consistent with this hypothesis.

In concept, the combination of an osteonabolic and an antiresorptive agent could be more beneficial than monotherapy with either drug alone, because the eventual increase in bone resorption with teriparatide, which is believed to limit PTH’s effects, would be controlled by the antiresorptive agent. However, most of the studies that have utilized combination therapy with PTH (1-84) or teriparatide and an antiresorptive have not been promising. Using alendronate as the antiresorptive agent, Black and cols. (37) studied postmenopausal women with 100 μg of PTH (1-84) while Finkelstein and cols. (38) studied men with 40 μg of teriparatide. In both cases, BTMs in the combination therapy group mirrored the effects of monotherapy with alendronate, with reductions in bone formation and bone resorption markers. It appeared that the potent antiresorptive effects of alendronate interfered with the potential actions of PTH (1-84) or teriparatide in this setting. This premise was tested by Deal and cols. (39) utilizing a less potent antiresorptive agent, raloxifene. In this study, the combination therapy arm showed an increase in bone formation markers similar to teriparatide alone. The increases in bone resorption markers, however, were reduced in comparison to teriparatide alone (39). The combination of teriparatide and risedronate in men also showed that BTMs mirrored the BTMs changes in the teriparatide-alone arm (40). The raloxifene (37) and risedronate (38) combination studies were small, and further data are needed, but they strengthened the idea that the anabolic window could be expanded by using combination therapy with teriparatide and an antiresorptive drug that does not have potent effects on bone resorption. Enforcing this notion is the combination therapy study of teriparatide and zoledronic acid. The pattern of change in BTMs with this combination is different from the combinations previously described. With combination therapy, there was a rapid, but transient, reduction in CTX during the first 2 months, with a subsequent and gradual increase with levels remaining above baseline for last 6 months of the study. Levels of both markers were significantly lower with combination therapy versus teriparatide alone (p<0.002) (41).

Combination therapy with teriparatide and denosumab is based upon a different hypothesis. The catabolic actions of PTH are believed to require RANK-L. If the RANK-L inhibitor denosumab is used with PTH, therefore, that catabolic pathway should be inhibited, thus “permitting” PTH to utilize more exclusively the osteonabolic Wnt signaling pathway. This hypothesis was tested in the Denosumab and Teriparatide Administration (DATA) (42). One hundred postmenopausal women with osteoporosis were randomized to receive teriparatide and denosumab, alone or in combination for 12 months. This study showed a densitometric benefit in year 1 in the combination arm which was sustained in year 2 (43). As anticipated, patients on monotherapy with denosumab showed a decrease in BTMs while patients in the teriparatide alone arm showed an increase of BTMs. In the combination therapy cohort, CTX falls with a time course and extent that is indistinguishable from the denosumab monotherapy arm. However, P1NP and osteocalcin decline with a much
slower time course and to a lesser extent (combination therapy: osteocalcin: -39 ± 22%, denosumab monotherapy: -55 ± 20%). A 12-month extension of the DATA Study showed that osteocalcin continued to decrease in the combination group, but still to a lesser extent than denosumab monotherapy. CTX suppression remained similar in the denosumab and in the combination therapy group (44). BMD increments during the two years of combination therapy with teriparatide and denosumab were higher than with either medication as monotherapy (44).

**Sclerostin antibodies**

Sclerostin is a glycoprotein product of the SOST gene and secreted mainly by osteocytes. It acts as an inhibitor of the anabolic Wnt signaling pathway by occupying the Wnt binding site at the LRP5/LRP6 complex (45-49). In the rare human diseases known as van Buchem or sclerosteosis, genetic mutations lead to loss of sclerostin expression. These individuals have high bone mass and do not fracture (49,50). These human diseases were a clue that eventually led to the development of humanized monoclonal sclerostin antibodies. These antisclerostin antibodies allow Wnt signaling pathway to function unimpeded by sclerostin and thus serve as a new pharmacologic osteoanabolic class.

**Romosozumab** (AMG 785/CDP7851, being developed by Amgen and UCB), is the first humanized monoclonal antibody to sclerostin for which clinical trials results were published. In the phase 1 trial, changes in BMD and BTMs were evaluated in 72 healthy subjects (51). Subjects were randomized to receive a single dose of placebo or either one dose of romosozumab SC (regimens 0.1, 0.3, 1, 3, 5 or 10 mg/kg) or one dose of romosozumab IV (regimens 1mg or 5 mg/kg). Bone formation markers P1NP, BSAP and osteocalcin showed a marked increase after a single SC injection, reaching maximum increments of 184%, 126% and 176% respectively with the 10 mg/kg SC, and 167%, 125%, 143% respectively with the 5 mg/kg IV regimen. Surprisingly, serum CTX decreased also in a dose-dependent manner, reaching nadirs of -54% with 10 mg/kg SC and -49% with 5 mg/kg IV (51). Ionized calcium concentration showed a small (4%) but transient reduction with levels returning to baseline thereafter. PTH levels increased transiently in the romosozumab cohorts possibly reflecting the changes in the ionized calcium concentration. In another phase I study, ascending multiple-doses of romosozumab were administered for 12 weeks to healthy men and postmenopausal women with low bone mass (52). Patients were randomized to receive either placebo or one of the SC regimens of romosozumab [1 or 2 mg/kg once every 2 weeks (Q2W) or 2 or 3 mg/kg once every 4 weeks (Q4W)]. Bone formation markers P1NP, osteocalcin and BSAP increased in the romosozumab groups. P1NP showed the greatest increments in the first 8 weeks of dosing compared to baseline and to smaller increases in the last 4 weeks of dosing, with levels returning to baseline within 4 to 8 weeks after the last romosozumab dose. Osteocalcin and BSAP changed in the same manner. P1NP levels increased by 106% and 147% in men, and by 83% and 129% in women at the romosozumab 1 mg/kg Q2W and at 3 mg/kg cohorts respectively. Changes in serum CTX levels were noteworthy for a decline with romosozumab treatment. Maximum reductions in CTX were -21% for placebo, and -35% and -37% for postmenopausal women in the romosozumab Q4W regimen at 2 or 3 mg/kg respectively. In men, CTX reached a nadir of -42% on the 1 mg/kg Q2W and -50% on the 3 mg/kg Q4W romosozumab cohorts (52). Changes in BTMs reflected the salutary effects seen at BMD, with lumbar spine BMD increasing between 4-7%, and total hip between 2-3% in patients taking romosozumab. These studies were followed by the results of the phase II study, which enrolled 419 postmenopausal women with low BMD (T-score ≤ -2.0 and > -3.5 at lumbar spine, total hip or femoral neck (53). Romosozumab dosing regimens were: monthly SC doses (70 mg, 140 mg or 210 mg), or Q 3-month SC doses (140 mg or 210 mg) for a total of 12 months. The controls included placebo or one of 2 active comparators: alendronate 70 mg weekly or teriparatide 20 µg SC daily. A rise in bone formation markers was noticed after one week of romosozumab treatment, reaching a peak after one month and decreasing thereafter to or below baseline levels (53). Conversely, CTX levels fell rapidly by the first week of romosozumab with CTX levels remaining below baseline values at 12 months. Similarly to results of the phase 1 trial, a transient reduction was noted in serum calcium concentration taking romosozumab, along with an also transient increase in PTH levels. Phase III trials of romosozumab are currently ongoing (54,55).

**Blosozumab** (Eli Lilly, Indianapolis, IN, USA) is another humanized sclerostin antibody that is being tested at this time. In a recent publication, results of two
phase I trials of blosozumab in postmenopausal women were reported. The first trial was a single-dose study, randomized, subject- and investigator blind, placebo-controlled, single-dose, dose-escalation study. A total of 60 subjects were randomized to 8 cohorts: 5 cohorts received IV regimens of blosozumab in a dose range (7.5, 25, 75, 225, and 750 mg). At each dose level during the dose-escalation phase, subjects received blosozumab or placebo. Another cohort received either blosozumab 150 mg or placebo SC. The other two cohorts with prior exposure to bisphosphonate received either 225 mg or 750 mg of IV blosozumab (56). The second phase I trial was a multiple-dose, multicenter, randomized, subject- and investigator blinded, placebo-controlled, parallel design study, in which 59 patients were randomized to either placebo or blosozumab SC (270 mg) or IV (750 mg) once every 2 weeks (Q2W), or blosozumab SC (180 or 270 mg) or IV 540 mg once every 4 weeks (Q4W) for 8 weeks. Dose-dependent responses were noted in BTMs levels of patients who received blosozumab. Bone formation markers OC, BSAP and P1NP increased in patients in the single- and multiple-dose regimens. CTX decreased after a single SC or IV dose of blosozumab, also in a dose-dependent manner, returning thereafter to baseline levels. In the trial with repeated doses of blosozumab, the reduction in CTX did not appear to have a clear dose-response relationship, but CTX levels returned to baseline except for patients on the 750 mg IV arm where CTX levels increased to nearly 100% above baseline. Total sclerostin (free and blosozumab-bound sclerostin) increased, with levels later decreasing in the same manner as the decline in blosozumab concentration. The similarity in this kinetics could reflect levels of sclerostin predominantly bound to blosozumab. BTMs in the subset of patients with previous bisphosphonate exposure showed similar dose-dependent responses, although with a lower magnitude (56).

**CONCLUSION**

BTMs have the potential to be useful monitoring tools in osteoporosis therapeutic regimens. Their change following treatment with an anti-absorptive or osteoanabolic agent may reflect a bone effect and should be considered in evaluating failure to therapy, along with BMD reductions and the presence of a fracture. Considering the significant change at 95% confidence, decrease of at least 25% following an anti-resorptive and an increase of at least 25% following an osteoanabolic agent are the minimal change required (57).

The data are still insufficient to relate BTMs changes alone to the outcome index of fracture risk reduction.

Disclosures: Dr. Francisco Bandeira is a consultant for Servier and Sanofi and receives research support from Amgen. Dr. John P. Rilezikian is a consultant for Amgen, Eli Lilly, Radius, NPS Pharmaceuticals, Merck, and GSK, and receives research support from NPS Pharmaceuticals and Amgen. Drs. Aline G. Costa, Manoel Anderson Soares and Lourena Lima: no conflicts of interest reported.

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